Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende lenvatinib i kombination med pembrolizumab til 1. linjebehandling af metastatisk nyre-cellekarcinom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. lenvatinib i kombination med pembrolizumab til 1. linjebehandling af metastatisk nyrecellekarcinom
2. Forhandlingsnotat fra Amgros vedr. lenvatinib i kombination med pembrolizumab til 1. linjebehandling af metastatisk nyrecellekarcinom
3. Ansøgers endelige ansøgning vedr. lenvatinib i kombination med pembrolizumab til 1. linjebehandling af metastatisk nyrecellekarcinom

Eisai response to DMC Draft Assessment Report for lenvatinib in combination with pembrolizumab for mRCC

Eisai would like to thank the Danish Medicines Council (DMC) for their draft assessment report. We acknowledge that there is uncertainty within the cost-effectiveness analysis, and scenarios that need to be further explored. We request that these be considered using the appropriate tools available, according to the DMC guidelines. A discussion of these scenarios and uncertainties is given below:

Overall Survival HR =1:
Based on the results of the network meta-analysis (NMA), overall survival (OS) has a hazard ratio (HR) of 0.95 [0.68; 1.34] when LEN+PEM is compared to NIVO+IPI. On this basis, the DMC assesses that there is no difference between treatment with LEN+PEM and NIVO+IPI and sets the HR = 1. This could be considered to be an overly simplistic assessment and approach. A more objective and academic approach is to use the data as calculated (i.e., using the mean point estimate from the NMA), and to incorporate any uncertainty using the probabilistic sensitivity analysis (PSA), as per DMC guidelines. Changing only the mean point estimate in the deterministic analysis undermines the data. Using PSA, rather than deterministic results allows parameter uncertainty to be explored.

Treatment capping
The DMC model base case utilizes data from the NIVO+IPI CheckMate trial. There are considerable differences between modelled costs and true efficacy when considering the use of this data in the DMC model base case. For example, in the CheckMate trial, NIVO use was not capped at 2 years. However, in the DMC model base case, checkpoint inhibitor treatments such as NIVO are capped at 2 years as a reflection of Danish clinical practice. Furthermore, in the DMC model base case, no reduction in efficacy for NIVO+IPI is assumed, even though treatment is capped. This potentially biases the calculation of NIVO+IPI costs and efficacy compared to LEN+PEM, since PEM was capped in the CLEAR trial.

Therefore, treatment capping should be tested in scenario analyses. The objective way to test this is to remove the treatment cap for both PEM and NIVO, resulting in efficacy being costed exactly as it is observed. This contrasts with the current approach taken in the DMC model base case, where the costs of NIVO+IPI treatment are artificially reduced by capping, without also reducing efficacy. As noted in Regan et al 2021, patients in general remain on treatment with NIVO+IPI much longer than two years, with 14% of patients still on treatment at 42 months. This suggests that there is a real-world benefit to NIVO+IPI treatment that extends beyond two years. Capping of treatment costs without also reducing efficacy therefore results in not costing the efficacy observed. This can lead to a significant underestimation of true costs, therefore biasing the calculation of NIVO+IPI costs and efficacy compared to LEN+PEM.

Extrapolation and time horizon:
Curve choices (and therefore also the time horizon) have been selected by the DMC based solely on the fit to landmark values in the CheckMate trial, without considering the long-term effect from the CLEAR trial. A more objective and pragmatic approach should be taken rather than biasing curve choices based on the fit to NIVO+IPI alone. When curves are chosen, a respective lifetime horizon should also be used.

Eisai AB
Svärdvägen 3A, SE-182 33 Danderyd, SWEDEN, Phone +46 501 01 600 · Fax +46 8 501 01 699
Org no 556683-3934 · VAT no SE556683-393401
www.eisai.co.uk

As per DMC guidelines, a time horizon should be long enough such that all costs and effects are captured, therefore a time horizon of 40 years should be used in contrast to the 20 years in the DMC model base case.

Summary and Results:
It is important to note that non-redacted ICERs presented in the assessment report only represent list prices. In reality, many treatments have significant discounts (such as pembrolizumab), and therefore the true ICERs are significantly lower than the list price ICERs presented.

In addition to treatment costs, overall survival is one of the main drivers of the results, and if extreme scenarios such as those in the DMC model base case are used, this drastically reduces the predicted incremental survival and incremental quality-adjusted life years (QALYs).

When more objective settings regarding survival are used, this results in incremental QALYs that are more than two times greater, with an estimated incremental QALY versus NIVO+IPI of 0.27 (compared to 0.12 in the DMC scenario), and significantly decreased ICERs.

Reference:
1. Regan, M.M., et al., Treatment-free Survival after Immune Checkpoint Inhibitor Therapy versus Targeted Therapy for Advanced Renal Cell Carcinoma: 42-Month Results of the CheckMate 214 Trial. Clinical Cancer Research, 2021. 27(24): p. 6687-6695.

Eisai AB
Svärdvägen 3A, SE-182 33 Danderyd, SWEDEN, Phone +46 501 01 600 · Fax +46 8 501 01 699
Org no 556683-3934 · VAT no SE556683-393401
www.eisai.co.uk

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

28. oktober 2022
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.11.2022
Leverandør	Eisai
Lægemiddel	Kisplyx (lenvatinib)
Ansøgt indikation	Kisplyx (lenvatinib) i kombination med Keytruda (pembrolizumab) til 1. linjebehandling af metastatisk nyrecellekarcinom.

Forhandlingsresultat

Amgros har opnået følgende pris på Kisplyx (lenvatinib):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke/form	Pakningsstørrelse	AIP	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Kisplyx (lenvatinib)	10 mg (kapsler)	30 stk.	12.237,92	[redacted]	[redacted]
Kisplyx (lenvatinib)	4 mg (kapsler)	30 stk.	12.237,92	[redacted]	[redacted]

Prisen er betinget af en anbefaling til en af de to populationer i Medicinrådets vurderingsrapport; 1. patienter med mRCC i god prognosegruppe, eller 2. patienter med mRCC i intermediær/dårlig prognosegruppe.

Leverandøren har markedsført to lægemidler med samme aktive indholdsstof og har ansøgt EMA om forskellige indikationer. Leverandøren har i forvejen Lenvima (lenvatinib), der tidligere er vurderet og godkendt af Medicinrådet til behandling af patienter med hepatocellulært carcinom. Kisplyx (lenvatinib) og Lenvima (lenvatinib) har samme ATC-kode, aktive indholdsstof, styrke og pakningsstørrelse.

Da lægemidlerne ligner hinanden, er det ikke muligt at forhandle på lægemidlerne eller nedsætte prisen i forbindelse med en prisjustering. Kisplyx (lenvatinib) og Lenvima (lenvatinib) indgår i samme udbud, som har aftale indtil d. 31.03.2023. Lægemidlerne vil blive udbudt med aftalestart den 01.04.2023.

Informationer fra forhandlingen

Leverandøren har mulighed for at komme med en ny pris på de to lægemidler i forbindelse med udbuddet, som har aftalestart d. 01.04.2023.

[redacted].

[redacted]

Konkurrencesituation og relation til behandlingsvejledning

Leverandøren har ansøgt på to patientpopulationer:

- God prognosegruppen med sunitinib som komparator
- Intermediær/dårlig prognosegruppe med Opdivo (nivolumab) i kombination med Yervoy (ipilimumab) som komparator.

Nedenstående tabel 2 viser udregninger for et års behandling af patienter i den intermediære/dårlige prognosegruppe. Der er ikke regnet på prisen for god prognosegruppe, da der har været patentudløb på Sutent (sunitinib), og der er derfor generisk konkurrence med markant lavere priser end tidligere. Kombinationen med inlyta (axitinib) og Keytruda (pembrolizumab) indgår også i tabellen, denne kombination er dog blevet afvist af Medicinrådet.

Tabel 2: Sammenligning af lægemiddeludgift til behandling af den intermediær/dårlige prognosegruppe

Lægemiddel	Dosering	Styrke og pakningsstørrelse	Pakningspris (SAIP, DKK)	Antal pakninger for perioden	Pris for 40 ugers behandling (SAIP, DKK)	I alt for kombinationer (DKK)
Kisplyx (lenvatinib)	20 mg PO/dag	10 mg (30 stk.)	[redacted]	9,3	[redacted]	[redacted]
Keytruda (pembrolizumab)	4 mg/kg* IV/6. uge	25 mg/ml (4 ml)	[redacted]	21	[redacted]	
Opdivo (nivolumab)	3 mg/kg* IV/3. uge 4 gange og herefter 6 mg/kg* IV/4. uge	240 mg/24 ml (1 stk.)	[redacted]	18	[redacted]	[redacted]
Yervoy (ipilimumab)	1 mg/kg* IV/3. uge 4 gange	5 mg/ml (40 ml)	[redacted]	1,6	[redacted]	
Inlyta (axitinib)	5 mg*2 PO/dag	1 mg (56 stk.)	[redacted]	50	[redacted]	[redacted]
Keytruda (pembrolizumab)	4 mg/kg* IV/6. uge	25 mg/ml (4 ml)	[redacted]	21	[redacted]	

*80 kg jf. Medicinrådets vurderingsrapport på Kisplyx (lenvatinib)

Status fra andre lande

Norge: Godkendt i juni 2022[1].
England: Under vurdering[2].

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/lenvatinib-kisplyx-pembrolizumab-keytruda
[2] https://www.nice.org.uk/guidance/indevelopment/gid-ta10629

Medicinrådet

Revised application for the assessment of lenvatinib with pembrolizumab for first line treatment of advanced renal cell carcinoma for adults

Table of contents

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Basic information

Contact information	
Name	**Sara Fredriksson Emrooz**
Title Phone number E-mail	Nordic Market Access Manager +46(0)73 143 53 91 Sara_FredrikssonEmrooz@eisai.net

Table 1. Overview of the pharmaceutical technology

Proprietary name	Kisplyx® Keytruda®
Generic name	Lenvatinib Pembrolizumab
Marketing authorization holder in Denmark	Eisai MSD
ATC code	L01EX08 L01XC18
Pharmacotherapeutic group	Antineoplastic agents, protein kinase inhibitors Antineoplastic agents, monoclonal antibodies
Active substance(s)	Lenvatinib Pembrolizumab
Pharmaceutical form(s)	Oral therapy IV therapy
Mechanism of action	Lenvatinib is an RTK inhibitor that selectively inhibits Vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2, and VEGFR3), as well as multiple other proangiogenic and oncogenic signalling pathways, including FGFR1, 2, 3, and 4, platelet-derived growth factor receptor alpha (PDGFRα), KIT, and RET. Pembrolizumab binds to the PD-1 receptor and blocks its interaction with the PD-L1 and PD-2 ligands, releasing PD-1-mediated inhibition of the immune response (including anti-tumour response).
Dosage regimen	The recommended dosage of lenvatinib is 20 mg orally once daily in combination with pembrolizumab administered as an IV infusion over 30 minutes: 200 mg every three weeks or 400 mg every 6 weeks Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, loss of clinical benefit, completion of 35 treatments (approximately 2 years) with pembrolizumab, or sponsor termination of the study. In the presence of clinical benefit, subjects in Arm B who discontinue pembrolizumab may continue treatment with lenvatinib alone unless any of the other discontinuation criteria apply. [1] This is in accordance with Danish clinical practice. [2]
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Kisplyx is indicated in combination with pembrolizumab for the first line treatment of adults with advanced renal cell carcinoma (RCC)

Other approved therapeutic indications

Kisplyx is also indicated in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.

Keytruda is also indicated for:

Melanoma

KEYTRUDA® as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

KEYTRUDA® as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.

Non-small cell lung carcinoma (NSCLC)

KEYTRUDA® as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

KEYTRUDA®, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.

KEYTRUDA®, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.

KEYTRUDA® as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA®.

Classical Hodgkin lymphoma (cHL)

KEYTRUDA® as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous 3 stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Urothelial carcinoma

KEYTRUDA® as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy

KEYTRUDA® as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10

Head and neck squamous cell carcinoma (HNSCC)

KEYTRUDA®, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1

KEYTRUDA® as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy

Renal cell carcinoma (RCC)

KEYTRUDA®, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults

Colorectal cancer (CRC)

	KEYTRUDA® as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults Oesophageal carcinoma KEYTRUDA® in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10 Triple-negative breast cancer (TNBC) KEYTRUDA® in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease [3]
Will dispensing be restricted to hospitals?	Dispensation of lenvatinib is not restricted to hospitals (oral form), pembrolizumab is to be dispensed at a hospital.
Combination therapy and/or co-medication	Yes
Packaging – types, sizes/number of units, and concentrations	Kisplyx® 4mg hard capsules – Each hard capsule contains 4mg of lenvatinib (as mesylate) Kisplyx® 10mg hard capsules – Each hard capsule contains 10mg of lenvatinib (as mesylate) [1] Keytruda® 25mg/ml – Each pack contains 4ml [3]
Orphan drug designation	No

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Abbreviations

Abbreviation	Full name
1L	First line
AVE+AXI	Avelumab with Axitinib
BSC	Best supportive care
ccRCC	Clear cell renal cell carcinoma
DCO	Data cut-off
DIC	Deviance Information Criterion
DOR	Duration of response
DRG	Diagnosis-related groups
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Cancer-Core 30 Module
EPAR	European public assessment report
EQ-5D	EuroQoL-5 Dimensions
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy-General
FAS	Full Analysis Set
FE	Fixed-effects
FGFR	Fibroblast growth factor receptors
FKSI-19	Functional Assessment of Cancer Therapy-Kidney Symptom Index-19
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index Disease-Related Symptoms
HR	Hazard ratio
HRQoL	Health-related Quality of life
IA	Interim analysis
IMDC	International Metastatic RCC Database Consortium
INV	Assessment between investigators
IRC	Independent review committee
ITC	Indirect treatment comparison
IV	Intravenous
KIT	Tyrosine-protein kinase
KM	Kaplan Meier
LEN+PEM	Lenvatinib in combination with pembrolizumab
LS	Least squares
m/aRCC	Metastatic/advanced RCC
m-ccRCC	Metastatic clear cell renal cell carcinoma
mDOR	Median duration of response
MID	Minimally important difference
MMRM	Mixed-model repeated measures
MSKCC	Memorial Sloan-Kettering Cancer Centre
MTD	Median treatment duration
NIVO+IPI	Nivolumab with ipilimumab
NMA	Network meta-analysis
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PEMBRO	Pembrolizumab
PDGFRα	Platelet-derived growth factor receptor alpha
PD-L	Programmed death-ligand
PFS	Progression-free survival
PICOS	Patient-intervention-comparator-outcome-study type
PH	Proportional hazard

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROs	Patient-reported outcomes
RCC	Renal Cell Carcinoma
RCTs	Randomized-controlled trials
RE	Random effects
RET	Rearranged during transfection proto-oncogene
RTK	Receptor tyrosine kinase
SLR	Systematic literature review
SYs	Subject-years
TEAEs	Treatment emergent adverse events
TKI	Tyrosine kinase inhibitor
TRAEs	Treatment related adverse events
TTD	Time to treatment-discontinuation
TTFD	Time to first deterioration
TuDD	Time until definitive deterioration
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptors

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Tables and Figures

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

1. Summary

1.1 Indication

This single technology assessment relates to lenvatinib plus pembrolizumab (LEN+PEM) for the first line treatment of adult patients with advanced renal cell carcinoma (aRCC). In Denmark approximately 250 patients are newly diagnosed with aRCC every year [4], making it the most common type of kidney cancer in Denmark [5].

LEN+PEM is expected to gain a broad European Commission indication for the first line treatment of aRCC in adult patients in November 2021, in alignment with the positive opinion of the CHMP published on the 14th of October 2021 [6]. This submission presents the case for the full indication based on the intention to treat (ITT) population of the Phase III CLEAR study of LEN+PEM versus sunitinib in patients with aRCC [7], as well as for two main patient subgroups of particular interest to the Danish Medicines Council (DMC) [8, 9]: patients who have favourable (good) prognosis and patients who have intermediate/poor prognosis according to the International Metastatic RCC Database Consortium (IMDC) classification [10].

1.2 The pharmaceutical

Lenvatinib is a Tyrosine Kinase Inhibitor (TKI) active against both VEGFR, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4) and FGFR, FGFR1, 2, 3, and 4. Lenvatinib also inhibits other Receptors Tyrosine Kinases (RTKs) that have been implicated in pathogenic angiogenesis, tumour growth, and cancer progression in addition to their normal cellular functions, including the platelet-derived growth factor receptor α (PDGFRα), KIT, and RET.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between the Programmed cell death protein 1 (PD-1) and its ligands, PD-L1 and PD-L2.

In the CLEAR trial [7], the combination of the immunomodulatory activity of LEN+PEM has been shown to produce potent antitumor activity beyond that observed with either agent alone [7, 11, 12]. These results demonstrate that LEN+PEM is a promising alternative treatment option for aRCC.

1.3 The comparators

Comparators were selected based on the DMC's recommendation and treatment guidance for aRCC. In accordance with the DMC's guidelines, which consider that sunitinib, tivozanib and pazopanib are clinically equivalent [8, 13], it is assumed in this submission that the evidence of sunitinib's efficacy can be used as a proxy of tivozanib's efficacy, which is recommended to be used in 80% of patients in the IMDC good prognosis population [8, 13]. In summary, for each population, the selected comparators are:

ITT overall population	• sunitinib
Good prognosis group	• sunitinib
Intermediate/poor prognosis group	• nivolumab in combination with ipilimumab

1.4 Most important efficacy endpoints

The primary endpoint of the CLEAR trial was progression-free survival (PFS) per independent review (IIR) as per RECIST 1.1. In accordance to previous submissions to the DMC in the same indication [8, 9], PFS and OS are the main endpoints of interest in demonstrating the efficacy of anti-tumour treatments within aRCC and they are also the main inputs in the economic model. Secondary endpoints include overall Response Rate (ORR), Complete Response (CR), Duration of Response (DOR) and Health Related Quality of life (HRQoL) as measured by Functional Assessment of Cancer Therapy Kidney Symptom Index Disease-Related Symptoms (FKSI-DRS), an instrument specifically designed to assess disease-related symptoms of kidney cancer and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Patients with Cancer-Core 30 Module (EORTC QLQ-C30).

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

In the CLEAR study, the LEN+PEM combination regimen produced a ~24-month median PFS in the overall population—an efficacy unparalleled among existing 1L aRCC regimens. LEN+PEM also resulted in significant improvement in OS versus sunitinib at median follow-up 33.7 (32.8, 34.4) months LEN+PEM arm and 33.4 (32.5, 34.1) months for the sunitinib arm, with a HR of 0.72 (95% CI 0.55, 0.93). The CR rate of 16% was also a notable result for LEN+PEM, as clinical expert recently highlighted CR is a good predictor of long-term survival. The CLEAR study demonstrated consistent clinical benefits across risk groups [14].

1.5 Safety of the pharmaceutical

The LEN+PEM regimen demonstrated tolerability in the CLEAR study, with a rate of discontinuation due to adverse events similar to sunitinib; individual adverse events were consistent with the established profile of each individual agent and typically manageable via dose modifications and standard medical care. The rate of grade ≥3 Treatment emergent adverse events (TEAEs) (82.4% in the LEN+PEM arm and 71.8% in the sunitinib arm) was equivalent to 2.0 and 2.1 per subject-year, respectively, when adjusted for drug exposure. The rate of fatal TEAEs (4.3% in the LEN+PEM arm and 3.2% in the sunitinib arm) was equivalent to 0.04 and 0.03 per subject-year, respectively, when adjusted for drug exposure. Finally, 13.4% of patients in the LEN+PEM arm discontinued both drugs due to a TEAE, vs 14.4% of patients in the sunitinib arm.

1.6 Structure of the economic analysis

The Cost-effectiveness model (CEM) was based on a three-state partitioned survival model with the following health states: progression-free, progressed, and dead. LEM+PEM was compared to the standard of care in Denmark for 1L treatment of aRCC. Sunitinib and nivolumab plus ipilimumab (NIVO+IPI) were included in the model as comparators.

The base case included the overall trial population with two additional subgroups included in the CEM: IMDC good prognosis risk, IMDC intermediate/poor prognosis. Eight subsequent treatments were included in the base-case: sunitinib, pazopanib, nivolumab, cabozantinib, axitinib, avelumab with axitinib (AVE+AXI) and pembrolizumab with axitinib (PEM+AXI). The time-horizon for the model was up to 40 years to cover/correspond the lifetime perspective , in accordance with the DMC requirements [15]. Deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA) and scenario analyses were conducted.

1.7 Sources of relative efficacy of the economic model

Survival analyses were conducted by fitting a series of distributions to the LEN+PEM and sunitinib data from CLEAR. These distributions were: Exponential, Weibull, Log-normal, log-logistic, Gompertz and Generalized Gamma. Single stratified fits and joint fits (with treatment as predictor) were fitted to the data. These parametric models were fitted to the OS, PFS and time to treatment discontinuation (TTD) data (joint fits were not fitted for the TTD data, but TTD was fitted separately for lenvatinib, pembrolizumab and sunitinib). These were also fitted for the intention-to-treat population and the two subgroups. All analyses were completed using SAS (version 9.4).

Specifications of different statistical fits for PFS, OS and TTD were taken from statistical analyses which followed the approach outlined in the NICE (National Institute for Health and Care Excellence) Decision Support Unit (DSU) technical support documentation [16]. In accordance with the DSU recommendations, proportional hazards (PH) assumptions were first tested though visual inspection of the log-cumulative hazard plot to assess if the LEN+PEM and sunitinib treatment curves cross for PFS and OS. In addition, formal testing through the Schoenfeld residuals test was performed with a p-value less than 0.05 suggesting that the proportional hazard assumption does not hold and that independent parametric fits are more suitable. Subsequently, the statistical fits for LEN+PEM and sunitinib for PFS and OS, and for lenvatinib, pembrolizumab and sunitinib for TTD were assessed using Akaike information criterion (AIC) and Bayesian information criterion (BIC) criteria, with the distribution producing the lowest AIC and BIC indicated as being the best fitting distribution. Similar to the approach adopted by the Evidence Review Group (ERG) in NICE TA640 [17], survival models were categorised in terms of statistic fit using modified Burnham [18] /Anderson and Raftery [19] rules of thumb to highlight the appropriateness of the remaining distributions relative to the model(s) with the best statistical fits.

To estimate the relative efficacy of LEN+PEM versus NIVO+IPI, constant hazards derived from a Network Meta Analysis (NMA) were applied in the economic model.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

1.8 Results of the economic analysis

Overall, treatment with LEN+PEM demonstrated to be a better treatment option in the ITT population producing better QALY gains and the best ICER outcomes compared to the IMDC good and intermediate/poor subgroups:

In the ITT population, LEN+PEM compared to Sunitinib provided a QALY gain of XXXX at an incremental cost of XXXXXXXXX resulting in an ICER of XXXXXXXXX DKK per QALY.

In the IMDC good prognosis population, LEN+PEM compared to Sunitinib provided a QALY gain of XXXX at an incremental cost of XXXXXXXXX resulting in an ICER of XXXXXXXXXX DKK per QALY.

In the IMDC intermediate/poor population, LEN+PEM compared to NIVO+IPI provided a QALY gain of XXXX at an incremental cost of XXXXXXXX DKK. This results in an overall ICER of XXXXXXXXX DKK.

Probabilistic results were consistent with deterministic results.

XLEN+PEM in the overall population is associated with a BI of XXXXXXXXXX in year 1, increasing annually until a BI of XXXXXXXXXX in year 5.

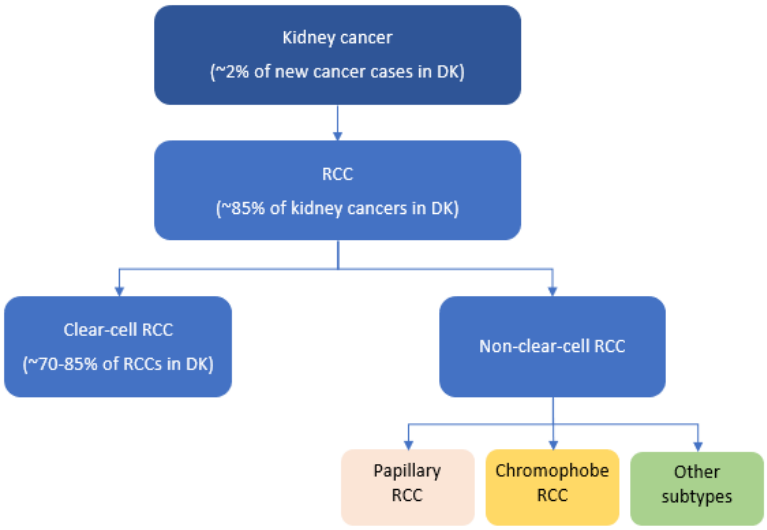
2. The patient population, the intervention and choice of comparator(s)

2.1 The medical condition and patient population

2.1.1 Pathophysiology and epidemiology of RCC

Kidney cancer is one of the most lethal genitourinary cancers, accounting for over 179,000 deaths per year worldwide [20]. Renal cell carcinoma (RCC) accounts for about 2% of all cancers in Denmark [5] and represents approximately 85% of all kidney cancers, in Denmark [5]. RCC includes many subtypes, including clear-cell, papillary, chromophobe, and other rarer forms (Figure 1) [8]. The most prevalent subtype, clear-cell RCC, has been the primary focus of RCC clinical trials [21, 22].

Figure 1. Common subtypes of RCC



Source: [8]
Abbreviations: DK, Denmark; RCC, Renal cell carcinoma.

The most recent report published by the Danish Renal Cell Cancer Database [4] describes that RCC most commonly onset at the age of 60-70 and rarely in people under the age of 40. RCC can develop due to sporadic mutations or hereditary variations in the genome, which most frequently occur on the short/p arm of chromosome 3 [23]. Well-established demographic, behavioural, and physiological risk factors associated with the development of RCC include obesity, hypertension, smoking, male sex, and older age [24, 25].

Most cases of RCC are discovered through unrelated imaging studies, while the tumour is still localised to the kidney [23, 26]. Most patients are asymptomatic at the time of diagnosis, however, the “classical triad” of RCC symptoms includes flank pain (discomfort in upper abdomen or back and sides), haematuria (blood in the urine), and palpable abdominal mass (abnormal growth in the abdomen [10, 23]. Patients may also exhibit signs of paraneoplastic syndromes, including hypertension, anaemia, cachexia (weakness), and

weight loss [23]. Patients with distant metastases at diagnosis (approximately 5% to 21% of cases) may also experience symptoms at sites of tumour spread [26-31].

Patients with RCC only localised to the kidney have relatively good outcomes, however, metastatic/advanced RCC (aRCC) is associated with much poorer prognosis [26, 27]. As described in detail in section 2.1.2, patients with aRCC are divided into three prognosis groups: good, intermediate, or poor. The median survival rate for aRCC is almost 4 years for patients in good, 2 years for intermediate and under 1 year for patients in poor prognosis group [32].

2.1.2 Prognostic risk stratification

RCC risk assessment strategies used in clinical guidelines consider several clinical and patient prognostic factors to stratify patients into prognostic risk groups [10]. The most commonly used prognostic risk stratification model for patients with aRCC is the IMDC prognosis groups [10, 27, 32], as described in Table 2.

Table 2: IMDC Prognostic Groups and Associated Outcomes

Prognostic factors	Risk group	Median OS	2-year OS
• Time from diagnosis to treatment <1 year[a] • Karnofsky PS <80% • Haemoglobin <LLN (normal: 12 g/dL) • Calcium >ULN (normal: 8.5–10.2 mg/dL) • Neutrophils >ULN (normal: 2.0–7.0 x 109/L) • Platelets >ULN (normal: 150,000–400,000)	Good prognosis (no risk factors)	Not reached	75%
	Intermediate prognosis (1 or 2 risk factors)	27 months	53%
	Poor prognosis (3–6 risk factors)	8.8 months	7%

Abbreviations: IMDC = International Metastatic RCC Database Consortium; LLN = lower limit of normal; OS = overall survival; PS = performance status; ULN = upper limit of normal; US = United States
aPatients included in the development of this risk model were treated with sunitinib, sorafenib, or bevacizumab
Note: this model was based on data from patients treated in the US and Canada [27, 32]
Source: [27, 32]

2.1.3 Patient populations relevant for this application

The population of interest for this submission is aRCC patients in first line (1L). In accordance with previous Danish Medicines Council (DMC) assessments of aRCC treatments [8], the population is analysed in its entirety and then subdivided into good risk disease and poor/intermediate risk disease groups, as defined by the IMDC [1, 27].

Danish renal cancer database for the years 2019-2020 [4] and the figures estimated by the DMC in a recent health technology assessment [8] indicate that there are approximately 240 patients newly diagnosed every year with aRCC in Denmark [9] [8] [33].

In line with Danish clinical opinion and it is estimated that approximately 25% of patients (n=60) are good prognosis, with the remaining 75% being intermediate poor (n=180) (Table 3). These proportions are also in line with the CLEAR clinical trial (Table 118).

Table 3. Estimated number of aRCC patients eligible for 1L treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
First-Line Treatment Population ITT	240	240	240	240	240
First-Line Treatment Population IMDC good prognosis	60	60	60	60	60
First-Line Treatment Population IMDC intermediate/poor prognosis	180	180	180	180	180

Abbreviations: aRCC, advanced renal cell carcinoma; 1L, first line
Source: [34]

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

2.2 Current treatment options and choice of comparator(s)

2.2.1 Current treatment options

2.2.1.1 Danish Medicines Council/ Medicinrådets guidelines

The DMC guidelines [13], published on the 21st of October 2020 and implemented since the 1st of January 2021, provide an overview of the treatments recommended in Denmark for aRCC. Curative treatment is mainly surgical and covers <5 % of the total number of patients who have local tumours or solitary metastases and are in good general condition [35]. When curative treatment is not an option, the patient is offered pharmacological treatment with the aim of symptom relief and life extension.

For the first line treatment of patients with clear cell aRCC in the good prognosis group, the DMC recommends tivozanib as first choice for at least 80% of patients, followed by sunitinib as second choice and pazopanib as third choice. The DMC considers that tivozanib, sunitinib and pazopanib are clinically equivalent. Moreover, the DMC acknowledges that PEM+AXI and AVE+AXI demonstrate better survival, hence these options are also included in the treatment guidance but are not recommended for this patient population as the DMC considers that there is no reasonable price/effect ratio [13].

For the first line treatment of patients in the intermediate/poor treatment group, the DMC recommends NIVO+IPI to treat up to 80% of patients in the intermediate/poor prognosis group. As second, third and fourth choice in this population, the DMC recommend tivozanib, pazopanib, and sunitinib. Similarly to the good prognosis group, PEM+AXI, AVE+AXI, and cabozantinib are included in the treatment guidance but are not recommended as the DMC considers that there is no reasonable price/effect ratio [13].

2.2.1.2 International guidelines

Table 4 presents a summary of the treatments recommended by different existing international guidelines. Figure 2 specifically describes the European Society of Medical Oncology (ESMO) guidelines.

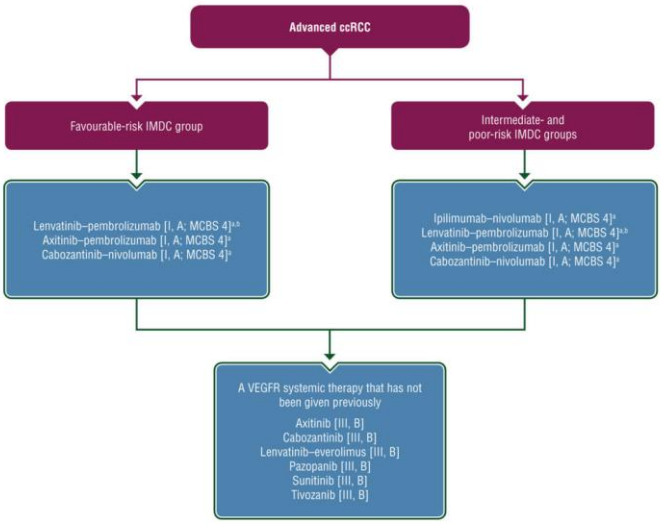
Table 4. International treatment guidelines applicable in the United States of America (US) and Europe

Region/country	Guideline	Good prognosis	Intermediate prognosis	Poor prognosis
US	NCCN	**LEN+PEM**	**LEN+PEM**	**LEN+PEM**
		CABO+NIVO	CABO+NIVO	CABO+NIVO
		PEM+AXI	PEM+AXI	PEM+AXI
		pazopanib	NIVO+IPI	NIVO+IPI
		sunitinib	cabozantinib	cabozantinib
Europe	ESMO	**LEN+PEM**	**LEN+PEM**	**LEN+PEM**
		CABO+NIVO	CABO+NIVO	CABO+NIVO
		PEM+AXI	PEM+AXI	PEM+AXI
			NIVO+IPI	NIVO+IPI
	EAU	**LEN+PEM**	**LEN+PEM**	**LEN+PEM**
		CABO+NIVO	CABO+NIVO	CABO+NIVO
		PEM+AXI	PEM+AXI	PEM+AXI
			NIVO+IPI	NIVO+IPI

EAU = European Association of Urology; ESMO = European Society of Medical Oncology; NCCN = National Comprehensive Cancer Network; US = United States

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 2. ESMO Algorithm for Systemic Treatment of 1L Advanced Clear-Cell RCC (September 2021 update)



Abbreviations: ccRCC, clear cell renal cell cancer; EMA, European Medicines Agency; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; IMDC, International Metastatic RCC Database Consortium; MCBS, ESMO-Magnitude of Clinical Scale; VEGFR, vascular endothelial growth factor receptor.
a ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA or FDA. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.
b FDA approved; not currently EMA approved. Source: [36]

Finally, the National Comprehensive Cancer Network (NCCN) recommends LEN+PEM as category 1, which indicates that the clinical evidence to support LEN+PEM was considered of the highest quality for both favourable and poor/intermediate [37].

2.2.1.3 Unmet need

Standard of care monotherapies for 1L aRCC (sunitinib, tivozanib, pazopanib) provide only ~2.5 years of OS and ~1 year of PFS; while immune-oncology combination (NIVO+IPI, AVE+AXI, and PEM+AXI) regimens offer improved efficacy both in OS and PFS, no approved regimen has extended PFS beyond 17 months [38-46]. Response rates have been shown to predict better prognosis in RCC, however, overall response rates are generally lower than 60%, with few deep and durable responses [40-42, 47-52]. Dose modifications are frequently required to manage treatment-related toxicities, ultimately leading to discontinuation of therapy in up to 41% of patients [39, 41, 44]. Thus, there remains an unmet need for efficacious 1L aRCC treatment regimens that are well-tolerated by patients and manageable by clinicians. Additional treatment options would also benefit patients who cannot receive current available options due to drug-to-drug interactions and/or comorbidities.

2.2.2 Choice of comparator(s)

Comparators were selected based on the DMC's recommendation and treatment guidance for aRCC. In accordance with the DMC's guidelines, which consider that sunitinib, tivozanib and pazopanib are clinically equivalent [8, 13], it is assumed in this submission that the evidence of sunitinib's efficacy, which is evaluated in the CLEAR trial, can be used as a proxy for tivozanib, which is recommended to be used in 80% of patients in the IMDC good prognosis population. Table 5 presents selected comparators for each prognosis group (good, and intermediate/poor).

Table 5. Summary of comparators for the treatment of 1L aRCC patients

Population	Comparator
ITT overall population	• sunitinib
Good prognosis group	• sunitinib
Intermediate/poor prognosis group	• NIVO+IPI

Abbreviations: ITT, intention to treat

2.2.3 Description of the comparator(s)

Sunitinib is approved in the EU and recommended in Denmark for the 1L treatment of patients with aRCC.

Table 6. Description of sunitinib for 1L aRCC for patients in the good prognosis treatment group [53, 54]

Subject	Description
Generic name (ATC-code)	Sunitinib (L01XE04)
Mode of action	Inhibits multiple RTKs involved in tumour growth, angiogenesis, and metastatic progression, including PDGFRs, VEGFRs, KIT, FLT3, CSF-1R, and RET
Pharmaceutical form	Tablets
Posology	50 mg orally QD for 4 weeks, followed by 2 weeks off
Method of administration	Oral
Should the pharmaceutical be administered with other medicines	No
Treatment duration / Criteria for end of treatment:	Until disease progression or unacceptable toxicity
Need for diagnostic or other test	No

Abbreviations: CSF-1R, Colony Stimulating Factor 1 Receptor; FLT3, Fms Related Receptor Tyrosine Kinase 3; KIT, tyrosine-protein kinase KIT; QD, once a day; RTKs, Receptor tyrosine kinases; PDGFRs, Platelet-derived growth factor receptors; RET, Rearranged during transfection proto-oncogen; VEGFRs Vascular endothelial growth factor receptor

Nivolumab in combination with ipilimumab is approved in the EU and recommended in Denmark for the 1L treatment of patients with aRCC.

Table 7. Description of NIVO+IPI for 1L aRCC for patients in the intermediate/poor prognosis treatment group [55]

Subject	Description
Generic name (ATC-code)	Nivolumab-Ipilimumab (L01XC17 - L01XC11)
Mode of action	PD-1 receptor is a negative regulator of T-cell activity that is involved in control of T-cell immune responses; binding of PD-1 with its ligands, PD-L1 and PD-L2 (which are expressed in antigen-presenting cells and may be expressed in by tumours or other cells in the tumour microenvironment), results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab is a monoclonal antibody which potentiates T-cell responses, including anti-tumour responses, through binding to the PD-1 receptor and blocking its interaction with PD-L1 and PD-L2 Ipilimumab is a monoclonal antibody that binds to CTLA-4, a negative regulator of T-cell activity, and blocks its interaction with its ligands (CD80/CD86); this blockade augments activation and proliferation of tumour infiltrating T-effector cells and reduces T-regulatory cell function Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumour responses in advanced RCC.
Pharmaceutical form	Infusion
Posology	Combination therapy phase: nivolumab 3 mg/kg over 30 minutes Q3W, ipilimumab 1 mg/kg over 30 minutes, followed by: Nivolumab monotherapy phase: 480 mg IV (over 60 minutes) Q4W
Method of administration	IV
Should the pharmaceutical be administered with other medicines	No
Treatment duration / Criteria for end of treatment:	Until disease progression or unacceptable toxicity. A protocol amendment in 2017 allowed discontinuation of nivolumab plus ipilimumab after 2 years of therapy without progression or toxicity.
Need for diagnostic or other test	No

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Abbreviations: aRCC, advanced renal cell carcinoma; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IV, intravenous; kg, kilograms; mg, milligrams, QW3, every three weeks; Q4W, every four weeks; PD-L1, Programmed death-ligand 1.

2.3 The intervention

Lenvatinib is a RTK inhibitor that selectively inhibits the kinase activities of VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including FGF receptors FGFR1, 2, 3, and 4, the PDGF receptor PDGFRα, KIT, and RET. Pembrolizumab is a monoclonal antibody that stimulates T-cell responses, including anti-tumour responses, through binding to the programmed death-1 (PD-1) receptor and blocking its interaction with PD-L1 and PD-L2 [50]. In the CLEAR trial [7], the combination of the immunomodulatory activity of LEN+PEM has been shown to produce potent antitumor activity beyond that observed with either agent alone [7, 11, 12]. If recommended LEN+PEM will constitute a promising alternative treatment option for 1L RCC patients in Denmark. Recently approved combination regimens offered improved efficacy (PFS) vs VEGF-targeted monotherapy, increasing PFS up to 17.0 months, but overall response rates are generally lower than 60% [40-42, 47-52]. Within the CLEAR study, LEN+PEM demonstrated an unparalleled efficacy outcome, with ~24-month median PFS in the ITT population. The potential of LEN+PEM in Danish clinical practice is further confirmed by the excellent and unprecedent results in response rates. LEN+PEM demonstrated 16% CR in the ITT population whereas current treatment options have until now demonstrated CR between 1% and 8% [38-41, 44, 45, 47, 48]. After assessing the most recent evidence of NIVO+IPI efficacy, experts have recently highlighted the importance of CR as a proxy for long-term survival [56] [57]. Therefore, LEN+PEM is likely to bring significant change to patients' overall survival. In addition to the aforementioned advantages, LEN+PEM will benefit patients who cannot receive current available options due to drug-to-drug interactions and/or comorbidities. In fact, there remains a sizeable proportion of patients for whom current recommended regimens are not suitable, due to drug interactions or labelled warnings/precautions, as indicated below [58-61].

> Drug interactions: strong cytochrome P450 (CYP3A) inhibitors/inducers should be avoided with axitinib, sunitinib, cabozantinib, and pazopanib, and drugs that raise gastric pH, or CYP substrates with narrow therapeutic windows, should also be avoided with pazopanib
> Tumor lysis syndrome: fatal cases of tumor lysis syndrome have occurred in patients with high tumor burden treated with sunitinib

If recommended, LEN+PEM will become the first combination therapy available for IMDC good prognosis patients and an important alternative option to NIVO+IPI in the IMDC intermediate/poor prognosis population [13].

Summary information is presented in Table 8.

Table 8. The intervention

	Lenvatinib in combination with pembrolizumab
Generic name (ATC-code)	L01EX08, lenvatinib L01FF02, pembrolizumab
Dosing	The recommended dosage of lenvatinib is 20 mg orally once daily in combination with pembrolizumab administered as an IV infusion over 30 minutes: 200 mg every three weeks or 400 mg every 6 weeks [1, 3]
Method of administration	Lenvatinib is for oral use Pembrolizumab is administered by IV infusion over 30 minutes
Treatment duration/ criteria for discontinuation	Subjects will continue to receive study treatment until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, loss of clinical benefit, completion of 35 treatments (approximately 2 years) with pembrolizumab, or sponsor termination of the study. In the presence of clinical benefit, subjects in Arm B who discontinue pembrolizumab may continue treatment with lenvatinib alone unless any of the other discontinuation criteria apply. This was confirmed to be more reflective of Danish clinical practice [2].
Should the pharmaceutical be administered with other medicine	No
Monitoring	Lenvatinib

	For patients with hypertension, blood pressure should be well controlled prior to treatment, and should be regularly monitored during treatment. Cases of nephrotic syndrome have been reported in patients using lenvatinib; urine protein should be monitored regularly to avoid proteinuria. Due to hepatotoxicity, close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment; liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. To avoid cardiac dysfunction, patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary. Electrolyte abnormalities should be monitored and corrected before starting treatment and electrocardiograms and should be monitored at baseline and periodically during treatment to avoid QT/QTc interval prolongation. Thyroid function should be monitored before initiation of, and periodically throughout, treatment with lenvatinib.[1] Pembrolizumab Patients should be monitored for signs and symptoms of immune-related: pneumonitis, colitis, changes in liver function (hepatitis), changes in renal function (nephritis), adrenal insufficiency and hypophysitis (endocrinopathies) and severe skin reactions. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. [3]
Diagnostic test	In the EU, no biomarker test or companion diagnostic is required for the use of LEN+PEM as the indication is for the overall patient population (all-comers).

3. Literature search and identification of efficacy and safety studies

3.1 Identification and selection of relevant studies

3.1.1 Global SLR

Two systematic literature reviews (SLR) have been conducted to investigate the efficacy and safety of all approved, recommended or under development 1L treatments for aRCC compared with each other or best supportive care (BSC) based on evidence from RCTs. The first SLR investigated efficacy and safety results, the second SLR investigated literature on Patient reported outcomes (PROs).

Systematic searches were conducted on June 4, 2021 (Three searches had been conducted on January 5, 2021, March 27, 2019, and September 1, 2020, as well) in Embase and MEDLINE (via PubMed), EconLit, Centre for Reviews and Dissemination, and the Cochrane Library using a combination of free-text search terms and controlled vocabulary terms (Emtree terms in embase.com). As per DMC guidelines, each SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [62] and the Cochrane Handbook for Systematic Reviews of Interventions [63] and followed an approved protocol developed specifically for this study. Abstracts and full-text publications were screened using a dual screening process and information from the accepted studies was extracted into a prespecified data extraction form. Quality assessments of the RCTs were conducted using the Cochrane Risk of Bias Assessment Tool 2.0 and economic evaluations with the Drummond Checklist.

One hundred and fifty-six publications corresponding to thirty-four unique RCTs evaluating the efficacy and safety of systemic 1L treatments for patients with advanced or metastatic RCC were identified. The majority of trials were open label; about half were phase III and half were phase II. No studies had a high risk of bias. The results of the global SLR on Efficacy and safety are presented in detail in

Appendix A Literature search for efficacy and safety of intervention and comparator(s). The SLR of PROs included 36 publications for 24 unique trials. Results of the SLR on PROs are presented in detail in Appendix H Literature search for HRQoL data. For full details on the relation between the global SLR, the NMA and publications providing inputs to the submission, please see XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

In this assessment, the two global SLRs were filtered to only report results that are relevant in the Danish context. Specifically, comparisons derived from the SLRs are only relevant for the assessment of the efficacy of LEN+PEM in the aRCC intermediate/poor

prognosis subgroup. In the assessment of the relative efficacy of LEN in the aRCC good prognosis subgroup, the existence of a head-to-head trial comparing LEN+PEM to the main relevant comparator (sunitinib) waves the need to refer to the SLRs.

3.1.2 Danish relevance

In this section, only studies investigating the efficacy and safety of treatments recommended in Denmark are reported. Specifically, as discussed in section 2.2.2, this section reports studies including sunitinib and nivolumab with ipilimumab (NIVO+IPI). In accordance with the DMC guidance, if a head-to-head study with a comparator relevant in Danish clinical practice exists, the literature search can be omitted [15]. Eisai and MSD have conducted the CLEAR trial [7], a randomised controlled trial conducted to compare the efficacy and safety of LEN+PEM versus sunitinib alone in 1L treatment of patients with aRCC. The evidence of the CLEAR trial was therefore considered sufficient to inform the comparison of LEN+PEM in the good prognosis 1L aRCC patient group.

Concerning the main comparator of relevance for the treatment of 1L aRCC patients with intermediate/poor prognosis, the above reasoning making the SLR obsolete. In the absence of a head-to-head trial comparing LEN+PEM to NIVO+IPI, the evidence of the global SLR was reviewed and studies that could inform an indirect comparison of LEN+PEM to NIVO+IPI were selected. For patients in the intermediate/poor prognosis group, four publication corresponding to one unique trial informing the efficacy and safety of NIVO+IPI are presented below, as well as the CLEAR trial [7]. The BIONIKK trial [64] has been excluded from this submission due to the very limited data reported (abstract) and to the focus of the analysis on the overall population, which is outside of the scope of a submission in the Danish context.

3.2 List of relevant studies

Table 9. Relevant studies informing efficacy and safety of treatments for 1L aRCC patients

Reference (title, author, journal, year)	Trial name	NCT #	Dates of study (start and expected completion date)	Used in comparison of
Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma, Motzer *et al.,* N Engl J Med, 2021 [65] Eisai, A Multicentre, Open-Label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination With Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects With Advanced Renal Cell Carcinoma (CLEAR) (DATA ON FILE), 2021 [7] Eisai, A Multicentre, Open-Label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination With Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects With Advanced Renal Cell Carcinoma (CLEAR), Quality of Life Report (DATA ON FILE), 2021 [14, 66]* Eisai, Merck, CLEAR307 RCC 1L September 2021 - OS update - Data on file [67].	CLEAR	NCT02811861	October 13, 2016 to July 31, 2022	Lenvatinib with pembrolizumab versus sunitinib in 1L aRCC good prognosis patients Lenvatinib with pembrolizumab versus nivolumab-ipilimumab in 1L aRCC intermediate/poor prognosis patients
Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial.	CHECKMATE214	NCT02231749	October 13, 2014 to March 5, 2021	Lenvatinib with pembrolizumab versus nivolumab and pembrolizumab in 1L aRCC patients in the intermediate/good prognosis group

Reference (title, author, journal, year)	Trial name	NCT #	Dates of study (start and expected completion date)	Used in comparison of
Albiges L, Tannir NM, Burotto M, et al. ESMO Open 2020;5:e001079. doi:10.1136/ esmoopen-2020-001079 [68]				
Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial Cella *et al,* 2019, The lancet oncology [69]*				
Quality of life in previously untreated patients with advanced renal cell carcinoma (aRCC) in CheckMate 214: Cella D, Escudier, B., Ivanescu, C., Mauer, M., Lord-Bessen, J., Gooden, K.,. Updated results. *Annals of Oncology.* 2020;30:v383-v384.[70]*				
"European Medicines Agency extension of indication to include the combination immunotherapy cancer drug treatment with nivolumab (Opdivo) and ipilimumab (Yervoy) for adults with intermediate/poor-risk advanced renal cell carcinoma."Ali, Sahra et al. ESMO open vol. 5,6 (2020): e000798. [71]				

Abbreviations: aRCC advanced renal cell carcinoma; ESMO, European society of medical oncology; TKI, tyrosine kinase inhibitor; VEGFR, Vascular endothelial growth factor receptor
*Informed the HRQoL data of this submission. These three studies are derived from the SLR 2 (PRO).

For detailed information about included studies, please refer to Appendix B.

4. Efficacy and safety

Chapter seven of this submission is structured around the overall/ITT population as well as the good and the intermediate/poor IMDC prognosis subgroups.

4.1 Efficacy and safety of LEN+PEM compared to sunitinib for 1L aRCC patients in the overall population

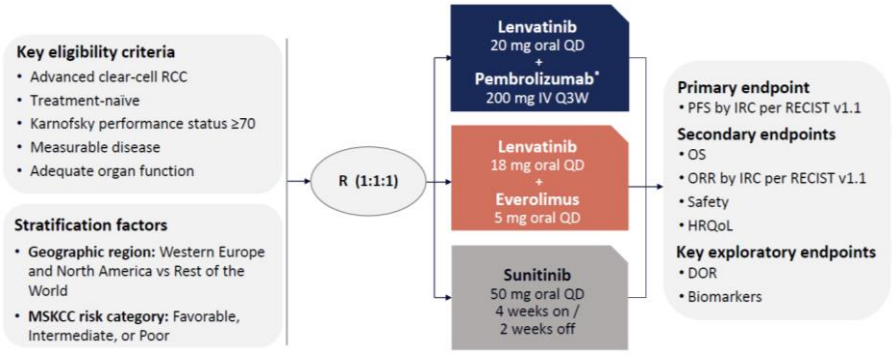
4.1.1 Relevant studies

4.1.1.1 CLEAR trial

CLEAR [7] is a head-to-head trial comparing LEN+PEM to the main comparator, sunitinib, which makes the SLR obsolete for the overall population (ITT) as well as for the good prognosis subgroup (IMDC), in terms of efficacy [15]. Therefore, only the CLEAR trial [7] and its results are presented in this section.

CLEAR is the largest study to date of an anti-PD-1/PD-L1 plus TKI regimen for the 1L treatment of RCC [7].The main characteristics of the CLEAR trial are presented in Table 10. Table 11 presents the main primary, secondary and exploratory endpoints. Table 10 summarises the main elements of the CLEAR clinical trial design. As discussed in section 2.2.1, both MSKCC and IMDC prognosis categorisation methods were included in the CLEAR trial, however this submission is based on the IMDC prognosis categorisation.

Figure 3. CLEAR study design.



Abbreviations: DOR, duration of response; QD, once a day; HRQoL, health-related quality of life; IRC, independent review committee; IV, intravenous; mg, milligrams; MSKCC, Memorial Sloan Kettering Cancer Centre; RECIST, response evaluation criteria; OS, overall survival; ORR, overall response rate; PFS, progression-free survival; RCC, renal cell carcinoma

Table 10. Summary presentation of CLEAR trial

Trial name	CLEAR
Trial design	CLEAR is a multicentre, open-label, randomised, Phase 3 trial to compare the efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab versus sunitinib alone in 1L treatment of subjects with aRCC. The trial design is summarised in Figure 3 .
Primary objective	To demonstrate that lenvatinib in combination with everolimus (Arm A) or pembrolizumab (Arm B) is superior compared with sunitinib alone (Arm C) in improving PFS by IIR using RECIST 1.1 as first-line treatment in subjects with advanced RCC.
Secondary objectives	• To compare OS of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib. • To compare ORR by IIR using RECIST 1.1 of subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib. • To compare safety and tolerability of treatment with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib, including the assessment of the proportion of subjects who discontinued treatment due to toxicity and time to treatment failure due to toxicity. • To compare the impact of treatment on HRQoL as assessed by using the Functional Assessment of Cancer Therapy Kidney Symptom Index Disease-Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-30), and the European Quality of Life 5 Dimension 3 Level Version (EuroQoL EQ-5D-3L) instruments for subjects treated with lenvatinib in combination with everolimus or pembrolizumab versus sunitinib. • To assess PFS on next line of therapy (PFS2) as reported by investigator. • To assess PFS based on investigator assessment per RECIST 1.1. • To characterise the population PK of lenvatinib when co-administered with everolimus or pembrolizumab. • To compare the PK of pembrolizumab from this study to historical data. • To characterise the population PK of everolimus when co-administered with lenvatinib. • To assess the PK/pharmacodynamic relationship between exposure and efficacy/biomarkers/safety, if possible, using a mechanistic approach.
Intervention and comparator	Patients in the CLEAR trial were randomised to one of the following treatment arms: Interventions: Arm A: lenvatinib 18 mg orally (PO) once daily (QD) plus everolimus 5 mg PO QD. N=355 Arm B: lenvatinib 20 mg PO QD plus pembrolizumab 200 mg intravenously (IV) every 3 weeks (Q3W). N=355 Comparator: Arm C: sunitinib 50 mg PO QD on a schedule of 4 weeks on treatment followed by 2 weeks off (Schedule 4/2). N=357 For the purpose of this submission, only results of arms B and C are presented. In the CLEAR trial, subjects continued to receive study treatment until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, loss of clinical benefit, completion of 35 treatments (approximately 2 years) with pembrolizumab, or sponsor termination of the study. In the presence of clinical benefit, subjects in Arm B who discontinued pembrolizumab could have continued treatment with lenvatinib alone unless any of the other discontinuation criteria apply. This is in accordance with Danish clinical practice. [2]

Trial name	CLEAR
Follow-up period	The data cut-off (DCO) of the 28th of August 2020 (DCO for the final PFS analysis and second interim analysis of OS) was planned to be performed after approximately 100% information fraction of PFS events (388 events) were observed for each comparison and after 182 deaths (60% information fraction of OS events) were observed for each comparison. At August 2020 DCO in the CLEAR study, the maturity of the OS data was 22.5% for LEN+PEM and 28.3% for sunitinib; this maturity is representative of the proportion of patients who died at the time of data cut off [7]. The median follow-up of August 2020 DCO was 26.7 (25.9, 27.4) months (LEN+PEM) and 26.3 (25.4, 27.2) months (sunitinib). Additionally, an OS update was conducted at the request of the EMA, DCO 31 March 2021. The OS update was performed at the approximate timing of the pre-specified DCO, per regulatory agency's request [14] [67]. The median follow-up for the March 2021 DCO was 33.7 (32.8, 34.4) months for the LEN+PEM arm and 33.4 (32.5, 34.1) months for the sunitinib arm.
Number of randomised patients	Planned: Approximately 1050 subjects were planned to be enrolled in the overall study. Randomised: 1069 subjects were randomised: 357 (Arm A), 355 (Arm B), 357 (Arm C).
Inclusion and exclusion criteria for patients	Adults (≥18 years of age) with a histologically or cytologically confirmed diagnosis of RCC with a clear-cell component and documented evidence of advanced disease, who had not received any previous systemic anticancer therapy for RCC were eligible for enrolment. Subjects had to have at least 1 measurable target lesion according to RECIST 1.1, adequate liver, bone marrow, blood coagulation, and renal function as defined in the protocol, Karnofsky Performance Status (KPS) of ≥70, and adequately controlled blood pressure (BP) with or without antihypertensive medications. Subjects with central nervous system metastases were eligible if they had completed local therapy (e.g., whole brain radiation therapy, surgery, or radiosurgery) and had discontinued the use of corticosteroids for at least 4 weeks before starting treatment in this study.
Analysis sets	Full Analysis Set (FAS) (Intent-to-Treat Analysis Population): All randomised subjects regardless of the treatment actually received. This is the primary analysis population used for all efficacy analyses, using the intent-to-treat principle. Per Protocol (PP) Analysis Set: Subjects who received at least 1 dose of any study drug, had no major protocol deviations, and had both baseline and at least 1 postbaseline tumour assessment. Subjects who died before the first postbaseline tumour assessment were also included. The PP Analysis Set was the secondary analysis set for efficacy endpoints. Safety Analysis Set (SAS): Subjects who received at least 1 dose of any study drug. This was the analysis population for all safety analyses, which was based on the as-treated principle. Population PK Analysis Set: All subjects who received at least 1 dose of study treatment, with documented dosing history in the lenvatinib plus everolimus combination arm (Arm A) or the LEN+PEM arm (Arm B) and had measurable plasma levels of lenvatinib or whole blood levels of everolimus. Pembrolizumab PK Analysis Set: All subjects who received at least 1 dose of study treatment, with documented dosing history in the LEN+PEM arm (Arm B) and had measurable serum concentrations of pembrolizumab. Pharmacodynamic Analysis Set: Subjects who received at least 1 dose of study drug and had sufficient pharmacodynamic data to derive at least 1 pharmacodynamic parameter and with documented dosing history. HRQoL Analysis Set: All subjects who had any HRQoL data and received at least 1 dose of study treatment.
Baseline characteristics	Baseline characteristics are presented in detail in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.
Relevant sub-groups	Exploratory analyses were conducted for the following subgroups: • Age • Sex • Race • Geographic region • Risk classification (MSKCC or IMDC) • Number of metastatic sites per IIR • KPS group • Baseline bone, liver, and lung metastasis status • Prior nephrectomy • Clear cell histology with sarcomatoid features

Abbreviations:, EORTC, the European Organization for the Research and Treatment of Cancer ; EuroQoL EQ-5D-3L European Quality of Life 5 Dimension 3 Level Version; FAS, full analysis set; HRQoL, Health-Related Quality of Life; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index Disease-Related Symptoms; IMDC, international metastatic RCC database consortium, Karnofsky Performance Status (KPS); MSKCC, Memorial Sloan Kettering Cancer Centre; ORR, overall response rate OS, overall survival; PO, per OS; PK, pharmacokinetics PP, per protocol; QD, once a day; QLQ-30, Quality of Life Questionnaire; PFS, progression-free survival; RCC, renal cell carcinoma; RECIST, response evaluation criteria; SAS, safety analysis set

Table 11. CLEAR trial summary of endpoints

Endpoint	Definition	Collection	Analysis
Primary			
PFS by IIR	Time from the date of randomisation to the date of the first documentation of disease progression or death as defined by RECIST 1.1	Data required by the protocol were collected on the Clinical report forms (CRFs) and entered into a validated data management system that was compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject. Data collection on the CRF followed the instructions described in the CRF Completion Guidelines. The investigator had ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 or Investigator and Site Information Form signed the completed CRF to attest to its accuracy, authenticity, and completeness. The data has been collected following the FDA censoring rule and has been accepted by the EMA [1]	PFS was evaluated using KM estimates and the difference in PFS for the 2 primary comparisons were each tested by stratified log-rank test, with geographic region and MSKCC prognostic groups as strata. The hazard ratio (HR) and its 95% confidence intervals (CIs) were estimated using the Cox regression model with Efron's method for ties, stratified by the factors used for stratified randomisation. Median PFS with 2-sided 95% CIs were presented, and the KM estimates of PFS were plotted over time.
Key secondary endpoints			
OS	Time from the date of randomisation to the date of death from any cause	See collection primary endpoint	The difference in OS for the 2 primary comparisons were each tested by stratified log-rank test, with geographic region and MSKCC prognostic groups as strata. The HR and its 95% CIs were estimated by a stratified Cox proportional hazards model with Efron's method for ties, stratified by the factors used for stratified randomisation. Median OS with 2-sided 95% CIs were calculated using KM product-limit estimates for each treatment arm, and KM estimates of OS were plotted over time.
ORR by IIR	Proportion of subjects who had best overall response (BOR) of CR or PR as defined by RECIST 1.1	See collection primary endpoint	ORR, estimated by treatment arms based on the tumour response evaluation by IIR per RECIST 1.1, was calculated with exact 95% CIs using the method of Clopper and Pearson within each arm. The difference in ORR for the 2 primary comparisons were each tested using the Cochran-Mantel-Haenszel test, with geographic region and MSKCC prognostic groups as strata. The 2-sided 95% CIs for the odds ratio and the difference in ORR were calculated. The P value for hypothesis testing of ORR will be based on the ORR data at the time of the PFS interim analysis. The ORR data available

Endpoint	Definition	Collection	Analysis
			at the time of this final PFS analysis and subsequent analysis time points are provided for supportive purposes.
Other secondary endpoints			
TEAEs and SAEs	Treatment emergent adverse events and Serious adverse events	See collection primary endpoint	All safety analyses were performed on the Safety Analysis Set. Safety was assessed by monitoring and recording all AEs and serious adverse events (SAEs) using Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grades, regular laboratory monitoring for haematology, blood chemistry, and urine values; regular performance of physical examinations, periodic measurement of vital signs, electrocardiograms (ECGs), and echocardiogram or multigated acquisition (MUGA) scans, including left ventricular ejection fraction (LVEF); and the performance of physical examinations.
Proportion of subjects who discontinued treatment due to toxicity	Proportion of subjects who discontinued study treatment due to TEAEs	See collection primary endpoint	
HRQoL	FKSI-DRS, the EORTC QLQ-C30, and the EuroQoL EQ-5D-3L	See collection primary endpoint	HRQoL was assessed at baseline (before first dose of study drug), on Day 1 of each subsequent cycle, at the time of withdrawal, and at the Off-Treatment Visit. Every effort was made to administer HRQoL surveys before study drug administration and before other assessments and procedures.
Exploratory endpoints			
DOR by IIR	Time from the date a response of CR or PR by IIR and investigator assessment	NA	DOR by IIR was first documented until the date of the first documentation of disease progression or date of death from any case

Abbreviations: CBR clinical benefit rate CR, complete response; DCR, disease control rate; DOR, duration of response; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer; EuroQoL EQ-5D, European Quality of Life 5 Dimension 3 Level Version; IIR, independent imaging review, ORR, overall response rate; OS, overall survival; PR, partial response; PFS, progression-free survival; SAEs, serious adverse events; TEAEs, treatment emergent adverse eve

4.1.2 Results Overall population

As mentioned previously in Table 10, only the results of treatment arms B (LEN+PEM) and C (sunitinib) of the CLEAR study are reported in this submission. Arm A investigated the efficacy and safety of lenvatinib in combination with everolimus, which is out of the scope of a submission to the DMC. Additionally, of the outcomes reported in Table 11, the results of PFS, OS, ORR, CR, DOR, HRQoL and safety are presented, in line with DMC's priorities, as described in previous DMC assessments of aRCC treatments [8, 9].

4.1.2.1 Results CLEAR - Efficacy (overall population)

4.1.2.1.1 CLEAR - PFS (overall population)

At August 2020 DCO, the 355 patients receiving LEN+PEM had a median PFS of 23.9 months (LEN+PEM vs sunitinib [95%CI] = 20.8, 27.7) whereas the 357 patients receiving sunitinib had a median PFS of 9.2 months (95% CI = 6.0, 11.0), (HR: 0.39 [CI=0.32, 0.49] p=0.0001). This is an unparalleled result among existing 1L aRCC regimens. It demonstrates a 2.5-fold increase in PFS, and a 61% reduction in the risk of disease progression or death with LEN+PEM compared with sunitinib. Kaplan-Meier (KM) PFS curves of the two treatment arms, assessed by independent imaging review (IIR), are presented in Figure 4.

Figure 4. CLEAR trial, Kaplan Meier PFS analysis for patients receiving LEN+PEM and patients receiving sunitinib, per IIR and RECIST v1.1 (August 2020 DCO), Full analysis set (FAS)

Abbreviations: DCO, Data cut-off; LEN+PEM, lenvatinib plus pembrolizumab; PFS, progression-free survival; OS, overall survival; RECIST, response evaluation criteria in solid tumours; IIR, independent imaging review

PFS favoured LEN+PEM vs. sunitinib across all pre-specified subgroups evaluated in the CLEAR trial, including all prognostic risk groups (Figure 5).

Figure 5. CLEAR trial: Subgroup Analysis of PFS per IIR and RECIST v1.1 (LEN+PEM vs Sunitinib; August 2020 DCO)

Abbreviations: CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan-Kettering Cancer Center; PD-L1, programmed cell death ligand-1

4.1.2.1.2 CLEAR - OS (overall population)

Results are presented in this section based on the OS update DCO of March 2021 requested by EMA [14] [67]. Despite the new DCO, with a 7-months longer follow-up compared to the previous August 2020 DCO, the median time for OS was still not reached in either groups of patients receiving LEN+PEM (n=355) (95% confidence interval LEN+PEM vs sunitinib [95%CI] = 41.5, NE) and sunitinib (n=357) (95%CI = 38.4, NE), (HR: 0.72 [CI=0.55, 0.93] p=0.0123). These results are consistent with results from previous DCO from August 2020, as showcased in Appendix K. Additional efficacy data. At all DCOs, the OS KM curves for LEN+PEM and sunitinib show clear separation in line with the OS HRs for LEN+PEM vs. sunitinib. However, the curves eventually converge and cross at month 33 at August 2020 DCO and month 43 at the OS update. This crossing should be interpreted cautiously as it is based on very few patients at remaining at risk; 5 and 3 for LEN+PEM and sunitinib respectively.

Figure 6. CLEAR trial, Kaplan Meier OS analysis for patients receiving LEN+PEM and patients receiving sunitinib, per IIR and RECIST v1.1 (March 2021 DCO), FAS

[redacted]progression-free survival; OS, overall survival; RECIST, response evaluation criteria in solid tumors; S, sunitinib

OS favoured LEN+PEM vs. sunitinib across all prognostic risk subgroups evaluated in the CLEAR trial, with the exception of the favourable prognostic risk subgroups (according to both IMDC and MSKCC) (Figure 7).

Figure 7. CLEAR trial, OS Subgroup Analysis (LEN+PEM; March 2021 DCO), (events is death)

[redacted]

Abbreviations: CI, confidence interval; IxRS, interactive voice and web response system; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; L + P, lenvatinib + pembrolizumab; MSKCC, Memorial Sloan-Kettering Cancer Center; NE, not estimable; S, sunitinib

[redacted]
12[redacted]

Table 12. CLEAR trial, Anticancer Medications Used During Survival Follow up (March 2021 DCO), FAS

	LEN+PEM (N=355) n (%)	Sunitinib (N=357) n (%)
[redacted]	[redacted]	[redacted]

[a]Discontinued patients also include those who were untreated (n = 3 lenvatinib + pembrolizumab, n = 2 lenvatinib + everolimus, and n = 17 sunitinib)
[b]Percentages based on the number of patients who discontinued treatment
2L = second line; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; August 2020 DCO = Interim Analysis 3; MTOR = mechanistic target of rapamycin; n = number; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand-1
Source: [72]

To investigate a potential impact of these imbalances on OS, a sensitivity analysis on the groups of patients who did not receive any subsequent treatment in the CLEAR trial is presented in Appendix K. Additional efficacy data (August 2020 DCO).

Additionally, a post-hoc sensitivity analysis was conducted to statistically adjust for these imbalances in subsequent treatment. This post-hoc scenario analysis is presented in sections 4.1.2.1.3.

4.1.2.1.3 CLEAR - OS (overall population) – subsequent treatment adjustment based on two stage estimation

This post-hoc sensitivity analysis was conducted with March 2021 DCO using two-stage estimation methods (TSE) [72]. [redacted] This result confirms the benefit for LEN+PEM versus sunitinib in OS, as OS was improved in comparison with the main ITT analysis. Additional details on the methods used for this analysis are presented in Appendix M. Methods of two stage estimation method.

Table 13. Acceleration factor estimation for switching to any anticancer medication by fitting Log-normal, log-logistic, and Weibull models to the observational datasets [72]

	LEN+PEM (N=220)	Sunitinib (N=272)
Switching to Any Anticancer Medication, n	[redacted]	[redacted]
Log-normal AFT model: AF (95% CI)	[redacted]	[redacted]
AIC / BIC	[redacted]	[redacted]
Log-logistic AFT model: AF (95% CI)	[redacted]	[redacted]
AIC / BIC	[redacted]	[redacted]
Weibull AFT model: AF (95% CI)	[redacted]	[redacted]
AIC / BIC	[redacted]	[redacted]

AF: Acceleration factor, AFT: Accelerated failure time, AIC: Akaike information criterion, BIC Bayesian information criterion, CI confidence interval;
The observational datasets consist of OS from the secondary baseline onwards in the subjects who discontinued study treatment and were still on survival follow-up afterwards, for each treatment arm.
An acceleration factor of >1.0 indicates anticancer treatment benefit after switching.

Table 14. Unadjusted and adjusted overall survival results for switching to any subsequent anticancer medication by 2-stage estimation method with different models [72]

	LEN+PEM (N=355)	Sunitinib (N=357)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

DCO date: March 2021 DCO
AF: Acceleration factor, HR = Hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IxRS= interactive voice and web response system; MSKCC = Memorial Sloan Kettering Cancer Center; RCC = renal cell carcinoma
a. HR (lenvatinib + pembrolizumab vs sunitinib) is based on a Cox proportional hazard model including treatment group as a factor, stratified by geographic region and MSKCC prognostic groups in IxRS.
[b] HR (lenvatinib + pembrolizumab vs sunitinib) is based on a Cox proportional hazard model including treatment group and the selected baseline covariates (IMDC prognostic risk group, number of metastatic organs/sites involved, and prior nephrectomy) as factors. The selected baseline covariates were determined by a multivariate Cox model on the unadjusted original OS data using the backward variable selection method with alpha=0.05.

[redacted]Abbreviations: L+P, lenvatinib plus pembrolizumab; S, sunitinib

[redacted]

Abbreviations: L+P, lenvatinib plus pembrolizumab; S, sunitinib

4.1.2.1.4 CLEAR - ORR (overall population)

At the August 2020 DCO, FAS, as assessed by IIR, an ORR of 71.0% (95%CI=66.3, 75.7) was observed in the 355 patients in the LEN+PEM arm. An ORR of36.1% (95%CI=31.2, 41.1) was observed in the 357 patients who received sunitinib. [redacted]

[redacted] demonstrating that patients receiving LEN+PEM had four-fold increase in the odds of responding to treatment compared to patients who received sunitinib [7].

4.1.2.1.5 CLEAR - CR (overall population)

At the August 2020 DCO, FAS, as assessed by IIR, CR was observed in 57 (16.1%) of the 355 patients in the LEN+PEM. CR was observed in 15 (4.2%) of the 357 patients who received sunitinib [7]. [redacted] This is a statistically significant and a clinically meaningful result as CR has previously been shown to be a proxy for long-term survival in aRCC [7, 57].

4.1.2.1.6 CLEAR - DOR (overall population)

DOR data was only collected for the overall population in the FAS with 355 patients in the LEN+PEM arm and 357 patients in the sunitinib arm. The included patients have good, intermediate, and poor disease prognosis according to IMDC categorisation. At the August 2020 DCO, the median DOR in the LEN+PEM arm was 25.8 months (95% CI: 22.1, 27.9) and in the sunitinib arm was 14.6 months (95% CI: 9.4, 16.7) [7].

4.1.2.1.7 CLEAR - HRQoL (overall population)

Methods

The following three HRQoL analyses were conducted in CLEAR trial:

- Time to first deterioration (TTFD): the number of weeks between randomization and the first deterioration event
    - Deterioration events were defined as detrimental changes in score relative to baseline that exceed the minimally important difference thresholds. Minimally important differences were a decrease of three or more points for the FKSI-DRS; a decrease of ten or more points for the EORTC QLQ-C30 functional and GHS/QoL scores; an increase of ten or more points for the EORTC QLQ-C30 symptom scores; a decrease of 0.08 or more points for the EQ-5D-3L index; and a decrease of 7 or more points for the EQ-5D-3L VAS.
- Time until definitive discontinuation (TuDD): the number of weeks between randomisation and the earliest deterioration event with no subsequent recovery above the deterioration threshold or no subsequent HRQoL assessment data
- Least square (LS) mean change from baseline [66, 73].

These analyses were applied to results from each of these three PRO instruments:

Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptom (FKSI-DRS)

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Cancer–Core 30 (EORTC QLQ-C30)

EuroQol five-dimensional three-level questionnaire (EQ-5D-3L) [66, 73].

The HRQoL instruments were administered at baseline (prior to the first dose of study drug), on day 1 of each subsequent cycle starting with Cycle 2, and at the off-treatment visit within 30 days of treatment discontinuation. [66, 73].

Population

Unless otherwise specified, all HRQoL analyses were based on the QoL analysis set. The QoL analysis set is defined as all participants of the safety population (who have received at least 1 dose of study treatment). Completion and compliance rates for HRQoL instruments and scores were computed based on the full analysis set, which included all participants who were randomized to treatment.

Change from baseline analysis

To assess the effect of treatment assignment on HRQoL outcomes, mixed models with random coefficients were fitted using the change from baseline for each HRQoL score as the response variable. Each model included treatment, time, a time by treatment interaction term, baseline HRQoL score, and the 2 randomization stratification variables (i.e., geographical region and prognostic group) along with patient-specific random intercept and slope terms. The covariance matrix for these random effects was assumed to be unstructured. The LS mean change from baseline for each treatment arm was estimated at each cycle, along with an overall LS mean estimated at the average follow-up time which was approximately 46 weeks (during Cycle 15). These means represent the model-adjusted average change from baseline within each treatment arm. The differences in LS means between each lenvatinib treatment arm (LEN+EVE and LEN+PEM) and SUN, along with associated 95% CIs and P values, were also estimated.

Time to deterioration analysis

For both TTFD and TuDD, the Kaplan-Meier method was used to estimate the distribution and median time-to-event value for each treatment arm. Comparisons were made between the distributions of each lenvatinib treatment arm (LEN+EVE and LEN+PEM) and that of the SUN

treatment arm using stratified log-rank tests. Cox models stratified by the randomization stratification variables (geographical region and MSKCC prognostic group) were fit for each score; hazard ratios (HRs) and associated 95% CIs were estimated to compare each lenvatinib treatment arm with the SUN treatment arm.

Results

[redacted] An overview of the Baseline HRQoL scores is presented in [redacted] Table 15. This is followed by an overview of HRQoL outcomes based on LS mean change from baseline to Cycle 15 (the average follow-up time for HRQoL) is presented in XXXXXX16 An overview of the median TTFD and median TuDD results is provided in XXXXXX17. Median times are estimated using the Kaplan-Meier method. [66]. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX reports completion rates at each cycle for EQ-5D-3L instrument ([redacted] 162[redacted] 164X and a summary of the reports completion rates for the other PROs instruments ([redacted] Table 166X. Appendix N also reports results of these PROs analyses for the IMDC good and intermediate/poor prognosis ([redacted] Table 168XXXXTable 173XXXXXXX

Table 15. Baseline HRQoL scores

Mean scores[a]	LEN + PEM (n = 351)	SUN (n = 340)
[redacted]		

[a]The FKSI-DRS instrument is measured on a scale of 0–36, with higher scores corresponding to better HRQoL. Scores on all scales of the EORTC QLQ-C30 range from 0–100, for the GHS/QoL and all functional scales, a higher scale corresponds to better HRQoL, for the symptom scales, a higher scale corresponds to worse symptoms. The EQ-5D-3L VAS is measured on a scale of 0–100, with higher scores corresponding to better HRQoL, and the EQ-5D-3L index ranges from 0–1, with higher scores representing better HRQoL.

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; EVE, everolimus; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease related Symptoms; GHS/QoL, global health status/quality of life; HRQoL, health-related quality of life; LEN, lenvatinib; PEMBRO, pembrolizumab; SUN, sunitinib; VAS, visual analog scale.

XXXXXX16XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX[X]

Scale	Difference in LS Mean Change from Baseline (95% CI) LEN+PEM versus sunitinib
[redacted]	
EORTC QLQ-C30	
Global health status/quality of life	0.81 (−1.42, 3.03)
Functional scales	
Physical	3.01 (0.48, 5.54)[b]
Role	3.09 (−0.24, 6.42)
Emotional	1.38 (−0.90, 3.66)
Cognitive	−0.61 (−2.89, 1.68)
Social	3.01 (−0.25, 6.26)

Scale	Difference in LS Mean Change from Baseline (95% CI) LEN+PEM versus sunitinib
Symptom scales	
Fatigue	−2.80 (−5.52, −0.08)[b]
Nausea and Vomiting	−1.54 (−3.14, 0.05)
Pain	−1.09 (−3.72, 1.53)
Dyspnoea	−2.79 (−5.33, −0.25)[b]
Insomnia	−0.73 (−3.57, 2.11)
Appetite Loss	0.18 (−2.64, 3.01)
Constipation	−2.19 (−4.19, −0.18)[b]
Diarrhoea	1.09 (−1.49, 3.67)
Financial Difficulties	0.23 (−2.98, 3.44)
[redacted]	[redacted]
VAS	1.68 (−0.57, 3.94)
[redacted]	

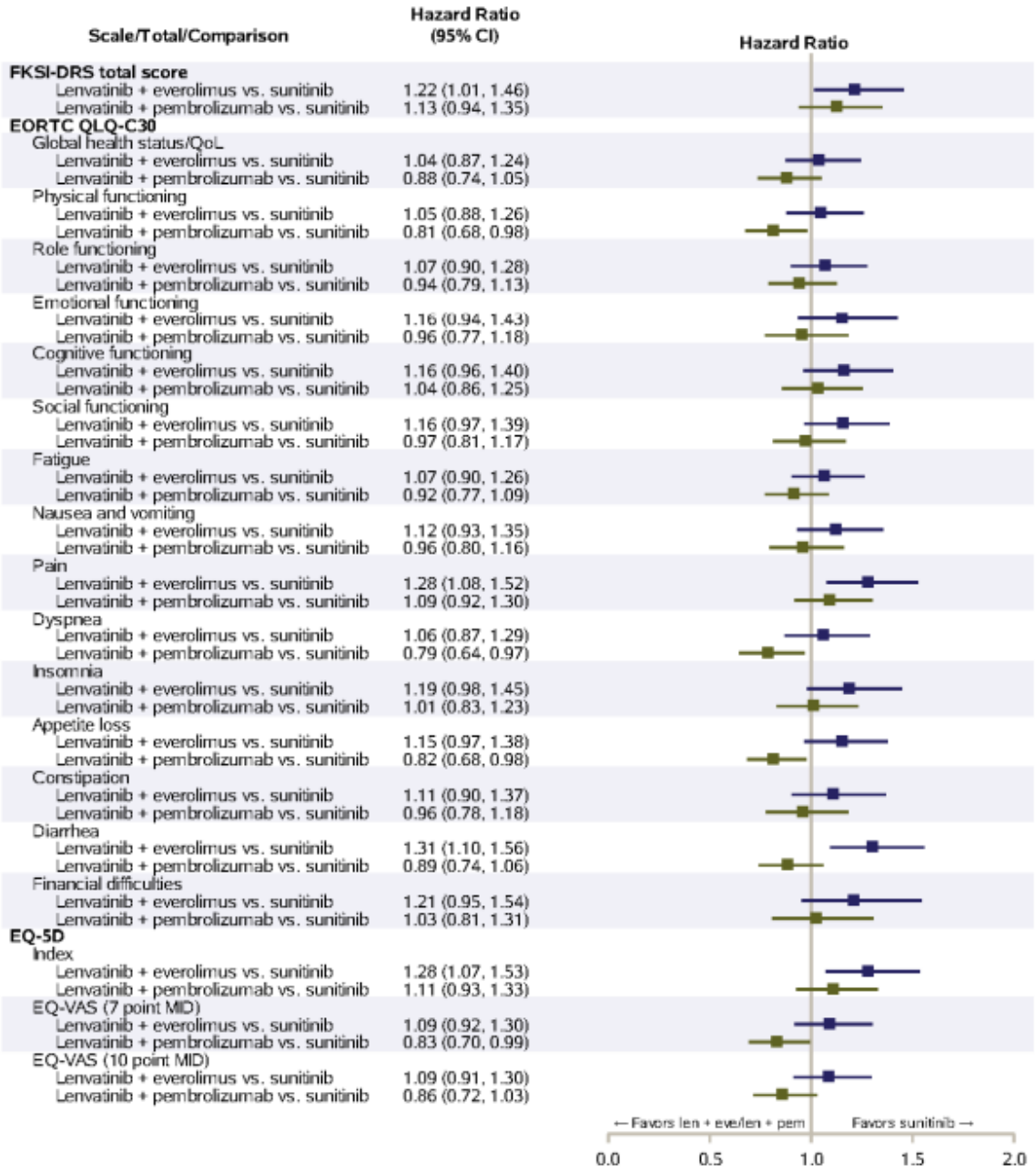
[redacted]

Scale	Median TTFD, weeks (95% CI)		Median TuDD, weeks (95% CI)	
	LEN+PEM	sunitinib	LEN+PEM	sunitinib
FKSI-DRS				
Total score (3-point MID)	9.14 (6.43, 12.14)	12.14 (9.14, 15.29)	134.14 (120.00, NE)[a]	117.43 (90.14, 131.29)
[redacted]				
EORTC QLQ-C30				
Global health status/quality of life	12.00 (7.29, 15.14)	9.14 (6.29, 12.14)	114.29 (102.14, 153.29)[a]	75.14 (57.29, 105.14)
Functional scales				
Physical	15.29 (12.29, 21.43)[a]	12.71 (9.29, 18.14)	134.14 (109.14, NE)[a]	78.14 (63.14, 111.00)
Role	9.14 (6.29, 12.14)	9.29 (6.29, 12.29)	105.43 (96.29, 117.29)[a]	78.29 (54.14, 96.14)
Emotional	45.14 (29.00, 68.14)	37.00 (22.43, 65.57)	NE (136.43, NE)[a]	147.00 (120.57, NE)
Cognitive	15.14 (12.14, 21.29)	16.00 (13.14, 21.29)	105.57 (96.43, 122.29)	135.00 (99.14, NE)
Social	12.14 (9.14, 15.14)	12.29 (9.14, 15.29)	120.14 (108.14, NE)[a]	93.14 (66.43, 115.29)
Symptom scales				
Fatigue	6.14 (4.00, 6.57)	6.00 (3.57, 6.14)	110.14 (96.29, 120.29)[a]	59.00 (45.14, 81.14)
Nausea and Vomiting	21.14 (18.14, 27.29)	16.00 (12.29, 21.14)	147.29 (143.86, 165.00)[a]	131.29 (120.57, NE)
Pain	7.14 (6.29, 9.29)	9.86 (9.14, 14.71)	119.71 (105.29, 138.29)[a]	105.29 (75.29, 130.29)
Dyspnoea	39.29 (24.43, 51.00)[a]	21.14 (15.43, 32.71)	153.14 (134.14, NE)[a]	126.14 (108.14, 158.29)
Insomnia	21.29 (15.29, 28.00)	19.14 (15.00, 30.43)	156.14 (128.71, NE)[a]	126.14 (111.14, 146.71)
Appetite Loss	18.29 (15.14, 21.71)[a]	9.14 (6.29, 15.14)	139.00 (134.71, NE)[a]	129.29 (117.29, 146.71)
Constipation	31.29 (24.14, 55.71)	32.71 (24.14, 50.86)	NE[a]	NE (126.14, NE)
Diarrhoea	15.43 (12.71, 20.86)	15.14 (12.14, 15.43)	126.29 (117.14, 146.29)[a]	120.43 (105.14, 131.29)
Financial Difficulties	76.14 (51.00, NE)	120.29 (58.57, NE)	153.57 (153.57, NE)	NE
EQ-5D				
Index	9.14 (6.29, 10.57)	15.00 (11.86, 18.14)	114.29 (102.14, 135.29)[a]	111.14 (84.14, 120.29)
VAS (7-point MID)	9.43 (6.43, 12.29)[a]	9.14 (6.29, 12.00)	124.86 (94.71, 134.57)[a]	74.86 (54.14, 96.00)
[redacted]				

[redacted]Hazard ratios are estimated from the Cox proportional hazards models and are measures of the comparative rates at which subjects in the two treatment arms experience deterioration events. HRs are generally based on the entire

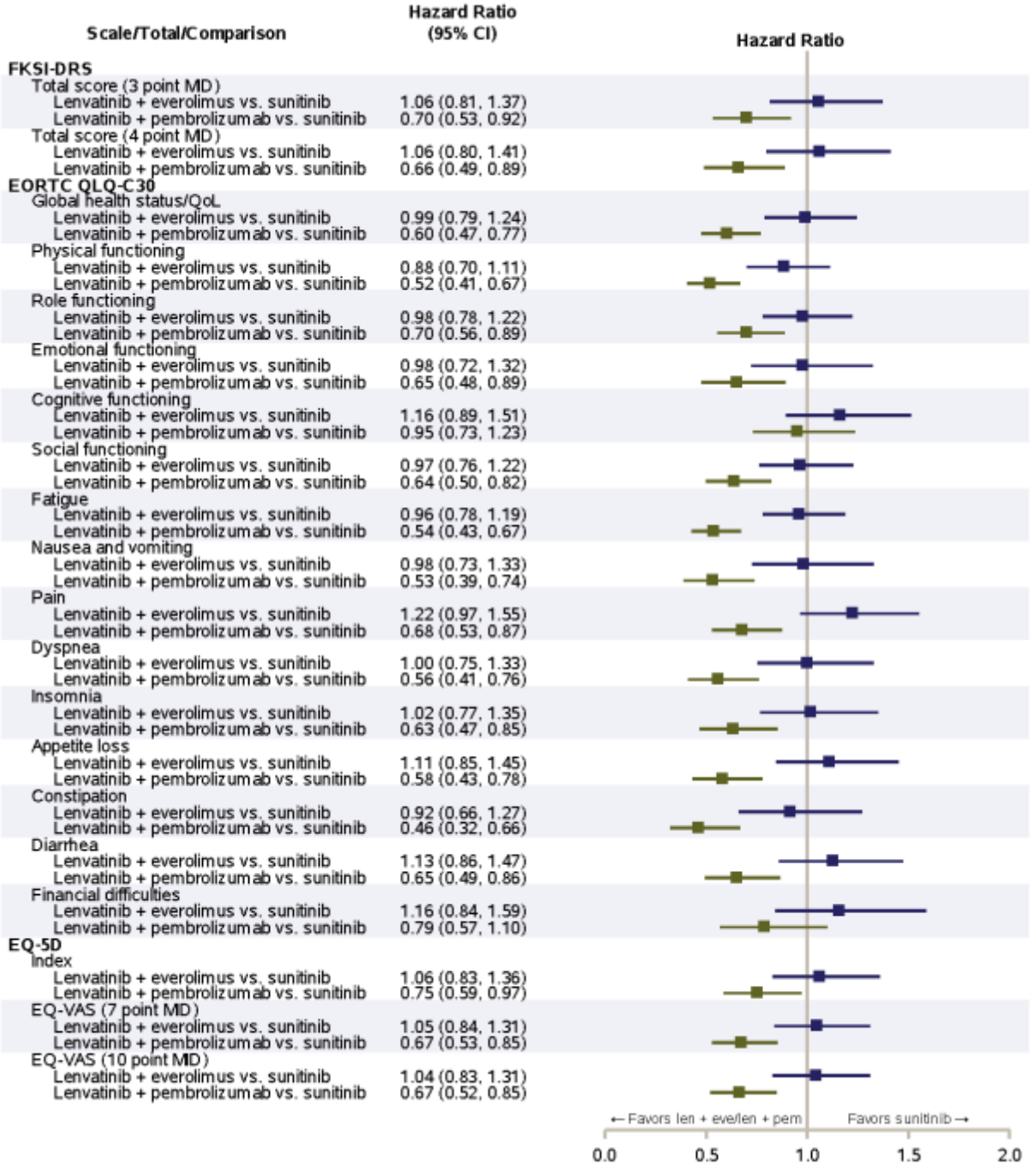
distribution of the survival curve. The HRs for time to first deterioration were nominally significant. These are presented in Figure 10 and Figure 11.

Figure 10. Hazard ratios for Time to First Deterioration



CI = confidence interval; FKSI-DRS = Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease-Related Symptoms, MID = minimally important difference; QoL = quality of Life; VAS = visual analog scale

Figure 11. Hazard ratio for Time until definitive deterioration



Source: [66].

Across instruments, comparisons of the overall change from baseline favoured LEN+PEM over sunitinib across the majority of scales, reaching significant improvement on the EORTC QLQ-C30 physical functioning scale (LS mean difference 3.0 [95% CI: 0.5, 5.5], p<0.05), and achieving significant reductions in the EORTC QLQ-C30 fatigue (−2.8 [−5.5, −0.1], p<0.05), dyspnoea (−2.8 [−5.3, −0.3], p<0.05), and constipation (−2.2 [−4.2, −0.2], p<0.05) symptom scales; however, these differences did not exceed the MID for clinical significance [66].

Based on TTFD analysis, the LEN+PEM arm was favoured over sunitinib across most EORTC QLQ-C30 measures, with the comparison reaching significance for the physical functioning score (HR 1.1 [95% CI: 0.9, 1.4]), and the symptom scales for dyspnoea (0.8 [0.6, 1.0]) and appetite loss (0.8 [0.7, 1.0]), as well as for the EQ-VAS (using a 7-point MID) (0.8 [0.7, 1.0]) [66, 73].

In the analysis of TuDD, all log-rank comparisons of LEN+PEM vs sunitinib significantly favoured LEN+PEM (p<0.05), with the exceptions of EORTC QLQ-C30 cognitive functioning and financial difficulties subscales Table 17) [66].

4.1.2.2 Results CLEAR - Safety (overall population)

Similarly, to DOR and HRQoL outcomes, safety outcomes are reported for the overall population. The relevant analysis set for these outcomes is the Safety analysis population defined as all patients who received ≥1 dose of study drug.

A summary of the safety outcomes reported in the CLEAR trial is presented in Table 18. A summary of safety outcomes adjusted by the total number of subject-years (SYs) of study drug exposure is then provided in Table 19.

Table 18. CLEAR trial, Summary of safety outcomes, safety analysis set, August 2020 DCO

Adverse event	lenvatinib + pembrolizumab (n=352)	sunitinib (n=340)
Median treatment duration, months (range)	17.0 (0.1 to 39.1)	7.8 (0.1 to 37.0)
Any grade TEAEs, n (%)	351 (99.7)	335 (98.5)
SAEs, n (%)	178 (50.6)	113 (33.2)
Any grade TEAEs leading to discontinuation, n (%)	131 (37.2)	49 (14.4)
Any grade TEAEs leading to discontinuation due to lenvatinib, n (%)[b]	90 (25.6)	NA
Any grade TEAEs leading to discontinuation due to pembrolizumab, n (%)[c]	101 (28.7)	NA
Any grade TEAEs leading to discontinuation of both lenvatinib and pembrolizumab, n (%)	47 (13.4) [a]	49 (14.4)
Total discontinuations, n (%)	210 (59.2)	273 (76.5)
Fatal TEAEs, %	15 (4.3%)	11 (3.2%)
Grade ≥3 TEAEs, n (%)	290 (82.4)	244 (71.8)
Grade ≥3 TRAE, n (%)	252 (71.6)	200 (58.8)

Abbreviations: AE, adverse event; N, number; SAE, severe adverse event; TEAE, treatment emergent adverse event. TRAE, treatment related adverse event.
a Discontinuation Both Lenvatinib and Pembrolizumab occurred at the same time due to the same AE
b Drug discontinuation (or interruption) for lenvatinib, regardless of the action taken for pembrolizumab
c Drug discontinuation (or interruption) for pembrolizumab, regardless of the action taken for lenvatinib

Table 19. CLEAR trial AEs, adjusted by Subjects-Year of Exposure to study drugs, safety analysis set, August 2020 DCO

Event	lenvatinib + pembrolizumab (n=352)	sunitinib (n=340)
Total number of SY (SY)	[redacted]	[redacted]
Any grade TEAEs per SY, n (AE rate)	[redacted]	[redacted]
Grade ≥3 TEAEs per SY, n (AE rate)	[redacted]	[redacted]
SAEs per SY, n (AE rate)	[redacted]	[redacted]
Fatal TEAEs per SY, n (AE rate)	[redacted]	[redacted]

Abbreviations: AE, adverse events; SAE = serious adverse events; SY = subject-year; TEAE = treatment-emergent adverse events
Source: [7]

Table 20. Grade ≥3 TRAEs (≥5% in Any Treatment Arm), safety analysis set, August 2020 DCO

Event	lenvatinib + pembrolizumab (n=352)	sunitinib (n=340)
Diarrhoea, n (%)	29 (8.2)	15 (4.4)
Amylase increased, n (%)	26 (7.4)	9 (2.6)
Lipase increased, n (%)	34 (9.7)	24 (7.1)
Weight decreased, n (%)	21 (6.0)	0 (0.0)
Hypertension, %	89 (25.3)	61 (17.9)
Proteinuria, n (%)	26 (7.4)	10 (2.9)
Platelet count decreased, n (%)	18 (5.3)	18 (5.3)
Neutrophil count decreased, n %	39 (11.5)	19 (5.6)
Neutropenia, n %	1 (0.3)	18 (5.3)
Thrombocytopenia, n %	1 (0.3)	18 (5.3)

Abbreviations: TRAE = treatment-related adverse event. Source: [7]; [65]

Overall, the safety outcomes observed with LEN+PEM were generally consistent with the established profile of each individual agent as monotherapy, with no new safety signals identified for the combination regimen [7]. Adverse events were manageable via dose modifications, which were implemented in in the majority of patients who reported adverse events across all treatment arms [65]. Grade ≥3 TEAEs occurred at a higher rate in the LEN+PEM arm than the sunitinib arm; however, when adjusting for duration of treatment exposure, the rates per patient-year were comparable [7].

Nearly all subjects in both the LEN+PEM (99.7%) and sunitinib (98.5%) arms had at least 1 TEAE (Table 18). However, patients treated with LEN+PEM had a longer median treatment duration (MTD) compared to patients treated with sunitinib [7]. AEs adjusted by the total number of subject-years (SYs) of study drug exposure are therefore presented in Table 19. The total number of SY of exposure, including dose interruptions, was 524.9 in the LEN+PEM arm and 344.2 in the sunitinib arm. The incidence of TEAEs adjusted for drug exposure was 15.7 per SY in the LEN+PEM arm and was similar at 18.2 per SY in the sunitinib arm.

Grade ≥3 TEAEs occurred in 82.4% of subjects in the LEN+PEM arm and 71.8% of subjects in the sunitinib arm. Adjusted by drug exposure, the rate of Grade ≥3 TEAEs was comparable at 2.0 and 2.1 per SY in the LEN+PEM and sunitinib arm, respectively.

Serious TEAEs (fatal and nonfatal) occurred in 50.6% of subjects in the LEN+PEM arm and 33.2% of subjects in the sunitinib arm; the difference was primarily due to nonfatal SAEs (50.0% vs 32.6%, respectively). When adjusted by treatment duration, the overall incidence of SAEs was higher in the LEN+PEM arm than in the sunitinib arm (0.7 vs 0.6 per SY, respectively).

Fatal TEAEs (Grade 5) were reported in 15 subjects (4.3%) in the LEN+PEM arm, which was similar to 11 subjects (3.2%) in the sunitinib arm. When adjusted by drug exposure, the incidence of fatal TEAEs was similar and low at <0.1 per SY in both the LEN+PEM arm and sunitinib arm (0.04 per SY, respectively).

4.2 Efficacy and safety of LEN+PEM compared to sunitinib for 1L aRCC patients in the IMDC good prognosis group

4.2.1 Relevant studies

A detailed description of the relevant trials can be found in 4.1.1.

Due to the DMC considering clinical equivalence of tivozanib, sunitinib and pazopanib [13], this section only presents IMDC good prognosis subgroup results for efficacy outcomes of the CLEAR trial which compares the efficacy and safety of LEN+PEM versus sunitinib.

4.2.2 Results – IMDC good prognosis

4.2.2.1 Results CLEAR - Efficacy (IMDC good prognosis)

In this section, PFS, OS and ORR are presented for the IMDC good prognosis subgroup of the CLEAR trial. Across all evaluated outcomes, the results of CLEAR favoured LEN+PEM, with statistically significant improvements in survival (PFS) and response outcomes (ORR) as compared to sunitinib monotherapy.

4.2.2.1.1 CLEAR - PFS (IMDC good prognosis)

At August 2020 DCO, IMDC good prognosis patients receiving LEN+PEM had a median PFS of [redacted] months (LEN+PEM vs sunitinib [95%CI] = [redacted]) whereas patients receiving sunitinib had a median PFS of [redacted] months (95% CI = [redacted]), (HR: 0.41 [redacted]). This is an unparalleled result among existing 1L aRCC regimens. It demonstrates a 2.5-fold increase in PFS, and a 58% reduction in the risk of disease progression or death with LEN+PEM compared with sunitinib. At 12 months, 79.9% (95% CI = 70.6, 86.5) of patients in the LEN+PEM arm versus 53.8% (95% CI = 43.4, 63.2) of the patients in the sunitinib arm were progression free. At 24 months, 55.8% (95% CI = 44.3, 65.9) of patients in the LEN+PEM arm versus 31.7% (95% CI = 21.3, 42.6) of the patients in the sunitinib arm were progression free. KM PFS curves of the two treatment arms, assessed by IIR, are presented in Figure 12. [65]

Figure 12. CLEAR trial, Kaplan Meier PFS analysis for patients receiving LEN+PEM and patients receiving sunitinib, per IRR and RECIST v1.1 (August 2020 DCO) – IMDC good prognosis subgroup, FAS

[redacted]

Abbreviations: DCO, Data cut-off; IIR, independent imaging review, LEN+PEM, lenvatinib plus pembrolizumab; L+P, lenvatinib plus pembrolizumab; PFS, progression-free survival; OS, overall survival; RECIST, response evaluation criteria in solid tumors; S, sunitinib

4.2.2.1.2 CLEAR - OS (IMDC good prognosis)

At updated OS DCO, median OS was not reached in either the LEN+PEM arm (n=110) (95% CI= NE, NE) nor the sunitinib arm (n=124) (95% CI = NE,NE), (HR: 1.22[CI=0.66, 2.26] p=0.5288). At 12 months, 97.2 (95% CI = 91.5, 99.1) of patients in the LEN+PEM arm versus 93.1 (86.7, 96.5) of the patients in the sunitinib arm were alive. At 24 months, 91.0 (95% CI = 83.4, 95.2) of patients in the LEN+PEM arm versus 86.9 (95% CI = 79.2, 91.9) of the patients in the sunitinib arm were alive. KM OS curves of the two treatment arms are presented in Figure 13. [75]

Figure 13. CLEAR trial, Kaplan Meier OS analysis for patients receiving LEN+PEM and patients receiving sunitinib, per IIR and RECIST v1.1 (March 2021 DCO) – IMDC good prognosis subgroup, FAS

[redacted]

Abbreviations: DCO, Data cut-off; IIR, independent imaging review, LEN+PEM, lenvatinib plus pembrolizumab; L+P, lenvatinib plus pembrolizumab; PFS, progression-free survival; OS, overall survival; RECIST, response evaluation criteria in solid tumors; S, sunitinib

[redacted]
21[redacted]

Table 21. CLEAR trial, Anticancer Medications Used During Survival Follow up (March 2021 DCO) – IMDC good prognosis subgroup, FAS

	LEN+PEM (N=110) n (%)	Sunitinib (N=114) n (%)
[redacted]	[redacted]	[redacted]

2L = second line; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; August 2020 DCO = Interim Analysis 3; MTOR = mechanistic target of rapamycin; n = number; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand-1
Source: [72]

4.2.2.1.3 CLEAR - ORR (IMDC good prognosis)

At the August 2020 DCO, as assessed by IIR, FAS, an ORR of [redacted] (95%CI=[redacted]) was observed among patients in the LEN+PEM arm (n=110), whereas an ORR of [redacted] (95%CI=[redacted]) was observed in patients who received sunitinib (n=124). The Odds ratio of the ORR in the LEN+PEM group versus the ORR in the sunitinib group was of [redacted] (95%CI=[redacted], p<[redacted]), indicating that patients who received LEN+PEM have [redacted] the odds of responding to treatment compared to patients who received sunitinib. [76]

4.2.2.1.4 CLEAR - CR (IMDC good prognosis)

At the August 2020 DCO, FAS, as assessed by IIR, an ORR of 71.0% (95%CI=66.3, 75.7) was observed in the 355 patients in the LEN+PEM arm. An ORR of 36.1% (95%CI=31.2, 41.1) was observed in [redacted] ([redacted] of the patients who received sunitinib (n=124). The Odds ratio of the CR in the LEN+PEM group versus the CR in the sunitinib group was [redacted] (CI:[redacted]; p=[redacted]), demonstrating a [redacted] increase in the odds of having a CR to treatment compared to patients who received sunitinib. [76]

4.2.2.1.5 CLEAR - Safety (IMDC good prognosis)

Due to the lack of subgroup specific data, safety for the IMDC good prognosis population should be assessed in relation to the data presented for the overall population in section 4.1.2.2.

4.2.2.1.6 CLEAR - HRQoL (IMDC good prognosis)

Due to lack of space, HRQoL data for the IMDC good prognosis subgroup has been added to Appendix N, in Table 167, Table 168, Table 170 and Table 172 [74]. Methods for the assessment of HRQoL outcomes in the IMDC good prognosis populations follow the methods used for the overall population (please see section 4.1.2.1.7) [66].

[redacted]

4.2.3 Comparative analyses Overall and IMDC good prognosis populations

4.2.3.1 Method of synthesis

The CLEAR trial provided direct head-to-head evidence of the relative efficacy and safety of LEN+PEM compared to sunitinib for the treatment of 1L aRCC patients.

4.2.3.2 Differences between trials

Not applicable.

4.2.3.3 Results from the comparative analysis

For detailed results from the head-to-head comparison of LEN+PEM versus sunitinib in the CLEAR trial, please see section 4.1.2 for the overall population and section 4.2.3 for the IMDC good prognosis population.

4.3 Efficacy and safety of LEN+PEM compared to NIVO+IPI for patients in the IMDC intermediate/poor prognosis subgroups

4.3.1 Relevant studies

Two studies were retained as relevant to inform the efficacy and safety assessment of LEN+PEM in the Danish context, where the combination is expected to be used in 1L treatment of patients with aRCC. The CLEAR trial investigated LEN+PEM versus sunitinib and the CHECKMATE 214 evaluated the combination of NIVO+IPI versus sunitinib, which evaluated the efficacy and safety of NIVO+IPI versus sunitinib.

4.3.1.1 CLEAR

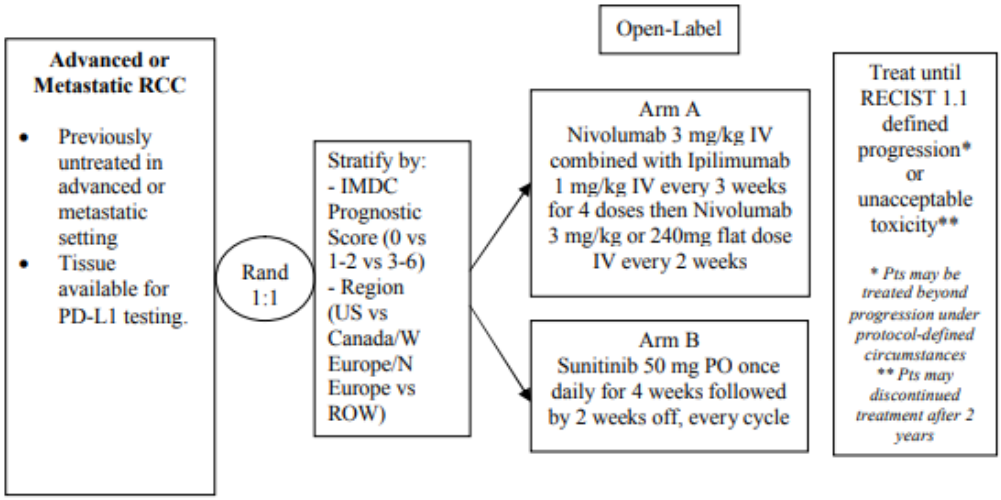
The CLEAR trial is presented in detail in section 4.2.1.

4.3.1.2 CHECKMATE 214

CHECKMATE 214 is a randomised, open-label, phase 3 trial of nivolumab plus ipilimumab followed by nivolumab monotherapy versus sunitinib monotherapy. Randomisation (in a 1:1 ratio) was performed with a block size of 4 with stratification according to IMDC risk score and geographic region. Nivolumab and ipilimumab were administered intravenously at a dose of 3 mg per kilogram over a period of 60 minutes and 1 mg per kilogram over a period of 30 minutes, respectively, every 3 weeks for four doses (induction phase), followed by nivolumab monotherapy at a dose of 3 mg per kilogram every 2 weeks (maintenance phase). Sunitinib was administered at a dose of 50 mg orally once daily for 4 weeks of each 6-week cycle.

Table 22 summarises the main characteristics of CHECKMATE 214. Full details on CHECKMATE 214 clinical trial are presented in Appendix B Main characteristics of included studies. Figure 14 illustrates CHECKMATE 214 clinical study design. Additionally, Table 23 presents the main primary, co-primary and secondary endpoints for which results are presented in this submission.

Figure 14. CHECKMATE 214 clinical study design



Abbreviations: IMDC, international metastatic RCC database consortium; kg, kilograms; mg, milligrams; RCC, renal cell carcinoma; PD-L1, PD-L1, Programmed death-ligand 1; PO, per OS, RECIST, response evaluation criteria; SAS, safety analysis set

Table 22. Summary presentation of CHECKMATE 214 clinical trial

Trial name	CHECKMATE 214
Trial design	Randomised, open-label, phase III trial of nivolumab plus ipilimumab followed by nivolumab monotherapy versus sunitinib monotherapy. The intervention model was parallel assignment, but after completion of final analysis eligible participants could switch from receiving Sunitinib to receiving nivolumab 3 mg/kg IV combined with Ipilimumab 1 mg/kg IV every 3 weeks for 4 doses then nivolumab 240mg flat dose IV every 2 weeks. Enrolled patients were randomly assigned 1:1 and stratified by IMDC prognostic score (0 vs 1-2 vs 3-6) and region (USA vs Canada/Western Europe/Northern Europe vs Rest of World).
Primary objective	The purpose of this phase III trial was to compare the objective response rate, progression-free survival, and overall survival of nivolumab plus ipilimumab with sunitinib for previously untreated clear-cell advanced renal-cell carcinoma among intermediate- and poor-risk patients.
Secondary objectives	Secondary end points: ORR in the intention-to-treat population (RECIST v1.1) PFS in the intention-to-treat population OS in the intention-to-treat population Incidence rate of adverse events among all treated patients ' Exploratory end points: ORR among favourable-risk patients PFS among favourable-risk patients OS among favourable-risk patients. Outcomes according to level of tumour programmed death ligand 1 (PD-L1) expression (≥1% vs. vs. <1%) Health-related quality of life on the basis of the score on the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy– Kidney Symptom Index (FKSI-19) both in intermediate- and poor-risk patients Health related quality of life for cancer Functional Assessment of Cancer Therapy–General (FACT-G)

Trial name	CHECKMATE 214
	EuroQol EQ-5D-3L
Intervention and comparator	Intervention: Nivolumab 3 mg/kg combined with Ipilimumab 1 mg/kg solutions intravenously every 3 weeks for 4 doses then nivolumab 3 mg/kg solutions intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends. Comparator Sunitinib 50 mg capsules by mouth once daily for 4 weeks then 2 weeks off, continuously until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends. After completion of final analysis eligible participants may switch from receiving Sunitinib to receiving nivolumab 3 mg/kg IV combined with Ipilimumab 1 mg/kg IV every 3 weeks for 4 doses then nivolumab 240mg flat dose IV every 2 weeks.
Follow-up period	The latest follow-up cut off was reported in Albiges et al., 2020. Here the minimum follow-up was 4 years (median follow-up=55 months).
Number of randomised patients	A total of 1096 patients were randomly assigned to treatment at 175 sites in 28 countries; 1082 patients received treatment (547 with nivolumab plus ipilimumab and 535 with sunitinib in the intention-to-treat population; 423 and 416, respectively, had intermediate or poor risk).
Inclusion an exclusion criteria for patients	Eligible patients were 18 years of age or older, with previously untreated advanced renal-cell carcinoma with a clear-cell component. Additional key inclusion criteria were measurable disease according to the RECIST, version 1.1,15 and a KPS score of at least 70 (on a scale from 0 to 100, with lower scores indicating greater disability). Key exclusion criteria were central nervous system metastases or autoimmune disease and glucocorticoid or immunosuppressant use. Patients were characterized according to IMDC risk (favourable [score of 0], intermediate [score of 1 or 2], or poor [score of 3 to 6]).
Baseline characteristics	Baseline characteristics are presented in detail in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.
Relevant sub-groups	Efficacy outcomes according to level of tumour programmed death ligand 1 (PD-L1) expression (≥1% vs. <1%): • ORR • PFS • OS Subgroup analyses for overall survival included the following subgroups: age, sex, region, prior nephrectomy, PD-L1 expression and prognostic scores

Abbreviations:, EORTC, the European Organization for the Research and Treatment of Cancer ; EuroQoL EQ-5D-3L European Quality of Life 5 Dimension 3 Level Version; HRQoL, Health-Related Quality of Life; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index Disease-Related Symptoms; IMDC, international metastatic RCC database consortium, Karnofsky Performance Status (KPS); IV, intravenous; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand 1, PO, per OS; QD, once a day; QLQ-30, Quality of Life Questionnaire; PFS, progression-free survival; RCC, renal cell carcinoma; RECIST, response evaluation criteria;

Table 23. CHECKMATE 214, main outcomes of interest

Endpoint	Definition	Collection	Analysis
Primary			
ORR for intermediate- and poor-risk patients.	The proportion of randomised subjects who achieved a best response of complete response (CR) or partial response (PR) using the RECIST v1.1 criteria based on IRRC assessment. Per RECIST v1.0 for target lesions and assessed by MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), greater than or equal to 30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR	From first dose until date of documented disease progression or subsequent therapy, whichever occurs first.	NA
OS for intermediate- and poor-risk patients.	Time from the date of randomisation to the date of death from any cause	From the date of randomisation to the date of death	Survival time was censored at the date of last contact ("last known alive date") for subjects who were alive.
PFS for intermediate- and poor-risk patients.	Time between the date of randomisation and the first date of documented progression, as determined by the IRRC (as per RECIST 1.1 criteria), or death due to any cause, whichever occurred first. Subsequent therapy included anticancer therapy, tumour directed radiotherapy, or tumour directed surgery. Subjects who died without a reported progression were considered to have progressed on the date of their death.	From date of first dose to date of documented disease progression or death due to any cause, whichever occurs first	Subsequent therapy included anticancer therapy, tumour directed radiotherapy, or tumour directed surgery. Subjects who died without a reported progression were considered to have progressed on the date of their death.
Secondary endpoints			
TEAEs	Incidence of adverse events	NA	Safety was assessed per the National Cancer Institute Common Terminology Criteria for Adverse Events, V.4.0.8 Treatment-related select AEs were prespecified and defined as events that might be immune-mediated, differ from those caused by non-immunotherapeutic drugs, might require immunosuppression for management and whose early recognition might mitigate severe toxicity (including events in the skin, gastrointestinal, endocrine, hepatic, pulmonary or renal systems).
Exploratory endpoints			
DOR	NA	NA	Post-hoc analysis
HRQoL	FKSI-DRS, the EORTC QLQ-C30, and the EuroQoL EQ-5D-3L	NA	HRQoL was assessed at baseline (before first dose of study drug), on Day 1 of each subsequent cycle, at the time of withdrawal, and at the Off-Treatment Visit. Every effort was made to administer HRQoL surveys before study drug administration and before other assessments and procedures.

Abbreviations: EORTC, the European Organization for the Research and Treatment of Cancer; EuroQoL EQ-5D-3L European Quality of Life 5 Dimension 3 Level Version; HRQoL, Health-Related Quality of Life; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index Disease-Related Symptoms; ; ORR, overall response rate; OS, overall survival; QLQ-30, Quality of Life Questionnaire; PFS, progression-free survival; RECIST, response evaluation criteria

4.3.2 Results CLEAR– Efficacy (IMDC intermediate/poor prognosis)

4.3.2.1.1 CLEAR - PFS (IMDC intermediate/poor prognosis)

At August 2020 DCO a median PFS of 22.1 months (95%CI=16.6–27.6) was observed in patients receiving LEN+PEM in the intermediate/poor prognosis subgroup (n=243). A median PFS of 5.9 months (95%CI=5.6–7.5), HR = 0.36 (0.28–0.47) p<0.0001 in patients receiving sunitinib (n=229). [76] At 12 months, 67.0% (95% CI= 60.4, 72.8) of patients in the LEN+PEM arm versus 29.7% (95% CI = 22.7, 37.1) of the patients in the sunitinib arm were progression free. At 24 months, 46.4% (95% CI= 38.8, 53.6) of patients in the LEN+PEM arm versus 14.1% (95% CI= 8.0, 21.9) of the patients in the sunitinib arm were progression free.

Figure 15. CLEAR trial, KM curve of PFS, by IIR, for IMDC intermediate and poor groups, FAS, August 2020 DCO

Abbreviations: DCO, Data cut-off; IIR, independent imaging review, LEN+PEM, lenvatinib plus pembrolizumab; L+P, lenvatinib plus pembrolizumab; PFS, progression-free survival; OS, overall survival; RECIST, response evaluation criteria in solid tumors; S, sunitinib

4.3.2.1.2 CLEAR - OS (IMDC intermediate/poor prognosis)

At the updated OS DCO, the median OS was [redacted] (95%CI=[redacted]) for patients receiving LEN+PEM in the intermediate/poor prognosis subgroup (n=243). Similarly, for patients receiving sunitinib (n=229) the median OS was [redacted] (95%CI= [redacted]), HR= [redacted] ([redacted]) p=[redacted][75]. At 12 months, [redacted] (95% CI= [redacted]) of patients in the LEN+PEM arm versus [redacted] (95% CI= [redacted]) of the patients in the sunitinib arm were alive. At 24 months, [redacted] (95% CI= [redacted]) of patients in the LEN+PEM arm versus [redacted] (95% CI = [redacted]) of the patients in the sunitinib arm were alive.

Figure 16. CLEAR trial, KM curve of OS, by IIR, for IMDC intermediate and poor groups, FAS, OS update DCO

Abbreviations: DCO, Data cut-off; IIR, independent imaging review, LEN+PEM, lenvatinib plus pembrolizumab; L+P, lenvatinib plus pembrolizumab; PFS, progression-free survival; OS, overall survival; RECIST, response evaluation criteria in solid tumors; S, sunitinib

Table 24

Table 24. CLEAR trial, Anticancer Medications Used During Survival Follow up (March 2021 DCO) – IMDC intermediate/poor prognosis subgroup, FAS

	LEN+PEM (N=243) n (%)	Sunitinib (N=229) n (%)

2L = second line; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; August 2020 DCO = Interim Analysis 3; MTOR = mechanistic target of rapamycin; n = number; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand-1

Source: [72]

4.3.2.1.3 CLEAR - ORR (IMDC intermediate/poor prognosis)

At August 2020 DCO, as assessed by IIR, FAS, an a statistically significantly higher ORR XXX was observed in the LEN+PEM arm (n=243) compared to the sunitinib arm (n=229) where an ORR was observed in XXX of patients. The Odds ratio of the ORR in the LEN+PEM versus the ORR in the sunitinib arm was XXX (CI= XXXXXXXX), , demonstrating that patients receiving LEN+PEM had six fold increase in the odds of responding to treatment compared to the patients who received sunitinib. [76]

4.3.2.1.4 CLEAR - CR (IMDC intermediate/poor prognosis)

At the August 2020 DCO, as assessed by IIR, FAS, a CR was observed in 34 (14.0%) of the IMDC intermediate/poor prognosis patients in the LEN+PEM arm (n=243). CR was observed in nine (3.9%) of the patients who received sunitinib (n=229). The Odds ratio of the CR in the LEN+PEM group versus the CR in the sunitinib group was 4.07 (CI:[1.89,8.79] p=0.0002), , demonstrating a four-fold increase in the odds of having a CR to treatment compared to patients who received sunitinib. [76]

4.3.2.1.5 CLEAR – Safety (IMDC intermediate/poor prognosis)

Due to the lack subgroup specific data for most outcomes, safety for the IMDC intermediate/poor population should be assessed in relation to the data presented for the overall population in section 4.1.2.2.

However, at the August 2020 DCO, a subgroup analysis was carried out to evaluated Grade 3-4 TRAEs for IMDC intermediate/poor populations for the purpose of the NMA [76].

Table 25. Grade3-4 TRAEs for the IMDC intermediate/poor subgroup

Subjects with Any Grade 3+ Treatment Related AEs	IMDC Intermediate/poor (N=241)
LEN+PEM	176 (73.0)
Sunitinib	123 (55.9)

4.3.2.1.6 CLEAR – HRQoL (IMDC intermediate/poor prognosis)

Due to lack of space, HRQoL data for the IMDC intermediate/poor prognosis subgroup has been added to Appendix N. Please see Table 167, Table 169, Table 171 and Table 173.

4.3.3 Results CHECKMATE 214 – IMDC intermediate/poor prognosis

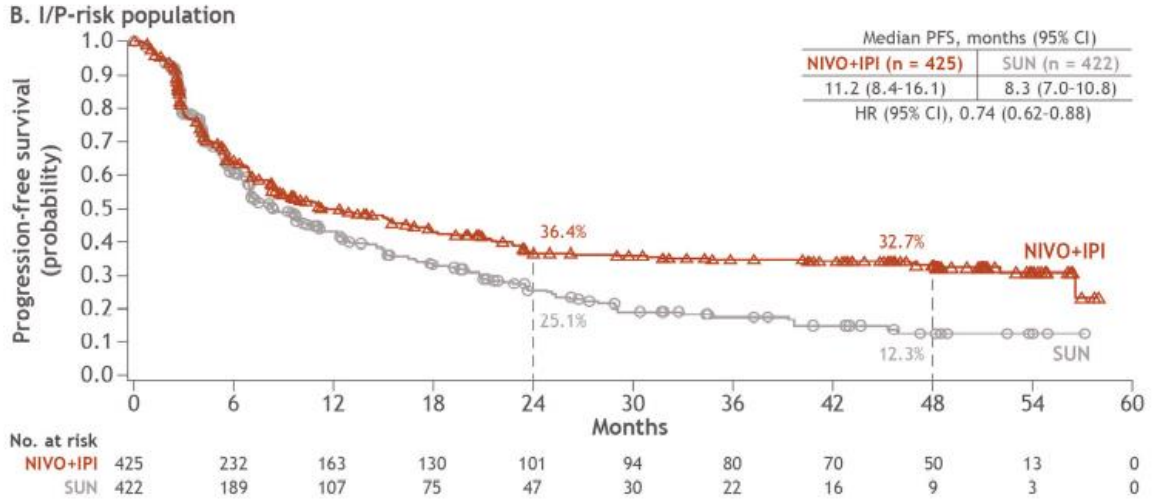
4.3.3.1 CHECKMATE 214 - Efficacy results (IMDC intermediate/poor)

The CHECKMATE 214 trial included efficacy outcomes for the intermediate/poor risk patient group as the primary outcome of the study. Results were not split between patients in the intermediate and the poor IMDC prognosis subgroups. Multiple publications have been issued based on the analyses CHECKMATE 214 data. However, the most recent publication by Albiges et al. [68] reported results for the outcomes selected as relevant for this assessment based on the most recent DCO (four years). Cella et al, 2019 [69, 70] reported HRQoL data. Finally, Ali et al, 2020 [71] reported Grade >3 TRAEs for the IMDC intermediate/poor population.

4.3.3.1.1 CHECKMATE 214 - PFS (IMDC intermediate/poor)

At a median follow up of 55 months (minimum 4 years), a median PFS of 11.6 months (95%CI= 8.4–16.1) was observed in patients receiving NIVO+IPI in the intermediate/poor prognosis subgroup. A median PFS of 8.3 months (95%CI=7–10.8) (HR= 0.74 (0.62–0.88) [68] was observed in patients receiving sunitinib.

Figure 17. CHECKMATE 214, Kaplan Meier curve for PFS, poor/intermediate prognosis group

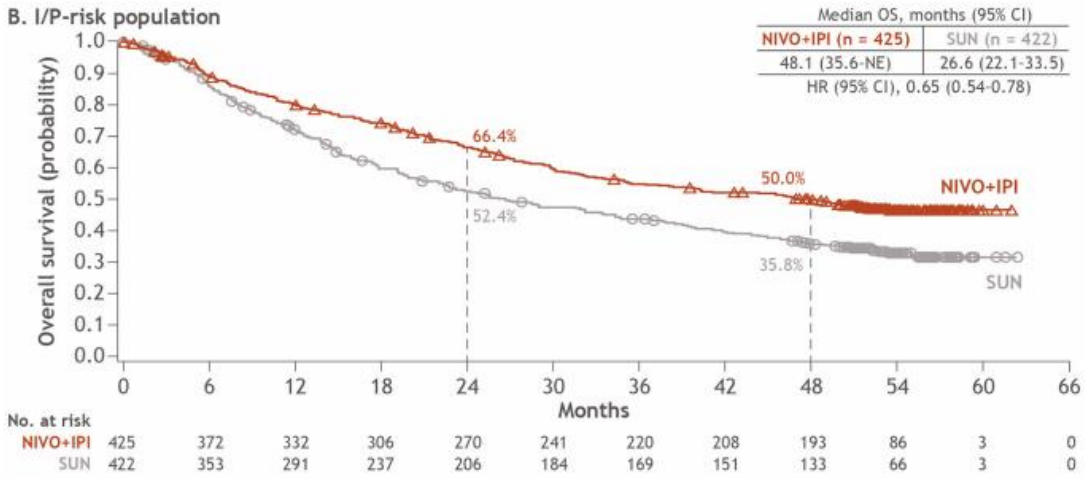


Abbreviations:; I/P, intermediate/poor; HR, hazard ratio; NIVO+IPI, nivolumab plus ipilimumab; PFS, progression-free survival; SUN, sunitinib

4.3.3.1.2 CHECKMATE 214 - OS (IMDC intermediate/poor)

A median OS of 48.1 months (95%CI= 35.6–NE) was observed at a median follow up of 55 months (minimum 4 years), patients receiving NIVO+IPI in the intermediate/poor prognosis subgroup. A median OS of 26.6 months (95%CI=22.1–33.5) (HR 0.65 (0.54–0.78)) [68] was observed in patients receiving sunitinib.

Figure 18. CHECKMATE 214, Kaplan Meier curve for OS, poor/intermediate prognosis group [68]



Abbreviations: I/P, intermediate/poor; HR, hazard ratio; NIVO+IPI, nivolumab plus ipilimumab; OS, overall survival; SUN, sunitinib

4.3.3.1.3 CHECKMATE 214 - ORR (IMDC intermediate/poor)

At a median follow-up of 55 months (minimum four years), [redacted] of the 425 patients in the IMDC intermediate/poor prognosis subgroup receiving NIVO+IPI were being responsive to the treatment. In the other treatment arm of the trail [redacted] of the 422 patients in the IMDC intermediate/poor prognosis subgroup receiving sunitinib demonstrated response to the treatment (p<0.0001). [68]

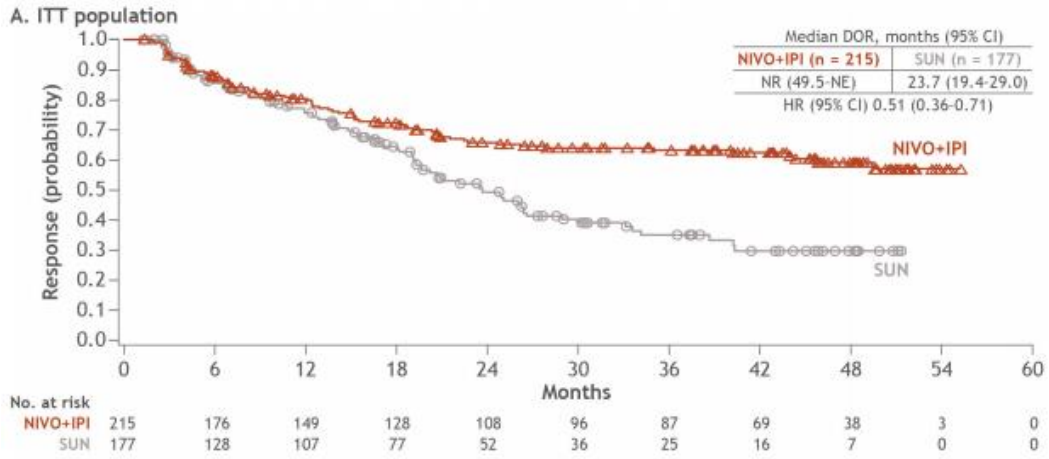
4.3.3.1.4 CHECKMATE 214 - CR (IMDC intermediate/poor)

At a median follow-up of 55 months (minimum four years), 44 (10.4%) of the 425 patients in the IMDC intermediate/poor prognosis subgroup receiving NIVO+IPI had a CR to the treatment. In the sunitinib arm of the trail, 6 (1.4%) of the 422 patients in the IMDC intermediate/poor prognosis subgroup receiving sunitinib demonstrated a complete response to the treatment (p<0.0001). [68]

4.3.3.1.5 CHECKMATE 214 - DOR (overall population)

At a median follow-up of 55 months (minimum four years), median duration of response (mDOR) with NIVO+IPI has not yet been reached , NR (45.8 – NE) whereas mDOR was 19.7 months for the IMDC intermediate/poor patients who received sunitinib (HR= 0.45, [95%CI=0.31, 0.65]). [68]

Figure 19. CHECKMATE 214, DOR in ITT patients



Abbreviations: I/P, intermediate/poor; ITT, intention to treat; DOR, duration of response; HR, hazard ratio; NIVO+IPI, nivolumab plus ipilimumab; SUN, sunitinib

4.3.3.1.6 CHECKMATE 214 - HRQoL (IMDC intermediate/poor)

HRQoL analyses were conducted in the CHECKMATE 214 trial using the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19), Functional Assessment of Cancer Therapy-General (FACT-G) and EQ-5D instruments [69]. PROs in all randomised participants were assessed as an exploratory endpoint. The analyses reported by Cella *et al,* 2019 [69] were conducted with a median follow-up was 25.2 months with the Mean change from baseline analysed at week 103. In the updated analyses, Cella et. *al* [70] also provided treatment differences at updated follow-up (week 145, approximately 33 months). These analyses were conducted for the IMDC intermediate/poor prognosis population.

A schedule of treatment and PRO assessments conducted in CHECKMATE214 is presented in Figure 20. PRO baseline scores are presented in Figure 21 and Mean changes from baseline are presented in Figure 22.

Figure 20. Schedule of treatment and PRO assessments [69]

	Cycle 1						Cycle 2						Cycle 3						Cycle 4						Cycle 5						Cycle 6+						Follow-up visit 1	Follow-up visit 2
Study week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36		
Nivolumab plus ipilimumab group	◄ Induction phase ►												◄ Maintenance phase ►																									
Nivolumab plus ipilimumab	✓			✓			✓			✓																											
Nivolumab													✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓		✓			
Sunitinib group																																						
Sunitinib	✓	✓	✓	✓			✓	✓	✓	✓			✓	✓	✓	✓			✓	✓	✓	✓			✓	✓	✓	✓			✓	✓	✓	✓				
PRO collection	X			X			X			X			X				X		X				X		X					X						X	X

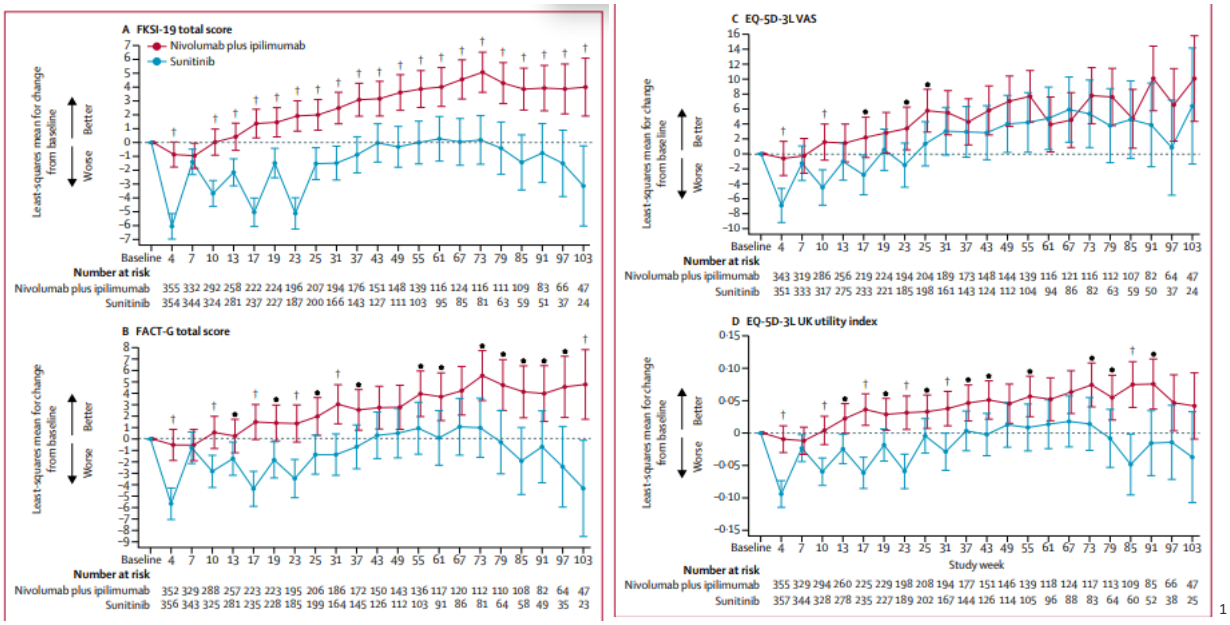
Figure 21. Baseline HRQoL cores for al randomized participants at intermediate or poor risk [69]

	Score ranges	Nivolumab plus ipilimumab group (n=425)	Sunitinib group (n=422)
FSKI-19			
Total score	0–76	60·07 (9·81)	59·05 (10·43)
DRS	0–36	30·74 (4·46)	30·13 (5·12)
DRS-P	0–48	38·97 (6·28)	38·30 (6·91)
DRS-E	0–4	2·17 (1·26)	2·05 (1·34)
TSE	0–12	11·22 (1·34)	11·21 (1·34)
FWB	0–12	7·75 (3·35)	7·49 (3·43)
FACT-G			
Total score	0–108	82·58 (15·04)	80·46 (15·79)
PWB	0–28	23·48 (4·71)	23·35 (4·87)
FWB	0–28	18·75 (6·44)	18·14 (6·66)
EWB	0–24	17·56 (4·37)	16·72 (4·71)
SWB	0–28	22·78 (5·27)	22·29 (5·28)
EQ-5D-3L			
VAS	0–100	70·45 (25·14)	69·61 (26·71)
Utility index	0–1	0·77 (0·25)	0·78 (0·25)

Data are mean (SD). Higher scores indicate better HRQoL (for FACT-G and FKSI-19), fewer symptoms (for FKSI-19), and better health status (EQ-5D-3L). EQ-5D-3L=EuroQoL five dimension three level. HRQoL=health-related quality of life. FKSI-19=functional assessment of cancer therapy-kidney symptom index. DRS=disease-related symptoms. DRS-P=disease-related symptoms physical. DRS-E=disease-related symptoms emotional. TSE=treatment side-effects. FWB=functional wellbeing. FACT-G=functional assessment of cancer therapy-general. PWB=physical wellbeing. EWB=emotional wellbeing. SWB=social and family wellbeing. VAS=visual analogue rating scale.

Table 2: **Baseline HRQoL cores for all randomised participants at intermediate or poor risk**

Figure 22 Mean change from baseline FKSI-19 total score (A), FACT-G total score (B), EQ-5D-3L VAS (C), and EQ-5D-3L UK utility index (D) in participants with intermediate or poor risk [69]



[1]

For completeness and to presented the latest available results, Table 26 reports updated results (change from baseline at 145 weeks), [70].

Table 26. 951P MMRM analysis (treatment differences at week 145) and time to deterioration for FKSI-19 [70].

Domain	LS Mean difference Nþl vs S [95% CI]	LS Mean difference N+I vs S [95% CI]	Time to deterioration (months) HR [95% CI]	Time to deterioration (months) HR [95% CI]
	All	Intermediate / Poor risk	All	Intermediate / Poor risk
Total	2.99 [0.92; 5.06] [a]	4.24 [1.38; 7.09] [a]	0.54 [0.47; 0.63] [a]	0.54 [0.46; 0.63] [a]
DRS	0.83 [-0.15; 1.82]	1.18 [-0.20; 2.56]	0.64 [0.55; 0.74] [a]	0.66 [0.56; 0.79] [a]
DRS-Physical	1.69 [0.33; 3.05] [a]	2.49 [0.58; 4.40] [a]	0.57 [0.49; 0.67] [a]	0.58 [0.49; 0.69] [a]
DRS-Emotional	0.23 [-0.04; 0.49]	0.10 [-0.26; 0.46]	0.90 [0.74; 1.09]	0.90 [0.73; 1.13]
Treatment side effects	0.73 [0.26; 1.20] [a]	1.01 [0.36; 1.65] [a]	0.42 [0.36; 0.49] [a]	0.45 [0.38; 0.53] [a]
Functional well-being	0.47 [-0.23; 1.18]	0.75 [-0.22; 1.72]	0.76 [0.66; 0.88] [a]	0.77 [0.66; 0.91] [a]

Abbreviations: CI confidence interval; DRS, disease-related symptoms; HR, hazard ratio; LS, least square. A positive LS Mean favours N+I vs S. A HR < 1 favour N+I vs S [a] P < 0.05 CI

4.3.3.1.7 CHECKMATE 214 - Safety results

Most of the safety outcomes were only measured for the overall population. Safety results for the overall population are derived from Albiges et *al.* [68] (four years minimum follow-up). [redacted] Safety results for the IMDC intermediate/poor population presented in Table 28 are derived from Ali *et al*, 2020 [71]. [redacted]

Table 27. CHECKMATE214, Summary of safety results for the overall population [68]

Adverse event	NIVO+IPI (n=547)	sunitinib (n=537)
Any grade TEAEs, n (%)	514 (94.7)	521 (97.4)
SAEs, n (%)	305 (55.76%)	213 (39.81%)
Any grade TEAEs leading to discontinuation, n (%)	NA	NA
Total discontinuations, n (%)	NA	NA

[1]

Adverse event	NIVO+IPI (n=547)	sunitinib (n=537)
Fatal TEAEs, %	NA	NA
Grade ≥3 TEAEs, n (%)	NA	NA
TRAE leading to discontinuation, n (%)	124 (22.7%) *	70 (13.1%)
Treatment-related Grade ≥3 AE (TRAE), n (%)	262 (47.9)	343 (64.1)
Fatigue	24 (4)	1 (<1)
Pruritus	3 (<1)	0
Diarrhoea	21 (4)	31 (6)
Rash	10 (2)	0
Nausea	8 (1)	7 (1)
Hypothyroisidm	2 (<1)	1 (<1)
Decreased appetite	7 (1)	6 (1)
Vomiting	4 (<1)	10 (2)
Dysgeusia	0	1 (<1)
Stomatitis	0	14 (3)
Mucosal inflammation	1 (<1)	15 (3)
Hypertension	4 (<1)	91 (17)
Palmoplantar erythema	1 (<1)	50 (9)

Abbreviations: AE, adverse event; N, number; SAE, severe adverse event; TEAE, treatment emergent adverse event. TRAE, treatment related adverse event.
*treatment related adverse events leading to discontinuation of both drugs

Table 28. CHECKMATE 214, Summary of Grade 3-4 drug- related adverse events (TRAEs) (equal of higher than 15% of any grade in either treatment group)— intermediate/poor- risk subjects, [71].

Grade 3-4 TRAE, n (%)	NIVO+IPI (n=423)	sunitinib (n=416)
All Grade 3-4 TRAE, n (%)	190 (44.9)	254 (61.1)
Fatigue	16 (3.8)	34 (8.2)
Asthenia	6 (1.4)	10 (2.4)
Mucosal inflammation	0	11 (2.6)
Pruritus	3 (0.7)	0
Rash	8 (1.9)	0
Palmar- plantar	0	32 (7.7)
Diarrhoea	15 (3.5)	19 (4.6)
Vomiting	3 (0.7)	9 (2.2)
Stomatitis	0	12 (2.9)
Dyspepsia	0	0
Lipase increased	40 (9.5)	26 (6.3)
Decreased appetite	4 (0.9)	4 (1.0)
Hypothyroidism	2 (0.5)	1 (0.2)
Dysgeusia	0	1 (0.2)
Anaemia	2 (0.5)	1 (0.2)
Hypertension	1 (0.2)	60 (14.4)
Thrombocytopenia	0	19 (4.6)

Abbreviations: TRAE, treatment-related adverse event; SUN, sunitinib

4.3.4 Comparative analyses IMDC intermediate/poor subgroup

No head-to-head studies are available that directly compare the efficacy of LEN+PEM and NIVO+IPI in the treatment if 1L aRCC patients. However, the two studies identified as relevant for this submission, CLEAR and CHECKMATE 214, both included an arm investigating the efficacy of sunitinib in 1L aRCC patients.

Following the global SLRs discussed in section 3.1.1, a global network meta-analysis (NMA) was carried-out to identify relevant clinical trials to be used for the comparative clinical efficacy and safety of LEN+PEM compared with other 1L treatments in aRCC based on evidence from RCTs. In alignment with the scope of the submission, this section reports on LEN+PEM relative efficacy and safety versus NIVO+IPI of the IMDC intermediate/poor prognosis subgroup for the outcomes of interest. For full results on the relative efficacy of LEM-PEM versus all other subgroups and all other comparators please see Appendix L. Global NMA Report. For full details on the relation between the global SLR, the NMA and publications providing inputs to the submission, please see XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

4.3.4.1 Methods of synthesis

In this section, the methods used to run the global NMA are briefly presented. For additional details on the methods and on the feasibility assessment, please see Appendix L.

The following seven outcomes that were included in the NMA:
OS

PFS (independent review committee (IRC) or assessment between investigators (INV) assessed)

ORR (defined as complete or partial response)

CR

Grade ≥ 3 all cause AEs

Grade ≥ 3 TRAEs

Treatment discontinuation due to AEs

Analyses of outcomes 5 and 7 were not carried out for versus NIVO+IPI due to lack of data in the IMDC intermediate/poor population.

As HRQoL was not included in the scope of the NMA, a narrative comparison is carried out in this section.

Models

Fixed-effects (FE) and random-effects (RE) Bayesian NMAs (where required due to the presence of multiple studies per comparison in case of substantial network heterogeneity) were conducted for the outcomes listed above using established methods. All Bayesian analyses were carried out by performing Markov Chain Monte Carlo simulations in OpenBUGS (version 3.2.3) and followed the coding and examples described by the DSU TSD2. Results were treated as significant if the CrI for the HR or did not cross 1, as in typical practice, although it should be noted that in some cases, a very high or very low probability of differentiating LEN + PEM from comparators was evident even if the criterion specified here were not satisfied. For details on how the choice between FE and RE was made, please see Appendix L.

As detailed in detail in Appendix L. , several subgroup and scenario analyses (SA) were planned, based on the availability of data. If both the IMDC and MSKCC definitions were available from a single trial, IMDC has been prioritized. Both MSKCC and IMDC definitions were used in CLEAR trial. In SA11, which was used for the analyses reported in this submission, it was assumed that IMDC (= MSKCC) SA11 included IMDC assessments from trials that provided both IMDC and MSKCC results in the analysis.

Network Diagram

The NMA network diagram included 22 comparators and 24 trials. Figure 23 below depicts the overall network, which includes all comparators and endpoints. Details of which specific trials and comparisons, relevant for this submission, were included in the outcome-specific network are provided in the descriptions of the results in the subsequent sections. Further details are provided in Appendix L.

Figure 23. Global Network Diagram

NOTE: Due to the enrolment of only intermediate- and poor-risk patients, the CABOSUN, Global ARCC, and TemPa trials were not included in the base-case analyses but were included in risk subgroup analyses. Only a treatment-naïve subgroup of patients from the TIVO-1 trial was included. Abbreviation: IFN = interferon; IL = interleukin

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

4.3.4.2 Differences between trials

To be included in the NMA and as detailed in the feasibility assessment report, the studies selected from the SLR underwent an assessment of their comparability. The studies selected from SLR to be included in the global NMA and their differences are presented in detail in Appendix L. In this paragraph, only the differences between CLEAR and CHECKMATE 214, the two trials relevant for the indirect comparison of LEN+PEM and NIVO+IPI are presented. Overall, the study populations of the CLEAR and the CHECKMATE 214 clinical trials are similar.

In the CLEAR trial, patients had a median (range) age of 62 (32–86) in the LEN+PEM arm and of 61 (29–82) in the sunitinib arm. In the CHECKMATE 214 trial, patients had a median age of 62 (26-85) in the NIVO+IPI arm and of 62 (21-85) in the sunitinib arm. Similarly, in the CLEAR trial, 74.5% and 77.0% of patients were male, in the LEN+PEM and sunitinib arms respectively, whereas 75% and 72% were male in the NIVO+IPI and sunitinib arms of the CHECKMATE 214 trial.

Additionally, in both studies, the lungs were the most common site of metastasis, representing >50% of reported metastatic sites.

Furthermore, outcomes were measured similarly in both trials. Both in the CLEAR trial and in the CHECKMATE 214 trial response outcomes were confirmed and reported per IRRC using RECIST 1.1. In both studies, PFS was evaluated per independent radiology review and OS was defined as tome from randomisation to death. The definition of the prognosis group was determined using MSKCC as a base-case in the CLEAR trial but additional results were also outputted based on the IMDC prognosis categorisation. This allowed the indirect comparison versus the CHECKMATE 214 trial, which defined prognosis groups based on the IMDC categorisation.

Finally, a similar proportion of patients enrolled belonged to the intermediate/poor prognosis group with 54.6% (LEN+PEM arm) and 53.8% (sunitinib arm) of intermediate patients in the CLEAR trial and 61% of intermediate prognosis patients in both arms of the CHECKMATE trial.

4.3.4.3 Results from the comparative analysis

NMA results

Figure 24 presents the forest plot result of the indirect comparison of LEN+PEM versus NIVO+IPI for IMDC intermediate/ poor patients in Grade 3+ TRAEs. Table 29 summarises the results of the indirect comparison of LEN+PEM efficacy and safety versus NIVO+IPI. Results carried out through a FE model as per SA11 (IMDC=MSKCC) of the NMA are presented for the IMDC intermediate/poor aRCC population. Additional details are presented in Appendix L.

Figure 24. Grade ≥ 3 TRAEs for LEN+PEM vs. NIVO+IPI for IMDC Intermediate/poor subgroup.

Table 29. Summary of NMA results for LEN+PEM vs NIVO+IPI

	LEN+PEM vs NIVO+IPI [95% CI]	Probability of treatment being better than comparator
OS (IMDC intermediate poor)	HR: 0.95 [0.68; 1.34]	60.6%
PFS (IMDC intermediate poor)	HR: 0.49 [0.36; 0.67]	100%
ORR (IMDC intermediate poor)	OR: 3.32 [2.03; 5.46]	100%
CR (IMDC intermediate poor)	[redacted]	[redacted]
Grade ≥ 3 TRAEs (IMDC intermediate poor)	[redacted]	[redacted]

The results of the NMA demonstrated:

- a numerical, but not significant advantage for LEN+PEM in OS in IMDC (= MSKCC) intermediate-/poor-risk subgroups was demonstrated vs NIVO+IPI (SA11)
- a significant advantage for LEN+PEM in PFS in IMDC (= MSKCC) intermediate-/poor-risk analyses vs NIVO+IPI
- a significant advantage for ORR in IMDC (= MSKCC) intermediate-/poor-risk analyses vs NIVO+IPI

[redacted]

Narrative comparison

It is not possible to carry out an indirect comparison of PROs between the CLEAR and CHECKMATE214 trial because:

- The outcomes measured are different (Table 30),
- Almost all instruments used are different (Table 31)

EQ-5D-3L being the only HRQoL instrument that was used in both trials, a narrative can be explored, but remains meaningless, due to the difference in the granularity of the health state utility values and the impossibility to access CHECKMATE 214 individual patient-level data (IPD).

HRQoL outcomes have been measured in the CLEAR trial [66, 74] and the CHECKMATE214 trial [69, 70, 77] for the IMDC intermediate/poor prognosis population. However, as showed in outcomes (Table 30), and instruments (Table 31) vary between the two trials, making it difficult to compare the results in an indirect comparison. As shown in Table 31, EQ-5D-3L is the only instrument that was used in both trials. In the CHECKMATE214 study by Cella et al, 2019 [69], reports EQ-5D-3L UK utility index calculated with UK tariffs. The utilities reported are: 0.77 (SD= 0.25) for the NIVO+IPI arm and 0.78 (0.25) for the sunitinib arm. As we do not have IPD for the CHECKMATE214 study, we are unable to calculate EQ-5D-3L utility index with Danish preference weights for NIVO+IPI. However, as we have IPD data from the CLEAR trial, we are able to generate EQ-5D-3L utilities with UK preferences for LEN+PEM and then compare these with the utilities reported in Cella et al, 2019 [69]. Utilities in the CLEAR trial were calculated based on the LEN+PEM arm only, and were stratified by pre-progression and post-progression. These utilities are: 0.79 (SE= 0.003) for patients in pre-progression and 0.68 (SE=0.038) in post-progression. Even if they are measured with the same instrument and the same tariffs, health state utilities of the two trials are not comparable due to differences in the level of granularity. As the comparator utilities published do not have the granularity needed to feed into the model (pre-progression and post-progression), it is standard practice in health economics to use the health state utilities that are available from the clinical trial. It could be considered appropriate to use LEN+PEM utility as a proxy for NIVO+IPI. Both CLEAR 307 and Checkmate 214 QoL analyses have the same conclusion. Quality of life was maintained or improved from baseline with immunotherapy-based combinations compared to Sunitinib in patients with advanced RCC. Also, the EQ-5D-3L was mapped to EQ-5D-5L and used Danish tariffs in accordance with the DMC preferences. The EQ-5D-5L utility based on Danish utility is not available for Checkmate 214. Without the patient level data from Checkmate 214, therefore it is not possible to conduct such utility analysis,(see also details in section 5.4).

Table 30. Comparison of HRQoL outcomes analysed in the CLEAR [66] and the CHECKMATE trials [77, 78]

PRO measure	CLEAR		CHECKMATE214	
	Is the outcome measured in the trial?	**Definition used**	**Is the outcome measured in the trial?**	**Definition used**
Time to first deterioration (TTFD)	Yes	Number of weeks between randomization and the first deterioration event. Deterioration events were defined as detrimental changes in score relative to baseline that exceed the minimally important difference thresholds. Minimally important differences were: a decrease of three or more points for the FKSI-DRS; a decrease of ten or more points for the EORTC QLQ-C30 functional and GHS/QoL scores; an increase of ten or more points for the EORTC QLQ-C30 symptom scores; a decrease of 0.08 or more points for the EQ-5D-3L index; and a decrease of 7 or more points for the EQ-5D-3L VAS. Death was considered a deterioration event if it occurred within 30 days of the last HRQoL assessment, regardless of the start date of any new anticancer treatment. Patients without a deterioration event at the analysis cutoff date were censored at the date of the last HRQoL assessment. However, in Checkmate 214,	Yes	Time from the date of randomisation to the date of the first clinically meaningful deterioration in PRO scores of at least one threshold unit compared with the baseline score. Clinically meaningful threshold values for changes from baseline were defined as:a decrease of 0.08 or more points for the EQ-5D-3L index; a decrease of 7 or more points for the EQ-5D-3L VAS. a decrease of one or more points for the FKIS-19 symptoms scales and an decrease in the Functional well-being score a decrease of three or more in the FACT-G domains and 7 points in total score Death was not included in the definition of first deterioration; therefore, participants who died and did not have a first deterioration before

		death was not included in the definition of first deterioration; therefore, participants who died and did not have a first deterioration before death were censored at the last completed assessment		death were censored at the last completed assessment.
Time to definitive deterioration (TuDD)	Yes	Number of weeks between randomisation and the earliest deterioration event with no subsequent recovery above the deterioration threshold or no subsequent HRQoL assessment data	No	NA
Time to confirmed deterioration	No	NA	Yes	Confirmed deterioration was defined as first clinically meaningful deterioration in the PRO score that was also followed by meaningful deterioration at the net consecutive visit or dropout, resulting in missing data[77]. Clinically meaningful threshold values for changes from baseline were defined as: a decrease of 0.08 or more points for the EQ-5D-3L index; a decrease of 7 or more points for the EQ-5D-3L VAS.
LS change mean from baseline	Yes	Least square (LS) mean change from baseline	Yes	Least square (LS) mean change from baseline

Table 31. Comparison of HRQoL instruments used in the CLEAR and the CHECKMATE trials [66] [69] [78]

PRO measure	CLEAR	CHECKMATE214
	Is the outcome measured in the trial?	**Is the outcome measured in the trial?**
EQ-5D-3L	Yes	Yes
FACT-G	No	Yes
FKSI-19	No	Yes
FKSI-DRS	Yes	No
EORTC QLQ-C30	Yes	No

5. Health economic analysis

5.1 Model

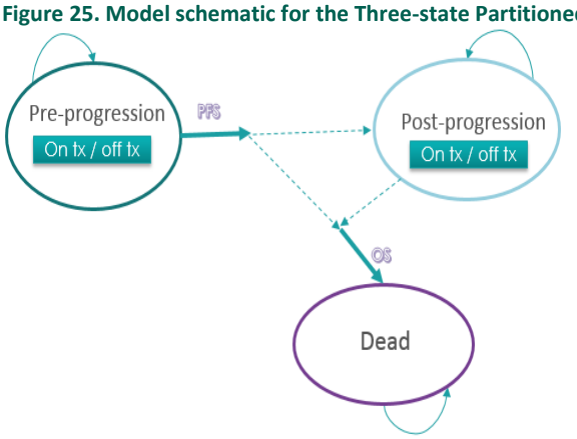
5.1.1 Model structure

A three-health state partitioned survival model is used to perform the cost-effectiveness analysis and estimate long-term costs and health benefits. The model schematic (Figure 25) aligns with previous RCC models submitted to the DMC [8]. Patients must be in any one of the three mutually exclusive health states at the end of each seven-day model cycle. The three health states are: pre-progression, post-progression, and death.

Based on this structure, to estimate the percentage of patients in each health state at each model cycle, survival distributions for PFS and OS were used. This enables the estimation of treatment costs, health state costs, and health state utility values to accrue quality-adjusted life years (QALY) and costs over the model time horizon. All patients are progression-free at the start of the model. At each cycle, state membership is calculated based on the PFS and OS curves, the PFS distribution is used to calculate the percentage of patients' remaining progression-free while the OS distributions is used to calculate the percentage of patients dead. The percentage of patients progressed will be inferred from the percentage difference between the patients alive and the progression-free patients.

Patients on-treatment, patients off-treatment, the number of incident progressed, incident dead, and incident treatment discontinuers are calculated for tracking purposes and to assign costs, they are not intended to be viewed as standalone health states. Progression-free, progressed, dead, patients on and off-treatment are half-cycle corrected. However, incident patients are not half-cycle corrected so that the number of new patients is captured at each cycle as opposed to the average number of new patients between cycles.

Figure 25. Model schematic for the Three-state Partitioned Survival Model



*Dashed lines indicate transitions that implied (but not explicitly modelled) while solid lines indicate explicit model transitions.
Abbreviations: OS = overall survival; PFS = progression-free survival; Tx = treatment

5.1.2 Patient population

The population included in the CEM are aRCC patients who are treatment-naive as defined in CLEAR. The model also includes two different subgroups to accommodate different local regulatory landscapes and reimbursement requirements, and to reflect previous submissions by competitors. The IMDC prognostic model is used to define the prognosis subgroups included in the model. Consequently, the CEM models the following target populations:

- Overall population with previously untreated aRCC (base case setting for CEM)
- Patients with favourable risk
- Patients with intermediate/poor risk

Typically, the inputs expected to change by subgroup are the efficacy data of treatments, list of comparators included in the analysis and utility values.

5.1.3 Perspective Time Horizon and cycle length

The model considers a Danish restrictive societal perspective, consistent with the guidelines presented by the DMC [15].

A lifetime horizon was selected to ensure the full impact of treatment in terms of cost and health outcomes are captured and is in line with time horizons used in previous HTA submission for NIVO+IPI [9], pembrolizumab plus axitinib (PEM+AXI) [79]. The model enables the time horizon to be set between one and 40 years.

A one-week time cycle is used in the model and the same cycle length has been used in previous HTA submissions and is of sufficient duration to capture differences in costs and effects between treatments.

5.1.4 Discounting

A discount rate of 3.5% until year 35 and 2.5% beyond year 35 was applied to costs, as defined by the Danish Ministry of Finance and in the DMC guidelines [15]. A discount rate of 0% was explored as scenario analysis.

5.1.5 Intervention

The CEM models three treatment regimens for 1L treatment as shown in Table 32.

Table 32. Rationale for inclusion of each comparator in the model

1L Treatment	Rationale for inclusion in the model
LEN+PEM	Intervention of interest
Sunitinib	Sunitinib is the active comparator in the CLEAR trial and it is recommended for 1L aRCC patients with good IMDC prognosis [13]. Also used in Denmark for patients in the intermediate/poor prognosis group.
NIVO+IPI	Used in Denmark in 80% of 1L aRCC patients with intermediate/poor IMDC prognosis group [13]

Abbreviations: aRCC, advanced renal cell carcinoma; IMDC, International Metastatic RCC Database Consortium.

Subsequent treatment regimens were chosen based on the DMC's guidelines for the treatment of aRCC, specifically for the second line treatment that have been exposed to PD-L1 in 1L and patients that have not been exposed to PD-L1 in 1L [13]. Sorafenib and everolimus were not included as the Danish clinical expert confirmed they are both very seldomly used in Denmark [57].

Table 33. Rationale for inclusion of each subsequent treatment in the model

Subsequent Treatment	Rationale for inclusion in the model
Cabozantinib	In Denmark, given to 80% of patients who have received a PD-L1 in 1L. [13]
Axitinib	In Denmark, given to patients who have received a PD-L1 in 1L. [13]
Tivozanib	In Denmark, given to patients who have received a PD-L1 in 1L. [13]
Pazopanib	In Denmark, given to patients who have received a PD-L1 in 1L. [13]
Sunitinib	In Denmark, given to patients who have received a PD-L1 in 1L. [13]
Nivolumab	In Denmark, given to 80% of patients who have not received a PD-L1 in 1L [13]
AVE+AXI	In Denmark, given to patients who have not received a PD-L1 in 1L [13]
PEM+AXI	In Denmark, given to patients who have not received a PD-L1 in 1L [13]

Abbreviations: AVE+AXI, avelumab plus axitinib; PD-L1, Programmed death-ligand 1; PEM+AXI, pembrolizumab plus axitinib; 1L, first line

5.1.6 Approach to Modelling Efficacy

5.1.6.1 General

The clinical effectiveness parameters for LEN+PEM and sunitinib in the cost-effectiveness model were estimated from the CLEAR trial [7] patient-level data on PFS, OS, Time to treatment discontinuation (TTD). PFS and TTD data were based on CLEAR August 2020 DCO whereas OS data was derived from the March 2021 DCO. The latest data available has been used throughout the model. The March 2021 data cut is an update of OS data only and it represents the latest OS data cut. The 28 August 2020 data cut represents the final data cut of IIR (independent imaging review) PFS. No further IIR PFS were collected beyond this data cut. TTD data is mature at the final PFS analysis, 76.5% in the sunitinib arm and 59.2% in the LEN+PEM arm had discontinued study treatment. CLEAR307 was the primary data source for the economic model. However, clinical effectiveness estimates of NIVO+IPI (in the intermediate/poor risk group) were applied by using constant HRs from the NMA.

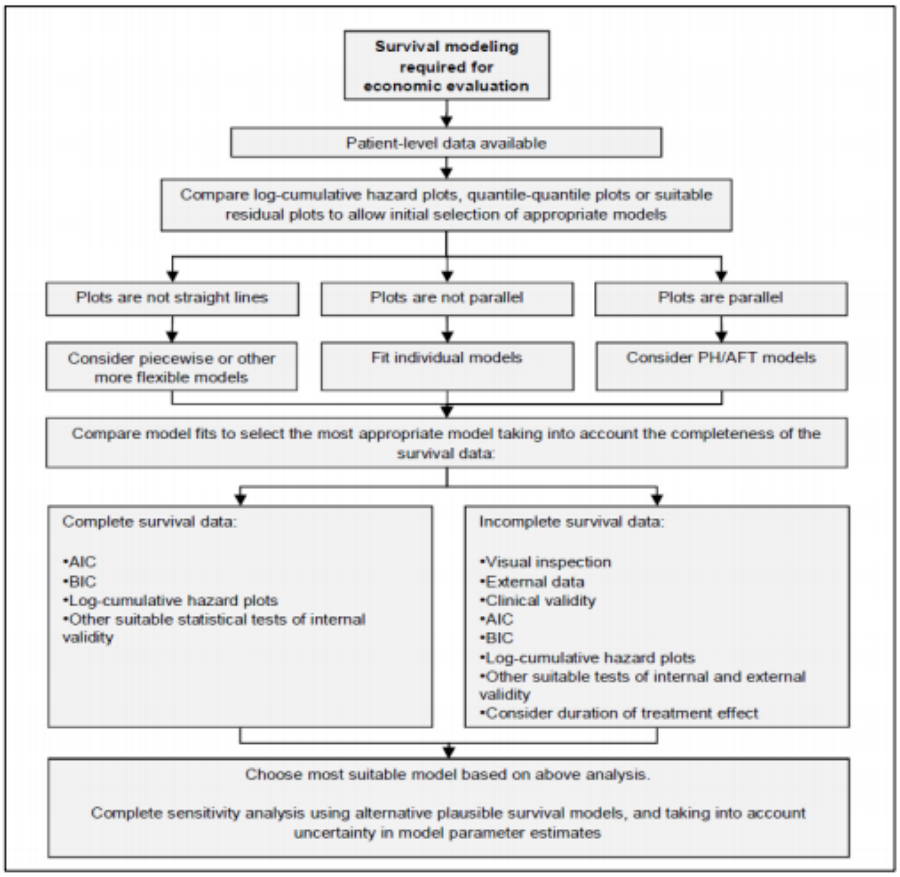
The follow-up period in CLEAR was much shorter than the time horizon of the economic model. Therefore, extrapolation of PFS, OS and TTD were required for the area under-the-curve (AUC) partitioned survival approach. Parametric models were fitted to the CLEAR KM data. In summary, the steps that were followed are presented in Figure 26 below.

Consistent with recommendations in the NICE DSU technical support document 14 [80], the selection of base case parametric functions for PFS and OS were informed by:

Goodness-of-fit statistics (i.e., Akaike information criterion [AIC] and Bayesian information criterion [BIC]) and visual inspection to assess the concordance between predicted and observed PFS and OS curves within the trial period; and

Clinical plausibility of long-term extrapolations beyond the trial period, which was evaluated based on published external sources, clinical expert opinion, and biological plausibility.

Figure 26. Survival Model Selection Process Algorithm by NICE DSU [16]



Abbreviations: AFT: Accelerated failure time; AIC: Akaike information criterion; BIC: Bayesian information criterion; PH: Proportional hazards Source.

5.1.6.2 Modelling PFS, OS and TTD for LEN+PEM and sunitinib

To keep the mortality risk of eligible patients, equivalent to or greater than the general population in all model cycles, all outcomes (OS, PFS, and TTD) were capped by general mortality using Danish life tables.

PFS

The log-cumulative hazard plot (Figure 27) showed that the plots for LEN+PEM and sunitinib remain separated and broadly parallel until the end of follow-up. This suggests that the proportional hazard assumption cannot be ruled out. This was confirmed by the formal assessment of the PH assumption via the Schoenfeld residuals test resulted in a p-value of XXXX, which suggested that the proportional hazard assumption holds (p>0.05), and that joint parametric fits for LEN+PEM and sunitinib are suitable.

Figure 27. Log-Cumulative Hazard Plots for PFS, overall population

Therefore, to model PFS in the populations of interest, a parametric joint fit using treatment as predictor was selected.

OS

To model long-term OS, the updated OS data-cut from March 2021 was used, which provided data for OS with a longer follow-up. The OS curves for LEN+PEM and sunitinib crossed at approximately 188 weeks, with log cumulative hazard plots for both treatment arms (Figure 28) appearing non-parallel. Formal assessment of the PH assumption via the Schoenfeld residuals test resulted in a p-value of XXXXX, suggesting that the proportional hazards assumption does not hold and that joint parametric distributions are not suitable for modelling of OS. While LEN+PEM showed improved OS in the short term, crossing occurs between the KM curves as the risk of death for LEN+PEM appears to increase and exceed the risk of mortality of sunitinib. However, it is important to note that there are a small number of patients at risk at the timepoint at which the curves intersect.

Figure 28. Log-cumulative Hazard Plot for OS using March 2021 DCO, overall population

Therefore, to model OS in the populations of interest, a stratified parametric single fit was selected for this submission. Different distributions can be selected for LEN+PEM and sunitinib. Time-to-event distributions and sunitinib are predicted independently of each other.

TTD

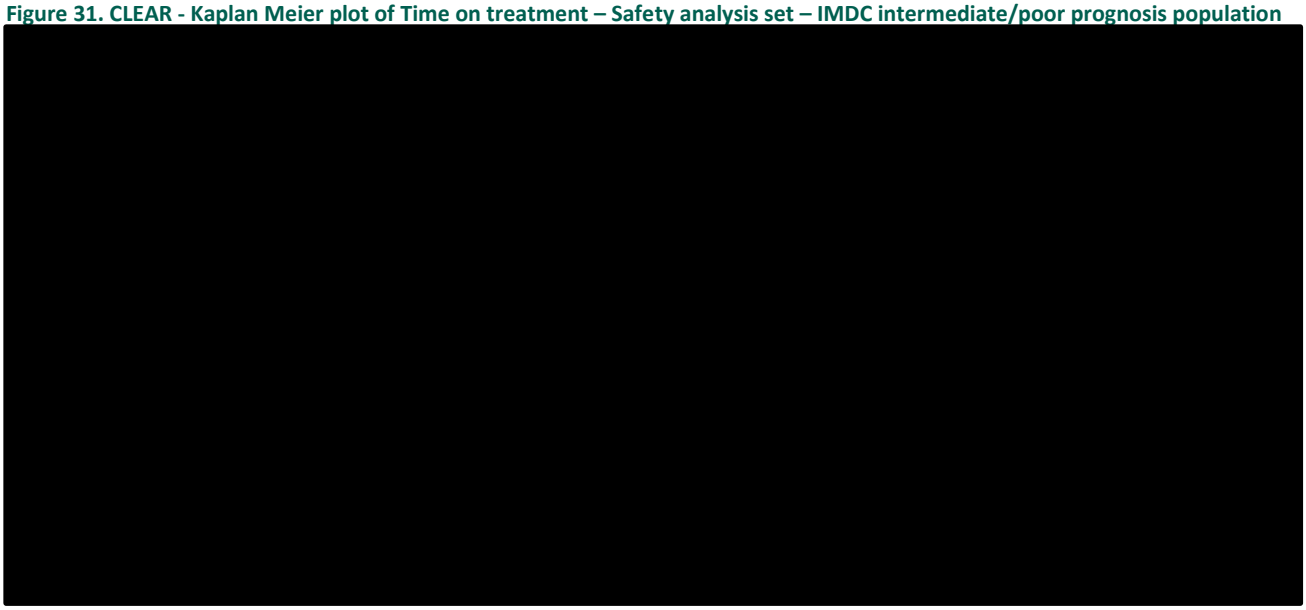
The CLEAR study protocol allowed patients to discontinue treatment upon progression but also for toxicity concerns [7]. For this reason, using the TTD curve rather than the PFS curve to estimate the time to treatment discontinuation gives an accurate reflection of the treatment actually

administered. TTD curves of the lenvatinib component and pembrolizumab component of the LEN+PEM combination are modelled separately as pembrolizumab has a fixed time on treatment duration of two years [79]. Figure 29, Figure 30, Figure 31 report the KM curves of the Time on treatment of the three populations of interest.

Figure 29. CLEAR - Kaplan-Meier plot of Time on treatment – Safety analysis set – ITT/overall population.

Figure 30. CLEAR- Kaplan Meier plot of Time on treatment – Safety analysis set – IMDC good prognosis population

Figure 31. CLEAR - Kaplan Meier plot of Time on treatment – Safety analysis set – IMDC intermediate/poor prognosis population



5.1.6.3 Modelling PFS, OS and TTD for NIVO+IPI

OS and PFS

For all non-CLEAR comparators, constant HR are applied to a reference curve (LEN+PEM or sunitinib) to allow PFS and OS to be modelled.

TTD

An exponential extrapolation is fitted to the median treatment duration as reported in literature for each 1L comparator outside of the CLEAR trial. This approach is taken when no KM curve for the comparator is available. Given that only 1 point of information is available (median), curves other than Exponential cannot be used, as it is not possible to calibrate curves with more than one parameter, when only one data point is known.

In scenario analyses, the impact of modelling TTD based on progression is tested.

5.1.7 Additional model assumptions

Modelling assumptions made during model development are described in Table 34. Modelling assumptions

Table 34. Modelling assumptions

Category	Assumption
Treatment efficacy	If PFS or OS are estimated by applying a constant HR, it is assumed that proportionality holds to the selected reference arm. When modelling TTD using the parametric fits for non-CLEAR comparators, the duration of TTD was assumed the same for all subgroups in the model due to lack of data. SE for median treatment duration was assumed to vary by 10% from the median treatment duration estimate. The two-year stopping rule for pembrolizumab is in line with the maximum treatment length of pembrolizumab from CLEAR and KEYNOTE-426 protocol in in NICE TA650 [79]. A two year stopping rule is also applied for nivolumab, in accordance with the DMC's guidelines for aRCC. [13]
Subsequent treatment	Patients are assumed to be eligible for subsequent treatment after 1L discontinuation. This assumption was in accordance with Danish clinical guidelines on RCC [8, 13]. Subsequent treatments are not modelled as individual line of therapies but represent an aggregated line of subsequent therapies due to lack of data for each subsequent treatment per line of therapy. In addition, this assumption has been made and accepted by DMC in previous RCC HTA assessments such as TA650 for PEM+AXI [79] and TA645 for AVE+AXI [81].

	The treatment duration on each individual subsequent treatment for patients who received a 1L treatment not included as comparator in the CLEAR trial were based on preferred assumptions from the Evidence Review Group who reviewed NICE TA650 and are assumed the same for all subgroups in the model [79].
Utilities	Utility values are distinguished for patients who are progression-free or post-progression and are reported by subgroup but are not assumed to be treatment specific. For treatment specific utilities, the progression-free utility of NIVO+IPI was assumed to be the same as LEN+PEM In the absence of pooled utility data for LEN+PEM with sunitinib from CLEAR, utility values for LEN+PEM were used in the model as the base progression-free and post-progression utility estimates, as there was no statistical difference between the LEN+PEM and sunitinib arms from CLEAR. Utility values for the intermediate and poor risk population were assumed the same as the intermediate risk group due to unavailable estimates for the intermediate and poor risk population. Utility estimates are age-adjusted in the base case as was the base case for the AVE+AXI TA645 submission. [81] Utility values derived from the CLEAR clinical trial were mapped to EQ-5D-5L, in accordance with the DMC's preferences [15]. The model allows the effect of AE disutilities to be applied, this uses data from NICE TA581 [82] (section 5.4.3)
Adverse events (AE)	Only grade ≥ 3 treatment-emergent adverse events (AEs) occurring in at least 5% of patients in any of the included treatments are included in the model. Use of a 5% threshold has also been used in previous RCC HTA assessments such as the DMC's Assessment of pembrolizumab and axitinib [8] Due to lack of data on TEAEs for the NIVO+IPI treatment regimen, TRAEs are included in the model for LEN+PEM, sunitinib and NIVO+IPI as a proxy for TEAEs. AEs costs are re applied as one-off costs. AE rates and AE unit costs are assumed equivalent across all subgroups due to a lack of subgroup specific estimates.
Drug acquisition costs	No vial sharing for infusions. Treatment dosing is subject to an observed estimate of dose intensity, for lenvatinib this was calculated based on the cumulative days per lenvatinib dose from CLEAR. For 1L treatments, a 100% dose intensity was assumed for drug components if this information was not available in the public literature as this approach prevents underestimating drug acquisition costs for comparators. For subsequent treatments, dose intensity is based on assumption used in TA650 [79] to ensure consistency with the data source used to obtain the duration and distribution of each subsequent treatment. Drug acquisition costs are assumed to be equivalent across all subgroups.
Drug administration costs	No administration cost was assumed for drugs taken orally. Drug administration costs for subsequent oral chemotherapy or subsequent intravenous (IV) chemotherapy drugs delivered on the same day were assumed to not incur any further cost i.e., if a two components of a combination therapy were delivered on the same day, only one drug would incur the administration cost, if applicable. Drug administration costs are assumed to be equivalent across all subgroups.
AE management costs	AE management costs are assumed equivalent across all subgroups. Unit cost per event for AEs were based on costs derived from the Danish DRG grouper, *interactive DRG [83].*
Disease management costs	Disease management costs are applied by health state and assumed to equivalent across all subgroups.

Other	To conduct the sensitivity analysis, in the absence of published ranges, higher and lower values were calculated as ± 10% of the mean/median base case value, with costs varied by ± 20 of the mean/median base case values.

5.1.8 Model Outcomes

A list of model outcomes reported for the base case in the model are reported in Table 35. Graphical representation of the sensitivity results in the form of a tornado diagram for deterministic sensitivity analysis (DSA) and cost-effectiveness acceptability curve (CEAC) for probabilistic sensitivity analysis (PSA) are also included, alongside the cost-effectiveness frontier.

Table 35. Model outputs

Cost Outcomes	Health Outcomes	Incremental and Cost-effectiveness Outcomes
Overall direct medical costs	Total LYs	Incremental costs
Overall costs disaggregated by each cost category within the model:	Progression-free	Incremental LYs
Drug acquisition	Post-progression	Incremental QALYs
Drug administration	On-treatment	Cost per life year gained
AE management	Off-treatment	Cost per QALY gained
Disease management	Total QALYs	INMB
Patient costs	Progression-free	
Subsequent treatment	Post-progression	

5.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

5.2.1 Presentation of input data used in the model and how they were obtained

5.2.1.1 Overall method

Table 36 summarises the inputs included in the model and how they were obtained/estimated. Details on the approach to modelling efficacy are presented in section 5.1.6 and in section 5.3. Details on Health state utility values (HSUV) are presented in section 5.4. Safety inputs, Grade ≥3 TEAE rates are presented in section 4.1.2.1.1 for LEN+PEM and sunitinib and See section 4.3.3 for NIVO+IPI.

Table 36. Summary of efficacy inputs included in the economic model

Name of estimates	Results from study or indirect treatment comparison (ITC)	Input value used in the model	How is the input value obtained/estimated
LEN+PEM and sunitinib			
PFS by IIR	See section 5.3	See section 5.3	CLEAR (August 2020 DCO) [7]
OS	See section 5.3	See section 5.3	CLEAR (March 2021 DCO) [65]
TTD	See section 5.3	See section 5.3	CLEAR (August 2020 DCO) [7]
Grade ≥3 TEAE	See section 4.1.2.1.1	See section 4.1.2.1.1	CLEAR, Motzer et *al*, 2021 [84] (August 2020 DCO)
Pre-progression utility	See section 5.4	See section 5.4	CLEAR (August 2020 DCO) [7]
Post-progression utility	See section 5.4	See section 5.4	CLEAR (August 2020 DCO) [7]
NIVO+IPI			
PFS by IIR	See section 5.3	See section 5.3	HR from NMA analysis [68]
OS	See section 5.3	See section 5.3	HR from NMA analysis [68]
TTD	See section 5.3	See section 5.3	HR from NMA analysis [68] [42]
Grade ≤3 TRAE	See section 4.3.3	See section 4.3.3	Model – Albiges 2020 [68] ITC - Ali et al, 2021 [71]
Pre-progression utility	See section 5.4	See section 5.4	CLEAR (August 2020 DCO) [7]
Post-progression utility	See section 5.4	See section 5.4	CLEAR (August 2020 DCO) [7]

Abbreviations: IIR, independent reviewer; ITT, intention to treat; I/P, intermediate/poor; LEN+PEM, lenvatinib pembrolizumab; NIVO+IPI, nivolumab ipilimumab; OS, overall survival; PFS, progression-free survival; TTD, Time-to-treatment discontinuation; TEAE, treatment emergent adverse events; TRAE, treatment-related adverse events

5.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

5.2.2.1 Patient population

The population for this economic assessment is 1L patients with aRCC. LEN+PEM is a treatment alternative to sunitinib for the patients with IMDC good prognosis and an alternative to NIVO+IPI for the IMDC intermediate/poor prognosis subgroup. The efficacy and safety of LEN+PEM in comparison to sunitinib has been investigated head-to-head in this population in the CLEAR clinical trial. Therefore, to fit the scope of this assessment, data from this trial is included in the model.

NIVO+IPI efficacy and safety has been investigated in the CHECKMATE 214 trial. Therefore, data from this trial is also included in the model. In Table 37, the age and sex distribution of the patients enrolled in these two trials have been compared to characteristics of the Danish aRCC patients included in the DaRenCa report [4]. The age and sex distribution are not expected to differ from Danish clinical practice, this has been confirmed by the Danish clinical expert [57].

Table 37. Patient population of CLEAR trial in the LEN+PEM and sunitinib arms, patient population of the CHECKMATE 214 trial and Danish clinical practice according to DenRenCa report.

Patient population Important baseline characteristics	Clinical documentation	Used in the model	Danish clinical practice
LEN+PEM			
Age, median (range)	62 (32–86) [7]	62 (32–86) [7]	67 (9;92) [4]
Men, %	74.5% [7]	74.5% [7]	62.7% [4]
Sunitinib			
Age, median (range)	61 (29–82) [7]	61 (29–82) [7]	See above
Men, %	77.0% [7]	77.0% [7]	See above
NIVO+IPI			
Age, median (range)	62 (26-85) [68]	62 (26-85) [68]	See above
Men, %	75% [68]	75% [68]	See above

Abbreviations: LEN+PEM, lenvatinib pembrolizumab

5.2.2.2 Intervention

In Denmark, LEN+PEM is expected to be positioned as 1L treatment for advanced or metastatic RCC patients, similarly to sunitinib (for patients with IMDC good prognosis) and similarly to NIVO+IPI (for patients with IMDC medium/poor prognosis group).

The dose of lenvatinib is 20 mg orally once daily in combination with pembrolizumab (200 mg as an IV infusion over 30 minutes) administered every three weeks ([3, 85]. A dose of 400mg to be infused every six weeks is available possible for Pembrolizumab. The impact of using 400mg every six weeks rather than the 200mg every three weeks is explored in a scenario analysis.

Regarding lenvatinib, the EU label [1] specifies that treatment should continue as long as there is clinical benefit or until unacceptable toxicity occurs. In the CLEAR trial, subjects continued to receive study treatment until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, loss of clinical benefit, completion of 35 treatments (approximately 2 years) with pembrolizumab, or sponsor termination of the study. In the presence of clinical benefit, subjects in Arm B who discontinued pembrolizumab could have continued treatment with lenvatinib alone unless any of the other discontinuation criteria apply.[3]. However, the economic model allows pembrolizumab to be administered for a duration of two years. This was confirmed to be more reflective of Danish clinical practice [2].

Table 38. Description of LEN+PEM as used in the model

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	Lenvatinib 20 mg orally once daily in combination with pembrolizumab (200mg) every three weeks administered as an intravenous (IV) infusion over 30 minutes (also available as 400mg to be administered every six weeks) [1] [3]	Lenvatinib 20 mg orally once daily in combination with pembrolizumab (200mg) every three weeks administered as an intravenous (IV) infusion over 30 minutes (also available as	Lenvatinib 20 mg orally once daily in combination with pembrolizumab (200mg) every three weeks administered as an intravenous (IV) infusion over 30 minutes (also available as

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice
		400mg to be administered every six weeks) [1] [3]	400mg to be administered every six weeks) [1] [3]
Length of treatment (time on treatment)/ criteria for discontinuation	Subjects continued to receive study treatment until disease progression, development of unacceptable toxicity, subject request, withdrawal of consent, loss of clinical benefit, completion of 35 treatments (approximately 2 years) with pembrolizumab, or sponsor termination of the study. In the presence of clinical benefit, subjects in Arm B who discontinued pembrolizumab could have continued treatment with lenvatinib alone unless any of the other discontinuation criteria apply [1] [3]	Lenvatinib: Until clinical benefit is observed or until unacceptable toxicity Pembrolizumab: Until disease progression or unacceptable toxicity, maximum for two years. [1] [3]	Lenvatinib: Until clinical benefit is observed or until unacceptable toxicity Pembrolizumab: Until disease progression or unacceptable toxicity, maximum for two years
The pharmaceutical's position in Danish clinical practice	NA	First line for advanced or metastatic RCC	First line for advanced or metastatic RCC

Abbreviations: IV, intravenous; mg, milligrams NA, not applicable; RCC, renal cell carcinoma.

5.2.2.3 Comparators

As discussed in 2.2.1, the Danish guidelines recommend that tivozanib should be used as first choice in 1L aRCC patients pertaining to the IMDC good prognosis group and that sunitinib is considered clinically equivalent to tivozanib. According to the guidelines, NIVO+IPI should be used as first choice for patients pertaining to the IMDC intermediate/poor prognosis group. Since the CLEAR trial presents direct evidence of the relative efficacy of LEN+PEM versus sunitinib, sunitinib was chosen as the relevant comparator for the ITT population and the IMDC good prognosis subgroup.

The economic model reflects these, and no discrepancies between the different SMPCs are to be mentioned.

Table 39. Description of comparators as used in the model

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Sunitinib [53]			
Posology	50 mg orally QD for 4 weeks, followed by 2 weeks off	50 mg orally QD for 4 weeks, followed by 2 weeks off	50 mg orally QD for 4 weeks, followed by 2 weeks off
Length of treatment	Until disease progression or unacceptable toxicity	Until disease progression or unacceptable toxicity	Until disease progression or unacceptable toxicity
The comparator's position in the Danish clinical practice	1L aRCC patients	1L aRCC patients	1L aRCC patients
NIVO+IPI [55] [54]			
Posology	Combination therapy phase (first four doses): nivolumab 3 mg/kg over 30 minutes Q3W, ipilimumab 1 mg/kg over 30 minutes, followed by:	Combination therapy phase (first four doses): nivolumab 3 mg/kg over 30 minutes Q3W, ipilimumab 1 mg/kg over 30 minutes, followed by:	Combination therapy phase (first four doses): nivolumab 3 mg/kg over 30 minutes Q3W, ipilimumab 1 mg/kg over 30 minutes, followed by:

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
	Nivolumab monotherapy phase: 480 mg IV (over 60 minutes) Q4W	Nivolumab monotherapy phase: 480 mg IV (over 60 minutes) Q4W	Nivolumab monotherapy phase: 480 mg IV (over 60 minutes) Q4W
Length of treatment	Until disease progression or unacceptable toxicity. (A protocol amendment in 2017 allowed discontinuation of nivolumab plus ipilimumab after 2 years of therapy without progression or toxicity)	Until disease progression or unacceptable toxicity and for a maximum of two years	Until disease progression or unacceptable toxicity and for a maximum of two years
The comparator's position in the Danish clinical practice	1L aRCC patients with IMDC intermediate/poor prognosis	1L aRCC patients with IMDC intermediate/poor prognosis	1L aRCC patients with IMDC intermediate/poor prognosis

Abbreviations: aRCC, advanced/metastatic renal cell carcinoma; 1L, first line; IMDC, International Metastatic RCC Database Consortium; IV, intravenous; QD, every day; QW4, every four week; mg, milligrams; QW3, every three weeks; kg, kilograms.

5.2.2.4 Relative efficacy outcomes

In the Danish clinical guidelines, PFS, OS and ORR are the three outcomes identified to assess the effect of a treatment for aRCC [13]. The manufacturer therefore believes that the included efficacy outcomes are highly relevant and would reflect Danish clinical practice to assess the value of LEN+PEM in 1L treatment of aRCC. This is summarised in Table 40 and Table 41.

Table 40. Relevance of model efficacy inputs in Danish clinical practice

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
PFS	See Table 11	Traditionally used in evaluations of drugs in oncology	Traditionally used in evaluations of drugs in oncology
OS	See Table 11	Traditionally used in evaluations of drugs in oncology	Traditionally used in evaluations of drugs in oncology

Table 41. Clinical documentation of outcomes included in model

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
LEN+PEM vs sunitinib		
PFS	CLEAR [7]	See Table 36
OS	CLEAR [7]	See Table 36
LEN+PEM vs NIVO+IPI		See Table 36
PFS	HR	See Table 36
OS	HR	See Table 36

5.3 Extrapolation of relative efficacy

5.3.1 Overall population

Due to space constraints and interest of the DMC, extrapolations for the overall population are presented in detail in Appendix G Extrapolation.

[redacted]

A short summary of the selected curves for each parameter is presented hereafter.

5.3.1.1 PFS extrapolations

Based on PFS data derived from the CLEAR August 2020 DCO, the Log-normal joint parametric model was selected for PFS to model both treatment arms. Based on the log cumulative hazard plot (broadly parallel) (Figure 27) and p-value from the Schoenfeld residual plot ([XXXX]), joint parametric fits were deemed suitable for PFS. Of the joint parametric models, the joint Log-normal model was selected based on having the best statistical fit according to both AIC and BIC, as well as the joint best visual fit to the tail for LEN+PEM and the best visual fit to the tail for sunitinib. Although the Log-normal model potentially overestimates PFS at ten-years for sunitinib when compared to clinical expert opinion from NICE TA645 [81], it represented a conservative long-term projection for sunitinib relative to LEN+PEM.

The generalised gamma joint parametric model was explored through scenario analysis, as this model produced a good relative statistical fit compared to the Log-normal model and one of the next best visual fits to the tails of the KM curves.

5.3.1.2 OS extrapolations

Based on data derived from the CLEAR March 2021 DCO, for the base case analysis, single Exponential distributions were applied for OS for both LEN+PEM (Figure 82) and sunitinib (Figure 85). Although the use of single Exponential distributions still assumes a proportional hazards relationship between LEN+PEM and sunitinib (due to hazards remaining constant over time), the Exponential models produced the most plausible set of single fit distributions given clinical expert expectations for long-term OS (<20% at ten years for patients starting treatment within the current clinical landscape). Other distributions provided unrealistic estimates of ten years survival for patients receiving sunitinib, ranging from 26.6% with the Log-logistic distribution to 43.9% with the Generalised Gamma distribution. Moreover, this is in line with the expectation that OS curves should not cross for LEN+PEM and sunitinib, with experts at the July 2021 advisory board [86] agreeing that statistical fit to the observed data had limited value when selecting the most appropriate set of extrapolations. This was also in line with guidance from NICE DSU TSD14 [16] which recommends that the same type of parametric model be applied unless sufficient justification is provided to warrant the use of separate types of parametric models based on “clinical expert judgement, biological plausibility and robust statistical analysis.”

In a scenario analysis, the impact of using the Log-normal distribution was assessed.

5.3.1.3 TTD extrapolations

Based on data derived from the CLEAR August 2020 DCO, and given the different treatment stopping rule for pembrolizumab (maximum treatment duration of ~two years) compared to lenvatinib and sunitinib (treatment until progression or unacceptable toxicity) and mechanisms of action, it was considered reasonable to apply different types of parametric survival models for pembrolizumab compared to lenvatinib and sunitinib.

For pembrolizumab, four of the distributions (Exponential, Weibull, Gompertz, generalized gamma) produced reasonable visual fits to the data up until the two-year treatment stopping point Figure 95. The generalized gamma model was excluded, however, due to unreasonable levels of uncertainty around the model parameters, with the standard errors being larger than the parameter values themselves, and a 95% CI around the median survival time of 1.30×10^{-141} to 4.04×10^{144} weeks. The Weibull model was selected as the base case TTD model for pembrolizumab, based on presenting both good visual fit and best statistical fit according to AIC BIC

For lenvatinib and sunitinib, the same type of distribution was applied based on guidance from NICE DSU TSD14 [16]. The generalized gamma model was the only distribution generating good statistical fits and good visual fits to the tails across both treatment arms, and hence this distribution was applied for the base case analysis (Figure 93 and Figure 97).

In a scenario analysis, the impact of generating a generating a TTD curve based on the PFS curve as an alternative method as described in section 5.1.6.3 was explored.

5.3.2 IMDC good prognosis population

5.3.2.1 PFS Extrapolations

The PFS data reported in this section derives from the August 2020 DCO of the CLEAR trial.

Figure 32. Log-Cumulative Hazard Plots for PFS (IMDC good prognosis subgroup)

The log cumulative hazard plots for LEN+PEM and sunitinib in The PFS data reported in this section derives from the August 2020 DCO of the CLEAR trial.

Figure 32 showed that the hazard plots cross very early on but that afterwards the curves remain separate and broadly parallel until the end of follow-up. In addition, formal testing of the PH assumption through the Schoenfeld residuals resulted in a p-value of 0.91, suggesting that the PH assumption cannot be ruled out. Therefore, a joint fit is applied to the PFS LEN+PEM and sunitinib data. The AIC and BIC of fittings for each distribution modelled in the IMDC good prognosis population are presented in Table 42 with the Log-normal distribution generating the lowest AIC and BIC highlighted in bold.

Table 42. AIC and BIC of Fittings for Joint Fits of LEN+PEM and Sunitinib for the IMDC good prognosis subgroup

Distribution	AIC	BIC
Weibull		
Log-normal		
Log-logistic		
Exponential		
Generalised Gamma		
Gompertz		

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 43. AIC and BIC Goodness-of-fit per each distribution relative to the distribution with the lowest AIC and BIC for EMA-based for PFS Joint Fits of LEN+PEM and Sunitinib for the IMDC good prognosis subgroup

Distribution	AIC relative goodness-of-fit classification	BIC relative goodness-of-fit classification
Weibull		
Log-normal		
Log-logistic		
Exponential		
Generalized gamma		
Gompertz		

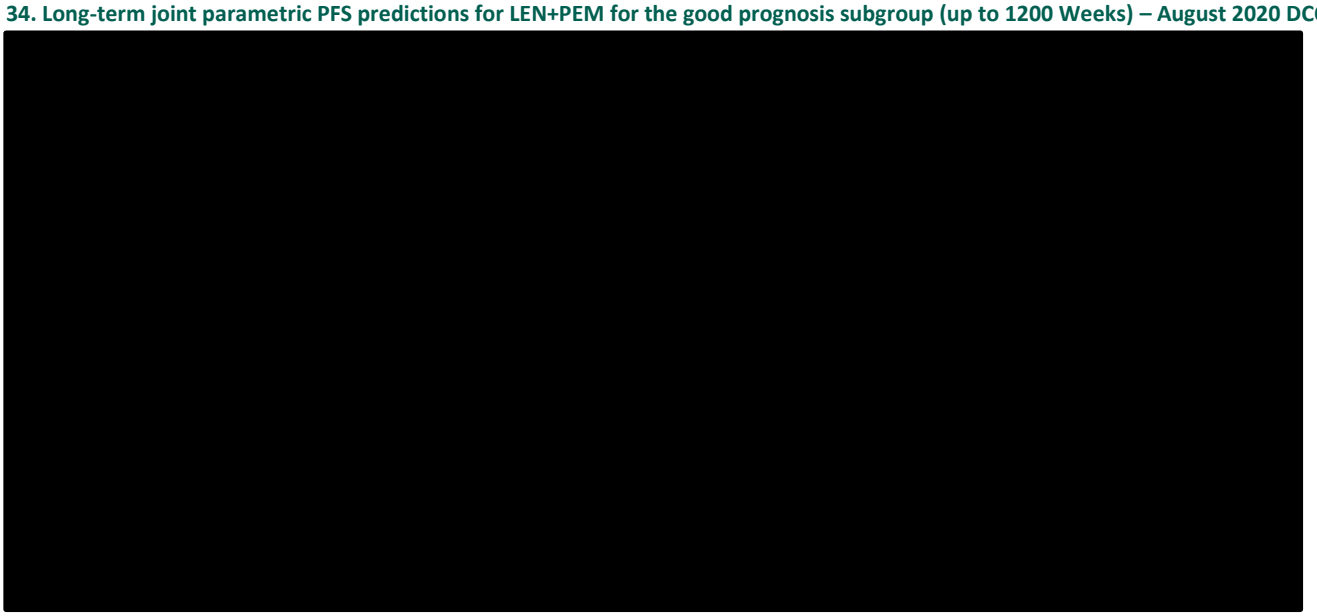
Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

The Log-normal distribution produced the best fit to the KM data, according to both AIC and BIC. The Weibull, Log-logistic and generalized gamma distributions also displayed good statistical fits to the KM curve as per AIC. The Exponential on the other hand produced a poor statistical fit relative to the Log-normal distribution whereas the Gompertz presented a relatively acceptable fit to the data (7-10 difference). Furthermore, as shown in Figure 33 (150weeks) and Figure 34 (1200 weeks), visual inspection of the joint parametric PFS curve for LEN+PEM overlaid by the KM curve showed that the Exponential distribution overestimates the tail of the curve, with the Log-normal, Log-logistic and generalised gamma models slightly overestimating the tail, and the remaining parametric models (Weibull, Gompertz) producing more significant underestimates of the tail and therefore relatively poor visual fits.

Figure 33. Comparison of observed PFS and joint parametric predictions for LEN+PEM during the observed period (up to 150 Weeks) – August 2020 DCO

XFigure 34. Long-term joint parametric PFS predictions for LEN+PEM for the good prognosis subgroup (up to 1200 Weeks) – August 2020 DCO



Abbreviation: LENVAT+PEMBRO = lenvatinib plus pembrolizumab

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 35. Long-term joint parametric PFS predictions for LEN+PEM for the good prognosis subgroup (up to 2500 Weeks) – August 2020 DCO

Similarly, the visual observation of the joint parametric PFS curve for Sunitinib overlaid by the KM curve in Figure 36 (150 weeks) and

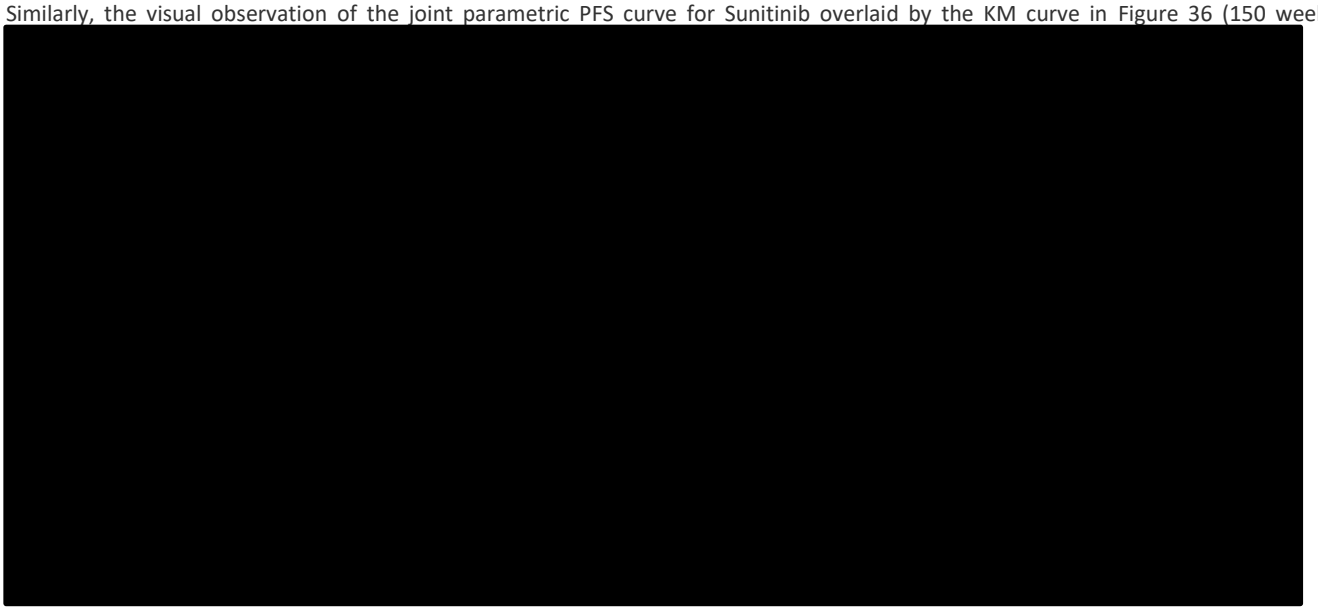


Figure 37 (1200 weeks) showed that the Log-normal distribution closely matched the tail of the KM curve, with the log-logistic, Exponential and Generalised Gamma slightly underestimating the tail and the remaining models (Weibull and Gompertz) producing more significant underestimates of the tail and therefore poor visual fits.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 36. Comparison of observed PFS and joint parametric predictions for Sunitinib during the observed period (up to 150 Weeks) – August 2020 DCO

Figure 37. Long-term joint parametric PFS predictions for Sunitinib for the good prognosis subgroup (up to 1200 Weeks) – August 2020 DCO

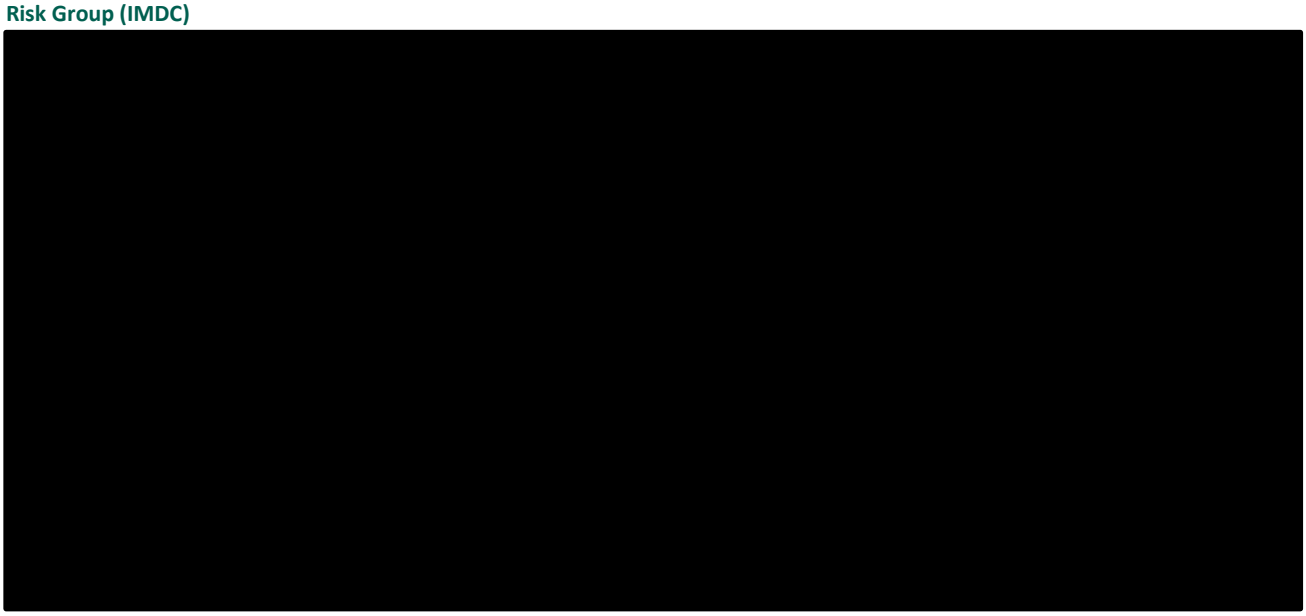
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 38 Long-term joint parametric PFS predictions for Sunitinib for the good prognosis subgroup (up to 2500 Weeks) – August 2020 DCO

Moreover, the expected percentages of progression-free patients at two-years, five-years and ten-years were extracted for the joint fits of LEN+PEM and Sunitinib.

The hazard profiles produced by each joint-fit parametric model for lenvatinib plus pembrolizumab and sunitinib were reviewed to assess the shape of the changing hazard over time, with the lenvatinib plus pembrolizumab hazard plots shown in Figure 39. As a joint parametric model was used to model both lenvatinib plus pembrolizumab and sunitinib, the hazard profiles for sunitinib were broadly similar (albeit with generally higher event risks for sunitinib over time).

Figure 39. Hazard Profiles from the Lenvatinib plus Pembrolizumab Joint-fit Parametric Model for PFS using FDA Censoring Rule – Favorable Risk Group (IMDC)



Abbreviation: LENVAT+PEMBRO = lenvatinib plus pembrolizumab

As shown in the smoothed hazard plot, the log-logistic, log-normal and generalized gamma models all produced similar increasing then decreasing hazards over time. The Weibull and Gompertz models both generated increasing hazard profiles, albeit with the Weibull hazards plateauing over time compared to continuously increasing rates of progression or death produced by the Gompertz model. The exponential model (by definition) produced a constant hazard profile. Further assessment of the appropriateness of the hazards will require additional validation with clinical experts.

As shown in Table 44, the estimated proportion of patients who are alive and progression-free treated with LEN+PEM at two-years ranges from XXXXXXXXXXXXXXX depending on the distribution selected. At five-years, the estimated proportion of alive and progression-free patients

decreases to between [redacted] and at ten-years the estimates further decrease to between [redacted] depending on the distribution selected.

Table 44. Expected PFS per Distribution with LEN+PEM (IMDC good prognosis)

Distribution for LEN+PEM	2-year PFS prediction	5-year PFS prediction	10-year PFS prediction
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LEN+PEM = lenvatinib plus pembrolizumab; PFS = progression-free survival

[redacted]

Distribution for sunitinib	2-year PFS prediction	5-year PFS prediction	10-year PFS prediction
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS = progression-free survival

Long-term progression-free survival estimates for sunitinib were searched for in published literature and from clinical commentary available in previous aRCC NICE TAs. These estimates were compared against the expected percentage of progression-free patients at two-years, five-years and ten-years extracted for the joint fits of sunitinib from this model. In the CheckMate 214 trial [68], which compared nivolumab plus ipilimumab against sunitinib in aRCC, 57.6% of IMDC favourable risk patients were progression-free at two-years In the KEYNOTE-426 trial [87], which evaluated PEM+AXI versus sunitinib in aRCC, 35.3% of IMDC favourable risk patients receiving sunitinib were progression-free at two-years. Moreover, the Danish clinical expert interviewed to inform this submission estimated that after two years, approximately 50% of patients receiving sunitinib will be progression-free, with 15% at 5 years and 5% at 10 years. It appears clear that there is high variability in the estimations of sunitinib PFS's values.

[redacted], with the Log-normal model and the Exponential model producing the highest and hence the closest estimates. While the Exponential model generated a 2-year PFS prediction that was slightly closer to the Danish clinical expert estimate compared to the Log-normal, the Exponential model underpredicted the PFS at 5 years and 10 years. Thus, the Log-normal joint parametric model was selected for PFS to model both treatment arms, based on the survival landmarks generated being the closest to Danish clinical practice ([redacted]). Moreover, the Log-normal model also had the best statistical fit according to both AIC and BIC, as well as good visual fit to the tail for sunitinib and the best visual fit to the tail for LEN+PEM. The loglogistic joint parametric model was explored through scenario analysis, as this model produced a good relative statistical fit and one of the next best visual fits to the tails of the KM curves.

5.3.2.2 OS extrapolations

The OS data reported in this section derives from the March 2021 DCO of the CLEAR trial.

Although formal assessment of the PH assumption via the Schoenfeld residuals test resulted in a p-value of [redacted], suggesting that the proportional hazards assumption may hold, the OS curves for LEN+PEM and sunitinib appear to cross at approximately 115 weeks in the IMDC favourable risk group, with log cumulative hazard plots for both treatment arms appearing more clearly non-parallel and fitted regression lines crossing before the end of follow-up, as shown in XXXXXXX40. As such, given the uncertainty in the PH assumption, single parametric fits were fitted for LEN+PEM and sunitinib independently. Clinical plausibility was then the main decision criteria to select the extrapolation model.

[redacted]

Abbreviation: LENVAT+PEMBRO = lenvatinib plus pembrolizumab

AIC and BIC estimates for the LEN+PEM OS distributions using the March 2021 DCO are shown in Table 46, with AIC and BIC classifications of relative fit shown in Table 47. The Gompertz distribution produced the lowest AIC and BIC, with the Log-logistic, the generalised gamma, the Weibull generating a good relative statistical fit (<4 difference) according to the AIC rules of thumb applied. The Exponential distribution produced an acceptable relative statistical fit to the Gompertz model in terms of AIC (7-10 difference). In terms of BIC, all the models generated an acceptable relative statistical fit (0 to 10 difference).

Table 46. AIC and BIC Estimates for LEN+PEM OS Distributions of the IMDC good prognosis subgroup, using March 2021 DCO

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 47. AIC and BIC Goodness-of-fit per Each Distribution Relative to the Distribution with the Lowest AIC and BIC for LEN+PEM OS using March 2021 DCO(IMDC good prognosis subgroup)

Distribution	AIC Relative Goodness-of-fit classification	BIC Relative Goodness-of-fit Classification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; G. Gamma, Generalised Gamma

AIC and BIC estimates for the sunitinib OS distributions are shown in Table 48, with AIC and BIC classifications of relative fit shown in Table 49. The Exponential distribution produced the best statistical fit with the lowest AIC, with all other models producing good relative statistical fits according to AIC. The Exponential model generated the best statistical fit and all other models producing good relative fits according to BIC.

Table 48. AIC and BIC Estimates for Sunitinib OS Distributions (IMDC good prognosis)

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; OS = overall survival

Table 49. AIC and BIC Goodness-of-fit per each distribution relative to the distribution with the lowest AIC and BIC for Sunitinib OS (IMDC good prognosis subgroup)

Distribution	AIC relative goodness-of-fit classification	BIC relative goodness-of-fit classification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; G. Gamma, Generalised Gamma; OS = overall survival

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Long-term single parametric predictions for LEN+PEM are shown in Figure 41 (200 weeks) and Figure 42 (1200 weeks) and for sunitinib in

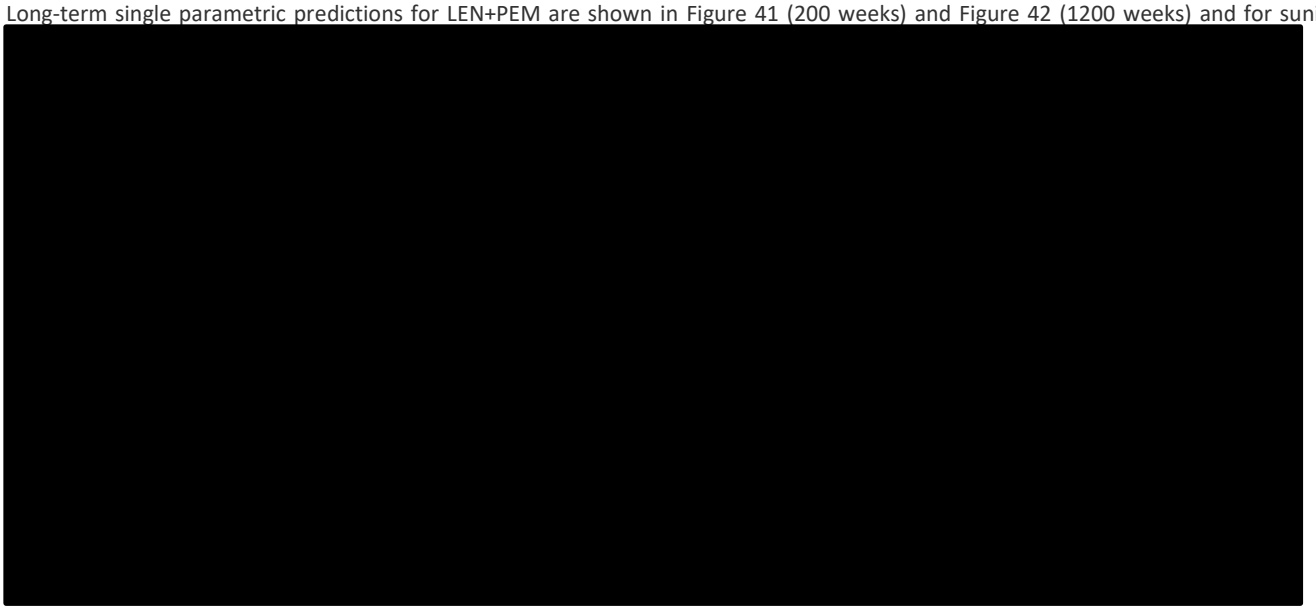


Figure 44 (250),
Figure 45 (1200 weeks), with OS fitted over their respective KM curves using the March 2021 DCO.

For LEN+PEM, the Exponential model produced a close fit to the tail of the KM curve. All other distributions underpredicted the tail, with the Log-normal model generating the smallest underprediction followed by the log-logistic. For sunitinib, the Log-logistic produced the closest fit to the tail of the KM curve. The Exponential, the Log-normal and the Gamma distributions generated clear overpredictions of the tail whereas all other models underpredicted the tail, with the Weibull distribution generating the smallest underprediction followed by the Gompertz model.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 41. Comparison of observed OS and single parametric predictions for LEN+PEM during the observed period for the IMDC good prognosis subgroups (up to 150 Weeks) – March 2021 DCO

Figure 42. Long-term single parametric OS predictions for LEN+PEM for the good prognosis subgroup (up to 1200 Weeks) - March 2021 DCO

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 43. Long-term single parametric OS predictions for LEN+PEM for the good prognosis subgroup (up to 2500 Weeks) - March 2021 DCO

Figure 44. Comparison of observed OS and single parametric predictions for Sunitinib during the observed period for the IMDC good prognosis subgroup (up to 250 Weeks) – March 2021 DCO

Figure 45. Long-term single parametric OS predictions for Sunitinib for the good prognosis subgroup (up to 1200 Weeks) – March 2021 - DCO

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 46. Long-term single parametric OS predictions for Sunitinib for the good prognosis subgroup (up to 2500 Weeks) – March 2021 - DCO

Smoothed hazard plots for lenvatinib plus pembrolizumab and sunitinib are shown in Figure 47 and Figure 48, respectively.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 47. Lenvatinib plus Pembrolizumab OS Hazard Profiles using March 2021 Data Cut - Favorable Risk Population (IMDC)

Abbreviation: LENVAT+PEMBRO = lenvatinib plus pembrolizumab

Figure 48. Sunitinib OS Hazard Profiles using March 2021 Data Cut - Favorable Risk Population (IMDC)

For lenvatinib plus pembrolizumab, the log-normal and log-logistic models both generated increasing then decreasing hazard profiles, with the log-normal model changing directions sooner than the log-logistic model and maintaining a lower risk of mortality over time. The Gompertz and generalized gamma models both produced continually increasing risk of deaths over time, with the Gompertz distribution showing a slightly sharper increasing hazard profile compared to the generalized gamma. The Weibull model produced an increasing but linear hazard plot that appeared to flatten very slowly over time, with the exponential distribution (by definition) generating a constant risk of mortality over time.

For sunitinib, the log-normal, log-logistic and generalized gamma models all generated increasing then decreasing hazard profiles, with the generalized gamma model producing a slightly sharper short-term increase followed by a sharper decline in hazards. The Gompertz model produced a steadily increasing risk of death over time. The Weibull model produced an increasing but slowly plateauing hazard plot, with the exponential distribution (by definition) generating a constant risk of mortality over time.

However, it is important to note that the appropriateness of the hazard profiles produced by each parametric model for each treatment arm requires clinical expert feedback.

Following review of statistical and visual fits, as well as analysis of life expectancy landmarks generated by all tested models as reported in Table 50 and Table 51, it appeared that none of the single fit extrapolations provided reasonable estimations of OS, with curves crossing between LEN+PEM and sunitinib. In fact, in accordance with NICE DSU21 [80], the selection of the parametric curve should primarily be based on the plausibility of long-term extrapolations. As discussed for the overall population, clinicians do not expect LEN+PEM and Sunitinib OS

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

curves to cross [86] . Moreover, all the distributions seemed to overestimate Sunitinib's life expectancy as compared to clinical expert expectations (<20% survival at ten years) [86].

Instead, the sunitinib equivalency mechanic in order to allow for a smoother convergence between LEN+PEM and sunitinib without actual crossing of the curves. Single Weibull parametric curves were applied to both LEN+PEM and Sunitinib curves until week 108, then Sunitinib OS HR for LEN+PEM was applied starting on week 108 (approximately 25 months). This time point was picked to match the point at which the OS KM data for the IMDC favourable risk group from the CLEAR trial March 2021 DCO appears to begin converging. Weibull curves were deemed appropriate as they provided a "middle of the batch" estimation of LEM+PEM and closely matched the tail of Sunitinib's KM curve.

Table 50. Expected OS per Distribution with LEN+PEM using March 2021 DCO (IMDC good prognosis)

Distribution for LEN+PEM	2-year OS prediction	5-year OS prediction	10-year OS prediction	40-year OS prediction
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LEN+PEM = lenvatinib plus pembrolizumab; OS = overall survival

Table 51. Expected OS per Distribution with Sunitinib using March 2021 DCO (IMDC good prognosis)

Distribution for Sunitinib	2-year OS prediction	5-year OS prediction	10-year OS prediction	40-year OS prediction
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: OS = overall survival

5.3.2.3 TTD extrapolations

The data reported in this section derives from the August 2020 DCO of the CLEAR trial.

Pembrolizumab

AIC and BIC estimates for the pembrolizumab TTD distributions are shown in [redacted] 52 with AIC and BIC classifications of relative fit shown in [redacted] 53. The Generalised Gamma produced the best statistical fit with the lowest AIC and BIC, with the Weibull, Loglogistic, Exponential and Gompertz distributions all displaying good relative statistical fits relative to the model with the lowest AIC (<4-point difference), reasonable (4-7 difference) and acceptable relative fits for BIC (<10 point difference). The Log-normal distribution produced a poor statistical fit relative to the Generalised Gamma distribution for both AIC and BIC.

Table 52. AIC and BIC Estimates for pembrolizumab TTD Distributions

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 53. AIC and BIC Goodness-of-fit per Each Distribution Relative to the Distribution with the Lowest AIC and BIC for pembrolizumab TTD

Distribution	AIC relative goodness-of-fit classification	BIC relative goodness-of-fit classification

[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

As mentioned before, in accordance with international and Danish clinical practice, the model sets a stopping rule for pembrolizumab at two years. This is observed in the KM curve for TTD reported in Figure 49. At week 104 (two years) the KM curve is complete, because all patients discontinue the treatment with pembrolizumab. Up until week 104, the Generalised Gamma, the Exponential and the Gompertz curves give a relatively good visual fit of the data, with all other models overestimating the time that patients receiving pembrolizumab spend on treatment. For the base case analysis, the Weibull distribution was selected for pembrolizumab TTD, based on the relatively good statistical fit and on the very good visual fit to the tail of the KM curve.

Figure 49. Long-term single parametric TTD predictions for Pembrolizumab (IMDC good prognosis group)

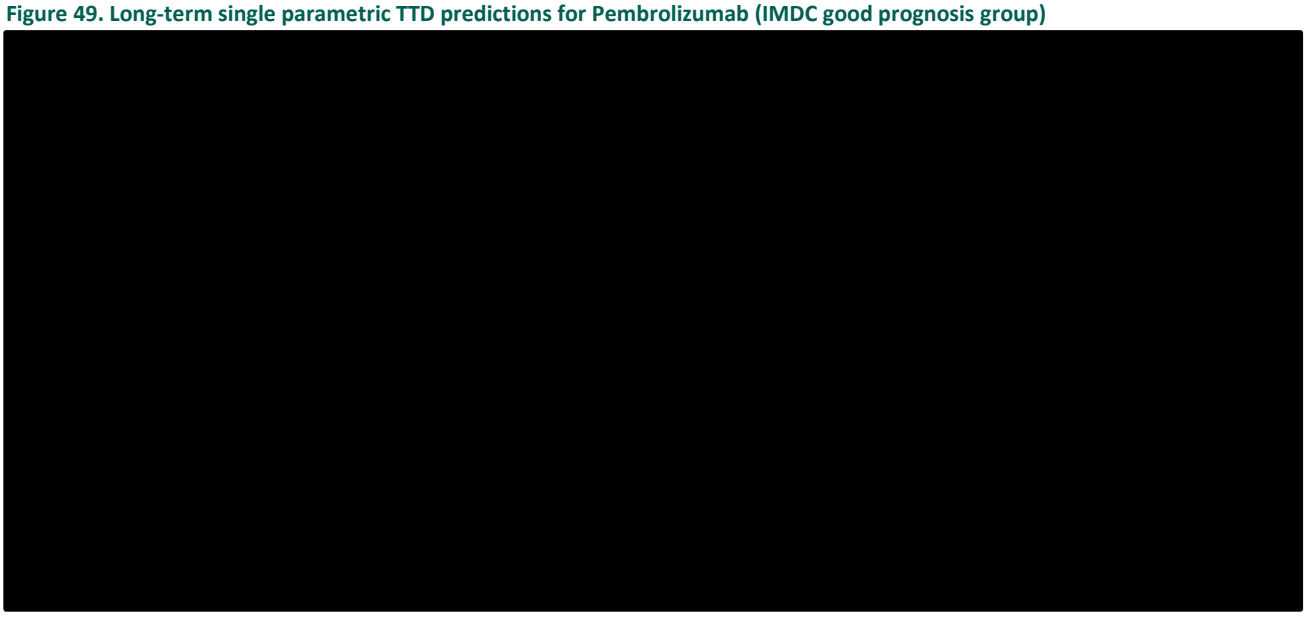
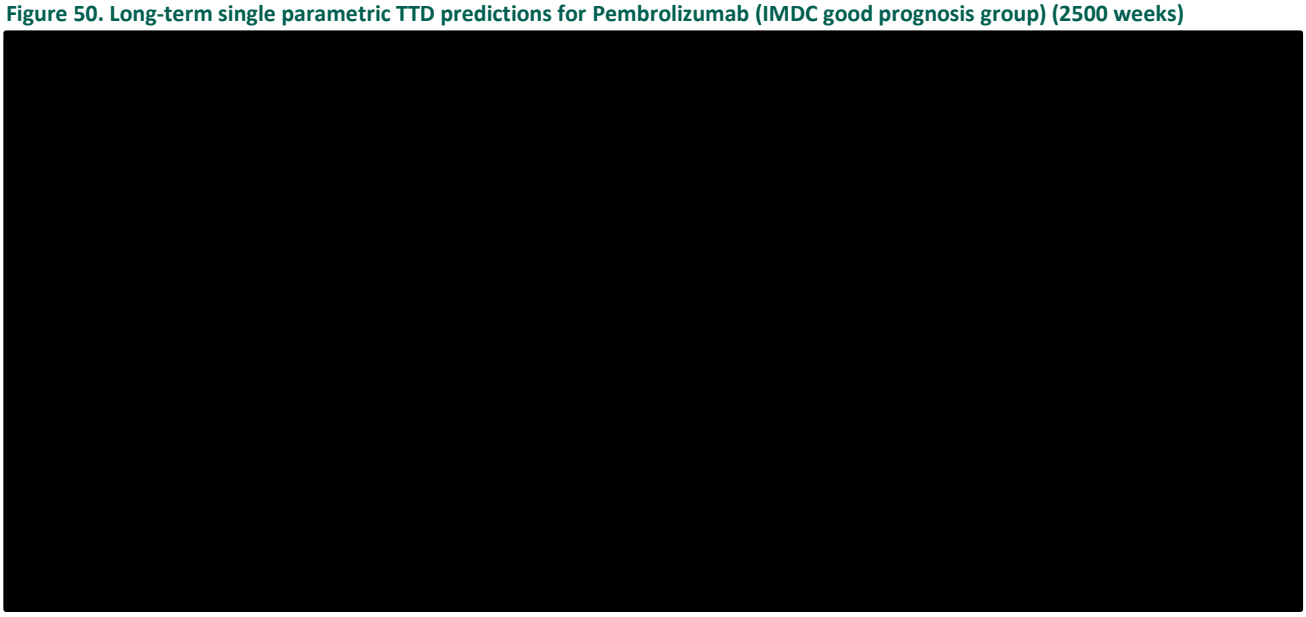


Figure 50. Long-term single parametric TTD predictions for Pembrolizumab (IMDC good prognosis group) (2500 weeks)



Lenvatinib

AIC and BIC estimates for the lenvatinib TTD distributions are shown in Table 54 with AIC and BIC classifications of relative fit shown in Table 55. The Exponential distribution produced the best statistical fit with the lowest AIC and BIC, with the Weibull, the Loglogistic, the Gompertz and the Generalised Gamma models producing good relative statistical fits according to AIC Good (0-4 difference), and only the Log-normal model producing an acceptable relative statistical fit.

Table 54. AIC and BIC Estimates for lenvatinib TTD Distributions

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

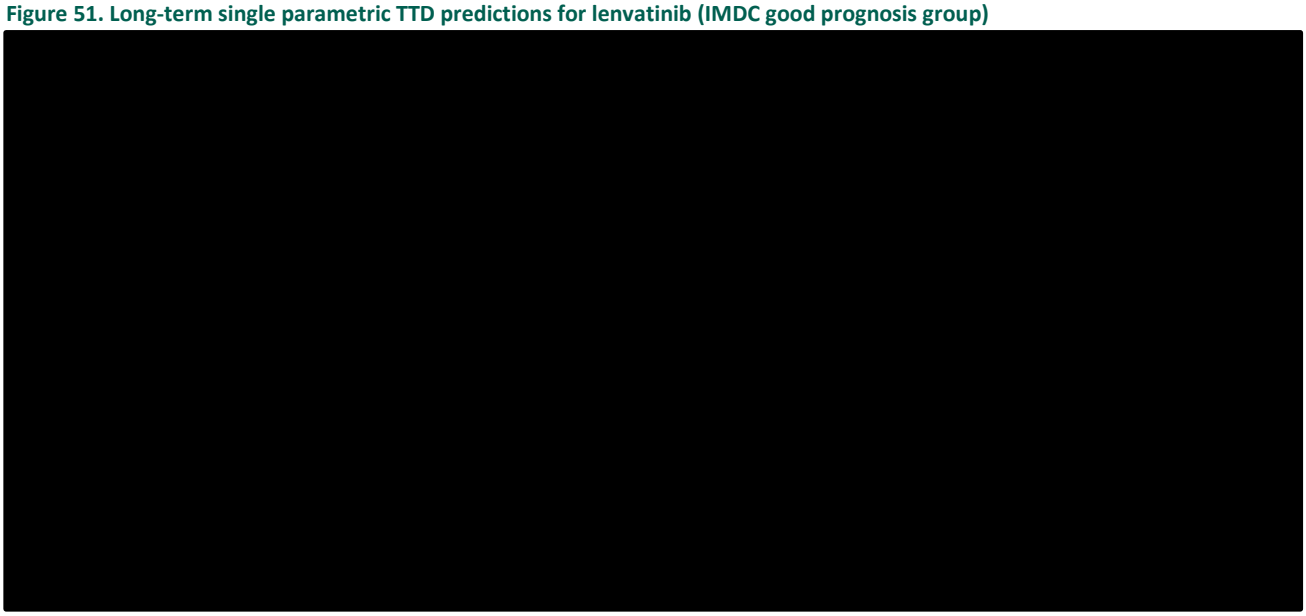
Table 55. AIC and BIC Goodness-of-fit per Each Distribution Relative to the Distribution with the Lowest AIC and BIC for lenvatinib TTD

Distribution	AIC relative goodness-of-fit classification	BIC relative goodness-of-fit classification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

As shown in Figure 51 visual inspection of the single parametric TTD curve for lenvatinib overlaid by the KM curve show that the Exponential, Weibull, Generalised Gamma and Gompertz distributions underestimate the tail of the curve, and the Log-normal model slightly overestimates the tail. Only the Loglogistic model seemed to produce a good visual fit of the TTD data. However, as defined in the CLEAR trial, TTD estimates cannot be bigger than PFS estimates for LEN+PEM. It appears clear that the Loglogistic and the Log-normal models overestimate lenvantinib long-term TTD. Therefore, the Exponential model was selected to model TTD for lenvantinib, as it provided with a more realistic estimate.

Figure 51. Long-term single parametric TTD predictions for lenvatinib (IMDC good prognosis group)



[redacted]

Sunitinib

AIC and BIC estimates for the sunitinib TTD distributions are shown in [redacted] with AIC and BIC classifications of relative fit shown in [redacted]. The Exponential distribution produced the best statistical fit with lowest AIC and BIC, with the other distributions all displaying good relative statistical fits relative to the model with the lowest AIC (<4-point difference) and reasonable relative fits for BIC (0-10 difference).

[redacted]

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

[redacted]

Distribution	AIC relative goodness-of-fit classification	BIC relative goodness-of-fit classification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

When checking the visual fit, the Log-normal, Loglogistic and Gamma models seem to produce a relatively appropriate fit of the tail of the curve. The Exponential, Weibull and Gompertz distributions produce a slight underestimation of the TTD observed data, with the Exponential model providing the smallest underestimation of the tail of the curve. The Exponential distribution was selected for sunitinib TTD as it had the best statistical fit and had a relatively close visual fit to the tail of the KM curve.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 53. Long-term single parametric TTD predictions for sunitinib (IMDC good prognosis group)

Figure 54. Long-term single parametric TTD predictions for sunitinib (IMDC good prognosis group) (2500 weeks)

In a scenario analysis, the impact of generating a generating a TTD curve based on the PFS curve as an alternative method as described in section 5.1.6.3 was explored.

5.3.3 IMDC intermediate/poor population

For PFS and OS, the relative efficacy of LEN+PEM versus NIVO+IPI was derived from the NMA, which assumed constant hazards. For PFS and and TTD, extrapolation of data are not presented for sunitinib as it is not a relevant comparator in this population in Denmark.

5.3.3.1 PFS Extrapolations

The PFS data reported in this section derives from the August 2020 DCO of the CLEAR trial.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 55. Log-Cumulative Hazard Plots for PFS (IMDC intermediate/poor prognosis subgroup)

[redacted]

The log cumulative hazard plots for LEN+PEM and sunitinib in [redacted] PFS data reported in this section derives from the August 2020 DCO of the CLEAR trial.

[redacted] 55 showed that the curves cross very early on but then remain separate and broadly parallel until the end of follow-up. In addition, formal testing of the PH assumption through the Schoenfeld residuals resulted in a p-value of [redacted], suggesting that the PH assumption cannot be excluded. However, because sunitinib is not a comparator in the IMDC intermediate/poor population, a single fit was applied to LEN+PEM data. The AIC and BIC treatment as predictor curves for each distribution modelled in the IMDC intermediate/poor prognosis population are presented in Table 58, with the Exponential distribution generating the lowest AIC and BIC highlighted in bold. [redacted]

Table 58. AIC and BIC of Fittings for MA-based PFS for single Fits of LEN+PEM for the IMDC intermediate/poor subgroup

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 59. AIC and BIC Goodness-of-fit per each distribution relative to the distribution with the lowest AIC and BIC for EMA-based for PFS single Fits of LEN+PEM for the IMDC intermediate/poor subgroup

Distribution	AIC relative goodness-of-fit classification	BIC relative goodness-of-fit classification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

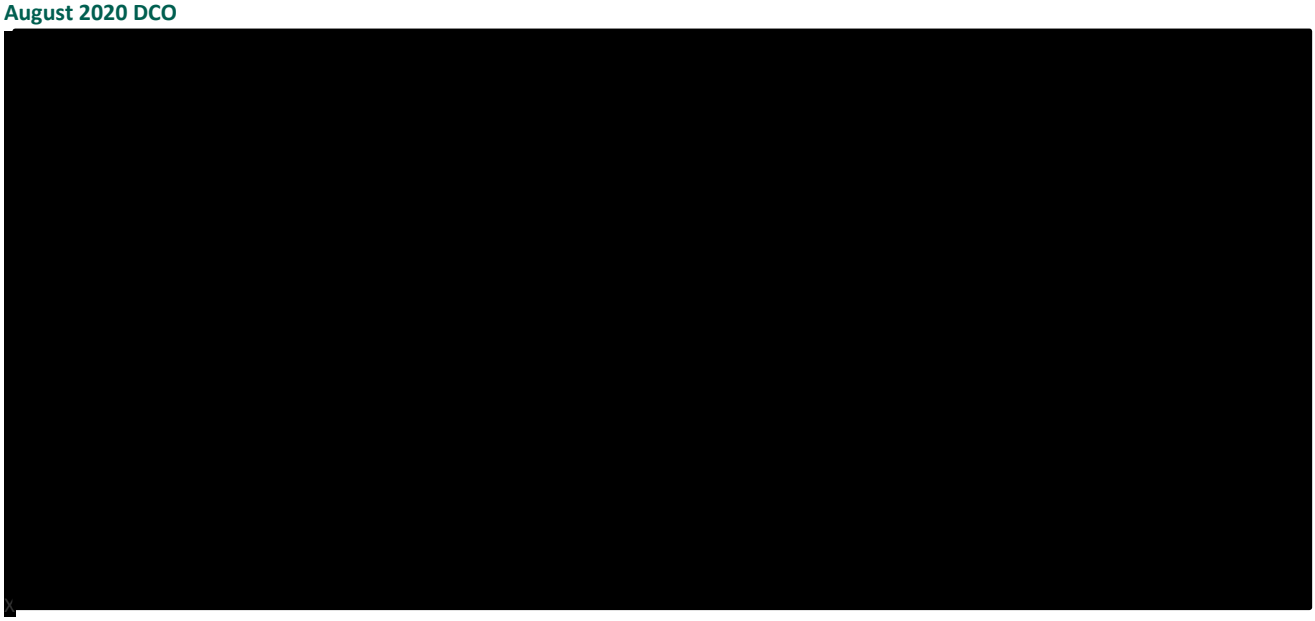
The weibull, loglogistic, gompertz and generalized gamma distributions displayed good statistical fits in terms of AIC, relatively to the model with the lowest AIC (exponential distribution). The lognormal distribution displayed a reasonable statistical fit relative to the Log-loglogistic distribution.

Furthermore, as shown in Figure 56 (160 weeks) and Figure 57 (1200 weeks), visual inspection of the single parametric PFS curve for LEN+PEM overlaid by the KM curve showed that the Loglogistic, the Gamma and the Exponential distributions provided the best visual fit of the tail of the KM curve, whereas the Lognormal overestimated the tail of the curve. All remaining models underestimated it.

Figure 56. Comparison of observed PFS and single parametric predictions for LEN+PEM during the observed period (up to 160 Weeks) – IMDC intermediate/poor prognosis subgroup – August 2020 DCO

Abbreviation: LENVAT+PEMBRO = lenvatinib plus pembrolizumab

Figure 57. Long-term single parametric PFS predictions for LEN+PEM for the intermediate/poor prognosis subgroup (up to 1200 Weeks) August 2020 DCO



Abbreviation: LENVAT+PEMBRO = lenvatinib plus pembrolizumab

Figure 58. Long-term single parametric PFS predictions for LEN+PEM for the intermediate/poor prognosis subgroup (up to 2500 Weeks) August 2020 DCO

Smoothed hazard profiles produced by each single-fit parametric model for lenvatinib plus pembrolizumab and sunitinib were reviewed to assess the shape of the changing hazard over time, with the lenvatinib plus pembrolizumab hazard plots shown in Figure 59. As a single

parametric model was used to model both lenvatinib plus pembrolizumab and sunitinib, the hazard profiles for sunitinib were broadly similar (albeit with generally higher event risks for sunitinib over time compared to lenvatinib plus pembrolizumab).

Figure 59. Hazard Profiles from the Lenvatinib plus Pembrolizumab single-fit Parametric Model for PFS using FDA Censoring Rule – Intermediate and Poor Risk Group (IMDC)

Abbreviation: LENVAT+PEMBRO = lenvatinib plus pembrolizumab

The log-normal, log-logistic and generalized gamma models all produced fairly similar increasing then decreasing hazard plots over time. The Weibull model generated an increasing but plateauing risk of progression or death over time, with the Gompertz model producing a decreasing hazard profile and the exponential model (by definition) producing a constant risk of progression or death. Further assessment of the appropriateness of the hazards will require additional validation with clinical experts.

The single exponential parametric model was selected to model LEN+PEM PFS, based on having a good statistical fit according to both AIC and BIC, as well as providing a middle of the batch fit to the tail for LEN+PEM. A scenario analysis was explored with the generalised gamma model.

To estimate the long-term relative efficacy of NIVO+IPI in terms of PFS, HR was taken from the network meta-analysis (Global NMA) which assumed constant hazards. The HR against the reference curve (LEN+PEM) was taken from the NMA and used in the model. In the case of PFS, the HR applied in the model was XXXXXXXXXXXXXXXXXXXX.

As shown in Figure 60, the curve obtained in the economic model with the constant HR produced an estimation of XXXXX of IMDC intermediate-poor patients being progression-free at two years.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 60. NIVO+IPI PFS long term estimation based on constant hazard ratio against LEN+PEM, IMDC intermediate/poor population

5.3.3.2 OS Extrapolations

The OS data reported in this section derives from the March 2021 DCO of the CLEAR trial. Given that in this population NIVO+IPI was the only comparator, proportional hazards were not required to be tested between LEN+PEM and sunitinib (as sunitinib is not a comparator). A single parametric fit was therefore considered for LEN+PEM.

AIC and BIC estimates for the LEN+PEM OS distributions using the March 2021 DCO are shown in Table 60, with AIC and BIC classifications of relative fit shown in Table 61. The Gompertz distribution produced the best statistical fit with the lowest AIC and BIC, with the Generalised Gamma and the Weibull generating a good relative statistical fit (<4 difference) according to the AIC rules of thumb applied. All other models produced reasonable fits to the Loglogistic model in terms of AIC (4-7 difference). In terms of BIC, the Log-normal distribution produced a poor fit, whereas all other models generated an acceptable relative statistical fit (0 to 10 difference).

Table 60. AIC and BIC Estimates for LEN+PEM OS Distributions of the IMDC intermediate/poor subgroup, using March 2021 DCO

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 61. AIC and BIC Goodness-of-fit per Each Distribution Relative to the Distribution with the Lowest AIC and BIC for LEN+PEM OS using March 2021 DCO (IMDC intermediate/poor subgroup)

Distribution	AIC Relative Goodness-of-fit classification	BIC Relative Goodness-of-fit Classification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; G. Gamma, Generalised Gamma

Long-term single parametric predictions for LEN+PEM are shown in Figure 61 (210 weeks) and Figure 62 (1200 weeks) with OS fitted over the respective KM curves using the March 2021 DCO.

For LEN+PEM, the Exponential model produced a close fit to the tail of the KM curve. All other distributions underpredicted the tail, with the Log-normal model generating the smallest underprediction followed by the loglogistic.

Figure 61. Comparison of observed OS and single parametric predictions for LEN+PEM during the observed period (up to 210 Weeks) - IMDC intermediate/poor prognosis subgroup (March 2021 DCO)

Figure 62. Long-term single parametric OS predictions for LEN+PEM for the IMDC intermediate/poor prognosis subgroup (up to 1200 Weeks) – March 2021 DCO

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 63. Long-term single parametric OS predictions for LEN+PEM for the IMDC intermediate/poor prognosis subgroup (up to 2500 Weeks) – March 2021 DCO

Smoothed hazard plots for lenvatinib plus pembrolizumab and sunitinib are shown in Figure 64 and Figure 65, respectively.

Figure 64. LEN+PEM OS Hazard Profiles using March 2021 Data Cut - Intermediate and Poor Risk Population (IMDC)

Abbreviation: LENVAT+PEMBRO = lenvatinib plus pembrolizumab

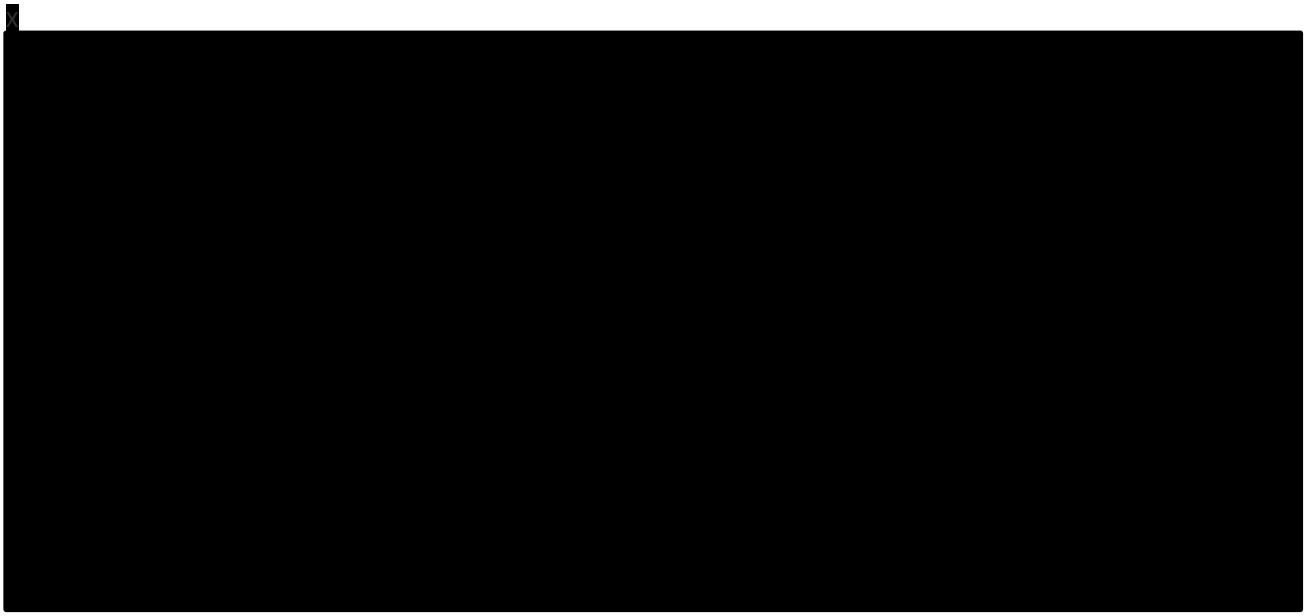
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 65. Sunitinib OS Hazard Profiles using March 2021 Data Cut - Intermediate and Poor Risk Population (IMDC)

For LEN+PEM, the log-normal and log-logistic models both generated increasing then decreasing hazard profiles, with the log-normal model changing from increasing to decreasing hazards earlier than the log-logistic model and maintaining a lower risk of mortality over time. The Gompertz and generalized gamma models both produced similar sharply increasing hazard profiles. The Weibull model produced an increasing but slowly flattening risk of death over time, with the exponential distribution (by definition) generating a constant mortality risk profile.
For sunitinib, the log-normal, log-logistic and generalized gamma models all generated increasing then decreasing hazard profiles, with the generalized gamma model producing a sharper short-term increase followed by a sharper decline in hazards. The Gompertz model produced a (fairly linearly) decreasing risk of death over time. The Weibull model produced a slightly increasing but plateauing hazard plot with almost constant hazards at 400 weeks, with the exponential distribution (by definition) generating a constant risk of mortality over time.
However, it is important to note that the appropriateness of the hazard profiles produced by each parametric model for each treatment arm requires clinical expert feedback.
The Exponential distribution was selected to model long-term OS for patients receiving LEN+PEM based on good statistical fit. As the Weibull model also produced a good statistical and clinical fit, it was explored in a scenario analysis.

To estimate the long-term relative efficacy of NIVO+IPI in terms of OS, the HR was taken from the network meta-analysis (Global NMA) which assumed constant hazards. The HR against the reference curve (LEN+PEM) was taken from the NMA and used in the model. In the case of OS, the HR of LEN+PEM versus NIVO+IPI applied in the model was XXXXXXXXXXXXXXXXXXXXX

Figure 66. NIVO+IPI OS long term estimation based on constant hazard ratio against LEN+PEM, IMDC intermediate/poor population



5.3.3.3 TTD Extrapolations

The data reported in this section derives from the August 2020 DCO of the CLEAR trial.

Pembrolizumab

AIC and BIC estimates for the pembrolizumab TTD distributions are shown in Table 62, with AIC and BIC classifications of relative fit shown in Table 63. The Generalised Gamma produced the best statistical fit with the lowest AIC and BIC, with the Weibull displaying acceptable statistical fit relative to the model with the lowest AIC (7-10 points difference) and BIC (0-10 points difference). All other distributions produced a poor statistical fit relative to the Generalised Gamma distribution in terms of AIC.

Table 62. AIC and BIC Estimates for pembrolizumab TTD Distributions (IMDC intermediate/poor subgroup)

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 63. AIC and BIC Goodness-of-fit per Each Distribution Relative to the Distribution with the Lowest AIC and BIC for pembrolizumab TTD (IMDC intermediate/poor subgroup)

Distribution	AIC relative goodness-of-fit classification	BIC relative goodness-of-fit classification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

As mentioned before, in accordance with the two years stopping rule mentioned previously, at week 104 (two years) the KM curve is complete, because all patients discontinue the treatment with pembrolizumab. Up until week 104, the Generalised Gamma, the Weibull and the Gompertz curves give a relatively good visual fit of the data, with all other models overestimating the time that patients receiving pembrolizumab spend on treatment. The Weibull distribution was selected for pembrolizumab TTD, based on the relatively good statistical fit and on the very good visual fit to the tail of the KM curve.

Figure 67. Long-term single parametric TTD predictions for Pembrolizumab (IMDC intermediate/poor prognosis group)

Figure 68. Long-term single parametric TTD predictions for Pembrolizumab (IMDC intermediate/poor prognosis group) (2500 weeks)

Lenvatinib

AIC and BIC estimates for the lenvatinib TTD distributions are shown in Table 64 with AIC and BIC classifications of relative fit shown in Table 65. The Exponential distribution produced the best statistical fit with the lowest AIC and BIC, with the Weibull, the Generalised Gamma and the Gompertz distribution producing good relative statistical fit according to AIC and the loglogistic distribution producing a poor relative statistical fit according to AIC. According to BIC, the Weibull, the Gompertz models and the Generalised Gamma model generated an acceptable relative fit. The Log-normal and loglogistic models produced poor statistical fits according to BIC.

Table 64. AIC and BIC Estimates for lenvatinib TTD Distributions (IMDC intermediate/poor prognosis)

Distribution	AIC	BIC
[redacted]	XXXXXXXX	XXXXXXXX
[redacted]	XXXXXXXX	XXXXXXXX
[redacted]	XXXXXXXX	XXXXXXXX
[redacted]	XXXXXXXX	XXXXXXXX
[redacted]	XXXXXXXX	XXXXXXXX
[redacted]	XXXXXXXX	XXXXXXXX

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 65. AIC and BIC Goodness-of-fit per Each Distribution Relative to the Distribution with the Lowest AIC and BIC for lenvatinib TTD (IMCC intermediate/poor prognosis)

Distribution	AIC relative goodness-of-fit classification	BIC relative goodness-of-fit classification
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

As shown in Figure 69, visual inspection of the single parametric TTD curve for lenvatinib overlaid by the KM curve show that the loglogistic and the Log-normal distributions clearly overestimate the tail of the curve, while Exponential, Weibull, Generalised Gamma and Gompertz distributions match quite closely the tail of the KM curve. The Generalised Gamma model was selected to model TTD for lenvatinib, based on good statistical fit and on good visual fit to the KM data.

Figure 69. Long-term single parametric TTD predictions for lenvatinib (IMDC intermediate/poor prognosis group)

[redacted]

Figure 70. Long-term single parametric TTD predictions for lenvatinib (IMDC intermediate/poor prognosis group) (2500 weeks)

[redacted]

As discussed in section 5.1.6.3, TTD for NIVO+IPI was estimated by using the median treatment duration of NIVO+IPI in the CHECKMATE214 trial as reported in the literature (Albiges et al, 2020 [68]). An Exponential curve was fitted to the median treatment duration of NIVO+IPI (7.9months) allowing a TTD curve to be generated.

In a scenario analysis, the impact of generating a generating a TTD curve based on the PFS curve as an alternative method as described in section 5.1.6.3 was explored.

5.4 Documentation of health-related quality of life (HRQoL)

The utility values of the model health states in the base case (pre-progression and post progression) were based on the LEN+PEM arm of the CLEAR trial (August 2020 DCO) and are applied to patients within relevant health states in order to capture the patient quality of life associated with treatment. Utility values in the model were derived from the analysis of EQ-5D-3L questionnaire in the CLEAR study. The utility values were subsequently mapped (using a reverse cross-walk algorithm [88]) to EQ-5D-5L values using Danish EQ-5D-5L weights, in accordance with the DMC preferences [15] and the Danish center for Healthcare Improvements recommendations [89]. Details on mapping of health state utility values are presented in Appendix I Mapping of HRQoL data . These are shown in Table 66 for the overall population, in Table 69 the IMDC good prognosis and Table 66 in the IMDC intermediate/poor prognosis subgroups.

If treatment specific utilities are chosen in the model, treatments are applied the utility of the same treatment class, for instance TKI's are assumed to have sunitinib utilities, and IOs are assumed to have LEN+PEM utilities. This assumption is not expected to have substantial impact on the results given the relatively small difference in utility between treatments when treatment specific utilities are chosen, and also given by the fact that utilities are not the main driver of cost effectiveness vs. NIVO+IPI in the intermediate/poor population. IPD for NIVO+IPI is not available and Danish weights cannot be calculated

5.4.1 Overview of health state utility values (HSUV)

Table 66. Summary of Denmark Utility Value (EQ-5D-3L to EQ-5D-5L Reverse Crosswalk) Quality of Life Analysis Set – Overall

	LEN+PEM (n=351)	Sunitinib (n=340)
Overall population		
Baseline		
Number of observations	[redacted]	[redacted]
Mean (SE) [95% CI]	[redacted]	[redacted]
Difference [95% CI]	[redacted]	
P value	[redacted]	
Progression-free survival		
Number of observations	[redacted]	[redacted]
Mean (SE) [95% CI]	[redacted]	[redacted]
Difference [95% CI]	[redacted]	
P value	[redacted]	[redacted]
Post-progression survival		
Number of observations	[redacted]	[redacted]
Mean (SE) [95% CI]	[redacted]	[redacted]
Difference [95% CI]	[redacted]	
P value	[redacted]	[redacted]

Table 67. Summary of Denmark Utility Value (EQ-5D-3L to EQ-5D-5L Reverse Crosswalk) Quality of Life Analysis Set - IMDC good prognosis population

	LEN+PEM (n=109)	Sunitinib (n=117)

Good prognosis population		
Baseline		
Number of observations	[redacted]	[redacted]
Mean (SE) [95% CI]	[redacted]	[redacted]
Difference [95% CI]	[redacted]	
P value	[redacted]	
Progression-free survival		
Number of observations	[redacted]	[redacted]
Mean (SE) [95% CI]	[redacted]	[redacted]
Difference [95% CI]	[redacted]	
P value	[redacted]	
Post-progression survival		
Number of observations	[redacted]	[redacted]
Mean (SE) [95% CI]	[redacted]	[redacted]
Difference [95% CI]	[redacted]	
P value	[redacted]	

Table 68. Summary of Denmark Utility Value (EQ-5D-3L to EQ-5D-5L Reverse Crosswalk) Quality of Life Analysis Set IMDC intermediate poor prognosis population

	LEN+PEM (n=240)	Sunitinib (n=220)
IMDC intermediate poor population		
Baseline		
Number of observations	[redacted]	[redacted]
Mean (SE) [95% CI]	[redacted]	[redacted]
Difference [95% CI]	[redacted]	
P value	[redacted]	
Progression-free survival		
Number of observations	[redacted]	[redacted]
Mean (SE) [95% CI]	[redacted]	[redacted]
Difference [95% CI]	[redacted]	
P value	[redacted]	
Post-progression survival		
Number of observations	[redacted]	[redacted]
Mean (SE) [95% CI]	[redacted]	[redacted]
Difference [95% CI]	[redacted]	
P value	[redacted]	

5.4.2 Health state utility values used in the health economic model

Utility values of the model health states are adjusted to account for the natural decrease in QoL associated with age. Adjusting utilities for age can prevent the overestimation of benefits associated with treatment that can occur if otherwise a baseline of perfect health is assumed. The data published by Wittrup-Jensen et al., 2009 [90, 91], is used in the model to provide general Danish population utility estimates is presented in Table 69.

In the absence of available data for the individual health states, the reference age for each health state are assumed the same as the age of participants from the CLEAR trial. Characteristics reported in CLEAR for the overall population were used to inform estimates for all other subgroups in the absence of subgroup-specific data. The starting age of the cohort was 61.7 years.

Table 69. EQ-5D Population Norms in the Denmark

Age Group	QoL	Source
18 –29	**0,871**	**Wittrup-Jensen et al., 2009 [90]**
30 –39	**0,848**	
40 –49	**0,834**	
50 –69	**0,818**	
70 –79	**0,813**	
80+	**0,721**	

5.4.3 Decrement to QoL due to AEs

AE disutilities are not applied in the base case, as utilities captured within the trial are expected to already have captured the detrimental effect of adverse events within the QoL value observed. However, the model allows the user to account for AE disutility that can arise with treatment. Disutility estimates and duration were taken from sunitinib arm of the NICE nivolumab plus ipilimumab submission TA581 [82] and assumed to be the same for all treatments and subgroups in the model. The total disutility decrement associated with each treatment was calculated as the sum product of the disutility associated with each AE, the duration of experiencing the disutility and the rate of experiencing an AE. Disutility due to AEs are not considered for subsequent treatments. Disutilities and duration per AE are presented in Table 70.

Table 70. Grade 3/4 Adverse Events Disutilities

Adverse Events	Grade 3/4 disutility	Grade 3/4 disutility duration (weeks)	Source	Comments
Anemia	0.081	3.14	NICE TA581*	Median utility duration based on sunitinib
Asthenia	0.204	3.14	NICE TA581*	Median utility duration based on sunitinib
Decreased appetite	0.038	3.42	NICE TA581*	Median utility duration based on sunitinib
Diarrhea	0.261	3.42	NICE TA581*	Median utility duration based on sunitinib
Dyspnea	0.204	15.43	Assumed same as fatigue	Median utility duration based on sunitinib
Fatigue	0.204	15.43	NICE TA581*	Median utility duration based on sunitinib
Hyperglycemia	0.081	3.14	Assumed same as increased lipase	-
Hypertension	0.015	3.14	NICE TA581*	Median utility duration based on sunitinib
Hypertriglyceridemia	0.081	3.14	Assumed same as increased lipase	-
Increased ALT	0.081	3.14	Assumed same as increased lipase	-
Increased amylase	0.081	3.14	Assumed same as increased lipase	-
Increased AST	0.081	3.14	Assumed same as increased lipase	-

Adverse Events	Grade 3/4 disutility	Grade 3/4 disutility duration (weeks)	Source	Comments
Increased lipase	0.081	3.14	NICE TA581*	Median utility duration based on sunitinib and assumed to be same as anemia
Lymphocytopenia	0.081	3.14	Assumed same as platelet count decrease	-
Nausea	0.255	3.42	NICE TA581*	Median utility duration based on sunitinib
Neutropenia	0.081	3.14	Assumed same as platelet count decrease	-
Palmar-plantar syndrome	0.040	15.00	NICE TA581*	Median utility duration based on sunitinib
Platelet count decrease	0.081	3.14	NICE TA581*	Median utility duration based on sunitinib and assumed to be same as anemia
Proteinuria	0.081	3.14	Assumed same as increased lipase	-
Stomatitis	0.040	15.00	NICE TA581*	Median utility duration based on sunitinib
Weight decreased	**0.038**	**3.42**	**Assumed same as decreased appetite**	-

*Source: NIVO+IPI submission, NICE TA581[82]

Abbreviations: ALT = alanine transaminase; AST = aspartate aminotransferase; NICE = National Institute for Health and Care Excellence

5.5 Resource use and costs

5.5.1 Treatment cost and dose

All pharmacy purchase prices (PPP) have been fetched for the drug acquisition cost from Medicinpriser.dk. The drug unit cost for each comparator is described below and summarized in Table 71.

Table 71. Drug acquisition unit costs

Drug	Units/Pack	Strength/unit (mg)	Pack cost (DKK)	Cost per unit (DKK)	Source
Lenvatinib	30 30	10 4	[redacted] [redacted]	[redacted] [redacted]	[redacted]
Pembrolizumab	1 (4 ml)	25/ml	23,799.60	23,799.60	Medicinpriser.dk [92]
Sunitinib	28 28 28	12.5 25 50	7,342.09 7,342.09 7,342.0914316,04 28631,00	262.22 262.22 262.22344,47 688.28 1375,91	Medicinpriser.dk [92]
Pazopanib	90	200	14,207.11	157.86	Medicinpriser.dk [92]
Nivolumab	1 (4 ml) 1 (10 ml)	10/ml 10/ml	3,785.32 9,403.31	3,785.32 9,403.31	Medicinpriser.dk [92]
Ipilimumab	1 (10 ml) 1 (40 ml)	5/ml 5/ml	26,311.31 105,010.82	26,311.31 105,010.82	Medicinpriser.dk [92]
Tivozanib	21	0.89	24,799.00	1,180.90	Medicinpriser.dk [92]

Abbreviations: DKK, Danish Kroner; mg, milligrams; ml, millilitre.

In Table 72 the dosing of each treatment is presented to enable the calculation of drug cost per patient.

Table 72. The dosing scheme

Drug	Dependency	Dose	Administrations per cycle	Treatment cycle length (weeks)	Dose intensity	Source
NIVO+IPI (combination therapy phase)						
Nivolumab	Weight	3.0 mg/kg	1	3	100%	Amgros, 2020 [93]

Ipilimumab	Weight	1.0 mg/kg	1	3	100%	
LEN + PEM						
Lenvatinib	Fixed dose	20.0 mg	21	3	71%	CLEAR [7]
Pembrolizumab	Fixed dose	200.0 mg	1	3	95%	
Sunitinib	Fixed dose	50 mg	28	4	79%	Amgros, 2020 [93]
NIVO+IPI (monotherapy phase)						
Nivolumab	Fixed dose	480.0 mg	1	4	100%	Amgros, 2020 [93]

Abbreviations: mg, milligrams; µg, micrograms

The total 1L drug acquisition costs were applied to the proportion of patients remaining on treatment in each model cycle within the model time horizon, determined by TTD. For the NIVO+IPI induction costs were applied from cycle one for the number of weeks of induction required after which maintenance costs begun to accumulate. For the other treatment regimens, maintenance costs were applied from cycle one. The exception to using the total 1L drug costs are for LEN+PEM as there is a maximum time on treatment of two years when pembrolizumab is used [79]. So, the per cycle drug acquisition cost of each drug component was applied individually to the proportion of patients remaining on treatment in each model cycle.

As discussed before, for the LEN+PEM combination, separate treatment discontinuation curves were modelled for each drug component. Therefore, the per cycle cost of lenvatinib is applied to the proportion of patients remaining on treatment with lenvatinib and the per cycle cost of pembrolizumab is applied to the proportion of patients remaining on treatment with pembrolizumab with the two costs summed at the end to provide the overall cost of treatment with LEN+PEM. Table 73 shows the per cycle drug acquisition costs of 1L treatment for induction and maintenance by each drug component of 1L intervention, if applicable and the total combined per cycle for each combination 1L treatment.

Should the user wish to change between flexible and fixed dosing, this can be directly changed in the model using the drop down in cells I114 and J114 etc of the "Drug cost details" sheet (i.e. it requires the user to change the dosing type fixed/weight/BSA and then also update the required dose mg/mg per kg/mg per m^2).

Table 73. Calculated 1L drug acquisition costs

Intervention	Drug	Induction Cost per Model Cycle	Maintenance Cost per Model Cycle
Lenvatinib +	Lenvatinib		[redacted]
Pembrolizumab	Pembrolizumab	-	[redacted]
Sunitinib	Sunitinib	-	DKK 3869
Nivolumab +	Nivolumab	DKK 7.855	DKK 11.296
Ipilimumab	Ipilimumab	DKK 2.625	DKK 0

*Induction duration for 12 model cycles
An induction period is not required for these drug components

5.5.2 Subsequent treatment

Subsequent treatment is applied to 50% of patients in line with previous assessments done by the DMC for aRCC treatments [8]. However, a scenario analysis also explored the impact of administering subsequent treatments to a different proportion of patients, based on data from the CLEAR trial.

The DMC guidelines on treatments for aRCC provide details on the preferred treatment options, depending on whether patients have received a PD-L1 inhibitor in 1L or not.

For patients that initially received LEN+PEM or NIVO+IPI as 1L treatment (treatment with PD-L1 inhibitor), the DMC recommends that 80% of patients receive cabozantinib. Based on minor adjustment following consultation with a Danish clinical expert [57], the patients receiving a subsequent treatment were allocated as follows in the economic model:

- 75% would receive cabozantinib
- 10% would receive tivozanib
- 5% would receive sunitinib
- 5% would receive pazopanib
- 5% would receive axitinib

For the patients that received subsequent treatment following first-line treatment with sunitinib, the DMC recommends that 80% of the patients receive nivolumab. Therefore, in the economic model, the allocation of subsequent treatments for these patients was estimated as follows:

- 80% would receive nivolumab
- 10% would receive avelumab + axitinib
- 10% would receive pembrolizumab + axitinib

The unit costs of subsequent treatments (not already used in 1L) are presented in Table 74.

Table 74. Subsequent treatment acquisition costs

Drug	Units/Pack	Strength/unit (mg)	Pack cost (DKK)	Cost per unit (DKK)	Source
Tivozanib	21	1340 µg	24,799.00	1,180.90	Medicinpriser.dk [92]
Pazopanib	90	200	14,207.11	157.86	Medicinpriser.dk [92]
Cabozantinib	30	20	49,400.00	1,646.67	Medicinpriser.dk [92]
Nivolumab	1	40 mg/4 ml	3.785,32	3.785,32	Medicinpriser.dk [92]
Axitinib	56,0	1mg	5.470,63	97.69	Medicinpriser.dk [92]

Abbreviations: DKK, Danish crowns; mg: milligrams

Subsequent treatment costs as per 1L treatment were calculated as the product of the per cycle drug acquisition and drug administration costs for each subsequent treatment, proportion of patients eligible to receive subsequent treatments by 1L treatment arm, the proportions receiving each subsequent treatment by 1L treatment arm and the duration of each subsequent treatment.

Table 75. Subsequent treatment costs

Treatment	One off cost
LEN + PEM	DKK 155,687
Sunitinib	DKK 213,596
NIVO+IPI	DKK 265,498

The model assumes that subsequent treatment costs are incurred at treatment discontinuation. The sum of incident treatment discontinuers within the model time horizon is multiplied by the one-off subsequent treatment cost associated with the 1L comparator.

5.5.3 Treatment administration

The unit costs of administration were obtained using the Danish DRG grouper, *interactive DRG*, and is applied to the administrations in the model. The unit cost of administration is presented in Table 76. The mode of administration which is presented for each type of drug is presented in Table 77. Sunitinib is delivered exclusively as oral treatment. Pembrolizumab and nivolumab are both delivered as parenteral chemotherapy, simple and complex, respectively. Lenvatinib is an oral therapy, whereas ipilimumab is both delivered as oral or IV chemotherapy, which is administrated subsequently the same day as the complementary drug, pembrolizumab and nivolumab, respectively.

Table 76: Unit costs of modes of administrations

Mode of administration	Unit cost (DKK)	Source
Exclusively oral chemotherapy	-	Assumption
Simple parenteral chemotherapy at first attendance	1,906.00	DRG 2021-DC649- 11MA98 - MDC11 1-dagsgruppe, pat. mindst 7 år - BWAA60 Medicingivning ved intravenøs injection [83]
Complex parenteral chemotherapy at first attendance	1,906.00	DRG 2021-DC649- 11MA98 - MDC11 1-dagsgruppe, pat. mindst 7 år - BWAA60 Medicingivning ved intravenøs injection [83]
Complex chemotherapy, including prolonged infusional treatment, at first attendance	1,906.00	DRG 2021-DC649- 11MA98 - MDC11 1-dagsgruppe, pat. mindst 7 år - BWAA60 Medicingivning ved intravenøs injection [83]
Subsequent elements of a chemotherapy cycle	1,906.00	DRG 2021-DC649- 11MA98 - MDC11 1-dagsgruppe, pat. mindst 7 år - BWAA60 Medicingivning ved intravenøs injection [83]
Subsequent oral chemotherapy or subsequent IV chemotherapy delivered on the same day	1,906.00	DRG 2021-DC649- 11MA98 - MDC11 1-dagsgruppe, pat. mindst 7 år - BWAA60 Medicingivning ved intravenøs injection [83]

Abbreviations: DRG, diagnosis-related group

Table 77: Mode of administration for each pharmaceutical treatment

Drug	Mode of administration	Source
Lenvatinib	Exclusively oral chemotherapy	Amgros, 2020 [93]
Pembrolizumab	Simple parenteral chemotherapy at first attendance	Amgros, 2020 [93]
Sunitinib	Exclusively oral chemotherapy	Amgros, 2020 [93]
Nivolumab	Complex parenteral chemotherapy at first attendance	Amgros, 2020 [93]
Ipilimumab	Subsequent oral chemotherapy or subsequent IV chemotherapy delivered on the same day	Amgros, 2020 [93]

5.5.4 Treatment monitoring

The rates of resource use associated with treatment monitoring was based on input from NICE TA650 and confirmed by the Danish clinician [2]. The cost of each category was sources using the Danish DRG grouper, *interactive DRG* and labportal.rh.dk. These unit costs are presented in Table 78. The frequency of use for each resource per cycle is reported for both progression-free (PF) patients and progressed patients in Table 79. As the scope of this submission did not include a subgroup analysis for PD-L1 patient, it was assumed that no biomarker testing was used. Outpatient consultations, blood test, and CT-scans were considered as the relevant direct non-medical costs for this submission. The frequencies of the direct non-medical resources for PF patients were estimated to be the same for all treatments. The frequencies of the direct non-medical resources for progressed patients were also estimated to be the same for all treatments, but lower compared to those applied for PF patients.

It is worth noting that Dispensation of lenvatinib is not restricted to hospitals (oral form), whereas pembrolizumab's administration is to be dispensed at a hospital only.

Table 78: Unit costs for monitoring of patients

Resource	Unit cost (DKK)	Source
Outpatient consultation medical oncology (first visit)	1,906.00	DRG 2021, 11MA98 MDC11 1-dagsgruppe, pat. mindst 7år Diagnosis: DC649: Nyrekræft
Outpatient consultation medical oncology (follow-up)	1,906.00	DRG 2021, 11MA98 MDC11 1-dagsgruppe, pat. mindst 7år Diagnosis: DC649: Nyrekræft
Blood test	31.00	B-Hæmoglobin; https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=2403
CT-scan	2,433.00	DRG 2021, 36PR07 - Klinisk fysiologi/nuklearmedicin grp. G / WDTCPXYXX

Table 79: The frequency of each unit per cycle

Resource frequency of use per model cycle – Progression- free patients (1 model cycle = 1 week)					
Treatment	**Outpatient consultation medical oncology (first visit)**	**Outpatient consultation medical oncology (follow-up)**	**Blood test**	**CT scan**	**Source**
LEN + PEM	1.00	0.25	0.25	0.08	KOL interview [2]
Sunitinib	1.00	0.25	0.25	0.08	
NIVO+IPI	1.00	0.25	0.25	0.08	
Resource frequency of use per model cycle - Progressed patients (1 model cycle = 1 week)					

Treatment	Outpatient consultation medical oncology (first visit)	Outpatient consultation medical oncology (follow-up)	Blood test	CT scan	Source
LEN + PEM	0.00	0.25	0.25	0.08	KOL interview [2]
Sunitinib	0.00	0.25	0.25	0.08	
NIVO+IPI	0.00	0.25	0.25	0.08	

Abbreviations: CT, Computed tomography; IPI, Ipilimumab; NIVO, nivolumab; LEN, lenvatinib; PEM, pembrolizumab

5.5.5 Adverse events cost

In order to capture the resource use associated with adverse events, the unit costs of adverse events were obtained from Danish DRG grouper, *interactive DRG [83].* The frequency of experiencing the ≥grade 3 adverse event while on treatment, was obtained from the CLEAR trial and from the literature for non-CLEAR treatment regimens, as described in section 5.2.1.1 . All unit costs were applied as one day costs.

Table 80. Adverse events costs

Adverse event	Cost (DKK)	Source
Anaemia	3,114	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD592: Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel
Asthenia	3,987	DRG 2021, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Decreased appetite	1,518	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR630: Appetitløshed
Diarrhoea	5,130	DRG 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS
Dyspnoea	1,732	DRG 2021, 04MA98: MDC04 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR060: Dyspnø
Fatigue	3,987	DRG 2021, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR539A: Udmattelse
Hyperglycaemia	3,987	DRG 2021, 23MA03: Symptomer og fund, u. kompl. bidiag., Diagnosis: DR739: Hyperglykæmi UNS
Hypertension	1,153	DRG 2021, 05MA98: MDC05 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DI109: Essentiel hypertension
Hypertriglyceridemia	1,518	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DE781: Hyperglyceridæmi
Increased ALT	1,626	DRG 2021, 23MA98: MDC23 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740: Transaminase- og laktatdehydrogenaseforhøjelse
Increased amylase	2,610	DRG 2021, 07MA98 - MDC07 1-day group, pat. at least 7 years, Diagnosis (DR748A): Abnorm serumamylase
Increased AST	3,987	DRG 2021, 23MA03 - Symptomer og fund, u. kompl. Bidiag, Diagnosis (DR740B) Transaminaseforhøjelse i serum
Increased lipase	2,610	DRG 2021, 07MA98 - MDC07 1-dagsgruppe, pat. mindst 7 år (DR748D) Abnorm serumlipase
Lymphocytopenia	3,114	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728: Anden forstyrrelse i hvide blodlegemer
Nausea	5,130	DRG 2021, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DR119C: Opkastning
Neutropenia	3,114	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Neutropeni UNS
Palmar-plantar syndrome	1,735	DRG 2021, 09MA98: MDC09 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DL271: Lokaliseret dermatitis forårsaget af indtaget lægemiddel
Platelet count decrease	3,114	DRG 2021, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD696: Trombocytopeni UNS
Proteinuria	1,906	DRG 2021 11MA98 - MDC11 1-dagsgruppe, pat. mindst 7 år, Diagnosis (DR809) Proteinuri UNS
Stomatitis	1,862	DRG 2021, 03MA98: MDC03 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DK121B: Stomatitis UNS
Weight decreased	1,518	DRG 2021, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR634: Abnormt vægttab

5.5.6 Patient cost and transportation cost

Productivity costs (defined as patient costs in DMC guidelines) and transportation cost are included in the model in line with the DMC method guidelines [95]. The unit cost per patient hour is assumed to be DKK 179 and the transportation cost per visit was assumed to be DKK 100 in line with the DMC guidelines, which was sourced from DMCs unit cost catalogue. Based on the resource use presented in Table 82, a total annual patient and transportation cost have been estimated for responders and non-responders, which are applied in the model.

Table 81. The unit cost of patient cost and transportation cost

Resource	Unit cost (DKK)	Source
Average hourly wage	179	Medicinrådet - [94]
Transportation cost per visit	100	Medicinrådet - [94]

Table 82. Estimated time usage for each resource

Resource	Frequency of use per week	Source
Outpatient consultation medical oncology (first visit)	0.25	KOL interview [57]
Outpatient consultation medical oncology (follow-up)	0.13	KOL interview [57]
Blood test	0.25	KOL interview [57]
CT-scan	0.08	KOL interview [57]

Table 83. Calculation of patient cost and transportation cost for responders and non-responders

Input	Cost per cycle (week) (DKK)
Progression-free	155
Progressed disease	66

5.6 Results

5.6.1 Modelling Overview

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 84. Modelling overview for the Overall Population

Overall ITT population	
Comparator	Sunitinib
Type of model	Partitioned survival model
Time horizon	40 years
Treatment line	1st line
Discount rate	3.5% until year 35 and 2.5% beyond year 35
Perspective	Restrictive societal perspective
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-3L in CLEAR trial, mapped to EQ-5D-5L.
Included costs	• Drug acquisition • Drug administration • AE management • Disease management • Patient costs • Subsequent treatment costs
Average time on treatment	Lenvatinib: single fit Generalised Gamma Pembrolizumab: single fit Weibull Sunitinib: single fit Generalised Gamma
Parametric function for PFS	LEN+PEM: joint fit Log-normal Sunitinib: joint fit Log-normal
Parametric function for OS	LEN+PEM: single fit Exponential Sunitinib: single fit Exponential
Stopping rule of pembrolizumab	Applied for two years
Stopping rule of nivolumab	Applied for two years
Subsequent treatment	• Sunitinib • Pazopanib • Nivolumab • Cabozantinib • Axitinib • Tivozanib • Avelumab + axitinib • Pembrolizumab + axitinib
Proportion of patients receiving subsequent treatment	Based on clinical expert opinion

Table 85. Modelling overview for the IMDC good prognosis population

IMDC good prognosis population	
Comparator	Sunitinib
Type of model	Partitioned survival model
Time horizon	40 years
Treatment line	1st line
Discount rate	3.5% until year 35 and 2.5% beyond year 35
Perspective	Restrictive societal perspective
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-3L in CLEAR trial, mapped to EQ-5D-5L.
Included costs	• Drug acquisition • Drug administration • AE management • Disease management • Patient costs • Subsequent treatment costs
Average time on treatment	Lenvatinib: single fit Exponential Pembrolizumab: single fit Weibull Sunitinib: single fit Exponential
Parametric function for PFS	LEN+PEM: joint fit Log-normal Sunitinib: joint fit Log-normal

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Parametric function for OS	LEN+PEM: Single fit Weibull. Sunitinib OS HR for LEN+PEM applied starting at week 108 Sunitinib: single fit Weibull
Stopping rule of pembrolizumab	Applied for two years
Stopping rule of nivolumab	Applied for two years
Subsequent treatment	• Sunitinib • Pazopanib • Nivolumab • Cabozantinib • Axitinib • Tivozanib • Avelumab + axitinib • Pembrolizumab + axitinib
Proportion of patients receiving subsequent treatment	Based on clinical expert opinion

Table 86. Modelling overview for the IMDC intermediate/poor prognosis population

IMDC intermediate/poor prognosis population	
Comparator	NIVO+IPI
Type of model	Partitioned survival model
Time horizon	40 years
Treatment line	1st line
Discount rate	3.5% until year 35 and 2.5% beyond year 35
Perspective	Restrictive societal perspective
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-3L in CLEAR trial, mapped to EQ-5D-5L.
Included costs	• Drug acquisition • Drug administration • AE management • Disease management • Patient costs • Subsequent treatment costs
Average time on treatment	Lenvatinib: single fit Generalised Gamma Pembrolizumab: single fit Weibull
Parametric function for PFS	LEN+PEM: single fit Exponential
Parametric function for OS	LEN+PEM: single fit Exponential
Stopping rule of pembrolizumab	Applied for two years
Stopping rule of nivolumab	Applied for two years
Subsequent treatment	• Sunitinib • Pazopanib • Nivolumab • Cabozantinib • Axitinib • Tivozanib • Avelumab + axitinib • Pembrolizumab + axitinib
Proportion of patients receiving subsequent treatment	Based on clinical expert opinion

Table 87. Summary of the Scenario analyses carried out for each population

Conducted scenario analyses	
ITT population	
Alternative OS distribution	• Single Log-normal parametric fit for LEN+PEM OS • Single Log-normal parametric fit for sunitinib OS

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Alternative PFS distribution	• Joint generalised gamma parametric fit for LEN+PEM PFS • Joint generalised gamma parametric fit for sunitinib PFS
	• Joint log-logistic parametric fit for LEN+PEM PFS • Joint log-logistic parametric fit for sunitinib PFS
Pembrolizumab posology	Administration every six weeks
Discount rate	0%
TTD	PFS curve
IMDC Good prognosis population	
Alternative PFS distribution	LEN+PEM: joint fit Log-logistic Sunitinib: joint fit Log-logistic
Pembrolizumab posology	Administration every six weeks
Discount rate	0%
TTD	PFS curve
IMDC intermediate/poor population	
Alternative OS distribution	• Single Weibull parametric fit for LEN+PEM OS
Alternative PFS distribution	• Single Weibull parametric fit for LEN+PEM PFS
Pembrolizumab posology	Administration every six weeks
Discount rate	0%
TTD	PFS curve

5.6.2 Results

5.6.2.1 Base case

5.6.2.1.1 ITT population

The results from Table 88 of the economic analysis for the overall population where LEN+PEM is compared to Sunitinib showed an overall QALY gain of [redacted] and an incremental cost 1,204,461 DKK. This results in an overall ICER of [redacted] per QALY gained.

Table 88. Results of economic analysis for the Overall population

Per patient	LEN + PEM	Sunitinib	Difference
Life years gained			
Total life years gained	[redacted]	[redacted]	1.21
Life years gained (Progression-free)	[redacted]	[redacted]	1.61
Life years gained (Post-progression)	[redacted]	[redacted]	-0.40
QALYs			
Total QALYs	[redacted]	[redacted]	0.98
QALYs (Progression-free)	[redacted]	[redacted]	1.28
QALYs (Post-progression)	[redacted]	[redacted]	-0.30
Costs (DKK)			
Total costs	[redacted]	[redacted]	1,204,461.16
Drug acquisition - Induction	[redacted]	[redacted]	0
Drug acquisition - Maintenance	[redacted]	[redacted]	1,166,537.02
Drug administration - Induction	0	0	0
Drug administration - Maintenance	40,089.03	0	40,089.03
AE management – PFS	1,390.40	720.81	669.59
AE management – PD	354.58	0	354.58
Disease management – PFS	111,216.33	54,307.35	56,908.97
Disease management – PD	106,062.12	120,276.79	-14,214.67
Subsequent treatment costs	78,407.63	150,637.23	-72,229.60
Patient and transport cost - PFS	39,871.70	12,136.81	27,734.89
Patient and transport cost - PD	10,302.81	11,691.46	-1,388.65
Incremental results	Intervention vs. Comparator		

Per patient	LEN + PEM	Sunitinib	Difference
ICER (DKK per QALY)	[redacted]		

5.6.2.1.2 IMDC good prognosis population

The results from Table 84 of the economic analysis for the good prognosis population where LEN+PEM is compared to Sunitinib showed an overall QALY gain of [redacted] and an incremental cost 1,310,834 DKK. This results in an overall ICER of [redacted] DKK per QALY gained.

Table 89. Results of economic analysis for the IMDC good prognosis population

Per patient	LEN + PEM	Sunitinib	Difference
Life years gained			
Total life years gained	[redacted]	[redacted]	0.05
Life years gained (Progression-free)	[redacted]	[redacted]	1.52
Life years gained (Post-progression)	[redacted]	[redacted]	-1.47
[redacted]			
Total QALYs	[redacted]	[redacted]	0.06
QALYs (Progression-free)	[redacted]	[redacted]	1.23
QALYs (Post-progression)	[redacted]	[redacted]	-1.18
Costs (DKK)			
Total costs	[redacted]	[redacted]	1,310,833.92
Drug acquisition - Induction	[redacted]	[redacted]	0
Drug acquisition - Maintenance	[redacted]	[redacted]	1,316,263.70
Drug administration - Induction	0	0	0
Drug administration - Maintenance	43,059.70	0	43,059.70
AE management – PFS	1,390.40	720.81	669.59
AE management – PD	442.93	0	442.93
Disease management – PFS	119,879.44	65,993.16	53,886.28
Disease management – PD	156,301.46	208,399.59	-52,098.13
Subsequent treatment costs	97,944.90	174,027.25	-76,082.35
Patient and transport cost - PFS	44,555.41	14,808.28	29,747.13
Patient and transport cost - PD	15,175.95	20,230.88	-5,054.93
Incremental results	Intervention vs. Comparator		
ICER (DKK per QALY)	[redacted]		

5.6.2.1.3 IMDC intermediate/poor population

The results from Table 85 of the economic analysis for the intermediate/poor population where LEN+PEM is compared to NIVO+IPI showed an overall QALY gain of [redacted] and an incremental cost 819,164 DKK. This results in an overall ICER of [redacted] DKK per QALY.

Table 90. Results of economic analysis for the IMDC intermediate/poor population

Per patient	LEN + PEM	NIVO +IPI	Difference
Life years gained			
Total life years gained	5.30	5.08	0.22
Life years gained (Progression-free)	2.39	1.22	1.16
Life years gained (Post-progression)	2.91	3.86	-0.95
QALYs			
Total QALYs	[redacted]	[redacted]	[redacted]
QALYs (Progression-free)	[redacted]	[redacted]	[redacted]
QALYs (Post-progression)	[redacted]	[redacted]	[redacted]
Costs (DKK)			
Total costs	[redacted]	[redacted]	[redacted]

Per patient	LEN + PEM	NIVO +IPI	Difference
Drug acquisition - Induction	[redacted]	[redacted]	[redacted]
Drug acquisition - Maintenance	[redacted]	[redacted]	[redacted]
Drug administration - Induction	0	DKK 13,543	-13,542.78
Drug administration - Maintenance	38,780.42	DKK 15,448	23,332.65
AE management – PFS	1,390.40	DKK 0	1,390.40
AE management – PD	389.97	DKK 539	-149.52
Disease management – PFS	86,474.29	DKK 45,257	41,217.00
Disease management – PD	103,199.11	DKK 136,757	-33,557.98
Subsequent treatment costs	86,234.93	DKK 203,442	-117,207.52
Patient and transport cost - PFS	33,323.07	DKK 11,023	22,299.93
Patient and transport cost - PD	10,029.98	DKK 16,675	-6,644.77

Incremental results	Intervention vs. Comparator
ICER (DKK per QALY)	[redacted]

5.6.2.2 Scenario analyses

5.6.2.2.1 ITT population

Table 91. Summary of the Scenario analyses carried out for each population

ITT population scenario analyses	ICER (DKK)
Basecase	[redacted]
Alternative OS distribution – Single fit: Log-normal	[redacted]
Alternative PFS distribution – Joint fit: Generalised gamma	[redacted]
Alternative PFS distribution – Joint fit: Log-logistic	[redacted]
TTD – estimated using PFS (for all non CLEAR treatments)	[redacted]
Discounting excluded	[redacted]
Pembrolizumab posology – 400mg Q6W	[redacted]

5.6.2.2.2 IMDC good prognosis population

Table 92. Summary of the Scenario analyses carried out for each population

IMDC good prognosis population scenario analyses	ICER (DKK)
Basecase	[redacted]
Alternative PFS distribution – Joint fit: Log-logistic	[redacted]
TTD – estimated using PFS (for all non CLEAR treatments)	[redacted]
Discounting excluded	[redacted]
Pembrolizumab posology – 400mg Q6W	[redacted]

5.6.2.2.3 IMDC intermediate/poor population

Table 93. Summary of the Scenario analyses carried out for each population

IMDC intermediate/poor population scenario analyses	ICER (DKK)
Basecase	[redacted]
Alternative OS distribution – Single fit: Weibull	[redacted]
Alternative PFS distribution – Single fit: Weibull	[redacted]
TTD – estimated using PFS (for all non CLEAR treatments)	[redacted]
Discounting excluded	[redacted]
Pembrolizumab posology – 400mg Q6W	[redacted]

5.7 Sensitivity analyses

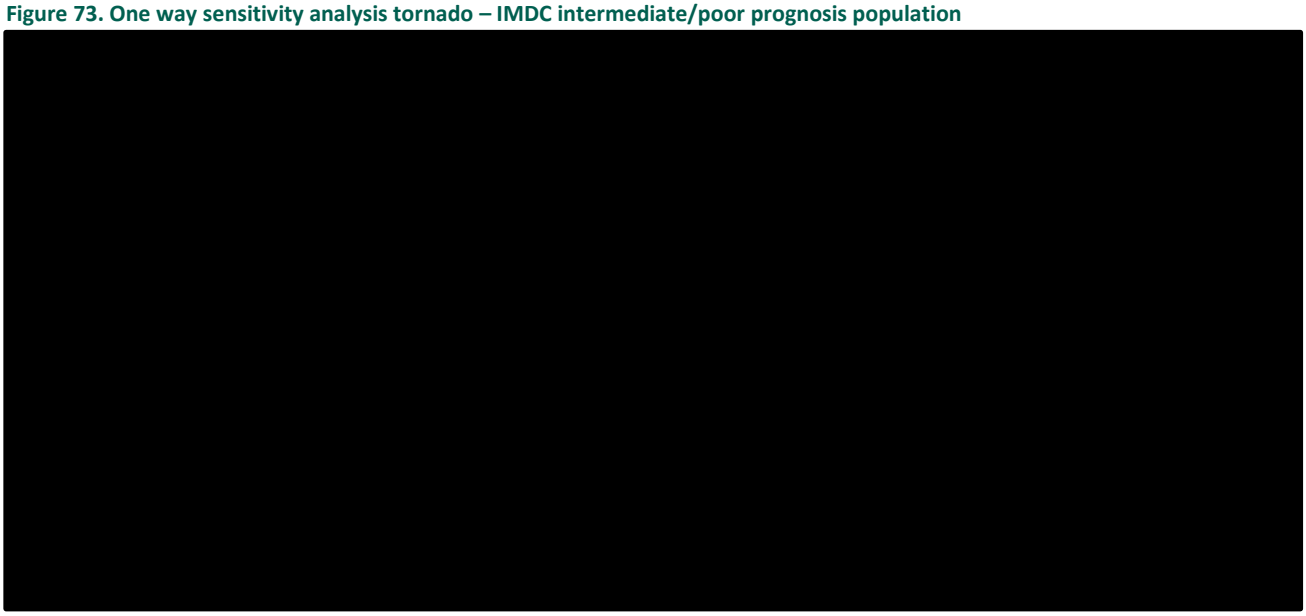
5.7.1 Deterministic sensitivity analyses

There is great concordance between the populations, within each the model is very sensitive to health state utilities, subsequent treatment cost and disease management. Drug costs were excluded from DSA and PSA as these are not uncertain.

Figure 71. One way-sensitivity analysis tornado – Overall population

Figure 72. One way sensitivity analysis tornado – IMDC good prognosis population

Figure 73. One way sensitivity analysis tornado – IMDC intermediate/poor prognosis population



Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

5.7.2 Probabilistic sensitivity analyses

See Appendix J Probabilistic sensitivity analyses for probabilistic sensitivity analyses results.

6. Budget impact analysis

The budget impact model (BIM) was developed to estimate the expected budget impact of recommending LEN+PEM as a possible standard treatment in Denmark. The budget impact was estimated per year for the first 5 years after the introduction of LEN+PEM in Denmark.

The budget impact model was partially nested within the cost-effectiveness model, and therefore any changes in the settings of the cost-effectiveness model would affect the results of the BIM. The budget impact result is representative of the population in the cost-effectiveness model and the survival outcome of this population (overall population). To calculate the budget impact of the sub-populations (IMDC good prognosis and IMDC intermediate/poor, the user can select these populations within the model, and the nested BIM will recalculate). The analysis was developed by comparing the costs for the Denmark per year over five years in the scenario where LEN+PEM is recommended as standard treatment and the scenario where LEN+PEM is not recommended as standard treatment in the relevant treatment comparison. The total budget impact per year is the difference between the two scenarios.

6.1 Number of patients and market uptake

As discussed in Section 2.1.3, Table 3, the expected number of incident patients is assumed to be 240 per year, and as such this BI analysis assumes 240 new incident patients per year. 240 patients per year aligns with each of the recent RCC appraisals to the DMC [9] [8] [33], and it is our assumption that this has not have changed. As also discussed in Section 2.1.3, Table 3, we estimate that there is approximately a 25%/75% split between those IMDC good prognosis and IMDC intermediate/poor. For the purpose of calculating the outcomes for the overall population, the BIM weights the market shares calculated for IMDC good prognosis and IMDC intermediate/poor respectively (given that different treatments are available in each sub-population.

It is our assumption that the market uptake of LEN+PEM is estimated to be 40% per year. This is an estimate which is simply a best guess, which cannot be further validated given that confidential discounts are applied to each of the treatments in the RCC therapeutic area. For all treatments other than LEN+PEM, market shares have been elicited from a Danish KOL. For the IMDC good prognosis subgroup, in the world without LEN+PEM, 10% of patients are assumed to have sunitinib, 20% pazopanib and 70% tivozanib, in the world with LEN+PEM, 10% are assumed to have pazopanib and 50% tivozanib. For the IMDC intermediate/poor prognosis subgroup, in the world without LEN+PEM, 10% of patients are assumed to have pazopanib, 75% NIVO+IPI and 15% tivozanib, in the world with LEN+PEM, 10% are assumed to have pazopanib and 40% NIVO+IPI and 10% tivozanib. It should be noted that given the agreed assumed equivalence of efficacy, pazopanib and tivozanib follow the exact same assumptions as sunitinib, with this reflected both in the cost effectiveness and budget impact analyses.

6.2 BI calculations

Applying the market shares and incidence as described in Section 6.1, and weighting the populations based on the expected 25%/75% split results in the following number of patients in each year (Table 94-Table 95)

Table 94. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration [9] [8] [33]	240	480	720	960	1,200
LEN + PEM	96	192	288	384	480
Sunitinib	0	0	0	0	0
Pazopanib	24	48	72	96	120
NIVO+IPI	72	144	216	288	360

	Year 1	Year 2	Year 3	Year 4	Year 5
Tivozanib	48	96	144	192	240
Total number of patients	240	480	720	960	1,200

Table 95. Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration [9] [8] [33]	240	480	720	960	1,200
LEN + PEM	0	0	0	0	0
Sunitinib	6	12	18	24	30
Pazopanib	30	60	90	120	150
NIVO+IPI	135	270	405	540	675
Tivozanib	69	138	207	276	345
Total number of patients	240	480	720	960	1,200

Using the calculations directly from the model the following per patient-costs are extracted, for each treatment (Table 96- Table 97)

Expenditure per patient

Table 96. Costs (DKK) per patient per year - if the pharmaceutical is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration, costs per patient					
LEN + PEM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO+IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tivozanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 97. Costs (DKK) per patient per year - if the pharmaceutical is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
For the pharmaceutical under consideration, costs per patient					
Sunitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NIVO+IPI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tivozanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Per-patient costs (Table 96- Table 97) are then multiplied the number of patients in each year (Table 94-Table 95) in order to give the total cost in each year for both the world where LEN+PEM is available and where it is not, these are then compared to give the budget impact (Table 98).

Budget impact

Table 98. Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minus: The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

10. Discussion on the submitted documentation

The documentation submitted for this single-technology assessment stems from a comprehensive clinical development program, where the efficacy and safety of combination treatment with LEN+PEM has been evaluated in adult patients with aRCC. For the scope of the assessment to reflect the clinical practice of aRCC treatment in Denmark, efficacy has been presented for the ITT population as well as for two patient population subgroups, good and intermediate/poor, based on IMDC categorisation, which were included as pre-determined subgroup analyses in the protocol of the CLEAR trial.

The CLEAR trial was a phase III, multicentre, randomized, open-label study to compare the efficacy and safety of first-line treatment with LEN+PEM or everolimus vs sunitinib in patients with Advanced Renal Cell Carcinoma (CLEAR [Study 307, NCT02811861]) [65]. With an enrolment of >1,000 patients, CLEAR is the largest study to date of an anti-PD-1/PD-L1 plus TKI regimen for the 1L treatment of advanced RCC [7]. The CLEAR trial hence presented direct head-to-head comparison of the efficacy and safety of LEN+PEM versus sunitinib, which is the standard of care in Denmark for the treatment of IMDC good prognosis patients. NIVO-IPI is the main treatment regimen recommended in Denmark for the IMDC intermediate/poor prognosis. As to the two main trials investigating LEN+PEM and NIVO+IPI, CLEAR and CHECKMATE214 [68], had a common comparator arm (sunitinib), it was possible to carry out an indirect treatment comparison of the two regimens.

LEN+PEM is part of new generation of combination therapy strategies which, as opposed to standard 1L monotherapy treatments for aRCC, targets different molecular pathways to increase response rate and avoid the resistance mechanisms that lead to failure with traditional therapies [7]. While newly approved immuno-oncology based combinations show improved efficacy vs VEGF-targeted monotherapy, overall response rates remain ≤60% [27, 40-42, 47, 48, 52, 95]. Patients receiving LEN+PEM in the CLEAR trial have demonstrated unprecedented results in median PFS (23.9 in the ITT population) as well as promising OS results, with a median OS of 43.0 months reported in the IMDC intermediate/poor subgroup. Patients receiving LEM+PEM in the CLEAR trial have also demonstrated high ORR [redacted] across ITT and both prognosis subgroups, with an ORR of [redacted] demonstrated in the IMDC intermediate/poor prognosis subgroup and 68.2% in the IMDC good prognosis. Most notably, patients achieved very high rates of CR in the ITT population (16.1% in the LEN+PEM arm vs. 4.2% in the sunitinib) and in both the subgroup populations (20.9% vs 4.8% in the IMDC good prognosis and 14.0% vs 3.9% in the IMDC intermediate/poor prognosis population). This almost four fold increase in the rates of CR represent a major change from alternative treatments and the hope for a radically positive impact on patients' life.

In summary, the CLEAR study provides direct evidence of the superiority of the lenvatinib plus pembrolizumab combination vs. sunitinib, in terms of OS, PFS, ORR, CR and QoL, and demonstrates a tolerable and manageable safety profile for the combination that is consistent with the safety profiles of each individual agent. Furthermore, the NMA suggests that LEN+PEM outperforms NIVO+IPI in terms of OS and ORR. Therefore, in alignment with the KOL interviewed for the purpose of this submission, the marketing authorisation holders expect LEN+PEM combination to be considered the preferred treatment option for patients with aRCC. In accordance with standard practice for modelling of oncology drugs, a partitioned survival model was used to model long-term efficacy and costs of LEN+PEM and relevant comparators. The base-case of the cost-utility analysis showed that in the ITT population LEN+PEM compared to Sunitinib provided a QALY gain of 0.98 at an incremental cost of 1,204,461 resulting in an ICER of DKK [redacted] per QALY. In the IMDC good prognosis population, where LEN+PEM is compared to Sunitinib showed an overall QALY gain of 0.06 and an incremental cost 1,310,834 DKK. This results in an overall ICER of [redacted] DKK per QALY gained. In the IMDC intermediate/poor population, LEN+PEM compared to NIVO+IPI provided a QALY gain of 0.27 at an incremental cost of 819.164 DKK. This results in an overall ICER of [redacted] DKK.

Sensitivity analyses determined that results do not vary significantly between deterministic and probabilistic analyses.

The budget impact analysis indicated that LEN+PEM results in additional cost burden, but that this is manageable (DKK 86,941,400 in year 5)

11. List of experts

Doctor Niels Fristrup, MD, PhD from Aarhus University Hospital | AUH · Department of Oncology, was consulted during the development of this application.

References

1. EuropeanCommission;, *KISPLYX (lenvatinib) Summary of Product Characteristics.* 2021.
2. Eisai, *KOL interviews - Niels Fristrup.* 2021.
3. Keytruda SmPC, *KEYTRUDA (pembrolizumab) Summary of Product Characteristics*. 2021, Merck Sharp & Dohme B.V.,.
4. Gruppe, D.U.C., *Dansk Renal Cancer Database (DaRenCaData) Årsrapport For opgørelsesperioden 1. august 2018 - 31. juli 2019 og 1. august 2019 – 31. juli 2020* 2021.
5. Danckert B, F.J., Engholm G , Hansen HL, Johannesen TB, Khan S, Køtlum JE, Ólafsdóttir E, Schmidt LKH, Virtanen A and Storm HH., *NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 8.2*. 2019.
6. (CHMP), C.f.M.P.f.H.U., *Summary of opinion1 (post authorisation)Kisplyx lenvatinib*. 2021.
7. Eisai CLEAR CSR, *A Multicenter, Open-Label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination With Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects With Advanced Renal Cell Carcinoma (CLEAR) (DATA ON FILE).* 2021.
8. Council, D.M., *Medicinrådets vurdering af pembrolizumab i kombination med axitinibtil førstelinjebehandling af metastaserende nyrecellekarcinom*. 2019.
9. Council, D.M., *Medicinrådets vurdering af nivolumab i kombination med ipilumab førstelinjebehandling af metastaserende nyrecellekarcinom.* 2019.
10. Escudier, B., et al., *Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†.* Annals of Oncology, 2019. **30**(5): p. 706-720.
11. Boss, D.S., et al., *A phase I study of E7080, a multitargeted tyrosine kinase inhibitor, in patients with advanced solid tumours.* Br J Cancer, 2012. **106**(10): p. 1598-604.
12. McDermott, D.F., et al., *Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma.* Nat Med, 2018. **24**(6): p. 749-757.
13. Medicinrådet, *Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til metastatisk nyrekræft* 2021.
14. Toni K. Choueiri, T.P., Camillo Porta, Masatoshi Eto, Viktor Grünwald, Thomas E. , et al., *A phase 3 trial of lenvatinib plus pembrolizumab versus sunitinib as a first-line treatment for patients with advanced renal cell carcinoma: overall survival follow-up analysis (the CLEAR study)*, in *Kidney Cancer Research Summit*. 2021.
15. Council, D.M., *The Danish Medicines Council methods guide for assessing new pharmaceuticals v1.2*. 2021.
16. Latimer, N.R., *Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: inconsistencies, limitations, and a practical guide.* Med Decis Making, 2013. **33**(6): p. 743-54.
17. National institute for Health and Care Excellence, *Treosulfan with fludarabine for malignant disease before allogeneic stem cell transplant. NICE TA640*. 2020.
18. Burnham, K.P. and D.R. Anderson, *Multimodel Inference: Understanding AIC and BIC in Model Selection.* Sociological Methods & Research, 2004. **33**(2): p. 261-304.
19. Raftery, A.E., *Bayesian Model Selection in Social Research.* Sociological Methodology, 1995. **25**: p. 111-163.
20. Sung, H., et al., *Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* CA: A Cancer Journal for Clinicians, 2021. **0**: p. 1-41.
21. Grunwald, V., et al., *Lenvatinib plus everolimus or pembrolizumab versus sunitinib in advanced renal cell carcinoma: study design and rationale.* Future Oncol, 2019. **15**(9): p. 929-941.
22. ACS. *What is Kidney Cancer?* 2020 [cited 2021 March 25]; Available from: https://www.cancer.org/cancer/kidney-cancer/about/what-is-kidney-cancer.html.
23. Capitanio, U. and F. Montorsi, *Renal cancer.* Lancet, 2016. **387**(10021): p. 894-906.
24. De, P., et al., *Trends in incidence, mortality, and survival for kidney cancer in Canada, 1986-2007.* Cancer Causes Control, 2014. **25**(10): p. 1271-81.
25. Capitanio, U., et al., *Epidemiology of Renal Cell Carcinoma.* Eur Urol, 2019. **75**(1): p. 74-84.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

26. NCI. *Cancer Stat Facts: Kidney and Renal Pelvis Cancer*. 2020 [cited 2021 March 25]; Available from: https://seer.cancer.gov/statfacts/html/kidrp.html.
27. NCCN. *Kidney Cancer Guidelines Version 4.2021*. 2021 [cited 2021 April 26]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.
28. Bai, T., et al., *Clinicopathologica Epidemiological Characteristics and Change Tendencies of Renal Cell Carcinoma in Shanxi Province of China from 2005 to 2014.* PLoS One, 2015. **10**(12): p. e0144246.
29. Chandrasekar, T., et al., *Metastatic renal cell carcinoma: Patterns and predictors of metastases-A contemporary population-based series.* Urol Oncol, 2017. **35**(11): p. 661.e7-661.e14.
30. Dabestani, S., et al., *Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: a population-based study.* World J Urol, 2016. **34**(8): p. 1081-6.
31. Kanayama, H.O., et al., *Clinicopathological characteristics and oncological outcomes in patients with renal cell carcinoma registered in 2007: The first large-scale multicenter study from the Cancer Registration Committee of the Japanese Urological Association.* Int J Urol, 2015. **22**(9): p. S1-7.
32. Heng, D.Y., et al., *Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study.* J Clin Oncol, 2009. **27**(34): p. 5794-9.
33. Medicinrådet, *Baggrund for Medicinrådets anbefaling vedrørende avelumab i kombination med axitinib som mulig standardbehandling til metastaserende nyrecellekarcinom*. 2020.
34. MSD, E.-. *RCC market research* 2021.
35. (RADS), C.f.t.U.o.A.H.M., *RADS Background note for the treatment of metastasizing kidney cancer.* 2017.
36. T. Powles, L.A., A. Bex, V. Grünwald, C. Porta, G. Procopio, M. Schmidinger, C. Suárez & G. de Velasco, on behalf of the ESMO Guidelines Committee, *ESMO Clinical Practice Guideline update on the use of immunotherapy in early stage and advanced renal cell carcinoma.* 2021.
37. Network, N.C.C. *NCCN Guidelines Version 3.2022 Kidney Cancer*. 2021; Available from: https://jnccn.org/view/journals/jnccn/18/9/article-p1160.xml.
38. Choueiri, T.K., et al., *Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update.* Eur J Cancer, 2018. **94**: p. 115-125.
39. Motzer, R.J., et al., *Pazopanib versus sunitinib in metastatic renal-cell carcinoma.* N Engl J Med, 2013. **369**(8): p. 722-31.
40. Motzer, R.J., et al., *Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial.* J Immunother Cancer, 2020. **8**(2).
41. Powles, T., et al., *Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial.* The Lancet Oncology, 2020. **21**(12): p. 1563-1573.
42. Albiges, L., et al., *Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma in CheckMate 214: 4-year follow-up and subgroup analysis of patients without nephrectomy*, in *ESMO Virtual Congress 2020*. 2020.
43. Motzer, R.J., et al., *Sunitinib versus interferon alfa in metastatic renal-cell carcinoma.* N Engl J Med, 2007. **356**(2): p. 115-24.
44. Motzer, R.J., et al., *Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma.* J Clin Oncol, 2009. **27**(22): p. 3584-90.
45. Motzer, R.J., et al., *Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial.* J Clin Oncol, 2013. **31**(30): p. 3791-9.
46. Fotivda SmPC, *FOTIVDA (tivozanib) Summary of Product Characteristics*. 2019, EUSA Pharma (Netherlands) B.V.,.
47. Choueiri, T.K., et al., *Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma.* Ann Oncol, 2020. **31**(8): p. 1030-1039.
48. Choueiri, T.K., et al., *Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma.* New England Journal of Medicine, 2021. **384**(9): p. 829-841.
49. Bavencio PI, *BAVENCIO (avelumab) US Prescribing Information*. 2020, EMD Serono Inc,.
50. Keytruda PI, *KEYTRUDA (pembrolizumab) US Prescribing Information*. 2021, Merck & Co Inc.,.
51. Opdivo PI, *OPDIVO (nivolumab) US Prescribing Information*. 2021, Bristol-Myers Squibb Company,.
52. Motzer, R., et al., *Nivolumab plus cabozantinib versus sunitinib for advanced renal cell carcinoma: outcomes by carcomatoid histology and updated trial results with extended follow-up of CheckMate-9ER*, in *ASCO GU*. 2021: Virtual.
53. Sutent SmPC, *SUTENT (sunitinib) Summary of Product Characteristics*. 2019, Pfizer Europe MA EEIG,.
54. Yervoy SmPC, *YERVOY (ipilimumab) Summary of Product Characteristics*. 2021, Bristol-Myers Squibb Pharma EEIG,.
55. Opdivo SmPC, *OPDIVO (nivolumab) Summary of Product Characteristics*. 2021, Bristol Myers Squibb Pharma EEIG,.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

56. Williams, L., *CHECKMATE 214 UPDATE CONFIRMS FIRST-LINE NIVOLUMAB–IPILIMUMAB BENEFIT. Patients with intermediate- or poor-risk renal cell carcinoma with a clear-cell component derive greater benefit in the long-term from nivolumab plus ipilimumab than with sunitinib*. 2019.
57. Niels Fristrup, M., PhD *Consultation on danish clinical practice in aRCC*. 2021.
58. Inlyta PI, *INLYTA (axitinib) US Prescribing Information*. 2020, Pfizer Inc,.
59. Sutent PI, *SUTENT (sunitinib) US Prescribing Information*. 2020, Pfizer Inc,.
60. Cabometyx PI, *CABOMETYX (cabozantinib) US Prescribing Information*. 2021, Exelixis Inc,.
61. Votrient PI, *VOTRIENT (pazopanib) US Prescribing Information*. 2020, Novartis Pharmaceuticals Corp.,.
62. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* PLoS Med, 2009. **6**(7): p. e1000100.
63. The Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions*. March 2011; Available from: http://handbook.cochrane.org/.
64. Vano Y, E.R., Bennamoun M, et al., *LBA25 Results from the phase II biomarker driven trial with nivolumab (N) and ipilimumab or VEGFR tyrosine kinase inhibitor (TKI) in naïve metastatic kidney cancer (m-ccRCC) patients (pts): The BIONIKK trial.* Ann Oncol, 2020. **31**: p. S1157.
65. Motzer, R., et al., *Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma.* N Engl J Med, 2021.
66. Eisai HRQoL Report, *A Multicenter, Open-Label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination With Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects With Advanced Renal Cell Carcinoma (CLEAR): Health-Related Quality of Life Outcomes Study Report*. 2021.
67. Eisai, *LEN+PEM CLEAR307 RCC 1L September 2021 - OS update - Data on file*. 2021.
68. Albiges, L., et al., *Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial.* ESMO Open, 2020. **5**(6): p. e001079.
69. Cella, D., et al., *Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial.* Lancet Oncol, 2019. **20**(2): p. 297-310.
70. Cella D, E., B., Ivanescu, C., Mauer, M., Lord-Bessen, J., Gooden, K., *Quality of life in previously untreated patients with advanced renal cell carcinoma (aRCC) in CheckMate 214: Updated results.* Annals of Oncology, 2020. **36**.
71. Ali, S., et al. *European Medicines Agency extension of indication to include the combination immunotherapy cancer drug treatment with nivolumab (Opdivo) and ipilimumab (Yervoy) for adults with intermediate/poor-risk advanced renal cell carcinoma*. in *ESMO*. 2021.
72. EISAI, *Statistical Report - Overall survival of lenvatinib plus pembrolizumab versus sunitinib adjusted for subsequent anticancer medication using 2-stage estimation and IPCW approach - Data on file*. 2021.
73. Motzer, R., C. Porta, and B. Alekseev, *Health-related quality-of-life (HRQoL) analysis from the phase 3 CLEAR trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) or everolimus (EVE) vs sunitinib (SUN) for patients (pts) with advanced renal cell carcinoma (aRCC)*, in *American Society of Clinical Oncology (ASCO) Annual Meeting*. 2021: Virtual.
74. Eisai, *Health-Related Quality of Life Outcomes in Patients With Advanced Renal Cell Carcinoma Treated with Lenvatinib Plus Pembrolizumab or Everolimus Versus Sunitinib (Randomized Phase 3 Study 307/KEYNOTE-581; CLEAR) DATA ON FILE*. 2022.
75. Eisai, *CLEAR 307 - subgroup analyses - March 2021 DCO - data on file*. 2021.
76. Eisai, *CLEAR 307 - subgroup analyses - August 2020 DCO - Data on file* 2020.
77. Cella, D., et al., *Health-related quality of life (HRQoL) in previously untreated patients with advanced renal cell carcinoma (aRCC) in CheckMate 214: Five-year follow-up results.* Journal of Clinical Oncology, 2022. **40**(6_suppl): p. 307-307.
78. D. Cella, V.G., B. Escudier, H. J. Hammers, S. George, P. Nathan, et al., ***Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial - SUPPLEMENTARY MATERIAL***. Lancet Oncol 2019. **20**(2): p. 297-310
79. National Institute for Health and Care Excellence, *Pembrolizumab with axitinib for untreated advanced renal cell carcinoma. TA650.* 2020.
80. NICE, *NICE DSU TECHNICAL SUPPORT DOCUMENT 21: Flexible Methods for Survival Analysis.* 2020.
81. National Institute for Health and Care Excellence, *Avelumab with axitinib for untreated advanced renal cell carcinoma. TA645.* 2020.
82. NICE, *Technology Appraisal Guidance: Nivolumab with Ipilimumab for Untreated Advanced Renal Cell Carcinoma*. 2019.
83. Sundhedsdatastyrelsen, *Interaktiv DRG.*
84. Motzer, R., et al., *Phase 3 trial of lenvatinib plus pembrolizumab or everolimus versus sunitinib monotherapy as a first-line treatment for patients with advanced renal cell carcinoma (CLEAR study)*, in *ASCO GU*. 2021: Virtual.
85. Agency, E.M., *Draft SmPC Kiplyx*. 2021.
86. Lightning Health, *LEN+PEM Advisory Meeting Report- FINAL (Eisai data on file).*

87. Powles, T., et al., *Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial.* Lancet Oncol, 2020. **21**(12): p. 1563-1573.
88. Ben van Hout 1, M.F.J., You-Shan Feng, Thomas Kohlmann, Jan Busschbach, Dominik Golicki, Andrew Lloyd, Luciana Scalone, Paul Kind, A Simon Pickard, *Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets.* Value Health, 2012. **15(5):708-15**.
89. Danishcenterforhealthcareimprovements. *THE DANISH EQ-5D-5L WEIGHTS, project quality of life*. 2021; Available from: https://www.dchi.aau.dk/forskning/livskvalitet/.
90. Kim U Wittrup-Jensen , J.L., Claire Gudex, Kjeld M Pedersen, *Generation of a Danish TTO value set for EQ-5D health states.* 2009.
91. Szende, A., B. Janssen, and J. Cabases, *Self-Reported Population Health: An International Perspective based on EQ-5D*, in *Self-Reported Population Health: An International Perspective based on EQ-5D*, A. Szende, B. Janssen, and J. Cabases, Editors. 2014: Dordrecht (NL).
92. Lægemiddelstyrelsen.
93. Amgros, *UDVIDET SAMMENLIGNINGSGRUNDLAG FOR TERAPIOMRÅDET NYREKRÆFT, RENALCELLECARCINOM. LÆGEMIDLER TIL BEHANDLING AF LOKALAVANCERET INOPERABELT ELLER METASTATISK NYREKRÆFT version 1.2.* 2020.
94. Medicinrådet, *Værdisætning af enhedsomkostninger. 2020;1–16.* 2020.
95. ESMO Guidelines Committee. *eUpdate--Renal Cell Carcinoma Algorithm (7 February 2020)*. 2020 [cited 2020 April 1]; Available from: https://www.esmo.org/guidelines/genitourinary-cancers/renal-cell-carcinoma/eupdate-renal-cell-carcinoma-algorithm.
96. National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisal 2013. Process and methods. Foreword*. 2013; Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword.
97. National Institute for Health and Care Excellence (NICE). *Single technology appraisal: User guide for company evidence submission template. Process and methods. Instructions for companies.* 2017; Available from: https://www.nice.org.uk/process/pmg24/chapter/instructions-for-companies.
98. Higgins, J., et al., *A revised tool for assessing risk of bias in randomized trials.* Cochrane Methods. Cochrane Database of Systematic Reviews, 2016. **10**(Suppl 1): p. 29-31.
99. Drummond, M. and T. Jefferson, *Guidelines for authors and peer reviewers of economic submissions to the BMJ.* British Medical Journal, 1996. **313**(7052): p. 275-284.
100. Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions*. 2017; Available from: http://training.cochrane.org/handbook
101. Healthcare Improvement Scotland (SIGN). *Home page*. March 1, 2021]; Available from: https://www.sign.ac.uk/what-we-do/methodology/search-filters/
102. Paisley S, B.A., Mensinkai S. , *Chapter 12: health-related quality of life studies. In: Etext on Health Technology Assessment (HTA) Information Resources*. 2005.
103. Wolters Kluwer. *Ovid Expert Searches*. March 1, 2021]; Available from: https://tools.ovid.com/ovidtools/expertsearches.html.
104. Higgins, J.P., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (Eds.), , *Cochrane handbook for systematic reviews of interventions*. 2019: John Wiley & Sons.
105. Bukowski, R.M., et al., *Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer.* J Clin Oncol, 2007. **25**(29): p. 4536-41.
106. Escudier, B., et al., *Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial.* Lancet, 2007. **370**(9605): p. 2103-11.
107. Rini, B.I., et al., *Axitinib with or without dose titration for first-line metastatic renal-cell carcinoma: a randomised double-blind phase 2 trial.* Lancet Oncol, 2013. **14**(12): p. 1233-42.
108. Sternberg, C.N., et al., *Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial.* J Clin Oncol, 2010. **28**(6): p. 1061-8.
109. Hudes, G., et al., *Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma.* N Engl J Med, 2007. **356**(22): p. 2271-81.
110. Lissoni, P., et al., *A randomized study of low-dose interleukin-2 subcutaneous immunotherapy versus interleukin-2 plus interferon-alpha as first line therapy for metastatic renal cell carcinoma.* Tumori, 1993. **79**(6): p. 397-400.
111. Negrier, S., et al., *Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial.* Cancer, 2007. **110**(11): p. 2468-77.
112. Armstrong, A.J., et al., *Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial.* Lancet Oncol, 2016. **17**(3): p. 378-88.
113. Tannir, N.M., et al., *Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma (ESPN): A Randomized Multicenter Phase 2 Trial.* Eur Urol, 2016. **69**(5): p. 866-74.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

114. Wan, X., et al., *First-line Nivolumab Plus Ipilimumab vs Sunitinib for Metastatic Renal Cell Carcinoma: A Cost-effectiveness Analysis.* JAMA Oncol, 2019. **5**(4): p. 491-496.
115. Choueiri, T.K., et al., *Cabozantinib Versus Sunitinib As Initial Targeted Therapy for Patients With Metastatic Renal Cell Carcinoma of Poor or Intermediate Risk: The Alliance A031203 CABOSUN Trial.* J Clin Oncol, 2017. **35**(6): p. 591-597.
116. Zurita, A.J., et al., *A randomized phase II trial of pazopanib (PAZ) vs. temsirolimus (TEM) in patients (pts) with advanced clear-cell renal cell carcinoma (accRCC) with intermediate or poor-risk disease (the TemPa trial).* Journal of Clinical Oncology, 2018. **36**(15_suppl): p. 4563-4563.
117. ClinicalTrials.gov. *Phase II Study of Afinitor vs. Sutent in Patients With Metastatic Non-Clear Cell Renal Cell Carcinoma*. 2018; Available from: https://clinicaltrials.gov/ct2/show/NCT01108445.
118. Escudier, B., et al., *A randomized, controlled, double-blind phase III study (AVOREN) of bevacizumab/interferon-α2a vs placebo/interferon- α2a as first-line therapy in metastatic renal cell carcinoma.* Journal of Clinical Oncology, 2007. **25**(18_suppl): p. 3-3.
119. Grünwald V., M.D.F., Atkins M., Motzer R., Rini B., Escudier B.,, et al., *A phase II study of atezolizumab (atezo) with or without bevacizumab (bev) vs sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC) patients (pts).* Oncol Res Treat, 2017. **40**(Suppl 3): p. 1-134.
120. ClinicalTrials.gov. *Bevacizumab, Sorafenib Tosylate, and Temsirolimus in Treating Patients With Metastatic Kidney Cancer*. 2018; Available from: https://clinicaltrials.gov/ct2/show/NCT00378703.
121. Rini, B.I., et al., *Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206.* J Clin Oncol, 2010. **28**(13): p. 2137-43.
122. Rini, B.I., et al., *Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206.* J Clin Oncol, 2008. **26**(33): p. 5422-8.
123. Tannir, N.M., et al., *Long-term response and time to response to pazopanib (PAZ) and sunitinib (SUN) in metastatic renal cell carcinoma (mRCC): COMPARZ subanalysis.* Journal of Clinical Oncology, 2017. **35**(15_suppl): p. 4572-4572.
124. Tomita, Y., et al., *Sunitinib versus sorafenib as first-line therapy for patients with metastatic renal cell carcinoma with favorable or intermediate MSKCC risk factors: A multicenter randomized trial, CROSS-J-RCC.* Journal of Clinical Oncology, 2014. **32**(4_suppl): p. 502-502.
125. Tomita, Y., et al., *Sunitinib versus sorafenib as first-line therapy followed by sorefenib and sunitinib for patients with metastatic renal cell carcinoma (RCC) with clear cell histology: A multicenter randomized trial, CROSS-J-RCC.* Journal of Clinical Oncology, 2017. **35**(6_suppl): p. 469-469.
126. Escudier, B., et al., *Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma.* J Clin Oncol, 2009. **27**(8): p. 1280-9.
127. Bayer, *Clinical Study Synopsis: A randomised, open-label, multi-center phase II study of first-line treatment with BAY 43-9006 (Sorafenib) versus standard treatment with Interferon alpha-2a in subjects with unresectable and/or metastatic renal cell carcinoma*.
128. ClinicalTrials.gov. *Study Evaluating Interferon And CCI-779 In Advanced Renal Cell Carcinoma (ARCC)*. 2017; Available from: https://clinicaltrials.gov/show/nct00065468.
129. Hutson TE, A.S.S., Stus VP, Lipatov ON, Shparyk Y, Bair AH, Rosbrook B, Andrews GI, Vogelzang NJ,, *Overall survival analysis from a randomised phase III trial of axitinib vs sorafenib as first-line therapy in patients with metastatic renal cell carcinoma.* Eur J Cancer, 2015. **51**: p. S476-S477.
130. Hutson, T.E., et al., *Axitinib Versus Sorafenib in First-Line Metastatic Renal Cell Carcinoma: Overall Survival From a Randomized Phase III Trial.* Clin Genitourin Cancer, 2017. **15**(1): p. 72-76.
131. Hutson, T.E., et al., *Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial.* Lancet Oncol, 2013. **14**(13): p. 1287-94.
132. Powles, T., et al., *LBA39IMmotion150: Novel radiological endpoints and updated data from a randomized phase II trial investigating atezolizumab (atezo) with or without bevacizumab (bev) vs sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC).* Annals of Oncology, 2017. **28**(suppl_5).
133. Motzer, R.J., et al., *IMmotion151: A Randomized Phase III Study of Atezolizumab Plus Bevacizumab vs Sunitinib in Untreated Metastatic Renal Cell Carcinoma (mRCC).* Journal of Clinical Oncology, 2018. **36**(6_suppl): p. 578-578.
134. Motzer, R.J., et al., *Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.* New England Journal of Medicine, 2019. **380**(12): p. 1103-1115.
135. Haanen, J., et al. *Efficacy of avelumab + axitinib (A + Ax) vs sunitinib (S) by IMDC risk group in advanced renal cell carcinoma (aRCC): extended follow-up results from JAVELIN Renal 101*. in *ASCO Annual Meeting*. 2021.
136. Rini, B.I., et al., *Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.* New England Journal of Medicine, 2019. **380**(12): p. 1116-1127.
137. Rini, B., et al. *Pembrolizumab plus Axitinib versus Sunitinib as First-line Therapy for Advanced Clear Cell Renal Cell Carcinoma: Results from 42-month Follow-up of KEYNOTE-426*. in *ASCO*. 2021.
138. ClinicalTrials.gov. *SU011248 Versus Interferon-Alfa As First-Line Systemic Therapy For Patients With Metastatic Renal Cell Carcinoma*. 2017; Available from: https://clinicaltrials.gov/show/nct00083889.

139. Negrier, S., et al., *Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Francais d'Immunotherapie.* N Engl J Med, 1998. **338**(18): p. 1272-8.
140. Ravaud, A., et al., *RECORD-2: phase II randomized study of everolimus and bevacizumab versus interferon alpha-2a and bevacizumab as first-line therapy in patients with metastatic renal cell carcinoma.* Ann Oncol, 2015. **26**(7): p. 1378-84.
141. EU Clinical Trials Register. *A randomized, open label, multi-center phase II study to compare bevacizumab plus RAD001 versus interferon alfa-2a and bevacizumab for the first-line treatment of patients with metastatic clear cell carcinoma of the kidney*. 2016; Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-000077-38/results.
142. Motzer, R.J., et al., *Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma.* J Clin Oncol, 2014. **32**(25): p. 2765-72.
143. ClinicalTrials.gov. *Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-line and Second-line Treatment of Patients With Metastatic Renal Cell Carcinoma*. 2016; Available from: https://clinicaltrials.gov/ct2/show/NCT00903175.
144. Tomita, Y., et al., *Key predictive factors for efficacy of axitinib in first-line metastatic renal cell carcinoma: subgroup analysis in Japanese patients from a randomized, double-blind phase II study.* Jpn J Clin Oncol, 2016. **46**(11): p. 1031-1041.
145. Cirkel, G.A., et al., *Alternating Treatment With Pazopanib and Everolimus vs Continuous Pazopanib to Delay Disease Progression in Patients With Metastatic Clear Cell Renal Cell Cancer: The ROPETAR Randomized Clinical Trial.* JAMA Oncol, 2017. **3**(4): p. 501-508.
146. Eichelberg, C., et al., *SWITCH: A Randomised, Sequential, Open-label Study to Evaluate the Efficacy and Safety of Sorafenib-sunitinib Versus Sunitinib-sorafenib in the Treatment of Metastatic Renal Cell Cancer.* Eur Urol, 2015. **68**(5): p. 837-47.
147. Retz, M., et al., *SWITCH II: Phase III randomized, sequential, open-label study to evaluate the efficacy and safety of sorafenib-pazopanib versus pazopanib-sorafenib in the treatment of advanced or metastatic renal cell carcinoma (AUO AN 33/11).* Eur J Cancer, 2019. **107**: p. 37-45.
148. Motzer, R.J., et al., *Supplement to Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial.* J Clin Oncol, 2013. **31**(30): p. 3791-9.
149. Bergmann, L., et al., *A Randomized Phase IIa Trial with Temsirolimus versus Sunitinib in Advanced Non-Clear Cell Renal Cell Carcinoma: An Intergroup Study of the CESAR Central European Society for Anticancer Drug Research-EWIV and the Interdisciplinary Working Group on Renal Cell Cancer (IAGN) of the German Cancer Society.* Oncol Res Treat, 2020. **43**(7-8): p. 333-339.
150. Choueiri TK, P.T., Burotto M, Bourlon MT, Zurawski B, Oyervides VM, et al. *Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial (Presentation Number 696O)*. in *Virtual 2020 ESMO Congress*. 2020.
151. Motzer, R.J., et al., *Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma.* New England Journal of Medicine, 2018. **378**(14): p. 1277-1290.
152. Eisai, *CLEAR 307 Top-line results PowerPoint*. 2020.
153. Tomita, Y., et al., *Sunitinib Versus Sorafenib as Initial Targeted Therapy for mCC-RCC With Favorable/Intermediate Risk: Multicenter Randomized Trial CROSS-J-RCC.* Clin Genitourin Cancer, 2020. **18**(4): p. e374-e385.
154. Hsieh, J.J., et al., *Genomic Biomarkers of a Randomized Trial Comparing First-line Everolimus and Sunitinib in Patients with Metastatic Renal Cell Carcinoma.* Eur Urol, 2017. **71**(3): p. 405-414.
155. Tannir NM, Frontera OA, and e.a. Hammers HJ. *Thirty-month follow-up of the phase III CheckMate 214 trial of first-line nivolumab + ipilimumab (N+I) or sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC)*. in *2019 Genitourinary Cancers Symposium*. 2019.
156. Albiges L, T.N., Burotto M, et al.,. *Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma 711P in CheckMate 214: 4-year follow-up and subgroup analysis of patients without nephrectomy*. in *ESMO Virtual Congress 2020*. 2020.
157. Motzer, R.J., et al. *Nivolumab plus cabozantinib versus sunitinib for advanced renal cell carcinoma: outcomes by sarcomatioid histology and updated trial results with extended follow-up of CheckMate 9ER*. in *Genitourinary Cancers Symposium*. 2021.
158. Apolo, A.B., et al. *Nivolumab plus cabozantinib versus sunitinib for advanced renal cell carcinoma: outcomes by baseline disease characteristics in phase 3 CheckMate 9ER trial*. in *ASCO Annual Meeting*. 2021.
159. Rini, B.I., et al., *Atezolizumab plus Bevacizumab Versus Sunitinib for Patients with Untreated Metastatic Renal Cell Carcinoma and Sarcomatoid Features: A Prespecified Subgroup Analysis of the IMmotion151 Clinical Trial.* Eur Urol, 2020.
160. EU Clinical Trials Register. *A randomised, double-blind phase III study to evaluate the efficacy and safety of bevacizumab in combination with interferon alfa-2a (Roferon) versus interferon alfa-2a and placebo as first line treatment administered to nephrectomised patients with metastatic clear cell renal cell carcinoma*. [refidGL-10] 2012 April 2021]; Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2004-000282-35/results.

161. Tomita, Y., et al., *Patients with metastatic renal cell carcinoma who benefit from axitinib dose titration: analysis from a randomised, double-blind phase II study.* BMC Cancer, 2019. **19**(1): p. 17.
162. European Medicines Agency. *ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS: MVASI, INN Bevacizumab*. Available from: https://www.ema.europa.eu/documents/product-information/mvasi-epar-product-information_en.pdf.
163. Motzer, R.J., et al., *Overall survival in renal-cell carcinoma with pazopanib versus sunitinib.* N Engl J Med, 2014. **370**(18): p. 1769-70.
164. National Institute of Health and Care Excellence. *Single Technology Appraisal, Tivozanib for treating renal cell carcinoma [ID591], Committee Papers* 2017 April 2021]; Available from: https://www.nice.org.uk/guidance/ta512/documents/committee-papers
165. Sternberg, C.N., et al., *A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update.* Eur J Cancer, 2013. **49**(6): p. 1287-96.
166. Albiges L, T.N., Burotto M, et al., *711P Nivolumab + ipilimumab (N+I) vs sunitinib (S) for first-line treatment of advanced renal cell carcinoma (aRCC) in CheckMate 214: 4-year follow-up and subgroup analysis of patients (pts) without nephrectomy.* Ann Oncol, 2020. **31**: p. S559-S560.
167. Knox, J.J., et al., *Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC.* Ann Oncol, 2017. **28**(6): p. 1339-1345.
168. Choueiri, T.K., et al., *Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma.* N Engl J Med, 2021. **384**(9): p. 829-841.
169. Eisai, *A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma (CLEAR).* 2021.
170. Rini, B.I., et al., *Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial.* Lancet, 2019. **393**(10189): p. 2404-2415.
171. Escudier, B., et al., *Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival.* J Clin Oncol, 2010. **28**(13): p. 2144-50.
172. Escudier, B., et al., *Efficacy of Nivolumab plus Ipilimumab According to Number of IMDC Risk Factors in CheckMate 214.* Eur Urol, 2020. **77**(4): p. 449-453.
173. European Medicines Agency. *ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS: OPDIVO*. Available from: https://www.ema.europa.eu/en/documents/product-information/opdivo-epar-product-information_en.pdf.
174. European Medicines Agency. *ANNEX I SUMMARY OF PRODUCT CHARACTERISTICS: VOTRIENT*. Available from: https://www.ema.europa.eu/documents/product-information/votrient-epar-product-information_en.pdf.
175. Choueiri, T.K., et al., *Subgroup analysis from JAVELIN Renal 101: Outcomes for avelumab plus axitinib (A + Ax) versus sunitinib (S) in advanced renal cell carcinoma (aRCC).* Journal of Clinical Oncology, 2019. **37**(7_suppl): p. 544-544.
176. Plimack ER, R.B., Stus V, et al.,. *Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced renal cell carcinoma: updated analysis of KEYNOTE-426*. in *2020 ASCO Annual Meeting*. 2020.
177. S.J. Hotte, M.M., G.A. Bjarnason, MD, [...], and F. Saad, MD, *Progression-free survival as a clinical trial endpoint in advanced renal cell carcinoma.* Current Oncology 2011. **18(Suppl 2) S11-S9**.
178. Pazdur, R., *Endpoints for assessing drug activity in clinical trials.* The oncologist. **vol. 13 Suppl 2 (2008): 19-21.**
179. E.A. Eisenhauera, et al., *New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1).* EUROPEAN JOURNAL OF CANCER, 2009. **45 (2009) 228 – 247**.
180. Sabrina H. Rossi1 · Tobias Klatte1, G.D.S., *Quality of life outcomes in patients with localised renal cancer: a literature review.* World Journal of Urology, 2018. **36:1961–1972**.
181. Cella, D., et al., *Development and validation of a scale to measure disease-related symptoms of kidney cancer.* Value Health, 2007. **10**(4): p. 285-93.
182. Pal, S.K., et al., *Real-World Survival Outcomes and Prognostic Factors Among Patients Receiving First Targeted Therapy for Advanced Renal Cell Carcinoma: A SEER-Medicare Database Analysis.* Clin Genitourin Cancer, 2017. **15**(4): p. e573-e582.
183. Gore, M.E., et al., *Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma.* Br J Cancer, 2015. **113**(1): p. 12-9.
184. Hammers, H.J., et al., *CheckMate 214: A phase III, randomized, open-label study of nivolumab combined with ipilimumab versus sunitinib monotherapy in patients with previously untreated metastatic renal cell carcinoma.* Journal of Clinical Oncology, 2015. **33**(15_suppl): p. TPS4578-TPS4578.
185. Motzer, R.J., et al., *Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.* N Engl J Med, 2019. **380**(12): p. 1103-1115.
186. Rini, B.I., et al., *Phase III Trial of Bevacizumab Plus Interferon Alfa Versus Interferon Alfa Monotherapy in Patients With Metastatic Renal Cell Carcinoma: Final Results of CALGB 90206.* Journal of Clinical Oncology, 2010. **28**(13): p. 2137-2143.

187. Cai, W., et al., *Comparison of efficacy, safety, and quality of life between sorafenib and sunitinib as first-line therapy for Chinese patients with metastatic renal cell carcinoma.* Chin J Cancer, 2017. **36**(1): p. 64.
188. Cohen, L., et al., *Depressive symptoms and cortisol rhythmicity predict survival in patients with renal cell carcinoma: role of inflammatory signaling.* PLoS One, 2012. **7**(8): p. e42324.
189. Wang, Y., et al., *Evaluation and predictive factors analyses for patient-self-reported depression, anxiety and quality of life in patients with metastatic renal cell carcinoma underwent interferon-α treatment: a prospective cohort study.* Transl Cancer Res, 2018. **7**(6): p. 1460-1473.
190. Swinburn, P., et al., *[Supplement] Elicitation of health state utilities in metastatic renal cell carcinoma.* Curr Med Res Opin, 2010. **26**(5): p. 1091-6.
191. Goebell, P.J., et al., *A cross-sectional investigation of fatigue in advanced renal cell carcinoma treatment: results from the FAMOUS study.* Urol Oncol, 2014. **32**(3): p. 362-70.
192. Schmidinger, M., et al., *Prospective Observational Study of Pazopanib in Patients with Advanced Renal Cell Carcinoma (PRINCIPAL Study).* Oncologist, 2019. **24**(4): p. 491-497.
193. Vuorinen, R.L., et al., *Sunitinib First-line Treatment in Metastatic Renal Cell Carcinoma: Costs and Effects.* Anticancer Res, 2019. **39**(10): p. 5559-5564.
194. Tannir, N.M., et al., *Temsirolimus versus Pazopanib (TemPa) in Patients with Advanced Clear-cell Renal Cell Carcinoma and Poor-risk Features: A Randomized Phase II Trial.* Eur Urol Oncol, 2020. **3**(5): p. 687-694.
195. Swinburn, P., et al., *Elicitation of health state utilities in metastatic renal cell carcinoma.* Curr Med Res Opin, 2010. **26**(5): p. 1091-6.
196. Bedke, J., Rini BI, Plimack ER, et al. *Health-Related Quality-of-Life Analysis From KEYNOTE-426: Pembrolizumab Plus Axitinib vs Sunitinib for Advanced Renal Cell Carcinoma*. in *EAU20*. 2020.
197. Cella, D., et al., *Treatment benefit of tivozanib hydrochloride versus sorafenib on health-related quality of life (HRQoL) among patients (pts) with advanced/metastatic renal cell carcinoma (mRCC): TIVO-1 study results.* J Clin Oncol, 2013. **31**(no. 6_suppl): p. 355.
198. Pickard, A.S., et al., *Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomized phase III trial.* J Clin Oncol, 2011. **29**(no. 15_suppl): p. 9096.
199. Cella, D., et al., *Quality of life in patients with advanced renal cell carcinoma in the randomized, open-label CheckMate 214 trial.* J Clin Oncol, 2018. **36**(no. 15_suppl): p. 3073.
200. Cella, D., Escudier, B., Ivanescu, C., Mauer, M., Lord-Bessen, J., Gooden, K.,, *Quality of life in previously untreated patients with advanced renal cell carcinoma (aRCC) in CheckMate 214: Updated results.* Annals of Oncology, 2020. **30**: p. v383-v384.
201. Escudier, B., et al., *Patient-reported outcomes (PROs) in IMmotion151: Atezolizumab (atezo) + bevacizumab (bev) vs sunitinib (sun) in treatment (tx) naive metastatic renal cell carcinoma (mRCC).* J Clin Oncol, 2018. **36**(no. 15_suppl): p. 4511.
202. Yang, S., et al., *Quality of life in patients with advanced renal cell carcinoma treated with temsirolimus or interferon-alpha.* Br J Cancer, 2010. **102**(10): p. 1456-60.
203. Castellano, D., et al., *Patient-reported outcomes in a phase III, randomized study of sunitinib versus interferon-{alpha} as first-line systemic therapy for patients with metastatic renal cell carcinoma in a European population.* Ann Oncol, 2009. **20**(11): p. 1803-12.
204. Cella, D., et al., *Quality of life predicts progression-free survival in patients with metastatic renal cell carcinoma treated with sunitinib versus interferon alfa.* J Oncol Pract, 2009. **5**(2): p. 66-70.
205. Cella, D., et al., *Health-related quality of life in patients with metastatic renal cell carcinoma treated with sunitinib vs interferon-alpha in a phase III trial: final results and geographical analysis.* Br J Cancer, 2010. **102**(4): p. 658-64.

Appendix A Literature search for efficacy and safety of intervention and comparator(s)

The goal of this project was to generate evidence that can be used to successfully demonstrate the value of LEN+PEM in the treatment of aRCC and to support reimbursement decisions by:

- Providing a comprehensive understanding of the clinical efficacy and safety of 1L treatments for aRCC
- Ensuring that the evidence generated meets the methodological rigor required by major HTA and regulatory bodies (e.g., FDA, the National Institute for Health and Care Excellence [NICE]) and is flexible enough to support future HTA submissions.

The following specific research questions were answered by the SLRs

SLR 1. Clinical Efficacy and Safety: What is the clinical efficacy and safety of approved, recommended, or under development 1L treatments for aRCC compared with each other or best supportive care (BSC) based on evidence from randomized controlled trials (RCT)?

SLR 2. Patient reported outcomes (PROs): What is the impact of 1L treatments approved, recommended, or under development on humanistic burden/patient-reported outcomes (PRO) in patients with aRCC based on evidence from observational studies and RCTs?

This appendix presents the details of SLR1. Clinical Efficacy and Safety. For full details on the relation between SLR, NMA and publications providing inputs to the submission, please see XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Methods

The SLRs were conducted in accordance with NICE technology appraisal guidance,[96, 97] the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [62] and the Cochrane Handbook for Systematic Reviews of Interventions [63] The quality of the identified evidence was assessed using well-established, recommended, quality score systems, when appropriate, including the Cochrane Risk of Bias Assessment Tool 2.0 [98] and the Drummond Checklist of Economic Evaluations [99].

Search strategy

Systematic searches for SLR 1 were conducted on June 4, 2021 (Three searches had been conducted on January 5, 2021, March 27, 2019, and September 1, 2020, as well) in Embase and MEDLINE (via PubMed), EconLit, Centre for Reviews and Dissemination, and the Cochrane Library using a combination of free-text search terms and controlled vocabulary terms (Emtree terms in embase.com), as recommended by the Cochrane Collaboration [100]. The searches identified relevant literature on the efficacy, safety, and PROs of 1L treatment options for aRCC; however, the search PROs and HRQoL data is presented in Appendix H . Search concepts were validated [101, 102] and modified, where appropriate, according to project-specific needs, using guidance from Ovid Expert Search Tools [103] and the Cochrane Handbook for Systematic Reviews of Interventions [104].

For conference proceedings with abstracts indexed in electronic literature databases (American Society of Clinical Oncology [ASCO], American Society of Clinical Oncology-Genitourinary (ASCO-GU), American Association for Cancer Research (AACR), American Urological Association (AUA), European Association of Urology (EUA), and European Society for Medical Oncology [ESMO]), Embase was searched. Abstracts from ASCO-GU were not indexed in Embase, and the conference website (https://meetinglibrary.asco.org/) was searched for relevant abstracts using keywords for aRCC (similar to those used in the electronic literature database searches).

SLRs identified by searches of the electronic databases were also reviewed. Specifically, the reference lists of these reviews were scrutinized—using the patient-intervention-comparator-outcome-study type (PICOS) criteria—as a supplemental data source to identify additional relevant publications. The SLRs were not processed further in the review, to avoid double-counting of relevant studies.
ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO iCTRP), and European Medicines Agency (EMA) European public assessment reports (EPAR) were also searched for relevant abstracts or documents explicating clinical evidence on aRCC.

The inclusion/exclusion criteria for the SLRs were based on the PICOS framework, as shown Table 99. These pre-defined inclusion and exclusion criteria were used to evaluate the titles/abstracts of records identified from the searches during the first level of review. Full-text articles were then retrieved and reviewed for abstracts that were deemed relevant during the first level of review. None of the exclusion criteria and all protocol-specified inclusion criteria must have been met for a study to pass this level.

PICOS

Table 99: PICOS inclusion/Exclusion Criteria

Category	SLR 1 (efficacy/safety)
Populations	Adults with aRCC with no prior lines of systemic therapy Subpopulations defined by histology, risk level, or mutation status.

	Exclusion: paediatric populations, early stage or locally advanced disease, carcinomas other than RCC/kidney cancer, prior systemic treatment experience
Interventions	1L systemic treatments for aRCC administered alone or in combination Exclusion: second or later lines of systemic treatment, surgery, radiotherapy, adjuvant or neo-adjuvant chemotherapy, treatments for symptom management
Comparators	BSC; placebo; other 1L treatments alone or in combination (as described above) Exclusions: surgery, radiotherapy, or other comparators that are not 1L systemic treatments for aRCC
Outcomes	Efficacy: PFS, OS, ORR, PD, duration of response, and time to next treatment Safety and treatment patterns: Patients with discontinuations, treatment discontinuation due to AEs, total all-cause grade 3+ AEs, total grade 3+ TRAEs; duration on intervention and subsequent treatments Exclusions: publications that do not report any outcome of interest listed above
Study design	RCTs (a minimum of two-arm parallel, phase II or III, trial) Exclusions: Single-arm trials, non-randomized trials, and other study designs not listed for each review.
Language	English language only
Publication year	No exclusion

Table 100: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	-	04.06.2021
Medline	PubMed	-	04.06.2021
CENTRAL+	Cochrane Library	-	04.06.2021
CDSR+	Cochrane Library	-	04.06.2021

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Collaboration Central Register of Clinical Trials.

*No time frame was added for the clinical efficacy and safety literature search. The time frame only applies to the literature searches on PROs.

Table 101: Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	Searched for relevant abstracts or documents explicating clinical evidence on aRCC	05.01.2021
WHO ICTRP registry	http://apps.who.int/trialsearch/Default.aspx	Searched for relevant abstracts or documents explicating clinical evidence on aRCC	05.01.2021
EMA EPAR	https://www.ema.europa.eu/en/medicines/download-medicine-data	Searched for relevant abstracts or documents explicating clinical evidence on aRCC	05.01.2021

Abbreviations: aRCC, advanced renal cell carcinoma; CEA, cost-effectiveness analysis; EMA, European Medicines Agency; EPAR, European public assessment reports; NIH, National Institutes of Health; WHO-iCTRP, World Health Organization International Clinical Trials Registry Platform

Table 102: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched
ASCO Annual Meeting	Embase.com	For conference proceedings with abstracts indexed in electronic literature databases Embase was searched using the strategy detailed in the search strategy below	See the search strategy further down
ASCO-GU Annual Meeting	https://meetinglibrary.asco.org/	Abstracts from ASCO-GU were not indexed in Embase, and the conference website was searched for relevant abstracts using keywords for aRCC (similar to those used in the electronic literature database searches).	The same words were used for this search, as those found in the search strategy in Embase

Conference	Source of abstracts	Search strategy	Words/terms searched
AACR	Embase.com	For conference proceedings with abstracts indexed in electronic literature databases Embase was searched using the strategy detailed in the search strategy below	See the search strategy further down
AUA	Embase.com	For conference proceedings with abstracts indexed in electronic literature databases Embase was searched using the strategy detailed in the search strategy below	See the search strategy further down
EAU	Embase.com	For conference proceedings with abstracts indexed in electronic literature databases Embase was searched using the strategy detailed in the search strategy below	See the search strategy further down
ESMO	Embase.com	For conference proceedings with abstracts indexed in electronic literature databases Embase was searched using the strategy detailed in the search strategy below	See the search strategy further down

Abbreviations: AACR, American Association for Cancer Research; ASCO, American Society of Clinical Oncology; ASCO-GU, American Society of Clinical Oncology-Genitourinary; AUA, American Urological Association; EAU, European Association of Urology; ESMO, European Society for Medical Oncology;

Moreover, hand searching of the bibliography list of relevant SLRs (published since 2015) was conducted. Websites of HTA bodies were not included as part of this grey literature search. In the tables below search strings from the SLR are presented.

Embase

Table 103: Embase Clinical Efficacy and Safety

Search Number	Search String	Hits (March 27, 2019)	Hits (September 1, 2020)	Hits (January 5, 2021)	Hits (June 4, 2021)
	'kidney carcinoma'/exp/mj OR 'kidney tumor'/exp/mj OR 'renal cell carcinoma'/exp/mj	78,089	78,950	80,669	82,348
	((renal OR kidney) NEAR/2 (carcinoma* OR adenocarcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignan*)):ab,ti	84,391	92,962	95,468	97,842
	#1 OR #2	108,258	113,080	115,898	118,424
	advanced:ab,ti OR unresect*:ab,ti OR 'un resect*':ab,ti OR nonresect*:ab,ti OR ((non NEAR/2 resect*):ab,ti) OR inopera*:ab,ti OR unopera*:ab,ti OR metastas*:ab,ti OR metastat*:ab,ti OR 'end stage':ab,ti OR 'late-stage':ab,ti OR 'late stage':ab,ti OR terminal:ab,ti OR 'stage 3':ab,ti OR 'stage iii':ab,ti OR 'stage three':ab,ti OR 'stage 4':ab,ti OR 'stage iv':ab,ti OR 'stage four':ab,ti	1,738,865	1,924,540	1,982,475	2,033,037
	#3 AND #4	39,181	43,514	44,762	45,900
	'naïve':ab,ti OR 'newly diagnosed':ab,ti OR 'frontline':ab,ti OR 'front line':ab,ti OR 'first line':ab,ti OR 'first-line':ab,ti OR '1st line':ab,ti OR 'induction therapy':ab,ti OR 'primary therapy':ab,ti OR 'primary treatment':ab,ti OR ((primary:ab,ti OR initial:ab,ti OR induction:ab,ti OR naïve:ab,ti) AND (therapy:ab,ti OR treatment:ab,ti)) OR (front:ab,ti AND line:ab,ti) OR (induction:ab,ti AND therapy:ab,ti) OR untreated:ab,ti OR 'un treated':ab,ti OR 'treatment naïve':ab,ti OR 'previously untreated':ab,ti	1,626,940	1,834,227	1,893,104	1,949,493
	#5 AND #6	8,942	10,435	10,844	11,201

	'randomized controlled trial'/exp OR random*:ab,ti OR placebo:ti OR trial:ab,ti OR 'phase ii':ab,ti OR 'phase 2':ab,ti OR 'phase iii':ab,ti OR 'phase 3':ab,ti OR ((singl*:ab,ti OR doubl*:ab,ti OR trebl*:ab,ti OR tripl*:ab,ti) AND (mask*:ab,ti OR blind*:ab,ti OR dumm*:ab,ti)) OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR 'random allocation':ab,ti OR 'placebo'/exp OR 'randomization'/exp OR 'randomized controlled trial (topic)'/de	2,199,171	2,444,238	2,519,893	2,592,394
	#7 AND #8	2,738	3,255	3,414	3,539
	'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'case report'/de OR 'phase 1 clinical trial'/de OR 'nonhuman'/de OR 'short survey'/it OR 'practice guideline'/de OR 'retrospective study'/de OR ('review'/it NOT (systematic:ab,ti OR meta* OR 'mixed treatment comparison':ab,ti OR 'indirect treatment comparison' OR 'meta analysis'/exp OR 'meta analysis (topic)' OR 'systematic review (topic)' OR 'systematic review'/exp OR 'network meta-analysis'/exp) AND [2015-2019]/py)	11,683,621	12,617,739	12,952,242	13,249,168
	'conference abstract'/it NOT ('2018 annual meeting of the american association for cancer research, aacr 2018':nc OR '2018 annual meeting of the american society of clinical oncology, asco 2018':nc OR '2017 annual meeting of the american society of clinical oncology, asco':nc OR '112th annual meeting of the american urological association, aua 2017':nc OR '2018 annual meeting, american urological association, aua 2018':nc OR '42nd esmo congress, esmo 2017':nc OR '33rd annual european association of urology congress, eau 2018':nc OR '32nd annual european association of urology congress, eau 2017':nc OR '2018 genitourinary cancers symposium':nc OR '2017 genitourinary cancers symposium':nc OR '2017 annual meeting of the american society of clinical oncology, asco 2017':nc OR 'american association for cancer research international conference on translational cancer medicine, aacr 2017':nc OR '23rd annual meeting of the international society for pharmacoeconomics and outcomes research, ispor 2018':nc OR 'ispor 22nd annual international meeting':nc OR 'ispor 20th annual european congress':nc)	3,283,691	3,835,981	3,960,832	4,079,774
	#9 NOT #10 NOT #11	1,066	1,157	1,191	1,308
	#12 AND [english]/lim AND [abstracts]/lim	1,010	-	-	1,237
	#12 AND [english]/lim AND [2019-2020]/py AND [abstracts]/lim	-	204	-	-
	#12 AND [english]/lim AND [2020-2021]/py AND [abstracts]/lim	-	-	88	-
	#12 AND [english]/lim AND dc="20201201-20210604"	-	-	-	101

MEDLINE (via PubMed.com)

Table 104: MEDLINE Clinical Search

Search Number	Search String	Hits (March 27, 2019)	Hits (September 1, 2020)	Hits (January 5, 2021)	Hits (June 4, 2021)
1.	"carcinoma, renal cell"[MeSH Terms]	30,774	33,360	33,940	34,911
2.	((renal[TIAB] OR kidney[TIAB]) AND (carcinoma*[TIAB] OR adenocarcinoma*[TIAB] OR cancer*[TIAB] OR neoplasm*[TIAB] OR tumor*[TIAB] OR tumour*[TIAB] OR malignan*[TIAB]))	135,013	134,899	137,983	14121

3.	#1 OR #2	129,264	138,028	141,140	144,480
4.	advanced[TIAB] OR unresect*[TIAB] OR "un resectable"[TIAB] OR nonresect*[TIAB] OR (non[TIAB] AND resect*[TIAB]) OR inopera*[TIAB] OR unopera*[TIAB] OR metastas*[TIAB] OR metastat*[TIAB] OR "end stage"[TIAB] OR "late-stage"[TIAB] OR "late stage"[TIAB] OR terminal[TIAB] OR "stage 3"[TIAB] OR "stage iii"[TIAB] OR "stage three"[TIAB] OR "stage 4"[TIAB] OR "stage iv"[TIAB] OR "stage four"[TIAB]	1,306,824	1,430,689	1,465,058	1,503,550
5.	#3 AND #4	39,136	42,464	43,473	44,590
6.	"naïve"[TIAB] OR "newly diagnosed"[TIAB] OR "frontline"[TIAB] OR "front line"[TIAB] OR "first line"[TIAB] OR "first-line"[TIAB] OR "1st line"[TIAB] OR "induction therapy"[TIAB] OR "primary therapy"[TIAB] OR "primary treatment"[TIAB] OR ((primary[TIAB] OR initial[TIAB] OR induction[TIAB] OR naïve[TIAB]) AND (therapy[TIAB] OR treatment[TIAB])) OR (front[TIAB] AND line[TIAB]) OR (induction[TIAB] AND therapy[TIAB]) OR untreated[TIAB] OR "un treated"[TIAB] OR "treatment naïve"[TIAB] OR "previously untreated"[TIAB]	1,109,975	1,185,624	1,216,938	1,252,264
7.	#5 AND #6	7,255	7,999	8,231	8,486
8.	"Randomized Controlled Trial"[Publication Type] OR random*[ti] OR placebo[ti] OR trial[ti] OR "phase ii"[ti] OR "phase 2"[ti] OR "phase iii"[ti] OR "phase 3"[ti] OR ((singl*[ti] OR doubl*[ti] OR trebl*[ti] OR tripl*[ti]) AND (mask*[ti] OR blind*[ti] OR dumm*[ti])) OR "Double-Blind Method"[MeSH] OR "Single-Blind Method"[MeSH] OR "random allocation"[TIAB] OR "Placebos"[MeSH] OR randomization[MeSH] OR "Randomized Controlled Trials as Topic"[MeSH]	878,371	914,968	933,208	957,849
9.	#7 AND #8	1,057	1,154	1,184	1,228
10.	"Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type] OR "Clinical Conference"[Publication Type]	3,312,612	3,542,989	3,599,184	3,671,774
11.	"review"[Publication Type] NOT (systematic OR meta-analysis OR meta-analyses OR metaanalysis OR metaanalyses OR ((indirect OR mixed) AND "treatment comparison")) AND 2015:2019[pdat]	410,331	2,688,839	2,742,419	2,809,541
12.	#9 NOT #10 NOT #11	1,029	1,020	1,047	1,081
13.	#12 AND English[Language] AND hasabstract[text]	976	-	-	-
14.	#12 AND English[Language] AND 2019:2020[pdat] AND hasabstract[text]	-	105	-	-
15.	#12 AND English[Language] AND 2020:2021[pdat] hasabstract[text]	-	-	68	-
16.	#12 AND English[Language] AND dt="20201201-20210604"	-	-	-	38

Table 105: MEDLINE PROs Search

No.	Query	Results (March 27, 2019)	Results (September 1, 2020)	Results (January 5, 2021)
	"carcinoma, renal cell"[MeSH Terms]	30,774	33,278	33,940
	((renal[TIAB] OR kidney[TIAB]) AND (carcinoma*[TIAB] OR adenocarcinoma*[TIAB] OR cancer*[TIAB] OR neoplasm*[TIAB] OR tumor*[TIAB] OR tumour*[TIAB] OR malignan*[TIAB]))	135,013	134,405	137,983
	#1 OR #2	129,264	137,530	141,140

	advanced[TIAB] OR unresect*[TIAB] OR "un resectable"[TIAB] OR nonresect*[TIAB] OR (non[TIAB] AND resect*[TIAB]) OR inopera*[TIAB] OR unopera*[TIAB] OR metastas*[TIAB] OR metastat*[TIAB] OR "end stage"[TIAB] OR "late-stage"[TIAB] OR "late stage"[TIAB] OR terminal[TIAB] OR "stage 3"[TIAB] OR "stage iii"[TIAB] OR "stage three"[TIAB] OR "stage 4"[TIAB] OR "stage iv"[TIAB] OR "stage four"[TIAB]	1,306,824	1,425,098	1,465,058
	#3 AND #4	39,136	42,291	43,473
	"quality of life"[MeSH] OR qol[TIAB] OR "quality of life"[TIAB] OR hrql[TIAB] OR hrqol[TIAB] OR "patient reported outcome"[TIAB] OR "patient reported outcomes"[TIAB] OR aqol[TIAB] OR "health utility"[TIAB] OR "health utilities"[TIAB] OR "health state utility"[TIAB] OR "health state utilities"[TIAB] OR "utility score*"[TIAB] OR "utility value*"[TIAB] OR "utility valuation"[TIAB] OR "disutility"[TIAB] OR "disutilities"[TIAB] OR "standard gamble"[TIAB] OR "time trade off"[TIAB] OR "time tradeoff"[TIAB] OR "visual analog scale"[TIAB] OR "visual analogue scale"[TIAB] OR "visual analog scales"[TIAB] OR "visual analogue scales"[TIAB] OR "discrete choice experiment"[TIAB] OR qwb[TIAB] OR 15d[TIAB] OR hui[TIAB] OR sf36[TIAB] OR "sf 36"[TIAB] OR sf6[TIAB] OR "sf 6"[TIAB] OR "short form 6"[TIAB] OR "eq 5d"[TIAB] OR eq5d[TIAB] OR euroqol[TIAB] OR "euro qol"[TIAB] OR "health status"[TIAB] OR "eortc qlq c30"[TIAB] OR "functional assessment of cancer therapy"[TIAB] OR "fksi"[TIAB] OR "fact-g"[TIAB]	391,441	454,990	454,990
	"Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type] OR "Clinical Conference"[Publication Type]	3,312,612	3,533,272	3,599,184
	"review"[Publication Type] NOT (systematic OR meta-analysis OR meta-analyses OR metaanalysis OR metaanalyses OR ((indirect OR mixed) AND "treatment comparison")) AND 2015:2019[pdat]	410,331	2,679,804	2742419
	#5 AND #6 AND English[Language] AND 2009:2019[pdat] AND hasabstract[text] NOT #7 NOT #8	515	-	-
	#5 AND #6 AND English[Language] AND 2019:2020[pdat] AND hasabstract[text] NOT #7 NOT #8	-	108	-
	#5 AND #6 AND English[Language] AND 2020:2021[pdat] AND hasabstract[text] NOT #7 NOT #8	-	-	90

CENTRAL and CDSR (via Cochrane Library)

Table 106. CENTRAL and CDSR Clinical Search

Search Number	Search String	Hits (March 27, 2019)	Hits (September 1, 2020)	Hits (January 5, 2021)	Hits (June 4, 2021)
	MeSH descriptor" [Carcinoma, Renal Cell] explode all trees	792	938	956	974
	((renal OR kidney) AND (carcinoma* OR adenocarcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignan*)):ti,ab	5,004	11,199	11,642	11,896
	#1 OR #2	5,073	11,291	11,735	11,990
	(advanced OR unresect* OR "un resectable" OR nonresect* OR (non AND resect*) OR inopera* OR unopera* OR metastas* OR metastat* OR "end stage" OR "late-stage" OR "late stage" OR terminal OR "stage 3" OR "stage iii" OR "stage three" OR "stage 4" OR "stage iv" OR "stage four"):ti,ab	71,721	112,239	116,199	11,9411
	#3 AND #4	2,657	5,777	5,981	6,098

("naïve" OR "newly diagnosed" OR "frontline" OR "front line" OR "first line" OR "first-line" OR "1st line" OR "induction therapy" OR "primary therapy" OR "primary treatment" OR ((primary OR initial OR induction OR naïve) AND (therapy OR treatment)) OR (front AND line) OR (induction AND therapy) OR untreated OR "un treated" OR "treatment naïve" OR "previously untreated"):ti,ab	165,614	315,457	330,264	340,892
#5 AND #6	1,184	3,437	3,586	3,661
#7 in trials	1,170	3,422	3,571	-
#7 with Cochrane Library publication date from Jan 2019 to Sep 2020, in Cochrane trials	-	308	-	-
#7 with Cochrane Library publication date from January 2020 to Jan 2021, in Cochrane reviews	-	-	197	-
#7 with Cochrane Library publication date from January 2015 to Feb 2019, in Cochrane reviews	0	-	-	-
#7 with Cochrane Library publication date from January 2015 to Sep 2020, in Cochrane reviews	-	5	-	-
#7 with Cochrane Library publication date from January 2020 to Jan 2021, in Cochrane reviews	-	-	1	-
#7 with Cochrane Library publication date from 2021 to current, in Cochrane reviews	-	-	-	24
#8 OR #11	1,170	-	-	-
#9 OR #12	-	308	-	-
#10 OR #13	-	-	198	-

Systematic selection of studies (clinical SLR)

Search results were uploaded to Distiller Systematic Review (DSR) software, an internet-based program that facilitates collaboration among reviewers during the study selection process. The team developed and tested screening questions and forms for level 1 (abstract) and level 2 (full-text) assessments based on the inclusion and exclusion criteria of each review. Citation abstracts and full-text articles were uploaded with screening questions to DSR. Prior to the formal screening process, a calibration exercise was conducted to pilot and refine the screening questions.

The SLRs followed a two-stage screening process:

Level 1: Titles and abstracts of studies identified by the search strategies were reviewed independently by two researchers to determine eligibility according to the inclusion and exclusion criteria. Disagreements between the reviewers were resolved by a third reviewer, as needed.

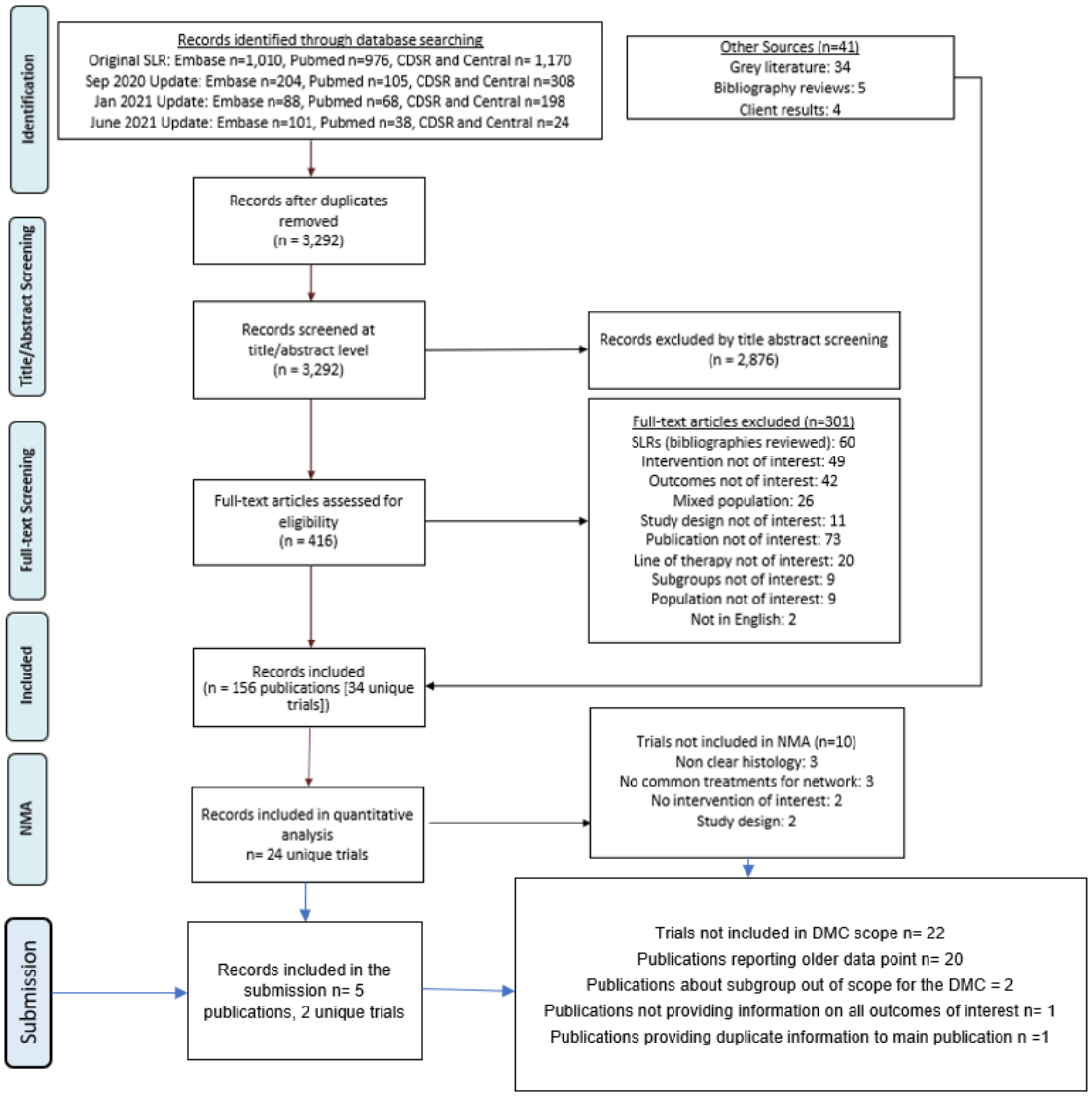
Level 2: All full-text articles deemed eligible during level 1 screening were reviewed independently by two researchers to determine eligibility according to the inclusion and exclusion criteria. Disagreements between the reviewers were resolved by a third reviewer, as needed.

After identifying the articles recommended for inclusion (in accordance with the PICOS criteria), lists of accepted studies and articles excluded at the full-text screening level were gathered. The flow of studies through the SLRs are documented in PRISMA diagrams, which map out the number of records identified, included, and excluded studies, and the reason for exclusion. Separate study listings and PRISMA diagrams are provided for each SLR topic.

The electronic database searches yielded 4,290 results. Grey literature searches identified 34 results. Nine results were included from additional hand-searches, including 5 from bibliography reviews and 4 slide deck containing data sourced directly from Eisai/Merck. After the removal of duplicates, 3,292 unique titles and abstracts were screened, of which 416 were considered admissible for full-text review. Ultimately, 156 publications (34 unique studies) were included.

This is presented in Figure 74.

Figure 74: PRISMA Study Flow Diagram for Clinical Efficacy and Safety reporting studies included in SLR, selected for the NMA and then selected for this submission.



Abbreviation: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Collaboration Central Register of Clinical Trials; SLR, systematic literature review

The summary of the studies selected is presented in Table 107 and the quality assessment of included studies is presented in Table 109.

Studies included in the clinical SLR

Details of the study design for the 34 included randomised trials on efficacy and safety outcomes are described in Table 107. The majority were open-label trials (28 studies), and the remainder were either double-blinded (four studies; [105-108] or did not specify whether blinding was performed (two studies; [109, 110]. Seventeen of the RCTs were phase III and 15 RCTs were phase II. Two studies [110, 111] did not report study phase. The majority of trials enrolled only patients with predominantly clear-cell histology or with a clear-cell component, but four studies (ASPEN [112], ESPN [113], Bergmann 2020 and SAVOIR [114]) limited enrollment to patients with non-clear cell RCC. Most studies enrolled mixed risk populations, but three studies (CABOSUN [115]), Global ARCC [109] and TemPa [116]) evaluated patients with intermediate- or poor-risk RCC. The largest included study was COMPARZ (N=1,100 [39]) and most studies randomized >100 patients, with the exception of ESPN (N=72 [113]), Lissoni 1993 (N=30) and Bergmann 2020 (N=22). Most studies recruited patients across multiple continents (19 studies), and the geographic location for the remaining studies were primarily based in Europe (8 studies), North America (5 studies). Sunitinib was the most commonly studied treatment, acting as an intervention or comparator in 16 studies, followed by pazopanib (eight studies), interferon (IFN) alfa-2a (seven studies), sorafenib (seven studies), and bevacizumab (seven studies).

Table 107. Summary of Study Design for RCC studies

Study	Country	Study Design	Years of Enrollment/Data Collection	Patient Population	Sample Size (Randomized)	Treatments (Intervention Followed by Comparator[s])	Duration of Follow-up	Available Outcomes	
								Efficacy	Safety
ASPEN [112, 117]	US, Canada, and the UK (17 sites)	Phase II RCT, open-label	September 2010 to October 2013	aRCC with non-clear-cell pathology	108	Everolimus Sunitinib	Median (IQR): 13 (6–22) months	?	?
AVOREN [106, 118, 119]	International (18 countries, 101 sites)	Phase III RCT, double-blind	Enrollment: June 2004 to October 2005 Data collection: June 2004 to September 2008	Previously untreated, predominantly clear-cell mRCC	649	Bevacizumab + IFN alfa-2a IFN alfa-2a + placebo	At primary analysis: Bevacizumab + IFN alfa-2a, median (range): 13.3 (0–25.6) months IFN alfa-2a + placebo, median (range): 12.8 (0–24.2) months At final analysis for OS: Bevacizumab + IFN alfa-2a, median: 22.9 months IFN alfa-2a + placebo, median: 20.6 months	?	?
BeST [120]	US	Phase II RCT, open-label	September 2007 to December 2010	Metastatic kidney cancer	361	Bevacizumab + temsirolimus Bevacizumab + sorafenib Sorafenib + temsirolimus Bevacizumab	NR	?	?
Bukowski, 2007 [105]	US (21 sites)	Phase II RCT, double-blind	March 2004 to October 2004	mRCC, predominantly clear-cell histology (>50%)	104	Bevacizumab + erlotinib Bevacizumab	Median: 9.8 months	?	?
CABOSUN [38, 115]	US	Phase II RCT, open-label	July 2013 to April 2015	Untreated clear-cell mRCC with ECOG performance score of 0–2 and IMDC intermediate or poor risk	157	Cabozantinib Sunitinib	At primary analysis, median: 21.4 months At final analysis for OS, median: 34.5 months At final analysis for PFS, median: 25 (IQR: 21.9–30.9) months	?	?
CALGB 90206 [121, 122]	US and Canada	Phase III RCT, open-label	October 2003 to July 2005	Previously untreated, clear-cell mRCC	732	Bevacizumab + IFN alfa-2b IFN alfa-2b	24 months	?	?
CheckMate 214 [68]	International (75 sites in 28 countries): US: n=307 Canada and Europe: n=400 Rest of world: n=389	Phase III RCT, open-label	Enrollment: October 2014 to February 2016 Database lock: August 2017	Previously untreated aRCC with a clear-cell component	1,096	Nivolumab + ipilimumab Sunitinib	Multiple data-cuts (48, 42, 30, and 24 months)	?	?
CLEAR (HOPE 307/KN-581) [7]	International	Phase III, RCT, open label	October 2016 to July 2019	Patients with treatment naïve RCC with a clear-cell component	1069	Lenvatinib + pembrolizumab Lenvatinib + everolimus Sunitinib	Median survival follow-up: 33.4 months for Sunitinib & 33.7 months for LEN+PEM ; 31 March 2021	?	?
COMPARZ [39, 123]	International (14 countries): Europe: n=310 North America: n=382 Asia: n=367 Australia: n=51	Phase III RCT, open-label	August 2008 to September 2011	Previously untreated, advanced or clear-cell mRCC	1,110	Pazopanib Sunitinib	NR	?	?

Study	Country	Study Design	Years of Enrollment/Data Collection	Patient Population	Sample Size (Randomized)	Treatments (Intervention Followed by Comparator[s])	Duration of Follow-up	Available Outcomes	
								Efficacy	Safety
CROSS-J-RCC [124, 125]	NR	Phase III RCT, open-label	February 2010 to July 2012	Treatment-naïve with clear-cell mRCC	124[a]	Sunitinib (1L)[b] Sorafenib (1L)[b]	NR, longest outcome reported (median total PFS): 38.4 months	?	?
Escudier, 2009 [126, 127]	International: Germany (6 sites), US (7 sites), France (5 sites), Poland (6 sites), Russia (3 sites), UK (1 sites) and Ukraine (3 sites)	Phase II RCT, open-label	Enrollment: June 2005 to September 2005 Data collection: June 2005 to March 2009	Unresectable and/or mRCC, predominantly clear cell, with no prior systemic therapy	189	IFN alfa-2a (1L)[b] Sorafenib (1L)[b]	24 months	?	?
ESPN [113]	NR	Phase II RCT, open-label	Enrollment: September 2010 to November 2013 Final analysis: May 2014	Non-clear cell mRCC, or clear-cell RCC with >20% sarcomatoid features	72	Everolimus Sunitinib	At final analysis, median: 23.6 (95% CI: 15.7, 30.2) months	?	?
Global ARCC [109, 128]	International: US, Western Europe, Australia, Canada, Asia-Pacific, Eastern Europe, Africa, and South America (153 sites total)	Phase III RCT, blinding NR	July 2003 to April 2005	Previously untreated, poor-prognosis mRCC	626	Temsirolimus IFN alfa-2a IFN alfa-2a + temsirolimus	Up to 80 months for final analysis	?	?
Hutson, 2013 [129-131]	International: Ukraine: n=61 Russia: n=58 India: n=34	Phase III RCT, open-label	Enrollment: June 2010 to April 2011 Primary DCO: July 2012	Confirmed mRCC with a clear-cell component	288	Axitinib Sorafenib	23 months	?	?
IMmotion150 [12, 132]	US and Europe (96 sites total)	Phase II RCT, open-label	Enrollment: January 2014 to March 2015 Final DCO: April 2017	Treatment-naïve mRCC	305	Atezolizumab + bevacizumab Sunitinib Atezolizumab	At survival follow-up, median: 20.7 months At final analysis, median: 25.7 months	?	?
IMmotion151 [133]	NR	Phase III RCT, blinding NR	NR	Untreated mRCC	915	Atezolizumab + bevacizumab Sunitinib	Median: 15 months	?	?
JAVELIN Renal 101 [134, 135]	International US: n=258 Canada and Western Europe: n=256 Rest of world: n=372	Phase III RCT, open-label	March 2016 to December 2017	Previously untreated with aRCC	886	Avelumab + axitinib Sunitinib	DCOoff April 2020, Minimum of 13 months	?	?
KEYNOTE-426 [136, 137]	International North America: n=207 Western Europe: n=210 Rest of world: n=444	Phase III RCT, open-label	October 2016 to January 2018	Previously untreated clear-cell aRCC	861	Pembrolizumab + axitinib Sunitinib	Median: 42.8 months (Range 35.6- 50.6 months)	?	?
Lissoni, 1993[110]	Italy	RCT, blinding NR Phase NR	NR	mRCC	30	IL-2 IL-2 + IFN alfa-2b	Mininum follow-up: 12 months	?	?
Motzer, 2007[43, 44, 138]	International: Australia, Brazil, Canada, France, Germany, Italy, Poland, Russia, Spain, UK, US (101 centers total)	Phase III RCT, open-label	August 2004 to October 2005	Treatment-naïve with, clear-cell mRCC	750	Sunitinib IFN alfa-2a	Final analysis: 123 weeks	?	?

Study	Country	Study Design	Years of Enrollment/Data Collection	Patient Population	Sample Size (Randomized)	Treatments (Intervention Followed by Comparator[s])	Duration of Follow-up	Available Outcomes	
								Efficacy	Safety
Negrier, 1998[139]	France	Phase III RCT, open-label	March 1992 to July 1995	mRCC	425	IL-2 + IFN alfa-2a IL-2 IFN alfa-2a	Median: 39 months	?	?
PERCY Quattro [111]	France (44 sites)	RCT, open-label Phase NR	January 2000 to July 2004	mRCC of intermediate prognosis	492	IFN alfa-2a + IL-2 Medroxy-progesterone IFN alfa-2a IL-2	Median: 29.2 (range: 0–54.6) months	?	?
RECORD-2 [140, 141]	International (108 sites)	Phase II RCT, open-label	NR	Predominantly clear-cell, mRCC	365	Bevacizumab + everolimus Bevacizumab + IFN alfa-2a	Up to 2 years for final analysis	?	?
RECORD-3 [142, 143]	International: Argentina, Australia, Brazil, Canada, Denmark, France, Germany, Hong Kong, Italy, Republic of Korea, Mexico, Netherlands, Peru, Spain, Taiwan, Thailand, Turkey, UK, US	Phase II RCT, open-label	Enrollment: October 2009 to June 2011 Primary DCO: September 2012	mRCC (clear cell or non-clear cell, with or without nephrectomy) receiving 1L therapy	471	Everolimus Sunitinib	NR	?	?
Rini, 2013 [107, 144]	International: Czech Republic, Germany, Japan, Russia, Spain, and US (49 sites total)	Phase II RCT, double-blind	September 2009 to February 2011	Previously untreated with mRCC	112	Axitinib à axitinib titration Axitinib à placebo titration	Axitinib à axitinib titration, median: 26.5 (IQR: 24.3–28.9) months Axitinib à placebo titration, median: 26.4 (IQR: 25.0–28.6) months	?	?
ROPETAR [145]	Netherlands (15 sites)	Phase II RCT, open-label	September 2012 to April 2014	Locally advanced or clear-cell mRCC	101	Pazopanib (1L) Everolimus + pazopanib (rotating)	At least 1 year (longest timepoint, median second-line PFS: 20.2 months)	?	?
SWITCH [146]	Germany, Austria, and Netherlands (72 sites total)	Phase III RCT, open-label	February 2009 to December 2011	aRCC/mRCC	365	Sorafenib (1L)[b] Sunitinib (1L)[b]	Mean: 10.3 months	?	?
SWITCH II [147]	Germany, Austria, and Netherlands (67 sites total)	Phase III RCT, open-label	June 2012 to November 2016	aRCC/mRCC	377	Sorafenib (1L)[b] Pazopanib (1L)[b]	NR, longest reported outcome (median total PFS): 12.9 months	?	?
TemPa [116]	NR	Phase II RCT, blinding NR	Through September 2017	Treatment-naïve with clear-cell aRCC with intermediate or poor-risk disease	NR	Pazopanib Temsirolimus	NR	?	?
TIVO-1 [148]	International (15 countries, 76 sites total): Central/Eastern Europe: n=457 North America/Western Europe: n=40 Rest of world: n=20	Phase II RCT, open-label	Enrollment: February 2010 to August 2010 DCO: December 2011	mRCC, with a clear-cell component, prior nephrectomy, measurable disease, and 0 or 1 prior therapies for mRCC	Overall: 517 Treatment-naïve: 362	Tivozanib Sorafenib	NR	?	?

Study	Country	Study Design	Years of Enrollment/Data Collection	Patient Population	Sample Size (Randomized)	Treatments (Intervention Followed by Comparator[s])	Duration of Follow-up	Available Outcomes	
								Efficacy	Safety
VEG105192 [108]	International: Europe, Asia, South America, North Africa, Australia, and New Zealand (80 sites total)	Phase III RCT, double-blind	Enrollment: April 2006 to April 2007 Primary DCO: May 2007 Final DCO: March 2010	Clear-cell or predominantly clear-cell, locally aRCC and/or mRCC	435	Pazopanib Placebo	NR		
BIONIKK [64]	France	Phase II, RCT, open-label	June 2017 to July 2019	Patients with metastatic ccRCC	202	Nivolumab Nivolumab+ Ipilimumab Sunitinib Pazopanib	Median: 16 months		
Bergmann 2020[149]	Central Europe	Phase IIa, RCT, open-label	NR	Previously untreated patients with advanced non-clear cell RCC	22	Temsirolimus sunitinib	NR		
CheckMate 9ER [71, 150]	International	Phase III, RCT, open-label	NR	Patients with advanced or metastatic clear-cell RCC	651	Nivolumab + cabozantinib Sunitinib	Multiple data-cuts (48, 42, 30, and 24 months)		

Studies excluded from the clinical SLR

The list of studies excluded from the SLR is presented in detail in Table 108.

Table 108: Excluded from the SLR 1 (Clinical efficacy and Safety)

ID	Bibliography	Exclusion Reason
4016	Euctr, I. T.. Targeted therapy with or without nephrectomy in metastatic renal cell carcinoma. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2015. 2015. #volume#:#pages#	Publication type not of interest
4028	Chen, R. C.,Choueiri, T. K.,Feuilly, M.,Meng, J.,Lister, J.,Marteau, F.,Falchook, A. D.,Morris, M. J.,George, D. J.,Feldman, D. R.. Quality-adjusted survival with first-line cabozantinib or sunitinib for advanced renal cell carcinoma in the CABOSUN randomized clinical trial (Alliance). Cancer. 2020. #volume#:#pages#	Outcomes not of interest
4075	Procopio, G.,Cognetti, F.,Miceli, R.,Milella, M.,Mosca, A.,Chiuri, V. E.,Bearz, A.,Morelli, F.,Ortega, C.,Atzori, F.,Donini, M.,Passalacqua, R.,Mennitto, A.,Sepe, P.,Martinetti, A.,Montone, R.,Apollonio, G.,Guadalupi, V.,Verzoni, E.,Claps, M.. Updated data on patients (pts) with metastatic renal cell carcinoma (mRCC) treated with sorafenib (SOR) vs observation (obs) after radical metastasectomy in the RESORT trial. Annals of oncology. 2020. 31:S574-S575	Outcomes not of interest
4077	Choueiri, T. K.,Powles, T.,Burotto, M.,Bourlon, M. T.,Zurawski, B.,Oyervides Juarez, V. M.,Hsieh, J. J.,Basso, U.,Shah, A. Y.,Suarez, C.,Hamzaj, A.,Barrios, C. H.,Richardet, M.,Pook, D.,Tomita, Y.,Escudier, B.,Zhang, J.,Simsek, B.,Apolo, A. B.,Motzer, R. J.. Nivolumab + cabozantinib vs sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase III CheckMate 9ER trial. Annals of oncology. 1159. 31:#pages#	Publication type not of interest
4128	Hofmann, F.,Hwang, E. C.,Lam, T. B.,Bex, A.,Yuan, Y.,Marconi, L. S.,Ljungberg, B.. Targeted therapy for metastatic renal cell carcinoma. The Cochrane database of systematic reviews. 2020. 10:CD012796	SLRs (bibliographies reviewed)
4129	Thana, M.,Wood, L. A.. First-Line Immune Checkpoint Inhibitor-Based Therapy for Metastatic Renal Cell Carcinoma: A Systematic Review. Kidney Cancer. 2020. 4:81-92	SLRs (bibliographies reviewed)
4132	Heo, J. H.,Park, C.,Ghosh, S.,Park, S. K.,Zivkovic, M.,Rascati, K. L.. A network meta-analysis of efficacy and safety of first-line and second-line therapies for the management of metastatic renal cell carcinoma. Journal of Clinical Pharmacy and Therapeutics.. 2020. #volume#:#pages#	SLRs (bibliographies reviewed)
4136	Kang, H. J.,Lee, S.. Tolerability of Alternative Dosing Schedules for Sunitinib: A Systematic Review and Meta-Analysis. Yonsei medical journal. 2020. 61:837-843	SLRs (bibliographies reviewed)
4139	Cao, G.,Wang, Z.,Tian, X.,Zhang, C.,Wu, X.,Zhang, H.,Jing, G.,Yan, T.. What is the optimum systemic treatment for advanced/metastatic renal cell carcinoma of favourable, intermediate and poor risk, respectively? A systematic review and network meta-analysis. BMJ Open. 2020. 10:#pages#	SLRs (bibliographies reviewed)
3005	Olid et al. Cabozantinib for the treatment of advanced renal cell carcinoma in treatment-naive adults. European journal of clinical pharmacy. 2020. 21160-163	Publication type not of interest
104	Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma: results from a phase III randomized, open-label, multicenter trial. Clinical advances in hematology & oncology. 2012. 10(9):4-6	Mixed Population
132	Ahrens M, Scheich S, Gokbuget N, et al. A randomised phase II study of nivolumab plus ipilimumab versus standard of care in previously untreated and advanced non-clear cell renal cell carcinoma (SUNIFORECAST). Oncology research and treatment. 2018. 4173-	Outcomes not of interest
241	Asakawa M, Maekawa T, Umeda M, et al. Comparative clinical study of single and combination therapy of human lymphoblastoid interferon (HLBI) with 5-FU in the treatment of advanced renal cell carcinoma. Hinyokika kiyo. Acta urologica japonica. 1989. 35(8):1451-1455	Not in English
245	Atkins MB, Gravis G, Drosik K, et al. Trebananib (AMG 386) in combination with sunitinib in patients with metastatic renal cell cancer: An open-label, multicenter, phase II study. Journal of Clinical Oncology. 2015. 33(30):3431-3438	Study design not of interest
253	Aulitzky WE, Aulitzky W, Ellerhorst J, et al. Intermittent low-dose IFN gamma treatment for metastatic renal cell carcinoma: Analysis of factors predicting clinical response and long-term survival. Onkologie. 1995. 18(4):339-345	Study design not of interest
290	Bay JO, Negrier S, Perol D, et al. Updated results on long-term overall survival (OS) of the French randomized phase II trial TORAVA in metastatic renal cell carcinoma (mRCC) patients. Journal of clinical oncology. 2012. 30(15 SUPPL. 1):	Mixed Population
316	Bergmann L, Grunwald V, Maute L, et al. A prospective randomized phase-II trial with temsirolimus vs. Sunitinib in non-clear renal cell carcinoma. A study of the CESAR central european society for anticancer drug research-EWIV and interdisciplinary renal cell carcinoma group of the German cancer society (IAGN). European journal of cancer.. 2015. 51S517	Mixed Population
352	Bjarnason GA, Kollmannsberger CK, Ahmad Q, et al. EFFects of pazopanib (PAZ) and sunitinib (SUN) dose modification on efficacy and safety in patients with metastatic renal cell carcinoma (mRCC) from COMPARZ. Journal of Clinical Oncology. 2017. 35(15):	Subgroups not of interest
355	Blagoev KB, Wilkerson J, Stein WD, et al. Effect of sunitinib (SU) administration on post-treatment survival in patients with metastatic renal cell carcinoma (mRCC) treated on the upfront randomized phase III trial of sunitinib or interferon alfa (IFN). Journal of clinical oncology. 2011. 29(15 SUPPL. 1):	Outcomes not of interest

395	Broom RJ, Hinder V, Sharples K, et al. Everolimus and zoledronic acid in patients with renal cell carcinoma with bone metastases: A randomized first-line phase II trial. Clinical Genitourinary Cancer. 2015. 13(1):50-58	Intervention not of interest
396	Broom RJ, Hinder V, Sharples K, et al. RAD001 and zoledronic acid in patients with renal cell carcinoma with bone metastases (RAZOR): a randomized phase II trial. Journal of clinical oncology. 2013. 31(6 SUPPL. 1):	Intervention not of interest
400	Bukowski RM. Cytokine combinations: Therapeutic use in patients with advanced renal cell carcinoma. Seminars in Oncology. 2000. 27(2):204-212	Publication type not of interest
456	Cella D, Bushmakin AG, Cappelleri JC, et al. Comparison of health-related quality of life (HRQoL) in patients reporting the same adverse event (AE) fatigue on different treatments. European journal of cancer. 2011. 47S233	Outcomes not of interest
464	Cella D, Ivanescu C, Skaltsa K, et al. Treatment benefit of tivozanib hydrochloride versus sorafenib on health-related quality of life (HRQoL) among patients (pts) with advanced/metastatic renal cell carcinoma (mRCC): tIVO-1 study results. Journal of clinical oncology. 2013. 31(6 SUPPL. 1):	Outcomes not of interest
465	Cella D, Li JZ, Cappelleri JC, et al. Quality of life in patients with metastatic renal cell carcinoma treated with sunitinib or interferon alfa: Results from a phase III randomized trial. Journal of Clinical Oncology. 2008. 26(22):3763-3769	Outcomes not of interest
478	Chang X, Zhang F, Liu T, et al. Comparative efficacy and safety of first-line treatments in patients with metastatic renal cell cancer: A network meta-analysis based on phase 3 RCTs. Oncotarget. 2016. 7(13):15801-15810	SLRs (bibliographies reviewed)
489	Chen RC, Feuilly M, Meng J, et al. Quality-adjusted time without symptoms or toxicity (Q-TWiST): Analysis of cabozantinib (Cabo) vs sunitinib (Sun) in patients with advanced renal cell carcinoma (aRCC) of intermediate or poor risk (Alliance A031203). Journal of Clinical Oncology. 2018. 36(15):	Outcomes not of interest
507	Choueiri TK, Cheng S, Qu AQ, et al. Carbonic anhydrase IX as a potential biomarker of efficacy in metastatic clear-cell renal cell carcinoma patients receiving sorafenib or placebo: analysis from the treatment approaches in renal cancer global evaluation trial (TARGET). Urol Oncol. 2013. 31(8):1788-93	Line of therapy not of interest
524	Choueiri TK, Rini BI, Cosgriff T, et al. JAVELIN renal 101: a phase 3 study of avelumab in combination with axitinib vs sunitinib as first-line treatment for patients with advanced renal cell carcinoma (aRCC). BJU international. 2016. 11829-30	Outcomes not of interest
668	Dufies M, Giuliano S, Viotti J, et al. CXCL7 is a predictive marker of sunitinib efficacy in clear cell renal cell carcinomas. British journal of cancer. 2017. 117(7):947-953	SLRs (bibliographies reviewed)
678	Ebbinghaus SW, Hussain M, Tannir NM, et al. A randomized phase 2 study of the thrombospondin-mimetic peptide ABT-510 in patients with previously untreated advanced renal cell carcinoma. Annual meeting proceedings of the american society of clinical oncology. 2005. 23404	Intervention not of interest
692	Eisen T, Shparyk Y, MacLeod NJ, et al. Effects of nintedanib (BIBF 1120) on QTc interval in previously untreated patients with renal cell cancer (RCC): results from an open-label, phase II study. Journal of clinical oncology. 2012. 30(15 SUPPL. 1):	Outcomes not of interest
724	Escudier B, Michaelson MD, Motzer RJ, et al. Axitinib versus sorafenib in advanced renal cell carcinoma: Subanalyses by prior therapy from a randomised phase III trial. British Journal of Cancer. 2014. 110(12):2821-2828	Line of therapy not of interest
728	Escudier B, Porta C, Bono P, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES study. Journal of Clinical Oncology. 2014. 32(14):1412-1418	Mixed Population
738	Escudier BJ, Cella D, Gschwend JE, et al. A randomized double-blind cross-over patient preference study of pazopanib versus sunitinib in treatment-naive locally advanced or metastatic renal cell carcinoma (mRCC). Journal of clinical oncology. 2010. 28(Suppl 15):40	Intervention not of interest
769	Fernández-Pello Montes S, Hofmann F, Tahbaz R, et al. A systematic review and meta-analysis comparing the effectiveness and adverse effects of different systemic treatments for non-clear cell renal cell carcinoma. European Urology, Supplements. 2018. 17(2):e1733-e1734	Study design not of interest
774	Figlin R, Nicolette C, Tannir N, et al. Interim analysis of the phase 3 ADAPT trial evaluating rocapuldencel-T (AGS-003), an individualized immunotherapy for the treatment of newly-diagnosed patients with metastatic renal cell carcinoma (mRCC). Annals of Oncology. 2017. 28v404	Intervention not of interest
778	Figlin RA, Wood CG. Patient identification and eligibility insights in the synchronous mRCC population: an update from the ongoing ADAPT* phase 3 study experience. BJU international.. 2014. 1147	Outcomes not of interest
780	Fischer Von Weikersthal L, Vervenne WL, Goebell PJ, et al. Phase III randomized sequential open-label study to evaluate efficacy and safety of sorafenib (SO) followed by sunitinib (SU) versus sunitinib followed by sorafenib in patients with advanced / metastatic renal cell carcinoma without prior systemic therapy (SWITCH Study)-Safety interim analysis results. Onkologie.. 2012. 35237	Outcomes not of interest
782	Fishman MN, Tomshine J, Fulp WJ, et al. A systematic review of the efficacy and safety experience reported for sorafenib in advanced renal cell carcinoma (RCC) in the post-approval setting. PLoS ONE. 2015. 10(4):	SLRs (bibliographies reviewed)
787	Flaherty KT, Manola JB, Pins M, et al. BEST: A randomized phase II study of vascular endothelial growth factor, RAF kinase, and mammalian target of rapamycin combination targeted therapy with bevacizumab, sorafenib, and temsirolimus in advanced renal cell carcinoma - A trial of the ECOG-ACRIN cancer research group (E2804). Journal of Clinical Oncology. 2015. 33(21):2384-2391	Mixed Population

923	Guo J, Jin J, Huang Y, et al. Comparison of PFS and safety for Asian compared to North American and European populations in the phase III trial of pazopanib versus sunitinib in patients with treatment-naive RCC (COMPARZ). Journal of clinical oncology. 2013. 31(6 SUPPL. 1):	Subgroups not of interest
924	Guo J, Jin J, Oya M, et al. Safety of pazopanib and sunitinib in treatment-naive patients with metastatic renal cell carcinoma: Asian versus non-Asian subgroup analysis of the COMPARZ trial. Journal of Hematology and Oncology. 2018. 11(1):	Subgroups not of interest
937	Hahn AW, Hale P, Maughan BL, et al. Optimal first-line treatment of metastatic renal-cell carcinoma: A network meta-analysis. Kidney Cancer. 2018. 2(2):115-121	SLRs (bibliographies reviewed)
939	Hahn RG, Bauer M, Wolter J. Phase II study of single-agent therapy with megestrol acetate, VP-16-213, cyclophosphamide, and dianhydrogalactitol in advanced renal cell cancer. Cancer Treatment Reports. 1979. 63(3):513-515	Mixed Population
941	Hahn RG, Temkin NR, Savlov ED. Phase II study of vinblastine, methyl-CCNU, and medroxyprogesterone in advanced renal cell cancer. Cancer Treatment Reports. 1978. 62(7):1093-1095	Mixed Population
945	Hainsworth JD, Shipley DL, Reeves Jr J, et al. High-dose bevacizumab in the treatment of patients with advanced clear cell renal carcinoma: A phase II trial of the sarah cannon oncology research consortium. Clinical Genitourinary Cancer. 2013. 11(3):283-289.e1	Mixed Population
949	Halabi S, Rini B, Escudier B, et al. Progression-free survival as a surrogate endpoint of overall survival in patients with metastatic renal cell carcinoma. Cancer. 2014. 120(1):52-60	SLRs (bibliographies reviewed)
950	Hale P, Hahn AW, Rathi N, et al. Treatment of metastatic renal cell carcinoma in older patients: A network meta-analysis. Journal of Geriatric Oncology. 2019. 10(1):149-154	SLRs (bibliographies reviewed)
963	Harmon CS, Figlin RA, Hutson TE, et al. Circulating protein biomarkers of sunitinib (SU) and interferon-alpha (IFN-alpha) efficacy in treatment (Tx)-naive patients (pts) with metastatic renal cell carcinoma (mRCC). Journal of clinical oncology. 2011. 29(15 SUPPL. 1):	Outcomes not of interest
977	Hawkins RE, Gore M, Shparyk Y, et al. A randomized phase II/III study of naptumomab estafenatox + IFNalpha versus IFNalpha in renal cell carcinoma: final analysis with baseline biomarker subgroup and trend analysis. Clinical cancer research. 2016. 22(13):3172-3181	Mixed Population
979	Hawkins RE, Gore ME, Shparyk Y, et al. A randomized phase II/III study of naptumomab estafenatox plus IFN-alpha versus IFN-alpha in advanced renal cell carcinoma. Journal of clinical oncology. 2013. 31(15 SUPPL. 1):	Mixed Population
981	Hegde PS, Jubb AM, Chen D, et al. Predictive impact of circulating vascular endothelial growth factor in four phase III trials evaluating bevacizumab. Clinical cancer research. 2013. 19(4):929-937	Study design not of interest
989	Heo JH, Park C, Rascati KL. Indirect comparisons of safety of targeted therapies for metastatic renal cell carcinoma: A network meta-analysis. Value in Health. 2017. 20(5):A87	Study design not of interest
1014	Hsieh JJ, Chen D, Wang PI, et al. Identification of efficacy biomarkers in a large metastatic renal cell carcinoma (mRCC) cohort through next-generation sequencing (NGS): results from RECORD-3. BJU international. Conference: 14th international kidney cancer symposium. Miami, FL united states. Conference start: 20151106. Conference end: 20151107. Conference publication: (var.pagings). 2015. 11613	Mixed Population
1029	Hurwitz HI, Douglas PS, Middleton JP, et al. Analysis of early hypertension and clinical outcome with bevacizumab: results from seven phase III studies. Oncologist. 2013. 18(3):273-280	Study design not of interest
1044	Hutson TE, Nosov D, Eisen T, et al. Subgroup analyses of a phase III trial comparing tivozanib hydrochloride versus sorafenib as initial targeted therapy for patients (pts) with metastatic renal cell carcinoma (mRCC). Journal of clinical oncology. 2013. 31(6 SUPPL. 1):	Subgroups not of interest
1047	Iacovelli R, Ciccarese C, Bria E, et al. Immunotherapy versus standard of care in metastatic renal cell carcinoma. A systematic review and meta-analysis. Cancer Treatment Reviews. 2018. 70112-117	SLRs (bibliographies reviewed)
1110	Kang SK, Volodarskiy A, Ohmann EL, et al. Efficacy and Safety of Selective Vascular Endothelial Growth Factor Receptor Inhibitors Compared with Sorafenib for Metastatic Renal Cell Carcinoma: A Meta-analysis of Randomised Controlled Trials. Clinical Oncology. 2016. 28(5):334-341	SLRs (bibliographies reviewed)
1114	Karakiewicz PI, Sun M, Bellmunt J, et al. Prediction of progression-free survival rates after bevacizumab plus interferon versus interferon alone in patients with metastatic renal cell carcinoma: Comparison of a nomogram to the Motzer criteria. European Urology. 2011. 60(1):48-56	Outcomes not of interest
1127	Kattan MW, Sternberg CN, Mehmud F, et al. Development and validation of a prognostic nomogram for progression-free survival in patients with advanced renal cell carcinoma treated with pazopanib. Oncology (Switzerland). 2015. 89(4):235-241	Outcomes not of interest
1145	Kilonzo M, Hislop J, Elders A, et al. Pazopanib for the first-line treatment of patients with advanced and/or metastatic renal cell carcinoma: A NICE single technology appraisal. PharmacoEconomics. 2013. 31(1):15-24	Publication type not of interest
1164	Knox JJ, Kay AC, Schiff E, et al. First-line everolimus followed by second-line sunitinib versus the opposite treatment sequence in patients with metastatic renal cell carcinoma (mRCC). Journal of clinical oncology. 2010. 28(Suppl 15):39	Outcomes not of interest
1206	Lalani AKA, McGregor BA, Albiges L, et al. Systemic Treatment of Metastatic Clear Cell Renal Cell Carcinoma in 2018: Current Paradigms, Use of Immunotherapy, and Future Directions. European Urology. 2019. 75(1):100-110	SLRs (bibliographies reviewed)
1211	Lamuraglia M, Raslan S, Elaidi R, et al. mTOR-inhibitor treatment of metastatic renal cell carcinoma: contribution of Choi and modified Choi criteria assessed in 2D or 3D to evaluate tumor response. European radiology. 2016. 26(1):278-285	Line of therapy not of interest

1233	Lavin PT, Maar R, Franklin M, et al. Autolymphocyte therapy for metastatic renal cell carcinoma: initial clinical results from 335 patients treated in a multisite clinical practice. Transplantation proceedings. 1992. 24(6):3059-3064	Intervention not of interest
1234	Le Saux O, Freyer G, Négrier S. First-Line Treatments for Poor-Prognosis Metastatic Renal Cell Carcinoma: Experts' Prescribing Practices and Systematic Literature Review. Clinical Drug Investigation. 2016. 36(5):389-399	SLRs (bibliographies reviewed)
1242	Lee CP, Patel PM, Selby PJ, et al. Randomized phase II study comparing thalidomide with medroxyprogesterone acetate in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology. 2006. 24(6):898-903	Mixed Population
1249	Lei Y, Yildiz S, Chen M. Re: james J. Hsieh, David Chen, Patricia I. Wang, et al. Genomic Biomarkers of a Randomized Trial Comparing First-line Everolimus and Sunitinib in Patients with Metastatic Renal Cell Carcinoma. Eur Urol. In press. http: //dx.doi.org/10.1016/j.eururo.2016.10.007. European urology. 2017. (no pagination)	Publication type not of interest
1274	Lister J, Schmidt E, Marteau F, et al. Cabozantinib versus standard of care in the first-line treatment of advanced/metastatic renal cell carcinoma: A network meta-analysis. Value in Health. 2018. 21S16	Study design not of interest
1355	McDermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology. 2005. 23(1):133-141	Mixed Population
1368	Méndez-Vidal MJ, Á Molina, Anido U, et al. Pazopanib: Evidence review and clinical practice in the management of advanced renal cell carcinoma. BMC Pharmacology and Toxicology. 2018. 19(1):	SLRs (bibliographies reviewed)
1427	Motzer RJ, Barrios CH, Kim TM, et al. Record-3: phase II randomized trial comparing sequential first-line everolimus (EVE) and second-line sunitinib (SUN) versus first-line SUN and second-line EVE in patients with metastatic renal cell carcinoma (mRCC). Journal of clinical oncology. 2013. 31(15 SUPPL. 1):	Intervention not of interest
1431	Motzer RJ, Choueiri T, Larkin J, et al. Phase 3 study of avelumab in combination with axitinib versus sunitinib as first-line treatment for patients with advanced renal cell carcinoma (aRCC). Annals of oncology. 2016. 27	Outcomes not of interest
1438	Motzer RJ, Grunwald V, Hutson TE, et al. A phase III trial to compare efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab vs sunitinib alone in first-line treatment of patients (Pts) with metastatic renal cell carcinoma (RCC). Journal of clinical oncology. 2017. 35(15):	Outcomes not of interest
1475	Mulders P, Hawkins R, Nathan P, et al. Cediranib monotherapy in patients with advanced renal cell carcinoma: Results of a randomised phase II study. European Journal of Cancer. 2012. 48(4):527-537	Mixed Population
1550	Nct. Pazopanib Versus Sunitinib in the Treatment of Asian Subjects With Locally Advanced and/or Metastatic Renal Cell Carcinoma. Https://clinicaltrials.gov/show/nct01147822. 2010.	Mixed Population
1568	Nct. Cabozantinib-s-malate or Sunitinib Malate in Treating Patients With Previously Untreated Locally Advanced or Metastatic Kidney Cancer. Https://clinicaltrials.gov/show/nct01835158. 2013.	Mixed Population
1571	Nct. A Study of Atezolizumab (an Engineered Anti-Programmed Death-Ligand 1 Antibody) as Monotherapy or in Combination With Bevacizumab (Avastin®) Compared to Sunitinib (Sutent®) in Participants With Untreated Advanced Renal Cell Carcinoma. Https://clinicaltrials.gov/show/nct01984242. 2013.	Mixed Population
1588	Nct. A Study of Atezolizumab in Combination With Bevacizumab Versus Sunitinib in Participants With Untreated Advanced Renal Cell Carcinoma. Https://clinicaltrials.gov/show/nct02420821. 2015.	Mixed Population
1664	Négrier S, Perol D, Ravaud A, et al. Randomized study of intravenous versus subcutaneous interleukin-2, and IFNα in patients with good prognosis metastatic renal cancer. Clinical Cancer Research. 2008. 14(18):5907-5912	Intervention not of interest
1667	Neidhart JA, Anderson SA, Harris JE, et al. Vinblastine fails to improve response of renal cancer to interferon alfa-n1: High response rate in patients with pulmonary metastases. Journal of Clinical Oncology. 1991. 9(5):832-837	Mixed Population
1707	Oudard S, Benhamouda N, Escudier B, et al. Decrease of pro-angiogenic monocytes predicts clinical response to anti-angiogenic treatment in patients with metastatic renal cell carcinoma (mRCC). European journal of cancer.. 2015. 51S89-S90	Outcomes not of interest
1762	Patil S, Figlin RA, Hutson TE, et al. Q-TWiST analysis to estimate overall benefit for patients with metastatic renal cell carcinoma treated in a phase III trial of sunitinib vs interferon-α. British Journal of Cancer. 2012. 106(10):1587-1590	Outcomes not of interest
1764	Patil S, Figlin RA, Hutson TE, et al. Prognostic factors for progression-free and overall survival with sunitinib targeted therapy and with cytokine as first-line therapy in patients with metastatic renal cell carcinoma. Annals of Oncology. 2011. 22(2):295-300	Outcomes not of interest
1794	Pickard AS, Cella D, Duh MS, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomized phase III trial. Journal of clinical oncology. 2011. 29(15 SUPPL. 1):	Outcomes not of interest
1821	Porta C, Gore ME, Rini BI, et al. Long-term Safety of Sunitinib in Metastatic Renal Cell Carcinoma. European Urology. 2016. 69(2):345-351	Mixed Population
1845	Procopio G, Cognetti F, Miceli R, et al. A randomized, open label, multicenter phase 2 study, to evaluate the efficacy of sorafenib (So) in patients (pts) with metastatic renal cell carcinoma (mRCC) after a radical resection of the metastases: RESORT trial. Journal of Clinical Oncology. 2018. 36(15):	Mixed Population

1861	Queirolo P, Spagnolo F. Atypical responses in patients with advanced melanoma, lung cancer, renal-cell carcinoma and other solid tumors treated with anti-PD-1 drugs: A systematic review. Cancer Treatment Reviews. 2017. 5971-78	SLRs (bibliographies reviewed)
1890	Reddy K, Bukowski RM. Phase III study of sunitinib malate (SU11248) versus interferon-alpha as first-line treatment in patients with metastatic renal cell carcinoma. Clinical genitourinary cancer. 2006. 5(1):23-25	Publication type not of interest
1922	Rini BI, Choueiri TK, Mariani M, et al. Avelumab in combination with axitinib versus sunitinib as first-line treatment for patients with advanced renal cell carcinoma: the phase III JAVELIN Renal 101 trial. Journal for immunotherapy of cancer. 2016. 4	Outcomes not of interest
1931	Rini BI, Hutson TE, Figlin RA, et al. Sunitinib in Patients With Metastatic Renal Cell Carcinoma: clinical Outcome According to International Metastatic Renal Cell Carcinoma Database Consortium Risk Group. Clinical genitourinary cancer. 2018. 16(4):298-304	Study design not of interest
1937	Rini BI, Powles T, Chen M, et al. Phase 3 KEYNOTE-426 trial: pembrolizumab (pembro) plus axitinib versus sunitinib alone in treatment-naive advanced/metastatic renal cell carcinoma (mRCC). Journal of clinical oncology. 2017. 35(15):	Outcomes not of interest
1938	Rini BI, Powles T, Chen M, et al. KEYNOTE-426: randomized phase III study of pembrolizumab in combination with axitinib versus sunitinib monotherapy in treatment-naive advanced/metastatic renal cell carcinoma (mRCC). Journal for immunotherapy of cancer. 2016. 4	Outcomes not of interest
1940	Rini BI, Stenzl A, Zdrojowy R, et al. IMA901, a multipeptide cancer vaccine, plus sunitinib versus sunitinib alone, as first-line therapy for advanced or metastatic renal cell carcinoma (IMPRINT): a multicentre, open-label, randomised, controlled, phase 3 trial. The Lancet Oncology. 2016. 17(11):1599-1611	Intervention not of interest
1950	Ritchie AWW, Griffiths G, Parmar M. Interferon-α and survival in metastatic renal carcinoma: Early results of a randomised controlled trial. Lancet. 1999. 353(9146):14-17	Mixed Population
1982	Rousseau B, Kempf E, Desamericq G, et al. First-line antiangiogenics for metastatic renal cell carcinoma: A systematic review and network meta-analysis. Critical Reviews in Oncology/Hematology. 2016. 10744-53	SLRs (bibliographies reviewed)
1984	Roviello G, Bachelot T, Hudis CA, et al. The role of bevacizumab in solid tumours: A literature based meta-analysis of randomised trials. European Journal of Cancer. 2017. 75245-258	SLRs (bibliographies reviewed)
2032	Schmidt E, Lister J, Neumann M, et al. Cabozantinib Versus Standard-of-Care Comparators in the Treatment of Advanced/Metastatic Renal Cell Carcinoma in Treatment-naïve Patients: a Systematic Review and Network Meta-Analysis. Targeted Oncology. 2018. 13(2):205-216	SLRs (bibliographies reviewed)
2073	Sheng X, Bi F, Ren X, et al. First-line axitinib versus sorafenib in Asian patients with metastatic renal cell carcinoma (mRCC): subgroup analysis of data from a phase III trial. Annals of oncology. 2017. 28x82-	Subgroups not of interest
2074	Sheng X, Bi F, Ren X, et al. First-line axitinib versus sorafenib in Asian patients with metastatic renal cell carcinoma: Exploratory subgroup analyses of Phase III data. Future Oncology. 2019. 15(1):3267-3277	Subgroups not of interest
2076	Sheng X, Jin J, He Z, et al. Efficacy and safety of pazopanib (PAZ) versus sunitinib (SUN) in patients (pts) with locally advanced or metastatic renal cell carcinoma (RCC): A pooled China subgroup analysis from COMPARZ studies. Journal of Clinical Oncology. 2018. 36(15):	Subgroups not of interest
2080	Shinohara N, Akaza H, Tomita Y, et al. Efficacy and safety of sunitinib (SU) in patients (pts) with metastatic renal cell carcinoma (mRCC) and lung metastases (mets) only at baseline. Journal of clinical oncology. 2012. 30(15 SUPPL. 1):	Mixed Population
2109	Song Y, Du C, Zhang W, et al. Body mass index and age are additional prognostic factors in patients with metastatic renal cell carcinoma treated with tyrosine kinase inhibitors. Urologic oncology. 2016. 34(6):258.e15-22	Outcomes not of interest
2112	Sorich MJ, Kichenadasse G, Rowland A, et al. Angiotensin system inhibitors and survival in patients with metastatic renal cell carcinoma treated with VEGF-targeted therapy: A pooled secondary analysis of clinical trials. International Journal of Cancer. 2016. 138(9):2293-2299	SLRs (bibliographies reviewed)
2125	Stadler WM, Rosner G, Small E, et al. Successful implementation of the randomized discontinuation trial design: an application to the study of the putative antiangiogenic agent carboxyaminoimidazole in renal cell carcinoma--CALGB 69901. Journal of clinical oncology. 2005. 23(16):3726-3732	Mixed Population
2134	Sternberg C, Bracarda S, Carteni G, et al. Sunitinib expanded-access trial in metastatic renal cell carcinoma (mRCC) - Final Italian results. European journal of cancer.. 2013. 49(var.pagings):S644	Study design not of interest
2140	Sternberg CN, Hawkins RE, Szczylik C, et al. A randomized, double-blind phase III study (VEG105192) of pazopanib (paz) versus placebo (pbo) in patients with advanced/metastatic renal cell carcinoma (mRCC): updated safety results. Journal of clinical oncology. 2011. 29(7 SUPPL. 1):	Mixed Population
2187	Takyar S, Diaz J, Sehgal M, et al. First-line therapy for treatment-naive patients with advanced/metastatic renal cell carcinoma: A systematic review of published randomized controlled trials. Anti-Cancer Drugs. 2016. 27(5):383-397	SLRs (bibliographies reviewed)
2244	Tran HT, Liu Y, Zurita AJ, et al. Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis of phase 2 and phase 3 trials. Lancet Oncol. 2012. 13(8):827-37	Mixed Population
2273	Unverzagt S, Moldenhauer I, Nothacker M, et al. Immunotherapy for metastatic renal cell carcinoma. Cochrane Database of Systematic Reviews. 2017. (5):	SLRs (bibliographies reviewed)
2334	Voss MH, Chen D, Marker M, et al. Tumor genomic analysis for 128 renal cell carcinoma (RCC) patients receiving firstline everolimus: Correlation between outcome and mutations status in MTOR, TSC1, and TSC2. Journal of Clinical Oncology. 2017. 35(6):	Study design not of interest

2338	Voss MH, Kuo F, Chen D, et al. Integrated biomarker analysis for 412 renal cell cancer (RCC) patients (pts) treated on the phase 3 COMPARZ trial: Correlating common mutation events in PBRM1 and BAP1 with angiogenesis expression signatures and outcomes on tyrosine kinase inhibitor (TKI) therapy. Journal of Clinical Oncology. 2017. 35(15):	Outcomes not of interest
2349	Wallis CJD, Klaassen Z, Bhindi B, et al. First-line Systemic Therapy for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis [Figure presented]. European Urology. 2018. 74(3):309-321	SLRs (bibliographies reviewed)
2352	Wang HT, Xia M. A meta-analysis of efficacy and safety of sorafenib versus other targeted agents for metastatic renal cell carcinoma. Medicine. 2019. 98(1):e13779	SLRs (bibliographies reviewed)
2354	Wang L, Ma L, Wang X, et al. Therapeutic effects and associated adverse events of first-line treatments of advanced renal cell carcinoma (RCC): a meta-analysis. International Urology and Nephrology. 2015.	SLRs (bibliographies reviewed)
2420	Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. New England Journal of Medicine. 2003. 349(5):427-434	Line of therapy not of interest
2456	Zibelman M, Barth P, Handorf E, et al. A review of interventional clinical trials in renal cell carcinoma: A status report from the clinicaltrials.gov website. Clinical Genitourinary Cancer. 2015. 13(2):142-149	Outcomes not of interest
1092	Jonasch E, Corn P, Pagliaro LC, et al. Upfront, randomized, phase 2 trial of sorafenib versus sorafenib and low-dose interferon alfa in patients with advanced renal cell carcinoma: Clinical and biomarker analysis. Cancer. 2010. 116(1):57-65	Intervention not of interest
1155	Kinouchi T, Sakamoto J, Tsukamoto T, et al. Prospective randomized trial of natural interferon-alpha versus natural interferon-alpha plus cimetidine in advanced renal cell carcinoma with pulmonary metastasis. Journal of Cancer Research and Clinical Oncology. 2006. 132(8):499-504	Intervention not of interest
1185	Kriegmair M, Oberneder R, Hofstetter A. Interferon alfa and vinblastine versus medroxyprogesterone acetate in the treatment of metastatic renal cell carcinoma. Urology. 1995. 45(5):758-762	Intervention not of interest
1276	Liu L, Zhang W, Qi X, et al. Randomized study of autologous cytokine-induced killer cell immunotherapy in metastatic renal carcinoma. Clinical Cancer Research. 2012. 18(6):1751-1759	Intervention not of interest
1296	Lümmen G, Goepel M, Möllhoff S, et al. Phase II study of interferon-gamma versus interleukin-2 and interferon-alpha 2b in metastatic renal cell carcinoma. Journal of urology. 1996. 155(2):455-458	Intervention not of interest
1354	McDermott DF, Manola J, Pins M, et al. The BEST trial (E2804): a randomized phase II study of VEGF, RAF kinase, and mTOR combination targeted therapy (CTT) with bevacizumab (bev), sorafenib (sor), and temsirolimus (tem) in advanced renal cell carcinoma (RCC). Journal of clinical oncology. 2013. 31(6 SUPPL. 1):	Intervention not of interest
1459	Motzer RJ, Rakhit A, Thompson JA, et al. Randomized multicenter phase II trial of subcutaneous recombinant human interleukin-12 versus interferon-α2a for patients with advanced renal cell carcinoma. Journal of Interferon and Cytokine Research. 2001. 21(4):257-263	Intervention not of interest
1522	Nct. A Study Evaluating the Efficacy and Safety of Sunitinib With or Without Bevacizumab in First-Line Patients With Metastatic Renal Cell Cancer (SABRE-R). Https://clinicaltrials.gov/show/nct00491738. 2007.	Intervention not of interest
1660	Négrier S, Gravis G, Pérol D, et al. Temsirolimus and bevacizumab, or sunitinib, or interferon alfa and bevacizumab for patients with advanced renal cell carcinoma (TORAVA): A randomised phase 2 trial. The Lancet Oncology. 2011. 12(7):673-680	Intervention not of interest
1847	Procopio G, Verzoni E, Bracarda S. Subgroup analysis and updated results of the randomized study comparing sorafenib (So) plus interleukin-2 versus So alone as first-line treatment in metastatic renal cell carcinoma. Journal of clinical oncology. 2010. 28 supplAbstract 4589	Intervention not of interest
1848	Procopio G, Verzoni E, Bracarda S, et al. Overall survival (OS) of sorafenib (So) plus interleukin-2 (IL-2) versus So alone in patients with treatment-naive metastatic renal cell carcinoma (mRCC): final update of the ROSORC trial. Journal of clinical oncology. 2013. 31(6 SUPPL. 1):	Intervention not of interest
1849	Procopio G, Verzoni E, Bracarda S, et al. A randomized, open label, prospective study comparing the association between sorafenib (So) and interleukin-2 (IL-2) versus So alone in advanced untreated renal cell cancer (RCC): rosorc Trial. Journal of clinical oncology. 2009. 27(15S Part I):258	Intervention not of interest
1850	Procopio G, Verzoni E, Bracarda S, et al. Sorafenib with interleukin-2 vs sorafenib alone in metastatic renal cell carcinoma: The ROSORC trial. British Journal of Cancer. 2011. 104(8):1256-1261	Intervention not of interest
1851	Procopio G, Verzoni E, Bracarda S, et al. Overall survival for sorafenib plus interleukin-2 compared with sorafenib alone in metastatic renal cell carcinoma (mRCC): Final results of the ROSORC trial. Annals of Oncology. 2013. 24(12):2967-2971	Intervention not of interest
1917	Rini B, Szczylik C, Tannir NM, et al. AMG 386 in combination with sorafenib in patients with metastatic clear cell carcinoma of the kidney: A randomized, double-blind, placebo-controlled, phase 2 study. Cancer. 2012. 118(24):6152-6161	Intervention not of interest
1920	Rini BI, Bellmunt J, Clancy J, et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. Journal of Clinical Oncology. 2014. 32(8):752-759	Intervention not of interest
1941	Rini BI, Szczylik C, Tannir NM, et al. AMG 386 in combination with sorafenib in patients (pts) with metastatic renal cell cancer (mRCC): a randomized, double-blind, placebo-controlled, phase II study. Journal of clinical oncology. 2011. 29(7 SUPPL. 1):	Intervention not of interest

2308	Verzoni E, Bracarda S, Ricci S, et al. Proof of concept of correlation between progression-free survival (PFS) and overall survival (OS) in treatment-naive patients with advanced renal-cell carcinoma (mRCC): final results of a randomized phase II study comparing sorafenib plus interleukin-2 (IL-2) versus sorafenib alone: the ROSORC trial. Journal of clinical oncology. 2013. 31(15 SUPPL. 1):	Intervention not of interest
2387	Witte RS, Hsieh P, Elson P, et al. A phase II trial of amonafide, caracemide, and homeharringtonine in the treatment of patients with advanced renal cell cancer. Investigational New Drugs. 1996. 14(4):409-413	Intervention not of interest
2452	Zhou AP, Bai Y, Song Y, et al. Anlotinib Versus Sunitinib as First-Line Treatment for Metastatic Renal Cell Carcinoma: A Randomized Phase II Clinical Trial. Oncologist. 2019.	Intervention not of interest
652	Donskov F, Jensen NV, Smidt-Hansen T, et al. A randomized phase II trial of interleukin-2 and interferon-α plus bevacizumab versus interleukin-2 and interferon-α in metastatic renal-cell carcinoma (mRCC): results from the Danish Renal Cancer Group (DaRenCa) study-1. Acta Oncologica. 2018. 57(5):589-594	Intervention not of interest
689	Eisen T, Loembé AB, Shparyk Y, et al. A randomised, phase II study of nintedanib or sunitinib in previously untreated patients with advanced renal cell cancer: 3-year results. British Journal of Cancer. 2015. 113(8):1140-1147	Intervention not of interest
690	Eisen T, Shparyk Y, Jones R, et al. Phase II efficacy and safety study of nintedanib versus sunitinib in previously untreated renal cell carcinoma (RCC) patients. Journal of clinical oncology. 2013. 31(15 SUPPL. 1):	Intervention not of interest
867	Gleave ME, Elhilali M, Fradet Y, et al. Interferon gamma-1b compared with placebo in metastatic renal-cell carcinoma. Canadian Urologic Oncology Group. New England journal of medicine. 1998. 338(18):1265-1271	Intervention not of interest
889	Gore ME, Griffin CL, Hancock B, et al. Interferon alfa-2a versus combination therapy with interferon alfa-2a, interleukin-2, and fluorouracil in patients with untreated metastatic renal cell carcinoma (MRC RE04/EORTC GU 30012): an open-label randomised trial. The Lancet. 2010. 375(9715):641-648	Intervention not of interest
940	Hahn RG, Begg CB, Davis T. Phase II study of vinblastine-CCNU, triazinate, and dactinomycin in advanced renal cell cancer. Cancer Treatment Reports. 1981. 65(7-8):711-713	Intervention not of interest
942	Hainsworth JD, Mace JR, Reeves JA, et al. Randomized phase II study of sunitinib + CXCR4 inhibitor LY2510924 versus sunitinib alone in first-line treatment of patients with metastatic renal cell carcinoma. Journal of clinical oncology. 2015. 33(15 SUPPL. 1):	Intervention not of interest
943	Hainsworth JD, Reeves JA, Mace JR, et al. A Randomized, Open-Label Phase 2 Study of the CXCR4 Inhibitor LY2510924 in Combination with Sunitinib Versus Sunitinib Alone in Patients with Metastatic Renal Cell Carcinoma (RCC). Targeted Oncology. 2016. 11(5):643-653	Intervention not of interest
986	Henriksson R, Nilsson S, Colleen S, et al. Survival in renal cell carcinoma - A randomized evaluation of tamoxifen vs interleukin 2, α-interferon (leucocyte) and tamoxifen. British Journal of Cancer. 1998. 77(8):1311-1317	Intervention not of interest
993	Hessel C, Mangeshkar M, Motzer RJ, et al. Evaluation of the novel "trial within a trial" design of METEOR, a randomized phase 3 trial of cabozantinib versus everolimus in patients (pts) with advanced renal cell carcinoma (RCC). Annals of oncology. Conference: 41st european society for medical oncology congress, ESMO 2016. Denmark. Conference start: 20161007. Conference end: 20161011. 2016. 27(no pagination):	Line of therapy not of interest
3177	Figlin, RA, Tannir, et al. Results of the ADAPT Phase 3 Study of Rocapuldencel-T in Combination with Sunitinib as First-Line Therapy in Patients with Metastatic Renal Cell Carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2020. 262327-2336	Intervention not of interest
3411	Rodriguez-Vida, A, Bamias, et al. Randomised Phase II study comparing alternating cycles of sunitinib and everolimus vs standard sequential administration in first-line metastatic renal carcinoma (SUNRISES study). BJU International.. 2020.	Intervention not of interest
3506	Zhou, AP, Bai, et al. Anlotinib Versus Sunitinib as First-Line Treatment for Metastatic Renal Cell Carcinoma: A Randomized Phase II Clinical Trial. Oncologist. 2020. 24e702-e708	Intervention not of interest
3117	Choueiri, TK, Heng, et al. Efficacy of Savolitinib vs Sunitinib in Patients with MET -Driven Papillary Renal Cell Carcinoma: The SAVOIR Phase 3 Randomized Clinical Trial. JAMA Oncology.. 2020.	Line of therapy not of interest
3205	Grunwald, V, Gru llich, et al. A phase II trial of TKI induction followed by a randomized comparison between nivolumab or TKI continuation in renal cell carcinoma (NIVOSWITCH). Annals of Oncology. 2020. 30 (Supplement 5)v388	Line of therapy not of interest
3206	Grunwald, V, Grullich, et al. A randomized phase II trial comparing switch to nivolumab with TKI continuation after 12 weeks of TKI induction therapy in metastatic renal cell carcinoma patients (NIVOSWITCH). Journal of clinical oncology. 2020. 38	Line of therapy not of interest
3207	Grunwald, V, Grullich, et al. TKI induction followed by a randomized comparison between nivolumab or TKI continuation in renal cell carcinoma (NiVOSWiTCH). Oncology research and treatment. 2020. 43	Line of therapy not of interest
3461	Tomita, Y, Fukasawa, et al. Nivolumab versus everolimus in advanced renal cell carcinoma: Japanese subgroup 3-year follow-up analysis from the Phase III CheckMate 025 study. Japanese Journal of Clinical Oncology. 2020. 49506-514	Line of therapy not of interest
3400	Rexer, H, Bergmann, et al. A Phase 2, Randomized, Open-Label Study of Nivolumab Combined with Ipilimumab Versus Sunitinib Monotherapy in Subjects with Previously Untreated and Advanced (unresectable or metastatic) non-clear Cell Renal Cell Carcinoma - SUNNIFORECAST AN 41/16 der AUO. Aktuelle Urologie. 2020. 51236-238	Not in English
3191	Glancszpigel, M, Valanzasca, et al. Assessing the Quality of the Evidence of Nivolumab According to the Hta Requirement in Argentina. Value in health regional issues. 2020. 19	Outcomes not of interest

3004	. Efficacy of Nivolumab plus Ipilimumab According to Number of IMDC Risk Factors in CheckMate 214. European urology. 2020.	Publication type not of interest
3006	. Correction to Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial (The Lancet Oncology (2019) 20(10) (1370a[Euro sign]"1385), (S1470204519304139), (10.1016/S1470-2045(19)30413-9)). Lancet oncology. 2020. 20e559-	Publication type not of interest
3007	. Efficacy and safety profile of sunitinib as a first line treatment for advanced/metastatic clear-cell renal cell carcinoma: pooled analysis of randomized controlled trials. Journal of clinical oncology. 2020. 37	Publication type not of interest
3013	. First-line axitinib versus sorafenib in Asian patients with metastatic renal cell carcinoma: exploratory subgroup analyses of Phase III data. Future oncology (London, England). 2020. 153267-3277	Publication type not of interest
3169	Euctr, GR. An Immunotherapy Study of Nivolumab Combined with Ipilimumab versus Nivolumab Monotherapy Alone in Participants with Advanced Kidney Cancer. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2018. 2020.	Publication type not of interest
3067	Bosse, D, Lin, et al. Response of Primary Renal Cell Carcinoma to Systemic Therapy. European Urology. 2020. 76852-860	SLRs (bibliographies reviewed)
3072	Buonerba, C, Dolce, et al. Outcomes associated with first-line anti-PD-1/ PD-L1 agents vs. Sunitinib in patients with sarcomatoid renal cell carcinoma: A systematic review and meta-analysis. Cancers. 2020. 12	SLRs (bibliographies reviewed)
3073	Buti, S, Petrelli, et al. Immunotherapy-based combinations versus standard first-line treatment for metastatic clear cell renal cell carcinoma: a systematic review and meta-analysis. Clinical and Translational Oncology. 2020. 221657-1663	SLRs (bibliographies reviewed)
3147	Deng, H, Huang, et al. Pazopanib has equivalent anti-tumor effectiveness and lower Total costs than Sunitinib for treating metastatic or advanced renal cell carcinoma: A meta-analysis. BMC Cancer. 2020. 19	SLRs (bibliographies reviewed)
3159	Elaidi, R, Phan, et al. Comparative efficacy of first-line immune-based combination therapies in metastatic renal cell carcinoma: A systematic review and network meta-analysis. Cancers. 2020. 121-13	SLRs (bibliographies reviewed)
3213	Hahn, AW, Klaassen, et al. First-line Treatment of Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis. European Urology Oncology. 2020. 2708-715	SLRs (bibliographies reviewed)
3217	Hale, P, Hahn, et al. Treatment of metastatic renal cell carcinoma in older patients: A network meta-analysis. Journal of Geriatric Oncology. 2020. 10149-154	SLRs (bibliographies reviewed)
3220	Haykal, T, Samji, et al. Efficacy and safety profile of sunitinib as a first line treatment for advanced/metastatic clear-cell renal cell carcinoma: Pooled analysis of randomized controlled trials. Journal of Clinical Oncology. Conference. 2020. 37	SLRs (bibliographies reviewed)
3267	Landre, T, Des Guetz, et al. Immune Checkpoint Inhibitors for Patients Aged >= 75 Years with Advanced Cancer in First- and Second-Line Settings: A Meta-Analysis. Drugs and Aging.. 2020.	SLRs (bibliographies reviewed)
3281	Manz, K, Fenchel, et al. Efficacy and safety of approved first-line tyrosine kinase inhibitor (TKI) treatment in patients with metastatic renal cell carcinoma (mRCC): A network meta-analysis based on phase II/III randomised clinical trials (RCTs). Journal of Clinical Oncology. Conference. 2020. 37	SLRs (bibliographies reviewed)
3282	Manz, KM, Fenchel, et al. Efficacy and Safety of Approved First-Line Tyrosine Kinase Inhibitor Treatments in Metastatic Renal Cell Carcinoma: A Network Meta-Analysis. Advances in Therapy. 2020. 37730-744	SLRs (bibliographies reviewed)
3296	Monteiro, FSM, Soares, et al. First-line Treatment of Metastatic Renal Cell Carcinoma in the Immuno-oncology Era: Systematic Review and Network Meta-analysis. Clinical Genitourinary Cancer. 2020. 18244-251.e4	SLRs (bibliographies reviewed)
3298	Moran, M, Nickens, et al. Augmenting the randomized controlled trial with real-world data to aid clinical decision making in metastatic renal cell carcinoma: A systematic review and meta-analysis. Future Oncology. 2020. 153987-4001	SLRs (bibliographies reviewed)
3299	Moran, M, Nickens, et al. Sunitinib for Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-Analysis of Real-World and Clinical Trials Data. Targeted Oncology. 2020. 14405-416	SLRs (bibliographies reviewed)
3366	Osterman, CK, Rose, et al. A Systematic Review of Systemic Treatment Options for Advanced Non-Clear Cell Renal Cell Carcinoma. Kidney Cancer. 2020. 415-27	SLRs (bibliographies reviewed)
3376	Papanikolaou, D, Ioannidou, et al. Systemic therapy for chromophobe renal cell carcinoma: A systematic review. Urologic Oncology: Seminars and Original Investigations. 2020. 38137-149	SLRs (bibliographies reviewed)
3380	Peinemann, F, Unverzagt, et al. Immunotherapy for metastatic renal cell carcinoma: A systematic review. Journal of Evidence-Based Medicine. 2020. 12253-262	SLRs (bibliographies reviewed)
3394	Ratto, BE, Chakraborty, et al. Systematic reiew and network metaanalysis of firstline treatments in mRCC. Journal of Clinical Oncology. Conference. 2020. 37	SLRs (bibliographies reviewed)
3413	Roviello, G, Corona, et al. Results from a meta-analysis of immune checkpoint inhibitors in first-line renal cancer patients: does PD-L1 matter?. Therapeutic Advances in Medical Oncology. 2020. 11	SLRs (bibliographies reviewed)
3440	Su, Y, Fu, et al. First-line treatments for advanced renal-cell carcinoma with immune checkpoint inhibitors: systematic review, network meta-analysis and cost-effectiveness analysis. Therapeutic Advances in Medical Oncology. 2020. 12	SLRs (bibliographies reviewed)
3456	Thein, KZ, Mogollon-Duffo, et al. Combination therapy with checkpoint inhibitors for first-line treatment of advanced renal cell carcinoma: A systematic review and metaanalysis of randomized controlled trials. Annals of Oncology. 2020. 30 (Supplement 5)v387-v388	SLRs (bibliographies reviewed)

3480	Varkaris, A, Xu, et al. Combining Immune Checkpoint and VEGFR Inhibition in Favorable Risk and Elderly Patients With Metastatic Renal Cell Carcinoma. Clinical Genitourinary Cancer. 2020. 18179-184.e3	SLRs (bibliographies reviewed)
3492	Wang, HT, Xia, et al. A meta-analysis of efficacy and safety of sorafenib versus other targeted agents for metastatic renal cell carcinoma. Medicine. 2020. 98e13779	SLRs (bibliographies reviewed)
3493	Wang, J, Li, et al. Role of immune checkpoint inhibitor-based therapies for metastatic renal cell carcinoma in the first-line setting: A Bayesian network analysis. EBioMedicine. 2020. 4778-88	SLRs (bibliographies reviewed)
3497	Win Htut, T, Swarup, et al. Treatment-related adverse events and tolerability in patients with advanced renal cell carcinoma treated with first-line combination therapy with checkpoint inhibitors. Annals of Oncology. 2020. 30 (Supplement 5)v527	SLRs (bibliographies reviewed)
3430	Singla, N. Re: brian I. Rini, Thomas Powles, Michael B. Atkins, et al. Atezolizumab plus Bevacizumab Versus Sunitinib in Patients with Previously Untreated Metastatic Renal Cell Carcinoma (IMmotion151): a Multicentre, Open-label, Phase 3, Randomised Controlled Trial. Lancet 2019;393: 2404-15: putting IMmotion into Motion: personalizing Frontline Treatment for Metastatic Renal Cell Carcinoma. European urology. 2020.	Study design not of interest
3425	Sheng, X., Jin, J., He, Z., Huang, Y., Zhou, A., Wang, J., Ren, X., Ye, D., Zhang, X., Qin, S., Zhou, F., Wang, B., Guo, J.. Pazopanib versus sunitinib in Chinese patients with locally advanced or metastatic renal cell carcinoma: Pooled subgroup analysis from the randomized, COMPARZ studies. BMC Cancer. 2020. 20:#pages#	Subgroups not of interest
3424	Sheng, X., Bi, F., Ren, X., Cheng, Y., Wang, J., Rosbrook, B., Jiang, M., Guo, J.. First-line axitinib versus sorafenib in Asian patients with metastatic renal cell carcinoma: Exploratory subgroup analyses of Phase III data. Future Oncology. 2020. 15:3267-3277	Subgroups not of interest
3407	Rini, B. I., Plimack, E. R., Stus, V., Gafanov, R., Hawkins, R., Nosov, D., Pouliot, F., Alekseev, B., Soulieres, D., Melichar, B., Vynnychenko, I., Kryzhanivska, A., Bondarenko, I., Azevedo, S. J., Borchiellini, D., Szczylik, C., Markus, M., McDermott, R. S., Bedke, J., Tartas, S., Chang, Y. H., Tamada, S., Shou, Q., Perini, R. F., Chen, M., Atkins, M. B., Powles, T.. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. New England Journal of Medicine. 2020. 380:1116-1127	Publication type not of interest
3305	Motzer, R. J., Penkov, K., Haanen, J., Rini, B., Albiges, L., Campbell, M. T., Venugopal, B., Kollmannsberger, C., Negrier, S., Uemura, M., Lee, J. L., Vasiliev, A., Miller, W. H., Gurney, H., Schmidinger, M., Larkin, J., Atkins, M. B., Bedke, J., Alekseev, B., Wang, J., Mariani, M., Robbins, P. B., Chudnovsky, A., Fowst, C., Hariharan, S., Huang, B., Di Pietro, A., Choueiri, T. K.. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. New England Journal of Medicine. 2020. 380:1103-1115	Publication type not of interest
4033	Motzer RJ, Robbins PB, Powles T, Albiges L, Haanen JB, Larkin J, Mu XJ, Ching KA, Uemura M, Pal SK, Alekseev B, Gravis G, Campbell MT, Penkov K, Lee JL, Hariharan S, Wang X, Zhang W, Wang J, Chudnovsky A, di Pietro A, Donahue AC, Choueiri TK. Avelumab plus axitinib versus sunitinib in advanced renal cell carcinoma: biomarker analysis of the phase 3 JAVELIN Renal 101 trial. Nature medicine. 2020. #volume#:#pages#	Publication type not of interest (duplicate)
4090	Choueiri, T. K.,Heng, D. Y. C.,Lee, J. L.,Cancel, M.,Verheijen, R. B.,Mellemgaard, A.,Ottesen, L.,Frigault, M. M.,L'Hernault, A.,Szijgyarto, Z.,Signoretti, S.,Albiges, L.. SAVOIR: a phase III study of savolitinib versus sunitinib in pts with MET-driven papillary renal cell carcinoma (PRCC). Journal of clinical oncology. 2020. 38:#pages#	Intervention not of interest
5057	Grunwald, V., Maute, L., Grimm, M. O., Weikert, S., Schleicher, J., Klotz, T., Greiner, J., Florcken, A., Hartmann, A., Gauler, T., Bergmann, L. A Randomized Phase IIa Trial with Temsirolimus versus Sunitinib in Advanced Non-Clear Cell Renal Cell Carcinoma: An Intergroup Study of the CESAR Central European Society for Anticancer Drug Research-EWIV and the Interdisciplinary Working Group on Renal Cell Cancer (IAGN) of the German Cancer Society. Oncology Research and Treatment.2020.43:7-8(333-339)	Publication type not of interest (duplicate)
5502	Abdelaziz, LA, Taha, HF, Ali, MM, Abdelgawad, MI, Elwan, A. Tolerability and outcome of sunitinib by giving 4/2 schedule versus 2/1 schedule in metastatic renal cell carcinoma patients: a prospective randomized multi-centric Egyptian study. Wspolczesna Onkologia. 2021;24(4):221-228.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5522	Ciccarese, C, Iacovelli, R, Bria, E, Schinzari, G, Rossi, E, Astore, S, Cannella, MA, D'Angelo, T, Cicala, CM, Maratta, MG, Tortora, G. Efficacy of VEGFR-TKI plus immune checkpoint inhibitor (ICI) in metastatic renal cell carcinoma (mRCC) patients with favorable IMDC prognosis. Journal of Clinical Oncology Conference. 2021;39(6 SUPPL).	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5540	Euctr, NL. Phase 2 Study of MK-6482 in Participants With Advanced Renal Cell Carcinoma. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2020. 2020.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)

5541	Gedye, C, Joshi, AJ, Zhang, AY, Martin, AJ, Joshua, AM, Harris, CA, Underhill, C, Pook, DW, Toner, GC, Kichenadasse, G, So, JY, Goh, JC, Morris, MF, Lawrence, NJ, Ferguson, T, Vasey, PA, Prithviraj, P, Subramaniam, S, Stockler, MR, Davis, ID. Denosumab and pembrolizumab in clear cell renal carcinoma (KEYPAD): A phase II trial (ANZUP1601). Journal of Clinical Oncology Conference. 2021;39(6 SUPPL).	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5546	Hutson, TE, Carthon, BC, Yorio, J, Babu, S, McKean, HA, Percent, IJ, Tykodi, SS, Harrison, MR, Zhang, J, Zoco, J, Johansen, JL, George, DJ. Efficacy and safety outcomes with nivolumab plus ipilimumab in patients with advanced renal cell carcinoma and low Karnofsky performance status: Results from the CheckMate 920 trial. Journal of Clinical Oncology Conference. 2021;39(6 SUPPL).	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5552	Kondoh, CN, Bae, WK, Tamada, S, Matsubara, N, Lee, HJ, Mizuno, R, Ani, S, Kimura, G, Tomita, Y, Chang, CH, Chang, J-C, Lin, J, Perini, R, Molife, LR, Powles, TB, Rini, B, Chung, HJ. Pembrolizumab plus axitinib (pembro + axi) vs sunitinib in metastatic renal cell carcinoma (mRCC) outcomes of the KEYNOTE-426 study in patients from eastern Asia. Annals of oncology. 1319;31.	Outcomes not of interest
5554	Liu, Z, Chen, Y, Wei, Z, He, Y, Wang, J, Mu, X, He, L, Li, R, Hu, X, Peng, X. Comparative efficacy and safety of immunotherapy in the first-line treatment of metastatic renal cell carcinoma: a systematic review and network meta-analysis. Annals of palliative medicine. 2021;10(3):2805-2814.	SLRs (bibliographies reviewed)
5580	Nct. A Study of Pembrolizumab (MK-3475) in Combination With Belzutifan (MK-6482) and Lenvatinib (MK-7902), or Pembrolizumab/Quavonlimab (MK-1308A) in Combination With Lenvatinib, Versus Pembrolizumab and Lenvatinib, for Treatment of Advanced Clear Cell Renal Cell Carcinoma (MK-6482-012). https://clinicaltrialsgov/show/NCT04736706. 2021.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5585	Pal, SK, Tangen, C, Thompson, IM, Balzer-Haas, N, George, DJ, Heng, DYC, Shuch, B, Stein, M, Tretiakova, M, Humphrey, P, Adeniran, A, Narayan, V, Bjarnason, GA, Vaishampayan, U, Alva, A, Zhang, T, Cole, S, Plets, M, Wright, J, Lara, PN. A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. The Lancet. 2021;397(10275):695-703.	Line of therapy not of interest (second-line or later)
5586	Pal, SK, Tangen, C, Thompson, IM, Haas, NB, George, DJ, Heng, DYC, Shuch, BM, Stein, MN, Tretiakova, MS, Humphrey, P, Adeniran, A, Narayan, V, Bjarnason, GA, Vaishampayan, UN, Alva, AS, Zhang, T, Cole, SW, Plets, M, Wright, J, Lara, PLN. Sunitinib versus cabozantinib, crizotinib or savolitinib in metastatic papillary renal cell carcinoma (pRCC): Results from the randomized phase II SWOG 1500 study. Journal of Clinical Oncology Conference. 2021;39(6 SUPPL).	Line of therapy not of interest (second-line or later)
5589	Plimack, ER, Powles, T, Bedke, J, Pouliot, F, Stus, V, Waddell, T, Gafanov, R, Nosov, D, Alekseev, B, McDermott, RS, Markus, M, Tartas, S, Kryzhanivska, A, Bondarenko, I, Szczylik, C, Lin, J, Perini, RF, Molife, LR, Atkins, MB, Rini, BI. Outcomes for patients in the pembrolizumab+axitinib arm with advanced renal cell carcinoma (RCC) who completed two years of treatment in the phase III KEYNOTE-426 study. Journal of Clinical Oncology Conference. 2021;39(6 SUPPL).	Outcomes not of interest
5593	Quhal, F, Mori, K, Bruchbacher, A, Resch, I, Mostafaei, H, Pradere, B, Schuettfort, VM, Laukhtina, E, Egawa, S, Fajkovic, H, Remzi, M, Shariat, SF, Schmidinger, M. First-line Immunotherapy-based Combinations for Metastatic Renal Cell Carcinoma: A Systematic Review and Network Meta-analysis. European Urology Oncology. 2021.	SLRs (bibliographies reviewed)
5594	Riaz, IB, He, H, Ryu, AJ, Siddiqi, R, Naqvi, SAA, Yao, Y, Husnain, M, Narasimhulu, DM, Mathew, J, Sipra, QUAR, Vandvik, PO, Joseph, RW, Liu, H, Wang, Z, Herasevich, V, Singh, P, Hussain, SA, Ho, TH, Bryce, AH, Pagliaro, LC, Murad, MH, Costello, BA. A Living, Interactive Systematic Review and Network Meta-analysis of First-line Treatment of Metastatic Renal Cell Carcinoma. European Urology. 2021.	SLRs (bibliographies reviewed)

5595	Rizzo, A, Mollica, V, Santoni, M, Ricci, AD, Rosellini, M, Marchetti, A, Montironi, R, Ardizzoni, A, Massari, F. Impact of Clinicopathological Features on Survival in Patients Treated with First-line Immune Checkpoint Inhibitors Plus Tyrosine Kinase Inhibitors for Renal Cell Carcinoma: A Meta-analysis of Randomized Clinical Trials. European Urology Focus. 2021.	SLRs (bibliographies reviewed)
5598	Sati, N, Boyne, DJ, Cheung, WY, Cash, SB, Arora, P. Factors Modifying the Associations of Single or Combination Programmed Cell Death 1 and Programmed Cell Death Ligand 1 Inhibitor Therapies with Survival Outcomes in Patients with Metastatic Clear Cell Renal Cell Carcinoma: A Systematic Review and Meta-analysis. JAMA Network Open. 2021.	SLRs (bibliographies reviewed)
5607	Tannir, NM, Motzer, RJ, Albiges, L, Plimack, ER, George, S, Powles, T, Donskov, F, Rini, BI, Grunwald, V, Hammers, HJ, Choueiri, TK, Gurney, H, Tykodi, SS, Porta, C, Burotto, M, Tomita, Y, Lee, CW, Tang, C, McDermott, DF, McKay, RR. Patterns of progression in patients treated with nivolumab plus ipilimumab (NIVO+IPI) versus sunitinib (SUN) for first-line treatment of advanced renal cell carcinoma (aRCC) in CheckMate 214. Journal of Clinical Oncology Conference. 2021;39(6 SUPPL).	Outcomes not of interest
5608	Tannir, NM, Signoretti, S, Choueiri, TK, McDermott, DF, Motzer, RJ, Flaifel, A, Pignon, JC, Ficial, M, Frontera, OA, George, S, Powles, T, Donskov, F, Harrison, MR, Emy, PB, Tykodi, SS, Kocsis, J, Ravaud, A, Rodriguez-Cid, JR, Pal, SK, Murad, AM, Ishii, Y, Saggi, SS, Brent McHenry, M, Rini, BI. Efficacy and safety of nivolumab plus ipilimumab versus sunitinib in first-line treatment of patients with advanced sarcomatoid renal cell carcinoma. Clinical Cancer Research. 2021;27(1):78-86.	Duplicated with RefID5159
5612	Tomita, Y, Motzer, RJ, Choueiri, TK, Rini, BI, Miyake, H, Uemura, H, Albiges, L, Fujii, Y, Umeyama, Y, Wang, J, Mariani, M, Schmidinger, M. Efficacy and safety of avelumab plus axitinib (A + Ax) versus sunitinib (S) in elderly patients with advanced renal cell carcinoma (aRCC): Extended follow-up results from JAVELIN Renal 101. Journal of Clinical Oncology Conference. 2021;39(6 SUPPL).	Outcomes not of interest
5615	Tykodi, SS, Gordan, LN, Alter, RS, Arrowsmith, E, Roger Harrison, M, John Percent, I, Singal, R, Van Veldhuizen, PJ, George, DJ, Hutson, TE, Zhang, J, Zoco, J, Johansen, JL, Kalebasty, AR. Nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma (nccRCC): Efficacy and safety from CheckMate 920. Journal of Clinical Oncology Conference. 2021;39(6 SUPPL).	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5619	Wallis, CJD, Lawson, K, Butaney, M, Satkunasivam, R, Parikh, J, Freedland, SJ, Patel, SP, Hamid, O, Pal, SK, Klaassen, Z. Association between PD-L1 status and immune checkpoint inhibitor response in advanced malignancies: A systematic review and meta-analysis of overall survival data. Japanese Journal of Clinical Oncology. 2020;50(7):800-809.	SLRs (bibliographies reviewed)
5622	Xie, Y, Chen, Z, Zhong, Q, Chen, Y, Shangguan, W, Xie, W. Efficacy and safety of immunological checkpoint inhibitors combined with anti-angiogenic drugs in first-line treatment of metastatic renal cell carcinoma: a systematic review and meta-analysis. Translational Andrology and Urology. 2021;10(1):300-309.	SLRs (bibliographies reviewed)
5625	Rini BI, Atkins MB, Choueiri TK, et al. Time to Resolution of Axitinib-Related Adverse Events After Treatment Interruption in Patients With Advanced Renal Cell Carcinoma. Clinical Genitourinary Cancer. 2021.	Outcomes not of interest
5626	Rizzo A, Mollica V, Santoni M, et al. Comparative effectiveness of first-line immune checkpoint inhibitors plus tyrosine kinase inhibitors according to IMDC risk groups in metastatic renal cell carcinoma: a meta-analysis. Immunotherapy. 2021;28.	SLRs (bibliographies reviewed)
5627	Effect of Dahuang Zhechong Pills combined with TACE on VEGF, MMP-2, TGF-[beta]1 and immune function of patients with primary liver cancer (blood stasis and collaterals blocking type). Zhongguo zhongyao zazhi. 2021;46(3):722-729.	Population not of interest (pediatric, not RCC/kidney cancer)
5628	Curigliano G, Martin M, Jhaveri K, et al. Alpelisib in combination with everolimus +/- exemestane in solid tumours: Phase Ib randomised, open-label, multicentre study. European Journal of Cancer. 2021;151:49-62.	Population not of interest (pediatric, not RCC/kidney cancer)

5629	Spaas M, Sundahl N, Hulstaert E, et al. Checkpoint inhibition in combination with an immunoboost of external beam radiotherapy in solid tumors (CHEERS): study protocol for a phase 2, open-label, randomized controlled trial. BMC Cancer. 2021;21(1).	Outcomes not of interest
5630	Gan CL, Stukalin I, Meyers DE, et al. Outcomes of patients with solid tumour malignancies treated with first-line immuno-oncology agents who do not meet eligibility criteria for clinical trials. European Journal of Cancer. 2021;151:115-125.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5632	Christensen BR, Hajja YM, Koshkin V, Barata PC. Update on First-Line Combination Treatment Approaches in Metastatic Clear-Cell Renal Cell Carcinoma. Current Treatment Options in Oncology. 2021;22(2).	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5633	Emamekhoo H. Efficacy and safety outcomes with nivolumab plus ipilimumab in patients with advanced renal cell carcinoma and brain metastases: results from the CheckMate 920 trial. 2021; ASCO Annual Meeting.	Population not of interest (pediatric, not RCC/kidney cancer)
5634	Grivas P. PrE0807: A phase Ib feasibility trial of neoadjuvant nivolumab (N) without or with lirilumab (L) in cisplatin-ineligible patients (pts) with muscle-invasive bladder cancer (MIBC). 2021; ASCO Annual Meeting.	Intervention not of interest
5635	Hah YS, Koo KC. Immunology and immunotherapeutic approaches for advanced renal cell carcinoma: A comprehensive review. International Journal of Molecular Sciences. 2021;22(9).	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5636	Kessler ER. Phase I/II trial of pembrolizumab and cabozantinib in the treatment of metastatic renal cell carcinoma (mRCC). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5637	Lee C-H. Nivolumab plus cabozantinib in patients with non-clear cell renal cell carcinoma: Results of a phase 2 trial. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5638	Lee C-H. Lenvatinib (LEN) + pembrolizumab (PEMBRO) treatment in patients (pts) with metastatic clear cell renal cell carcinoma (RCC): Final results of a phase 1b/2 trial. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5639	McKay RR. A randomized trial of radium-223 (Ra-223) dichloride and cabozantinib in patients (pts) with advanced renal cell carcinoma (RCC) with bone metastases (RADICAL/Alliance A031801). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5640	Motzer RJ. Health-related quality-of-life (HRQoL) analysis from the phase 3 CLEAR trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) or everolimus (EVE) versus sunitinib (SUN) for patients (pts) with advanced renal cell carcinoma (aRCC). 2021; ASCO Annual Meeting.	Outcomes not of interest
5641	Natesan DV. Updated results of phase II trial using escalating doses of neoadjuvant atezolizumab for cisplatin-ineligible patients with nonmetastatic urothelial cancer (NCT02451423). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to

		2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5642	Procopio G. A phase 2 prospective trial of cabozantinib as first-line treatment for metastatic collecting ducts renal cell carcinoma: The BONSAI trial (Meeturo 2) clinical trial information—NCT03354884. 2021; ASCO Annual Meeting.	Population not of interest (pediatric, not RCC/kidney cancer)
5643	Procopio G. A phase 2 single-arm study of cabozantinib in patients with advanced or unresectable renal cell carcinoma pretreated with one immune checkpoint inhibitor: The BREAKPOINT trial (MeetUro trial 03-NCT03463681). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5644	Quhal F, Mori K, Remzi M, Fajkovic H, Shariat SF, Schmidinger M. Adverse events of systemic immune-based combination therapies in the first-line treatment of patients with metastatic renal cell carcinoma: systematic review and network meta-analysis. Current opinion in urology. 2021;06.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5645	Runcie K. Cyto-KIK: A phase II trial of cytoreductive surgery in kidney cancer plus immunotherapy (nivolumab) and targeted kinase inhibition (cabozantinib). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5646	Shah AY. Cabozantinib (C) exposure-response (ER) analysis for the phase 3 CheckMate 9ER (CM 9ER) trial of nivolumab plus cabozantinib (N+C) versus sunitinib (S) in first-line advanced renal cell carcinoma (1L aRCC). 2021; ASCO Annual Meeting.	Outcomes not of interest
5647	Kollmannsberger C, Choueiri TK, Heng DY, George S, Jie F, Croitoru R, Poondru S, Thompson JA. A Randomized Phase II Study of AGS-16C3F Versus Axitinib in Previously Treated Patients with Metastatic Renal Cell Carcinoma. The Oncologist. 2021 Mar;26(3):182-e361.	Line of therapy not of interest (second-line or later)
5648	Staehler M, Stöckle M, Christoph DC, Stenzl A, Potthoff K, Grimm MO, Klein D, Harde J, Brüning F, Goebell PJ, Augustin M. Everolimus after failure of one prior VEGF-targeted therapy in metastatic renal cell carcinoma: Final results of the MARC-2 trial. International Journal of Cancer. 2021 Apr 1;148(7):1685-94.	Line of therapy not of interest (second-line or later)
5649	Rini BI, Motzer RJ, Powles T, McDermott DF, Escudier B, Donskov F, Hawkins R, Bracarda S, Bedke J, De Giorgi U, Porta C. Atezolizumab plus bevacizumab versus sunitinib for patients with untreated metastatic renal cell carcinoma and sarcomatoid features: a prespecified subgroup analysis of the IMmotion151 clinical trial. European Urology. 2021 May 1;79(5):659-62.	Outcomes not of interest
5650	Wang K, Wu Z, Wang G, Shi H, Xie J, Yin L, Xu T, Mao W, Peng B. Survival nomogram for patients with bone metastatic renal cell carcinoma: A population-based study. International braz j urol. 2021 Mar;47(2):333-49.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5651	Harada H, Shikama N, Wada H, Uchida N, Nozaki M, Hayakawa K, Yamada K, Nagakura H, Ogawa H, Miyazawa K, Katagiri H. A phase II study of palliative radiotherapy combined with zoledronic acid hydrate for metastatic bone tumour from renal cell carcinoma. Japanese Journal of Clinical Oncology. 2021 Jan;51(1):100-5.	Intervention not of interest
5652	Berezowska A, Passchier E, Bleiker E. Professional patient navigation in a hospital setting: a randomized controlled trial. Supportive Care in Cancer. 2021 Apr;29(4):2111-23.	Intervention not of interest
5653	Heo JH, Park C, Ghosh S, Park SK, Zivkovic M, Rascati KL. A network meta-analysis of efficacy and safety of first-line and second-line therapies for the management of metastatic renal cell carcinoma. Journal of Clinical Pharmacy and Therapeutics. 2021 Feb;46(1):35-49.	SLRs (bibliographies reviewed)
5654	Calais, J, Gafita, A, Eiber, MR, Armstrong, WR, Gartmann, J, Thin, P, Nguyen, K, Lok, V, Gosa, L, Grogan, T, Esfandiari, R, Ranganathan, D, Allen-Auerbach, MS, Quon, A, Bahri, S, Gupta, P,	Population not of interest (pediatric, not RCC/kidney cancer)

	Gardner, L, Slavik, R, Dahlbom, M, Herrmann, K, Delpassand, ES, Fendler, WP, Czernin, J. Prospective phase 2 trial of PSMA-targeted molecular RadiothErapy with ¹⁷⁷Lu-PSMA-617 for metastatic Castration-reSISTant Prostate Cancer (RESIST-PC): Efficacy results of the UCLA cohort. J Nucl Med. 2021;20:20.	
5655	Yu, EY, Petrylak, DP, O'Donnell, PH, Lee, JL, van der Heijden, MS, Loriot, Y, Stein, MN, Necchi, A, Kojima, T, Harrison, MR, Hoon Park, S, Quinn, DI, Heath, EI, Rosenberg, JE, Steinberg, J, Liang, SY, Trowbridge, J, Campbell, M, McGregor, B, Balar, AV. Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2021;12:12.	Population not of interest (pediatric, not RCC/kidney cancer)
5656	Ahrens, M. A randomized phase II study of nivolumab plus ipilimumab versus standard of care in previously untreated and advanced non-clear cell renal cell carcinoma (SUNIFORECAST). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5658	Allaf, ME. PROSPER: Phase III RandOmized Study Comparing PERioperative nivolumab versus observation in patients with renal cell carcinoma (RCC) undergoing nephrectomy (ECOG-ACRIN EA8143). 2021; ASCO Annual Meeting.	Intervention not of interest
5657	Albiges, L. Outcomes of patients who progressed while receiving avelumab + axitinib (A + Ax) and received subsequent treatment (Tx) in JAVELIN Renal 101. 2021; ASCO Annual Meeting.	Line of therapy not of interest (second-line or later)
5659	Atkins, MB. Phase II study of nivolumab and salvage nivolumab + ipilimumab in treatment-naïve patients (pts) with advanced non-clear cell renal cell carcinoma (nccRCC) (HCRN GU16-260-Cohort B). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5660	Basso, U, Facchinetti, A, Rossi, E, Maruzzo, M, Conteduca, V, Aieta, M, Massari, F, Fraccon, AP, Mucciarini, C, Sava, T, Santoni, M, Pegoraro, C, Durante, E, Nicodemo, M, Perin, A, Bearz, A, Gatti, C, Fiduccia, P, Diminutto, A, Barile, C, De Giorgi, U, Zamarchi, R, Zagonel, V. Prognostic Role of Circulating Tumor Cells (CTCS) in Metastatic Renal Cell Carcinoma: A Large, Multicenter Prospective Trial. Oncologist. 2021;02:02.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5661	Bex, A. Dynamic changes of the immune infiltrate after neoadjuvant avelumab/axitinib in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy (NeoAvAx). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5662	Cella, D. Quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST) of nivolumab plus cabozantinib (N+C) versus sunitinib (SUN) in treatment-naïve, advanced/metastatic renal cell carcinoma (aRCC): A post-hoc analysis of CheckMate 9ER (CM 9ER) data. 2021; ASCO Annual Meeting.	Outcomes not of interest
5663	Choueiri, TK. Integrating peripheral biomarker analyses from JAVELIN Renal 101: Avelumab + axitinib (A + Ax) versus sunitinib (S) in advanced renal cell carcinoma (aRCC). 2021; ASCO Annual Meeting.	Outcomes not of interest
5664	Donas, JG. Retrospective study for the characterization of COVID-19 in renal cancer (COVID-REN) patients treated with antiangiogenics or immunotherapy and outcome comparison with non-infected cases. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5665	Duarte, C. Treatment outcomes in renal cell carcinoma patients with metastases to the pancreas and other sites. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)

5666	Ernst, MS. The impact of antibiotic (Ab) exposure on clinical outcomes in patients with metastatic renal cell carcinoma (mRCC) treated with immune checkpoint inhibitors (ICI) or VEGF targeted therapy (VEGF-TT). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5667	Fallah, J. Survival benefit of nephrectomy prior to immunotherapy-based combinations in patients with metastatic renal cell carcinoma: An FDA pooled analysis. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5668	Farha, M. Characterization of the tumor immune microenvironment in clear cell renal cell carcinoma (ccRCC): Prognostic value and therapeutic implications of an M0-macrophage enriched subtype. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5669	Gan, CL. Outcomes of first-line (1L) ipilimumab and nivolumab (IPI-NIVO) and subsequent therapy in metastatic renal cell carcinoma (mRCC): Results from the International mRCC Database Consortium (IMDC). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5670	Gedye, C. Ipilimumab + nivolumab in people with rare variant renal cell carcinoma refractory to nivolumab alone: Part 2 of UNISON (ANZUP 1602) nivolumab then ipilimumab + nivolumab in advanced non-clear cell renal cell carcinoma. 2021; ASCO Annual Meeting.	Line of therapy not of interest (second-line or later)
5671	Ghatalia, P. Role of cytoreductive nephrectomy (CN) in metastatic renal cell carcinoma (mRCC). 2021; ASCO Annual Meeting.	Intervention not of interest
5672	Giles, RH. Patient-reported experience of diagnosis, management, and burden of renal cell carcinomas: Results from the 2020 Global Patient Survey from 41 countries. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5673	Gopalakrishnan, D. Immune checkpoint inhibitors (ICI) in advanced sarcomatoid renal cell carcinoma (sRCC): A multicenter study. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5675	Grigg, C. Survival trends of men and women with metastatic clear cell renal cell carcinoma. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5676	Grimm, M-O. Efficacy of nivolumab/ipilimumab in patients with initial or late progression with nivolumab: Updated analysis of a tailored approach in advanced renal cell carcinoma (TITAN-RCC). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5678	Haas, NB. Disease-free survival as a predictor of overall survival in localized renal cell carcinoma (RCC) following first nephrectomy. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)

5679	Hannan, R. Phase II trial of stereotactic ablative radiation (SAbR) for oligoprogressive kidney cancer. 2021; ASCO Annual Meeting.	Intervention not of interest
5680	Hutson, TE. Post hoc analysis of the CLEAR study in advanced renal cell carcinoma (RCC): Effect of subsequent therapy on survival outcomes in the lenvatinib (LEN) + everolimus (EVE) versus sunitinib (SUN) treatment arms. 2021; ASCO Annual Meeting.	Outcomes not of interest
5681	Kilari, D. Outcomes with novel combinations in non-clear cell renal cell carcinoma(nccRCC): ORACLE study. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5682	Kilari, D. Making Strides in the Treatment of Non-Clear Cell Carcinoma: Are We Ready for Adaptive and Biomarker-Driven Strategies? 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5683	Labaki, C. Effect of high-dose corticosteroid use on efficacy of immune checkpoint inhibitors in patients with renal cell carcinoma (RCC). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5684	Lee, C-H. KEYNOTE-B61: Open-label phase 2 study of pembrolizumab in combination with lenvatinib as first-line treatment for non-clear cell renal cell carcinoma (nccRCC). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5685	Lee, D. An FDA-pooled analysis of frontline combination treatment benefits by risk groups in metastatic renal cell carcinoma (mRCC). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5686	Masini, C. Programmed death ligand-1 (PD-L1) expression in patients (pts) with metastatic renal cell carcinoma (mRCC) treated with nivolumab (NIVO) in combination with stereotactic body radiotherapy (SBRT) in NIVES study. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5687	McGregor, BA. Cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) (CaNI) for advanced renal cell carcinoma with variant histology (aRCCVH). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5688	McGregor, BA. Efficacy outcomes of nivolumab + cabozantinib versus pembrolizumab + axitinib in patients with advanced renal cell carcinoma (aRCC): Matching-adjusted indirect comparison (MAIC). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5689	Meza, LA. First results of a randomized phase IB study comparing nivolumab/ipilimumab with or without CBM-588 in patients with metastatic renal cell carcinoma. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)

5690	Motzer, RJ. Long-term trend of quality-adjusted time without symptoms or toxicities (Q-TWiST) of nivolumab+ipilimumab (N+I) versus sunitinib (SUN) for the first-line treatment of advanced renal cell carcinoma (aRCC). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5691	Nazha, B. Circulating tumor DNA (ctDNA) in patients with advanced adrenocortical carcinoma. 2021; ASCO Annual Meeting.	Population not of interest (pediatric, not RCC/kidney cancer)
5692	O'Shea, PJ. Outcomes of immunotherapy (ICI) alone vs tyrosine kinase inhibitors (TKI) alone versus ICI and TKI combined in renal cell carcinoma brain metastasis. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5693	Pal, SK. Temporal characteristics of treatment-emergent adverse events and dose modifications with tivozanib and sorafenib in the phase 3 TIVO-3 study of relapsed or refractory mRCC. 2021; ASCO Annual Meeting.	Line of therapy not of interest (second-line or later)
5694	Perez-Gracia, JL. Randomized phase Ib study to evaluate safety, pharmacokinetics and therapeutic activity of simlukafusp α in combination with atezolizumab ± bevacizumab in patients with unresectable advanced/ metastatic renal cell carcinoma (RCC) (NCT03063762). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5695	Plimack, ER. A phase 1b/2 umbrella study of investigational immune and targeted combination therapies as first-line therapy for patients with advanced renal cell carcinoma (RCC). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5697	Rodriguez, CS. Clinical activity of durvalumab and savolitinib in MET-driven, metastatic papillary renal cancer. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5698	Seitz, R. Association with immune checkpoint inhibitor efficacy of a 27-gene classifier in renal cell cancer. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5699	Sheng, X. Vorolanib, everolimus, and the combination in patients with pretreated metastatic renal cell carcinoma (CONCEPT study): A randomized, phase 3, double-blind, multicenter trial. 2021; ASCO Annual Meeting.	Line of therapy not of interest (second-line or later)
5700	Soleimani, M. Plasma exosome microRNA-155 expression in patients with metastatic renal cell carcinoma treated with immune checkpoint inhibitors: A potential biomarker of response to systemic therapy. 2021; ASCO Annual Meeting.	Outcomes not of interest
5701	Srinivasan, R. Phase 2 study of belzutifan (MK-6482), an oral hypoxia-inducible factor 2α (HIF-2α) inhibitor, for Von Hippel-Lindau (VHL) disease-associated clear cell renal cell carcinoma (ccRCC). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5702	Tannir, NM. CANTATA: Primary analysis of a global, randomized, placebo (Pbo)-controlled, double-blind trial of telaglenastat (CB-839) + cabozantinib versus Pbo + cabozantinib in advanced/metastatic renal cell carcinoma (mRCC) patients (pts) who progressed on immune checkpoint inhibitor (ICI) or anti-angiogenic therapies. 2021; ASCO Annual Meeting.	Line of therapy not of interest (second-line or later)

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

5703	Tomita, Y. Association of C-reactive protein (CRP) with efficacy of avelumab + axitinib (A + Ax) in advanced renal cell carcinoma (aRCC): Long-term follow-up results from JAVELIN Renal 101. 2021; ASCO Annual Meeting.	Population not of interest (pediatric, not RCC/kidney cancer)
5704	Toni K. Choueiri, PT, Se Hoon Park, Balaji Venugopal, Tom Ferguson, Yen-Hwa Chang, Jaroslav Hajek, Stefan N. Symeonides, Jae-Lyun Lee, Naveed Sarwar, Antoine Thiery-Vuillemin, Marine Gross-Goupil, Mauricio Mahave, Naomi B. Haas, Piotr Sawrycki, Eric (Pingye) Zhang, Jaqueline Willemann Rogerio, Kentaro Imai, David I. Quinn, Thomas Powles. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for patients with renal cell carcinoma: Randomized, double-blind, phase III KEYNOTE-564 study. Paper presented at: ASCO Annual Meeting.	Intervention not of interest
5705	Tucker, MD. Association between neutrophil-to-eosinophil ratio (NER) and efficacy outcomes in the JAVELIN Renal 101 study. 2021; ASCO Annual Meeting.	Population not of interest (pediatric, not RCC/kidney cancer)
5706	Tucker, MD. Association of baseline neutrophil-to-eosinophil ratio (NER) and neutrophil-to-lymphocyte ratio (NLR) with response to combination immunotherapy (IO) with ipilimumab plus nivolumab (ipi/nivo) in patients with metastatic renal cell carcinoma (mRCC). 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5707	Verzoni, E. TIVO-3: Durability of response and updated overall survival of tivozanib versus sorafenib in metastatic renal cell carcinoma (mRCC). 2021; ASCO Annual Meeting.	Line of therapy not of interest (second-line or later)
5708	Wadiwala, J. Health care disparities and barriers to palliative care among metastatic renal cell carcinoma patients: An NCDB analysis. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5709	Zalcberg, JR. Multi-center phase 1 efficacy and safety study of nivolumab in renal transplant patients with metastatic malignancy. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5710	Zarrabi, K. Real-world outcomes in patients with metastatic clear cell renal cell carcinoma receiving front-line axitinib plus pembrolizumab versus ipilimumab plus nivolumab. 2021; ASCO Annual Meeting.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5711	Velasco, Gd. Novel Strategies to Improve Outcomes in Advanced Renal Cell Carcinoma. Paper presented at: ASCO Annual Meeting2021.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)
5712	Kapoor, A. Unanswered Questions in the Management of Advanced Renal Cell Carcinoma. Paper presented at: ASCO Annual Meeting2021.	Publication type/Study design not of interest (editorial, letter, commentary, SLR/MA/NMA prior to 2015, single-arm trials, case series, narrative review, pre-clinical, etc.)

Quality assessment of included studies

Quality of RCTs was assessed using the Cochrane Risk of Bias Assessment Tool 2.0 [98]. This tool agrees with the "Quality assessment of the relevant RCTs," which was described in the NICE single technology appraisal user guide for company evidence submission. This tool summarizes how well each study meets seven quality criteria on study randomization, concealment of treatment allocation, baseline differences, blinding

of patients and assessors, imbalances in withdrawals, completeness of reporting of outcomes, and use of intention-to-treat analyses, with an overall quality score awarded to each study.

Table 109: Cochrane Risk of Bias Assessment for Included Clinical Studies

Trial Name	Intervention	Risk of Bias Judgement					
		Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall
ASPEN [112]	Everolimus vs. sunitinib	?	?	?	?	?	?
AVOREN [106]	Bevacizumab + IFN alfa-2a vs. IFN alfa-2a + placebo	?	?	?	?	?	?
BeST [120]	Bevacizumab + temsirolimus vs. bevacizumab + sorafenib vs. sorafenib + temsirolimus vs. Bevacizumab	?	?	?	?	?	?
Bergmann 2020 [149]	Temsirolimus vs. sunitinib	?	?	?	?	?	?
BIONIKK [64]	Nivolumab vs. nivolumab + ipilimumab vs. sunitinib or pazopanib	?	?	?	?	?	?
Bukowski 2007[105]	Bevacizumab + erlotinib vs. bevacizumab	?	?	?	?	?	?
CABOSUN [115]	Cabozantinib vs. sunitinib	?	?	?	?	?	?
CALGB 90206 [121, 122]	Bevacizumab + IFN alfa-2b vs. IFN alfa-2b	?	?	?	?	?	?
CheckMate 214 [151]	Nivolumab + ipilimumab vs. sunitinib	?	?	?	?	?	?
CheckMate 9ER [150]	Nivolumab + cabozantinib vs. sunitinib	?	?	?	?	?	?
CLEAR [152]	Lenvatinib + pembrolizumab vs. lenvatinib + everolimus vs. sunitinib	?	?	?	?	?	?
COMPARZ [39]	Pazopanib vs. sunitinib	?	?	?	?	?	?
CROSS-J-RCC [153]	Sunitinib (1L)[a] vs. sorafenib (1L)[a]	?	?	?	?	?	?
Escudier 2009 [126]	IFN alfa-2a (1L)[a] vs. sorafenib (1L)[a]	?	?	?	?	?	?
ESPN [113]	Everolimus vs. sunitinib	?	?	?	?	?	?
Global ARCC [109]	Temsirolimus vs. IFN alfa-2a vs. IFN alfa-2a + temsirolimus	?	?	?	?	?	?
Hutson 2013 [131]	Axitinib vs. sorafenib	?	?	?	?	?	?
IMmotion150 [12]	Atezolizumab + bevacizumab vs. sunitinib vs. atezolizumab	?	?	?	?	?	?
IMmotion151 [133]	Atezolizumab + bevacizumab vs. sunitinib	?	?	?	?	?	?
JAVELIN Renal 101 [134]	Avelumab + axitinib vs. sunitinib	?	?	?	?	?	?
KEYNOTE-426 [136]	Pembrolizumab + axitinib vs. sunitinib	?	?	?	?	?	?
Lissoni 1993 [110]	IL-2 vs. IL-2 + IFN alfa-2b	?	?	?	?	?	?
Motzer 2007 [43]	Sunitinib vs. IFN alfa-2a	?	?	?	?	?	?

Trial Name	Intervention	Risk of Bias Judgement					
		Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall
Negrier 1998 [139]	IL-2 + IFN alfa-2° vs. IL-2 vs. IFN alfa-2a	?	?	?	?	?	?
PERCY Quattro [111]	IFN alfa-2a + IL-2 vs. Medroxy-progesterone vs. IFN alfa-2a vs. IL-2	?	?	?	?	?	?
RECORD-2 [140, 141]	Bevacizumab + everolimus vs. bevacizumab + IFN alfa-2a	?	?	?	?	?	?
RECORD-3 [142]	Everolimus vs. sunitinib	?	?	?	?	?	?
Rini 2013 [107]	Axitinib à axitinib titration vs. axitinib à placebo titration	?	?	?	?	?	?
ROPETAR [145]	Pazopanib (1L) vs. everolimus + pazopanib (rotating)	?	?	?	?	?	?
SWITCH [146]	Sorafenib (1L)[a] vs. sunitinib (1L)[a]	?	?	?	?	?	?
SWITCH II [147]	Sorafenib (1L)[a] vs. pazopanib (1L)[a]	?	?	?	?	?	?
TemPa [116]	Pazopanib vs. temsirolimus	?	?	?	?	?	?
TIVO-1 [148]	Tivozanib vs. sorafenib	?	?	?	?	?	?
VEG105192 [108]	Pazopanib vs. placebo	?	?	?	?	?	?

? = Low Risk; ?= Some Concerns; ?= High Risk; ? = Not Assessable

a These studies had protocol-defined treatments upon progression during 1L treatment; only 1L data is described in this report

Abbreviations: 1L, first-line; IFN, interferon; IL-2, interleukin-2

Unpublished data

No unpublished data was included.

Summary of Results

Table 110. Summary of PFS results

Study	Treatment (Intervention Followed by Comparators)	Duration of Follow-Up	Median PFS (95% CI), in Months	PFS HR (95% CI)
mTOR inhibitors				
RECORD-2 [140]	Bevacizumab + IFN alfa-2a (n=183)	NR	IRC: 10.02 (8.3, 12.9) p=0.485 INV: 10.5 (NR) (p value NR for INV)	IRC, unadjusted, stratified: 0.91 (0.69, 1.19) INV, unadjusted, stratified: 0.9 (0.71, 1.15) p=0.423
	Bevacizumab + everolimus (n=182)	NR	IRC: 9.3 (8.1, 11.2) INV: 9.2 (NR)	Reference
RECORD-3 [142, 154]	Everolimus (n=238)	NR	7.9 (5.6, 8.2)	1.4 (1.2, 1.8)
	Sunitinib (n=233)	NR	10.7 (8.2, 11.5)	Reference
ROPETAR [145]	Everolimus + pazopanib (rotating) (n=52)	NR	7.4 (5.6, 18.4) p=0.37	0.81 (0.5, 1.31) p=0.39
	Pazopanib (n=49)	NR	9.4 (6.6, 11.9)	Reference
Multikinase inhibitors				
CROSS-J-RCC [153]	Sunitinib (n=57)	NR	8.7 (5.5, 21.1)	0.67 (0.42, 1.08)[a] p=0.095
	Sorafenib (n=63)	NR	7.0 (6.1, 12.2)	Reference
Escudier 2009 [126]	IFN alfa-2a (n=92)	24 months	7 (NR)	0.88 (NR) p=0.47
	Sorafenib (n=97)	24 months	5.6 (NR)	Reference
Hutson, 2013 [131]	Axitinib (n=192)	23 months	10.1 (7.1, 12.1)	0.77 (0.56, 1.05)

Study	Treatment (Intervention Followed by Comparators)	Duration of Follow-Up	Median PFS (95% CI), in Months	PFS HR (95% CI)
				p=0.038
	Sorafenib (n=96)	23 months	6.5 (4.7, 8.3)	Reference
Motzer, 2007 [138]	Sunitinib (n=375)	NR	IRC: 48.3 (46.4, 58.3) weeks INV: 47.7 (46.3, 58.1) weeks	IRC: 0.514 (0.42, 0.63) p<0.00001 INV: 0.542 (0.45, 0.65) p<0.00001
	IFN alfa-2a (n=375)	NR	IRC: 22.1 (17.1, 24) weeks INV: 22.1 (16.7, 27.4) weeks	Reference
Rini, 2013 [107]	Axitinib à axitinib titration (n=56)	Median: 26.5 months	14.5 (9.2, 24.5)	0.85 (0.54, 1.35) p=0.24
	Axitinib à placebo titration (n=56)	Median: 26.4 months	15.7 (8.3, 19.4)	Reference
SWITCH [146]	Sorafenib (n=182)	Mean: 10.3 months	5.9 (90% CI: 5.5, 7.9)	1.19 (90% CI: 0.97, 1.47) p=0.9
	Sunitinib (n=183)	Mean: 10.3 months	8.5 (90% CI: 7.1, 11.2)	Reference
SWITCH II [147]	Sorafenib (n=189)	NR	5.6 (4.7, 6.3)	NR
	Pazopanib (n=188)	NR	9.3 (7.4, 10.6)	NR
Tyrosine kinase inhibitors				
Bukowski, 2007 [105]	Bevacizumab + erlotinib (n=50)	Median: 9.8 months	9.9 (NR)	0.86 (0.5, 1.49) p=0.58
	Bevacizumab + placebo (n=53)	Median: 9.8 months	8.5 (NR)	Reference
COMPARZ [39]	Pazopanib (n=557)	NR	IRC: 8.4 (8.3, 10.9) INV: 10.5 (8.3, 11.1)	IRC: 1.05 (0.9, 1.22) INV: 1 (0.86, 1.15)
	Sunitinib (n=553)	NR	IRC: 9.5 (8.3, 11.1) INV: 10.2 (8.3, 11.1)	Reference
TIVO-1 [148]	Tivozanib (n=181)	Minimum 20 months	12.7 (9.1, 15)	0.756 (0.58, 0.985) p=0.037
	Sorafenib (n=181)	Minimum 20 months	9.1 (7.3, 10.8)	Reference
VEG105192 [108]	Pazopanib (n=155)	NR	11.2 (NR)	0.4 (0.27, 0.6) p<0.0001
	Placebo (n=78)	NR	2.8 (NR)	Reference
Cytokines				
Lissoni, 1993 [110]	IL-2 (n=15)	Minimum 12 months	Mean: 10 (NR)	NR
	IL-2 + IFN alfa-2b (n=15)	Minimum 12 months	Mean: 11 (NR)	NR
PERCY Quattro [111]	IFN alfa-2a + IL-2 (n=122)	Median: 29.2 months	3.8 (3, 5.9)	NR
	IFN alfa-2a (n=122)	Median: 29.2 months	3.4 (3, 5.6)	NR
	IL-2 (n=125)	Median: 29.2 months	3.4 (2.9, 5.8)	NR
	Medroxyprogesterone (n=123)	Median: 29.2 months	3 (2.9, 3.6)	NR
PD-1 inhibitors/PD-L1 antibodies				
BIONIKK [64]	Nivolumab (n=NR)	Median: 16 months	4.9 (NR)	NR
	Nivolumab + ipilimumab (n=NR)	Median: 16 months	10.4 (NR)	NR
	Sunitinib or Pazopanib (n=NR)	Median: 16 months	Not yet reached	NR
CheckMate 214 [40, 155, 156]	Nivolumab + ipilimumab (n=550)	Minimum 30 months	9.7 (8.1, 11.1)	0.85 (0.73, 0.98)[a] p=0.027
		Median: 43.6 months	12.4 (9.8, 16.5)	0.88 (0.75, 1.04) p=0.1268
		4 years	12.2 (9.7, 16.5)	0.89 (0.76, 1.05)
	Sunitinib (n=546)	Minimum 30 months	9.7 (8.3, 11.1)	Reference
		Median: 32.3 months	12.3 (9.8, 15.4)	Reference
		4 years	12.3 (9.8, 15.2)	Reference
CheckMate 9ER [150, 157, 158]	Nivolumab + cabozantinib (n=323)	Median: 18.1 months	IRC: 16.6 (12.5, 24.9) INV: 19.4 (16.6, NE)	IRC: 0.51 (0.41, 0.64) p<0.0001 INV: 0.46 (0.36, 0.57) p<0.0001
		Median: 23.5 months	17 (12.6, 19.4)	0.52 (0.43, 0.64) p<0.0001
	Sunitinib (n=328)	Median: 18.1 months	IRC: 8.3 (7.0, 9.7) INV: 9.2 (7.1, 11.0)	Reference
		Median: 23.5 months	8.3 (6.9, 9.7)	Reference

Study	Treatment (Intervention Followed by Comparators)	Duration of Follow-Up	Median PFS (95% CI), in Months	PFS HR (95% CI)
CLEAR [152]	Lenvatinib + pembrolizumab (n=355)	Median: 26.7 months	IRC: 23.9 (20.8, 27.7) INV: 22.1 (17.1, 26.9)	IRC, vs. sunitinib: 0.39 (0.32, 0.49) p<0.0001 IRC, vs. lenvatinib + everolimus: 0.59 (0.48, 0.73) p<0.0001 INV, vs. sunitinib: 0.47 (0.38, 0.58) p<0.0001
	Lenvatinib + everolimus (n=357)	Median: 26.6 months	IRC: 14.7 (11.1, 16.7) INV: 14.6 (11.2, 18.0)	IRC: 0.65 (0.53, 0.80) p<0.0001 INV: 0.70 (0.57, 0.85) p=0.0004
	Sunitinib (n=357)	Median: 26.3 months	IRC: 9.2 (6.0, 11.0) INV: 9.5 (7.9, 11.1)	Reference
IMmotion150 [12]	Atezolizumab + bevacizumab (n=101)	33 months	IRC: 11.7 (8.4, 17.3) INV: 11.1 (8.2, 13.5)	IRC: 1 (0.69, 1.45) p=0.982 INV: 0.82 (0.59, 1.15) p=0.254
	Atezolizumab (n=103)	33 months	IRC: 6.1 (5.4, 13.6) INV: 5.5 (3, 8.4)	IRC: 1.19 (0.82, 1.71) p=0.358 INV: 1.18 (0.86, 1.63) p=0.31
	Sunitinib (n=101)	33 months	IRC: 8.4 (7, 14) INV: 7.8 (5.7, 11.2)	Reference
IMmotion151 [159]	Atezolizumab + bevacizumab (n=454)	Median: 15 months	IRC: 9.6 (8.3, 11.5) INV: 11.2 (9.6, 13.3)	IRC: 0.88 (0.74, 1.04) (p-value NR for IRC) INV: 0.83 (0.7, 0.97) p=0.0219
	Sunitinib (n=461)	Median: 15 months	IRC: 8.3 (7.0, 9.7) INV: 8.4 (7.5, 9.7)	Reference
JAVELIN Renal 101 [47, 134, 135]	Avelumab + axitinib (n=442)	Median: 9.9 months	13.8 (11.1, NE)	0.69 (0.56, 0.84) p<0.001
		Minimum 13 months	13.3 (11.1, 15.3)	0.69 (0.57, 0.82)
		NR	13.9 (11.1, 16.6)	0.67 (0.57, 0.79) P=0.012
	Sunitinib (n=444)	Median: 8.4 months	8.4 (6.9, 11.1)	Reference
		Minimum 13 months	8.0 (6.7, 9.8)	Reference
		NR	8.5 (8.2, 9.7)	Reference
KEYNOTE-426 [87, 136, 137]	Pembrolizumab + axitinib (n=432)	Median: 12.8 months	15.1 (12.6, 17.7)	0.69 (0.57, 0.84) p<0.001
		Median: 30.6 months	15.4 (12.7, 18.9)	0.71 (0.60, 0.84) p<0.0001
		Median: 42.8 months	15.7 (13.6, 20.2)	0.68 (0.58, 0.8) p<0.001
	Sunitinib (n=429)	Median: 12.8 months	11.1 (8.7, 12.5)	Reference
		Median: 30.6 months	11.1 (9.1, 12.5)	Reference
		Median: 42.8 months	11.1 (8.9, 12.5)	Reference
VEGF ligand inhibitor				
AVOREN [160]	Bevacizumab + IFN alfa-2a (n=327)	Median: 23 months	10.2 (NR)	Unstratified: 0.75 (0.64, 0.88) p=0.0004
	IFN alfa-2a + placebo (n=322)	Median: 21 months	5.5 (NR)	Reference
BeST [120]	Bevacizumab + temsirolimus (n=80)	NR	7.6 (90% CI: 6.7, 9.2) p=0.89	NR
	Sorafenib + temsirolimus (n=84)	NR	7.4 (90% CI: 5.6, 7.9) p=0.68	NR
	Bevacizumab + sorafenib (n=83)	NR	9.2 (90% CI: 7.5, 11.4) p=0.54	NR
	Bevacizumab (n=84)	NR	7.5 (90% CI: 5.8, 10.8)	NR
CALGB 90206 [122]	Bevacizumab + IFN alfa-2b (n=369)	24 months	8.5 (7.5, 9.7) p<0.0001	0.67 (0.57, 0.79) p<0.0001
	IFN alfa-2b (n=363)	24 months	5.2 (3.1, 5.6)	Reference

Table 111. Summary OS results

Study	Treatment (Intervention Followed by Comparators)	Duration of Follow-Up	Median OS (95% CI), in Months	OS HR (95% CI)
mTOR inhibitors				
RECORD-2 [140]	Bevacizumab + IFN alfa-2a (n=183)	NR	27.1 (20.4, 30.8)	Unadjusted, stratified: 1.01 (0.75, 1.34) p=0.961
	Bevacizumab + everolimus (n=182)	NR	27.1 (19.9, 35.3)	Reference
ROPETAR [145]	Everolimus + pazopanib (rotating) (n=52)	NR	35 (>12.2, NR)	0.9 (0.51, 1.58) p=0.7
	Pazopanib (n=49)	NR	18.5 (>14.7, NR)	Reference
Multikinase inhibitors				
Hutson, 2013[131]	Axitinib (n=192)	23 months	21.7 (18, 31.7)	0.995 (0.731, 1.356) p=0.4883
	Sorafenib (n=96)	23 months	23.3 (18.1, 33.2)	Reference
Motzer, 2007 [44, 138]	Sunitinib (n=375)	123 weeks	26.4 (23, 32.9) weeks	0.818 (0.669, 0.9995) p=0.049
	IFN alfa-2a (n=375)	123 weeks	21.8 (17.9, 26.9) weeks	Reference
Rini, 2013 [161]	Axitinib à axitinib titration (n=56)	NR (final analysis)	42.7 (24.7, NR)	0.79 (0.49, 1.27) p=0.162
	Axitinib à placebo titration (n=56)	NR (final analysis)	30.4 (23.7, 45.0)	Reference
Tyrosine kinase inhibitors				
Bukowski, 2007 [162]	Bevacizumab + erlotinib (n=50)	Median: 9.8 months	NR	1.764 (NR) p=0.1789
	Bevacizumab + placebo (n=53)	Median: 9.8 months	NR	Reference
COMPARZ [163]	Pazopanib (n=557)	NR	28.3 (26, 35.5)	0.92 (0.79, 1.06) p=0.24
	Sunitinib (n=553)	NR	29.1 (25.4, 33.1)	Reference
TIVO-1 [164]	Tivozanib (n=181)	NR	NR	Unadjusted for crossover: 1.230 (0.671, 1.553)
	Sorafenib (n=181)	NR	NR	Reference
VEG105192 [165]	Pazopanib (n=155)	NR	22.9 (17.6, 25.4)	1.01 (0.72, 1.42)
	Placebo (n=78)	NR	23.5 (12, 34.3)	Reference
Cytokines				
Negrier 1998 [139]	IFN alfa-2a + IL-2 (n=140)	Median: 39 months	17 (NR)	NR
	IFN alfa-2a (n=147)	Median: 39 months	13 (NR)	NR
	IL-2 (n=138)	Median: 39 months	12 (NR)	NR
PERCY Quattro [111]	IFN alfa-2a + IL-2 (n=122)	Median: 29.2 months	16.8 (14, 18.9)	NR
	IFN alfa-2a (n=122)	Median: 29.2 months	15.2 (12.8, 19.9)	NR
	IL-2 (n=125)	Median: 29.2 months	15.3 (13.3, 20)	NR
	Medroxyprogesterone (n=123)	Median: 29.2 months	14.9 (11.7, 19.2)	NR
PD-1 inhibitors/PD-L1 antibodies				
CheckMate 214 [40, 155, 156]	Nivolumab + ipilimumab (n=550)	Minimum 30 months	Not reached (NE)	0.71 (0.59, 0.86)[a] p=0.0003
		Median: 43.6 months	Not reached (46.3, NE)	0.72 (0.61, 0.86)
		4 years	Not reached (46.7, NE)	0.69 (0.59, 0.81)
	Sunitinib (n=546)	Minimum 30 months	37.9 (32.2, NE)	Reference
		Median: 32.3 months	38.4 (32.0, 44.7)	Reference
		4 years	38.4 (32.0, 45.0)	Reference
CheckMate 9ER [150, 158]	Nivolumab + cabozantinib (n=323)	Median: 18.1 months	Not reached (NE)	0.60 (0.40, 0.89) p=0.0010
		Median: 23.5 months	Not reached (NE)	0.66 (0.5, 0.87) P=0.0034
	Sunitinib (n=328)	Median: 18.1 months	Not reached (22.6, NE)	Reference
		Median: 23.5 months	29.5 (28.4, NE)	Reference
CLEAR [152]	Lenvatinib + pembrolizumab (n=355)	Median: 26.7 months	Not reached (33.6, NE)	0.66 (0.49, 0.88) p=0.0049
		Median: 33.7 months	Not reached (41.5, NE)	0.72 (0.55, 0.93)
	Lenvatinib + everolimus (n=357)	Median: 26.6 months	Not reached (NE)	1.15 (0.88, 1.50) p=0.2975
	Sunitinib (n=357)	Median: 26.3 months	Not reached (NE)	Reference
		Median: 33.4 months	Not reached (38.4, NE)	Reference
IMmotion151 [159]	Atezolizumab + bevacizumab (n=454)	Median: 15 months	33.6 (29.0, NE)	0.93 (0.76, 1.14) p=0.4751
	Sunitinib (n=461)	Median: 15 months	34.9 (27.8, NE)	Reference
JAVELIN Renal 101 [47, 134, 135]	Avelumab + axitinib (n=442)	Median: 9.9 months	Not reached (NR)	0.78 (0.554, 1.084) p=0.14
		Minimum 13 months	Not reached (30.0, NE)	0.80 (0.616, 1.027) RPSFT adjusted: 0.65 (0.41, 0.93)
		NR	Not reached (42.2, NE)	0.79 (0.64, 0.97)

Study	Treatment (Intervention Followed by Comparators)	Duration of Follow-Up	Median OS (95% CI), in Months	OS HR (95% CI)
				p=0.012
	Sunitinib (n=444)	Median: 8.4 months	Not reached (NR)	Reference
		Minimum 13 months	Not reached (27.4, NE)	Reference
		NR	37.8 (31.4, NE)	Reference
KEYNOTE-426 [87, 136, 137]	Pembrolizumab + axitinib (n=432)	Median: 12.8 months	Not reached (NR)	0.53 (0.38, 0.74) p<0.0001
		Median: 30.6 months	Not reached (NR)	0.68 (0.55, 0.85) p=0.0003
		Median: 42.8 months	45.7 (43.6, NE)	0.73 (0.6, 0.88) p<0.001
	Sunitinib (n=429)	Median: 12.8 months	Not reached (NR)	Reference
		Median: 30.6 months	35.7 (33.3, NE)	Reference
		Median: 42.8 months	40.1 (34.3, 44.2)	Reference
VEGF ligand inhibitor				
AVOREN [160]	Bevacizumab + IFN alfa-2a (n=327)	Median: 23 months	23.3 (NR)	Unstratified: 0.91 (0.76, 1.1) p=0.336
	IFN alfa-2a + placebo (n=322)	Median: 21 months	21.3 (NR)	Reference
BeST [120]	Bevacizumab + temsirolimus (n=80)	NR	24.7 (90% CI: 21.4, 35.3)	NR
	Sorafenib + temsirolimus (n=84)	NR	24.3 (90% CI: 19.7, 34.7)	NR
	Bevacizumab + sorafenib (n=83)	NR	27.5 (90% CI: 21.5, 37.4)	NR
	Bevacizumab (n=84)	NR	28.6 (90% CI: 22.3, 34.9)	NR
CALGB 90206 [121]	Bevacizumab + IFN alfa-2b (n=369)	24 months	18.3 (16.5, 22.5) p=0.097	0.86 (0.73, 1.01) p=0.069
	IFN alfa-2b (n=363)	24 months	17.4 (14.4, 20)	Reference

Table 112. Summary of Response Outcomes

Study	Timeframe of Response Assessment	Treatment (Intervention Followed by Comparators)	ORR, n (%)	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	DOR, Median (95% CI)
mTOR inhibitors								
RECORD-2 [141]	From randomization to December 2011 DCO	Bevacizumab + everolimus (n=182)	49 (26.9%)	0 (0%)	49 (26.9%)	90 (49.5%)	25 (13.7%)	13.3 (10.7, 16.7) months
		Bevacizumab + IFN alfa-2a (n=183)	51 (27.9%)	1 (0.5%)	50 (27.3%)	84 (45.9%)	26 (14.2%)	11.3 (10.4, not estimatible) months
RECORD-3 [143]	Up to 35 months	Everolimus (n=238)	19 (8.0%)	1 (0.4%)	18 (7.6%)	NR	NR	All responders: 13.37 (8.3, NE) months Responders still alive at final analysis (n=7): NR (range: 3.1–4.9) years
		Sunitinib (n=233)	62 (26.6%)	3 (1.3%)	59 (25.3%)	NR	NR	All responders: 17.25 (11.4, NE) months Responders still alive at final analysis (n=4): NR (range: 3.1–4.2) years
Multikinase inhibitors								
CROSS-J-RCC [153]	NR	Sunitinib (n=57)	14 (29.8%)	2 (4.3%)	12 (25.5%)	14 (30.0%)	19 (40.4%)	32.0 (NR) monhts
		Sorafenib (n=63)	10 (21.3%)	1 (2.1%)	9 (19.1%)	22 (46.8%)	15 (31.9%)	14.9 (NR) months
Escudier, 2009[126]	24 months	IFN alfa-2a (n=92)	NR	1 (1.1%)	7 (7.6%)	51 (55.4%)	24 (26.1%)	NR
		Sorafenib (n=97)	NR	0 (0%)	5 (5.2%)	72 (74.2%)	10 (10.3%)	NR
Hutson, 2013[131]	At primary analysis (follow-up NR)	Axitinib (n=192)	62 (32%)	0 (0%)	62 (32%)	Duration of SD: ≥20 weeks: 45 (23%) <20 weeks: 38 (20%)	20 (10%)	14.7 (11, NE) months
		Sorafenib (n=96)	14 (15%)	0 (0%)	14 (15%)	Duration of SD: ≥20 weeks: 26 (27%) <20 weeks: 25 (26%)	12 (13%)	14.3 (11.3, NE) months
Motzer, 2007 [44, 138]	Over duration of treatment phase	Sunitinib (n=375)	IRC: 145 (38.7%)[a] INV: 176 (47%)	INV: 11 (3%)	INV: 165 (44%)	INV: 150 (40%)	INV: 26 (7%)	IRC: 56.3 (48.4, 64.9) weeks INV: 52.9 (46.1, 60.1) weeks
		IFN alfa-2a (n=375)	IRC: 29 (7.7%)[a] INV: 46 (12%)	INV: 4 (1%)	INV: 42 (11%)	INV: 202 (54%)	INV: 69 (18%)	IRC: 48.1 (42.1, 120.1) weeks INV: 64.9 (41.9, 82) weeks
Rini, 2013 [107, 161]	At follow-up, median (IQR): 26.5 (24.3–28.9) months	Axitinib à axitinib titration (n=56)	30 (54%)	1 (2%)	29 (52%)	13 (23%)	13 (23%)	Not reached (NR)
	At follow-up, median (IQR): 26.4 (25.0–28.6) months	Axitinib à placebo titration (n=56)	19 (34%)	0 (0%)	19 (34%)	24 (43%)	11 (20%)	21.2 (11.1, 25.8) months
	At the final analysis (follow-up duration NR)	Axitinib à axitinib titration (n=56)	NR	NR	NR	NR	35 (63%)	NR
		Axitinib à placebo titration (n=56)	NR	NR	NR	NR	40 (71%)	NR
SWITCH [146]	During 1L treatment	Sorafenib (n=177)	55 (31%)	5 (2.8%)	50 (28%)	68 (38%)	NR	NR
		Sunitinib (n=176)	51 (29%)	6 (3.4%)	45 (26%)	61 (35%)	NR	NR

Study	Timeframe of Response Assessment	Treatment (Intervention Followed by Comparators)	ORR, n (%)	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	DOR, Median (95% CI)
SWITCH II [147]	During 1L treatment	Sorafenib (n=189)	54 (28.6%)	5 (2.6%)	49 (25.9%)	74 (39.2%)	33 (17.5%)	NR
		Pazopanib (n=188)	87 (46.3%)	5 (2.7%)	82 (43.6%)	59 (31.4%)	21 (11.2%)	NR
Tyrosine kinase inhibitors								
Bukowski, 2007[105]	2 years for complete response assessment, NR for other outcomes	Bevacizumab + erlotinib (n=50)	7 (14%)	1 (2.0%)[a]	NR	34 (68%)	8 (16%)	9.1 (range: 1.6–13.9) months
		Bevacizumab + placebo (n=53)	7 (13%)	0 (0%)	NR	36 (68%)	9 (17%)	6.7 (range: 1.8–9.2) months
COMPARZ [39]	At primary analysis (follow-up NR)	Pazopanib (n=557)	IRC: 171 (31%) INV: 186 (33%)	IRC: 1 (<1%) INV: 3 (<1%)	IRC: 170 (31%) INV: 183 (33%)	IRC: 216 (39%) INV: 231 (41%)	IRC: 97 (17%) INV: 78 (14%)	NR
		Sunitinib (n=553)	IRC: 137 (25%) INV: 160 (29%)	IRC: 3 (<1%) INV: 8 (1%)	IRC: 134 (24%) INV: 152 (27%)	IRC: 242 (44%) INV: 239 (43%)	IRC: 105 (19%) INV: 93 (17%)	NR
VEG105192 [108]	At primary analysis (follow-up NR)	Pazopanib (n=155)	49 (32%)	NR	NR	NR	NR	NR
		Placebo (n=78)	3 (4%)	NR	NR	NR	NR	NR
Cytokines								
Lissoni, 1993[110]	12 month minimum follow-up	IL-2 (n=15)	NR	0 (0%)	5 (33%)	7 (47%)	3 (20%)	PR, mean: 15 (NR) months SD, mean: 7 (NR) months
		IL-2 + IFN alfa-2b (n=15)	NR	0 (0%)	4 (27%)	7 (47%)	4 (27%)	PR, mean: 10 (NR) months SD, mean: 13 (NR) months
Negrier, 1998[139]	10 weeks	IL-2 + IFN alfa-2a (n=140)	NR	1 (0.7%)[a]	25 (17.9%)[a]	31 (22.1%)[a]	63 (45.0%)[a]	NR
		IFN alfa-2a (n=147)	NR	0 (0%)[a]	11 (7.5%)[a]	46 (31.3%)[a]	87 (59.2%)[a]	NR
		IL-2 (n=138)	NR	2 (1.4%)[a]	7 (5.1%)[a]	30 (21.7%)[a]	78 (56.5%)[a]	NR
PERCY Quattro [111]	12 weeks	IFN alfa-2a + IL-2 (n=110)	NR	0 (0%)[a]	12 (10.9%)[a]	41 (37.3%)[a]	57 (51.8%)[a]	NR
		IFN alfa-2a (n=115)	NR	1 (0.9%)[a]	4 (3.5%)[a]	49 (42.6%)[a]	61 (53%)[a]	NR
		IL-2 (n=120)	NR	1 (0.8%)	4 (3.3%)	52 (43.3%)	63 (52.5%)	NR
		Medroxyprogesterone (n=120)	NR	1 (0.8%)	2 (1.7%)	43 (35.8%)	74 (61.7%)	NR
	6 months	IFN alfa-2a + IL-2 (n=113)	NR	0 (1.7%)	8 (3.4%)	27 (17.5%)	78 (77.5%)	NR
		IFN alfa-2a (n=115)	NR	3 (0.4%)	7 (2.5%)	23 (18.4%)	82 (78.7%)	NR
		IL-2 (n=119)	NR	0 (0%)	5 (5.6%)	26 (22.8%)	88 (71.6%)	NR
		Medroxyprogesterone (n=120)	NR	1 (1.3%)	1 (6.6%)	18 (21.9%)	100 (70.2%)	NR
PD-1 inhibitors/PD-L1 antibodies								
BIONIKK [64]	At first interim analysis, median: 16 months	Nivolumab (n=NR)	NR (30%)	NR	NR	NR	NR	NR
		Nivolumab + ipilimumab (n=NR)	NR (44%)	NR	NR	NR	NR	NR
		Sunitinib or Pazopanib (n=NR)	NR (50%)	NR	NR	NR	NR	NR
CheckMate 214 [40, 68, 155, 156, 166]	For ORR: 30 month minimum follow-up	Nivolumab + ipilimumab (ITT: n=550) (int/poor-risk: n=425)	NR (41%)	NR (11%)	NR	NR	NR	IMDC intermediate-/ poor-risk only: Not reached (21.8 months, NE)

Study	Timeframe of Response Assessment	Treatment (Intervention Followed by Comparators)	ORR, n (%)	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	DOR, Median (95% CI)
	For response duration: median 25.2 month follow-up	Sunitinib (ITT: n=535) (int/poor risk: n=422)	NR (34%)	NR (2%)	NR	NR	NR	IMDC intermediate-/ poor-risk only: 18.2 (14.8, NE) months
	Median: 43.6 months	Nivolumab + ipilimumab (n=550)	NR (39.1%)	NR (10.7%)	NR (28.4%)	NR (35.8%)	NR (18.2%)	Not reached (NE)
	Median: 32.3 months	Sunitinib (n=535)	NR (32.6%)	NR (2.4%)	NR (30.2%)	NR (41.6%)	NR (14.5%)	24.8 (19.4, 27.3)
	Minimum 48 months	Nivolumab + ipilimumab (n=550)	NR (39.1%)	59 (10.7%)	156 (28.4%)	198 (36.0%)	97 (17.6%)	Not reached (49.5, NE)
		Sunitinib (n=535)	NR (32.4%)	14 (2.6%)	163 (29.9%)	230 (42.1%)	77 (14.1%)	23.7 (19.4, 29.0)
	At 4 years	Nivolumab + ipilimumab (n=550)	NR (39%)	NR (11%)	NR	NR	NR	NR
		Sunitinib (n=535)	NR (32%)	NR (3%)	NR	NR	NR	NR
CheckMate 9ER [150, 158]	At first interim follow-up, median: 18.1 months	Nivolumab + cabozantinib (n=323)	IRC: NR (55.7%) INV: NR (59.4%)	IRC: NR (8.0%) INV: NR (3.4%)	IRC: NR (47.7%) INV: NR (56.0%)	IRC: NR (32.2%) INV: NR (30.0%)	IRC: NR (5.6%) INV: NR (5.3%)	20.2 (17.3, NE)
		Sunitinib (n=328)	IRC: NR (59.4%) INV: NR (55.7%)	IRC: NR (8.0%) INV: NR (3.4%)	IRC: NR (47.7%) INV: NR (56.0%)	IRC: NR (32.2%) INV: NR (30.0%)	IRC: NR (5.6%) INV: NR (5.3%)	11.5 (8.3, 18.4)
	At second follow-up, median: 23.5 months	Nivolumab + cabozantinib (n=323)	NR (54.8%)	30 (9.3%)	NR	NR	NR	NR
		Sunitinib (n=328)	NR (28.4%)	14 (4.3%)	NR	NR	NR	NR
CLEAR [152]	At first analysis (Nov. 2019, follow-up duration NR)	Lenvatinib + pembrolizumab (n=355)	IRC: 239 (67.3%) INV: NR	IRC: 39 (11.0%) INV: NR	IRC: 200 (56.3%) INV: NR	IRC: 81 (22.8%) INV: NR	IRC: 17 (4.8%) INV: NR	IRC: 25.8 (20.1, NE) INV: NR
		Lenvatinib + everolimus (n=357)	IRC: 181 (50.7%) INV: NR	IRC: 23 (6.4%) INV: NR	IRC: 158 (44.3%) INV: NR	IRC: 131 (36.7%) INV: NR	IRC: 25 (7.0%) INV: NR	IRC: 16.1 (13.1, NE) INV: NR
		Sunitinib (n=357)	IRC: 125 (35.0%) INV: NR	IRC: 14 (3.9%) INV: NR	IRC: 111 (31.1%) INV: NR	IRC: 144 (40.3%) INV: NR	IRC: 48 (13.4%) INV: NR	IRC: 14.7 (9.4, 18.4) INV: NR
	At second analysis (Aug. 2020, follow-up duration NR)	Lenvatinib + pembrolizumab (n=355)	IRC: 252 (71.0%) INV: 244 (68.7%)	IRC: 57 (16.1%) INV: 36 (10.1%)	IRC: 195 (54.9%) INV: 208 (58.6%)	IRC: 68 (19.2%) INV: 74 (20.8%)	IRC: 19 (5.4%) INV: 22 (6.2%)	IRC: NR INV: 26.3 (20.6, 28.7)
		Lenvatinib + everolimus (n=357)	IRC: 191 (53.5%) INV: 192 (54.3%)	IRC: 35 (9.8%) INV: 9 (2.5%)	IRC: 156 (43.7%) INV: 185 (51.8%)	IRC: 120 (33.6%) INV: 127 (35.6%)	IRC: 26 (7.3%) INV: 13 (3.6%)	IRC: NR INV: 18.4 (15.0, 22.4)
		Sunitinib (n=357)	IRC: 129 (36.1%) INV: 122 (34.2%)	IRC: 15 (4.2%) INV: 7 (2.0%)	IRC: 114 (31.9%) INV: 115 (32.2%)	IRC: 136 (38.1%) INV: 159 (44.5%)	IRC: 50 (14.0%) INV: 33 (9.2%)	IRC: NR INV: 14.8 (11.2, 19.7)
IMmotion150 [12]	At survival analysis, median follow-up: 20.7 months	Atezolizumab + bevacizumab (n=101)	32 (32%)	NR (7%)	NR (25%)	NR	NR	NR
		Atezolizumab (n=103)	26 (25%)	NR (11%)	NR (14%)	NR	NR	NR
		Sunitinib (n=101)	29 (29%)	NR (5%)	NR (24%)	NR	NR	NR
IMmotion151 [133, 159]	At primary analysis, median follow-up: 13 months	Atezolizumab + bevacizumab (n=454)	IRC: NR INV: 168 (36%)[a]	IRC: 49 (11%) INV: 24 (5%)	IRC: NR INV: 142 (31%)	IRC: NR INV: 178 (39%)	IRC: NR INV: 80 (18%)	NR
		Sunitinib (n=460)	IRC: NR INV: 153 (33%)[a]	IRC: 32 (7%) INV: 10 (2%)	IRC: NR INV: 143 (31%)	IRC: NR INV: 178 (39%)	IRC: NR INV: 87 (19%)	NR
	At survival analysis, median follow-up: 15 months	Atezolizumab + bevacizumab (n=454)	IRC: 151 (33%) INV: 166 (37%)	NR	NR	NR	NR	16.6 (15.4, NE) months

Study	Timeframe of Response Assessment	Treatment (Intervention Followed by Comparators)	ORR, n (%)	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	DOR, Median (95% CI)
		Sunitinib (n=460)	IRC: 144 (31%) INV: 153 (33%)	NR	NR	NR	NR	14.2 (11.3, NE) months
JAVELIN Renal 101 [47, 134]	At primary analysis, median follow-up: 9.9 months	Avelumab + axitinib (n=442)	IRC: 227 (51.4%) INV: NR (55.9%)	IRC: 15 (3.4%) INV: 14 (3.2%)	IRC: 212 (48%) INV: 233 (52.7%)	IRC: 131 (29.6%) INV: 127 (28.7%)	IRC: 51 (11.5%) INV: 38 (8.6%)	IRC: not reached (NE) INV: not reached (11.9 months, NE)
	At primary analysis, median follow-up: 8.4 months	Sunitinib (n=444)	IRC: 114 (25.7%) INV: NR (30.2%)	IRC: 8 (1.8%) INV: 10 (2.3%)	IRC: 106 (23.9%) INV: 124 (27.9%)	IRC: 202 (45.5%) INV: 202 (45.5%)	IRC: 83 (18.7%) INV: 68 (15.3%)	IRC: not reached (11.2 months, NE) INV: 12.6 (8.3, 15.3) months
	Minimum 13 months follow-up	Avelumab + axitinib (n=442)	IRC: 232 (52.5%) INV: NR	IRC: 17 (3.8%) INV: NR	IRC: 215 (48.6%) INV: NR	IRC: 125 (28.3%) INV: NR	IRC: 55 (12.4%) INV: NR	18.5 (17.8, NE)
		Sunitinib (n=444)	IRC: 121 (27.3%) INV: NR	IRC: 9 (2.0%) INV: NR	IRC: 112 (25.2%) INV: NR	IRC: 194 (43.7%) INV: NR	IRC: 86 (19.4%) INV: NR	Not reached (16.4, NE)
KEYNOTE-426 [87, 136, 137]	At primary analysis, median follow-up: 12.8 months	Pembrolizumab + axitinib (n=432)	NR (59.3%)	25 (5.8%)	231 (53.5%)	106 (24.5%)	47 (10.9%)	Not reached (range: 1.4+–18.2+ months)
		Sunitinib (n=429)	NR (35.7%)	8 (1.9%)	145 (33.8%)	169 (39.4%)	73 (17.0%)	15.2 (range: 1.1+–15.4+) months
	Median follow-up: 30.6 months	Pembrolizumab + axitinib (n=432)	260 (60%)	38 (9%)	222 (51%)	100 (23%)	49 (11%)	23.5 (19.4, 29.0)
		Sunitinib (n=429)	171 (40%)	13 (3%)	158 (37%)	150 (35%)	74 (17%)	15.9 (13.8, 20.4)
	Median follow-up: 42.8 monts	Pembrolizumab + axitinib (n=432)	NR (60.4%)	43 (10%)	NR	NR	NR	23.6 (range: 1.4+–43.4+)
		Sunitinib (n=429)	NR (39.6%)	15 (3.5%)	NR	NR	NR	15.3 (range: 2.3 –42.8+)
VEGF ligand inhibitors								
AVOREN [106]	At primary clinical DCO, median (range) follow-up: 13.3 (0–25.6) months	Bevacizumab + IFN alfa-2a (n=306)	96 (31%)	4 (1%)	92 (30%)	141 (46%)	61 (20%)	13.5 (range: 1.8–20.3) months
	At primary clinical DCO, median (range) follow-up: 12.8 (0–24.2) months	IFN alfa-2a + placebo (n=289)	37 (13%)	6 (2%)	31 (11%)	144 (50%)	95 (33%)	11.1 (range: 3.7–19.5) months
BeST [120]	At 6 months for stable disease assessment Up to 5 years for ORR assessment	Bevacizumab + temsirolimus (n=80)	NR (31.6%)	NR	NR	NR (56.2%)	NR	NR
		Sorafenib + temsirolimus (n=84)	NR (20.2%)	NR	NR	NR (52.4%)	NR	NR
		Bevacizumab (n=84)	NR (13.3%)	NR	NR	NR (54.8%)	NR	NR
		Bevacizumab + sorafenib (n=83)	NR (30.5%)	NR	NR	NR (59.0%)	NR	NR

Study	Timeframe of Response Assessment	Treatment (Intervention Followed by Comparators)	ORR, n (%)	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	DOR, Median (95% CI)
CALGB 90206 [122]	At primary analysis (follow-up duration NR)	Bevacizumab + IFN alfa-2b (n=NR)	NR (25.5%)	NR	NR	NR	NR	11.9 (8.3, 14.8) months
		IFN alfa-2b (n=NR)	NR (13.1%)	NR	NR	NR	NR	8.7 (5.6, 11.4) months

Table 113 Summary of Safety Results

Study	Treatment (Intervention Followed by Comparators)	Grade 3+ AEs, n (%)	Grade 3+ TRAEs, n (%)	Total Discontinuations, n (%)	AE-related Discontinuations, n (%)
mTOR inhibitors					
Bergmann, 2020[149]	Temsirolimus (n=12)	NR	NR	NR	1 (8.3) [a]
	Sunitinib (n=10)	NR	NR	NR	0 (0) [a]
RECORD-2 [140]	Bevacizumab + everolimus (n=182, ITT) (n=180, mITT)	mITT, grade 3; Grade 4: 106 (58.9); 39 (21.7)	NR	ITT: 175 (96.2)	ITT: 41 (23.4)
	Bevacizumab + IFN alfa-2a (n=183, ITT) (n=181, mITT)	mITT, grade 3; Grade 4: 99 (54.7); 39 (21.5)	NR	ITT: 175 (95.6)	ITT: 47 (26.9)
RECORD-3 [142, 167]	Everolimus (n=238)	NR	Grade 3/4: NR (47)	201 (85)	NR
	Sunitinib (n=233)	NR	Grade 3/4: NR (63)	192 (82)	NR
ROPETAR [145]	Pazopanib (n=49)	NR	NR	42 (86)	5 (10)
	Everolimus + pazopanib (rotating) (n=52)	NR	NR	40 (78)	6 (12)
Multikinase inhibitors					
CROSS-J-RCC [124, 153]	Sunitinib (n=57)	NR	NR	54 (95)	13 (22.8)
	Sorafenib (n=63)	NR	NR	62 (98)	12 (19)
Escudier, 2009 [126, 127]	IFN alfa-2a (n=92)	Interim, grade 3+: 49 (54.4)	Interim, grade 3+: 32 (35.6)	Interim: 16 (17)[a]	Interim: 14 (15)[a] Final: NR (22)
	Sorafenib (n=97)	Interim, grade 3+: 68 (70.1)	Interim, grade 3+: 40 (41.2)	Interim: 15 (15)[a]	Interim: 11 (11)[a] Final: NR (25)
Hutson, 2013 [131]	Axitinib (n=189, mITT)	NR	NR	NR	10 (5)
	Sorafenib (n=96, mITT)	NR	NR	NR	4 (4)
Motzer, 2007 [44, 138]	Sunitinib (n=375, PP) (n=375, ITT)	NR	NR	PP: 323 (86)[a]	ITT: 76 (20)[a]
	IFN alfa-2a (n=360, PP) (n=375, ITT)	NR	NR	PP: 354 (98)[a]	ITT: 86 (23)[a]
Rini, 2013 [107, 161]	Axitinib à Axitinib titration (n=56)	NR	NR	47 (84)	Interim: 5 (9)[a] Final: 8 (14)
	Axitinib à Placebo titration (n=56)	NR	NR	55 (98)	Interim: 4 (7)[a] Final: 5 (9)
SWITCH [146]	Sorafenib (n=182, ITT) (n=177, mITT)	Grade 3/4, mITT: 117 (66)	NR	ITT: 161 (88)[a]	ITT: 19 (10)[a]
	Sunitinib (n=183, ITT) (n=176, mITT)	Grade 3/4, mITT: 118 (67)	NR	ITT: 156 (85)[a]	ITT: 29 (16)[a]
SWITCH II [147]	Sorafenib (n=189)	Grade 3/4: 108 (59)	NR	115 (61)	28 (15)
	Pazopanib (n=188)	Grade 3/4: 117 (64)	NR	110 (59)	25 (13)
Tyrosine kinase inhibitors					
Bukowski, 2007[105]	Bevacizumab + erlotinib (n=51)	Grade 3/4: NR (65)	NR	NR	4 (8)[a]
	Bevacizumab + placebo (n=53)	Grade 3/4: NR (59)	NR	NR	3 (6)[a]

Study	Treatment (Intervention Followed by Comparators)	Grade 3+ AEs, n (%)	Grade 3+ TRAEs, n (%)	Total Discontinuations, n (%)	AE-related Discontinuations, n (%)
COMPARZ [39]	Pazopanib (n=554, PP)	Grade 3: 327 (59) Grade 4: 85 (15) Grade 5: 13 (2)	Drug-related fatal AEs: 3 (1)	486 (88)	135 (24)
	Sunitinib (n=548, PP)	Grade 3: 311 (57) Grade 4: 91 (17) Grade 5: 19 (3)	Drug-related fatal AEs: 8 (1)	483 (88)	112 (20)
Cytokines					
PERCY Quattro [111]	IFN alfa-2a + IL-2 (n=119, PP)	Grade 3/4: 89 (74.8)	NR	NR	NR
	IL-2 (n=124, PP)	Grade 3/4: 77 (62.1)	NR	NR	NR
	IFN alfa-2a (n=122, PP)	Grade 3/4: 49 (40.2)	NR	NR	NR
	Medroxyprogesterone (n=121, PP)	Grade 3/4: 12 (9.9)	NR	NR	NR
PD-L1 antibody/PD-1 inhibitors					
CheckMate-214 [40, 68, 151]	Nivolumab + ipilimumab (n=547)	NR	Interim: 250 (46) Final, grade 3/4: 259 (47.9)	Final: 494 (90.3) [a]	Interim: 118 (22) Final: 121 (22.1)
	Sunitinib (n=535)	NR	Interim: 335 (63) Final, grade 3/4: 343 (64.1)	Final: 520 (97.2) [a]	Interim: 63 (12) Final: 69 (12.9)
CheckMate 9ER [150, 157, 168]	Nivolumab + cabozantinib (n=323, ITT) (n=320, As treated)	Interim, As treated: 241 (75.3)[b] Final, As treated: NR (78.4)[b]	Interim, ITT: NR (60.6) Final, As treated: NR (62.2)[b]	NR	Interim, ITT: NR (5.6)
	Sunitinib (n=328, ITT) (n=320, As treated)	Interim, As treated: 226 (70.6)[b] Final, As treated: NR (73.1)[b]	Interim, ITT: NR (50.9) Final, As treated: NR (52.5)[b]	NR	Interim, ITT : NR (16.9)
CLEAR [152, 169]	Lenvatinib + pembrolizumab (n=352)	Interim: 290 (82.4)	Interim: 252 (71.6)	Interim: 210 (59.2) Final: 238 (67)[c]	Interim: 131 (37.2) Final: 68 (19.2)[c]
	Lenvatinib + everolimus (n=355)	Interim: 295 (83.1)	Interim: 259 (73.0) [a,d]	Interim: 243 (68.1)	Interim: 96 (27)
	Sunitinib (n=340)	Interim: 244 (71.8)	Interim: 200 (58.8)	Interim: 273 (76.5) Final: 291 (81.5)[d]	Interim: 49 (14.4) Final: 43 (12)[d]
IMmotion150 [12]	Atezolizumab + bevacizumab (n=101)	Grade 3/4: 64 (63)	Grade 3/4: 40 (40)	NR	15 (15)
	Atezolizumab (n=103)	Grade 3/4: 41 (40)	Grade 3/4: 17 (17)	NR	7 (7)
	Sunitinib (n=100)	Grade 3/4: 69 (69)	Grade 3/4: 57 (57)	NR	10 (10)
IMmotion151 [133, 170]	Atezolizumab + bevacizumab (n=454)	NR	Grade 3/4: NR (40)	NR	Discontinuation of treatment regimen: 24 (5) Discontinuation of any component: 53 (12)
	Sunitinib (n=461)	NR	Grade 3/4: NR (54)	NR	Discontinuation of treatment regimen: 37 (8) Discontinuation of any component: 37 (8)
JAVELIN Renal 101 [47, 134]	Avelumab + axitinib (n=434, as treated)	Grade 3+: 309 (71.2)	Grade 3+: 246 (56.7)	242 (54.8)[f]	33 (7.6)
	Sunitinib (n=439, as treated)	Grade 3+: 314 (71.5)	Grade 3+: 243 (55.4)	336 (75.7)[g]	59 (13.4)
KEYNOTE-426 [87, 136]	Pembrolizumab + axitinib (n=429)	Initial: NR (75.8)	Initial: Grade 3+: 270 (62.9) Interim: Grade 3: 250 (58) Grade 4: 33 (8) Grade 5: 4 (1) Final: 291 (67.8)	Initial: 176 (41)[a] Interim: 312 (72.7) [a] Final: 349 (82.4) [a]	Initial: NR (10.7) Interim: 78 (18.2) [a] Final: 83 (19.3) [a]

Study	Treatment (Intervention Followed by Comparators)	Grade 3+ AEs, n (%)	Grade 3+ TRAEs, n (%)	Total Discontinuations, n (%)	AE-related Discontinuations, n (%)
	Sunitinib (n=425)	Initial: NR (70.6)	Initial: grade 3+: 247 (58.1) Interim: Grade 3: 233 (55) Grade 4: 26 (6) Grade 5: 6 (1) Final: 271 (63.8)	Initial: 242 (57)[a] Interim: 349 (82.1)[a] Final: 385 (90.6)[a]	Initial: NR (13.9) Interim: 69 (16.2)[a] Final: 78 (18.4)[a]
VEGF ligand inhibitors					
AVOREN [160]	Bevacizumab + IFN alfa-2a (n=337, Safety population, not described further)	Grade 3–5: 211 (63)	NR	NR	105 (31)
	IFN alfa-2a + placebo (n=304, Safety population, not described further)	Grade 3–5: 139 (46)	NR	NR	37 (12)
BeST [120]	Bevacizumab + temsirolimus (n=91)	NR	NR	91 (100)[a]	17 (19)[a]
	Sorafenib + temsirolimus (n=91)	NR	NR	91 (100)[a]	18 (20)[a]
	Bevacizumab (n=89)	NR	NR	89 (100)[a]	11 (12)[a]
	Bevacizumab + sorafenib (n=90)	NR	NR	90 (100)[a]	20 (22)[a]
CALGB 90206 [121, 122]	Bevacizumab + IFN alfa-2b (n=369, ITT)(N=362, mITT)	NR	Final, mITT, grade 3+: 290 (80)	Interim, ITT: 355 (96)[a]	Interim, ITT: 85 (24)
	IFN alfa-2b (n=363, ITT) (n=347, mITT)	NR	Final, mITT, grade 3+: 217 (63)	Interim, ITT: 355 (98)[a]	Interim, ITT: 66 (19)

Table 114. PFS and OS Effect Modification by Risk Score

Study	Risk Group	Treatment (Intervention Followed by Comparator)	Median PFS (95% CI), in months	HR for PFS (95% CI)	Median OS (95% CI), in months	HR for OS (95% CI)
ASPEN [112]	MSKCC Favorable + non-clear cell histology	Everolimus (n=14)	5.7 (5.6–8.4)	2.9 (80% CI: 1.5–5.7)	NR	NR
		Sunitinib (n=15)	14 (11.5–19.7)	Reference	NR	NR
	MSKCC Intermediate + non-clear cell histology	Everolimus (n=32)	4.9 (3–5.6)	1.38 (80% CI: 0.96–2)	NR	NR
		Sunitinib (n=32)	6.5 (5.7–11)	Reference	NR	NR
	MSKCC Poor + non-clear cell histology	Everolimus (n=11)	6.1 (3.1–7.3)	0.3 (80% CI: 0.1–0.7)	NR	NR
		Sunitinib (n=4)	4 (0.9–5.8)	Reference	NR	NR
AVOREN [106, 171]	MSKCC Favorable	Bevacizumab + IFN alfa-2a (n=87)	NR	0.6 (0.42–0.85)	35.1 (25–45.6)	0.92 (0.62–1.37) p=0.6798
		IFN alfa-2a + placebo (n=93)	NR	Reference	37.2 (25–47.7)	Reference
	MSKCC Intermediate	Bevacizumab + IFN alfa-2a (n=183 for PFS, n=200 for OS)	NR	0.55 (0.44–0.7)	22.6 (18.3–25.8)	0.83 (0.65–1.05) p=0.1230
		IFN alfa-2a + placebo (n=180 for PFS, n=192 for OS)	NR	Reference	19.3 (14.8–22.8)	Reference
	MSKCC Poor	Bevacizumab + IFN alfa-2a (n=29 for PFS, n=30 for OS)	NR	0.81 (0.46–1.42)	6 (2.8–11.8)	0.85 (0.49–1.47) p=0.5594
		IFN alfa-2a + placebo	NR	Reference	5.1 (2.6–10.5)	Reference

Study	Risk Group	Treatment (Intervention Followed by Comparator)	Median PFS (95% CI), in months	HR for PFS (95% CI)	Median OS (95% CI), in months	HR for OS (95% CI)
		(n=25 for PFS, n=29 for OS)				
CABOSUN [38]	IMDC Intermediate and Poor	Cabozantinib (n=79)	IRC: 8.6 (6.8–14) INV: 8.3 (6.5–12.4)	IRC: 0.48 (0.31–0.74) p=0.0008 INV: 0.56 (0.37–0.83) p=0.0042	26.6 (14.6, Not estimable)	0.8 (0.53–1.21) p=0.27
		Sunitinib (n=78)	IRC: 5.3 (3–8.2) INV: 5.4 (3.4–8.2)	Reference	21.2 (16.3–27.4)	Reference
	IMDC Intermediate	Cabozantinib (n=64)	11.4 (NR)	0.52 (0.32–0.82)	NR	NR
		Sunitinib (n=63)	6.1 (NR)	Reference	NR	NR
	IMDC Poor	Cabozantinib (n=15)	6.8 (NR)	0.31 (0.11–0.92)	NR	NR
		Sunitinib (n=15)	2.7 (NR)	Reference	NR	NR
CALGB 90206 [121, 122]	MSKCC Favorable	Bevacizumab + IFN alfa-2b (n=97)	11.1 (9–13.8)	NR	32.5 (21.6–43.7)	0.895 (0.64–1.253)[b] p=0.5189
		IFN alfa-2b (n=95)	5.7 (3.6–8.3)	NR	33.5 (24.3–39.4)	Reference
	MSKCC Intermediate	Bevacizumab + IFN alfa-2b (n=234)	8.4 (6.1–9.9)	NR	17.7 (15.6–22.5)	0.867 (0.708–1.062)[b] p=0.1688
		IFN alfa-2b (n=231)	5.3 (3.1–5.7)	NR	16.1 (13.4–19.9)	Reference
	MSKCC Poor	Bevacizumab + IFN alfa-2b (n=38)	3.3 (2.2–4.7)	NR	6.6 (5.9–8.9)	0.748 (0.458–1.219)[b] p=0.2439
		IFN alfa-2b (n=37)	2.6 (1.6–3.1)	NR	5.7 (4.4–9.2)	Reference
CheckMate 214 [40, 155, 156, 172, 173]	IMDC Favorable	Nivolumab + ipilimumab (n=125)	Minimum 30 months: 13.9 (9.9–17.9) Median 43.6 months: 17 (9.7–20.7) Minimum 48 months: 12.4 (9.7–18)	Minimum 30 months: 1.23 (0.9–1.69) p=0.443 Median 43.6 months: 1.65 (1.16–2.35) p=0.0049 Minimum 48 months: 1.84 (1.29–2.62)	Minimum 30 months: Not yet reached (Not estimable) Median 43.6 months: Not yet reached (Not estimable) Minimum 48 months: Not yet reached (Not estimable)	Minimum 30 months: 1.13 (0.64–1.99) p=0.671 Median 43.6 months: 1.19 (0.77–1.85) p=0.4383 Minimum 48 months: 0.93 (0.62–1.40)
		Sunitinib (n=124)	Minimum 30 months: 19.9 (15.1–23.5)	Reference	Minimum 30 months: Not yet reached (Not estimable)	Reference

Study	Risk Group	Treatment (Intervention Followed by Comparator)	Median PFS (95% CI), in months	HR for PFS (95% CI)	Median OS (95% CI), in months	HR for OS (95% CI)
			Median 32.3 months: 28.8 (23.2–34.5) Minimum 48 months: 28.9 (22.1–38.4)		Median 32.3 months: Not yet reached (Not estimable) Minimum 48 months: Not yet reached (56–Not estimable)	
	IMDC Intermediate and Poor	Nivolumab + ipilimumab (n=425)	Minimum 30 months: 8.2 (6.9–10) Median 43.6 months: 11.6 (8.4–15.5) Minimum 48 months: 11.2 (8.4–16.1)	Minimum 30 months: 0.77 (0.65–0.9) p=0.001 Median 43.6 months: 0.75 (0.62–0.90) p=0.0015 Minimum 48 months: 0.74 (0.62–0.88)	Minimum 30 months: Not reached (32.49, Not reached) Median 32.3 months: 47.0 (35.6–Not estimable) Minimum 48 months: 48.1 (35.6–Not estimable)	Minimum 30 months: 0.66 (0.48–0.91) p<0.0001 Median 43.6 months: 0.72 (0.61–0.86) p=0.0002 Minimum 48 months: 0.65 (0.54–0.78)
		Sunitinib (n=422)	Minimum 30 months: 8.3 (7–8.8) Median 32.3 months: 8.3 (7–10.8) Minimum 48 months: 8.3 (7–10.8)	Reference	Minimum 30 months: 26.97 (22.08–34.83) Median 32.3 months: 26.6 (22.1–33.5) Minimum 48 months: 26.6 (22.1–33.5)	Reference
	1 IMDC risk factor	Nivolumab + ipilimumab (n=189)	Minimum 30 months: 10.1 (8.1–14.0)	Minimum 30 months: 0.77 (0.60–0.99)	Minimum 30 months: Not reached (Not estimable)	Minimum 30 months: 0.62 (0.44–0.87)
		Sunitinib (n=172)	Minimum 30 months: 8.9 (8.3–12.2)	Reference	Minimum 30 months: 37.8 (32.3–Not estimable)	Reference
	2 IMDC risk factors	Nivolumab + ipilimumab (n=172)	Minimum 30 months: 6.9 (5.5–9.5)	Minimum 30 months: 0.83 (0.62–1.12)	Minimum 30 months: Not reached (32.1–Not estimable)	Minimum 30 months: 0.72 (0.51–1.02)
		Sunitinib (n=125)	Minimum 30 months: 8.3 (5.6–9.7)	Reference	Minimum 30 months: 28.6 (17–Not estimable)	Reference
	3 IMDC risk factors	Nivolumab + ipilimumab (n=55)	Minimum 30 months: 10.7 (3.0–15.0)	Minimum 30 months: 0.44 (0.27–0.73)	Minimum 30 months: 25.8 (18.5–35.2)	Minimum 30 months: 0.50 (0.31–0.82)
		Sunitinib (n=47)	Minimum 30 months: 5.4 (2.9–7.0)	Reference	Minimum 30 months: 11.9 (6.2–16.2)	Reference
	4–6 IMDC risk factors	Nivolumab + ipilimumab (n=35)	Minimum 30 months: 4.5 (2.5–8.5)	Minimum 30 months: 0.86 (0.5–1.49)	Minimum 30 months: 13.9 (7.4–25.2)	Minimum 30 months: 0.63 (0.36–1.10)

Study	Risk Group	Treatment (Intervention Followed by Comparator)	Median PFS (95% CI), in months	HR for PFS (95% CI)	Median OS (95% CI), in months	HR for OS (95% CI)
		Sunitinib (n=38)	Minimum 30 months: 4.0 (2.7–4.4)	Reference	Minimum 30 months: 5.7 (4.1–10.5)	Reference
CheckMate 9ER [150, 158]	IMDC Favorable	Nivolumab + cabozantinib (n=74)	At 23.5 months:[c] 24.7 (13.1-NE)	At 18.1 months:[c] 0.62 (0.38–1.01) At 23.5 months:[c] 0.58 (0.36-0.93)	At 23.5 months:[c] Not estimable (Not estimable–Not estimable)	At 18.1 months:[c] 0.84 (0.35–1.97) At 23.5 months:[c] 0.94 (0.46-1.92)
		Sunitinib (n=72)	At 23.5 months:[c] 12.8 (9.6-18.5)	Reference	At 23.5 months:[c] Not estimable (28.4–Not estimable)	Reference
	IMDC Intermediate	Nivolumab + cabozantinib (n=188)	At 23.5 months:[c] 17.5 (11.3-19.4)	At 18.1 months:[c] 0.54 (0.40–0.72) At 23.5 months:[c] 0.58 (0.45 - 0.76)	At 23.5 months:[c] Not estimable (Not estimable–Not estimable)	At 18.1 months:[c] 0.70 (0.46–1.07) At 23.5 months:[c] 0.74 (0.5-1.08)
		Sunitinib (n=188)	At 23.5 months:[c] 8.5 (7-9.8)	Reference	At 23.5 months:[c] Not estimable (Not estimable–Not estimable)	Reference
	IMDC Poor	Nivolumab + cabozantinib (n=61)	At 23.5 months:[c] 9.9 (5.9-17.7)	At 18.1 months:[c] 0.37 (0.23–0.58) At 23.5 months:[c] 0.36 (0.23 - 0.56)	At 23.5 months:[c] Not estimable (21.4– Not estimable)	At 18.1 months:[c] 0.37 (0.21–0.66) At 23.5 months:[c] 0.45 (0.27-0.76)
		Sunitinib (n=68)	At 23.5 months:[c] 4.2 (2.9-5.6)	Reference	At 23.5 months:[c] 11.2 (6.8 - 19.8)	Reference
CLEAR [152, 169][d]	IMDC Favorable	Lenvatinib + pembrolizumab (n=110)	28.1 (22–Not estimable)	0.41 (0.28–0.62) p<0.0001	At 26.6 months:[c] Not estimable (33.6–Not estimable) At 33.7 months:[c] Not estimable (Not estimable–Not estimable)	At 26.6 months:[c] 1.15 (0.55–2.4) At 33.7 months:[c] 1.22 (0.66–2.26)
		Lenvatinib + everolimus (n=114)	20.2 (NR)	0.55 (0.38–0.81)	Not estimable (NR)	1.01 (0.46–2.19)
		Sunitinib (n=124)	12.9 (11.1–18.4)	Reference	At 26.6 months:[c] Not estimable (Not estimable–Not estimable)	Reference

Study	Risk Group	Treatment (Intervention Followed by Comparator)	Median PFS (95% CI), in months	HR for PFS (95% CI)	Median OS (95% CI), in months	HR for OS (95% CI)
					At 33.4 months:[c] Not estimable (Not estimable–Not estimable)	
	IMDC Intermediate	Lenvatinib + pembrolizumab (n=210)	22.1 (16.6–27.7)	0.39 (0.29–0.52) p<0.0001	At 26.6 months:[c] Not estimable (32.4–Not estimable) At 33.7 months:[c] 43 (40.2–Not estimable)	At 26.6 months:[c] 0.72 (0.50–1.05) At 33.7 months:[c] 0.72 (0.52–1)
		Lenvatinib + everolimus (n=195)	12.7 (NR)	0.67 (0.51–0.88)	Not estimable (NR)	1.22 (0.86–1.72)
		Sunitinib (n=192)	7.1 (5.6–9.4)	Reference	At 26.6 months:[c] Not estimable (Not estimable–Not estimable) At 33.4 months:[c] 41.1 (32–Not estimable)	Reference
	IMDC Poor	Lenvatinib + pembrolizumab (n=33)	22.1 (10.8–Not estimable)	0.28 (0.13–0.6) p=0.0009	At 26.6 months:[c] Not estimable (19.4–Not estimable) At 33.7 months:[c] 36.9(19.4–Not estimable)	At 26.6 months:[c] 0.30 (0.14–0.64) At 33.7 months:[c] 0.39 (0.2–0.77)
		Lenvatinib + everolimus (n=42)	5.6 (NR)	0.73 (0.42–1.29)	8.0 (NR)	0.90 (0.52–1.54)
		Sunitinib (n=37)	4.0 (2.4–5.6)	Reference	At 26.6 months:[c] 10.4 (4.2–12.7) At 33.4 months:[c] 10.4 (4.2–12.7)	Reference
	IMDC Intermediate + Poor	Lenvatinib + pembrolizumab (n=243)	22.1 (16.6–27.6)	0.36 (0.28–0.47) p<0.0001	Not estimable (32.4–Not estimable)	At 26.6 months:[c] 0.58 (0.42–0.80) p=0.001 At 33.7 months:[c] 0.62 (0.46–0.83)
		Sunitinib (n=229)	5.9 (5.6–7.5)	Reference	Not estimable (30.7–Not estimable)	Reference

Study	Risk Group	Treatment (Intervention Followed by Comparator)	Median PFS (95% CI), in months	HR for PFS (95% CI)	Median OS (95% CI), in months	HR for OS (95% CI)
	MSKCC Favorable	Lenvatinib + pembrolizumab (n=96)	27.6 (20.3–29.7)	0.36 (0.23–0.54) p<0.0001	At 26.6 months:[c] Not estimable (33.6–Not estimable) At 33.7 months:[c] Not estimable (Not estimable–Not estimable)	At 26.6 months:[c] 0.86 (0.38–1.92) p=0.706 At 33.7 months:[c] 1 (0.51–1.96)
		Lenvatinib + everolimus (n=98)	20.3 (NR)	0.45 (0.30–0.67)	Not estimable (NR)	0.54 (0.21–1.35)
		Sunitinib (n=97)	11.1 (10.1–13.1)	Reference	At 26.6 months:[c] Not estimable (Not estimable–Not estimable) At 33.4 months:[c] Not estimable (Not estimable–Not estimable)	Reference
	MSKCC Intermediate	Lenvatinib + pembrolizumab (n=227)	24.3 (17.5–28.6)	0.44 (0.34–0.58) p<0.0001	At 26.6 months:[c] Not estimable (33.1–Not estimable) At 33.7 months:[c] 43 (40.2–Not estimable)	At 26.6 months:[c] 0.66 (0.47–0.94) p=0.0196 At 33.7 months:[c] 0.71 (0.52–0.97)
		Lenvatinib + everolimus (n=227)	12.8 (NR)	0.75 (0.59–0.97)	Not estimable (NR)	1.19 (0.87–1.62)
		Sunitinib (n=228)	7.9 (6.0–11.0)	Reference	At 26.6 months:[c] Not estimable (Not estimable–Not estimable) At 33.4 months:[c] 41.1 (34.5–Not estimable)	Reference
	MSKCC Poor	Lenvatinib + pembrolizumab (n=32)	11.8 (9.1–23.4)	0.18 (0.08–0.42) p<0.0001	At 26.6 months:[c] Not estimable (16.6–Not estimable) At 33.7 months:[c] 33 (16.6–Not estimable)	At 26.6 months:[c] 0.50 (0.23–1.08) p=0.0775 At 33.7 months:[c] 0.5 (0.25–1.02)
		Lenvatinib + everolimus (n=32)	5.5 (NR)	0.68 (0.36–1.28)	7.5 (NR)	[c] 1.50 (0.78–2.88)
		Sunitinib (n=32)	5.6 (3.4–5.6)	Reference	At 26.6 months:[c] 16.5 (8.9–Not estimable)	Reference

Study	Risk Group	Treatment (Intervention Followed by Comparator)	Median PFS (95% CI), in months	HR for PFS (95% CI)	Median OS (95% CI), in months	HR for OS (95% CI)
					At 33.4 months:[c] 17.1 (8.9–32.7)	
	MSKCC Intermediate + Poor	Lenvatinib + pembrolizumab (n=259)	22.1 (16.7–27.6)	0.44 (0.34–0.56) p<0.0001	Not estimable (33.1–Not estimable)	At 26.6 months:[c] 0.66 (0.48–0.90) p=0.0093 At 33.7 months:[c] 0.67 (0.51–0.90)
		Sunitinib (n=260)	7.2 (5.6–9.2)	Reference	Not estimable (Not estimable–Not estimable)	Reference
COMPARZ [163, 174]	MSKCC Favorable	Pazopanib (n=151)	NR	NR	42.5 (37.9, Not reached)	0.88 (0.63–1.21)
		Sunitinib (n=152)	NR	NR	43.6 (37.1–47.4)	Reference
	MSKCC Intermediate	Pazopanib (n=322)	NR	NR	26.9 (23.1–35.6)	0.9 (0.74–1.09)
		Sunitinib (n=328)	NR	NR	26.1 (20.7–31.6)	Reference
	MSKCC Poor	Pazopanib (n=67)	NR	1.472 (0.937–2.313)	9.9 (7.3–12.3)	0.85 (0.56–1.28)
		Sunitinib (n=52)	NR	Reference	7.7 (5.4–11.9)	Reference
CROSS-J-RCC [124, 153]	MSKCC Favorable	Sunitinib (n=NR)	31.2 (NR)	0.27 (0.08–0.9) p=0.023	NR	NR
		Sorafenib (n=NR)	6.2 (NR)	Reference	NR	NR
	All risk groups (primary analysis population)	Sunitinib (n=57)	8.7 (NR)	0.67 (0.42–1.08)	NR	NR
		Sorafenib (n=63)	7 (NR)	Reference	NR	NR
Global ARCC [128]	Modified MSKCC Poor[a]	IFN alfa-2a + temsirolimus (n=210)	4.9 (3.9–6)	0.76 (0.62–0.94) p=0.0107	8.4 (6.6–10.3)	0.93 (0.75–1.15) p=0.4902
		Temsirolimus (n=209)	5.6 (3.9–7.2)	0.74 (0.6–0.91) p=0.0042	10.9 (8.6–12.7)	0.78 (0.63–0.97) p=0.0252
		IFN alfa-2a (n=207)	3.2 (2.2–4)	Reference	7.3 (6.1–8.8)	Reference
Hutson, 2013 [131]	MSKCC Favorable	Axitinib (n=94)	NR	0.64 (0.4–1.02)	NR	NR
		Sorafenib (n=53)	NR	Reference	NR	NR
	MSKCC Intermediate, Poor, or Not available	Axitinib (n=NR)	NR	0.83 (0.54–1.28)	NR	NR
		Sorafenib (n=NR)	NR	Reference	NR	NR
IMmotion150 [12]	MSKCC Favorable	Atezolizumab + bevacizumab (n=30)	NR	0.75 (NR)	NR	NR
		Atezolizumab (n=26)	NR	1.54 (NR)	NR	NR

Study	Risk Group	Treatment (Intervention Followed by Comparator)	Median PFS (95% CI), in months	HR for PFS (95% CI)	Median OS (95% CI), in months	HR for OS (95% CI)
		Sunitinib (n=21)	NR	Reference	NR	NR
	MSKCC Intermediate	Atezolizumab + bevacizumab (n=62)	NR	1.06 (NR)	NR	NR
		Atezolizumab (n=69)	NR	1.08 (NR)	NR	NR
		Sunitinib (n=70)	NR	Reference	NR	NR
	MSKCC Poor	Atezolizumab + bevacizumab (n=9)	NR	0.91 (NR)	NR	NR
		Atezolizumab (n=8)	NR	0.68 (NR)	NR	NR
		Sunitinib (n=10)	NR	Reference	NR	NR
JAVELIN Renal 101 [47, 134, 175]	IMDC Favorable	Avelumab + axitinib (n=94)	At 9.9 months:[c]. Not estimable (16.1–Not estimable) Minimum 13 months: 24.0 (20.7–not estimable) DCO (April 2020): 20.7 (16.6-26.3)	At 9.9 months:[c].0.54 (0.321–0.907)[b] Minimum 13 months: 0.626 (0.397–0.986) DCO (April 2020): 0.71 (0.49-1.02)	At 9.9 months:[c].NR Minimum 13 months: Not estimable DCO (April 2020): Not estimable (Not estimable–Not estimable)	At 9.9 months:[c].NR Minimum 13 months: 0.812 (0.336–1.96) DCO (April 2020): 0.66 (0.36-1.22)
		Sunitinib (n=96)	At 8.4 months:[c]. 13.8 (11.1–18.6) Minimum 13 months: 16.7 (12.6–not estimable) DCO (April 2020): 13.8 (11.1-23.5)	Reference	At 8.4 months:[c].NR Minimum 13 months: Not estimable DCO (April 2020): Not estimable (39.8–Not estimable)	Reference
	IMDC Intermediate	Avelumab + axitinib (n=271)	At 9.9 months:[c]. 13.8 (9.7–not estimable) Minimum 13 months: 11.6 (8.4–15.2) DCO (April 2020): 12.9 (11.1-6.6)	At 9.9 months:[c].0.74 (0.57–0.95)[b] Minimum 13 months: 0.756 (0.603–0.948) DCO (April 2020): 0.71 (0.58-0.86)	At 9.9 months:[c].NR Minimum 13 months: 30.0 (30.0–not estimable) DCO (April 2020): 42.2 (33.1-Not Estimatable)	At 9.9 months:[c].NR Minimum 13 months: 0.86 (0.615–1.202) DCO (April 2020): 0.84 (0.65-1.08)
		Sunitinib (n=276)	At 8.4 months:[c]. 8.4 (7.0–11.2) Minimum 13 months: 8.3 (6.9–11.0) DCO (April 2020): 8.4 (7.9-10.1)	Reference	At 8.4 months:[c].NR Minimum 13 months: 28.6 (27.4–not estimable) DCO (April 2020): 37.8 (29.6-Not Estimatable)	Reference

Study	Risk Group	Treatment (Intervention Followed by Comparator)	Median PFS (95% CI), in months	HR for PFS (95% CI)	Median OS (95% CI), in months	HR for OS (95% CI)
	IMDC Poor	Avelumab + Axitinib (n=72)	At 9.9 months:[c]. 6.0 (3.6–8.7) Minimum 13 months: 6.0 (3.0–9.0) DCO (April 2020): 8.7 (5.6-11.1)	At 9.9 months:[c].0.57 (0.375–0.88)[b] Minimum 13 months: 0.514 (0.342–0.774) DCO (April 2020): 0.45 (0.30-0.68)	At 9.9 months:[c].NR Minimum 13 months: 21.2 (14.7–26.3) DCO (April 2020): 21.3 (14.7-33.1)	At 9.9 months:[c].NR Minimum 13 months: 0.57 (0.363–0.895) DCO (April 2020): 0.6 (0.40-0.91)
		Sunitinib (n=71)	At 8.4 months:[c]. 2.9 (2.7–5.5) Minimum 13 months: 2.9 (2.7–5.6) DCO (April 2020): 4.2 (2.8-5.5)	Reference	At 8.4 months:[c].NR Minimum 13 months: 11.0 (7.8–16.5) DCO (April 2020): 11 (7.8-16.5)	Reference
	IMDC Intermediate + Poor	[redacted]	DCO (April 2020): 11.1 (9.8-14.6)	DCO (April 2020): 0.66 (0.55-0.79)	DCO (April 2020): 40 (30.5-Not Estimatable)	DCO (April 2020): 0.79 (0.64-0.98)
		[redacted]	DCO (April 2020): 8.2 (6.9-8.4)	Reference	DCO (April 2020): 29.5 (24.8-38)	Reference
	MSKCC Favorable	Avelumab + axitinib (n=96)	At 9.9 months:[c]. Not estimable (12.6–Not estimable) Minimum 13 months: NR	At 9.9 months:[c].0.65 (0.397–1.072)[b] Minimum 13 months: 0.726 (0.466–1.132) DCO (April 2020): 0.8 (0.56-1.11)	NR	At 9.9 months:[c].NR Minimum 13 months: 1.198 (0.517–2.775) DCO (April 2020): 0.80 (0.45-1.45)
		Sunitinib (n=100)	At 8.4 months:[c]. 16.7 (11.1–18.6) Minimum 13 months: NR	Reference	NR	Reference
	MSKCC Intermediate	Avelumab + axitinib (n=283)	At 9.9 months:[c]. 13.3 (8.5–not estimable) Minimum 13 months: NR	At 9.9 months:[c].0.72 (0.559–0.915) Minimum 13 months: 0.715 (0.575–0.889) DCO (April 2020): 0.66 (0.54-0.81)	NR	At 9.9 months:[c].NR Minimum 13 months: 0.724 (0.527–0.995) DCO (April 2020): 0.73 (0.57-0.94)
		Sunitinib (n=294)	At 8.4 months:[c]. 7.9 (6.7–9.8) Minimum 13 months: NR	Reference	NR	Reference

Study	Risk Group	Treatment (Intervention Followed by Comparator)	Median PFS (95% CI), in months	HR for PFS (95% CI)	Median OS (95% CI), in months	HR for OS (95% CI)
KEYNOTE-426 [87, 136, 137, 176]	MSKCC Poor	Avelumab + axitinib (n=51)	At 9.9 months:[c]. 5.6 (2.6–11.2) Minimum 13 months: NR	At 9.9 months:[c].0.5 (0.296–0.827) Minimum 13 months: 0.465 (0.283–0.763) DCO (April 2020): 0.39 (0.24-0.62)	NR	At 9.9 months:[c].NR Minimum 13 months: 0.638 (0.371–1.099) DCO (April 2020): 0.74 (0.45-1.21)
		Sunitinib (n=44)	At 8.4 months:[c]. 2.8 (1.5–2.9) Minimum 13 months: NR	Reference	NR	Reference
	IMDC Favorable	Pembrolizumab + axitinib (n=138)	At 12.8 months:[c] 17.7 (15.2, not evaluable) At 30.6 months:[c] 20.8 (15.4–28.8) At 42.8 months: [c] 20.7 (NR)	At 12.8 months:[c] 0.81 (0.53–1.24)[b] At 30.6 months:[c] 0.79 (0.57–1.09) p=0.078 At 42.8 months: [c] 0.76 (0.56, 1.03)	At 12.8 months:[c] NR At 30.6 months:[c] Not reached (NR)	At 12.8 months:[c] 0.64 (0.24–1.68)[b] At 30.6 months:[c] 1.06 (0.6–1.86) p=0.58 At 42.8 months: [c] 1.17 (0.76, 1.8)
		Sunitinib (n=131)	At 12.8 months:[c] 12.7 (11.5–not evaluable) At 30.6 months:[c] 18.0 (12.5–20.8) At 42.8 months: [c] 17.8 (NR)	Reference	At 12.8 months:[c] NR At 30.6 months:[c] Not reached (NR)	Reference
	IMDC Intermediate	Pembrolizumab + axitinib (n=238)	At 12.8 months:[c] 14.5 (12.4–18.0) At 30.6 months:[c] NR	At 12.8 months:[c] 0.70 (0.54–0.91)[b] At 30.6 months:[c] 0.72 (0.57–0.90)	NR	At 12.8 months:[c] 0.53 (0.35–0.82)[b] At 30.6 months:[c] 0.63 (0.47–0.83)
		Sunitinib (n=246)	At 12.8 months:[c] 9.5 (8.0–12.5) At 30.6 months:[c] NR	Reference	NR	Reference
	IMDC Poor	Pembrolizumab + axitinib (n=56)	At 12.8 months:[c] 4.9 (2.9–12.4) At 30.6 months:[c] NR	At 12.8 months:[c] 0.58 (0.35–0.94)[b] At 30.6 months:[c] 0.54 (0.34–0.86)	NR	At 12.8 months:[c] 0.43 (0.23–0.81)[b] At 30.6 months:[c] 0.59 (0.37–0.96)
		Sunitinib (n=52)	At 12.8 months:[c] 2.9 (2.7–4.2) At 30.6 months:[c] NR	Reference	NR	Reference

Study	Risk Group	Treatment (Intervention Followed by Comparator)	Median PFS (95% CI), in months	HR for PFS (95% CI)	Median OS (95% CI), in months	HR for OS (95% CI)
	IMDC Intermediate or Poor	Pembrolizumab + axitinib (n=294)	At 12.8 months:[c] NR At 30.6 months:[c] 12.7 (11.3–18.0) At 42.8 months:[c] 13.8 (NR)	At 12.8 months:[c] NR At 30.6 months:[c] 0.69 (0.56–0.84) p=0.0002 At 42.8 months:[c] 0.67 (0.55, 0.81)	At 12.8 months:[c] NR At 30.6 months:[c] Not reached (NR)	At 12.8 months:[c] NR At 30.6 months:[c] 0.63 (0.50–0.81) p=0.0001 At 42.8 months:[c] 0.64 (0.52, 0.8)
		Sunitinib (n=298)	At 12.8 months:[c] NR At 30.6 months:[c] 8.3 (6.7–10.1) At 42.8 months:[c] 8.2 (NR)	Reference	At 12.8 months:[c] NR At 30.6 months:[c] 28.9 (23.7–34.3)	Reference
Motzer, 2007 [43, 44]	MSKCC Favorable	Sunitinib (n=143)	Not reached (NR)	0.37 (0.21–0.64)	Not reached (NR)	NR
		IFN alfa-2a (n=121)	8 (NR)	Reference	Not reached (NR)	NR
	MSKCC Intermediate	Sunitinib (n=209)	11 (NR)	0.39 (0.28–0.54)	20.7 (18.2–25.6)	0.787 (0.617–1.004)
		IFN alfa-2a (n=212)	4 (NR)	Reference	15.4 (13.6–18.2)	Reference
	MSKCC Poor	Sunitinib (n=23)	4 (NR)	0.53 (0.23–1.23)	5.3 (4.2–10)	0.66 (0.36–1.207)
		IFN alfa-2a (n=25)	1 (NR)	Reference	4 (2.7–7.2)	Reference
RECORD-3 [142]	MSKCC Favorable	Everolimus (n=70)	11.1 (8.3–15.9)	1.2 (0.8–1.8)[b]	NR	NR
		Sunitinib (n=69)	13.4 (11–18.2)	Reference	NR	NR
	MSKCC Intermediate	Everolimus (n=132)	5.7 (5.1–8.1)	1.5 (1.1–2)[b]	NR	NR
		Sunitinib (n=131)	8.2 (7.4–11.2)	Reference	NR	NR
	MSKCC Poor	Everolimus (n=35)	2.6 (1.4–4.2)	1.7 (1–3.1)[b]	NR	NR
		Sunitinib (n=32)	3 (2–8.1)	Reference	NR	NR
SWITCH [146]	MSKCC Favorable	Sorafenib (n=71)	NR	1.3 (0.87–1.94)[b] p=0.9	NR	NR
		Sunitinib (n=82)	NR	Reference	NR	NR
	MSKCC Intermediate	Sorafenib(n=108)	NR	1.14 (0.82–1.57)[b] p=0.8	NR	NR
		Sunitinib (n=94)	NR	Reference	NR	NR
TemPa [116]	IMDC Intermediate or Poor	Pazopanib (n=35)	First analysis: 5.2 (3.6–7.4) Final analysis: 5.2 (NR)	First analysis: p=0.16 Final analysis: 1.36 (0.84–2.22) p=0.21	First analysis: 12 (8.3–20.1) Final analysis: 11.9 (NR)	First analysis: p=0.56 Final analysis: 1.16 (0.7–1.93) p=0.558
		Temsirolimus (n=34)	First analysis: 2.6 (1.9–4.2)	Reference	First analysis: 7.3 (5.8–17.4)	Reference

Study	Risk Group	Treatment (Intervention Followed by Comparator)	Median PFS (95% CI), in months	HR for PFS (95% CI)	Median OS (95% CI), in months	HR for OS (95% CI)
			Final analysis: 2.7 (NR)		Final analysis: 7.1 (NR)	
	IMDC Intermediate	Pazopanib (n=15)	First analysis: 7.3 (NR) Final analysis: 5.7 (1.7–10)	First analysis: 0.38 (NR)[b] p=0.03 Final analysis: NR	First analysis: NR Final analysis: 14.5 (4.2–22.9)	NR
		Temsirolimus (n=10)	First analysis: 3.7 (NR) Final analysis: 3.8 (1.8–10.8)	Reference	First analysis: NR Final analysis: 15.0 (5.9–32.6)	NR
	IMDC Poor	Pazopanib (n=26)	First analysis: NR Final analysis: 4.9 (2.5–6.5)	NR	First analysis: NR Final analysis: 9.6 (4.6–15.5)	NR
		Temsirolimus (n=24)	First analysis: NR Final analysis: 1.9 (1.8–3.1)	NR	First analysis: NR Final analysis: 7.1 (NR–NR)	NR

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix B Main characteristics of included studies

Table 115: Characteristics of the CLEAR study

Trial name: Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab Versus Sunitinib Alone as Treatment of Advanced Renal Cell Carcinoma (CLEAR)	**NCT number:** NCT02811861
Objective	Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma
Publications – title, author, journal, year	LEN+PEM or Everolimus for Advanced Renal Cell Carcinoma, Motzer et al., The New England Journal of Medicine, 2021.
Study type and design	Multicentre, Open-label, Randomized, Phase 3 Trial. Randomization in a 1:1:1 ratio. Randomisation was stratified according to geographic region (Western Europe and North America or the rest of the world) and Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic risk group (favourable, intermediate, or poor risk). The intervention model was parallel assignment.
Sample size (n)	1,069 participants

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Trial name: Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab Versus Sunitinib Alone as Treatment of Advanced Renal Cell Carcinoma (CLEAR) **NCT number:** NCT02811861

Main inclusion and exclusion criteria	**Inclusion Criteria:** Histological or cytological confirmation of renal cell carcinoma (RCC) with a clear-cell component At least 1 measurable target lesion according to Response Evaluation in Solid Tumours (RECIST) 1.1 Karnofsky Performance Status (KPS) of ≥70 Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP ≤150/90 mmHg at Screening and no change in antihypertensive medications within 1 week prior to Cycle 1/Day 1 (C1/D1) Adequate organ function per blood work **Exclusion Criteria:** Participants who have received any systemic anticancer therapy for RCC, including anti-vascular endothelial growth factor (VEGF) therapy, or any systemic investigational anticancer agent Participants with central nervous system (CNS) metastases are not eligible, unless they have completed local therapy (e.g., whole brain radiation therapy (WBRT), surgery or radiosurgery) and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (e.g., radiologic) or symptoms of CNS metastases must be stable for at least 4 weeks before starting study treatment Active malignancy (except for RCC, definitively treated basal or squamous cell carcinoma of the skin, and carcinoma in-situ of the cervix or bladder) within the past 24 months. Participants with history of localized & low risk prostate cancer are allowed in the study if they were treated with curative intent and there is no prostate specific antigen (PSA) recurrence within the past 5 years Prior radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks prior to study treatment start Received a live vaccine within 30 days of planned start of study treatment Participants with urine protein ≥1 gram/24 hour Fasting total cholesterol >300 milligram per decilitre (mg/dL) (or >7.75 millimole per litre (mmol/L)) and/or fasting triglycerides level >2.5 x upper limit of normal (ULN). Note: these participants can be included after initiation or adjustment of lipid-lowering medication Uncontrolled diabetes as defined by fasting glucose >1.5 times the ULN. Note: these participants can be included after initiation or adjustment of glucose-lowering medication Prolongation of corrected QT (QTc) interval to >480 milliseconds (ms) Bleeding or thrombotic disorders or participants at risk for severe haemorrhage. The degree of tumour invasion/infiltration of major blood vessels should be considered because of the potential risk of severe haemorrhage associated with tumour shrinkage/necrosis following lenvatinib therapy Clinically significant haemoptysis or tumour bleeding within 2 weeks prior to the first dose of study drug Significant cardiovascular impairment within 12 months of the first dose of study drug: history of congestive heart failure greater than New York Heart Association Class II, unstable angina, myocardial infarction, cerebrovascular accident, or cardiac arrhythmia associated with hemodynamic instability. The following is also excluded: left ventricular ejection fraction below the institutional normal range as determined by multiple-gated acquisition scan or echocardiogram Active infection (any infection requiring systemic treatment) Participants known to be positive for Human Immunodeficiency Virus (HIV). Known active Hepatitis B (e.g., Hepatitis B surface antigen (HBsAg) reactive) or Hepatitis C (e.g., hepatitis C virus ribonucleic acid (HCV RNA) [qualitative] is detected) Known history of, or any evidence of, interstitial lung disease Has a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis Participants with a diagnosis of immunodeficiency or who are receiving chronic systemic steroid therapy (doses exceeding 10 mg/day of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment. Physiologic doses of corticosteroids (up to 10 mg/day of prednisone or equivalent) may be used during the study Active autoimmune disease (with the exception of psoriasis) that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment. Known intolerance to any of the study drugs (or any of the excipients) Participant has had an allogenic tissue/solid organ transplant.

Trial name: Lenvatinib/Everolimus or Lenvatinib/Pembrolizumab Versus Sunitinib Alone as Treatment of Advanced Renal Cell Carcinoma (CLEAR)	**NCT number:** NCT02811861
Intervention	Lenvatinib 18 milligrams (mg) administered orally, once daily, plus everolimus 5 mg administered orally, once daily ***Or*** Lenvatinib 20 mg administered orally, once daily, plus pembrolizumab 200 mg administered intravenously (IV), every 3 weeks
Comparator(s)	Sunitinib 50 mg administered orally, once daily, on a schedule of 4 weeks on treatment followed by 2 weeks off treatment
Follow-up time	The median follow-up of August 2020 DCO: • ITT - Median follow up time was 26.7 (25.9, 27.4) months for the LEN+PEM arm and 26.3 (25.4, 27.2) months for the sunitinib arm • IMDC good prognosis – Median follow up time was 26.8 (24.7, 28.2) months for the LEN+PEM arm and 25.7 (24.4, 27.2) months for the sunitinib arm • IMDC intermediate/poor prognosis – Median follow up time was 26.7 (25.9, 27.5) months for the LEN+PEM arm and 26.6 (25.7, 27.9) months for the sunitinib arm The median follow-up for the March 2021 DCO: • ITT - Median follow up time was 33.7 (32.8, 34.4) months for the LEN+PEM arm and 33.4 (32.5, 34.1) months for the sunitinib arm. • IMDC good prognosis – Median follow up time was 33.8 (30.9, 35.3) months for the LEN+PEM arm and 32.7 (31.1, 34.3) months for the sunitinib arm • IMDC intermediate/poor prognosis – Median follow up time was 33.6 (32.5, 34.5) months for the LEN+PEM arm and 33.6 (32.5, 34.7) months for the sunitinib arm
Is the study used in the health economic model?	Yes
Primary, secondary, and exploratory endpoints	The primary endpoint was progression-free survival as assessed by independent review. The secondary outcome measures were: Objective response rate (ORR) Overall survival (OS) Number of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) Number of participants who discontinued treatment due to toxicity Time to treatment failure due to toxicity Health-Related Quality of Life (HRQoL) scores PFS on next-line of therapy (PFS2) PFS by investigator assessment Model-predicted clearance for lenvatinib and everolimus AUC for lenvatinib and everolimus
Method of analysis	Efficacy was assessed in the intention-to-treat population, which included all the patients who underwent randomization. Progression-free survival and overall survival were evaluated with KM estimates and two-sided 95% confidence intervals. Differences between each combination regimen and sunitinib were evaluated with the stratified log-rank test. A stratified Cox regression model with Efron's method for handling tied results was used to estimate the hazard ratios and 95% confidence intervals. Between-group differences in the percentage of patients with an objective response were evaluated with a stratified Cochran–Mantel–Haenszel test; the stratified relative risk and 95% confidence intervals are provided. The duration of response in patients with a confirmed response was estimated by the KM method. Safety analyses included all the patients who received at least one dose of any trial drug.
Subgroup analyses	All subgroup analyses were prespecified in the statistical analysis plan. The subgroups were defined based on age, sex, geographical region, MSKCC risk group, IMDC risk group, baseline Karnofsky performance status, no. of organs with metastases, and PD-L1 combined positive score. free survival was assessed according to Response Evaluation Criteria in Solid Tumours, version 1.1, by an independent review committee. Differences between the treatment groups were evaluated with the stratified log-rank test, stratified according to geographic region and Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic risk group. A stratified Coxregression model was used to estimate the hazard ratio for disease progression or death and 95% confidence intervals (CIs). Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability. The programmed cell death ligand 1 (PD-L1) combined positive score is defined as the number of PD-L1–staining cells (tumour cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.
Other relevant information	None

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 116. Summary of endpoints evaluated in the CLEAR trial

Endpoint	Definition	Collection	Analysis
Primary			
PFS	Time from the date of randomisation to the date of the first documentation of disease progression or death as defined by RECIST 1.1	Data required by the protocol were collected on the Clinical report forms (CRFs) and entered into a validated data management system that was compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject. Data collection on the CRF followed the instructions described in the CRF Completion Guidelines. The investigator had ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 or Investigator and Site Information Form signed the completed CRF to attest to its accuracy, authenticity, and completeness.	PFS was evaluated using KM estimates and the difference in PFS for the 2 primary comparisons were each tested by stratified log-rank test, with geographic region and MSKCC prognostic groups as strata. The hazard ratio (HR) and its 95% confidence intervals (CIs) were estimated using the Cox regression model with Efron's method for ties, stratified by the factors used for stratified randomization. Median PFS with 2-sided 95% CIs were presented, and the KM estimates of PFS were plotted over time.
Key secondary endpoints			
OS	Time from the date of randomization to the date of death from any cause	See Collection for PFS	The difference in OS for the 2 primary comparisons were each tested by stratified log-rank test, with geographic region and MSKCC prognostic groups as strata. The HR and its 95% CIs were estimated by a stratified Cox proportional hazards model with Efron's method for ties, stratified by the factors used for stratified randomization. Median OS with 2-sided 95% CIs were calculated using KM product-limit estimates for each treatment arm, and KM estimates of OS were plotted over time.
ORR	Proportion of subjects who had best overall response (BOR) of CR or PR as defined by RECIST 1.1	See Collection for PFS	ORR, estimated by treatment arms based on the tumour response evaluation by IIR per RECIST 1.1, was calculated with exact 95% CIs using the method of Clopper and Pearson within each arm. The difference in ORR for the 2 primary comparisons were each tested using

Endpoint	Definition	Collection	Analysis
			the Cochran-Mantel-Haenszel test, with geographic region and MSKCC prognostic groups as strata. The 2-sided 95% CIs for the odds ratio and the difference in ORR were calculated. The P value for hypothesis testing of ORR will be based on the ORR data at the time of the PFS interim analysis. The ORR data available at the time of this final PFS analysis and subsequent analysis time points are provided for supportive purposes.
Other secondary endpoints			
TEAEs and SAEs	Treatment emergent adverse events and Serious adverse events	See Collection for PFS	Safety was assessed by monitoring and recording all AEs and serious adverse events (SAEs) using Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grades, regular laboratory monitoring for haematology, blood chemistry, and urine values; regular performance of physical examinations, periodic measurement of vital signs, electrocardiograms (ECGs), and echocardiogram or multigated acquisition (MUGA) scans, including left ventricular ejection fraction (LVEF); and the performance of physical examinations.
Proportion of subjects who discontinued treatment due to toxicity	Proportion of subjects who discontinued study treatment due to TEAEs	See Collection for PFS	
Time to treatment failure due to toxicity	Time from the date of randomization to the date that a subject discontinued study treatment due to TEAEs	See Collection for PFS	
HRQoL	FKSI-DRS, the EORTC QLQ-C30, and the EuroQoL EQ-5D-3L	See Collection for PFS	HRQoL was assessed at baseline (before first dose of study drug), on Day 1 of each subsequent cycle, at the time of withdrawal, and at the Off-Treatment Visit. Every effort was made to administer HRQoL surveys before study drug administration and before other assessments and procedures.
PFS2	Time from randomization to disease progression as assessed by investigator on next-line	See Collection for PFS	

Endpoint	Definition	Collection	Analysis
	treatment or death from any cause (whichever occurred first)		
PFS by investigator assessment	Time from the date of randomization to the date of first documentation of disease progression based on the investigator assessment per RECIST 1.1 or death (whichever occurred first)	See Collection for PFS	
Pembrolizumab PK comparison to historical data		See Collection for PFS	
Model-predicted clearance and area under the concentration-time curve (AUC) for lenvatinib in Arms A and B		See Collection for PFS	
Model-predicted clearance and AUC for everolimus in Arm A		See Collection for PFS	
Exploratory endpoints			
ORR	Proportion of subjects who had BOR of CR or PR as determined by investigator assessment using RECIST 1.1	See Collection for PFS	
DOR	Time from the date a response of CR or PR by IIR and investigator assessment was first documented until the date of the first documentation of disease progression or date of death from any case	See Collection for PFS	

Endpoint	Definition	Collection	Analysis
DCR	Proportion of subjects who had BOR of CR, PR, or stable disease by IIR and investigator assessment. Stable disease had to be achieved at ≥7 weeks after randomization to be considered BOR	See Collection for PFS	
CBR	Proportion of subjects who had BOR of CR, PR, or durable stable disease (duration of stable disease ≥23 weeks after randomization) by IIR and investigator assessment	See Collection for PFS	

Abbreviations: CBR clinical benefit rate CR, complete response; DCR, disease control rate; DOR, duration of response; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer; EuroQoL EQ-5D, European Quality of Life 5 Dimension 3 Level Version; ORR, overall response rate; OS, overall survival; PR, partial response; PFS, progression-free survival; SAEs, serious adverse events; TEAEs, treatment emergent adverse events.

Table 117: Main characteristics of the CheckMate 214 study

Trial name: Nivolumab Combined with Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 214)	**NCT number:** NCT02231749
Objective	The purpose of this phase III trial was to compare the objective response rate, progression-free survival, and overall survival of nivolumab plus ipilimumab with sunitinib for previously untreated clear-cell advanced renal-cell carcinoma among intermediate- and poor-risk patients.
Publications – title, author, journal, year	Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial, Albiges, ESMO Open, 2020. Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial, Motzer, Journal for ImunnoTherapy of Cancer, 2020. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial, The Lancet Oncology, 2019. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma, Motzer, New England Journal of Medicine, 2018.
Study type and design	Randomized, open-label, phase III trial of nivolumab plus ipilimumab followed by nivolumab monotherapy versus sunitinib monotherapy. The intervention model was parallel assignment, but after completion of final analysis eligible participants may switch from receiving Sunitinib to receiving Nivolumab 3 mg/kg IV combined with Ipilimumab 1 mg/kg IV every 3 weeks for 4 doses then Nivolumab 240mg flat dose IV every 2 weeks. Enrolled patients were randomly assigned 1:1 and stratified by IMDC prognostic score (0 vs 1-2 vs 3-6) and region (USA vs Canada/Western Europe/Northern Europe vs Rest of World). A total of 1096 patients were randomly assigned to treatment at 175 sites in 28 countries; 1082 patients received treatment (547 with nivolumab plus ipilimumab and 535 with sunitinib in the intention-to-treat population; 423 and 416, respectively, had intermediate or poor risk).
Sample size (n)	1,390 participants

Trial name: Nivolumab Combined with Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 214) **NCT number:** NCT02231749

Main inclusion and exclusion criteria	**Inclusion Criteria:** Histological confirmation of renal cell carcinoma (RCC) with a clear-cell component Advanced (not amenable to curative surgery or radiation therapy) or metastatic (AJCC Stage IV) RCC No prior systemic therapy for RCC with the following exception: One prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets vascular endothelial growth factor (VEGF) or VEGF receptors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy Karnofsky Performance Status (KPS) of at least 70% Measurable disease as per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 Tumour tissue [formalin-fixed paraffin-embedded (FFPE) archival or recent acquisition] must be received by the central vendor (block or unstained slides) in order to randomize a subject to study treatment. (Note: Fine Needle Aspiration [FNA] and bone metastases samples are not acceptable for submission) **Exclusion Criteria:** Any history of or current central nervous system (CNS) metastases. Baseline imaging of the brain is required within 28 days prior to randomization Prior systemic treatment with VEGF or VEGF receptor targeted therapy (including, but not limited to, sunitinib, pazopanib, axitinib, tivozanib, and bevacizumab) Prior treatment with an anti-programmed death (PD)-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways Any active or recent history of a known or suspected autoimmune disease or recent history of a syndrome that required systemic corticosteroids (>10 mg daily Prednisone equivalent) or immunosuppressive medications except for syndromes which would not be expected to recur in the absence of an external trigger. Subjects with vitiligo or type I diabetes mellitus or residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement are permitted to enrol Any condition requiring systemic treatment with corticosteroids (>10 mg daily Prednisone equivalents) or other immunosuppressive medications within 14 days prior to first dose of study drug. Inhaled steroids and adrenal replacement steroid doses >10 mg daily Prednisone *equivalents are permitted in the absence of active autoimmune disease*
Intervention	Nivolumab 3 mg/kg combined with Ipilimumab 1 mg/kg solutions intravenously every 3 weeks for 4 doses then Nivolumab 3 mg/kg solutions intravenously every 2 weeks until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends.
Comparator(s)	Sunitinib 50 mg capsules by mouth once daily for 4 weeks then 2 weeks off, continuously until documented disease progression, discontinuation due to toxicity, withdrawal of consent or the study ends. After completion of final analysis eligible participants may switch from receiving Sunitinib to receiving Nivolumab 3 mg/kg IV combined with Ipilimumab 1 mg/kg IV every 3 weeks for 4 doses then Nivolumab 240mg flat dose IV every 2 weeks.
Follow-up time	The latest follow-up cut off was reported in Albiges et al., 2020. Here the minimum follow-up was 4 years (median follow-up=55 months).

Trial name: Nivolumab Combined with Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 214) **NCT number:** NCT02231749

Is the study used in the health economic model?	Yes
Primary, secondary, and exploratory endpoints	Co-primary end points: Objective response rate in intermediate- and poor-risk patients Progression-free survival in intermediate- and poor-risk patients Overall survival in intermediate- and poor-risk patients Secondary end points: Objective response rate in the intention-to-treat population Progression-free survival in the intention-to-treat population Overall survival in the intention-to-treat population Incidence rate of adverse events among all treated patients ' Exploratory end points: • Objective response rate among favourable-risk patients • Progression free survival among favourable-risk patients • Overall survival among favourable-risk patients. • Outcomes according to level of tumour programmed death ligand 1 (PD-L1) expression (≥1% vs. vs. <1%) • Health-related quality of life on the basis of the score on the National Comprehensive Cancer Network Functional Assessment of Cancer Therapy– Kidney Symptom Index (FKSI-19) both in intermediate- and poor-risk patients • Health related quality of life for cancer Functional Assessment of Cancer Therapy–General (FACT-G) • EuroQol EQ-5D-3L.
Method of analysis	The overall alpha level was 0.05, split among three co-primary end points (α=0.001 for ORR; α=0.009 for PFS; and α=0.04 for OS) and will affect the width of the confidence interval. Overall survival, progression-free survival, and duration of response were estimated with the use of KM methods. For quality-of-life assessments, descriptive statistics and change from baseline were conducted for the FKSI-19 score. Calculations of P values, to evaluate the between-group difference in mean change from baseline, were based on an independent-samples t-test under the assumption that variances were unequal. Both a pattern-mixture model and a restricted maximum likelihood-based repeated-measures approach were used to confirm descriptive data.
Subgroup analyses	Efficacy outcomes according to level of tumour programmed death ligand 1 (PD-L1) expression (≥1% vs. <1%): Objective response rate Progression-free survival Overall survival Subgroup analyses for overall survival included the following subgroups: age, sex, region, prior nephrectomy, PD-L1 expression and prognostic scores
Other relevant information	None

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 118: Baseline characteristics of the two main studies for the comparative analysis of efficacy and safety

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety – overall population					
	CLEAR			CHECKMATE 214*	
Intervention	lenvatinib& everolimus (n=355)	lenvatinib& pembrolizumab (n=355)	sunitinib (n = 357)	nivolumab& ipilimumab (n=550)	sunitinib (n=546)
Median age (range)	64 (34–88)	62 (32–86)	61 (29–82)	62 (26-85)	62 (21-85)
Male	255 (71.8%)	266 (74.5%)	275 (77.0%)	413 (75%)	395 (72%)
Karnofsky performance-status score†					
100-90	295 (83.1%)	286 (80.1%)	294 (82.4%)	NR	NR
80-70	60 (16.9%)	70 (19.6%)	62 (17.4%)	NR	NR
MSKCC risk group‡					
Favourable (0)	96 (27.0%)	98 (27.5%)	97 (27.2%)	NR	NR
Intermediate (1-2)	227 (63.9%)	227 (63.6%)	228 (63.9%)	NR	NR
Poor (3-6)	32 (9.0%)	32 (9.0%)	32 (9.0%)	NR	NR
IMDC risk group|					
Favourable (0)	110 (31.0%)	114 (31.9%)	124 (34.7%)	125 (23%)	124 (23%)
Intermediate (1-2)	210 (59.2%)	195 (54.6%)	192 (53.8%)	334 (61%)	333 (61%)
Poor (3-6)	33 (9.3%)	42 (11.8%)	37 (10.4%)	91 (17%)	89 (16%)
Could not be evaluated	2 (0.6%)	6 (1.7%)	4 (1.1%)	0	0
Region (IVRS)					
Western Europe or Northern America	198 (55.8%)	200 (56.0%)	199 (55.7%)	355 (65%)	352 (64%)
Rest of the world	157 (44.2%)	157 (44.0%)	158 (44.3%)	195 (35%)	194 (36%)
PD-L1 combined positive score¶					
<1%	107 (30.1%)	116 (32.5%)	119 (33.3%)	386/499 (77%)	376/503 (75%)
>1%	112 (31.5%)	118 (33.1%)	103 (28.9%)	113/499 (23%)	127/503 (25%)
Unavailable	136 (38.3%)	123 (34.5%)	135 (37.8%)	0	0
Previous radiotherapy	NR	NR	NR	63 (11%)	70 (13%)
Previous nephrectomy	262 (73.8%)	260 (72.8%)	275 (77.0%)	453 (82%)	437 (80%)
Sarcomatoid features	28 (7.9%)	24 (6.7%)	21 (5.9%)	NR	NR

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

No. of sites with target or nontarget lesions‡					
1	NR	NR	NR	123 (22%)	118 (22%)
≥2	NR	NR	NR	427 (78%)	427 (78%)
No. of metastatic organs or sites					
1	97 (27.3%)	125 (35.0%)	108 (30.3%)	NR	NR
≥2	254 (71.5%)	229 (64.1%)	246 (68.9%)	NR	NR
Sites of metastasis					
Lung	249 (70.1%)	245 (68.6%)	239 (66.9%)	381 (69%)	373 (68%)
Lymph node	170 (47.9%)	163 (45.7%)	159 (44.5%)	246 (45%)	268 (49%)
Bone	85 (23.9%)	86 (24.1%)	97 (27.2%)	112 (20%)§	119 (22%)§
Liver	60 (16.9%)	62 (17.4%)	61 (17.1%)	99 (18%)	107 (20%)

* Percentages may not total 100 because of rounding.
† Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability. Scores were missing for 1 patient each in the lenvatinib-plus-everolimus and sunitinib groups (CLEAR trial).
‡ A Memorial Sloan Kettering Cancer Centre (MSKCC) score of 0 indicates favourable risk, a score of 1 or 2 intermediate risk, and a score of 3 or higher poor risk.
| An International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) score of 0 indicates favourable risk, a score of 1 or 2 intermediate risk, and a score of 3 to 6 poor risk.
¶Programmed cell death ligand 1 (PD-L1) expression was assessed with the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) and reported as the combined positive score, defined as the number of PD-L1–staining cells (tumour cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.
‡The number of target or nontarget lesions at baseline was not reported for one patient in the sunitinib group (CHECKMATE 214 trial).
§Shown are patients who had bone metastases with or without a soft-tissue component.
* Percentages may not total 100 because of rounding.
† Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability.

Table 119: Baseline characteristics (poor and intermediate IMDC group) of the two main studies for the comparative analysis of efficacy and safety

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety – Poor and intermediate risk group IMDC population					
	CLEAR			**CHECKMATE 214***	
Intervention	lenvatinib& everolimus (n=237)	lenvatinib& pembrolizumab (n=243)	sunitinib (n=229)	nivolumab& ipilimumab (n=425)	sunitinib (n=422)
Median age (range)	63 (32-86)	63 (34-86)	60 (30-82)	62 (26-85)	61 (21-85)
Male	173 (73.0%)	180 (74.1%)	176 (76.9%)	314 (74%)	301 (71%)
Karnofsky performance-status score†					
100-90	181 (76.4%)	193 (79.4%)	180 (78.6%)	NR	NR
80-70	56 (23.6%)	50 (20.6%)	49 (21.4%)	NR	NR
Region (IVRS)					

Western Europe or Northern America	135 (57.0%)	140 (57.6%)	124 (54.1%)	260 (74%)	257 (74%)
Rest of the world	102 (43.0%)	103 (42.4%)	105 (45.9%)	165 (39%)	165 (39%)
Race group					
White	174 (73.4%)	187 (77.0%)	173 (75.5%)	NR	NR
Asian	47 (19.8%)	52 (21.4%)	42 (18.3%)	NR	NR
All others	7 (3.0%)	2 (0.8%)	7 (3.1%)	NR	NR
Unavailable	9 (3.8%)	2 (0.8%)	7 (3.1%)	NR	NR
PD-L1 combined positive score¶					
<1%	NR	NR	NR	284/384 (74%)	278/392 (71%)
>1%	NR	NR	NR	100/384 (26%)	114/392 (29%)
Unavailable	NR	NR	NR	NR	NR
Previous radiotherapy	NR	NR	NR	52 (12%)	52 (12%)
Previous nephrectomy	NR	NR	NR	341 (80%)	319 (76%)
No. of sites with target or nontarget lesions					
1	NR	NR	NR	NR	NR
≥2	NR	NR	NR	NR	NR
No. of metastatic organs or sites					
1	NR	NR	NR	90 (21%)	84 (20%)
≥2	NR	NR	NR	335 (79%)	337 (80%)
Sites of metastasis					
Lung	NR	NR	NR	294 (69%)	296 (70%)
Lymph node	NR	NR	NR	190 (45%)	216 (51%)
Bone§	NR	NR	NR	95 (22%)§	97 (23%)§
Liver	NR	NR	NR	88 (21%)	89 (21%)

* Percentages may not total 100 because of rounding.

† Karnofsky performance-status scores range from 0 to 100, with lower scores indicating greater disability.

¶Programmed cell death ligand 1 (PD-L1) expression was assessed with the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) and reported as the combined positive score, defined as the number of PD-L1–staining cells (tumour cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.

§Shown are patients who had bone metastases with or without a soft-tissue component.

Table 120: Baseline characteristics (favourable IMDC group) of the CLEAR study for the analysis of efficacy and safety

Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety – Favourable risk group IMDC population			
	CLEAR		
	Lenvatinib+Everolimus (N = 110)	Lenvatinib+Pembrolizumab (N = 114)	Sunitinib (N = 124)
Age (years)			
Mean (SD)	61.5 (10.09)	63.2 (9.07)	61.9 (8.89)
Median	61.0	64.0	62.0
Q1, Q3	55.0, 68.0	58.0, 70.0	57.0, 68.5
Min, Max	35.0, 83.0	36.0, 88.0	29.0, 79.0
Age Group, n (%)			
<65 years	68 (59.6)	60 (54.5)	78 (62.9)
>=65 years	46 (40.4)	50 (45.5)	46 (37.1)
>=65-<75 years	32 (28.1)	35 (31.8)	39 (31.5)
>=75 years	14 (12.3)	15 (13.6)	7 (5.6)
Sex, n (%)			
Male	89 (78.1)	74 (67.3)	97 (78.2)
Female	25 (21.9)	36 (32.7)	27 (21.8)
Race, n (%)			
White	74 (64.9)	75 (68.2)	94 (75.8)
Black or African American	0 (0.0)	1 (0.9)	0 (0.0)
Asian	30 (26.3)	28 (25.5)	25 (20.2)
Japanese	16 (14.0)	16 (14.5)	11 (8.9)
Chinese	0 (0.0)	1 (0.9)	0 (0.0)
Other Asian	14 (12.3)	11 (10.0)	14 (11.3)
American Indian or Alaskan Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	3 (2.6)	3 (2.7)	2 (1.6)
Missing	7 (6.1)	3 (2.7)	3 (2.4)
Race group, n (%)			
White	74 (64.9)	75 (68.2)	94 (75.8)
Asian	30 (26.3)	28 (25.5)	25 (20.2)
All Others	3 (2.6)	4 (3.6)	2 (1.6)
Missing	7 (6.1)	3 (2.7)	3 (2.4)
Ethnicity, n (%)			
Hispanic or Latino	8 (7.0)	1 (0.9)	7 (5.6)
Non Hispanic or Latino	104 (91.2)	107 (97.3)	117 (94.4)
Missing	2 (1.8)	2 (1.8)	0 (0.0)
Weight (kg)			
n	114	110	124
Mean (SD)	86.6 (19.54)	81.5 (17.68)	84.7 (18.45)
Median	86.0	81.3	81.6
Q1, Q3	72.7, 98.4	68.0, 94.0	73.0, 96.4
Min, Max	41.7, 132.0	48.0, 129.0	48.0, 140.9
Height (cm)			
n	113	110	123
Mean (SD)	171.9 (10.00)	169.4 (9.46)	171.9 (9.60)
Median	172.7	170.0	172.3
Q1, Q3	166.0, 178.0	163.0, 175.0	167.0, 178.0
Min, Max	147.6, 197.5	149.0, 190.5	144.7, 194.0
BMI (kg/m^2)			
n	113	110	124
Mean (SD)	29.2 (5.78)	28.2 (4.97)	28.6 (5.44)
Median	29.0	27.9	27.6
Q1, Q3	25.4, 32.8	25.0, 31.6	25.0, 31.7
Min, Max	1.3, 2.6	1.5, 2.6	1.4, 2.6
Geographic Region per IxRS, n (%)			
Western Europe and North America	59 (51.8)	56 (50.9)	71 (57.3)
Rest of the World	55 (48.2)	54 (49.1)	53 (42.7)

Geographic Region per CRF, n (%)			
Western Europe and North America	59 (51.8)	57 (51.8)	71 (57.3)
Rest of the World	55 (48.2)	53 (48.2)	53 (42.7)
KPS Score at Baseline, n (%)			
100	66 (57.9)	70 (63.6)	81 (65.3)
90	36 (31.6)	31 (28.2)	32 (25.8)
80	12 (10.5)	9 (8.2)	11 (8.9)
70	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Baseline KPS Score Group, n (%)			
100-90	102 (89.5)	101 (91.8)	113 (91.1)
80-70	12 (10.5)	9 (8.2)	11 (8.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)

Comparability of patients across studies

A review of the baseline characteristics of the two phase-III trials, CLEAR and CHECKMATE 214, demonstrated that the two trials had similar baseline characteristics. Some differences were notified between the two trials concerning the allocation of participants in the IMDC risk groups.

Moreover, the inclusion and exclusion criteria were also mostly similar, despite the CLEAR trial had some additional exclusion criteria compared to the CHECKMATE 214 trial.

Comparability of the study populations with Danish patients eligible for treatment

Patients in the studies were mainly recruited in North America and Europe, and the inclusion criteria and patient characteristics (IMDC prognosis categorisation) were consistent with the criteria for treatments in Denmark. Therefore, no important differences exist between the study populations and the Danish patient population. This was confirmed with a Danish key opinion leader.

Appendix D Efficacy and safety results per study

Definition, validity, and clinical relevance of included outcome measures

Table 121: Description and definition of outcome measures

Outcome measure	Definition	Validity	Clinical relevance
PFS by IIR	Time from the date of randomization to the date of the first documentation of disease progression or death as defined by RECIST 1.1	The standard outcome for trials investigating cancer. In general, a positive difference in PFS was correlated with a positive difference in OS, and no improvement in PFS was correlated with no improvement in OS. Additionally, the DMC has requested the specific measure in the assessment of Avelumab looking at PFS at 12 month as a measure for OS and the assessment of NIVO+IPI [177] [33]	The PFS is a validated measure used in clinical trials to assess the time patients live with the disease without getting worse. PFS is the way to see how well the treatment with LEN+PEM works in patients with aRCC.
OS	Time from the date of randomization to the date of death from any cause.	The gold standard in cancer trials (FDA)(EMA) [178]. Additionally, the DMC has requested the specific measure in the assessment of Avelumab [33] and NIVO+IPI [9]	The OS is a validated measure used in clinical trials to assess the time patients remain alive on treatment. The median survival rate for target treatment is almost 4 years for patients in good, 2 years for intermediate and under 1 year for patients in poor prognosis group, for this reason, OS is clinically relevant to see if patients with aRCC live longer when treated with LEN+PEM compared to treatment comparators.
ORR	The proportion of subjects who had the best overall response (BOR) of complete response (CR) or partial response (PR) as determined by IIR using RECIST 1.1.	Part of the RECIST criteria [179]. Furthermore, the DMC has requested the specific measure in the assessment of Avelumab [33] and the protocol of NIVO+IPI [9].	The ORR is measured to assess the patient's response of treatment with LEN+PEM vs sunitinib for patients with aRCC.
HRQoL	Multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning.	HRQoL is a widely used and validated outcome measure [180]	HRQoL was used to measure if the treatment with LEN+PEM was associated with an improved quality of life compared to the other treatment comparators.

Outcome measure	Definition	Validity	Clinical relevance
			Important difference was found to be ≤0.2 points, 0.2 points ≈ 1 point on the FKSI-DRS score [181]
DOR	Time from the date a response of CR or PR by IIR and investigator assessment was first documented until the date of the first documentation of disease progression or date of death from any case	DMC has required this measure in the assessment of NIVO+IPI [9].	Only collected for the overall population, to assess the duration of response difference between patients treated with LEN+PEM and sunitinib

Results

Table 122: Study results of CLEAR study

Results of [CLEAR (NCT02811861**)]**											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
OS ITT population	LEN+PEM	355	XXXXX	NA	NA	NA	XXXXX	XXXXX	XXXXX	Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ties.	CLEAR March 2021 DCO
	sunitinib	357	XXXXX								
PFS IRR ITT population	LEN+PEM	355	XXXXX	NA	NA	NA	XXXXX	XXXXX	XXXXX	PFS was evaluated using KM estimates and the difference in PFS for the 2 primary comparisons were each tested by stratified log-rank test, with geographic region and MSKCC prognostic groups as strata. The hazard ratio (HR) and its 95% confidence intervals (CIs) were estimated using the Cox regression	CLEAR August 2020 DCO
	sunitinib	357	XXXXX								

										model with Efron's method for ties, stratified by the factors used for stratified randomisation. Median PFS with 2-sided 95% CIs were presented, and the KM estimates of PFS were plotted over time.	
ORR ITT population	LEN+PEM	355	[redacted]				[redacted]	[redacted]	[redacted]	ORR, estimated by treatment arms based on the tumour response evaluation by IIR per RECIST 1.1, was calculated with exact 95% CIs using the method of Clopper and Pearson within each arm. The difference in ORR for the 2 primary comparisons were each tested using the Cochran-Mantel-Haenszel test, with geographic region and MSKCC prognostic groups as strata. The 2-sided 95% CIs for the odds ratio and the difference in ORR were calculated. The P value for hypothesis testing of ORR will be based on the ORR data at the time of the PFS interim analysis. The ORR data available at the time of this final PFS analysis and subsequent analysis time points are provided for supportive purposes.	CLEAR August 2020 DCO
	sunitinib	357	[redacted])								
CR ITT population	LEN+PEM	355	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]	RECIST 1.1	CLEAR August 2020 DCO
	sunitinib	357	[redacted]								
	LEN+PEM	355	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]	RECIST 1.1	

Results of [CLEAR (NCT02811861)]										
DOR ITT population	sunitinib	357	XXXXX							CLEAR August 2020 DCO
PFS IRR *IMDC Good prognosis*	LEN+PEM	110	XXXXX	14.7	NR	NR	XXXXX	XXXXX	XXXXX	PFS was evaluated using KM estimates and the difference in PFS for the 2 primary comparisons were each tested by stratified log-rank test, with geographic region and MSKCC prognostic groups as strata. The hazard ratio (HR) and its 95% confidence intervals (CIs) were estimated using the Cox regression model with Efron's method for ties, stratified by the factors used for stratified randomisation. Median PFS with 2-sided 95% CIs were presented, and the KM estimates of PFS were plotted over time.	CLEAR August 2020 DCO
	Sunitinib	124	XXXXX							
PFS IRR *IMDC Intermediate /poor prognosis*	LEN+PEM	243	XXXXX	16.2	NR	NR	XXXXX	XXXXX	XXXXX	PFS was evaluated using KM estimates and the difference in PFS for the 2 primary comparisons were each tested by stratified log-rank test, with geographic region and MSKCC prognostic groups as strata. The hazard ratio (HR) and its 95% confidence intervals (CIs) were estimated using the Cox regression model with Efron's method for ties, stratified by the factors used for stratified randomisation. Median PFS with 2-sided 95% CIs were	CLEAR August 2020 DCO
	Sunitinib	229	XXXXX							

Results of [CLEAR (NCT02811861)]

										presented, and the KM estimates of PFS were plotted over time.	
ORR *IMDC Good prognosis*	LEN+PEM	110	[redacted]	17.4	NR	NR	[redacted]	[redacted]	[redacted]	ORR, estimated by treatment arms based on the tumour response evaluation by IIR per RECIST 1.1, was calculated with exact 95% CIs using the method of Clopper and Pearson within each arm. The difference in ORR for the 2 primary comparisons were each tested using the Cochran-Mantel-Haenszel test, with geographic region and MSKCC prognostic groups as strata. The 2-sided 95% CIs for the odds ratio and the difference in ORR were calculated. The P value for hypothesis testing of ORR will be based on the ORR data at the time of the PFS interim analysis. The ORR data available at the time of this final PFS analysis and subsequent analysis time points are provided for supportive purposes.	CLEAR August 2020 DCO
	Sunitinib	124	[redacted]								
ORR *IMDC Intermediate /poor prognosis*	LEN+PEM	243	[redacted]	43.6	NR		6.6	[redacted]	[redacted]	[redacted]	CLEAR August 2020 DCO
	Sunitinib	229	[redacted]								
CR IMDC good prognosis	LEN+PEM	110	[redacted]	NA	NA		[redacted]	[redacted]	[redacted]	RECIST 1.1	CLEAR August 2020 DCO
	Sunitinib	124	[redacted]								

Results of [CLEAR (NCT02811861)]											
CR IMDC intermediate/ poor prognosis	LEN+PEM	243	[redacted]				[redacted]	[redacted]	[redacted]		
	Sunitinib	229	[redacted]	NA	NA		[redacted]	[redacted]	[redacted]		
OS *IMDC Good prognosis*	LEN+PEM	110	[redacted]	NR	NR		[redacted]	[redacted]	[redacted]	Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ties.	CLEAR March 2021 DCO
	Sunitinib	124	[redacted]								
OS *IMDC Intermediate /poor prognosis*	LEN+PEM	243	[redacted]	NR	NR	NR	[redacted]	[redacted]	[redacted]	Hazard ratio is based on a Cox Proportional Hazards Model including treatment group as a factor; Efron method is used for ties.	CLEAR March 2021 DCO
	Sunitinib	229	[redacted]								

Appendix E Safety data for intervention and comparator(s)

Table 123: Safety data from the CLEAR trial, Overall Population

Adverse event	lenvatinib + pembrolizumab (n=352)	sunitinib (n=340)
Median treatment duration, months (range)	17.0 (0.1 to 39.1)	7.8 (0.1 to 37.0)
Any grade TEAEs, n (%)	351 (99.7)	335 (98.5)
SAEs, n (%)	178 (50.6)	113 (33.2)
Any grade TEAEs leading to discontinuation, n (%)	47 (13.4) [a]	49 (14.4)
Total discontinuations, n (%)	210 (59.2)	273 (76.5)
Fatal TEAEs, %	15 (4.3%)	11 (3.2%)
Grade ≥3 TEAEs, n (%)	290 (82.4)	244 (71.8)
Drug-related Grade ≥3 AE (TRAE), n (%)	252 (71.6)	200 (58.8)
Total number of SY (SY)	524.9	344.2
Any grade TEAEs per SY, n (AE rate)	8211 (15.7)	6266 (18.2)
Grade ≥3 TEAEs per SY, n (AE rate)	1023 (2.0)	709 (2.1)
SAEs per SY, n (AE rate)	378 (0.7)	188 (0.6)
Fatal TEAEs per SY, n (AE rate)	19 (0.1)	12 (0.1)
Grade ≥3 TRAEs (≥5% in Any Treatment Arm),		
Diarrhoea, n (%)	29 (8.2)	15 (4.4)
Amylase increased, n (%)	26 (7.4)	9 (2.6)
Lipase increased, n (%)	34 (9.7)	24 (7.1)
Weight decreased, n (%)	21 (6.0)	0 (0.0)
Hypertension, %	89 (25.3)	61 (17.9)
Proteinuria, n (%)	26 (7.4)	10 (2.9)
Platelet count decreased, n (%)	18 (5.3)	18 (5.3)
Neutrophil count decreased, n %	39 (11.5)	19 (5.6)
Neutropenia, n %	1 (0.3)	18 (5.3)
Thrombocytopenia, n %	1 (0.3)	18 (5.3)

[a] Discontinuation of lenvatinib and pembrolizumab due to the same adverse event.

Appendix F Comparative analysis of efficacy and safety

Table 124. HRs of relative efficacy of LEN+PEM versus NIVO+IPI derived from the global NMA (IMDC intermediate/poor population)

Meta-analysis of studies comparing LEN+PEM to NIVO+IPI for patients with aRCC									
Outcome	**Studies included in the analysis**	**Absolute difference in effect**			**Relative difference in effect**			**Method used for quantitative synthesis**	**Result used in the health economic analysis?**
		Difference	**CI**	***P* value**	**Difference**	**CI**	***P* value**		
Overall survival (IMDC intermediate/poor)		NA	NA	NA	HR: XXX	XXXXXXXX	NA	*The HRs for the included studies were synthesized using a fixed effect model*	*Yes*
Progression-free survival (IMDC intermediate/poor)		NA	NA	NA	HR: XXX	XXXXXXXX	NA	*The HRs for the included studies were synthesized using a fixed effect model*	*Yes*
Overall Response Rate (IMDC intermediate/poor)		NA	NA	NA	OR: XXX	XXXXXXXX	NA	*The HRs for the included studies were synthesized using a fixed effect model*	*No*
Complete response rate (IMDC intermediate/poor)		NA	NA	NA	OR: XXX	XXXXXXXX	NA	*The HRs for the included studies were synthesized using a fixed effect model*	*No*
Grade ≥ 3 TRAEs (IMDC intermediate/poor)		NA	NA	NA	OR: XXX	XXXXXXXX	NA	*The HRs for the included studies were synthesized using a fixed effect model*	*No*

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix G Extrapolation

In this appendix related to section 5.3, the marketing authorisation holder is presenting detailed information regarding the extrapolation of relative efficacy for overall ITT population of the CLEAR trial (March 2021 DCO). This data will be instrumental to the DMC to appraise the relative efficacy of LEN+PEM in all populations of interest.

PFS extrapolations

As discussed in section 5.1.6.2, the PH assumption seems reasonable and is not rejected. Therefore, a joint fit is applied to the PFS LEN+PEM and sunitinib data.

Table 125. AIC and BIC of Fittings for Joint Fits of LEN+PEM and Sunitinib for the overall population

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 126. AIC and BIC Goodness-of-fit per each distribution relative to the distribution with the lowest AIC and BIC for PFS Joint Fits of LEN+PEM and Sunitinib for the overall population

Distribution	AIC relative goodness-of-fit classification	BIC relative goodness-of-fit classification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

The log-logistic and generalized gamma distributions display good relative statistical fits relative to the model with the lowest AIC and BIC (Log-normal distribution). The Exponential, Weibull and Gompertz distributions all produced a poor statistical fit relative to the Log-normal distribution.

Furthermore, as shown in Figure 75, and

Figure 76, visual inspection of the joint parametric PFS curve for LEN+PEM overlaid by the KM curve show that all parametric models underestimate the tail of the KM curve, with the log-logistic and Log-normal curves producing the smallest underestimates.

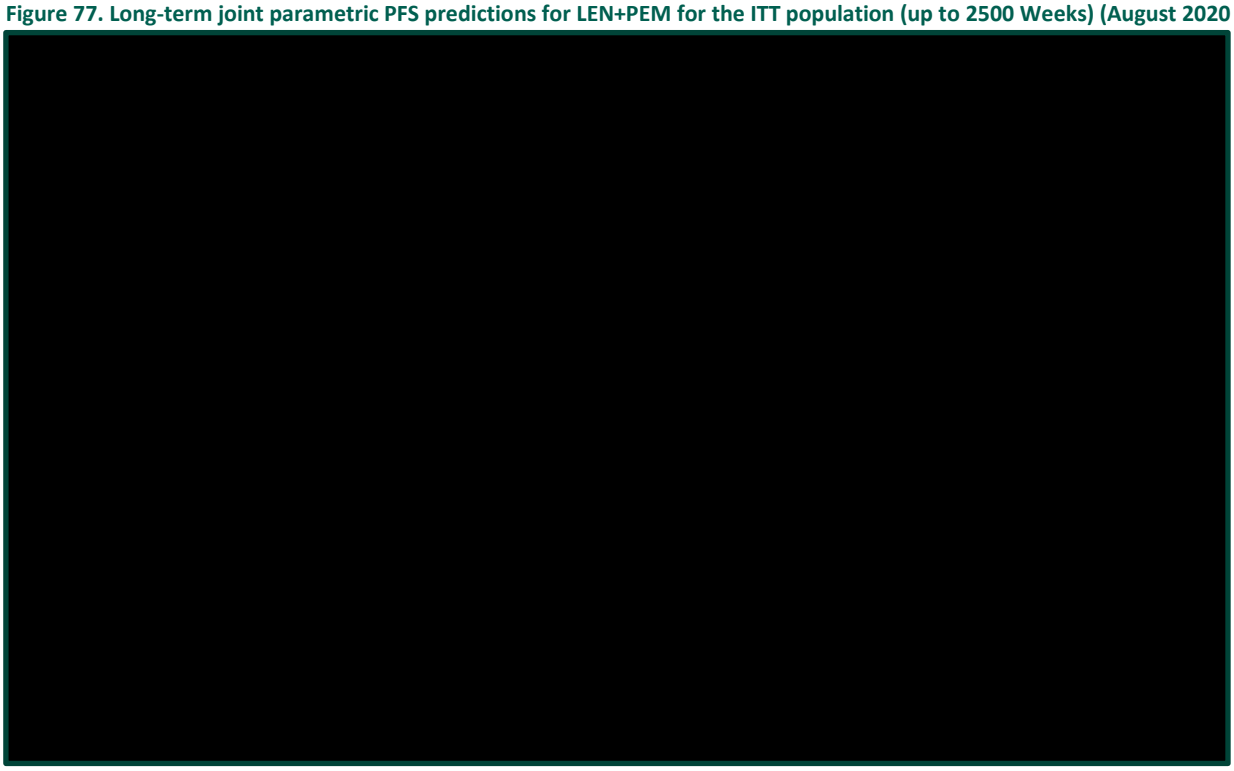
Figure 75. Comparison of observed PFS and joint parametric predictions for LEN+PEM during the observed period (up to 160 Weeks) – ITT population (August 2020 DCO)

xx

Figure 76. Long-term joint parametric PFS predictions for LEN+PEM for the ITT population (up to 1200 Weeks) (August 2020 DCO)

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 77. Long-term joint parametric PFS predictions for LEN+PEM for the ITT population (up to 2500 Weeks) (August 2020 DCO)



Similarly, Visual inspection of the joint parametric PFS curves for sunitinib overlaid by the KM curve (Figure 78 and

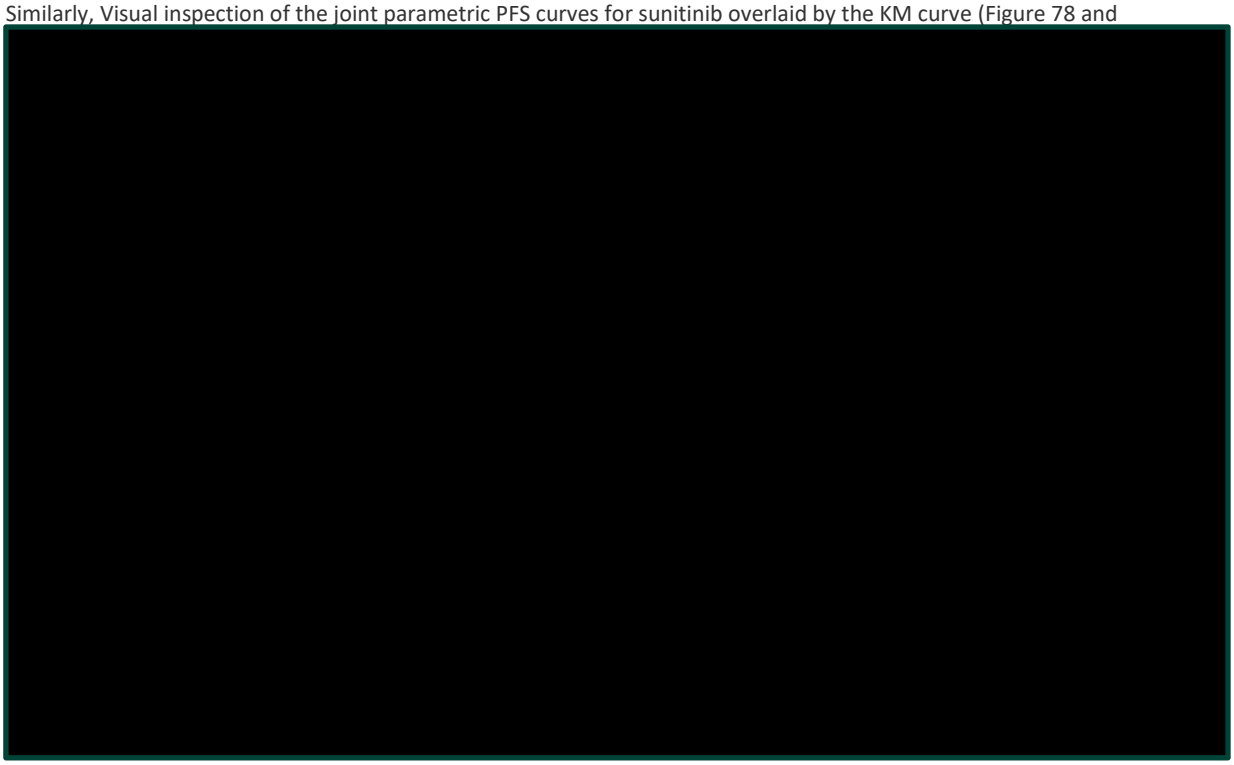
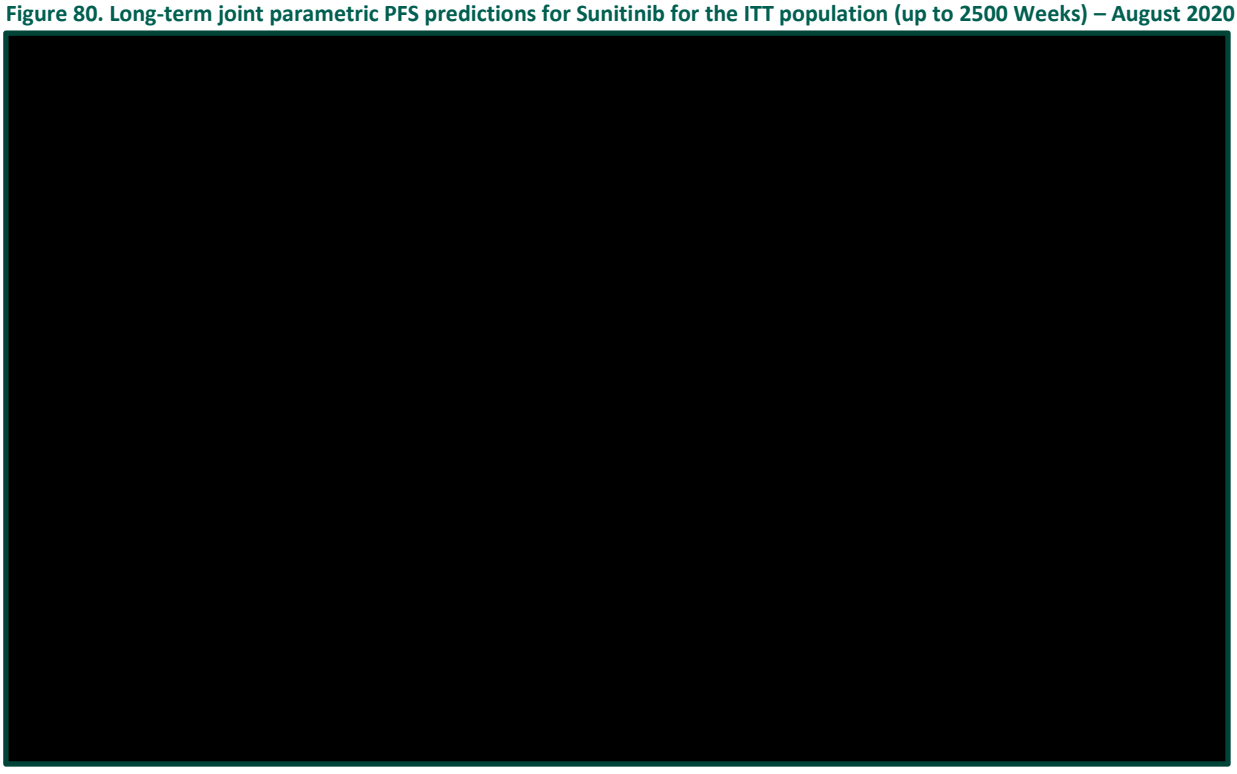


Figure 79) indicated that the Log-normal distribution closely matched the tail of the KM curve, with the log-logistic and generalized gamma models slightly underestimating the tail, and the remaining parametric models (Exponential, Weibull, Gompertz) producing more significant underestimates of the tail and therefore relatively poor visual fits.

Figure 78. Comparison of observed PFS and joint parametric predictions for Sunitinib during the observed period (up to 160 Weeks) – ITT population – (August 2020 DCO)

Figure 79. Long-term joint parametric PFS predictions for Sunitinib for the ITT population (up to 1200 Weeks) – August 2020 DCO

Figure 80. Long-term joint parametric PFS predictions for Sunitinib for the ITT population (up to 2500 Weeks) – August 2020 DCO



The hazard profiles produced by each joint-fit parametric model for LEN+PEM and sunitinib were analysed to assess the shape of the changing hazard over time as shown in Figure 81.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 81. Hazard Profiles from Each Joint-fit Parametric Model for PFS

Abbreviation: LENVAT+PEMBRO = lenvatinib plus pembrolizumab

As shown by the smoothed hazard plot in Figure 81, the log-logistic, Log-normal and generalized gamma all produced fairly similar hazard profiles, with increasing hazards of death or progression in the short-term followed by decreasing hazards in the long-term. The Weibull distribution produced an increasing (but plateauing) hazard profile over time, while the Gompertz model produced a broadly linear increasing risk of death or progression over time. By definition, the Exponential model produced a constant hazard profile. As a joint parametric fit was considered appropriate for PFS, and therefore a proportional hazards assumption applied for sunitinib, the sunitinib models produced the same hazard profiles as their corresponding LEN+PEM curves (albeit with proportional increases in hazards).

Moreover, the expected percentage of progression-free patients at two-years, five-years and ten-years were extracted for the joint fits of LEN+PEM (and including capping by Danish background mortality). As shown in Table 127, the estimated proportion of patients who are alive and progression-free treated with LEN+PEM at two-years ranges from [redacted] depending on the distribution selected. At five-years, the estimated proportion of alive and progression-free patients decreases to between [redacted] and at ten-years the estimates further decrease to between [redacted] depending on the distribution selected. Over the lifetime time horizon of the model, the estimated proportion of alive and progression-free patients decreases to between [redacted] depending on the distribution selected.

Table 127. Expected PFS per Distribution with LEN+PEM – overall population

Distribution for LEN+PEM	2-year PFS prediction	5-year PFS prediction	10-year PFS prediction
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LEN+PEM = lenvatinib plus pembrolizumab; PFS = progression-free survival

Long-term progression-free survival estimates for sunitinib were searched for in published literature and from clinical commentary available in previous aRCC NICE TAs. These estimates were compared against the expected percentage of progression-free patients at two-years, five-years and ten-years extracted for the joint fits of sunitinib from this model. In the COMPARZ trial [39], which evaluated pazopanib and sunitinib in aRCC, approximately 25% of sunitinib patients were progression-free at two-years. In addition, KEYNOTE-426 which evaluated PEM+AXI versus sunitinib in aRCC demonstrated that 26.5% of sunitinib patients were progression-free at two-years [87].

[redacted]

[redacted]Table 128[redacted] Furthermore, clinical feedback from the AVE+AXI NICE TA645 suggests 0% of sunitinib patients would be alive and progression-free beyond ten years [81]. This is broadly in line with the projected estimates of this model which vary between 0% to 2.34% depending on the distribution selected.

Table 128. Expected PFS as per Distribution with Sunitinib – overall population

Distribution for sunitinib	2-year PFS prediction	5-year PFS prediction	10-year PFS prediction
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PFS = progression-free survival

The Log-normal joint parametric model was selected for PFS to model both treatment arms, based on having the best statistical fit according to both AIC and BIC, as well as the joint best visual fit to the tail for LEN+PEM and the best visual fit to the tail for sunitinib. In addition, the joint parametric Log-normal model produced the closest estimates as seen in the literature at two-years for the number of patients estimated to be progression-free with sunitinib, followed by the log-logistic model. Although the Log-normal model overestimates the proportion progression-free at ten-years, when compared against clinical opinion from NICE TA645 [81], it represented a conservative long-term projection for sunitinib relative to LEN+PEM. The loglogistic and generalised gamma joint parametric models were explored through scenario analysis, as these models produced a good relative statistical fit and one of the next best visual fits to the tails of the KM curves.

OS extrapolations

This section outlines the rationale for the selection of the best extrapolation model for long term OS. Statistical fits are considered but the final decision was based on clinical plausibility, as described below.

AIC and BIC estimates for the LEN+PEM OS distributions using the March 2021 DCO are shown in Table 129. The Gompertz distribution produced the best statistical fit with the lowest AIC and BIC, with none of the remaining distributions generating a good relative statistical fit (<4 difference) according to the AIC rules of thumb applied. The Weibull and the generalized gamma models produced a reasonable relative statistical fit (4 to 7 difference), with the log-logistic model generating an acceptable relative statistical fit for AIC. Both the Log-normal and the log-logistic distributions produced poor relative statistical fits to the Gompertz model in terms of AIC (>10 difference). In terms of BIC, all models except for Log-normal produced an acceptable statistical fit, with the Log-normal distribution producing a poor relative statistical fit (>10 difference) compared to the Gompertz model.

Table 129. AIC and BIC Estimates for LEN+PEM OS Distributions using March 2021 DCO

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 130. AIC and BIC Goodness-of-fit per Each Distribution Relative to the Distribution with the Lowest AIC and BIC for LEN+PEM OS using March 2021 DCO

Distribution	AIC Relative Goodness-of-fit classification	BIC Relative Goodness-of-fit Classification
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

AIC and BIC estimates for the sunitinib OS distributions using the March 2021 DCO are also shown in [redacted] 131. The generalized gamma distribution produced the best statistical fit with the lowest AIC and BIC. The log-logistic and generalized gamma produced acceptable relative statistical fits according to AIC (7 to 10 difference) but the Weibull, Exponential, and Gompertz curves producing poor relative statistical fits according to AIC (>10 difference). For BIC, only the Log-normal distribution generated an acceptable relative statistical fit according to BIC (0 to 10 difference), with all other models having a poor relative statistical fit (>10 difference).

Table 131. AIC and BIC Estimates for Sunitinib OS Distributions using March 2021 DCO

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 132. AIC and BIC Goodness-of-fit per Each Distribution Relative to the Distribution with the Lowest AIC and BIC for Sunitinib OS using March 2021 DCO

Distribution	AIC Relative Goodness-of-Fit Classification	BIC Relative Goodness-of-fit Classification
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Long-term single parametric predictions for LEN+PEM are shown in Figure 82
Figure 83 and sunitinib in Figure 85 and Figure 86 with OS fitted over their respective KM curves using the March 2021 DCO.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 82. Comparison of observed OS and single parametric Predictions for LEN+PEM using March 2021 DCO (up to 210 Weeks) – ITT population

[redacted]

[redacted]

Figure 83. Long-term Single Parametric OS single parametric Predictions for LEN+PEM Using March 2021 DCO (up to 1200 Weeks) – ITT population

[redacted]

Abbreviations: LEN + PEM = lenvatinib plus pembrolizumab; OS = overall survival

Figure 84 Long-term Single Parametric OS single parametric Predictions for LEN+PEM Using March 2021 DCO (up to 2500 Weeks) – ITT population

Figure 85. Comparison of observed OS and single parametric predictions for Sunitinib during the observed period for the ITT population (up to 150 Weeks) – March 2021 DCO

Abbreviations: OS = overall survival; SUN = sunitinib

Figure 86. Long-term single parametric OS predictions for Sunitinib for the ITT population (up to 1200 Weeks) – March 2021 DCO

Abbreviations: OS = overall survival; SUN = sunitinib

Figure 87 Long-term single parametric OS predictions for Sunitinib for the ITT population (up to 2500 Weeks) – March 2021 DCO

For LEN+PEM, the Weibull model produced a close fit to the tail of the KM curve. The Gompertz and the generalized gamma distribution underpredicted the tail, while the log-logistic, Exponential, and Log-normal curves overpredicted the tail, with the log-logistic model generating the smallest overprediction followed by the Exponential model.

For sunitinib, the generalized gamma produced the closest fit to the tail of the KM curve, albeit with a slight overprediction. All other models underpredicted the tail, with the Gompertz distribution generating the smallest underprediction followed by the Log-normal model.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

The hazard profiles produced by each parametric model for LEN+PEM and sunitinib were analysed to assess the shape of the changing hazard over time as shown Figure 88 and Figure 89.

Figure 88 LEN+PEM OS Hazard Profiles using March 2021 DCO

Abbreviation: LENVAT+PEMBRO = lenvatinib plus pembrolizumab

Figure 89. Sunitinib OS Hazard Profiles using March 2021 DCO

For LEN+PEM, the generalized gamma and Gompertz models both produced sharply increasing hazard profiles. The Log-normal and log-logistic models both generated increasing then decreasing hazard profiles, with the Log-normal model producing a shorter-term increase in hazards

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

compared to the log-logistic distribution. The Weibull model produced an increasing but plateauing hazard plot, with the Exponential distribution (by definition) generating a constant risk of mortality over time.

For sunitinib, the generalized gamma, Log-normal, and log-logistic models all generated short-term increasing then decreasing hazard profiles, with the generalized gamma model producing a larger increase in short-term mortality risk before generating a faster decline in hazards compared to the Log-normal and log-logistic models (which had fairly similar hazard plots). The Gompertz models generated a decreasing hazard profile with a similar long-term mortality risk to the generalized gamma distribution. Similar to the Exponential distribution, the Weibull model produced a fairly flat and broadly constant (albeit slightly increasing) risk of mortality over time.

Moreover, the expected percentage of patients remaining alive at two years, five years, and ten years was extracted for each parametric distribution for LEN+PEM. As shown in [redacted] 133, the estimated proportion of patients who are alive and treated with LEN+PEM at two years ranges from [redacted] depending on the distribution selected. At five years, the estimated proportion of patients who are alive decreases to between [redacted] and at 10 years the estimates further decrease to between [redacted] depending on the distribution selected, indicating substantial variability in long-term predictions across survival models. However, the long-term predictions of 0% of patients who are alive at ten years estimated from the Gompertz and generalized gamma models are likely to be clinically implausible in relation to those generated by the sunitinib arm and the ten-year PFS model predictions ([redacted] Over the model lifetime of 40 years, the estimated proportion of patients who are alive decreases to between [redacted] depending on the distribution selected.

As shown in [redacted] 133, four of the six distributions (Weibull, log-logistic, Gompertz and generalized gamma) resulted in crossing of the OS extrapolations when assuming the same type of distribution for both LEN+PEM and sunitinib. Clinical and economic experts interviewed during the July 2021 advisory board meeting [86] noted that the crossing of the OS KM curves in the trial was not expected, and that the crossing was likely related to the subsequent treatments being received by sunitinib patients after progression or a lack of maturity in the data. In addition, it was noted that a relatively small group of patients at risk may be having a significant impact on the position of the OS curve at the tail, which is supported by the idea that the point of crossing in the KM curves shifts between the August 2020 and March 2021 DCOs. Furthermore, when discussing the use of a mechanic of setting the hazard for LEN+PEM equal to sunitinib at the point of crossing, this approach was challenged by clinicians and health economists due to the belief that the OS curves in reality should not cross. As such, this suggests that the extrapolations produced by these four models are clinically implausible.

Table 133. Expected OS per Distribution with LEN+PEM using March 2021 DCO

Distribution for LEN+PEM	2-year OS prediction	5-year OS prediction	10-year OS prediction	40-year OS prediction
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LEN+PEM = LEN+PEM; OS = overall survival

Table 134. Expected OS per Distribution with Sunitinib using March 2021 DCO

Distribution for Sunitinib	2-year OS prediction	5-year OS prediction	10-year OS prediction	40-year OS prediction
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: OS = overall survival

Long-term OS estimates for sunitinib were searched for in published literature and from clinical commentary available in previous aRCC NICE TAs. These estimates were compared against the expected percentage of alive patients at two years, five years, and ten-years for each individual parametric fit for sunitinib. In the COMPARZ trial [39], which evaluated pazopanib and sunitinib in aRCC, approximately 56% of sunitinib patients were alive at two years. KEYNOTE-426 [87], which evaluated PEM+AXI versus sunitinib in untreated aRCC, demonstrated

that 65.5% of sunitinib patients were alive at two years. In a recent SEER publication [182] for first line aRCC, two-year OS of <40% was observed for sunitinib.

A summary of two-, five-, and ten-year predictions from the parametric models for sunitinib are shown in Table 135, with external data estimates [39, 87, 182-185] and KOL opinion from the PEM+AXI appraisal (NICE TA650 [79]). The two-year OS from the trial (69.7%) and the estimates from the parametric models [redacted], particularly the SEER study (<40% alive at two years) [182]. As such, it is difficult to assess the clinical plausibility of the extrapolations using the two-year external data, with most of the studies having similar follow-up durations to the CLEAR August 2020 DCO for OS. In terms of the five-year OS for sunitinib, both external data (25.9%, 26.73%) and KOL opinion from TA650 [79] (20% to 25%) [redacted], with the Weibull model generating the closest estimate. In terms of the ten-year OS predictions [redacted] in relation to the range of values provided by KOLs in TA650 (10% to15%), although the Weibull (17.3%) and Exponential models (18.1%) produced fairly close estimates to the upper bound of the KOL predictions. Given the available external data and expectations from KOLs from TA650, this suggests that the Gompertz and generalized gamma models are clinically implausible, with ten-year estimates (35.0% and 43.9%) far above the upper bound of values expected by clinical experts in TA650 (15%).

Table 135. External Data and TA650 KOL Opinion for Sunitinib OS

Data source	2 years	5 years	10 years
Gore 2015 [183]	~41.3%	~25.9%	-
Pooled studies (Hammers 2015, Motzer 2019, Motzer 2013) [39, 184, 185]	60.0%	~26.73%	-
COMPARZ trial (Motzer 2013) [39]	~56%	-	-
KEYNOTE-426 trial (Powles 2020) [87]	65.5%	-	-
SEER data (Pal 2017) [182]	~39.0%	-	-
TA650 KOL opinion	-	20%–25%	10%–15%

Abbreviation: KOL = key opinion leader

While no long-term data is currently available for LEN+PEM, clinical experts interviewed during the July 2021 advisory board meeting[86] suggested that in the current clinical landscape, patients starting on treatment would likely have five-year OS of around 50% and ten-year OS below 20%. In addition, clinical experts interviewed as part of the NICE appraisal for PEM+AXI (TA650 [79]) indicated a ten-year OS expectation of 25% for PEM+AXI.

[redacted]

[redacted]

As shown in Figure 90 overlaying the KM plots of sunitinib OS alongside prior clinical trials shows that the CLEAR trial sunitinib arm produced much higher OS in the long-term compared to previous studies, while Figure 91 shows that PFS from the CLEAR trial is relatively typical for sunitinib relative to other studies. Although differences between trials may be a result of differences in underlying patient characteristics and naïve comparisons across clinical trials should be interpreted with caution, the fact that sunitinib OS from the CLEAR trial is atypically high while PFS is around the average of other sunitinib trials further suggests that subsequent treatments may be impacting the results and contributing to the crossing of curves not necessarily observed in previous clinical trials for aRCC treatments.

Figure 90. Overlaid KM Plots of Sunitinib OS Across Clinical Trials[redacted]

Abbreviations: KM = Kaplan-Meier; OS = overall survival; SUN = sunitinib Source: Alliance A031203 CABOSUN (Choueiri 2018) [38], Gore 2015 [183], SEER (Pal 2017) [182], Immotion 151 (Rini 2019) [170], CheckMate 214 (Albiges 2020) [68], CheckMate 9ER (Choueiri 2021) [168], COMPARZ (Motzer 2014) ([39, 163], KEYNOTE-426 (Powles 2020) [87], JAVELIN101 update (Choueiri 2020) [47]

Figure 91. Overlaid KM Plots of Sunitinib PFS Across Clinical Trials

Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival; SUN = sunitinibn Source: Alliance A031203 CABOSUN (Choueiri 2018) [38], Gore 2015 [183], SEER (Pal 2017) [182], Immotion 151 (Rini 2019) [170], CheckMate 214 (Albiges 2020) [68], CheckMate 9ER (Choueiri 2021) [168], COMPARZ (Motzer 2014) ([39, 163], KEYNOTE-426 (Powles 2020) [87], JAVELIN101 update (Choueiri 2020) [47]

As shown in Figure 92 overlaying the KM plots of LEN+PEM OS alongside other combination immunotherapies showed more favorable outcomes with the LEN+PEM combination than with any other immunotherapies, until at least approximately 36 months. NIVO+IPI does show better survival outcomes after approximately 44 months but also has more mature data available than LEN+PEM. This further supports the idea that the curve crossing observed in CLEAR is due to uncharacteristically high OS observed with sunitinib compared to other clinical trials, although naïve comparisons across clinical trials should be interpreted with caution.

Figure 92. Overlaid KM plots of LEN+PEM vs Combination Immunotherapies Across Clinical Trials

Abbreviations: ATE + BEV = atezolizumab plus bevacizumab; AVE + AXI = avelumab plus axitinib; BEV + IFN = bevacizumab plus interferon alpha; LEN + PEM = lenvatinib plus pembrolizumab; NIVO + CABO = nivolumab plus cabozantinib; NIVO+IPI = nivolumab plus ipilimumab; PEM + AXI = pembrolizumab plus axitinib
Source: PEM + AXI - KEYNOTE-426 (Powles 2020) [87], AVE + AXI - JAVELIN101 update (Choueiri 2020), NIVO+IPI - CheckMate 214 (Albiges 2020) [68], ATE + BEV - Immotion 151 (Rini 2019) [170], NIVO + CABO - CheckMate 9ER (Choueiri 2021) [168], BEV + IFN - CALGB 90206 (Rini 2010) [186]

NICE Decision Support Unit (DSU) TSD14 [16] recommends that the same type of parametric model be applied unless sufficient justification is provided to warrant the use of separate types of parametric models based on "clinical expert judgement, biological plausibility and robust statistical analysis." Although the use of the Exponential model for both treatment arms implies a proportional hazards relationship for both treatments, given comments from clinical experts about the implausibility of the curves actually crossing and long-term OS expectations for the existing treatment landscape for aRCC (<20% at 10 years), the Exponential model appears to be the most plausible set of single fit parametric models. In addition, although the log-logistic, generalized gamma and Gompertz distributions produced better overall statistical fits to the data across both treatment arms, the long-term extrapolations from these distributions were substantially less plausible, particularly for the generalized gamma and Gompertz models. This was also acknowledged by clinical and economic experts during the UK July advisory board meeting where it was noted that statistical fit based on AIC and BIC had limited value in informing the selection of base case OS distributions, and that it was not surprising that statistical measures for goodness-of-fit do not reveal a clear choice of base case extrapolations for LEN+PEM and sunitinib. As such, single Exponential distributions were applied in the base case analysis for OS for both LEN+PEM and sunitinib and the lognormal extrapolations were tested in a scenario analysis.

TTD extrapolations

TTD curves are generated separately for lenvatinib and pembrolizumab as they are administered separately and pembrolizumab has a fixed time on treatment duration of two years [79]. As pembrolizumab has different stopping rules compared to lenvatinib and sunitinib, a PH assumption was not applied and independent models were instead fitted for each treatment, with the hazards for each treatment expected to be sufficiently different to justify the use of different types of parametric model for each treatment.

As for PFS and OS, parametric models for TTD were also selected on the basis of statistical fit (AIC/BIC), visual fit and clinical plausibility based on available external data, with modified Burnham/Anderson and Raftery criteria used to categorize models based on statistical fit relative to the model with the lowest AIC and BIC, respectively.

AIC and BIC estimates for the lenvatinib TTD distributions are shown Table 136. The Exponential distribution produced the best statistical fit with the lowest AIC and BIC, with the Weibull, Gompertz and generalized gamma distributions all displaying good relative statistical fits relative

to the model with the lowest AIC (<4 point difference) and acceptable relative fits for BIC (<10 point difference). The Log-normal and Log-logistic distributions both produced a poor statistical fit relative to the Exponential distribution for both AIC and BIC.

Table 136. AIC and BIC Estimates for Lenvatinib TTD Distributions

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 137. AIC and BIC Goodness-of-fit per Each Distribution Relative to the Distribution with the Lowest AIC and BIC for Lenvatinib TTD

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

AIC and BIC estimates for the pembrolizumab TTD distributions are also shown in Table 137. The generalized gamma distribution produced the best statistical fit with the lowest AIC and BIC, with all other models producing poor relative statistical fits according to AIC (>10-point difference), and only the Weibull model producing an acceptable relative statistical fit according to BIC.

Table 138. AIC and BIC Estimates for Pembrolizumab TTD Distributions

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 139. AIC and BIC Goodness-of-fit per Each Distribution Relative to the Distribution with the Lowest AIC and BIC for Pembrolizumab TTD

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Similarly, AIC and BIC estimates for the sunitinib TTD distributions are reported in Table 138. The Log-normal distribution produced the best statistical fit with lowest AIC and BIC, with the log-logistic and generalized gamma distributions all displaying good relative statistical fits relative

to the model with the lowest AIC (<4 point difference) and acceptable relative fits for BIC (<10 point difference). The Weibull, Exponential and Gompertz distributions all produced a poor statistical fit relative to the Exponential distribution according to both AIC and BIC.

Table 140. AIC and BIC Estimates for Sunitinib TTD Distributions

Distribution	AIC	BIC
[redacted]	[redacted]	[redacted]

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 141. AIC and BIC Goodness-of-fit per Each Distribution Relative to the Distribution with the Lowest AIC and BIC for Sunitinib TTD

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Long-term predictions for each model fitted to the TTD KM curve for lenvatinib are shown in Figure 93. The generalized gamma model produced a close fit to the tail of the KM curve, with all other models overestimating the tail. The Gompertz, Exponential and Weibull models slightly overestimated the tail of the KM curve, with the Log-normal and log-logistic distributions producing fairly large overestimates of the tail.

Figure 93. Long-term Single Parametric TTD Predictions for Lenvatinib – ITT population

Figure 94. Long-term Single Parametric TTD Predictions for Lenvatinib – ITT population (2500 weeks)

Long-term predictions for each model fitted to the TTD KM curve for pembrolizumab are shown in Figure 95. All models produced significant overestimates of the tail, due to the sharp drop in the curve at approximately 120 weeks, as a result of the 2-year stopping applied for pembrolizumab in the CLEAR trial. The generalized gamma model produced the closest fit to the tail followed by the Exponential, Gompertz and Weibull models, with the Log-normal and log-logistic distributions producing the largest overestimates of the tail.

Figure 95. Long-term Single Parametric TTD Predictions for Pembrolizumab- ITT population

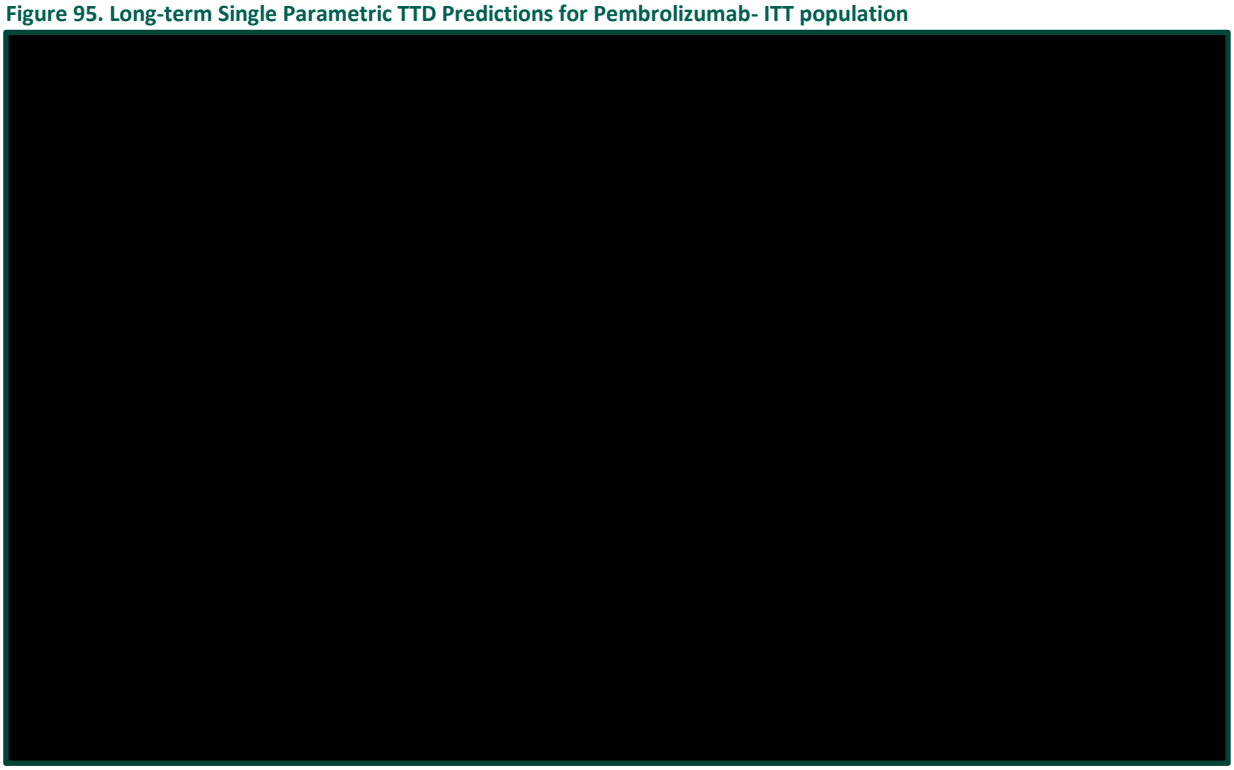


Figure 96. Long-term Single Parametric TTD Predictions for Pembrolizumab- ITT population (2500 weeks)

Long-term predictions for each model fitted to the TTD KM curve for sunitinib are shown in Figure 97. The log-logistic, Log-normal, generalized gamma and Gompertz models all generated similar close fits to the tail of the KM curve, with the Exponential and Weibull models both moderately underestimating the tail.

Figure 97. Long-term Single Parametric TTD Predictions for Sunitinib- ITT population

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 98 Long-term Single Parametric TTD Predictions for Sunitinib- ITT population (2500 weeks)

Given the lack of long-term external data for validating the longer-term predictions from the parametric models and that all models appeared reasonable in relation to the base case PFS extrapolations, selection of base case TTD distributions was primarily based on statistical and visual fit.

For pembrolizumab, while the generalized gamma model appeared to produce the best statistical and visual fit to the TTD KM curve for pembrolizumab, it is important to note that the poor relative statistical fits of other models compared to the generalized gamma distribution and fairly poor visual fits in general are due to the sharp drop in the tail associated with the two-year stopping rule for pembrolizumab, and therefore may produce fairly unreliable indications of the most appropriate parametric model for pembrolizumab TTD. Furthermore, considerable uncertainty was observed around the generalized gamma parameters, with the standard errors being larger than the parameter values themselves, and a 95% CI around the median survival time of 1.30×10^{-141} to 4.04×10^{144} weeks. As the Exponential, Weibull and Gompertz models all produced similar visual fits to the generalized gamma distribution up until the sharp drop in the tail (at approximately 100 weeks), and a hard stopping rule for treatment continuation was applied at two years in the base case model, the Weibull distribution was selected for use in the base case analysis based on having a good statistical and visual fit to the end of the KM curve.

Compared to pembrolizumab, lenvatinib and sunitinib have different treatment stopping rules (treatment until progression or unacceptable toxicity) and mechanisms of action, therefore it was considered reasonable to apply different types of parametric survival models to these treatments compared to pembrolizumab. The only distribution that generated good statistical and good visual fits to the tails across both treatment arms was the generalized gamma model, and hence this distribution was applied for the base case analysis.

Appendix H Literature search for HRQoL data

As mentioned in

Appendix A Literature search for efficacy and safety of intervention and comparator(s), the goal of this project was to generate evidence that can be used to successfully demonstrate the value of LEN+PEM in the treatment of aRCC and to support reimbursement decisions by:

- Providing a comprehensive understanding of the clinical efficacy and safety of 1L treatments for aRCC
- Ensuring that the evidence generated meets the methodological rigor required by major HTA and regulatory bodies (e.g., FDA, the National Institute for Health and Care Excellence [NICE]) and is flexible enough to support future HTA submissions.

The following specific research questions were answered by the systematic literature reviews (SLR):

> **SLR 1. Clinical Efficacy and Safety:** What is the clinical efficacy and safety of approved, recommended, or under development 1L treatments for aRCC compared with each other or best supportive care (BSC) based on evidence from randomized controlled trials (RCT)?

SLR 2. PROs: What is the impact of 1L treatments approved, recommended, or under development on humanistic burden/patient-reported outcomes (PRO) in patients with aRCC based on evidence from observational studies and RCTs?

This appendix presents the details of SLR2. PROs

Search strategy

The SLRs were conducted in accordance with NICE technology appraisal guidance,[96, 97] the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [62] and the Cochrane Handbook for Systematic Reviews of Interventions [63] The quality of the identified evidence was assessed using well-established, recommended, quality score systems, when appropriate, including the Cochrane Risk of Bias Assessment Tool 2.0 [98] and the Drummond Checklist of Economic Evaluations [99].

Systematic searches for SLR 2 were conducted on January 5, 2021 (Two searches had been conducted on March 27, 2019, and September 1, 2020, as well) in Embase and MEDLINE (via PubMed), EconLit, Centre for Reviews and Dissemination, and the Cochrane Library using a combination of free-text search terms and controlled vocabulary terms (Emtree terms in embase.com), as recommended by the Cochrane Collaboration [100]. Search concepts were validated [101, 102] and modified, where appropriate, according to project-specific needs, using guidance from Ovid Expert Search Tools [103] and the Cochrane Handbook for Systematic Reviews of Interventions [104].
For conference proceedings with abstracts indexed in electronic literature databases (American Society of Clinical Oncology [ASCO], American Society of Clinical Oncology-Genitourinary (ASCO-GU), American Association for Cancer Research (AACR), American Urological Association (AUA), European Association of Urology (EUA), and European Society for Medical Oncology [ESMO]), Embase was searched. Abstracts from ASCO-GU were not indexed in Embase, and the conference website (https://meetinglibrary.asco.org/) was searched for relevant abstracts using keywords for aRCC (similar to those used in the electronic literature database searches).
SLRs identified by searches of the electronic databases were also reviewed. Specifically, the reference lists of these reviews were scrutinized—using the patient-intervention-comparator-outcome-study type (PICOS) criteria—as a supplemental data source to identify additional relevant publications. The SLRs were not processed further in the review, to avoid double-counting of relevant studies.
ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO iCTRP), and European Medicines Agency (EMA) European public assessment reports (EPAR) were also searched for relevant abstracts or documents explicating clinical evidence on aRCC.

The inclusion/exclusion criteria for the SLRs were based on the PICOS framework, as shown in Table 142. These pre-defined inclusion and exclusion criteria were used to evaluate the titles/abstracts of records identified from the searches during the first level of review. Full-text articles were then retrieved and reviewed for abstracts that were deemed relevant during the first level of review. None of the exclusion criteria and all protocol-specified inclusion criteria must have been met for a study to pass this level.

PICOS

Table 142. PICOS SLR2

Category	SLR2 (PROs)
Populations	Adults with aRCC with no prior lines of systemic therapy Subpopulations defined by histology, risk level, or mutation status. Exclusion: paediatric populations, early stage or locally advanced disease, carcinomas other than RCC/kidney cancer, prior systemic treatment experience
Interventions	1L systemic treatments for aRCC administered alone or in combination Exclusions: second or later lines of systemic treatment, surgery, radiotherapy, adjuvant or neo-adjuvant chemotherapy, treatments for symptom management
Comparators	1L systemic treatments administered alone or in combination, or no comparator (i.e., single arm) Exclusions: surgery, radiotherapy, or other comparators that are not 1L systemic treatments for aRCC
Outcomes	PROs (including HRQoL or utility weights) assessed based on the following instruments: EQ-5D, SF-36, SF-12, SF-6, EORTC QLQ-C30, FACT-G, FKSI, or direct utility elicitation (time trade-off or standard gamble methods). Exclusions: publications that do not report any outcome of interest listed above.
Study design	RCTs (a minimum of two-arm parallel, phase II or III, trial) Exclusions: publications that do not report any outcome of interest listed above

Language	English language only
Publication year	Studies published since 2009

Embase

Table 143. Embase PROs Search

Search Number	Search String	Hits (March 27, 2019)	Hits (September 1, 2020)	Hits (January 5, 2021)
	'kidney carcinoma'/exp/mj OR 'kidney tumor'/exp/mj OR 'renal cell carcinoma'/exp/mj	78,089	78,656	80,669
	((renal OR kidney) NEAR/2 (carcinoma* OR adenocarcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignan*)):ab,ti	84,391	92,594	95,468
	#1 OR #2	108,258	112,657	115,898
	advanced:ab,ti OR unresect*:ab,ti OR 'un resect*':ab,ti OR nonresect*:ab,ti OR ((non NEAR/2 resect*):ab,ti) OR inopera*:ab,ti OR unopera*:ab,ti OR metastas*:ab,ti OR metastat*:ab,ti OR 'end stage':ab,ti OR 'late-stage':ab,ti OR 'late stage':ab,ti OR terminal:ab,ti OR 'stage 3':ab,ti OR 'stage iii':ab,ti OR 'stage three':ab,ti OR 'stage 4':ab,ti OR 'stage iv':ab,ti OR 'stage four':ab,ti	1,738,865	1,916,352	1,982,475
	#3 AND #4	39,181	43,352	44,762
	'quality of life'/exp OR qol:ab,ti OR 'quality of life':ab,ti OR hrql:ab,ti OR hrqol:ab,ti OR 'patient reported outcome':ab,ti OR 'patient reported outcomes':ab,ti OR aqol:ab,ti OR 'quality of well being scale':ab,ti OR 'health utility':ti,ab OR 'health utilities':ti,ab OR 'health state utility':ti,ab OR 'health state utilities':ti,ab OR 'utility score*':ti,ab OR 'utility value*':ti,ab OR 'utility valuation':ti,ab OR 'disutility':ab,ti OR 'disutilities':ab,ti OR 'standard gamble':ab,ti OR 'time trade off':ab,ti OR 'time tradeoff':ab,ti OR 'visual analog scale':ab,ti OR 'visual analogue scale':ab,ti OR 'visual analog scales':ab,ti OR 'visual analogue scales':ab,ti OR 'discrete choice experiment':ab,ti OR qwb:ab,ti OR 15d:ab,ti OR hui:ab,ti OR sf36:ab,ti OR 'sf 36':ab,ti OR sf6:ab,ti OR 'sf 6':ab,ti OR 'short form 6':ab,ti OR 'eq 5d':ab,ti OR eq5d:ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti OR 'health status':ab,ti OR 'eortc qlq c30':ab,ti OR 'functional assessment of cancer therapy':ab,ti OR 'fksi':ab,ti OR 'fact-g':ab,ti	654,938	752,382	785,473
	'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'case report'/de OR OR 'methodology'/de OR 'clinical protocol'/de OR 'nonhuman'/de OR 'short survey'/it OR 'practice guideline'/de OR ('review'/it NOT (systematic:ab,ti OR meta* OR 'mixed treatment comparison':ab,ti OR 'indirect treatment comparison' OR 'meta analysis'/exp OR 'meta analysis (topic)' OR 'systematic review (topic)' OR 'systematic review'/exp OR 'network meta-analysis'/exp) AND [2015-2019]/py)	12,413,644	12,549,039	12,549,039
	'conference abstract'/it NOT ('2018 annual meeting of the american association for cancer research, aacr 2018':nc OR '2018 annual meeting of the american society of clinical oncology, asco 2018':nc OR '2017 annual meeting of the american society of clinical oncology, asco':nc OR '112th annual meeting of the american urological association, aua 2017':nc OR '2018 annual meeting, american urological association, aua 2018':nc OR	3,283,691	3,830,779	3,960,832

	'42nd esmo congress, esmo 2017':nc OR '33rd annual european association of urology congress, eau 2018':nc OR '32nd annual european association of urology congress, eau 2017':nc OR '2018 genitourinary cancers symposium':nc OR '2017 genitourinary cancers symposium':nc OR '2017 annual meeting of the american society of clinical oncology, asco 2017':nc OR 'american association for cancer research international conference on translational cancer medicine, aacr 2017':nc OR '23rd annual meeting of the international society for pharmacoeconomics and outcomes research, ispor 2018':nc OR 'ispor 22nd annual international meeting':nc OR 'ispor 20th annual european congress':nc)			
	#5 AND #6 AND [english]/lim AND [abstracts]/lim AND [2008-2019]/py NOT #7 NOT #8	476	-	-
	#5 AND #6 AND [english]/lim AND [abstracts]/lim AND [2019-2020]/py NOT #7 NOT #8	-	88	-
	#5 AND #6 AND [english]/lim AND [abstracts]/lim AND [2008-2021]/py NOT #7 NOT #8	-	-	57

MEDLINE (via Pubmed.com)

Table 144: MEDLINE PROs Search

No.	Query	Results (March 27, 2019)	Results (September 1, 2020)	Results (January 5, 2021)
	"carcinoma, renal cell"[MeSH Terms]	30,774	33,278	33,940
	((renal[TIAB] OR kidney[TIAB]) AND (carcinoma*[TIAB] OR adenocarcinoma*[TIAB] OR cancer*[TIAB] OR neoplasm*[TIAB] OR tumor*[TIAB] OR tumour*[TIAB] OR malignan*[TIAB]))	135,013	134,405	137,983
	#1 OR #2	129,264	137,530	141,140
	advanced[TIAB] OR unresect*[TIAB] OR "un resectable"[TIAB] OR nonresect*[TIAB] OR (non[TIAB] AND resect*[TIAB]) OR inopera*[TIAB] OR unopera*[TIAB] OR metastas*[TIAB] OR metastat*[TIAB] OR "end stage"[TIAB] OR "late-stage"[TIAB] OR "late stage"[TIAB] OR terminal[TIAB] OR "stage 3"[TIAB] OR "stage iii"[TIAB] OR "stage three"[TIAB] OR "stage 4"[TIAB] OR "stage iv"[TIAB] OR "stage four"[TIAB]	1,306,824	1,425,098	1,465,058
	#3 AND #4	39,136	42,291	43,473
	"quality of life"[MeSH] OR qol[TIAB] OR "quality of life"[TIAB] OR hrql[TIAB] OR hrqol[TIAB] OR "patient reported outcome"[TIAB] OR "patient reported outcomes"[TIAB] OR aqol[TIAB] OR "health utility"[TIAB] OR "health utilities"[TIAB] OR "health state utility"[TIAB] OR "health state utilities"[TIAB] OR "utility score*"[TIAB] OR "utility value*"[TIAB] OR "utility valuation"[TIAB] OR "disutility"[TIAB] OR "disutilities"[TIAB] OR "standard gamble"[TIAB] OR "time trade off"[TIAB] OR "time tradeoff"[TIAB] OR "visual analog scale"[TIAB] OR "visual analogue scale"[TIAB] OR "visual analog scales"[TIAB] OR "visual analogue scales"[TIAB] OR "discrete choice experiment"[TIAB] OR qwb[TIAB] OR 15d[TIAB] OR hui[TIAB] OR sf36[TIAB] OR "sf 36"[TIAB] OR sf6[TIAB] OR "sf 6"[TIAB] OR "short form 6"[TIAB] OR "eq 5d"[TIAB] OR eq5d[TIAB] OR euroqol[TIAB] OR "euro	391,441	454,990	454,990

	qol"[TIAB] OR "health status"[TIAB] OR "eortc qlq c30"[TIAB] OR "functional assessment of cancer therapy"[TIAB] OR "fksi"[TIAB] OR "fact-g"[TIAB]			
	"Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type] OR "Clinical Conference"[Publication Type]	3,312,612	3,533,272	3,599,184
	"review"[Publication Type] NOT (systematic OR meta-analysis OR meta-analyses OR metaanalysis OR metaanalyses OR ((indirect OR mixed) AND "treatment comparison")) AND 2015:2019[pdat]	410,331	2,679,804	2742419
	#5 AND #6 AND English[Language] AND 2009:2019[pdat] AND hasabstract[text] NOT #7 NOT #8	515	-	-
	#5 AND #6 AND English[Language] AND 2019:2020[pdat] AND hasabstract[text] NOT #7 NOT #8	-	108	-
	#5 AND #6 AND English[Language] AND 2020:2021[pdat] AND hasabstract[text] NOT #7 NOT #8	-	-	90

PsycINFO (via EBSCOhost)

Table 145. PsycINFO PRO Search

Search Number	Search String	Hits (March 27, 2019)	Hits (September 1, 2020)	Hits (January 5, 2021)
S1	AB (((renal OR kidney) AND (carcinoma* OR adenocarcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignan*))) OR TI (((renal OR kidney) AND (carcinoma* OR adenocarcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignan*)))	884	947	951
S2	AB (advanced OR unresect* OR 'un resect*' OR nonresect* OR ((non-resect*):ab,ti) OR inopera* OR unopera* OR metastas* OR metastat* OR "end stage" OR "late-stage" OR "late stage" OR terminal OR "stage 3" OR "stage iii" OR "stage three" OR "stage 4" OR "stage iv" OR "stage four") OR TI (advanced OR unresect* OR 'un resect*' OR nonresect* OR ((non-resect*):ab,ti) OR inopera* OR unopera* OR metastas* OR metastat* OR "end stage" OR "late-stage" OR "late stage" OR terminal OR "stage 3" OR "stage iii" OR "stage three" OR "stage 4" OR "stage iv" OR "stage four")	73,932	91,908	74,397
S3	S1 AND S2	210	232	230
Limiters	Publication Year: 2009-2019; Publication Type: All Journals; English	100	-	-
Limiters	Publication Year: 2019-current; Publication Type: All Journals; English	-	18	-
Limiters	Publication Year: 2020-current; Publication Type: All Journals; English	-	-	8

EconLit (via EBSCOhost)

Table 146. EconLit PROs

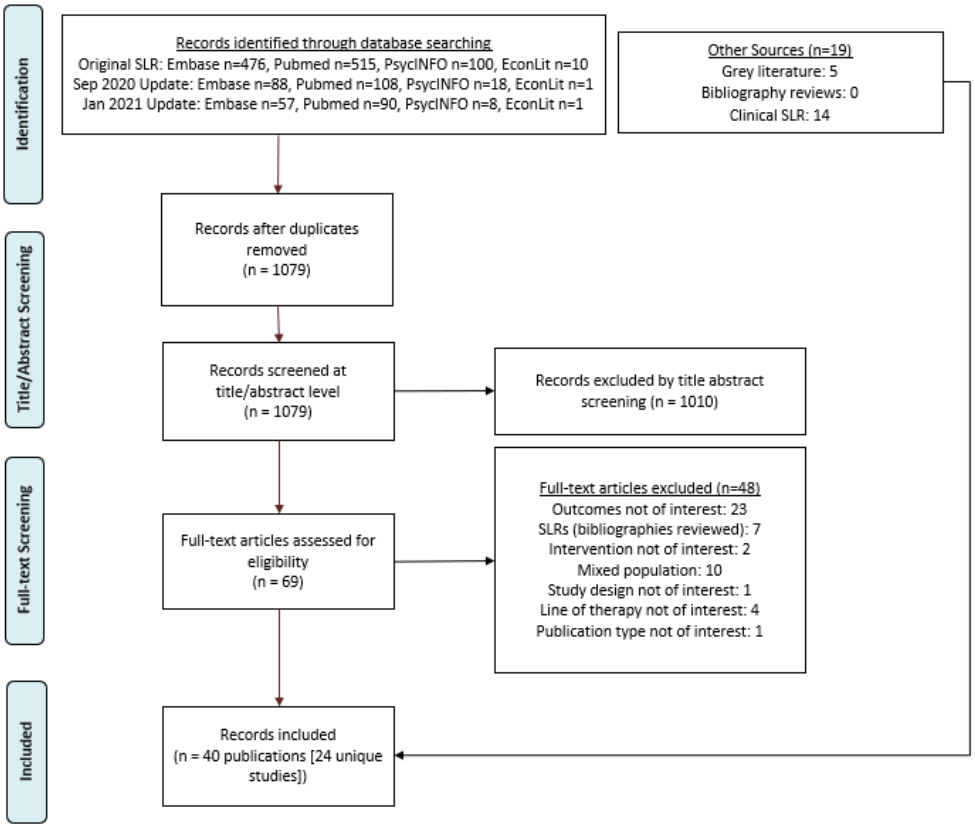
No.	Query	Results (March 27, 2019)	Results (September 1, 2020)	Results (January 5, 2021)
S1	AB (((renal OR kidney) AND (carcinoma* OR adenocarcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignan*))) OR TI (((renal OR kidney) AND (carcinoma* OR adenocarcinoma* OR cancer* OR neoplasm* OR tumor* OR tumour* OR malignan*)))	17	18	18

Limiters	Published Date: 20090101-20191231; Publication Type: Journal Article	10	-	-
Limiters	Published Date: 20190101-20201001; Publication Type: Journal Article	-	1	-
Limiters	Published Date: 20200101-20210105; Publication Type: Journal Article	-	-	1

Systematic selection of studies (PROs)

The searches yielded 1,472 records across literature databases, of which 69 were selected for review at the full-text level. Following review of the full texts, 21 publications met the criteria for inclusion in the review of humanistic burden for aRCC. Five additional sources were identified from the grey literature sources, and 14 full-text studies were identified by a reference check of the included clinical trials from clinical efficacy and safety SLR. These 40 publications reported PRO data for 24 unique studies. The flow of this literature is presented in Figure 99.

Figure 99: PRISMA Study Flow Diagram for PROs



Abbreviation: SLR, systematic literature review

Studies included in the SLR are presented in Table 147 and the studies excluded from the PRO SLR are presented in Table 149.

Studies included in the PRO SLR

Details on the studies included in the PRO SLR are presented in Table 147. Twenty-four unique studies reported PRO data for patients with aRCC receiving 1L treatments. A summary of available PRO outcomes of interest across the included studies is presented in Table 148. Seventeen studies were RCTs and the remaining seven were observational studies [187-193]. Median study follow-up ranged from 8.5 [193] to 30 [192] months. Study sample sizes ranged from 69 [194] to 1,110 [39]; additionally, 11 studies included more than 400 patients.

Eight studies were conducted in a single country, one each in Finland [193], Germany [191], France [111] the UK [190], and two each in China [189] and the US. [188, 194]. Fifteen were conducted across multiple countries, and one study did not report the country of region of study participants [133]; see Table 147). The majority of participants were from Europe (12 studies), North America (nine studies), and Asia and Australia (four studies). South America and Africa were less common in the studies (three and two studies, respectively). Study years spanned 2000 to 2018.

Table 147. Study Characteristics of studies included in the PRO SLR

Study	Country	Study Design	Years of Enrollment/Data Collection	Patient Population	Sample Size (Randomized)	Treatments	Duration of Follow-up
			North America				
TemPa [116, 194]	US (1 site)	Phase II RCT, open-label	November 2012 to June 2017	Treatment-naïve with aRCC with intermediate or poor-risk disease	69	Temsirolimus and Pazopanib	NR
Cohen, 2012 [188]	Multiregional (14 countries): Europe: n=310 North America: n=382 Asia: n=367 Australia: n=51	Phase III RCT, open-label	August 2008 to September 2011	Previously untreated, clear-cell aRCC or mRCC	1,110	Pazopanib and sunitinib	NR
			Europe				
Vuorinen, 2019 [193]	Finland (5 sites)	Prospective; phase NR	January 2010 to November 2014	mRCC	81	Sunitinib	Mean: 253 days (range: 3–728)
PERCY Quattro [111]	France (44 sites)	RCT, open-label; phase NR	January 2000 to July 2004	mRCC of intermediate prognosis	492	Medroxyprogesterone and IFN alfa-2a IL-2 IFN alfa-2a + IL2	Median: 29.2 (range: 0–54.6) months
FAMOUS [191]	Germany/100 sites	Cross-sectional; phase NA	December 2007 to December 2012	Receiving systemic treatment for aRCC or mRCC	NA	NR	NA
Swinburn, 2010 [195]	UK	Cross-sectional; phase NA	NR	Receiving newly developed treatments for mRCC	100	Newly developed treatments for mRCC (otherwise not specified)	NR
			Rest of World				
Wang, 2018 [189]	China	Prospective; phase NA	January 2013 to December 2016	mRCC who reciving IFN-alfa treatment	NA	IFN-alfa	12 weeks

Study	Country	Study Design	Years of Enrollment/Data Collection	Patient Population	Sample Size (Randomized)	Treatments	Duration of Follow-up
Cai, 2017 [187]	China	Retrospective observational; phase NA	March 2006 to July 2015	Chinese patients with mRCC	184	Sorafenib and sunitinib	Median: 23
International or Unclear							
CheckMate 9ER [150]	US, Argentina, Australia, Brazil, Chile, Czechia, Germany, Greece, Israel, Italy, Japan, Mexico, Poland, Romania, Russia, Spain, Turkey, UK (sites NR)	Phase III, RCT, open-label	NR	aRCC or mRCC	651	Nivolumab + cabozantinib and sunitinib	Median: 18.1 months
KEYNOTE-426 [196]	Multiregional: North America, Western Europe, other countries	Phase III RCT, open-label	October 2016 to January 2018	Advanced clear-cell RCC	861	Pembrolizumab + axitinib and sunitinib	Median: 30.6 months
PRINCIPAL [192]	International	Prospective; phase NR	NR	Primarily clear-cell aRCC/mRCC	657	Pazopanib	30 months
SWITCH II [147]	Germany, Austria, and Netherlands (67 sites total)	Phase III RCT, open-label	June 2012 to November 2016	aRCC/mRCC	377	Sorafenib (1L)[b] and pazopanib (1L)[b]	NR, longest reported outcome (median total PFS): 12.9 months
CheckMate 214 [151]	Multiregional (75 sites in 28 countries): US: n=307 Canada and Europe: n=400 Rest of world: n=389	Phase III RCT, open-label	Enrollment: October 2014 to February 2016 Database lock: August 2017	Previously untreated aRCC with a clear-cell component	1,096	Nivolumab + ipilimumab and sunitinib	Median: 25.2 months Minimum: 17.5 months
IMmotion151 [133]	NR	Phase III RCT, blinding NR	NR	Untreated mRCC	915	Atezolizumab + bevacizumab and sunitinib	Median: 15 months
ASPEN [112, 117]	US, Canada, and the UK (17 sites)	Phase II RCT, open-label	September 2010 to October 2013	aRCC with non-clear-cell pathology	108	Everolimus and sunitinib	Median (IQR): 13 (6–22) months

Study	Country	Study Design	Years of Enrollment/Data Collection	Patient Population	Sample Size (Randomized)	Treatments	Duration of Follow-up
RECORD-2 [140, 141]	Multiregional (108 sites)	Phase II RCT, open-label	NR	Predominantly clear-cell, mRCC	365	Bevacizumab + everolimus and bevacizumab + IFN alfa-2a	Up to 2 years for final analysis
RECORD-3 [142, 143]	Multiregional: Argentina, Australia, Brazil, Canada, Denmark, France, Germany, Hong Kong, Italy, Republic of Korea, Mexico, Netherlands, Peru, Spain, Taiwan, Thailand, Turkey, UK, and US	Phase II RCT, open-label	Enrollment: October 2009 to June 2011 Primary DCO: September 2012	mRCC (clear cell or non–clear cell, with or without nephrectomy) receiving 1L therapy	471	Everolimus and sunitinib	NR
Hutson, 2013 [129-131]	Multiregional: Ukraine: n=61 Russia: n=58 India: n=34	Phase IIIRCT, open-label	Enrollment: June 2010 to April 2011 Primary DCO: July 2012	Confirmed mRCC with a clear-cell component	288	Axitinib and sorafenib	23 months
TIVO-1 [148, 197]	Multiregional (15 countries, 76 sites total): Central/Eastern Europe: n=457 North America/Western Europe: n=40 Rest of world: n=20	Phase II RCT, open-label	Enrollment: February 2010 to August 2010 DCO: December 2011	mRCC, with a clear cell component, prior nephrectomy, measurable disease, and 0 or 1 prior therapies for mRCC	Overall: 517 Treatment-naïve: 362	Tivozanib and sorafenib	NR
VEG105192 [198]	Multiregional: Europe, Asia, South America, North Africa, Australia, and New Zealand (80 sites total)	Phase III RCT, double-blind	Enrollment: April 2006 to April 2007 Primary DCO: May 2007 Final DCO: March 2010	Clear-cell or predominantly clear-cell, locally aRCC and/or mRCC	435	Pazopanib and placebo	NR
Escudier, 2009 [126, 127]	Multiregional: Germany (6 sites), US (7 sites), France (5 sites), Poland (6 sites), Russia (3 sites), UK (1 sites), and Ukraine (3 sites).	Phase II RCT, open-label	Enrollment: June 2005 to September 2005 Data collection: June 2005 to March 2009	Unresectable and/or mRCC, predominantly clear cell, with no prior systemic therapy	189	Sorafenib and IFN alfa-2a	24 months

Study	Country	Study Design	Years of Enrollment/Data Collection	Patient Population	Sample Size (Randomized)	Treatments	Duration of Follow-up
Global ARCC [109, 128]	Multiregional: US, Western Europe, Australia, Canada, Asia-Pacific, Eastern Europe, Africa, and South America (153 sites total)	Phase III RCT, blinding NR	July 2003 to April 2005	Previously untreated, poor-prognosis mRCC	626	IFN alfa-2a + temsirolimus IFN alfa-2a + temsirolimus	Up to 80 months for final analysis
Motzer, 2007 [43, 44, 138]	Multiregional: Australia, Brazil, Canada, France, Germany, Italy, Poland, Russia, Spain, UK, and US (101 centers total)	Phase III RCT, open-label	August 2004 to October 2005	Treatment-naïve with clear-cell mRCC	750	Sunitinib and IFN alfa-2a	Final analysis: 123 weeks

Abbreviations: 1L = first line; aRCC = advanced renal cell carcinoma; IFN = interferon; IL-2 = interleukin-2; IQR = interquartile range; mRCC = metastatic renal cell carcinoma; NA = not applicable; NR = not reported; PFS = progression-free survival; RCC = renal cell carcinoma; RCT = randomized controlled trial; UK = United Kingdom; US = United States

*Administered treatments included sunitinib, sorafenib, and bevacizumab combined with IFN alpha, temsirolimus, everolimus, or IFN alpha alone. Outcomes were not stratified by specific treatment received.

Table 148. Summary of available PRO measures in the studies included in the PRO SLR

Study	Country	Intervention	PRO Measures					
			EQ-5D	EORTC	FACT-G	FKSI	SF-6/12/36	Utilities
North America								
Cohen, 2012 [188]	US	NA	☐	☐	☐	☐	☐	☐
TemPa [194]	US	Pazopanib	☐	☐	☐	☐	☐	☐
Europe								
Vuorinen, 2019 [193]	Finland	Sunitinib	☐	☐	☐	☐	☐	☐
PERCY Quattro [111]	France	IFN alfa-2a + IL-2	☐	☐	☐	☐	☐	☐
FAMOUS [191]	Germany	NA	☐	☐	☐	☐	☐	☐
Swinburn, 2010 [190]	UK	NA	☐	☐	☐	☐	☐	☐
Rest of the world								
Wang, 2018 [189]	China	IFN alfa-2a	☐	☐	☐	☐	☐	☐
Cai, 2017 [187]	China	Sorafenib	☐	☐	☐	☐	☐	☐
International or unclear								
CheckMate 9ER [150]	US, Argentina, Australia, Brazil, Chile, Czechia, Germany, Greece, Israel, Italy, Japan, Mexico, Poland, Romania, Russia, Spain, Turkey, UK	Nivolumab + cabozantinib	☐	☐	☐	☐	☐	☐
KEYNOTE-426 [196]	North America, Western Europe, and rest of the world	Axitinib + pembrolizumab	☐	☐	☐	☐	☐	☐
PRINCIPAL [192]	US, Argentina, Australia, Brazil, Canada, Denmark, France, Germany, Hong Kong, Italy, South Korea, Mexico, Netherlands, Peru, Spain, Taiwan, Thailand, Turkey, UK	Pazopanib	☐	☐	☐	☐	☐	☐

Study	Country	Intervention	PRO Measures					
			EQ-5D	EORTC	FACT-G	FKSI	SF-6/12/36	Utilities
SWITCH II [147]	Germany, Austria, and Netherlands	Sorafenib	☐	☐	☐	☐	☐	☐
CheckMate 214 [69, 151, 199, 200]	US, Canada, Europe, and rest of the world	Nivolumab + ipilimumab	☐	☐	☐	☐	☐	☐
IMmotion151 [201]	NR	Atezolizumab + bevacizumab	☐	☐	☐	☐	☐	☐
ASPEN [112]	US, Canada, and the UK	Everolimus	☐	☐	☐	☐	☐	☐
RECORD-2 [141]	International	Bevacizumab + everolimus	☐	☐	☐	☐	☐	☐
RECORD-3 [143]	Argentina, Australia, Brazil, Canada, Denmark, France, Germany, Hong Kong, Italy, Republic of Korea, Mexico, Netherlands, Peru, Spain, Taiwan, Thailand, Turkey, UK, US	Everolimus	☐	☐	☐	☐	☐	☐
COMPARZ [39]	Asia, Australia, Europe, and North America	Pazopanib	☐	☐	☐	☐	☐	☐
Hutson, 2013 [131]	India, Russia, and Ukraine	Axitinib	☐	☐	☐	☐	☐	☐
TIVO-1 [197]	Central/Eastern Europe, North America/Western Europe, and ROW	Tivozanib	☐	☐	☐	☐	☐	☐
VEG105192 [198]	Europe, Asia, South America, North Africa, Australia, and New Zealand	Pazopanib	☐	☐	☐	☐	☐	☐
Global ARCC [202]	US; Western Europe, Australia, and Canada; or Asia-Pacific, Eastern Europe, Africa, and South America	Temsirolimus	☐	☐	☐	☐	☐	☐
Escudier, 2009 [126]	Germany, US, France, Poland, Russia, UK, and Ukraine	IFN alfa-2a	☐	☐	☐	☐	☐	☐
Motzer, 2007 [43, 138, 203, 204]	Australia, Brazil, Canada, France, Germany, Italy, Poland, Russia, Spain, UK, and US	Sunitinib	☐	☐	☐	☐	☐	☐

Studies excluded from the PRO SLR

Table 149: Excluded from SLR 2

ID	Bibliography	Exclusion Reason
6524	Chen, R. C.,Choueiri, T. K.,Feuilly, M.,Meng, J.,Lister, J.,Marteau, F.,Falchook, A. D.,Morris, M. J.,George, D. J.,Feldman, D. R.. Quality-adjusted survival with first-line cabozantinib or sunitinib for advanced renal cell carcinoma in the CABOSUN randomized clinical trial (Alliance). Cancer. 2020. 126:5311-5318	Outcomes not of interest
6525	Hofmann, F.,Hwang, E. C.,Lam, T. B.,Bex, A.,Yuan, Y.,Marconi, L. S.,Ljungberg, B.. Targeted therapy for metastatic renal cell carcinoma. The Cochrane database of systematic reviews. 2020. 10:CD012796	SLRs (bibliographies reviewed)
6533	Bergerot, C. D.,Philip, E. J.,Bergerot, P. G.,Hsu, J.,Dizman, N.,Salgia, M.,Salgia, N.,Vaishampayan, U.,Battle, D.,Loscalzo, M.,Dale, W.,Pal, S. K.. Discrepancies between genitourinary cancer patients' and clinicians' characterization of the Eastern Cooperative Oncology Group performance status. Cancer.. 2020. #volume#:#pages#	Mixed Population
5018	Cella D, Motzer RJ, Rini BI, et al. Important Group Differences on the Functional Assessment of Cancer Therapy-Kidney Symptom Index Disease-Related Symptoms in Patients with Metastatic Renal Cell Carcinoma. Value Health. 2018. 21(12):1413-1418	SLRs (bibliographies reviewed)
5074	Bedke J, Welslau M, Boegemann M, et al. Interim results from PAZOREAL: A non-interventional study to assess effectiveness and safety of pazopanib and everolimus in the changing mRCC treatment landscape. Annals of Oncology. 2017. 28v318-v319	Outcomes not of interest
5083	Bergerot CD, Bergerot PG, Philip EJ, et al. Perception of cure among patients with metastatic genitourinary cancer initiating immunotherapy. Journal for ImmunoTherapy of Cancer. 2019. 7(1):	Mixed Population
5097	Boegemann M, Bedke J, Schostak M, et al. Effectiveness and safety of pazopanib (PAZO) and everolimus (EVE) in a changing treatment (Tx) landscape: Interim results of the non-interventional study PAZOREAL. Journal of Clinical Oncology. 2018. 36(15):	Outcomes not of interest
5131	Carmichael C, Yuh BE, Sun V, et al. Quality of life in patients with metastatic renal cell carcinoma: Assessment of long-term survivors. Clinical Genitourinary Cancer. 2013. 11(2):149-154	Mixed Population
5146	Cella D, Motzer R, Rini BI, et al. Important group differences on the functional assessment of cancer therapy-kidney symptom index disease-related symptoms (FKSI-DRS) in patients with metastatic renal cell carcinoma. Value in Health. 2017. 20(9):A456-A457	Outcomes not of interest
5147	Cella D, Pickard AS, Duh MS, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomised phase III trial. European Journal of Cancer. 2012. 48(3):311-323	Mixed Population
5175	Cirkel GA, Hamberg P, Sleijfer S, et al. Alternating Treatment With Pazopanib and Everolimus vs Continuous Pazopanib to Delay Disease Progression in Patients With Metastatic Clear Cell Renal Cell Cancer: The ROPETAR Randomized Clinical Trial. JAMA oncology. 2017. 3(4):501-508	Outcomes not of interest
5213	Denouel A, Heutte N, Escudier B, et al. Sexual Disorders of Patients With Metastatic Renal Cell Carcinoma (mRCC) Treated With Antiangiogenic Therapies. Clinical Genitourinary Cancer. 2018. 16(5):369-375.e1	Mixed Population
5224	Dos Santos M, Brachet PE, Chevreau C, et al. Impact of targeted therapies in metastatic renal cell carcinoma on patient-reported outcomes: Methodology of clinical trials and clinical benefit. Cancer Treat Rev. 2017. 5353-60	SLRs (bibliographies reviewed)
5248	Escudier B, Porta C, Bono P, et al. Randomized, controlled, double-blind, cross-over trial assessing treatment preference for pazopanib versus sunitinib in patients with metastatic renal cell carcinoma: PISCES study. Journal of Clinical Oncology. 2014. 32(14):1412-1418	Outcomes not of interest

5392	Joly F, Heutte N, Duclos B, et al. Prospective Evaluation of the Impact of Antiangiogenic Treatment on Cognitive Functions in Metastatic Renal Cancer. European Urology Focus. 2016. 2(6):642-649	Outcomes not of interest
5471	Luo X, Cappelleri JC, Cella D, et al. Using the Rasch model to validate and enhance the interpretation of the Functional Assessment of Cancer Therapy-Kidney Symptom Index--Disease-Related Symptoms scale. Value Health. 2009. 12(4):580-6	Outcomes not of interest
5507	Méndez-Vidal MJ, Á Molina, Anido U, et al. Pazopanib: Evidence review and clinical practice in the management of advanced renal cell carcinoma. BMC Pharmacology and Toxicology. 2018. 19(1):	SLRs (bibliographies reviewed)
5520	Miyake H, Harada KI, Inoue TA, et al. Assessment of health-related quality of life in Japanese patients with metastatic renal cell carcinoma during treatment with tyrosine kinase inhibitors. Medical Oncology. 2014. 31(9):	Mixed Population
5521	Miyake H, Harada KI, Kumano M, et al. Assessment of efficacy, safety and quality of life of 55 patients with metastatic renal cell carcinoma treated with temsirolimus: A single-center experience in Japan. International Journal of Clinical Oncology. 2014. 19(4):679-685	Outcomes not of interest
5522	Miyake H, Harada KI, Kusuda Y, et al. Health-related quality of life in Japanese patients with metastatic renal cell carcinoma treated with sunitinib. International Journal of Clinical Oncology. 2013. 18(2):220-225	Outcomes not of interest
5526	Miyake H, Miyazaki A, Harada KI, et al. Assessment of efficacy, safety and quality of life of 110 patients treated with sunitinib as first-line therapy for metastatic renal cell carcinoma: Experience in real-world clinical practice in Japan. Medical Oncology. 2014. 31(6):	Outcomes not of interest
5541	Motzer RJ, Grünwald V, Hutson TE, et al. A phase III trial to compare efficacy and safety of lenvatinib in combination with everolimus or pembrolizumab vs sunitinib alone in first-line treatment of patients (Pts) with metastatic renal cell carcinoma (RCC). Journal of Clinical Oncology. 2017. 35(15):	Outcomes not of interest
5550	Mudd A, Bakker R, Malcolm B, et al. Reported utilities for patients with untreated advanced/ metastatic renal cell carcinoma-a systematic literature review. Value in Health. 2017. 20(9):A449	Study design not of interest
5584	Pan X, Huang H, Huang Y, et al. Sunitinib dosing schedule 2/1 improves tolerability, efficacy, and health-related quality of life in Chinese patients with metastatic renal cell carcinoma. Urologic Oncology: Seminars and Original Investigations. 2015. 33(6):268.e9-268.e15	Intervention not of interest
5620	Powles T, McDermott DF, Rini B, et al. IMmotion150: Novel radiological endpoints and updated data from a randomized phase II trial investigating atezolizumab (atezo) with or without bevacizumab (bev) vs sunitinib (sun) in untreated metastatic renal cell carcinoma (mRCC). Annals of Oncology. 2017. 28v624	Outcomes not of interest
5707	Schmidinger M, Bamias A, Procopio G, et al. Prospective Observational Study of Pazopanib in Patients with Advanced Renal Cell Carcinoma (PRINCIPAL Study). Oncologist. 2019.	Outcomes not of interest
5745	Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial. Journal of Clinical Oncology. 2010. 28(6):1061-1068	Mixed Population
5757	Takyar S, Diaz J, Sehgal M, et al. First-line therapy for treatment-naive patients with advanced/metastatic renal cell carcinoma: A systematic review of published randomized controlled trials. Anti-Cancer Drugs. 2016. 27(5):383-397	SLRs (bibliographies reviewed)
5792	Unverzagt S, Moldenhauer I, Nothacker M, et al. Immunotherapy for metastatic renal cell carcinoma. Cochrane Database Syst Rev. 2017. 5Cd011673	SLRs (bibliographies reviewed)
5199	de Groot S, Redekop WK, Versteegh MM, et al. Health-related quality of life and its determinants in patients with metastatic renal cell carcinoma. Quality of Life Research. 2018. 27(1):115-124	Line of therapy not of interest
5603	Pickard AS, Jiang R, Lin HW, et al. Using Patient-reported Outcomes to Compare Relative Burden of Cancer: EQ-5D and Functional Assessment of Cancer Therapy-General in Eleven Types of Cancer. Clinical Therapeutics. 2016. 38(4):769-777	Line of therapy not of interest

5665	Rini BI, Bellmunt J, Clancy J, et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. Journal of Clinical Oncology. 2014. 32(8):752-759	Intervention not of interest
5685	Rothrock NE, Jensen SE, Beaumont JL, et al. Development and initial validation of the NCCN/FACT symptom index for advanced kidney cancer. Value in Health. 2013. 16(5):789-796	Line of therapy not of interest
6004	Appleman, L. J., Puligandla, M., Pal, S. K., Harris, W., Agarwal, N., Costello, B. A., Ryan, C. W., Pins, M., Kolesar, J., Vaena, D. A., Parikh, R. A., Hashmi, M., Dutcher, J. P., DiPaola, R. S., Haas, N. B., Carducci, M. A.. Randomized, double-blind phase study of pazopanib versus placebo in patients with metastatic renal cell carcinoma who have no evidence of disease following metastasectomy: A trial of the ECG-ACRN cancer research group (E10). Journal of Clinical Oncology. Conference. 2020. 37:#pages#	Outcomes not of interest
6007	Atkins, M. B., Rini, B. I., Motzer, R. J., Powles, T., McDermott, D. F., Suarez, C., Bracarda, S., Stadler, W. M., Donskov, F., Gurney, H., Oudard, S., Uemura, M., Lam, E. T., Grullich, C., Quach, C., Carroll, S., Ding, B., Zhu, Q. C., Piault-Louis, E., Schiff, C., Escudier, B.. Patient-Reported Outcomes from the Phase III Randomized IMmotion151 Trial: Atezolizumab + Bevacizumab versus Sunitinib in Treatment-Naive Metastatic Renal Cell Carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2020. 26:2506-2514	Outcomes not of interest
6014	Berezowska, A., Passchier, E., Bleiker, E.. Professional patient navigation in a hospital setting: a randomized controlled trial. Supportive Care in Cancer. 2020. 31:31	Mixed Population
6015	Bergerot, C. D., Bergerot, P. G., Philip, E. J., Hsu, J., Dizman, N., Vaishampayan, U. N., Dorff, T. B., Pal, S. K.. Expectations of cure among patients with advanced genitourinary cancer treated with immunotherapy. Journal of Clinical Oncology. Conference. 2020. 37:#pages#	Mixed Population
6016	Bergerot, C. D., Bergerot, P. G., Philip, E. J., Hsu, J. A., Dizman, N., Vaishampayan, U., Dorff, T., Pal, S. K.. Perception of cure among patients with metastatic genitourinary cancer initiating immunotherapy. Journal for ImmunoTherapy of Cancer. 2020. 7:#pages#	Mixed Population
6035	Chung, D. Y., Kang, D. H., Kim, J. W., Kim, D. K., Lee, J. Y., Hong, C. H., Cho, K. S.. Does an alternative sunitinib dosing schedule really improve survival outcomes over a conventional dosing schedule in patients with metastatic renal cell carcinoma? An updated systematic review and meta-analysis. Cancers. 2020. 11:#pages#	Outcomes not of interest
6052	Grimm, M. O., Schmidinger, M., Duran Martinez, I., Schinzari, G., Esteban, E., Schmitz, M., Schumacher, U., Baretton, G., Barthelemy, P., Melichar, B., Charnley, N., Schrijvers, D., Albiges, L.. Tailored immunotherapy approach with nivolumab in advanced renal cell carcinoma (TITAN-RCC). Annals of Oncology. 2020. 30 (Supplement 5):v892	Outcomes not of interest
6062	Jeong, C. W., Suh, J., Yuk, H. D., Tae, B. S., Kim, M., Keam, B., Kim, J. H., Kim, S. Y., Cho, J. Y., Kim, S. H., Moon, K. C., Cheon, G. J., Ku, J. H., Kim, H. H., Kwak, C.. Establishment of the Seoul National University Prospectively Enrolled Registry for Genitourinary Cancer (SUPER-GUC): A prospective, multidisciplinary, bio-bank linked cohort and research platform. Investigative And Clinical Urology. 2020. 60:235-243	Outcomes not of interest
6105	Pal, S. K., McDermott, D. F., Atkins, M. B., Escudier, B., Rini, B. I., Motzer, R. J., Fong, L., Joseph, R. W., Oudard, S., Ravaud, A., Bracarda, S., Rodriguez, C. S., Lam, E. T., Choueiri, T. K., Ding, B., Quach, C., Hashimoto, K., Schiff, C., Piault, E., Powles, T.. Patient-reported outcomes (PROs) in IMmotion150: Atezolizumab (atezo) alone or with bevacizumab (bev) versus sunitinib (sun) in first-line metastatic renal cell carcinoma (mRCC). Journal of Clinical Oncology. Conference. 2020. 37:#pages#	Outcomes not of interest
6106	Pal, S. K., McDermott, D. F., Atkins, M. B., Escudier, B., Rini, B. I., Motzer, R. J., Fong, L., Joseph, R. W., Oudard, S., Ravaud, A., Bracarda, S., Suarez, C., Lam, E. T., Choueiri, T. K., Ding, B., Quach, C., Hashimoto, K., Schiff, C., Piault-Louis, E., Powles, T.. Patient-reported outcomes in	Outcomes not of interest

	a phase 2 study comparing atezolizumab alone or with bevacizumab vs sunitinib in previously untreated metastatic renal cell carcinoma. BJU International. 2020. 126:73-82	
6110	Peinemann, F., Unverzagt, S., Hadjinicolaou, A. V., Moldenhauer, I.. Immunotherapy for metastatic renal cell carcinoma: A systematic review. Journal of Evidence-Based Medicine. 2020. 12:253-262	SLRs (bibliographies reviewed)
6123	Rossi, S. H., Blick, C., Handforth, C., Brown, J. E., Stewart, G. D.. Essential Research Priorities in Renal Cancer: A Modified Delphi Consensus Statement. European Urology Focus. 2020. 6:991-998	Outcomes not of interest
6125	Schmidinger, M., Porta, C., Oudard, S., Denechere, G., Brault, Y., Serfass, L., Costa, N. M., James, M. G.. Real-world experience with sunitinib treatment in patients with metastatic renal cell carcinoma: Clinical outcome according to risk score. Journal of Clinical Oncology. Conference. 2020. 37:#pages#	Outcomes not of interest
6140	Tomita, Y., Fukasawa, S., Shinohara, N., Kitamura, H., Oya, M., Eto, M., Tanabe, K., Saito, M., Kimura, G., Yonese, J., Yao, M., Uemura, H.. Nivolumab versus everolimus in advanced renal cell carcinoma: Japanese subgroup 3-year follow-up analysis from the Phase III CheckMate 025 study. Japanese Journal of Clinical Oncology. 2020. 49:506-514	Line of therapy not of interest
6029	Cella, D., Grunwald, V., Escudier, B., Hammers, H. J., George, S., Nathan, P., Grimm, M. O., Rini, B. I., Doan, J., Ivanescu, C., Paty, J., Mekan, S., Motzer, R. J.. Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial. The Lancet Oncology. 2020. 20:297-310	Publication type not of interest (duplicate)

Unpublished data

No unpublished data was included.

Summary of results

Among the identified studies, the instruments of interest utilized to derive PRO/utilities included EQ-5D index scores and visual analog scales (VAS), European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30), Functional Assessment of Cancer Therapy-General (FACT-G), Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI), and direct utility elicitation as a time trade-off method. These data were reported for the overall study population and a separate section on data by subgroup population of interest including histology, risk score, and PD-L1 status was also reported (see below).

EQ-5D Results

Five studies, three prospective and two RCTs, reported EQ-5D outcomes, including EQ-5D index scores (four studies[131, 138, 192, 193, 203, 205] and VAS (three studies[138, 192, 196, 203, 204] for overall populations with aRCC. One study included participants from Ukraine, Russia, and India [131], one included patients from Finland [193] while the remaining three studies represented international patient populations [138, 196, 203, 204]. Two additional studies provided EQ-5D outcomes in risk subgroups.

EQ-5D Index Scores

Among the studies reporting data on the overall aRCC populations, four studies reported EQ-5D index scores, two RCTs and two prospective studies, evaluating the following treatments:

- Sunitinib vs. IFN alfa-2a
- Sorafenib vs. axitinib
- Sunitinib
- Pazopanib

1L systemic treatments on patients' quality of life (QoL) measured by EQ-5D showed a similar trend across all treatments. At baseline, mean scores were similar and ranged between 0.71 [131] to 0.76 [138]. Post-treatment scores in trials of IFN alfa-2a, sunitinib, sorafenib, or axitinib ranged from 0.59 [131] to 0.86 [138]. IFN alfa-2a and sunitinib showed some numerical improvements in EQ-5D scores compared to pre-

treatment scores (no within-arm statistical comparisons provided). Sunitinib showed mixed results compared to IFN alfa-2a in a multiregional study [43]. While patients reported superior EQ-5D scores with sunitinib vs. IFN alfa-2a through the interim analysis (median treatment duration, sunitinib: six months and IFN alfa-2a: four months), additional follow-up showed more favorable scores with the latter than the former (maximum follow-up, 123 weeks, [43, 205]. Small sample sizes during the additional follow-up period (IFN alfa-2a: 9 subjects) may account for these discrepant findings.

Some between treatment differences were observed across available RCTs; at the end of treatment higher EQ-5D scores were reported with:

- Sunitnib compared to IFN alfa-2a (maximum follow-up 80 weeks; [205]
- Axitinib compared to sorafenib (follow-up, 23 weeks[131]

Additionally, prospective observational studies found that sunitinib and pazopanib improved EQ-5D scores over time (sunitinib: 0.755 to 0.781[193]; pazopanib: 0.757 to 0.815[192].

EQ-5D VAS

Two RCTs and one prospective study reported the use of EQ-5D VAS to measure PRO in patients with aRCC [138, 192, 196, 203, 204]. The RCTs both enrolled international patient populations. The following treatments were evaluated:

- Pembrolizumab + axitinib vs. sunitinib
- Sunitinib vs. IFN alfa-2a
- Pazopanib

Combination treatment with pembrolizumab + axitinib did not improve EQ-5D VAS scores compared with sunitinib monotherapy over a 30 week follow-up duration (difference in least square means between treatments: -1.4 [95% CI: -3.9, 1.1; [196]. Treatment with sunitinib improved QoL as measured by EQ-5D VAS in patients with aRCC compared with IFN alfa-2a.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix I Mapping of HRQoL data

The algorithm used in this submission to map utilities derived from the CLEAR trial to EQ-5D-5L was built into EuroQol's spreadsheet model and based on the work done by Ben van Hout and colleagues [88], in accordance with the recommendations of the Danish Center for Healthcare improvements. The objective of their study was to develop values sets for the EQ-5D-5L by means of a mapping ("crosswalk") approach to the currently available three-level version of the EQ-5D (EQ-5D-3L) values sets [88].

Respondents completed both the 3L and the 5L in six countries: Denmark, England, Italy, the Netherlands, Poland, and Scotland. The official EQ-5D-5L language version for each country was used. Different subgroups were targeted, and in most countries, a screening protocol was implemented to capture a broad spectrum of health across the EQ-5D dimensions for both the 5L and 3L descriptive systems. The screening protocol was operationalized as follows. First, conditions were identified that would provide varying levels of problems on each dimension based on existing data sets and literature (e.g., stroke and rheumatoid arthritis for problems with mobility, depression and personality disorder for problems related to anxiety/depression). Second, after data were collected from approximately 100 patients with the selected condition, the frequency distributions for each dimension were examined. If only a limited range of responses to the various levels described by each system were endorsed, a screening question was added to filter out relatively healthy patients less likely to report any problems. The severity assurance protocol was followed in all countries except Italy, which did not administer a severity screening protocol for patients with liver disease. The 5L was administered first, followed by the visual analogue scale and a number of demographic questions, and finally the 3L. A previous study showed that when respondents scored the 3L first, there was a tendency to avoid the in-between levels 2 and 4 of the 5L, and therefore all respondents scored the 5L first [88].

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix J Probabilistic sensitivity analyses

The results of the probabilistic sensitivity analyses were obtained by running 5000 simulations. 5000 simulations was chosen based on the findings of converge testing.

Overall population

Table 150. Settings of the Probabilistic sensitivity analyses carried out for the Overall population

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
PFS Joint Parametric Fit - Parameter 1: LEN+PEM & Sunitinib	3,7006		Normal/ Cholesky	α: 0,79	β: 0,06	Settings!N16
PFS Joint Parametric Fit - Parameter 2: LEN+PEM & Sunitinib	1,2184		Normal/ Cholesky	α: -1,18	β:0,01	Settings!N17
PFS Joint Parametric Fit - Parameter 3: LEN+PEM & Sunitinib	0,8479		Normal/ Cholesky	α: 1,20	β:0,01	Settings!N18
PFS Constant HR: Sunitinib	2,5641	0,227554702	Log-normal	μ: 0.94	SD: 0.23	Settings!N22
PFS Constant HR: NIVO+IPI	2,2727	0,324298059	Log-normal	μ: 0.82	SD: 0.32	Settings!N26
Tx Disc Single Parametric Fit - Parameter 1: LEN	4,7677	--	Normal/ Cholesky	α: -0,02	β:0,00	Settings!N104
Tx Disc Single Parametric Fit - Parameter 1: PEM	4,7121	--	Normal/ Cholesky	α: -0,06	β:-0,01	Settings!N108
Tx Disc Single Parametric Fit - Parameter 2: PEM	1,2267	--	Normal/ Cholesky	α: -1,66	β:0,00	Settings!N116
Tx Disc Single Parametric Fit - Parameter 1: Sunitinib	4,1163	--	Normal/ Cholesky	α: -0,02	β:0,00	Settings!N117
Tx Disc Median Treatment Duration: NIVO+IPI	34,3509	3,4351	Gamma	α: 100	β:0,343508929	Settings!N145
OS Single Parametric Fit - Parameter 1: LEN + PEM	5,7085	--	Normal/ Cholesky	α: 0,04	β:0,00	Settings!N149
OS Single Parametric Fit - Parameter 2: LEN + PEM	0,7397	--	Normal/ Cholesky	α: 0,97	β:0,00	Settings!N150

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Efficacy: OS Single Parametric Fit - Parameter 1: Sunitinib	5,7032	--	Normal/ Cholesky	α: 0,65	β:0,07	Settings!N160
Efficacy: OS Single Parametric Fit - Parameter 2: Sunitinib	0,9821	--	Normal/ Cholesky	α: 1,88	β:0,03	Settings!N161
Effficacy: OS Constant HR: NIVO+IPI	0,9615	0,156130837	Log-normal	μ: 0.03	SD: 0.15	Settings!N283
Starting Age	61,7000	0,32	Gamma	α: 37916,52	β:0,00	Settings!N284
Gender (% male)	0,7450	0,01	Beta	α: 796	β:272,60	Settings!N285
Body surface area: Overall population	0,0000	0,00	Gamma			Settings!N383
Mean weight: Overall population	80,0000	0,57	Gamma	α: 19577,32	β:0,00	Settings!N385
AE Mgmt Progression-free Cost: LEN + PEM	1390,4006	DKK 278	Gamma	α: 25,00	β:55,62	Settings!N386
AE Mgmt Progression-free Cost: Sunitinib	720,8147	DKK 144	Gamma	α: 25,00	β:28,83	Settings!N387
AE Mgmt Progression-free Cost: NIVO+IPI	0,0000	DKK 0	Gamma	NA	NA	Settings!N399
AE Mgmt Progressed Cost: LEN + PEM	704,0477	DKK 141	Gamma	α: 25,00	β:28,16	Settings!N402
AE Mgmt Progressed Cost: Sunitinib	0,0000	DKK 0	Gamma	NA	NA	Settings!N403
AE Mgmt Progressed Cost: NIVO+IPI	704,0477	DKK 141	Gamma	α: 25,00	β:28,16	Settings!N415
Disease Mgmt Cost - Progression-free one-off cost: LEN + PEM	1906,0000	DKK 381	Gamma	α: 25,00	β:76,24	Settings!N418
Disease Mgmt Cost - Progression-free one-off cost: Sunitinib	1906,0000	DKK 381	Gamma	α: 25,00	β:76,24	Settings!N419
Disease Mgmt Cost - Progression-free one-off cost: NIVO+IPI	1906,0000	DKK 381	Gamma	α: 25,00	β:76,24	Settings!N431
Disease Mgmt Cost - Progression-free cycle cost: LEN + PEM	678,8900	DKK 136	Gamma	α: 25,00	β:27,16	Settings!N434
Disease Mgmt Cost - Progression-free cycle cost: Sunitinib	678,8900	DKK 136	Gamma	α: 25,00	β:27,16	Settings!N435

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Disease Mgmt Cost - Progression-free cycle cost: NIVO+IPI	678,8900	DKK 136	Gamma	α: 25,00	β:27,16	Settings!N447
Disease Mgmt Cost - Progressed one-off cost: LEN + PEM	0,0000	DKK 0	Gamma	NA	NA	Settings!N450
Disease Mgmt Cost - Progressed one-off cost: Sunitinib	0,0000	DKK 0	Gamma	NA	NA	Settings!N451
Disease Mgmt Cost - Progressed one-off cost: NIVO+IPI	0,0000	DKK 0	Gamma	NA	NA	Settings!N463
Disease Mgmt Cost - Progressed cycle cost: LEN + PEM	678,8900	DKK 136	Gamma	α: 25,00	β:27,16	Settings!N466
Disease Mgmt Cost - Progressed cycle cost: Sunitinib	678,8900	DKK 136	Gamma	α: 25,00	β:27,16	Settings!N467
Disease Mgmt Cost - Progressed cycle cost: NIVO+IPI	678,8900	DKK 136	Gamma	α: 25,00	β:27,16	Settings!N479
BSC for progression after 1L	0,0000	DKK 0	Gamma	NA	NA	Settings!N481
Disease Mgmt Cost - One-off cost of mortality	0,0000	DKK 0	Gamma	NA	NA	Settings!N483
% receiving subsequent treatment after taking: LEN + PEM	0,5000	0,1	Beta	α: 50	β:49,50	Settings!N483
% receiving subsequent treatment after taking: Sunitinib	0,5000	0,1	Beta	α: 50	β:49,50	Settings!N484
% receiving subsequent treatment after taking: NIVO+IPI	0,5000	0,1	Beta	α: 50	β:49,50	Settings!N487
Subsequent treatment drug cost: LEN + PEM	649762,1810	DKK 129.952	Gamma	α: 25,00	β:25990,49	Settings!N499
Subsequent treatment drug cost: Sunitinib	264510,2459	DKK 52.902	Gamma	α: 25,00	β:10580,41	Settings!N500
Subsequent treatment drug cost: NIVO+IPI	1270922,0047	DKK 254.184	Gamma	α: 25,00	β:50836,88	Settings!N503
Direct Non-medical Costs: Progression-free	0,0000	DKK 0	Gamma	NA	NA	Settings!N514
Direct Non-medical Costs: Progressed	0,0000	DKK 0	Gamma	NA	NA	Settings!N517
Health states utility: Progression-free	0,8100	0,00	Beta	α: 31164	β:7310,06	Settings!N518

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Health states utility: Post progression	0,7300	0,03	Beta	α: 229	β:84,88	Settings!N518
Health states utility: Progression-free - Sunitinib	0,7700	0,00	Beta	α: 15151	β : 4525,66	Settings!N521
Health states utility: Progression-free - NIVO+IPI	0,7900	0,00	Beta	α: 32764	β 8709,54	Settings!N523
Regression parameters - Constant	0,9546	-	Normal/ Cholesky	α: -0,36	β:0,00	Settings!N539
Regression parameters - Sex (male)	0,0253	-	Normal/ Cholesky	α: -0,32	β:0,00	Settings!N540
Regression parameters - Age	-0,0011	-	Normal/ Cholesky	α: 1,04	β:0,00	Settings!N541
Regression parameters - Age squared	0,0000	-	Normal/ Cholesky	α: 0,31	β:0,00	Settings!N542

Table 151. Results of economic analysis for the Overall population

Per patient	LEN + PEM	Sunitinib
Mean Total Costs	[redacted]	[redacted]
• **Lower: 95% CI**	[redacted]	[redacted]
• **Upper: 95% CI**	[redacted]	[redacted]
Mean QALYs	[redacted]	[redacted]
Lower: 95% CI	[redacted]	[redacted]
Upper: 95% CI	[redacted]	[redacted]
Mean LYs	[redacted]	[redacted]
Lower: 95% CI	[redacted]	[redacted]
Upper: 95% CI	[redacted]	[redacted]
Incremental Cost	Ref	[redacted]
Incremental QALYs	Ref	[redacted]
ICER (£/QALYs)	Ref	[redacted]
INMB (/QALYs)	Ref	[redacted]

Figure 100. CEAC derived from PSA for Overall population

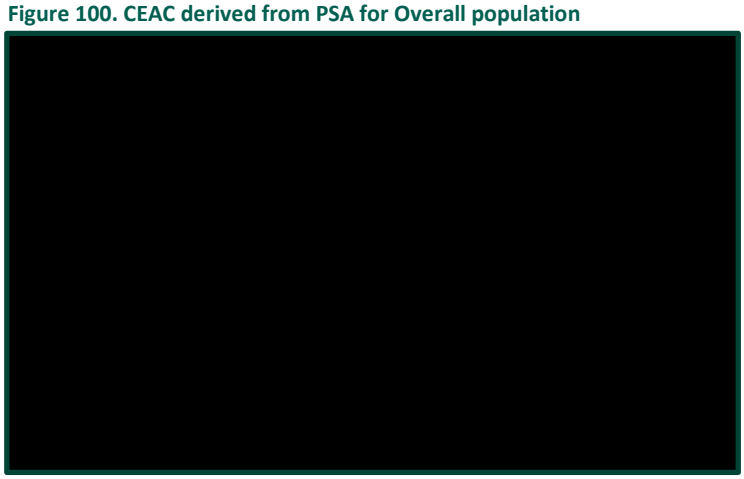


Figure 101. Scatter plot derived from PSA for Overall population

Table 152. Comparison of deterministic and probabilistic results, overall population

Deterministic (Base Case) Results	LEN + PEM	Sunitinib
Incremental Costs	--	XXXXX
Incremental Benefits QALYs	--	XXXXX
ICER (£/QALYs)	--	XXXXX
INMB (/QALYs)	--	XXXXX
Probabilistic Results	**LEN + PEM**	**Sunitinib**
Incremental Costs	--	XXXXX
Incremental Benefits QALYs	--	XXXXX
ICER (£/QALYs)	--	XXXXX
INMB (/QALYs)	--	XXXXX

In the overall population, as shown in Table 152, the probabilistic results align with the deterministic results. The probabilistic ICER for the cost effectiveness comparison of LEN+PEM versus sunitinib in the overall population was DKK XXXXXXXXX per QALY, compared to an ICER of DKK XXXXXXXXX per QALY in the deterministic analysis. Moreover, as shown in Figure 101, almost all points are in the north east quadrant, indicating that in the overall population, LEN+PEM is associated with higher costs but also provides higher efficacy, compared to sunitinib. Finally, as shown in Figure 100, at a threshold of DKK 2.000.000, LEN+PEM is cost effective in 82.1% of the iterations and Sunitinib is cost effective in 17.9% of the iterations.

IMDC good prognosis population

Table 153. Settings of the Probabilistic sensitivity analyses carried out for the IMDC good prognosis population

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Efficacy: PFS Joint Parametric Fit -	4,0632	NA	Normal/ Cholesky	α: -2,04	β: -0,23	Settings!N16

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Parameter 1: LEN+PEM & Sunitinib						
Efficacy: PFS Joint Parametric Fit - Parameter 2: LEN+PEM & Sunitinib	1,0692	NA	Normal/ Cholesky	α: 1,19	β: -0,04	Settings!N17
Efficacy: PFS Joint Parametric Fit - Parameter 3: LEN+PEM & Sunitinib	0,6925	NA	Normal/ Cholesky	α: -0,78	β: 0,21	Settings!N18
Effficacy: PFS Constant HR: Sunitinib	2,4390	0,322880008	Log-normal	--	--	Settings!N22
Effficacy: PFS Constant HR: NIVO+IPI	4,5455	0,457089896	Log-normal	--	--	Settings!N26
Efficacy: Tx Disc Single Parametric Fit - Parameter 1: LEN	4,9924	NA	Normal/ Cholesky	α: -2,62	β: -0,56	Settings!N101
Efficacy: Tx Disc Single Parametric Fit - Parameter 2: LEN	1,0266	NA	Normal/ Cholesky	α: 1,22	β: 0,51	Settings!N102
Efficacy: Tx Disc Single Parametric Fit - Parameter 3: LEN	1,1132	NA	Normal/ Cholesky	α: 1,17	β: -1,11	Settings!N103
Efficacy: Tx Disc Single Parametric Fit - Parameter 1: PEM	4,9903	NA	Normal/ Cholesky	α: -1,52	β: -0,29	Settings!N104
Efficacy: Tx Disc Single Parametric Fit - Parameter 2: PEM	1,3156	NA	Normal/ Cholesky	α: 0,36	β: -0,10	Settings!N105
Efficacy: Tx Disc Single Parametric Fit - Parameter 1: Sunitinib	4,2206	NA	Normal/ Cholesky	α: -0,23	β: -0,05	Settings!N108
Efficacy: Tx Disc Single Parametric Fit - Parameter 2: Sunitinib	1,1775	NA	Normal/ Cholesky	α: -2,01	β: 0,02	Settings!N109
Efficacy: Tx Disc Single Parametric Fit - Parameter 3: Sunitinib	0,3695	NA	Normal/ Cholesky	α: -0,45	β: -0,08	Settings!N110
Efficacy: Tx Disc Median Treatment Duration: NIVO+IPI	34,3509	3,4351	Gamma	α: 100	β: 0,343508929	Settings!N117
Efficacy: OS Single Parametric Fit -	5,7297	NA	Normal/ Cholesky	α: 0,77	β: 0,15	Settings!N149

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Parameter 1: LEN + PEM						
Efficacy: OS Single Parametric Fit - Parameter 2: LEN + PEM	0,5154	NA	Normal/ Cholesky	α: 1,90	β: 0,06	Settings!N145
Efficacy: OS Single Parametric Fit - Parameter 1: Sunitinib	6,3189	NA	Normal/ Cholesky	α: 0,28	β: 0,10	Settings!N283
Efficacy: OS Single Parametric Fit - Parameter 2: Sunitinib	0,8175	NA	Normal/ Cholesky	α: 0,17	β: 0,04	Settings!N283
Effficacy: OS Constant HR: NIVO+IPI	0,7634	0,375934554	Log-normal	--	--	Settings!N285
Starting Age	61,7000	0,32	Gamma	α: 37916,52	β: 0,00	Settings!N385
Gender (% male)	0,7450	0,01	Beta	α: 796	β: 272,60	Settings!N386
Body surface area: Favourable risk population	1,9600	0,20	Gamma	α: 100,00	β: 0,02	Settings!N387
Mean weight: Favourable risk population	81,0700	0,57	Gamma	α: 20104,51	β: 0,00	Settings!N389
AE Mgmt Progression-free Cost: LEN + PEM	1390,4006	DKK 278	Gamma	α: 25,00	β: 55,62	Settings!N399
AE Mgmt Progression-free Cost: Sunitinib	720,8147	DKK 144	Gamma	α: 25,00	β: 28,83	Settings!N401
AE Mgmt Progression-free Cost: NIVO+IPI	0,0000	DKK 0	Gamma	NA	NA	Settings!N403
AE Mgmt Progressed Cost: LEN + PEM	704,0477	DKK 141	Gamma	α: 25,00	β: 28,16	Settings!N415
AE Mgmt Progressed Cost: Sunitinib	0,0000	DKK 0	Gamma	NA	NA	Settings!N417
AE Mgmt Progressed Cost: NIVO+IPI	704,0477	DKK 141	Gamma	α: 25,00	β: 28,16	Settings!N419
Disease Mgmt Cost - Progression-free one-off cost: LEN + PEM	1906,0000	DKK 381	Gamma	α: 25,00	β: 76,24	Settings!N431
Disease Mgmt Cost - Progression-free one-off cost: Sunitinib	1906,0000	DKK 381	Gamma	α: 25,00	β: 76,24	Settings!N433
Disease Mgmt Cost - Progression-free one-off cost: NIVO+IPI	1906,0000	DKK 381	Gamma	α: 25,00	β: 76,24	Settings!N435
Disease Mgmt Cost - Progression-free	678,8900	DKK 136	Gamma	α: 25,00	β: 27,16	Settings!N447

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
cycle cost: LEN + PEM						
Disease Mgmt Cost - Progression-free cycle cost: Sunitinib	678,8900	DKK 136	Gamma	α: 25,00	β: 27,16	Settings!N449
Disease Mgmt Cost - Progression-free cycle cost: NIVO+IPI	678,8900	DKK 136	Gamma	α: 25,00	β: 27,16	Settings!N451
Disease Mgmt Cost - Progressed one-off cost: LEN + PEM	0,0000	DKK 0	Gamma	NA	NA	Settings!N463
Disease Mgmt Cost - Progressed one-off cost: Sunitinib	0,0000	DKK 0	Gamma	NA	NA	Settings!N465
Disease Mgmt Cost - Progressed one-off cost: NIVO+IPI	0,0000	DKK 0	Gamma	NA	NA	Settings!N467
Disease Mgmt Cost - Progressed cycle cost: LEN + PEM	678,8900	DKK 136	Gamma	α: 25,00	β: 27,16	Settings!N479
Disease Mgmt Cost - Progressed cycle cost: Sunitinib	678,8900	DKK 136	Gamma	α: 25,00	β: 27,16	Settings!N480
Disease Mgmt Cost - Progressed cycle cost: NIVO+IPI	678,8900	DKK 136	Gamma	α: 25,00	β: 27,16	Settings!N483
BSC for progression after 1L	0,0000	DKK 0	Gamma	NA	NA	Settings!N484
Disease Mgmt Cost - One-off cost of mortality	0,0000	DKK 0	Gamma	NA	NA	Settings!N485
% receiving subsequent treatment after taking: LEN + PEM	0,5000	0,1	Beta	α: 50	β: 49,50	Settings!N487
% receiving subsequent treatment after taking: Sunitinib	0,5000	0,1	Beta	α: 50	β: 49,50	Settings!N497
% receiving subsequent treatment after taking: NIVO+IPI	0,5000	0,1	Beta	α: 50	β: 49,50	Settings!N500
Subsequent treatment drug cost: LEN + PEM	649762,1810	DKK 129.952	Gamma	α: 25,00	β: 25990,49	Settings!N503
Subsequent treatment drug cost: Sunitinib	265150,4971	DKK 53.030	Gamma	α: 25,00	β: 10606,02	Settings!N513
Subsequent treatment drug cost: NIVO+IPI	1270922,0047	DKK 254.184	Gamma	α: 25,00	β: 50836,88	Settings!N517
Direct Non-medical Costs: Progression-free	0,0000	DKK 0	Gamma	NA	NA	Settings!N518
Direct Non-medical Costs: Progressed	0,0000	DKK 0	Gamma	NA	NA	Settings!N521

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Health states utility: Progression-free	0,8000	0,00	Beta	α: 14221	β: 3555,36	Settings!N522
Health states utility: Post progression	0,7900	0,04	Beta	α: 95	β: 25,24	Settings!N523
Health states utility: Progression-free - Sunitinib	0,7700	0,00	Beta	α: 15151	β: 4525,66	Settings!N525
Health states utility: Progression-free - NIVO+IPI	0,7900	0,00	Beta	α: 32764	β: 8709,54	Settings!N540
Regression parameters - Constant	0,9546	NA	Normal/ Cholesky	α: -0,05	β: 0,00	Settings!N542
Regression parameters - Sex (male)	0,0253	NA	Normal/ Cholesky	α: 1,41	β: 0,00	Settings!N542
Regression parameters - Age	-0,0011	NA	Normal/ Cholesky	α: -0,34	β: 0,00	Settings!N542
Regression parameters - Age squared	0,0000	NA	Normal/ Cholesky	α: 1,26	β: 0,00	Settings!N542

Table 154. Results of economic analysis for the good prognosis population

Per patient	LEN + PEM	Sunitinib
Mean Total Costs	[redacted]	[redacted]
• **Lower: 95% CI**	[redacted]	[redacted]
• **Upper: 95% CI**	[redacted]	[redacted]
Mean QALYs	[redacted]	[redacted]
Lower: 95% CI	[redacted]	[redacted]
Upper: 95% CI	[redacted]	[redacted]
Mean LYs	[redacted]	[redacted]
Lower: 95% CI	[redacted]	[redacted]
Upper: 95% CI	[redacted]	[redacted]
Incremental Cost	--	[redacted]
Incremental QALYs	--	[redacted]
ICER (£/QALYs)	--	[redacted]
INMB (/QALYs)	--	[redacted]

Figure 102. CEAC derived from PSA for IMDC good prognosis population

Figure 103. Scatter plot derived from PSA for IMDC good prognosis population

Table 155. Comparison of deterministic and probabilistic results, good prognosis population

Deterministic (Base Case) Results	LEN + PEM	Sunitinib
Incremental Costs	--	XXXXX
Incremental Benefits QALYs	--	XXXXX
ICER (£/QALYs)	--	XXXXX
INMB (/QALYs)	--	XXXXX
Probabilistic Results	**LEN + PEM**	**Sunitinib**

Incremental Costs	--	XXXXX
Incremental Benefits QALYs	--	XXXXX
ICER (£/QALYs)	--	XXXXX
INMB (/QALYs)	--	XXXXX

In the IMDC good prognosis population, as shown in Table 155, the probabilistic results align with the deterministic results. The probabilistic ICER for the cost effectiveness comparison of LEN+PEM versus sunitinib in the overall population was DKK XXXXXXXXX per QALY, compared to an ICER of DKK XXXXXXXXX per QALY in the deterministic analysis. As shown in Figure 103, at a threshold of DKK 20.000.000, LEN+PEM is cost effective in 39.3% of the iterations and Sunitinib is cost effective in 60.7% of the iterations.

IMDC intermediate/poor prognosis population

Table 156. Settings of the Probabilistic sensitivity analyses carried out for the IMDC intermediate/poor population

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Efficacy: PFS Joint Parametric Fit - Parameter 1: LEN+PEM & Sunitinib	3,4894	--	Normal/ Cholesky	α: 0,22	β 0,02	Settings!N16
Efficacy: PFS Joint Parametric Fit - Parameter 2: LEN+PEM & Sunitinib	1,2317	--	Normal/ Cholesky	α: -1,34	β 0,00	Settings!N17
Efficacy: PFS Joint Parametric Fit - Parameter 3: LEN+PEM & Sunitinib	0,9584	--	Normal/ Cholesky	α: 0,44	β -0,02	Settings!N18
Effficacy: PFS Constant HR: Sunitinib	2,7778	0,132130768	Log-normal	--	--	Settings!N22
Effficacy: PFS Constant HR: NIVO+IPI	2,0408	0,154629322	Log-normal	--	--	Settings!N26
Efficacy: Tx Disc Single Parametric Fit - Parameter 1: LEN	4,8619	--	Normal/ Cholesky	α: -0,77	β -0,11	Settings!N101
Efficacy: Tx Disc Single Parametric Fit - Parameter 2: LEN	0,7528	--	Normal/ Cholesky	α: -0,35	β 0,12	Settings!N102
Efficacy: Tx Disc Single Parametric Fit - Parameter 3: LEN	1,5910	--	Normal/ Cholesky	α: -0,96	β -0,36	Settings!N103
Efficacy: Tx Disc Single Parametric Fit - Parameter 1: PEM	4,6097	--	Normal/ Cholesky	α: 1,97	β 0,20	Settings!N104
Efficacy: Tx Disc Single Parametric Fit - Parameter 2: PEM	1,2001	--	Normal/ Cholesky	α: 0,92	β 0,04	Settings!N105

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
Efficacy: Tx Disc Single Parametric Fit - Parameter 1: Sunitinib	3,3593	--	Normal/ Cholesky	α: 0,09	β: 0,01	Settings!N108
Efficacy: Tx Disc Single Parametric Fit - Parameter 2: Sunitinib	1,2382	--	Normal/ Cholesky	α: -0,83	β 0,00	Settings!N109
Efficacy: Tx Disc Single Parametric Fit - Parameter 3: Sunitinib	0,0354	--	Normal/ Cholesky	α: -1,76	β 0,02	Settings!N110
Efficacy: Tx Disc Median Treatment Duration: NIVO+IPI	34,3509	3,4351	Gamma	α: 100	β 0,343508929	Settings!N117
Efficacy: OS Single Parametric Fit - Parameter 1: LEN + PEM	5,6263	--	Normal/ Cholesky	α: 1,71	β 0,19	Settings!N149
Efficacy: OS Single Parametric Fit - Parameter 2: LEN + PEM	0,7930	--	Normal/ Cholesky	α: -1,60	β 0,09	Settings!N145
Efficacy: OS Single Parametric Fit - Parameter 1: Sunitinib	5,3581	--	Normal/ Cholesky	α: 0,35	β 0,04	Settings!N283
Efficacy: OS Single Parametric Fit - Parameter 2: Sunitinib	0,9775	--	Normal/ Cholesky	α: 0,09	β 0,01	Settings!N283
Effficacy: OS Constant HR: NIVO+IPI	1,0526	0,173047082	Log-normal	--	--	Settings!N285
Starting Age	61,7000	0,32	Gamma	α: 37916,52	β 0,00	Settings!N385
Gender (% male)	0,7450	0,01	Beta	α: 796	β 272,60	Settings!N386
Body surface area: Intermediate and poor risk population	1,9600	0,20	Gamma	α: 100,00	β 0,02	Settings!N387
Mean weight: Intermediate and poor risk population	81,0700	0,57	Gamma	α: 20104,51	β 0,00	Settings!N389
AE Mgmt Progression-free Cost: LEN + PEM	1390,4006	DKK 278	Gamma	α: 25,00	β 55,62	Settings!N399
AE Mgmt Progression-free Cost: Sunitinib	720,8147	DKK 144	Gamma	α: 25,00	β 28,83	Settings!N401
AE Mgmt Progression-free Cost: NIVO+IPI	0,0000	DKK 0	Gamma	NA	NA	Settings!N403
AE Mgmt Progressed Cost: LEN + PEM	704,0477	DKK 141	Gamma	α: 25,00	β 28,16	Settings!N415

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
AE Mgmt Progressed Cost: Sunitinib	0,0000	DKK 0	Gamma	NA	NA	Settings!N417
AE Mgmt Progressed Cost: NIVO+IPI	704,0477	DKK 141	Gamma	α: 25,00	β 28,16	Settings!N419
Disease Mgmt Cost - Progression-free one-off cost: LEN + PEM	1906,0000	DKK 381	Gamma	α: 25,00	β 76,24	Settings!N431
Disease Mgmt Cost - Progression-free one-off cost: Sunitinib	1906,0000	DKK 381	Gamma	α: 25,00	β 76,24	Settings!N433
Disease Mgmt Cost - Progression-free one-off cost: NIVO+IPI	1906,0000	DKK 381	Gamma	α: 25,00	β 76,24	Settings!N435
Disease Mgmt Cost - Progression-free cycle cost: LEN + PEM	678,8900	DKK 136	Gamma	α: 25,00	β 27,16	Settings!N447
Disease Mgmt Cost - Progression-free cycle cost: Sunitinib	678,8900	DKK 136	Gamma	α: 25,00	β 27,16	Settings!N449
Disease Mgmt Cost - Progression-free cycle cost: NIVO+IPI	678,8900	DKK 136	Gamma	α: 25,00	β 27,16	Settings!N451
Disease Mgmt Cost - Progressed one-off cost: LEN + PEM	0,0000	DKK 0	Gamma	NA	NA	Settings!N463
Disease Mgmt Cost - Progressed one-off cost: Sunitinib	0,0000	DKK 0	Gamma	NA	NA	Settings!N465
Disease Mgmt Cost - Progressed one-off cost: NIVO+IPI	0,0000	DKK 0	Gamma	NA	NA	Settings!N467
Disease Mgmt Cost - Progressed cycle cost: LEN + PEM	678,8900	DKK 136	Gamma	α: 25,00	β 27,16	Settings!N479
Disease Mgmt Cost - Progressed cycle cost: Sunitinib	678,8900	DKK 136	Gamma	α: 25,00	β 27,16	Settings!N480
Disease Mgmt Cost - Progressed cycle cost: NIVO+IPI	678,8900	DKK 136	Gamma	α: 25,00	β 27,16	Settings!N483
BSC for progression after 1L	0,0000	DKK 0	Gamma	NA	NA	Settings!N484
Disease Mgmt Cost - One-off cost of mortality	0,0000	DKK 0	Gamma	NA	NA	Settings!N485
% receiving subsequent treatment after taking: LEN + PEM	0,5000	0,1	Beta	α: 50	β 49,50	Settings!N487
% receiving subsequent	0,5000	0,1	Beta	α: 50	β 49,50	Settings!N497

	Expected value	Standard error	Probability distribution	Parameter distribution (Name: Value)	Parameter distribution (Name: Value)	Refers to cell (in the Excel model)
treatment after taking: Sunitinib						
% receiving subsequent treatment after taking: NIVO+IPI	0,5000	0,1	Beta	α: 50	β 49,50	Settings!N500
Subsequent treatment drug cost: LEN + PEM	649762,1810	DKK 129.952	Gamma	α: 25,00	β 25990,49	Settings!N503
Subsequent treatment drug cost: Sunitinib	265150,4971	DKK 53.030	Gamma	α: 25,00	β 10606,02	Settings!N513
Subsequent treatment drug cost: NIVO+IPI	1270922,0047	DKK 254.184	Gamma	α: 25,00	β 50836,88	Settings!N517
Direct Non-medical Costs: Progression-free	0,0000	DKK 0	Gamma	NA	NA	Settings!N518
Direct Non-medical Costs: Progressed	0,0000	DKK 0	Gamma	NA	NA	Settings!N521
Health states utility: Progression-free	0,7800	0,00	Beta	α: 8365	β 2359,28	Settings!N522
Health states utility: Post progression	0,6600	0,05	Beta	α: 52	β 26,82	Settings!N523
Health states utility: Progression-free - Sunitinib	0,7700	0,00	Beta	α: 15151	β 4525,66	Settings!N525
Health states utility: Progression-free - NIVO+IPI	0,7900	0,00	Beta	α: 32764	β 8709,54	Settings!N540
Regression parameters - Constant	0,9546	NA	Normal/ Cholesky	α: 0,13	β 0,00	Settings!N542
Regression parameters - Sex (male)	0,0253	NA	Normal/ Cholesky	α: -0,09	β 0,00	Settings!N542
Regression parameters - Age	-0,0011	NA	Normal/ Cholesky	α: 2,47	β 0,00	Settings!N542
Regression parameters - Age squared	0,0000	NA	Normal/ Cholesky	α: 1,34	β 0,00	Settings!N542

Table 157. Results of economic analysis for the intermediate/poor prognosis population

Per patient	LEN + PEM	NIVO+IPI
Mean Total Costs	[redacted]	[redacted]
• **Lower: 95% CI**	[redacted]	[redacted]
• **Upper: 95% CI**	[redacted]	[redacted]
Mean QALYs	[redacted]	[redacted]
Lower: 95% CI	[redacted]	[redacted]
Upper: 95% CI	[redacted]	[redacted]
Mean LYs	[redacted]	[redacted]
Lower: 95% CI	[redacted]	[redacted]
Upper: 95% CI	[redacted]	[redacted]
Incremental Cost	Ref	[redacted]

Per patient	LEN + PEM	NIVO+IPI
Incremental QALYs	Ref	XXXXX
ICER (£/QALYs)	Ref	XXXXX
INMB (/QALYs)	Ref	XXXXX

Figure 104. CEAC derived from PSA for IMDC intermediate/poor population

Figure 105. Scatter plot derived from PSA for IMDC intermediate/poor population

Table 158. Comparison of deterministic and probabilistic results, intermediate/poor prognosis population

Deterministic (Base Case) Results	LEN + PEM	NIVO+IPI

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Incremental Costs	--	XXXXX
Incremental Benefits QALYs	--	XXXXX
ICER (£/QALYs)	--	XXXXX
INMB (/QALYs)	--	XXXXX
Probabilistic Results	**LEN + PEM**	**NIVO+IPI**
Incremental Costs	--	XXXXX
Incremental Benefits QALYs	--	XXXXX
ICER (£/QALYs)	--	XXXXX
INMB (/QALYs)	--	XXXXX

In the IMDC intermediate/poor population, as shown in Table 158, the probabilistic results align with the deterministic results. The probabilistic ICER for the cost effectiveness comparison of LEN+PEM versus NIVO+IPI in the IMDC intermediate prognosis population was DKK XXXXXXXXX per QALY, compared to an ICER of DKK XXXXXXXXX per QALY in the deterministic analysis. Moreover, as shown in Figure 105, at a threshold of DKK 5.000.000, LEN+PEM is cost effective in 58.2% of the iterations and NIVO+IPI is cost effective in 41.8% of the iterations.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix K. Additional efficacy data (August 2020 DCO)

In this Section, OS results of the CLEAR trial are reported for the ITT population, based on the August 2020 DCO. A sensitivity analysis for subgroup of patients who did not receive any subsequent treatment is also presented.

OS results at August 2020 DCO, based on an extended median follow-up of 26.6 months, showed a significant improvement in OS with LEN+PEM vs sunitinib (HR 0.66 [95% CI: 0.49, 0.88]; p=0.005), corresponding to a 34% reduction in the risk of death [65]. At 24 months, more patients in the lenvatinib + pembrolizumab arm were alive (79.2%) compared to the sunitinib arm (70.4%) [65]. Median OS was not estimable for any treatment group at August 2020 DCO [65]. The KM curves are presented in Figure 106.

Figure 106. CLEAR trial, KM analysis of OS (August 2020 DCO) overall population

Subgroup analyses of OS at the August 2020 DCO favored LEN+PEM over sunitinib across nearly all predefined subgroups, including all MSKCC risk groups. In the IMDC risk groups, OS benefit in favor of LEN+PEM was observed in the intermediate and poor risk groups, but not in the favorable risk group as the HR crossed 1 (

Figure 107) [65]. However, small event size and wide confidence intervals limit interpretation of these data.

Figure 107. CLEAR trial, OS Subgroup Analysis (LEN+PEM vs Sunitinib; August 2020 DCO) overall population

Note that, as discussed in the main section for the March 2021 DCO, the crossover in the KM curve may be attributable to the high level of censoring prior to the crossover point, as well as an increased frequency of patients in the sunitinib arm switching to subsequent immunotherapy [65]. A summary of anticancer medications/therapies used in discontinued patients is reported in Appendix M. Methods of CLEAR Study: Anticancer Medications Used During Survival Follow up (August 2020 DCO).

CLEAR – OS (overall population) – sensitivity analysis – patients who did not receive subsequent treatment

A sensitivity analysis of the CLEAR trial provides additional evidence of the benefit of OS in the comparison of LEN+PEN versus sunitinib. This sensitivity analysis was carried out on the August 2020 DCO.

XXXXXXX108 presents KM plots for OS in patients who did not receive any subsequent systemic anticancer medication.

[redacted]

[redacted]

Abbreviations: L+P; IIR, independent imaging review lenvatinib plus pembrolizumab; NE, not estimable; OS, overall survival; S, sunitinib

Appendix L. Global NMA Report

The Global NMA from which relative efficacy estimates were derived is embedded here.

[redacted]

[redacted]

Appendix M. Methods of two stage estimation method

The objective of the analysis was to estimate the treatment effect of LEN+PEM versus sunitinib on OS follow up (DCO of 31 March 2021) with adjustment for treatment with any subsequent anticancer medication in both LEN+PEM and sunitinib arms using 2-stage estimation and IPCW approach.

Use of subsequent anticancer medicines

[redacted] 12[redacted] 12[redacted]

Baseline covariates

Both 2-stage estimation and IPCW methods considered covariates in Table 159 with selection based on clinical expert opinion and prior knowledge of the disease. The covariates included in models may vary depending on the approach to incorporate the time-dependent covariates in the model, the model fitting and model convergence.

For both 2-stage estimation and IPCW approach, the HR was estimated using the Cox regression model stratified by the factors used for stratified randomization, similar to the ITT analysis. Additionally, Cox regression models with treatment arm as a factor and with adjustment of additional baseline covariates in Table 159 were also explored.

Table 159. Covariates considered in the 2-stage estimation and inverse probability of censoring weights methods

Baseline covariates (at study entry):
• MSKCC prognostic risk group: favorable risk, intermediate risk or poor risk • IMDC prognostic risk group: favorable risk, intermediate risk or poor risk • Region: Western Europe and North America or Rest of the world • Age group (years): <65 or ≥65 • Sex: Female or Male • Prior Nephrectomy: Yes or No • RCC Sarcomatoid component by Histology: Yes or No • Bone Metastasis: Yes or No • Liver Metastasis: Yes or No • Lung Metastasis: Yes or No • Number of metastatic organs/sites involved: 0-1, 2 or ≥3
Secondary baseline covariates (at study treatment discontinuation) in 2-stage estimation/Time dependent covariates in IPCW:
• Disease progression during the study treatment: Yes or No • Treatment-related TEAE leading to study treatment discontinuation: Yes or No • Time from randomization to study treatment discontinuation in months (continuous) • IMDC prognostic risk group[a]: favorable risk, intermediate risk or poor risk • Sum of diameters in target lesions (continuous) • Bone Metastasis: Yes or No • Liver Metastasis: Yes or No • Lung Metastasis: Yes or No • Number of metastatic organs/sites involved: 0-1, 2 or ≥3

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IPCW = Inverse Probability of Censoring Weights, MSKCC = Memorial Sloan Kettering Cancer Center; RCC = renal cell carcinoma, TEAE=Treatment-emergent Adverse Event.
a. Derived from time from diagnosis to study treatment, and Karnofsky Performance Status score, hemoglobin, corrected calcium, neutrophil count, and platelet count at secondary baseline.

Two stage estimation method

In the 2-stage estimation, OS is defined similarly as in the ITT, but the survival time for subjects switching to subsequent anticancer medication is adjusted. Specifically, the survival time after discontinuation from study treatment is adjusted using acceleration factor (AF) determined in Stage 1. The primary 2-stage estimation approach applies the adjustment for switching without re-censoring due to the potentially substantial impact of re-censoring.

The secondary baseline for the 2-stage estimation method was defined as the study treatment discontinuation date. Acceleration factors calculated by fitting log-normal, log-logistic, and Weibull models to the observational datasets (OS from the secondary baseline onwards in the subjects who discontinued study treatment and were still on survival follow-up afterwards) for each treatment arm (220 subjects in the LEN+PEM arm and 272 subjects in the sunitinib arm) are shown in XXXXXX160.

X[redacted]160[redacted]

[redacted]

	Lenvatinib + Pembrolizumab (N=220)	Sunitinib (N=272)
Switching to Any Anticancer Medication, n	[redacted]	[redacted]
Log-normal AFT model: AF (95% CI)	[redacted]	[redacted]
AIC / BIC	[redacted]	[redacted]
Log-logistic AFT model: AF (95% CI)	[redacted]	[redacted]
AIC / BIC	[redacted]	[redacted]
Weibull AFT model: AF (95% CI)	[redacted]	[redacted]
AIC / BIC	[redacted]	[redacted]

AF: Acceleration factor, AFT: Accelerated failure time, AIC: Akaike information criterion, BIC Bayesian information criterion, CI confidence interval;
The observational datasets consist of OS from the secondary baseline onwards in the subjects who discontinued study treatment and were still on survival follow-up afterwards, for each treatment arm.
An acceleration factor of >1.0 indicates anticancer treatment benefit after switching.

Acceleration factors of >1.0 (ranging from 2.34 to 2.84 in the LEN+PEM arm, and 3.60 to 4.49 in the sunitinib arm for switching to any subsequent anticancer medication) indicated that switchers experienced extended survival time compared with subjects who have not received any subsequent anticancer medication in both randomized treatment arms (XXXXXX160).
Followed the approach in the LP 2-stage estimation and IPCW report, the full model with a log-normal was considered as the preferred model fitting to both the treatment arms. OS results from Cox regression analyses undertaken on the counterfactual datasets obtained using the acceleration factors from each model are shown in (XXXXXX161).
Based on the counterfactual OS data with the AF estimation from the log-normal model, the adjusted HRs (LEN+PEM vs. sunitinib) using the Cox regression model stratified by randomization factor were 0.56 (95% CI: 0.43, 0.73) without re-censoring, and 0.29 (95% CI: 0.18, 0.45) with re-censoring, while the original unadjusted HR was 0.72 (95% CI: 0.55, 0.93). The estimated HRs from Cox regression model with treatment arm as a factor adjusting for selected covariates are further reduced (XXXXXX161).Figure 109 and

Figure 110 depict the survival curves from the original observed OS (unadjusted) and the counterfactual OS (adjusted) without and with re-censoring, respectively.

[redacted]

[redacted]

	Lenvatinib + Pembrolizumab (N=355)	Sunitinib (N=357)
[redacted]		
[redacted]	[redacted]	[redacted]

[redacted]

DCO date: March 2021 DCO

AF: Acceleration factor, HR = Hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IxRS= interactive voice and web response system; MSKCC = Memorial Sloan Kettering Cancer Center; RCC = renal cell carcinoma

b. HR (lenvatinib + pembrolizumab vs sunitinib) is based on a Cox proportional hazard model including treatment group as a factor, stratified by geographic region and MSKCC prognostic groups in IxRS.

[b] HR (lenvatinib + pembrolizumab vs sunitinib) is based on a Cox proportional hazard model including treatment group and the selected baseline covariates (IMDC prognostic risk group, number of metastatic organs/sites involved, and prior nephrectomy) as factors. The selected baseline covariates were determined by a multivariate Cox model on the unadjusted original OS data using the backward variable selection method with alpha=0.05.

Figure 109. Kaplan-Meier curves of adjusted overall survival for switching to any anticancer medication by 2-stage estimation method without re-censoring based on Log-normal model for acceleration factor estimation

[redacted]

Figure 110. Kaplan-Meier curves of adjusted overall survival for switching to any anticancer medication by 2-stage estimation method with re-censoring based on log-normal model for acceleration factor estimation

[redacted]

[redacted]

Table 162. Instrument completion Rates – Full analysis set – Instrument EQ-5D-3L (cycle 1-15) [redacted]

[redacted]

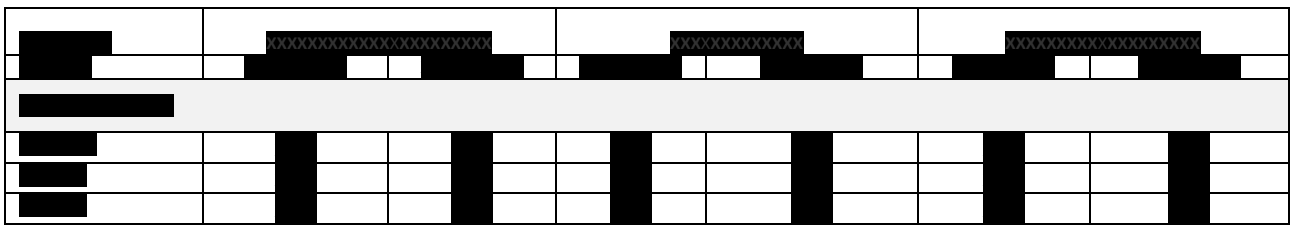
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

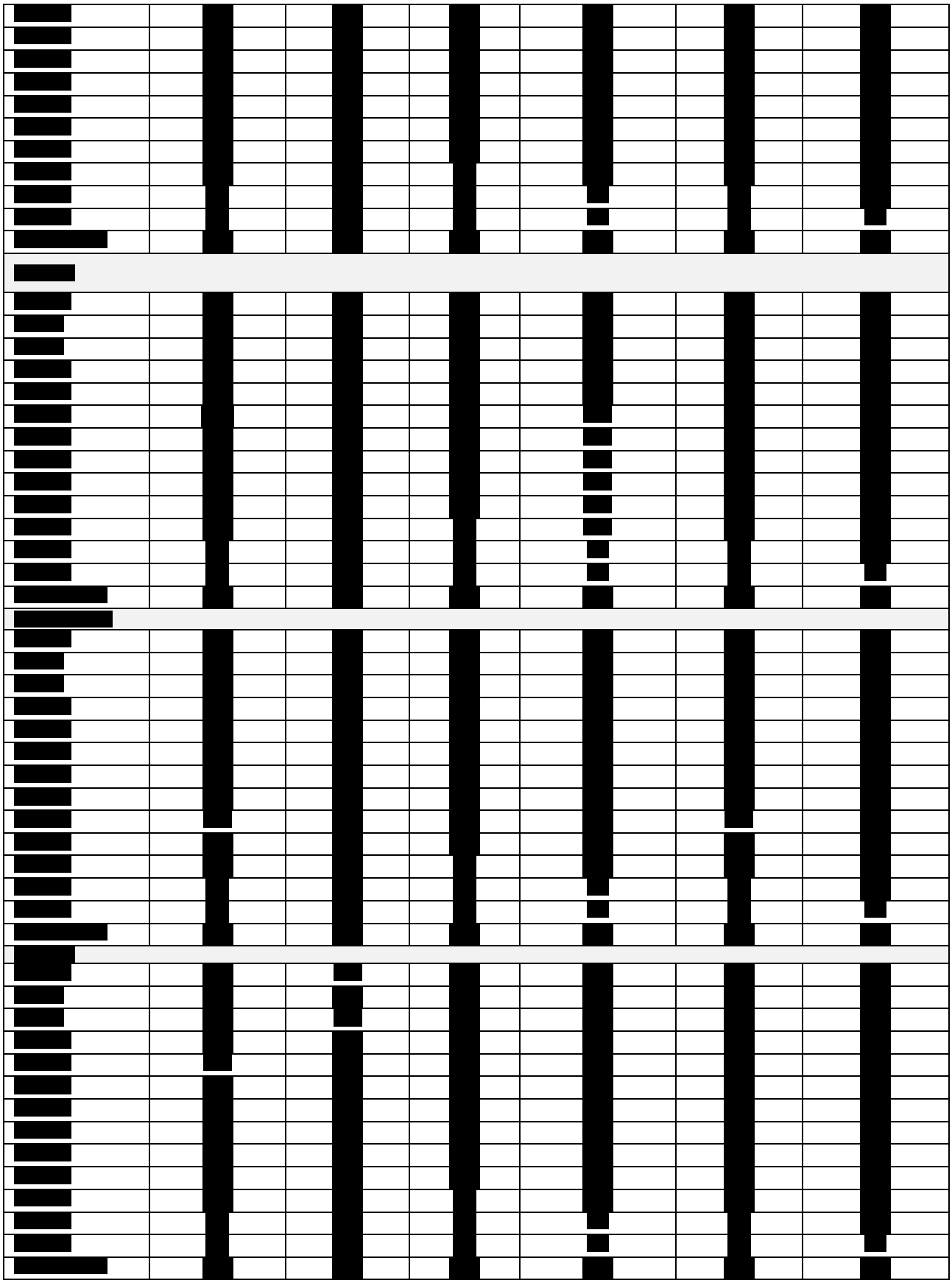
Table 163. Instrument completion Rates – Full analysis set – Instrument EQ-5D-3L (cycles 16-30) [66]

Table 164. Instrument completion Rates – Full analysis set – Instrument EQ-5D-3L (cycles 31-45) [66]

Table 165. Instrument completion Rates – Full analysis set – Instrument EQ-5D-3L (cycles 46-59) [66]

Table 166. HrQoL Completion and Compliance rates [66]





Completion rates: percentage of patients who completed the instrument among all patients who were enrolled in the full analysis set at baseline and were assessed for each of the HRQoL outcomes by assessment time point and treatment arm. Compliance rates: percentage of patients who completed the instrument among all patients who were still enrolled in the study and on study treatment at a particular postbaseline time point and were, therefore, expected to complete the instrument. Please note that these data are only available for the ITT population and are not available split by the IMDC risk groups.

EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; EVE, everolimus; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease related Symptoms; LEN, lenvatinib; PEMBRO, pembrolizumab.

Table 167. Mean baseline HRQoL scores by IMDC Risk Group and Treatment Quality of life analysis set. [74]

	Favorable Risk		Intermediate or Poor Risk	
Mean Score	LEN + PEMBRO (N = 109)	SUN (N = 117)	LEN + PEMBRO (N = 240)	SUN (N = 220)
[redacted]				

EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Cancer - Core 30; FKSI-DRS = Functional Assessment of Cancer Therapy Kidney Symptom Index - Disease-Related Symptoms; GHS = global health status; HRQoL = health-related quality of life; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; QoL = quality of life; VAS = visual analog scale.

Table 168. IMDC good prognosis Subgroup Analyses of Least Squares Mean Change From Baseline in Lenvatinib + Pembrolizumab and Sunitinib Arms [74][redacted]

Table 169. IMDC intermediate/poor prognosis Subgroup Analyses of Least Squares Mean Change From Baseline in Lenvatinib + Pembrolizumab and Sunitinib Arms [74]

*Denotes a statistically significant log-rank difference ($P < 0{\cdot}05$). For presentation, scores from the FKSI-DRS and EQ-5D-3L Index instruments were transformed to the scale of 0–100 (FKSI-DRS transformed score = (raw score/36)*100; EQ-5D-3L Index transformed score = (raw score)*100).
CI, confidence interval; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease related Symptoms; LS, least squares; GHS/QoL, global health status/quality of life; IMDC, International Metastatic RCC Database Consortium; LEN, lenvatinib; MSKCC, Memorial Sloan Kettering Cancer Center; PEMBRO, pembrolizumab; SUN, sunitinib; VAS, visual analog scale.

Table 170. IMDC good prognosis Subgroup Analyses of Time to First Deterioration in Lenvatinib + Pembrolizumab and Sunitinib Arms [74]

Table 171. IMDC intermediate/poor prognosis Subgroup Analyses of Time to First Deterioration in Lenvatinib + Pembrolizumab and Sunitinib Arms [74]

*Denotes a statistically significant log-rank difference ($P < 0{\cdot}05$).

CI, confidence interval; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L, EuroQol 5 Dimensions 3 Levels; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index–Disease related Symptoms; GHS/QoL, global health status/quality of life; IMDC, International Metastatic RCC Database Consortium; L / LEN, lenvatinib; MSKCC, Memorial Sloan Kettering Cancer Center; P / PEMBRO, pembrolizumab; S / SUN, sunitinib; VAS, visual analog scale.

Table 172. IMDC good prognosis Subgroup Analyses of Time to Definitive Deterioration in Lenvatinib + Pembrolizumab and Sunitinib Arms [74]

Table 173. IMDC intermediate/poor prognosis Subgroup Analyses of Time to Definitive Deterioration in Lenvatinib + Pembrolizumab and Sunitinib Arms [74]

Below there are also tables detailing the number of patients included in the assessment of each PRO. Full details of all analyses are included in the PRO report.

It should be noted that:

- Cycle 15 corresponds to the average HRQoL follow-up time (which was approximately 46 weeks).
- Time to first deterioration (TTfD) and time until definitive discontinuation (TuDD) are defined as follows:[66]
  - TTfD: the number of weeks between randomization and the first deterioration event

- TuDD: the number of weeks between randomisation and the earliest deterioration event with no subsequent recovery above the deterioration threshold or no subsequent HRQoL assessment data
- In both TTfD and TuDD cases, death was considered a deterioration event if it occurred within 30 days of the last HRQoL assessment (for consistency with the timing of the off-treatment visit), regardless of the start date of any new anticancer treatment. Participants without a deterioration event at the analysis cutoff date were censored at the date of the last HRQoL assessment.
- Deterioration events were defined as detrimental changes in score relative to baseline that exceed the minimally important difference thresholds. Minimally important differences were a decrease of three or more points for the FKSI-DRS; a decrease of ten or more points for the EORTC QLQ-C30 functional and GHS/QoL scores; an increase of ten or more points for the EORTC QLQ-C30 symptom scores; a decrease of 0.08 or more points for the EQ-5D-3L index; and a decrease of 7 or more points for the EQ-5D-3L VAS.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 174. Time first deterioration (FKSI-DRS total score and EORTC QLQ-C30)

[redacted]

[redacted]

CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Cancer - Core 30; EQ-VAS = EuroQol visual analog scale; FKSI-DRS = Functional Assessment of Cancer Therapy Kidney Symptom Index - Disease-Related Symptoms; HR = hazard ratio; NE = not estimable; TTD = time to deterioration; QoL = quality of life.
[1] HR and 95% CI are from a Cox regression model comparing lenvatinib + everolimus or lenvatinib + pembrolizumab to sunitinib, stratified by the randomization stratification variables (geographic region and Memorial Sloan-Kettering Cancer Center prognostic group).
For each scale, N represents the number of participants with a baseline score and at least one post-baseline score.

[redacted]

Table 175. Time first deterioration (EQ-5D Index, EQ-VAS 7 point MID and EQ-VAS 10-point MID)

[redacted]

[redacted]

CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Cancer - Core 30; EQ-VAS = EuroQol visual analog scale; FKSI-DRS = Functional Assessment of Cancer Therapy Kidney Symptom Index - Disease-Related Symptoms; HR = hazard ratio; NE = not estimable; TTD = time to deterioration; QoL = quality of life.
[1] HR and 95% CI are from a Cox regression model comparing lenvatinib + everolimus or lenvatinib + pembrolizumab to sunitinib, stratified by the randomization stratification variables (geographic region and Memorial Sloan-Kettering Cancer Center prognostic group).
For each scale, N represents the number of participants with a baseline score and at least one post-baseline score.

[redacted]

Overall population	IMDC favourable subgroup	IMDC intermediate/poor subgroup
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Patients With Cancer - Core 30; EQ-VAS = EuroQol visual analog scale; FKSI-DRS = Functional Assessment of Cancer Therapy Kidney Symptom Index - Disease-Related Symptoms; HR = hazard ratio; NE = not estimable; TuDD = time until definitive deterioration; QoL = quality of life.

[1] HR and 95% CI are from a Cox regression model comparing lenvatinib + everolimus or lenvatinib + pembrolizumab to sunitinib, stratified by the randomization stratification variables (geographic region and Memorial Sloan-Kettering Cancer Center prognostic group).

For each scale, N represents the number of participants with a baseline score and at least one post-baseline score.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 178. Time to definitive deterioration (FKSI-DRS total score and EQ-5D-3L by subgroup)

Overall population	IMDC favourable subgroup	IMDC intermediate/poor subgroup
[redacted]	[redacted]	[redacted]

[redacted]

This appendix explains the relation and the attrition rate between the efficacy and safety SLR presented in Appendix A Literature search for efficacy and safety of intervention and comparator(s), the global Network Meta Analysis discussed in section 4.3.4 (and attached to the documents of this application) and the efficacy and safety inputs to this application to the DMC, in regards to the IMDC intermediate/poor prognosis population of RCC patients.

We are providing below

- In Table 179**,** a list of trials included in the SLR, in the NMA, and the reason for exclusion from the NMA
- In Table 180, a list of publications included in the SLR, considered eligible for the NMA and finally which contributed data to the NMA. The publications that did not contribute due to data from a later time point being available, or data not eligible for analysis.
- In Table 181 and Table 182, a list of publications for CLEAR and CheckMate214 respectively, which were included in the SLR, considered eligible for the NMA, contributed data to the NMA and was included in the DMC submission

The 5 publications which provide direct input to this submission are highlighted yellow. Please note that some publications included in the SLR are repetitive. For example, for the conference presentation, the SLR included both the abstract and poster/slides/full text as they are identified by database search and meets the inclusion criteria of SLR.). Moreover, please note that this SLR was conducted in a global setting, hence the scope of the SLR was larger than the scope of interest for this submission to the DMC. Generally, the publications retained to inform this submission have been selected based on the following criteria:

- Comparators of interest to the DMC in the population of interest to the DMC
- Latest available data for each outcome of interest

Table 179. List of trials included in SLR (n=34), in the NMA (n=24) and reason for exclusion from the NMA.

XXXXX	XXXXXXXXXXX	XXXXXXXXXXXXXXXX XXXXXXXX	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
[redacted]			

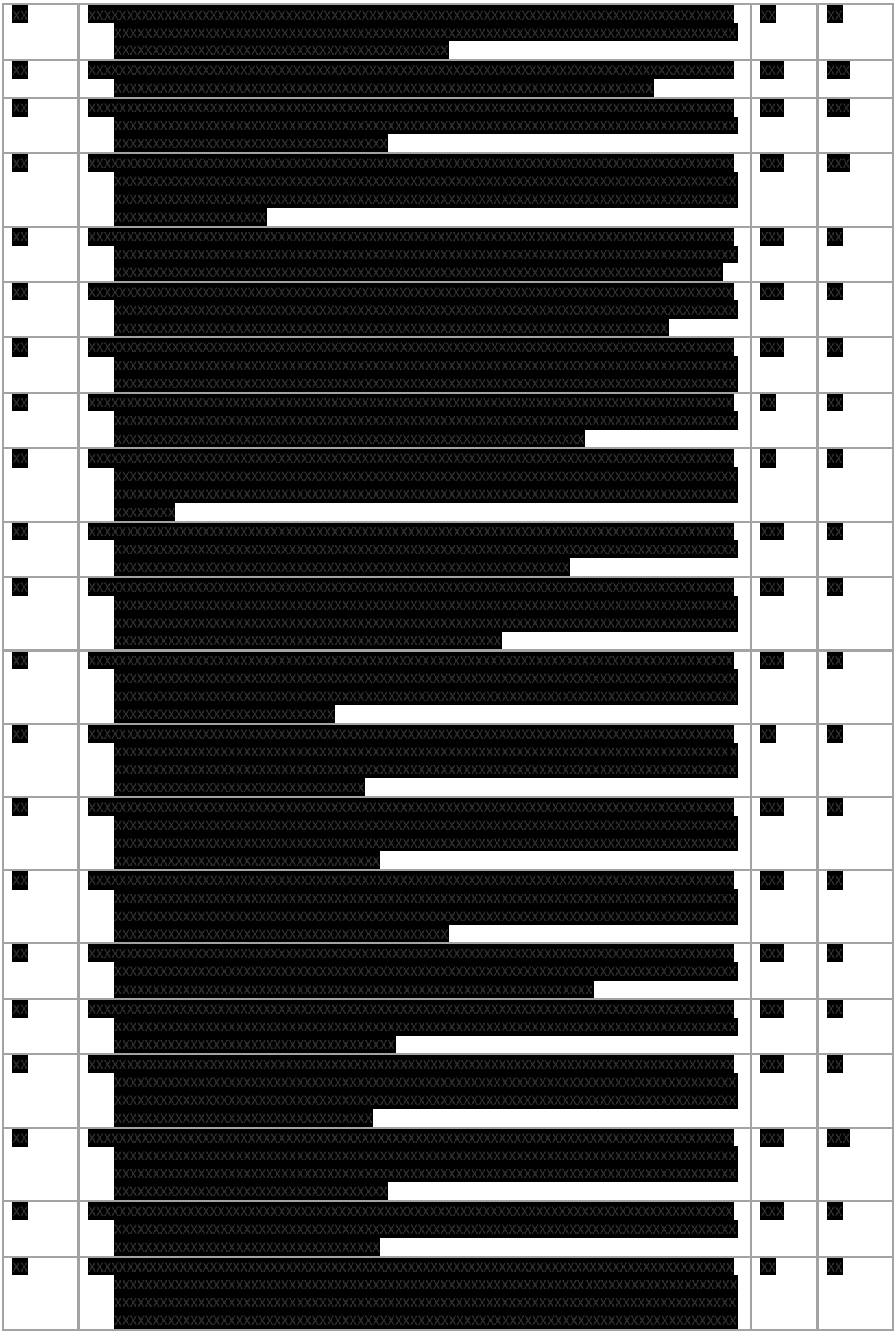
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 180. List of the 156 publications included in the SLR, with indication of those that were considered eligible for the NMA (n= 138) and finally those that actually contributed data to the NMA (n=58)

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk



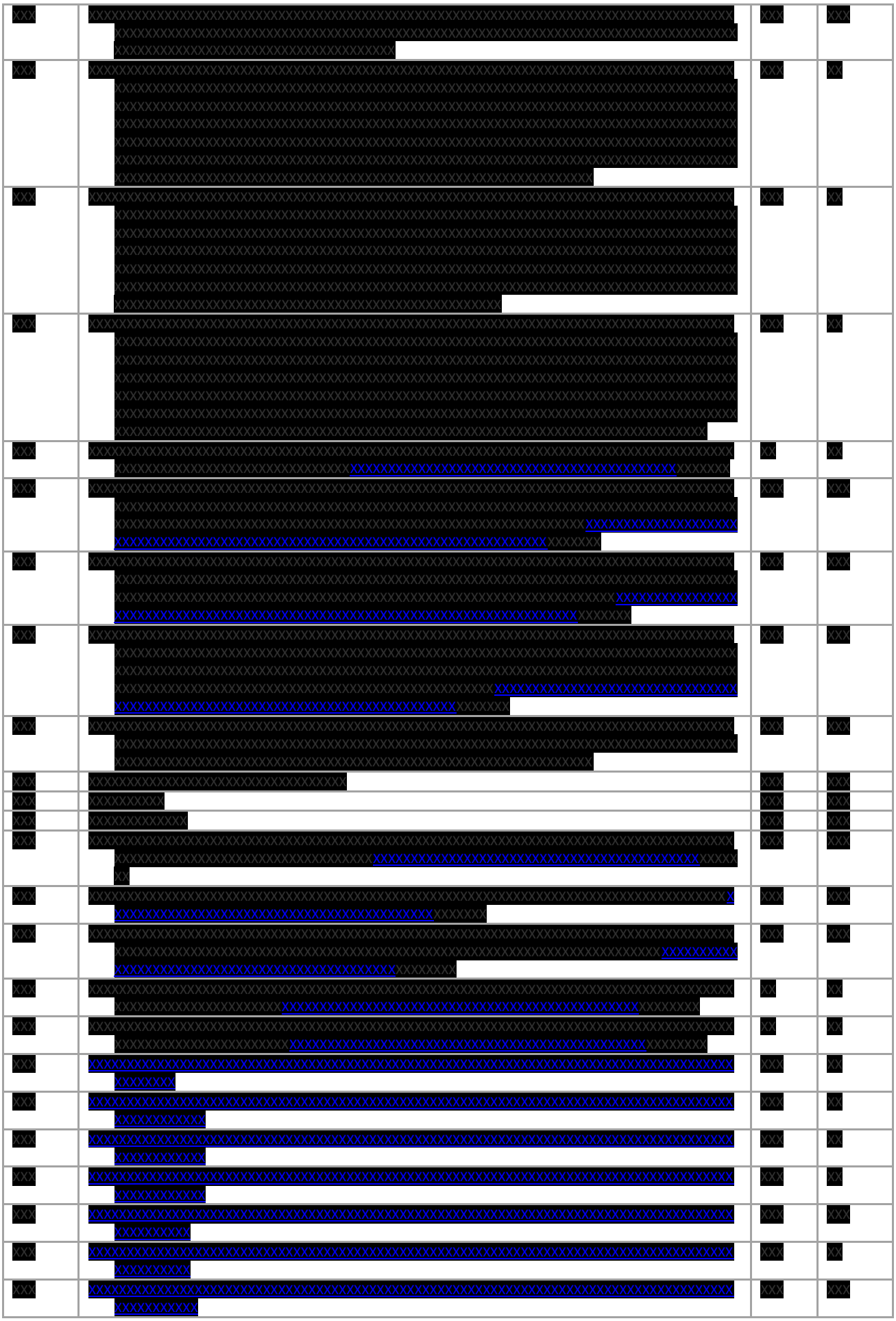
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

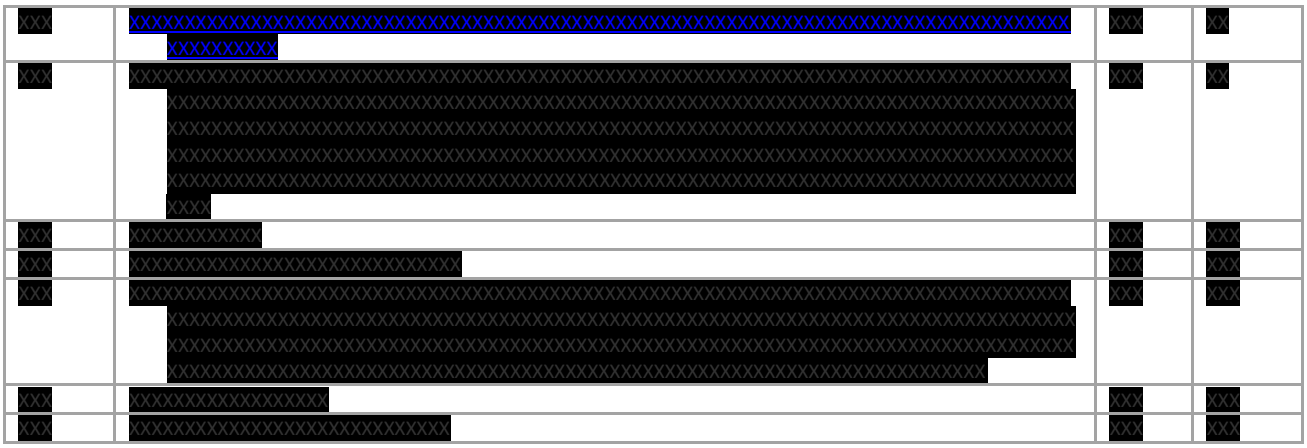
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

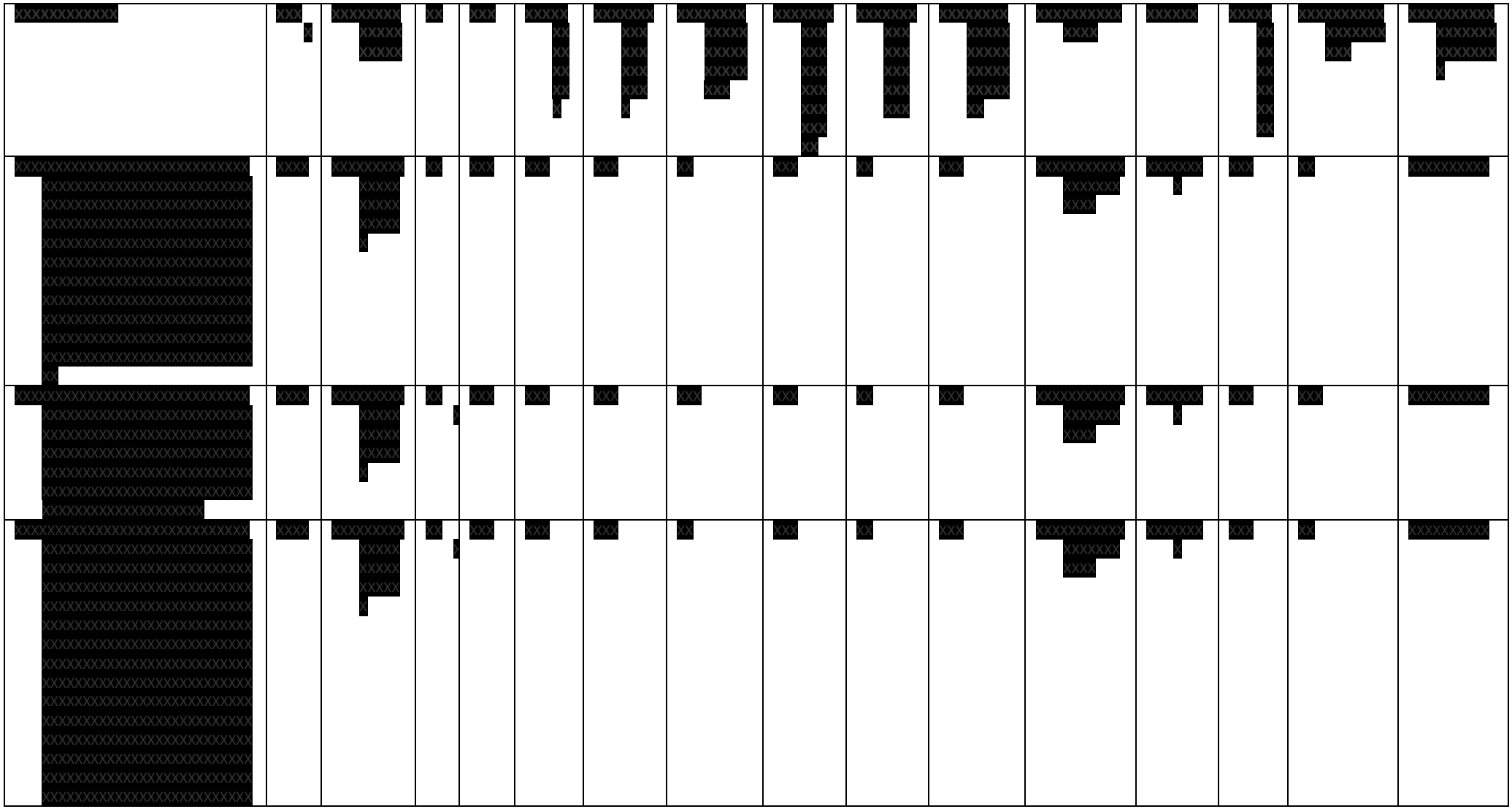


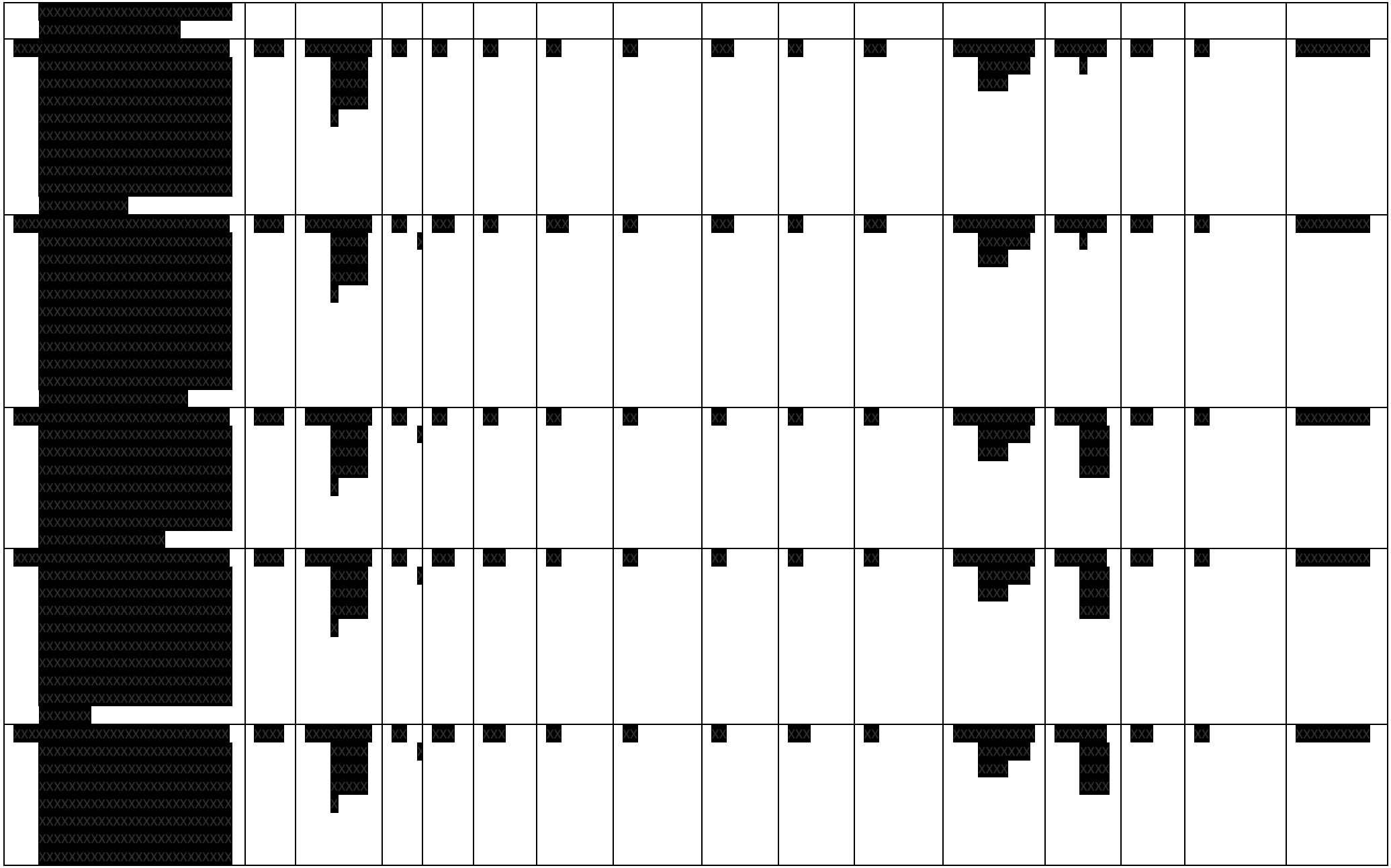
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk



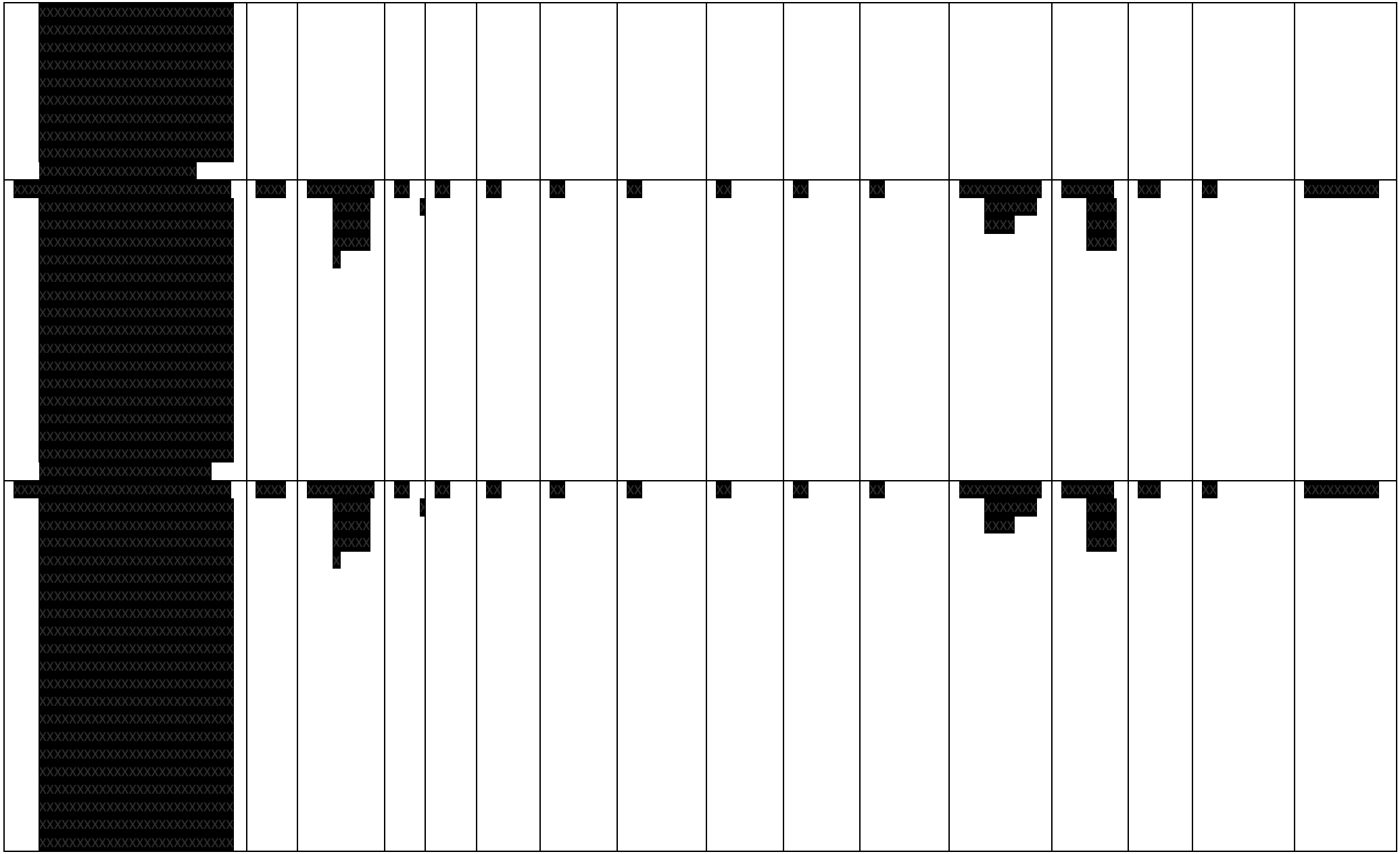
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 181. List of publications for CheckMate214 which were included in the SLR, considered eligible for the NMA, contributed data to the NMA and was included in the DMC submission

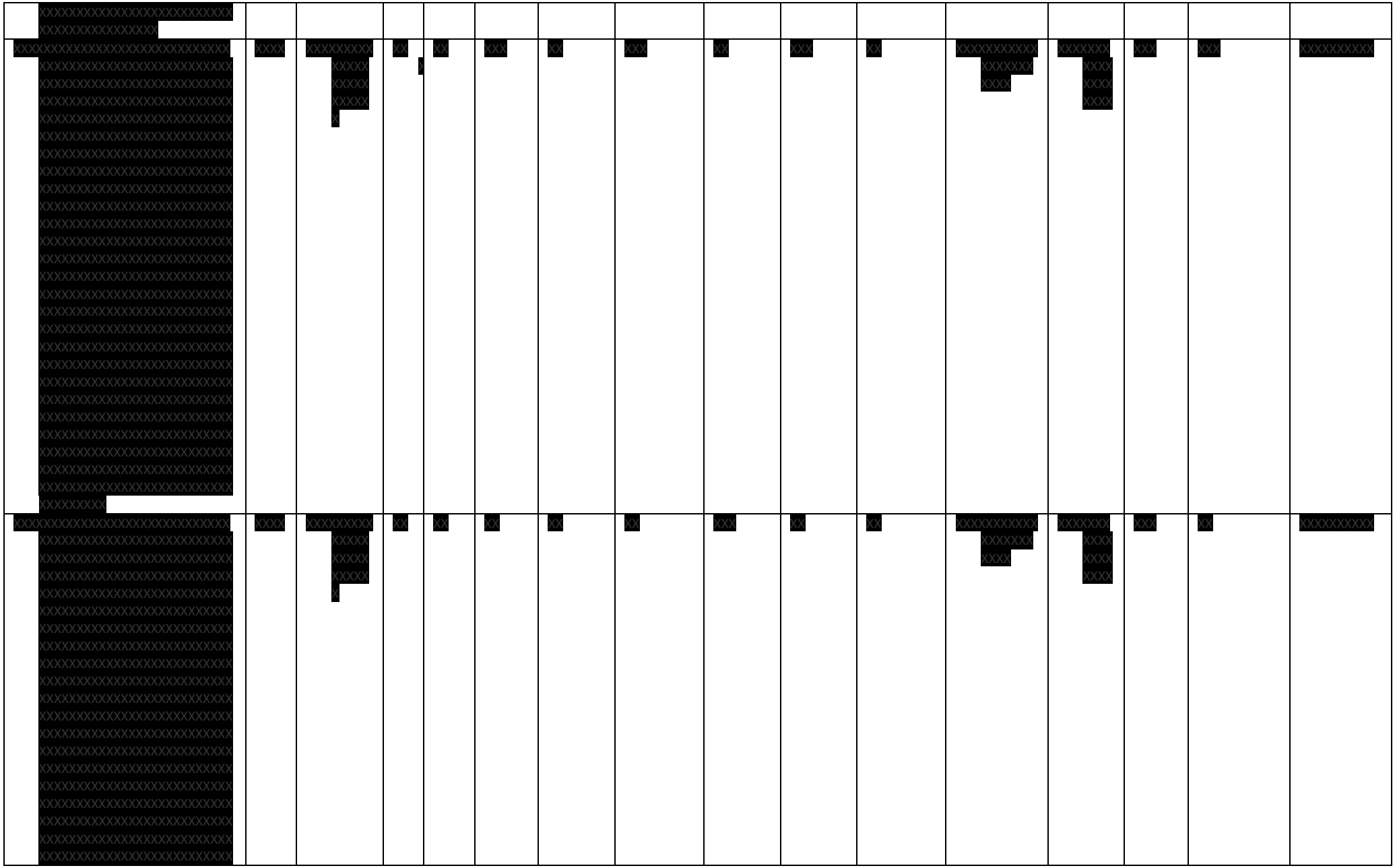




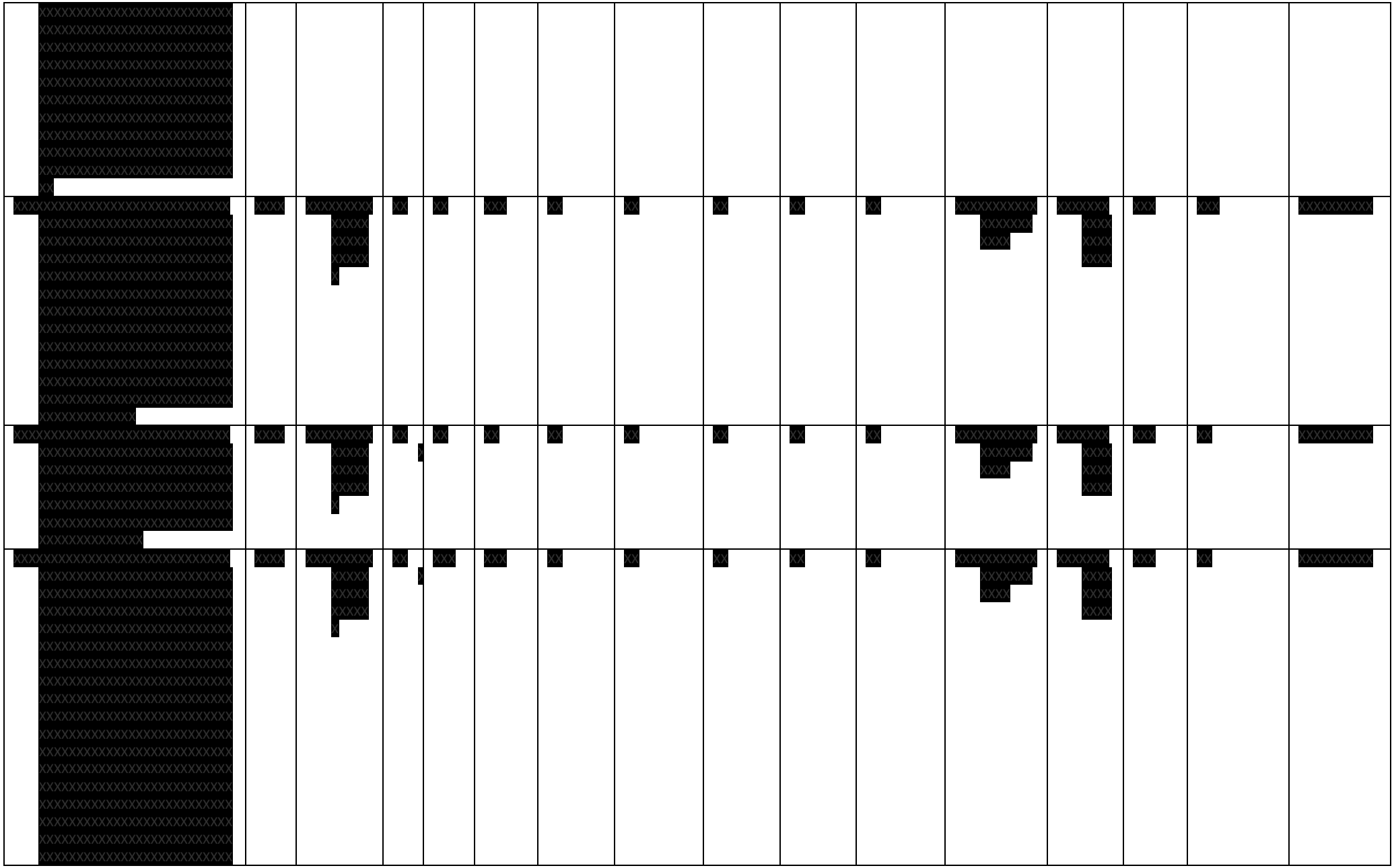
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk



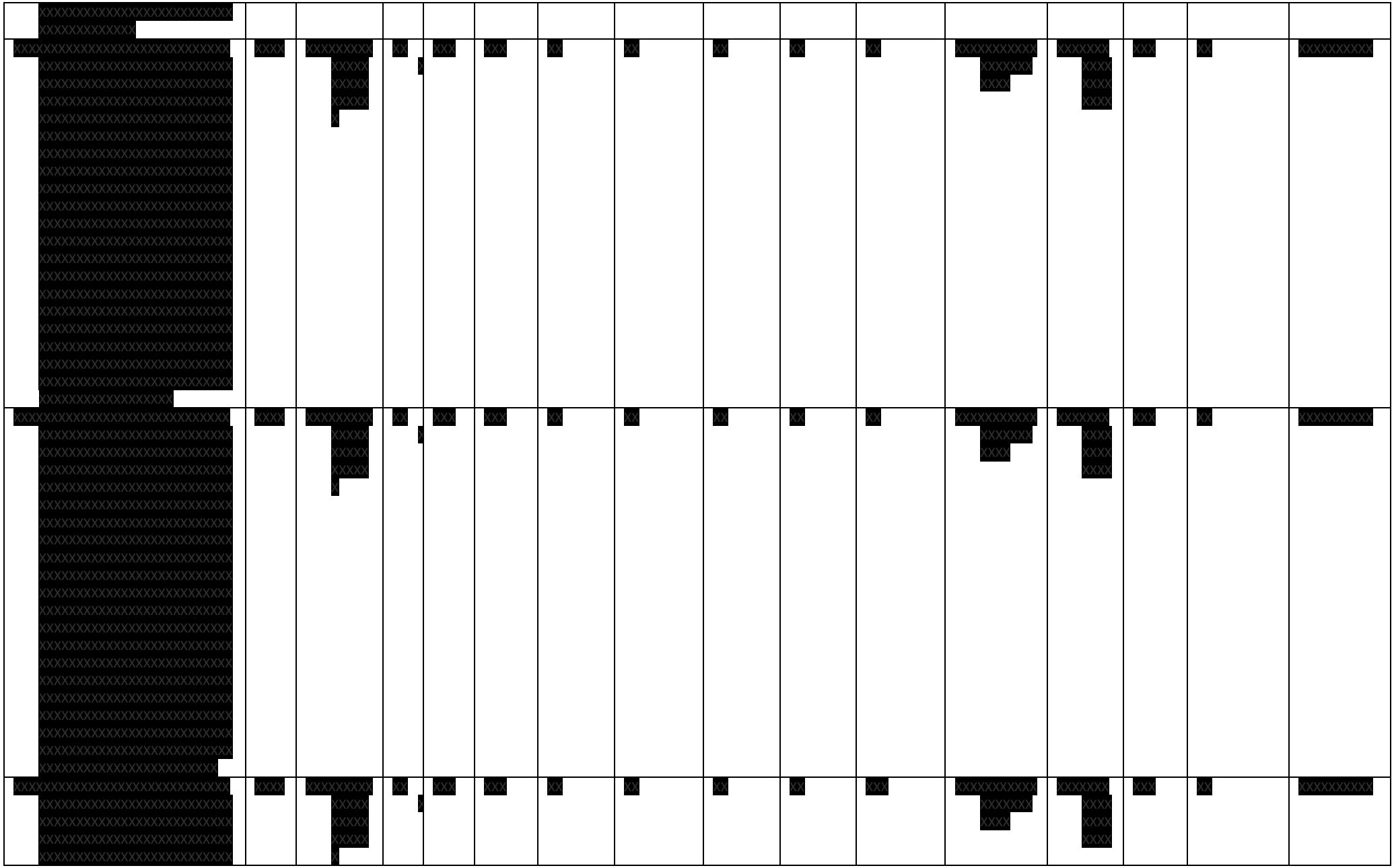
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk



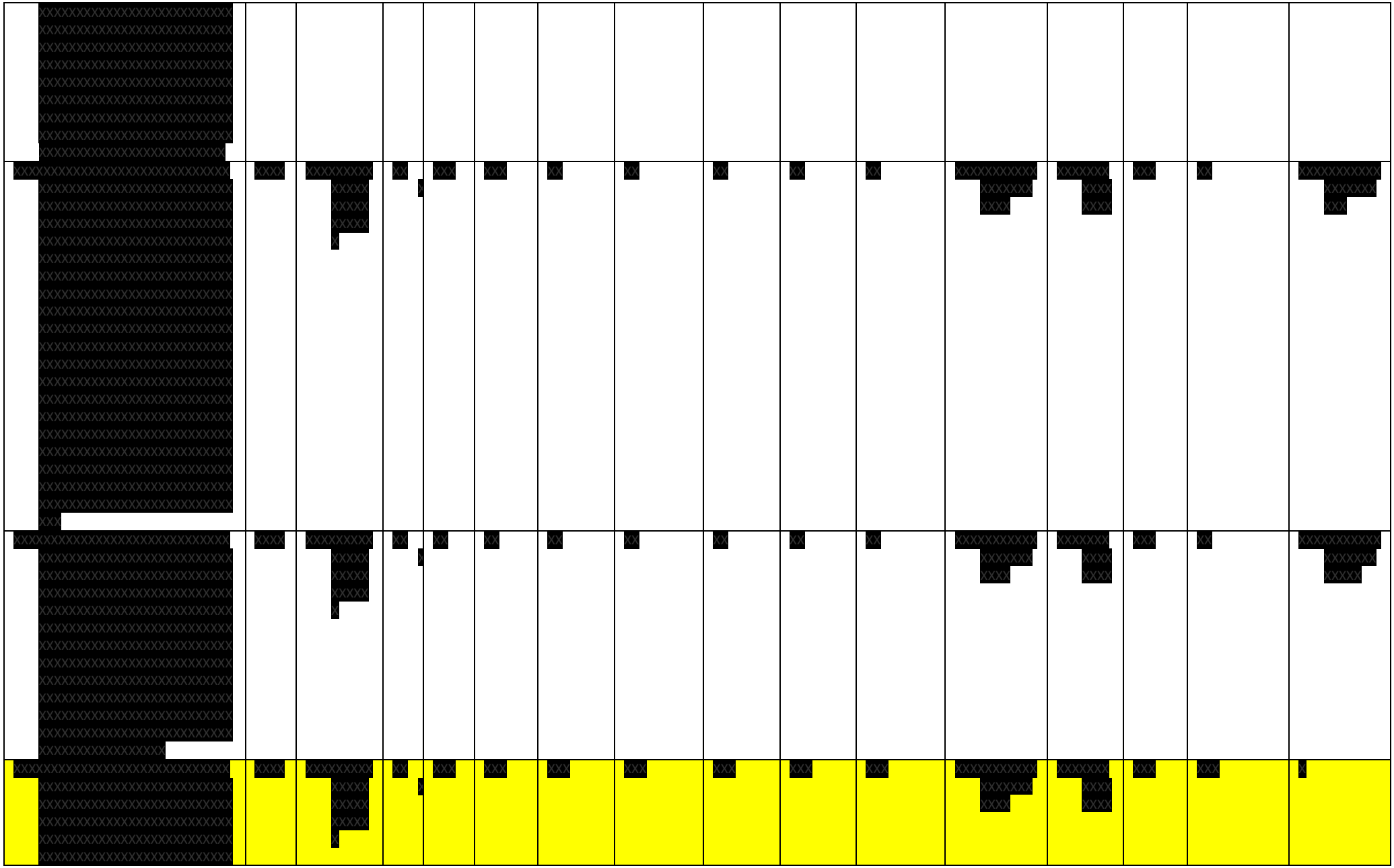
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk



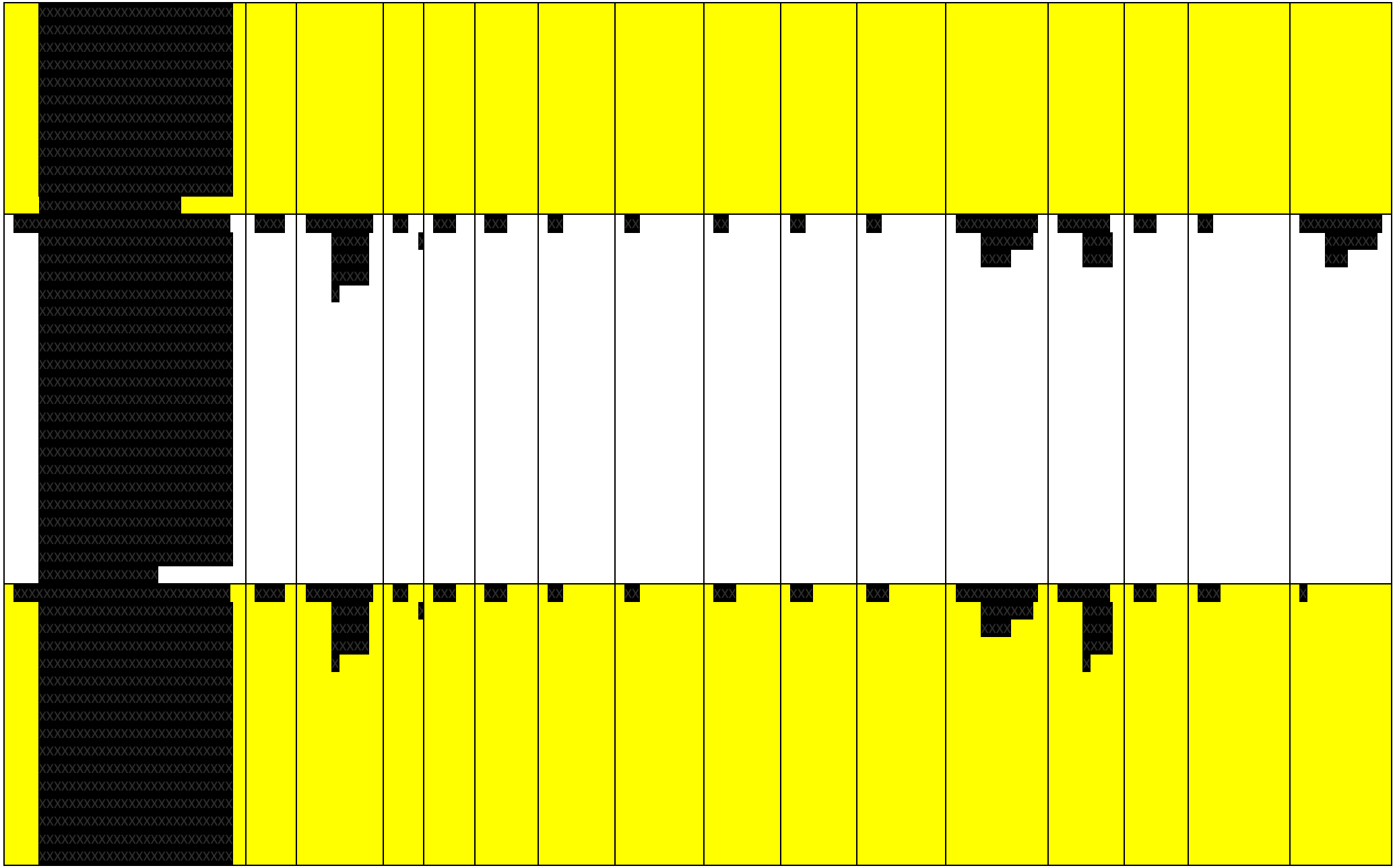
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk



Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk



Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk



Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

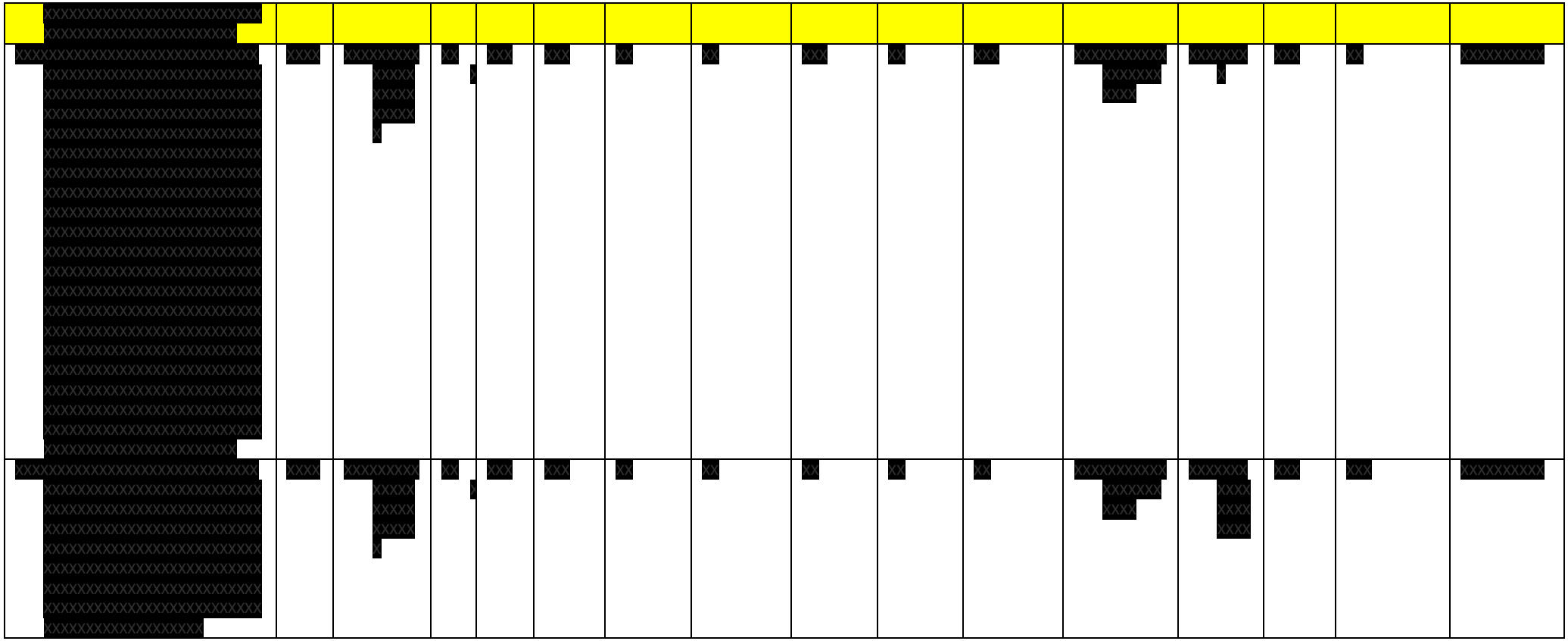


Table 182. List of publications for CLEAR which were included in the SLR, considered eligible for the NMA, contributed data to the NMA and was included in the DMC submission

Bibliography	Year	Trial Name / Number	OS	PFS	Response Rates	Duration of Response	All-cause Discontinuations	AE-related Discontinuations	All-cause Grade 3+ AEs	Treatment-related Grade 3+ AEs	Intervention 1	Search	Eligible for NMA	Data included in NMA	Exclusion from submission

Grunwald, V. Analysis of the CLEAR study in patients (pts) with advanced renal cell carcinoma (RCC): Depth of response and efficacy for selected subgroups in the lenvatinib (LEN) + pembrolizumab (PEMBRO) and sunitinib (SUN) treatment arms. 2021; ASCO Annual Meeting.	[redacted]														
[redacted]															
[redacted]															

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

[redacted]

Log cumulative hazard plots for the ITT population are presented here:

OS

Figure 111. Log-Cumulative hazard plots of observed data, sunitinib and LEN+PEM, Overall population, Overall survival, March 2021 DCO

PFS

Figure 112. Log-Cumulative hazard plots of observed data, sunitinib and LEN+PEM, Overall population, Progression-free survival, August 2020 DCO

TTD LEN

Figure 113. Log-Cumulative hazard plots of observed data, lenvatinib, Overall population, Time to treatment discontinuation, August 2020 DCO

TTD PEM

Figure 114. Log-Cumulative hazard plots of observed data, pembrolizumab, Overall population, Time to treatment discontinuation, August 2020 DCO

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

TTD sunitinib

Figure 115. Log-Cumulative hazard plots of observed data, sunitinib, Overall population, Time to treatment discontinuation, August 2020 DCO

Log cumulative hazard plots for the IMDC good prognosis population are presented here:

OS

Figure 116. Log-Cumulative hazard plots of observed data, sunitinib and LEN+PEM, IMDC good prognosis population, Overall survival March 2021 DCO

PFS

Figure 117. Log-Cumulative hazard plots of observed data, sunitinib and LEN+PEM, IMDC good prognosis population, Progression-free survival, August 2020 DCO

TTD LEN

Figure 118. Log-Cumulative hazard plots of observed data, lenvatinib, IMDC good prognosis population, Time to treatment discontinuation, August 2020 DCO

TTD PEM

Figure 119. Log-Cumulative hazard plots of observed data, pembrolizumab, IMDC good prognosis population, Time to treatment discontinuation, August 2020 DCO

TTD Sunitinib

Figure 120. Log-Cumulative hazard plots of observed data, sunitinib, IMDC good prognosis population, Time to treatment discontinuation, August 2020 DCO

Log cumulative hazard plots for the IMDC intermediate/poor population are presented here:

OS

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 121. Log-Cumulative hazard plots of observed data, sunitinib and LEN+PEM, IMDC intermediate/poor prognosis population, Overall survival March 2021 DCO

PFS

Figure 122. Log-Cumulative hazard plots of observed data, sunitinib and LEN+PEM, IMDC intermediate/poor prognosis population, Progression-free survival, August 2020 DCO

TTD LEN

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 123. Log-Cumulative hazard plots of observed data, lenvatinib, IMDC intermediate/poor prognosis population, Time to treatment discontinuation, August 2020 DCO

TTD PEM

Figure 124. Log-Cumulative hazard plots of observed data, pembrolizumab, IMDC intermediate/poor prognosis population, Time to treatment discontinuation, August 2020 DCO

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

TTD Sunitinib

Figure 125 Log-Cumulative hazard plots of observed data, sunitinib, IMDC intermediate/poor prognosis population, Time to treatment discontinuation, August 2020 DCO

Schoenfeld residual plots for the ITT population are presented here:

OS

Figure 126. Schoenfeld Residual Plot of Overall survival, Overall population, March 2021 DCO

PFS

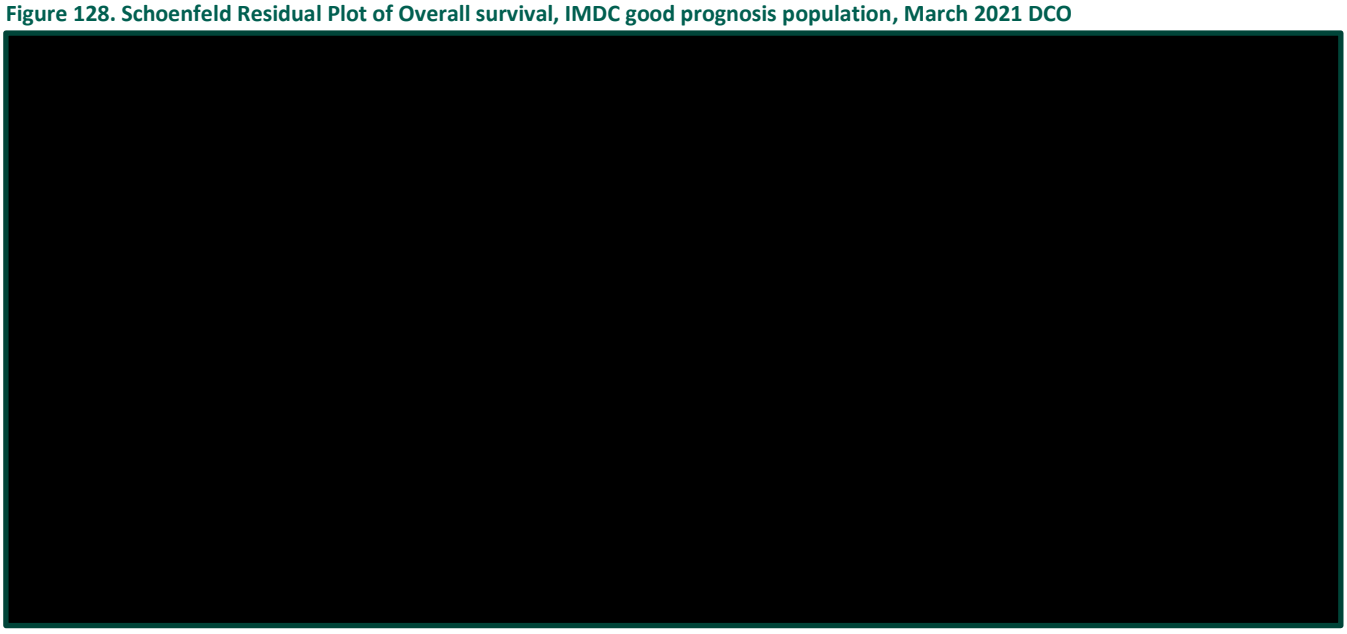
Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 127. Schoenfeld Residual Plot of Progression-free survival, Overall population, August 2020 DCO

Schoenfeld residual plots for the IMDC good prognosis population are presented here:

OS

Figure 128. Schoenfeld Residual Plot of Overall survival, IMDC good prognosis population, March 2021 DCO



PFS.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 129. Schoenfeld Residual Plot of Progression-free survival, IMDC good prognosis population, August 2020 DCO

Schoenfeld residual plots for the IMDC intermediate/poor population are presented here:

OS

Figure 130. Schoenfeld Residual Plot of Overall survival, IMDC intermediate poor prognosis population, March 2021 DCO

PFS

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Figure 131. Schoenfeld Residual Plot of Progression-free survival, IMDC intermediate poor prognosis population, August 2020 DCO

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk