Medicinrådet

# Bilag til Medicinrådets anbefaling vedrørende cabozantinib (Cabometyx) i kombination med nivolumab (Opdivo) til behandling af metastatisk nyrecelle-karcinom

*Vers. 1.0*

# Bilagsoversigt

1. Ansøgers notat til Rådet vedr. cabozantinib i kombination med nivolumab til behandling af metastatisk nyrekræft
2. Amgros' forhandlingsnotat vedr. cabozantinib i kombination med nivolumab til behandling af metastatisk nyrekræft
3. Ansøgning vedr. cabozantinib i kombination med nivolumab til behandling af metastatisk nyrekræft

Aalborg, May 11th, 2023

# Ipsen's response to the Danish Medicines Council's draft assessment report for cabozantinib in combination with nivolumab for first-line treatment of aRCC

Ipsen would like to thank the Danish Medicines Council (DMC) for their draft assessment report and appreciates the opportunity to provide our comments. Our response letter focuses on vital factors that must be considered by the DMC to ensure that the final recommendation on cabozantinib in combination with nivolumab (CaboNivo) in 1L aRCC is based on correct assumptions.

**The DMC takes an unscientific approach and undermines the data for CaboNivo**

The DMC concludes that, based on a naïve comparison of OS results demonstrated for CaboNivo and IpiNivo in their respective pivotal clinical trials, a difference in OS has not been documented between CaboNivo and IpiNivo. However, using this conclusion to justify the DMC's approach in which the OS curve for IpiNivo is assumed to be identical to the one for CaboNivo over the entire time horizon in the health economic (HE) model is directly misleading. In our base case analysis submitted, the curves used to model OS for both CaboNivo and IpiNivo reflect the best-fitting curves resulting from the fractional polynomial (FP) network meta-analysis (NMA) conducted, including data from the pivotal clinical trials for CaboNivo and IpiNivo. Simply disregarding the FP NMA curve for IpiNivo in the DMC's base case analysis by replacing this with the FP NMA curve for CaboNivo undermines the clinical trial data and the FP NMA results completely. The FP NMA curves used in our base case was chosen based on commonly accepted HE analysis methodologies, and the choice of NMA methodology itself is in alignment with the DMC's guidance document for survival extrapolations in HE evaluations [1]. Also, important to note is that the marginal OS HR benefit for CaboNivo vs. sunitinib (HR=0.66) compared to IpiNivo vs. sunitinib (HR=0.68) would in fact be more supportive of the OS assumptions used in our base case analysis than the ones used in the DMC's base case analysis. Any uncertainty or validity questions around the assumptions used in our model should be addressed by the DMC through sensitivity analyses, not by simply replacing the comparator OS curve with the intervention OS curve in the base case analysis. Unfortunately, the approach taken by the DMC ultimately results in an extremely overestimated incremental cost-effectiveness ratio (ICER), as OS is one of the main drivers of the results, and assuming 100% identical OS curves for CaboNivo and IpiNivo over the time horizon reduces the incremental quality-adjusted life years (QALYs) dramatically to a very small value. We find the approach taken to be unscientific and contrasting to the DMC's own guidelines and therefore request a reconsideration of this, both in relation to OS and PFS.

**The DMC ignores a critical bias caused by a difference in the discontinuation criteria for nivolumab in the CheckMate 214 trial and in Danish clinical practice**

The DMC has implemented a 2-year stopping rule for nivolumab when used in combination with ipilimumab in their base case analysis, referencing that "this is standard clinical practice". However, no rationale for the 2-year restriction is provided in the DMC's drug recommendation [2], and the DMC instruction is **not** in alignment with the treatment protocol used in the CheckMate 214 trial[1] nor with the EMA SmPC for nivolumab[2] [3]. Considering that the optimal duration of immune checkpoint inhibitors in aRCC specifically and in solid tumors in general has not yet been fully established [4-8], the appropriateness of the DMC instruction deviating from both the treatment regimen used in this pivotal trial and the SmPC is highly remarkable.

What is of critical importance for the DMC's assessment of CaboNivo is that the discrepancy between the discontinuation criteria for nivolumab in the CheckMate 214 trial for IpiNivo and in the DMC's drug recommendation leads to a serious biasing of the results in the DMC's base case analysis. By implementing a 2-year stopping rule for IpiNivo in the HE model, the treatment costs are assumed to be zero after year 2. As just discussed, the DMC is also assuming completely identical OS curves for CaboNivo and IpiNivo in the HE model based on a conclusion of "no documented OS benefit" for CaboNivo. However, even if this approach was valid,

[1]The CheckMate 214 trial compared the efficacy and safety of IpiNivo to sunitinib in 1L aRCC. Treatment with nivolumab continued as long as clinical benefit was observed or until treatment was no longer tolerated, with no specific maximum duration of therapy specified [8]).

[2]The EMA SmPC for nivolumab specifies that nivolumab, when used in combination with ipilimumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient (and up to maximum duration of therapy if specified for an indication). However, no such maximum duration of therapy is specified for the IpiNivo aRCC indication [3].

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the efficacy and safety profiles of IpiNivo demonstrated in the CheckMate 214 trial are based on a setting where the 2-year stopping rule did **not** exist. In other words, in the DMC's base case analysis, the efficacy modelled for IpiNivo is not being costed, as the CheckMate 214 data reflect a patient population in which a considerable proportion of patients continued treatment with nivolumab much longer than two years[3]. Without implementing any effect of the treatment capping on the efficacy profile of IpiNivo, the DMC assumes that any nivolumab treatment administered after 2 years in the CheckMate 214 trial would have had zero benefit for the patients. This assumption is to be considered clinically implausible and no data is available to support it. It should be noted that, in contrast to the CheckMate 214 trial, a maximum 2-year duration of nivolumab treatment **was** specified in the CheckMate 9ER trial, and the clinical trial data for CaboNivo therefore reflects this setting. Thus, the approach taken by the DMC ultimately results in a biased comparison of the efficacy and costs of IpiNivo compared to CaboNivo, and we also request this approach to be reconsidered. As an alternative, we strongly urge the DMC to base the recommendation of CaboNivo in 1L aRCC on the results of a HE analysis **without** a 2-year stopping rule for IpiNivo, reflecting the highest level of certainty. Reluctance to assess our case without the 2-year stopping rule for IpiNivo would demand us to request to include treatment efficacy reduction assumptions for IpiNivo, even though we understand the complexity, simply because the current approach chosen by the DMC is not acceptable from a scientific nor a health technology assessment perspective.

Of critical importance for this discussion is also that we have consulted a Danish clinical expert to understand more fully the actual clinical practice for IpiNivo treatment in Denmark. The clinical expert described that, even though the standard practice is to stop nivolumab treatment after 2 years, it is also clinical praxis in Denmark to re-initiate the treatment with nivolumab if the disseminated kidney cancer starts to grow after the 2-year stopping rule for nivolumab has been implemented. Therefore, the clinical expert confirmed that a substantial number of patients who are stopped due to the 2-year stopping rule will be re-initiated on nivolumab, meaning that the DMC's assumption is not even fully reflective of true clinical practice.

**Summary**

The DMC's base case ICER of approx. 772 mio. DKK/QALY (AIP level) is extremely overestimated due to highly questionable approaches leading to extreme underestimation of incremental QALYs (0.001) and extreme overestimation of incremental costs for CaboNivo vs. IpiNivo (approx. 1,000,000 DKK). The ICER level appears unbelievable considering our base case ICER of approx. 1.46 mio. DKK/QALY (AIP level), based on a QALY gain of 0.125 and incremental costs of approx. 182,000 DKK. Important to note is also that when comparing the DMC's base case analysis results in our case to those in the DMC's analysis for LenPem in 1L aRCC, CaboNivo leads to a higher total QALY value (CaboNivo: 3.59, LenPem: 3.28) in the comparison to IpiNivo. The higher total QALY value for IpiNivo in our case is therefore the main factor driving the extreme ICER, which seems misleading.

In the respect of both patients and clinicians, we encourage the DMC to reconsider their approaches in evaluating the TKI+IO combinations in aRCC to be more balanced and respectful of the existing data. We are aware that DaRenCa submitted a letter to the DMC following the negative decision on LenPem in 1L aRCC in December last year, criticizing the DMC's approach to the evidence on the TKI+IO combinations and highlighting the fact that Denmark is now the only country in Western Europe where no TKI+IO combinations are available. Furthermore, the DMC has on several occasions acknowledged that not all intermediate/poor risk patients are eligible for IpiNivo and that TKI+IO treatment is also an important option here. This population of IpiNivo ineligible patients **was** included in our DMC application, using the currently available clinical trial evidence for CaboNivo. However, the DMC has decided to exclude this population from the assessment report completely, leaving no new hope for a vulnerable patient population for which TKI monotherapy is the only treatment option currently available. Ipsen can only fully support all the views expressed by DaRenCa and hope for a change in the DMC's approaches, using the CaboNivo case as the first example.

[3] Regan et al. have reported that 14% of patients in the IpiNivo arm in the CheckMate 214 trial still remained on nivolumab treatment at 42 months [9], and according to Albiges et al., with a further median follow-up of 55 months, 10% of patients remained on treatment with nivolumab [10].

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25.04.2023

DBS og CAF

# Forhandlingsnotat

| | |
|---|---|
| Dato for behandling i Medicinrådet | 26.04.2023 |
| Leverandør | Ipsen |
| Lægemiddel | Cabometyx (cabozantinib) + Opdivo (nivolumab) |
| Ansøgt indikation | Cabozantinib i kombination med nivolumab til behandling af metastatisk nyrekræft |
| Nyt lægemiddel / indikationsudvidelse | Indikationsudvidelse |

## Prisinformation

Amgros har følgende aftalepris på Cabometyx og Opdivo:

*Tabel 1: Aftalepris Cabometyx*

| Lægemiddel | Styrke | Pakningsstørrelse | AIP (DKK) | Nuværende SAIP (DKK) | Rabatprocent ift. AIP |
|---|---|---|---|---|---|
| Cabometyx (cabozantinib) | 20 mg | 30 stk. | 49.400 | [redacted] | [redacted] |
| Cabometyx (cabozantinib) | 40 mg | 30 stk. | 49.400 | [redacted] | [redacted] |
| Cabometyx (cabozantinib) | 60 mg | 30 stk. | 49.400 | [redacted] | [redacted] |

*Tabel 2: Aftalepris Opdivo*

| Lægemiddel | Styrke | Pakningsstørrelse | AIP (DKK) | Nuværende SAIP (DKK) | Rabatprocent ift. AIP |
|---|---|---|---|---|---|
| Opdivo (nivolumab) | 40 mg/4 ml | 1 stk. | 3.508,46 | [redacted] | [redacted] |
| Opdivo (nivolumab) | 100 mg/10 ml | 1 stk. | 8.715,54 | [redacted] | [redacted] |
| Opdivo (nivolumab) | 120 mg/12 ml | 1 stk. | 10.458,66 | [redacted] | [redacted] |
| Opdivo (nivolumab) | 240 mg/24 ml | 1 stk. | 20.917,31 | [redacted] | [redacted] |

## Aftaleforhold

[redacted]

## Konkurrencesituationen

Cabometyx indgår i behandlingsvejledningen for nyrekræft, og er 1. valg i 2. linje til behandling af patienter med clearcelle mRCC, der opfylder opstartskriterierne, og som har modtaget immunterapi i 1. linje.

Tidligere har Medicinrådet vurderet Kisplyx (lenvatinib) i kombination med Keytruda (pembrolizumab), Bavencio (avelumab) i kombination med Inlyta (axitinib) og Keytruda (pembrolizumab) i kombination med Inlyta (axitinib) til behandling af metastaserende nyrekræft, men ingen af disse er anbefalet.

*Tabel 3: Sammenligning af lægemiddeludgifter*

| Lægemiddel | Styrke | Pakningsstørrelse | Dosering | Pris pr. pakning (SAIP, DKK) | Lægemiddeludgift for 40 ugers behandling (SAIP, DKK) | Kombinationsbehandling – 40 ugers behandling |
|---|---|---|---|---|---|---|
| Cabometyx (cabozantinib) | 40 mg | 30 stk. | 40 mg PO/dag | [redacted] | [redacted] | [redacted] |
| Opdivo (nivolumab) | 240 mg/24 ml | 1 stk. | 6 mg/kg hver 4. uge | [redacted] | [redacted]* | |
| Yervoy (ipilimumab) | 5 mg/ml | 40 ml | 1 mg/kg IV/3. uge 4 gange | [redacted] | [redacted] | [redacted] |
| Opdivo (nivolumab) | 240 mg/24 ml | 1 stk. | 3 mg/kg IV/3. uge 4 gange og herefter 6 mg/kg IV/4. uge | [redacted] | [redacted] | |
| Kisplyx (lenvatinib) | 10 mg | 30 stk. | 20 mg PO/dag | [redacted] | [redacted] | [redacted] |
| Keytruda (pembrolizumab) | 25 mg/ml | 4 ml | 4 mg/kg IV hver 6. uge | [redacted] | [redacted] | |

*gennemsnitsvægt 79,8 kg.

## Status fra andre lande

| Land | Status | Kommentar | Link |
|---|---|---|---|
| Norge | Anbefalet | Nivolumab + ipilimumab, nivolumab + kabozantinib, pembrolizumab + aksitinib, pembrolizumab + lenvatinib og avelumab + aksitinib vil bli sammenlignet med hverandre for førstelinjebehandling av nyrecellekarsinom | /Metodevurderinger/Cabometyx+Opdivo_1.linjebehandling avansert nyrecellekarsinom_2021 |
| England | Anbefalet | | https://www.nice.org.uk/guidance/indevelopment/Cabozantinib with nivolumab |

Konklusion

[redacted]

# Application for the assessment of CABOMETYX® (cabozantinib) in combination with OPDIVO® (nivolumab) for first-line treatment of patients with advanced renal cell carcinoma (aRCC)



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# Table of contents






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[redacted]

# 1. Basic information

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| Overview of the pharmaceutical [1, 2] | |
|---|---|
| **Proprietary name** | CABOMETYX® in combination with OPDIVO®. |
| **Generic name** | Cabozantinib in combination with nivolumab. |
| **Marketing authorization holder in Denmark** | Ipsen (CABOMETYX®) & Bristol-Myers Squibb (OPDIVO®). |
| **ATC code** | L01EX07 (CABOMETYX®) & L01XC17 (OPDIVO®). |
| **Pharmacotherapeutic group** | CABOMETYX®: Antineoplastic agent, protein kinase inhibitor.<br>OPDIVO®: Antineoplastic agent, monoclonal antibody. |
| **Active substance(s)** | Cabozantinib and nivolumab. |
| **Pharmaceutical form(s)** | Oral tablet (CABOMETYX®), concentrate solution for intravenous (IV) infusion (OPDIVO®). |
| **Mechanism of action** | **Cabozantinib** inhibits multiple receptor tyrosine kinases involved in tumour growth, angiogenesis and metastatic progression of cancer including MET (hepatocyte growth factor receptor protein), AXL (GAS6 receptor), and vascular endothelial growth factor receptor (VEGFR). It is the only approved TKI that, in addition to VEGFR, targets both MET and AXL receptors, which play an important role in the emergence of resistance mechanisms to anti-VEGFR inhibitors.<br>**Nivolumab** is a human monoclonal antibody that targets the PD-1 receptor and blocks its interaction with its ligands, PD-L1 and PD-L2. Tumours use PD-L1 expression as defence or escape mechanism against the host's anti-tumour T cell response; inhibiting PD-L1 restores the function of these anti-tumour T cells which have become ineffective or suppressed. Therefore, the efficacy of PD-L1 inhibition relies on a pre-existing immune response. |

| Overview of the pharmaceutical [1, 2] | |
|---|---|
| **Dosage regimen** | Cabozantinib is administered 40 mg orally (PO) once daily (QD) in combination with nivolumab 240 mg every 2 weeks (Q2W) or 480 mg every 4 weeks (Q4W) IV (30 minutes IV infusion). |
| **Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)** | First-line treatment of adult patients with advanced renal cell carcinoma (RCC). The European Commission approved cabozantinib in combination with nivolumab for this indication on April 21, 2021. |
| **Other approved therapeutic indications** | CABOMETYX® in combination with OPDIVO® has no other approved indication but both individual treatment options have several. |
| **Will dispensing be restricted to hospitals?** | Yes. |
| **Combination therapy and/or co-medication** | Yes, CABOMETYX® in combination with OPDIVO®. |
| **Packaging – types, sizes/number of units, and concentrations [3]** | **Cabozantinib:**<br>Type: Film-coated tablets.<br>Package size (regardless of concentration): 30 tablets.<br>Concentrations: 20, 40 and 60 mg.<br><br>**Nivolumab:**<br>Type: concentrate solution for IV infusion.<br>Concentration: each ml of concentrate contains 10 mg nivolumab. |
| **Orphan drug designation** | No. |

# 2. Abbreviations

**List of abbreviations and definition of terms**

| | |
|---|---|
| 1L | First-line |
| 2L | Second-line |
| 3L | Third-line |
| AE | Adverse event |
| aRCC | Advanced renal cell carcinoma |
| Ave/Axi | Avelumab + Axitinib combined therapy |
| Axi/Pembro | Axitinib + Pembrolizumab combined therapy |
| AXL | Receptor tyrosine kinase for GAS6 |
| BICR | Blinded independent central review |
| BMS | Bristol Myers-Squibb |
| BOR | Best overall response |
| Cabo/Nivo | Cabozantinib + Nivolumab combined therapy |
| ccmRCC | Clear cell metastatic renal cell cancer |
| ccRCC | Clear cell renal cell carcinoma |
| CE | Cost-effectiveness |
| CHMP | The Committee for Medicinal Products for Human Use |
| CI | Confidence interval |
| CPI | Checkpoint inhibitor |
| CR | Complete response |
| CTLA-4 | Cytotoxic T-lymphocyte-associated protein 4 |
| CUA | Cost-utility analysis |
| DBL | Database lock |
| DMC | Danish Medicines Council |
| DoR | Duration of response |
| EMA | European Medicines Agency |
| EQ-5D | EuroQol Health Questionnaire Instrument |
| ESMO | European Society of Medical Oncology |
| FDA | Food and Drug Administration |
| FKSI | Functional Assessment of Cancer Therapy-Kidney Symptom Index |
| GAS6 | Growth-arrest specific gene 6 |
| GIST | Gastrointestinal stromal tumour |
| HE | Health economic |
| HGF | Hepatocyte growth factor |
| HR | Hazard ratio |
| HRQoL | Health-related quality-of-life |
| HSUV | Health state utility value |
| HTA | Health technology assessment |
| ICER | Incremental cost-effectiveness ratio |
| IFN-α | Interferon-α |
| IMAE | Immune-mediated adverse event |
| IMDC | International Metastatic Renal Cell Carcinoma Database Consortium |
| Ipi/Nivo | Ipilimumab + Nivolumab combined therapy |
| ITT | Intention-to-treat |
| IV | Intravenous |
| KM | Kaplan-Meier |
| MET | Receptor tyrosine kinase for HGF |
| mRCC | Metastatic renal cell carcinoma |
| MSKCC | Memorial Sloan Kettering Cancer Centre |
| NCCN | National Comprehensive Cancer Network |
| nccRCC | Non-clear cell renal cell carcinoma |

| | |
|---|---|
| NCI | National Cancer Institute |
| NMA | Network meta-analysis |
| NS | Not significant |
| OESI | Other event(s) of special interest |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progressed disease |
| PD-1 | Programmed cell death immune receptor |
| PD-L1 | Programmed cell death ligand 1 |
| PF | Progression-free |
| PFS | Progression-free survival |
| PFS-2 | Progression-free survival after next line of treatment |
| PPES | Palmar-plantar erythrodysaesthesia syndrome |
| PR | Partial response |
| PRO | Patient reported outcomes |
| Q2W | Administration every 2 weeks |
| Q4W | Administration every 4 weeks |
| QALY | Quality-adjusted life year |
| QD | Administration once daily |
| QoL | Quality-of-life |
| RCC | Renal cell carcinoma |
| RCT | Randomised control trial |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| RTK | Receptor tyrosine kinase |
| SAE | Serious adverse event |
| SD | Stable disease |
| SE | Standard error |
| SLR | Systematic literature review |
| TKI | Tyrosine kinase inhibitor |
| TTR | Time to response |
| US | United States (of America) |
| UTD | Unable to determine |
| VAS | Visual analogue scale |
| VEGF | Vascular endothelial growth factor |
| VEGFR | Vascular endothelial growth factor receptor |
| Vs. | Versus |

# 3. Tables and figures

**List of tables**





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## Appendix tables

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## List of figures





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## Appendix figures

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# 4. Summary

## 4.1 The disease: Renal cell carcinoma

Renal cell carcinoma (RCC) is the most common type of kidney cancer and accounts for approximately 1.8% of all cancer deaths and 3% of all new cancer cases per year globally.[4] In Denmark, the incidence is around 900-950 cases annually. The incidence is around 1.8 times more prevalent in men than in women.[5, 6]

In its early stages, RCC is asymptomatic or presents with unspecific symptoms at disease onset.[7, 8] Patients with metastatic (m)RCC experience rapid disease progression, heightening their already declining performance, quality-of-life (QoL) deterioration, and poor prognosis.[9-11] According to the European Society of Medical Oncology (ESMO), the 5-year overall survival (OS) is 32% in patients in the low-risk prognostic category and 19.5% in the intermediate-risk category.[12-15]

Advanced RCC (aRCC) requires a variety of therapeutic options to allow for treatment approaches that take into account both the patient's and the tumour's characteristics.[16, 17] Sunitinib has been the standard of care in advanced (a)RCC for over a decade and is the most widely used approved first-line (1L) therapy.[18-22] Prior to the approval of the immune checkpoint inhibitor (CPI) combinations, 1L monotherapy agents had not demonstrated significant OS improvement over sunitinib.[2, 23-27] In 2019, ipilimumab and nivolumab (Ipi/Nivo, a combination of two CPIs) was approved for the management of intermediate and poor risk aRCC patients. Approval was based on the demonstration of significant OS improvement (hazard ratio [HR]=0.63, p<0.001).[1]

## 4.2 The intervention: Cabozantinib + Nivolumab

Cabometyx® (cabozantinib; oral tablets) is a tyrosine kinase inhibitor agent (TKI), targeting multiple receptors. Cabozantinib targets both angiogenesis and tumour progression with a unique mode of action and therefore shows a key advantage over other TKIs used in 1L RCC that mainly inhibit the vascular endothelial growth factor receptor (VEGFR) signal pathway. Cabozantinib is being developed as a new 1L treatment for aRCC in combination with nivolumab (a human monoclonal antibody that targets the programmed cell death immune [PD-1] receptor); this combination will hereafter be referred to as "Cabo/Nivo". Considering the need for improved benefit over standard of care in the 1L setting regardless of prognostic group, Bristol Myers-Squibb (BMS) initiated the CheckMate 9ER study to assess the efficacy and safety of Cabo/Nivo in 1L aRCC treatment which serves the basis for this submission.

## 4.3 Indication/population covered in the application and comparators

According to the most recent label issued by the European Medicines Agency (EMA), the indication of Cabometyx® is now extended to also include the combination with nivolumab (Cabo/Nivo) in aRCC patients regardless of IMDC prognostic risk group (i.e., favourable, intermediate, and poor). This reflects the study population in the pivotal CheckMate 9ER phase 3 clinical trial. [2] However, as described below, the current application focuses on two separate subgroups of patients with IMDC intermediate/poor prognostic risk.

In Denmark, the standard treatment for patients in the IMDC favourable prognostic group is TKI monotherapy, and for patients in the IMDC intermediate/poor prognostic group, the standard treatment is double checkpoint immunotherapy with Ipi/Nivo. For IMDC intermediate/poor risk patients who do not tolerate Ipi/Nivo, tivozanib, pazopanib, sunitinib and cabozantinib monotherapy are considered clinically-equivalent alternatives [28, 29], with sunitinib being the preferred choice based on price [30]. Thus, patients with IMDC intermediate/poor risk can be divided in two different subpopulations based on their tolerability to treatment with Ipi/Nivo: an Ipi/Nivo eligible patient population where Ipi/Nivo is current standard treatment, and an Ipi/Nivo ineligible patient population where TKI monotherapy is current standard treatment. Cabo/Nivo is not only a relevant treatment alternative for patients who do tolerate Ipi/Nivo, but also for patients who do not, as it is expected that Cabo/Nivo will be an alternative treatment option for approximately 20% of these patients [31] (please see section 5.2 for a more detailed description of the patient populations relevant

for this application). Furthermore, both of these patient populations have a significant unmet need for an effective, tolerable new option which improves OS, delays disease progression and improves disease control, while maintaining or improving patients' QoL. Consequently, the following two clinically relevant target populations are covered in the current application:

1. *IMDC intermediate/poor prognostic risk patients who are eligible for Ipi/Nivo treatment*
2. *IMDC intermediate/poor prognostic risk patients who are ineligible for Ipi/Nivo treatment but eligible for Cabo/Nivo treatment*

In the Ipi/Nivo eligible patient population, Ipi/Nivo is currently the only standard treatment recommended, meaning that it is the only appropriate comparator treatment in this population. In the Ipi/Nivo ineligible patient population, TKI monotherapy (tivozanib, pazopanib and sunitinib) would theoretically be the relevant comparators, but as these treatments are considered clinically equivalent, comparison of Cabo/Nivo to one of these treatments (sunitinib) is considered representative of comparison to the other alternatives. Further, of the TKI monotherapies available as comparators, the Danish Medicines Council (DMC's) drug recommendation specifies that sunitinib is the preferred choice, and comparison of Cabo/Nivo with sunitinib will provide the strongest quality of evidence, as the CheckMate 9ER trial comparing Cabo/Nivo with sunitinib is the only head-to-head study available with a direct comparison of Cabo/Nivo to one of these TKIs.

## 4.4 CheckMate 9ER trial

The CheckMate 9ER trial was a robust, multicentre, multinational, randomized phase III control trial which included 651 1L aRCC patients. It was designed to compare the efficacy and safety of Cabo/Nivo vs. sunitinib. The primary endpoint was progression-free survival (PFS), as determined by blinded independent central review (BICR). Secondary endpoints included OS, objective response rate (ORR) as determined by BICR (including also duration of response [DOR] and time to response [TTR]), and safety. Health-related quality-of-life (HRQoL) was an exploratory endpoint. The overall efficacy results include the primary and secondary endpoints in all randomised subjects (intention-to-treat [ITT] population) at three different database locks (DBL): DBL 30 March, 2020 with median follow up for OS of 18.1 months, DBL 10 Sept, 2020 with median follow up for OS of 23.5 months and DBL 24 June, 2021 with median follow up for OS of 32.9 months. To reflect the anticipated position of Cabo/Nivo in the Danish clinical setting (IMDC intermediate/poor risk patients), efficacy results from the IMDC intermediate/poor subgroup are presented in detail in this application. Data from the ITT population are also presented in the application for reference. The application generally includes data from the third, most recent DBL and from the first DBL, which serve to demonstrate that results with longer follow-up confirm those from the original analyses.

The CheckMate 9ER trial met all study endpoints, and a summary of the results is presented here:

In all randomized subjects, the primary endpoint of PFS per BICR and both secondary endpoints (OS and ORR per BICR) were statistically significant for Cabo/Nivo vs. sunitinib, indicating substantial response and improved disease control and demonstrating improved survival. The favourable OS and PFS outcomes were consistent across all subgroups analysed (see Table A 15 [32-34]. The results from DBL March 30, 2020 were confirmed at DBL June 24, 2021, where Cabo/Nivo continued to show both PFS, OS and ORR benefits over sunitinib. [35]

Efficacy results for the IMDC intermediate/poor risk subgroup at DBL June 24, 2021 were as follows:

- Median PFS for Cabo/Nivo was [redacted]
- Median OS was reached in the sunitinib treatment group at 29.47 months, and at 37.6 months in the Cabo/Nivo arm. Relative difference in effect: HR=0.66, 95% CI: 0.50, 0.85, p=0.002 [37]. [redacted]

- ORR was 52.6% [redacted] 23.8% [redacted] for Cabo/Nivo vs. sunitinib, respectively. Relative difference in effect: OR: [redacted] and absolute difference in effect: [redacted]
- Median DOR was [redacted], for Cabo/Nivo vs. sunitinib, respectively [36], and median TTR was [redacted], for Cabo/Nivo vs. sunitinib, respectively [36].

In the overall safety population, Cabo/Nivo demonstrated a clinically acceptable safety and tolerability profile, and treatment-related adverse events (AE) were manageable. The safety profile of Cabo/Nivo was as expected on the basis of the known profile of the two potent agents as monotherapies, without any new safety signals. [redacted] Since the primary analysis (DBL March 30, 2020), no new deaths that investigators considered to be related to treatment occurred with Cabo/Nivo; one additional death that was considered to be related to treatment occurred with sunitinib (sudden death) [35].

HRQoL results from the CheckMate 9ER trial was published by Cella *et al.*, describing the patient-reported outcome (PRO) of the trial at DBL, Sept 10, 2020, [41], and updated results from DBL June 24, 2021, were recently presented [42]. Disease-related symptoms were evaluated using the Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI-19), and global health status was assessed by the three-level EuroQol Health Questionnaire Instrument (EQ-5D-3L). Based on the most recent data from DBL June 24, 2021, change from baseline in PRO scores indicated that Cabo/Nivo was associated with more favourable outcomes vs. sunitinib (treatment difference 2.37 (95% CI: 1.19, 3.54), nominal p<0.0001 for FKSI-19 total score; treatment difference 1.17 (95% CI: 0.68, 1.66), nominal p<0.0001 for FKSI-19 disease-related symptoms (DRS) version 1; treatment difference 3.68 (95% CI: 1.83, 5.54), nominal p=0.0001 for EQ-5D-3L visual analogue scale (VAS); and treatment difference 0.05 (95% CI: N/A), nominal p=0.001 for EQ-5D-3L UK utility index), reaching significance at most timepoints. Overall, PROs were maintained or improved with Cabo/Nivo vs. sunitinib and significantly delayed time to deterioration of PRO scores, suggesting a benefit for Cabo/Nivo compared with sunitinib, with the additional benefit of improved HRQoL being maintained with longer follow-up. [42, 43]

In summary, in the CheckMate 9ER Phase III trial, Cabo/Nivo significantly improved survival, delayed disease progression, increased both ORR and DOR and shortened TTR in comparison to sunitinib, while maintaining or improving QoL. The benefits on OS and PFS were consistent across all subgroups analysed (see Table A 15). Cabo/Nivo demonstrated an acceptable safety and tolerability profile, and treatment-related AEs were manageable. The positive results of CheckMate 9ER prompted the inclusion of Cabo/Nivo in the ESMO guidelines as a 1L therapy in aRCC. [44]

## 4.5 CheckMate 214

CheckMate 214 was a randomized, open-label, phase 3 trial of nivolumab plus ipilimumab followed by nivolumab monotherapy versus sunitinib monotherapy, with the purpose to compare the ORR (with DOR) , PFS and OS in patients with previously untreated advanced RCC. Randomization (in a 1:1 ratio) was performed with a block size of 4 with stratification according to IMDC risk score (0 vs. 1 or 2 vs. 3 to 6) and geographic region (United States vs. Canada and Europe vs. the rest of the world). Efficacy was assessed in ITT, IMDC intermediate/poor risk, and favourable risk populations.

In summary, based on the data from the most recent DBL (24 February, 2021), with a median follow-up of 67.7 months, Ipi/Nivo showed benefits over sunitinib with respect to PFS, OS, ORR and HRQoL in patients with previously untreated aRCC. Efficacy results for the IMDC intermediate/poor risk population were as follows:

- Median PFS was 11.6 (95% CI: 8.4, 16.5) vs. 8.3 (95% CI: 7.0, 10.4) months for Ipi/Nivo vs. sunitinib. [45]
- Median OS was 47.0 (95% CI: 35.4, 57.4) months in the Ipi/Nivo arm vs. 26.6 (95% CI: 22.1, 33.5) months in the sunitinib arm, HR=0.68 (95% CI: 0.58-0.81), p<0.0001. [45]
- ORR was 42.1% (95% CI: 37.4, 47.0) vs. 26.8% (95% CI: 22.6, 31.3) for Ipi/Nivo vs. sunitinib. [45]
- Median TTR was 2.8 (IQR: 2.6, 3.8) months for Ipi/Nivo and 3.1 (IQR: 2.8, 5.4) months for sunitinib. [45]
- Median DOR was not reached (95% CI: 50.9, NE) for Ipi/Nivo and 19.7 (95% CI: 15.4, 25.1) months for sunitinib. [45]

There is no head-to-head study comparing Cabo/Nivo and Ipi/Nivo in the treatment of aRCC. An indirect treatment comparison was therefore undertaken to explore the relative treatment efficacy and safety of these treatments based on aggregated data from the CheckMate 9ER and CheckMate 214 trials, which shared sunitinib as the common comparator.

## 4.6 Health economic analysis

A partitioned-survival model was used to assess long-term costs and effects associated with Cabo/Nivo compared with sunitinib and Ipi/Nivo treatment, respectively, in the management of aRCC. For the comparison with sunitinib, patient-level survival data for PFS and OS from the CheckMate 9ER trial were extrapolated by fitting the data to parametric survival models and selecting the best-fit models. For the comparison with Ipi/Nivo, PFS and OS curves were modelled based on a fractional polynomial (FP) network-meta analysis (NMA) which included the CheckMate 9ER and CheckMate 214 studies with sunitinib as the common comparator (the network also included two additional studies which had no influence on the Cabo/Nivo and Ipi/Nivo survival curves, as shown in Appendix G). In both comparisons, data for the IMDC intermediate/poor prognostic risk subpopulations was used. The analysis was performed over a lifetime horizon, with 1-week cycles during the first 24 months to capture short-term health effects and fit with the dosing schedules of the treatments, followed by 6-month cycles beyond 24 months to make the model calculations more efficient in the longer-term of this lifetime model. Health effects were estimated as quality-adjusted life years (QALYs). HRQoL data were collected in the CheckMate 9ER trial using the EQ-5D-3L instrument, which were mapped to the five-level EQ-5D (EQ-5D-5L) and recalibrated with the Danish tariff-weighting algorithm [46] to generate health-state HRQoL utilities for the model. Adverse event rates were based on CheckMate 9ER and CheckMate 214 trial data. The cost analysis was performed to reflect the Danish setting, applying unit costs from local price lists of drugs and health care resources used. Pharmaceutical, hospital, adverse event, second line treatment, and patient costs were considered in the model.

The cost-effectiveness (CE) analysis comparing Cabo/Nivo with sunitinib indicated that treatment with Cabo/Nivo is expected to generate [redacted] incremental QALY and [redacted] life years. The additional cost with Cabo/Nivo treatment was [redacted] which generated an incremental CE ratio (ICER) of [redacted] with Cabo/Nivo as compared with sunitinib treatment over a lifetime horizon. [redacted].

The CE analysis comparing Cabo/Nivo with Ipi/Nivo indicated that treatment with Cabo/Nivo is expected to generate 0.125 incremental QALY and 0.161 life years. The additional cost with Cabo/Nivo treatment was DKK 182,483 which generated an ICER of DKK 1,461,841 per QALY gained with Cabo/Nivo as compared with Ipi/Nivo treatment over a lifetime horizon. Deterministic and probabilistic sensitivity analyses suggested that the CE results were robust and indicated that the most influential parameter was baseline age where higher ages were associated with higher ICERs.

The budget impact analysis was based on an estimated number of up to [redacted] receiving Cabo/Nivo treatment annually. Cabo/Nivo was estimated to generate an additional annual health care expenditure of around [redacted] five years from now, if recommended as a treatment for the suggested patient populations. Budget impact scenario analyses indicated that recommending Cabo/Nivo as standard treatment only for target population 1 (IMDC intermediate/poor prognostic risk patients who are eligible for Ipi/Nivo treatment) or target population 2 (IMDC intermediate/poor

prognostic risk patients who are ineligible for Ipi/Nivo treatment but eligible for Cabo/Nivo treatment) would be associated with a budget impact 5 years from now of [redacted] and [redacted] respectively.

## 4.7 Conclusion

While there have been advances in the treatment of aRCC, there remains a need for effective, tolerable therapeutic options which improve OS, delay progression, and improve disease control. In the CheckMate 9ER trial, Cabo/Nivo significantly improved OS, delayed disease progression, and increased ORR vs. sunitinib while maintaining or improving QoL. The favourable OS and PFS outcomes were consistent across all subgroups analysed (see Table A 15). The safety profile of Cabo/Nivo was as expected on the basis of the known profile of the two potent agents as monotherapy, without any new safety signals. Recently presented results on HRQoL indicated that for patients with aRCC, treatment with Cabo/Nivo was associated with maintenance or improvement of HRQoL in contrast to treatment with sunitinib.[41]

In Denmark, the two patient populations expected to use Cabo/Nivo are (1) patients with IMDC intermediate/poor prognostic risk who are eligible for Ipi/Nivo treatment and (2) patients with IMDC intermediate/poor prognostic risk who are ineligible for Ipi/Nivo treatment but eligible for Cabo/Nivo treatment. These patient populations are clinically relevant target populations for the current application as it is expected that Cabo/Nivo will be an alternative treatment option for the full population of Ipi/Nivo eligible patients, but also for approximately 20% of the Ipi/Nivo-ineligible patient population, corresponding to approximately 84% of the total population of IMDC intermediate/poor risk patients receiving 1L treatment. [31]

The results of the CE analyses comparing Cabo/Nivo with sunitinib and Ipi/Nivo, respectively, indicate that by delaying the progression of the disease and extending survival, Cabo/Nivo is a superior treatment option to both comparators. Better clinical outcomes with Cabo/Nivo in terms of improved survival as well as improved HRQoL to the patients generated a higher number of QALYs, with a larger difference demonstrated in the comparison with sunitinib. These patient populations have a significant unmet need for an effective, tolerable new option which improves OS, delays disease progression and improves disease control, while maintaining or improving patients' QoL. The recommendation of Cabo/Nivo as a standard treatment would therefore be a valuable contribution to the treatment alternatives currently available for these patient populations.

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

## 5.1 The medical condition and patient population

### 5.1.1 Renal cell carcinoma

Renal cell carcinoma (RCC) accounts for 85% to 90% of all kidney malignancies.[9-11] The most common and most aggressive RCC subtype is clear cell (cc)RCC, which accounts for 75%-90% of RCC tumours [12, 14, 15, 47]. RCC is a slow-progressing tumour with a relatively late onset of symptoms, making it difficult to diagnose. While few patients (6–10%) present with a classic triad of flank pain, gross haematuria (visible blood in urine), and palpable abdominal mass, the majority of patients are asymptomatic or exhibit nonspecific symptoms such as fatigue, weight loss, or anaemia.[7] Consequently, RCC is often diagnosed incidentally, typically during an abdominal ultrasound or a computerized tomography scan prescribed for other medical reasons. [9, 48] As a result of delayed diagnosis, a considerable proportion of RCC patients (between 25% and 40% of cases) present with disease that has already progressed to advanced stages.[49-53]

RCC metastasize most commonly in the lung, bone, lymph nodes, and liver [54]. By affecting vital organs such as these, metastatic disease increases the symptom burden, leading to significant morbidity and poor prognosis (Table 1). Between 20%-50% of patients diagnosed at early stages progress to metastatic cancer following surgical resection; in Denmark, it is reported that approximately 20% of RCC patients undergoing surgical resection will experience metastatic relapse [28]. Advanced (a)RCC or metastatic (m)RCC are currently incurable. In a Swedish population-based study, 3- and 5-year survival rates for patients diagnosed with advanced RCC (aRCC) were estimated at 21% and 13%, respectively [55]. The 5-year age-standardized survival from diagnosis for patients with distant metastatic disease (stage IV) is less than 10% [56]. To better understand the risks associated with the outcomes, a number of prognostic models have been developed, including the Memorial Sloan Kettering Cancer Centre (MSKCC) criteria model and the International Metastatic RCC Database Consortium (IMDC) model.[57] The latter was developed based on 6 adverse prognostic factors categorized into favourable risk (0 factors), intermediate risk (1-2 factors), and poor risk (3-6 factors) groups. The majority (at least 80%) of mRCC patients are classified as intermediate and poor risk per the IMDC model. [57] These patients have poorer prognosis compared with those in the favourable risk group, as reported from large real-world data sets (Table 1). [57, 58]

**Table 1: Survival of metastatic RCC patients**

| | Overall survival, median (95% CI) | Progression-free survival, median (95% CI) |
|---|---|---|
| **Untreated patients** | 9.2 months (9.7 for patients treated with non-tyrosine kinase inhibitors)<br>(population-based study)[55] | 3 months<br>(phase III trial placebo arm of treatment-naïve subgroup; n=78)[59] |
| **Patients receiving 1L targeted therapy** | | |
| **All risk categories** | 20.9 months (19.6, 22.5)<br>(real-world data from the IMDC reports) [58] | 7.2 months (6.7, 7.7)[58] |
| **Favourable risk** | 43.2 months (31.4, 50.1)<br>(IMDC Consortium database)[57] | -- |
| **Intermediate and poor risk** | 14.7 (13.3, 16.5) [58] | 5.6 months (5.3, 6.1) [58] |

According to the European Society of Medical Oncology (ESMO), the 5-year overall survival (OS) is 32% in patients in the low-risk prognostic category and 19.5% in the intermediate-risk category [47]. In recent real-world studies, the median OS was reported to be 39.7 months in the IMDC favourable risk patients and 6.1 months in the poor risk category [19, 21, 60]. In Denmark, the median survival with targeted treatment has been reported to be almost 4 years for favourable risk patients, 2 years for intermediate risk patients and less than 1 year for poor risk patients [28].

Patients with mRCC generally experience rapid disease progression, strongly impacting their already declining performance, QoL, and poor prognosis.[57] In clinical practice, approximately half (42% - 65%; in Denmark approx. 55%) of first-line (1L) patients receive a second-line (2L) therapy and 16% of those progress to a third-line (3L) treatment [30, 61-66]. Thus, it is expected that between 35-58% of aRCC patients will only receive one line of therapy [61-66], which highlights the need to maximise survival benefits of the 1L therapy.

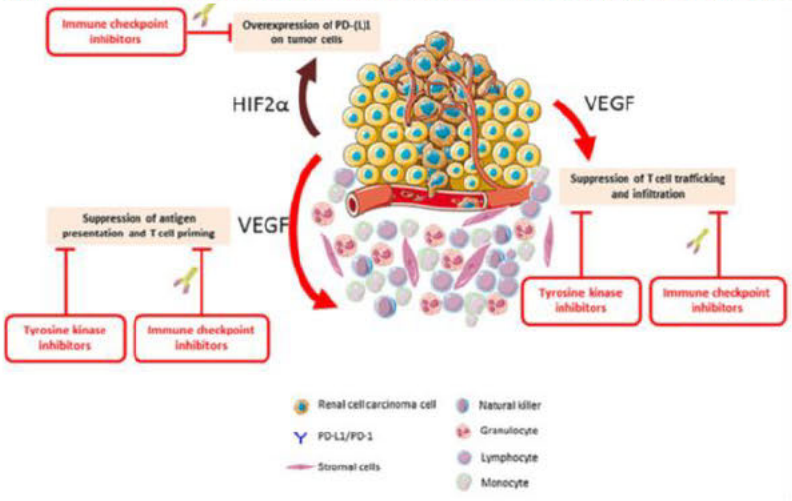
### 5.1.2 Molecular pathways involved in renal cell cancer tumourigenesis

RCC is a heterogeneous disease caused by a multitude of environmental and genetic factors.[14, 67] Identification of the diverse factors involved in renal cell tumourigenesis has led to the development of targeted therapies.[68] Among genetic alterations in RCC, the most recognized is inactivation of the *VHL* tumour suppressor gene, which causes approximately 60% of clear cell tumours [7, 68]. *VHL* inactivation plays a pivotal role in tumour development of clear cell RCC (ccRCC), and involves several signalling pathways [68]. In normal cells, VHL suppresses the transcription of pro-angiogenic and growth factors; in the absence of normal VHL function, these factors are overexpressed, thereby promoting cell proliferation, migration, survival, and angiogenesis [69-72]. Downstream of VHL inactivation, overexpression of the vascular endothelial growth factor (VEGF) contributes to renal tumour hyper-vascularization[73] and promotion of micro vessel formation by human microvascular endothelial cultured cells.[12, 74]

VHL loss of function also results in upregulated expression of the receptor tyrosine kinases (RTK) MET (receptor for hepatocyte growth factor [HGF]) and AXL (receptor for the vitamin K-dependent protein growth-arrest-specific gene 6 [GAS6]).[72, 75] HGF/MET signalling regulates tubule formation during renal development; deregulated activation of this pathway induces cell scatter and invasion.[48, 76] AXL promotes cell growth and survival.[54, 77] Overexpression of MET and AXL in RCC was shown to promote cell growth and invasiveness and was associated with poor prognosis.[78] HGF/MET is also believed to promote tumour progression by bypassing VEGF pro-angiogenic signals and acting as an alternative angiogenic pathway. [79, 80] In addition, activation of MET and AXL have been shown to mediate *a priori* drug resistance. [78, 81]

There is an interaction between angiogenesis and immunosuppression in tumour development and progression (Figure 1).[82] VEGF inhibits the innate immune system by inducing upregulation of the Programmed cell death ligand 1 (PD-L1) expression, upregulating the expression of immune checkpoint Programmed cell death immune receptor (PD-1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) on immune cells and increasing the levels of regulatory T-cells results in maintenance of an immunosuppressive context. In addition, antiangiogenic activity leads to normalization of the tumour vasculature and hypoxia alleviation which exhibit a positive effect on immune cell infiltration into tumours.[82]

**Figure 1: The interplay between the immune system and angiogenesis in renal cell carcinoma**




*Source: Rassy 2018 [82].*
*Abbreviations: HIF2a=hypoxia-inducible factor; VEGF=vascular endothelial growth factor.*

### 5.1.3 Epidemiology

In Denmark, the incidence is around 950 new RCC cases annually and an estimated 300 patients are diagnosed with clear cell metastatic RCC (ccmRCC) each year. The median age of disease onset is 68 years and the age-standardized incidence is 16.0 per 100,000 inhabitants (21.5 for men and 9.3 for women). [5, 6]

Table 2 below shows the incidence and prevalence of renal cancer in the past 5 years.

**Table 2: Incidence and prevalence of renal cancer in the past five years**

| Year | [2015-2016] | [2016-2017] | [2017-2018] | [2018-2019] | [2019-2020] |
|---|---|---|---|---|---|
| **Incidence in Denmark** | 931 | 928 | 972 | 1,018 | 979 |
| **Prevalence in Denmark** | N/A | N/A | 8,025 (5,196 men and 2,829 women) | N/A | N/A |

*Sources: [5, 6]*

## 5.2 Patient populations relevant for this application

### 5.2.1 Patient population expected to use Cabo/Nivo in Denmark

Cabozantinib is approved for patients with aRCC on the basis of studies mostly focusing on clear-cell histology. However, a few available studies provide evidence to support the anti-tumour activity and safety of cabozantinib across non-ccRCC (nccRCC). In a recent phase II study by Lee et al., treatment with Cabo/Nivo showed promising efficacy in metastatic nccRCC patients [83]. Two further retrospective cohort studies in advanced/metastatic nccRCC showed data on the clinical activity and safety of cabozantinib, suggesting that the antitumour activity of cabozantinib is not limited to the ccRCC subgroup [84, 85]. Both Campbell et al. and Martinez Chanzá et al. are included as references for the efficacy of cabozantinib in the Danish Medicines Council (DMC's) treatment guideline for RCC [28]. Further, based on the findings by Martinez Chanzá et al., European Medicines Agency (EMA) acknowledged the inclusion of nccRCC in the

sought indication of cabozantinib. However, the evidence currently published on the use of Cabo/Nivo in nccRCC does not allow for inclusion of the non-clear-cell subpopulation specifically in this application.

As described in the application summary (see Section 4), two patient populations are expected to use Cabo/Nivo in Denmark:

1. *IMDC intermediate/poor prognostic risk patients who are eligible for Ipi/Nivo treatment*
2. *IMDC intermediate/poor prognostic risk patients who are ineligible for Ipi/Nivo treatment but eligible for Cabo/Nivo treatment*

As previously described, Ipi/Nivo is currently the only standard treatment recommended for the general patient population with IMDC intermediate/poor risk disease, i.e., Ipi/Nivo eligible patients, meaning that it would be the only appropriate comparator treatment in this population. The following points support that Cabo/Nivo is a clinically relevant alternative for the Ipi/Nivo eligible patients:

1. In the in the newest update of the ESMO Clinical Practice Guidelines for RCC, Cabo/Nivo is recommended as a first-line treatment for advanced ccRCC irrespective of IMDC risk group. In patients with IMDC intermediate/poor risk, Cabo/Nivo and Ipi/Nivo have the same level of recommendation [86].
2. A recent review by Kim and Lee [87] discusses the current evidence and clinical perspectives of frontline immunotherapy-based treatments used in aRCC. In the section discussing how to select the most appropriate first-line treatment in patients with different disease characteristics, the authors note that, for patients with intermediate/poor risk, several issues must be considered for decision making in practice and states directly that in patients with symptomatic, high disease burden who require rapid disease control, a VEGF inhibitor + checkpoint inhibitor (CPI) combination, i.e., Cabo/Nivo, can be a better option than Ipi/Nivo. It is specifically highlighted that the low progressive disease rate, which is of critical importance in patients with high tumour burden, is an important advantage of VEGF inhibitor + CPI combinations, including Cabo/Nivo. Furthermore, Cabo/Nivo makes it possible to achieve a fast response and keep the patient from progressing soon after. The authors also note that toxicity profiles are different between Ipi/Nivo and VEGF inhibitor + CPI combinations, and that Ipi/Nivo can induce higher rates of immune-related adverse events (AEs), which can be fatal and require high doses of steroids. In addition, when discussing how to choose across the different VEGF inhibitor + CPI combinations, Cabo/Nivo is highlighted to be a good option for patients who need a tolerable treatment with a good response, and it is emphasized that in particular, Cabo/Nivo showed improved quality of life compared to sunitinib.
3. In another very recent review by Ha *et al.* published in July 2022 [88], the American Society of Clinical Oncology value framework (ASCO VF) v2.0 and European Society for Medical Oncology-magnitude of clinical benefit scale (ESMO-MCBS) v1.1 were applied to evaluate the newly emerging drugs in RCC and assess their value. The ASCO VF net health benefit of each therapy was evaluated based on individual scores for efficacy, toxicity, plus bonus items, such as quality of life. Importantly, it was determined that **Cabo/Nivo offers the most significant net health benefit of any 1L treatment within aRCC**, as Cabo/Nivo scored higher (50.8) than both Axi/Pembro (48.7), Ipi/Nivo (41.9), Lenva/Pembro (35.2) and Axi/Ave (22.4).

Cabo/Nivo is also a clinically relevant alternative for some Ipi/Nivo ineligible patients, which is supported by the points described above and in the following. Generally, patient ineligibility for Ipi/Nivo treatment can have diverse causes, including current use of immunosuppressive treatments, poor performance status (≤2) and co-occurrence of specific active autoimmune diseases (i.e., Morbus Crohn, colitis ulcerosa, rheumatoid arthritis and hepatitis). For some of these Ipi/Nivo ineligible patients, Cabo/Nivo can be an alternative treatment option. [31] It is not possible to describe *all* types of patients who would be candidates to Cabo/Nivo, as the mix of individual characteristics in each patient will always be essential in deciding the most optimal treatment on a patient-by-patient basis. However, examples of Ipi/Nivo ineligible patients for who Cabo/Nivo can be an alternative treatment option include selected patients with autoimmune disease and patients with brain metastases (and specifically patients who need systemic prednisolone treatment for

these metastases). Furthermore, in those patients with brain metastases where Ipi/Nivo would be considered, Cabo/Nivo would also generally be a preferred option over Ipi/Nivo to maximize the opportunity for achieving rapid disease control and decrease/cease the use of metastasis-related prednisolone treatment. The same is true in some patients with poor performance status who (theoretically) can start Ipi/Nivo treatment and would do so in current clinical practice, but for who Cabo/Nivo would be the preferred treatment option. Although these examples represent general populations within the Ipi/Nivo ineligible population, it will always be a patient-to-patient level decision whether an Ipi/Nivo ineligible patient is eligible for Cabo/Nivo as an alternative treatment option. In addition, it is important to keep in mind that only approximately half of the first line patients will receive later treatment lines. It is therefore of critical importance to use the best available treatment option for each individual patient already in the first line setting even if in this case the ineligible Ipi/Nivo population is limited as described in Section 5.2.2 [89]

For patients with autoimmune disease, the possibility of using Cabo/Nivo as an alternative to Ipi/Nivo in selected patients is supported further by comparing the Summary of Product Characteristics (SmPCs) for ipilimumab, nivolumab and cabozantinib. Of these SmPCs, only the one for **ipilimumab** has a disease-specific precaution for avoiding its use in patients with autoimmune diseases: *"…Ipilimumab is a T-cell potentiator that enables the immune response (see section 5.1) and may interfere with immunosuppressive therapy, resulting in an exacerbation of the underlying disease or increased risk of graft rejection. Ipilimumab should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening. In other patients with a history of autoimmune disease, ipilimumab should be used with caution after careful consideration of the potential risk-benefit on an individual basis.*" [90]

Specifically for RCC patients, the nivolumab SmPC includes a disease-specific precaution stating that in patients with brain metastases, autoimmune disease or medical conditions requiring systemic immunosuppression, nivolumab, nivolumab in combination with ipilimumab or nivolumab in combination with cabozantinib should be used with caution after careful consideration of the potential benefit/risk on an individual basis [1].

As the text regarding patients with autoimmune diseases in the ipilimumab SmPC is fairly strong *"…ipilimumab should be avoided…"*, and the expression for using the combination therapies in RCC in the nivolumab SmPC is "*..to be used with caution",* it seems that the precaution stems primarily from ipilimumab rather than nivolumab. Furthermore, seen in a Nordic perspective, the Finnish national treatment guidelines for RCC published in 2021 states that for the patient to receive double immunological treatment, there must NOT be any autoimmune disease that needs an immunosuppressive treatment. So, in clinical practice, the Finnish guidelines denies the use of Ipi/Nivo in patients with autoimmune disease. Nothing like this is mentioned for any other treatment, including Cabo/Nivo. Therefore, these guidelines further supports the use of Cabo/Nivo in 1L for such Ipi/Nivo ineligible patients. [91] It should also be noted that clinical experts generally recognize that the risk is much greater for a treatment with two immunological compounds (especially with ipilimumab) than one. This explains why many clinical experts would consider treating patients with autoimmune disease with a combination of TKI/CPI instead of Ipi/Nivo and supports that for some Ipi/Nivo ineligible patients, Cabo/Nivo can be a treatment option.

### 5.2.2 Expected number of patients eligible for Cabo/Nivo treatment

Figure 2 shows how the annual number of Cabo/Nivo eligible patients has been estimated. According to the DMC treatment guidelines, 210 ccmRCC patients with IMDC intermediate/poor risk receive 1L treatment each year. [28, 29] About 20% of these patients (i.e., 42 patients per year) are estimated to be ineligible for Ipi/Nivo treatment based on DK clinical expert input collected by IPSEN during the application process and by Amgros during previous assessment processes of new drugs used for renal cancer [31, 92]. Of the Ipi/Nivo ineligible patients, about 20% are estimated to be eligible for Cabo/Nivo as an alternative treatment option [31]. This Cabo/Nivo target population is a small and diverse patient population with different mixes of individual patient characteristics making each patient ineligible for Ipi/Nivo, but eligible for Cabo/Nivo. Some of these characteristics were described in Section 5.2.1 (i.e., autoimmune disease, brain metastases, poor performance status), and the 20 % estimate would as a minimum include patients with such

characteristics. In addition, the 168 (80%) of the 210 ccmRCC patients with IMDC intermediate/poor risk who would be expected to be Ipi/Nivo eligible are part of the total Cabo/Nivo target patient population. The two Cabo/Nivo target populations combined correspond to 176 patients annually and approximately 84% of the total population of IMDC intermediate/poor risk patients receiving 1L treatment.

**Figure 2. Estimation of number of patients eligible for Cabo/Nivo treatment**


*Left panel: Target patient population 1: IMDC intermediate/poor prognostic risk patients who are eligible for Ipi/Nivo treatment.*
*Right panel: Target patient population 2: IMDC intermediate/poor prognostic risk patients who are ineligible for Ipi/Nivo treatment but eligible for Cabo/Nivo treatment*
*Sources: Left panel: outer circle [29], inner circle [31, 92]. Right panel: outer circle [29], middle circle [31, 92], inner circle [31].*

Table 3 summarizes the number of new patients in Denmark who are expected to receive Cabo/Nivo treatment in the next 5 years. The numbers are based on assumptions of a [redacted] Cabo/Nivo market share in the Ipi/Nivo eligible patient population and a [redacted] Cabo/Nivo market share in the Ipi/Nivo ineligible + Cabo/Nivo eligible patient population, combined with an assumption of a gradual market uptake. In the first year after introduction, it is assumed that 50% of the total number of expected patients based on the market share assumptions actually receive Cabo/Nivo. After the first year, all expected Cabo/Nivo patients are assumed to receive the treatment.

[redacted]

## 5.3 Current treatment options and choice of comparator(s)

### 5.3.1 Current treatment options

Advanced RCC requires a variety of therapeutic options to allow for treatment approaches that take into account both the patient's and the tumour's characteristics. [16, 17] Since the introduction of VEGF tyrosine kinase inhibitors (TKIs), the RCC treatment landscape, particularly in the front-line, has been rapidly evolving. Monotherapies have been developed based on the identification of multiple signalling factors involved in renal cell tumourigenesis. Combining therapies with a synergistic antitumour effect also aimed to address the rising issue of drug resistance.[82]

In Denmark, the treatment choice for patients with mRCC is guided by "*Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til metastatisk nyrekræft*" (published by the DMC in October 2020) [30] and "*Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til metastatisk nyrekræft*" (published by the DMC in June 2022 and valid from September 1, 2022) [93]. In addition to the national treatment guideline published by the DMC, a new national clinical treatment guideline for the oncological treatment of RCC was published by the Danish Renal Cancer Group (DaRenCa) in June 2021.[94] However, in contrast to the drug recommendation published by the DMC [93], recommendations in the DaRenCa treatment guideline are based on clinical aspects only and do not include costs as a factor in the choice between medical treatments. Therefore, in clinical practice, the treatment choice for patients with mRCC is still guided by the DMC drug recommendation, and based on that, general recommendations from the DaRenCa treatment guideline are not described in more detail in the application.

In the DMC treatment guideline and drug recommendation [28, 93], the choice of 1L medical treatment is based on the patient's prognosis using the IMDC prognostic stratification tool, as well as the patient's general condition and comorbidities [29, 93].

IMDC is used to classify patients into three different prognostic risk groups (i.e., favourable, intermediate, and poor) based on the following risk factors:

- Karnofsky Performance Status <80%
- <1 year from time of primary diagnosis to initiation of systemic therapy for metastatic disease
- Hemoglobin < lower limit of normal
- Corrected calcium > upper limit of normal
- Neutrophils > upper limit of normal
- Platelets > upper limit of normal

IMDC divides patients into the three prognostic groups based on the status of above risk factors:

- 0 risk factors: favourable prognostic group
- 1-2 risk factors: intermediate prognostic group
- ≥ 3 risk factors: poor prognostic group

A short summary of the drug recommendations for patients with advanced ccRCC is given in the table below (Table 4) [93].

**Table 4: Treatment choice for patients with advanced clear cell RCC in Denmark**

| | First-line treatment | | Second-line treatment | |
|---|---|---|---|---|
| Patient group | IMDC favourable prognosis | IMDC intermediate/poor prognosis | Did not receive checkpoint immunotherapy in first-line | Received checkpoint immunotherapy in first-line |
| **First-choice treatment (use in at least 80% of all patients)** | Sunitinib Teva | Opdivo (nivolumab)/ Yervoy (ipilimumab) | Opdivo (nivolumab) | Cabometyx (cabozantinib) |
| **Treatment alternatives that may be considered (prioritized list)** | Fotivda (tivozanib)<br>Votrient (pazopanib) | Sunitinib Teva<br>Fotivda (tivozanib)<br>Votrient (pazopanib) | Bavencio (avelumab)/Inlyta (axitinib)<br>Keytruda (pembrolizumab)/ Inlyta (axitinib)<br>Opdivo (nivolumab)/ Yervoy (ipilimumab) | Sunitinib Teva<br>Sorafenib Mylan<br>Fotivda (tivozanib)<br>Votrient (pazopanib)<br>Inlyta (axitinib)<br>Everolimus Sandoz |

*Source: [93]*

As evident from Table 4, the standard treatment for patients with IMDC intermediate/poor prognosis is double checkpoint immunotherapy with Ipi/Nivo. For IMDC intermediate/poor risk patients who do not tolerate checkpoint immunotherapy (i.e., in accordance with the DMC drug recommendation, combination treatment with Ipi/Nivo) [93], tivozanib, pazopanib, sunitinib and cabozantinib monotherapy are considered clinically-equivalent alternatives. [28, 29]. Thus, patients with IMDC intermediate/poor prognosis can be divided in two different subpopulations based on their tolerability to treatment with Ipi/Nivo: an Ipi/Nivo eligible patient population where Ipi/Nivo is current standard treatment, and an Ipi/Nivo ineligible patient population where TKI monotherapy is current standard treatment, with sunitinib being the preferred choice based on price [93]. Cabozantinib monotherapy and the combinations of axitinib and pembrolizumab/avelumab are included as 1L treatments in the DMC treatment guideline and drug recommendation, but are currently not reimbursed for 1L treatment [28, 93].

### 5.3.2 Choice of comparator(s)

As described in Section 5.2.1, Cabo/Nivo is a clinically relevant alternative for both the general patient population with IMDC intermediate/poor risk disease, i.e., Ipi/Nivo eligible patients, and for some Ipi/Nivo ineligible patients. In the Ipi/Nivo eligible patient population, Ipi/Nivo is currently the only standard treatment recommended, meaning that it is the only appropriate comparator treatment in this population. In the Ipi/Nivo ineligible patient population, TKI monotherapy (tivozanib, pazopanib and sunitinib) would theoretically be the relevant comparators. However, sunitinib is included as the only comparator in the Ipi/Nivo ineligible population for the following reasons:

- As tivozanib, pazopanib and sunitinib are considered clinically equivalent alternatives by the DMC, comparison of Cabo/Nivo to one of these treatments is considered representative of comparison to the other alternatives. DK expert input collected by IPSEN during the application process confirms that there are no significant differences between the use of tivozanib, pazopanib and sunitinib in clinical practice, which supports this approach. [31]
- Of the TKI monotherapies available as comparators, the DMC drug recommendation specifies that sunitinib is the preferred choice [93]. In addition, comparison of Cabo/Nivo with sunitinib will provide the strongest quality of evidence, as the CheckMate 9ER trial comparing Cabo/Nivo with sunitinib is the only head-to-head study

available with a direct comparison of Cabo/Nivo to one of these TKIs. Choosing the most appropriate comparator based on the evidence available is in line with the approach used in previous assessments of new drugs within renal cancer. [92, 95]

### 5.3.3 Description of the comparator(s)

#### 5.3.3.1 Sunitinib

Sunitinib was the first anti-VEGF receptor (VEGFR) monotherapy to demonstrate delayed disease progression over interferon- α (IFN-α), although it did not significantly improve OS. Prior the approval of Ipi/Nivo, sunitinib was considered the first choice and standard of care in the management of 1L aRCC. A description of sunitinib is given in Table 5 below.

**Table 5: Description of comparator: Sunitinib/Sutent**

| Overview of the comparator | |
|---|---|
| **Proprietary name** | Sutent [23] |
| **Generic name** | Sunitinib [23] |
| **ATC code** | L01EX01 [23] |
| **Pharmaceutical form(s)** | Oral tablet, hard capsule [23] |
| **Mechanism of action** | **Sunitinib** is a small-molecule that inhibits cellular signalling by targeting multiple receptor tyrosine kinases (RTKs). These include all receptors for platelet-derived growth factor (PDGF-Rs) and vascular endothelial growth factor receptors (VEGFRs) which play a role in both tumour angiogenesis and tumour cell proliferation. Sunitinib was approved by the FDA for the treatment of RCC and imatinib-resistant gastrointestinal stromal tumour (GIST) on January 26, 2006.[96] |
| **Dosage regimen** | The recommended dose of sunitinib is 50 mg taken orally once daily, for 4 consecutive weeks, followed by a 2-week rest period (Schedule 4/2) to comprise a complete cycle of 6 weeks. [23, 97] |
| **Combination therapy and/or co-medication** | No |
| **Packaging – types, sizes/number of units, and concentrations** | 12.5 mg, 25 mg, 37.5 mg, 50 mg hard capsules.<br>Package sizes: bottle 30 capsules, blister 28 capsules. [97] |
| **Treatment duration/criteria for end of treatment** | Treatment duration is not clearly defined, continue according to progression-free survival or unacceptable toxicity. [23] |
| **Monitoring required during administration and treatment period** | Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of sunitinib treatment. During sunitinib treatment, routine monitoring of thyroid function should be performed every 3 months. [23] |

#### 5.3.3.2 Ipilimumab/Nivolumab

A description of Ipi/Nivo is given in Table 6 below.

**Table 6: Description of comparator: ipilimumab (Yervoy) in combination with nivolumab (Opdivo)**

| Overview of the comparator | |
|---|---|
| **Proprietary name** | YERVOY® [90]; OPDIVO®. [1] |
| **Generic name** | ipilimumab; nivolumab. |
| **ATC code** | L01XC11 ; L01XC17 |
| **Pharmaceutical form(s)** | **Ipilimumab:**<br>Type: concentrate solution for IV infusion.<br>Concentration: each ml of concentrate contains 5 mg ipilimumab. [90]<br><br>**Nivolumab:**<br>Type: concentrate solution for IV infusion.<br>Concentration: each ml of concentrate contains 10 mg nivolumab. [1] |
| **Mechanism of action** | **Ipilimumab** is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intratumoural T-effector/T-regulatory cell ratio which drives tumour cell death. [90]<br><br>**Nivolumab** is a human monoclonal antibody that targets the PD-1 receptor and blocks its interaction with its ligands, PD-L1 and PD-L2. Tumours use PD-L1 expression as defence or escape mechanism against the host's anti-tumour T cell response; inhibiting PD-L1 restores the function of these anti-tumour T cells which have become ineffective or suppressed. Therefore, the efficacy of PD-L1 inhibition relies on a pre-existing immune response. |
| **Dosage regimen** | For treatment of RCC, the recommended dose is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg over 30 minutes every 2 weeks, or at 480 mg over 60 minutes every 4 weeks. [1]. For the monotherapy phase, the first dose of nivolumab should be administered 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks or 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480 mg every 4 weeks. |
| **Combination therapy and/or co-medication** | Yes, YERVOY® in combination with OPDIVO®. [1] |

| Overview of the comparator | |
|---|---|
| **Packaging – types, sizes/number of units, and concentrations** | **Ipilimumab**: [98]<br>Type: concentrate solution for IV infusion.<br>Concentration: each ml of concentrate contains 5 mg of ipilimumab.<br>Available as 10 ml vial with 50 mg and<br>40 ml vial with 200 mg.<br><br>**Nivolumab:** [99]<br>Type: concentrate solution for IV infusion.<br>Concentration: each ml of concentrate contains 10 mg nivolumab.<br>Available as 4 ml vial with 40 mg , 10 ml vial with 100 mg, 12 ml vial with 120 mg and 24 ml vial with 240 mg. |
| **Treatment duration/criteria for end of treatment** | Treatment with nivolumab, either as monotherapy or in combination with ipilimumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient [1].<br><br>Treatment with ipilimumab, in combination with nivolumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient, up to a maximum of 4 doses (12 weeks) [90]. |
| **Monitoring required during administration and treatment period** | Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy [1, 90]. |

## 5.4 The intervention

Based on cabozantinib monotherapy's superior efficacy in the 1L setting in patients with IMDC intermediate or poor prognostic risk (CABOSUN trial) and nivolumab's clinical activity and OS improvement, it was hypothesized that the different mechanisms of action of these two compounds would results in additive clinical activity. Considering the need for improved benefit over standard of care in the first-line setting regardless of prognostic group, Bristol Myers-Squibb (BMS) initiated the CheckMate 9ER study to assess the efficacy and safety of Cabo/Nivo in 1L aRCC treatment. Cabo/Nivo demonstrated significantly improved OS, delayed disease progression and increased objective response rate (ORR) in comparison to sunitinib while maintaining or improving patients' QoL. [41, 100]

### 5.4.1 Dosing & Method of administration

The recommended dose of cabozantinib is 40 mg once daily in combination with nivolumab administered intravenously at either 240 mg every 2 weeks or 480 mg every 4 weeks. [2]

### 5.4.2 Treatment duration

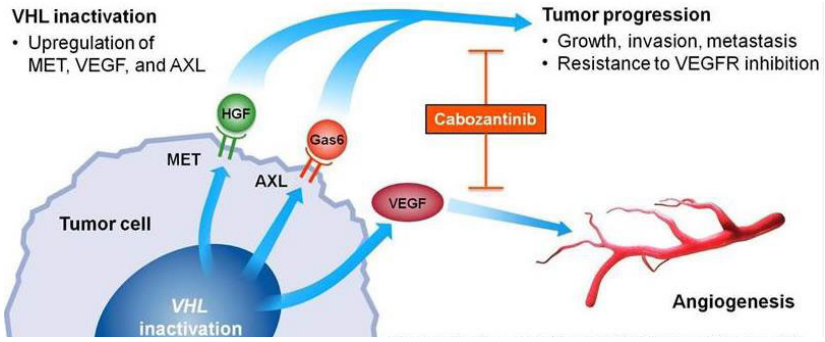
Cabozantinib treatment should continue until disease progression or unacceptable toxicity. Nivolumab should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.[3]

### 5.4.3 Mechanism of action

Cabozantinib (XL184) is a small molecule that inhibits numerous RTKs involved in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer (Figure 3). [2] Cabozantinib is a potent inhibitor of multiple RTKs known to play important roles in tumour cell proliferation and/or tumour neovascularization, including VEGFR, MET, AXL, and RET. In particular, it is the only approved drug in RCC that – in addition to VEGFR – also inhibits the MET and AXL receptors associated with disease progression and metastasis. [78, 101] With this unique mode of action, cabozantinib targets both angiogenesis and tumour progression and therefore shows a key advantage over other TKIs used in 1L RCC that mainly inhibit the VEGFR signal pathway. It also has the potential to overcome drug resistance.

Preclinical studies and clinical observations on circulating immune suppressive cells and immune effector cells in cancer patients suggest that cabozantinib promotes an immune-permissive environment, which may present an opportunity for synergistic effects from combination treatment with CPIs independent of tumour PD-L1 expression.[102]

**Figure 3: Molecular targets of cabozantinib inhibition**



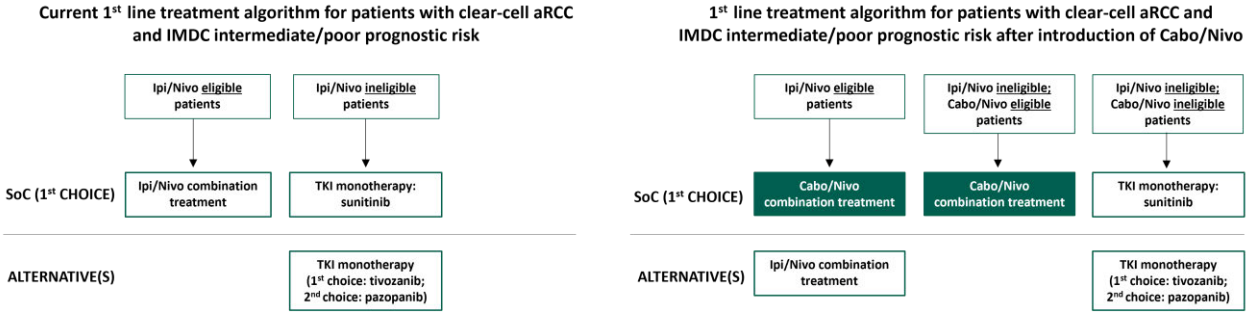

*Abbreviations: AXL=receptor for the vitamin K-dependent protein growth-arrest-specific gene 6 [GAS6]; MET=Mesenchymal epithelial transition; VHL=von Hipple-Lindau; VEGF=vascular endothelial growth factor; VEGFR=vascular endothelial growth factor receptor.*
*Sources: Shen 2013[103]; Zhou 2016.[78]*

Nivolumab is a human monoclonal antibody that targets the PD-1 receptor and blocks its interaction with its ligands, PD-L1 and PD-L2. Tumours use PD-L1 expression as defence or escape mechanism against the host's anti-tumour T-cell response; inhibiting PD-L1 restores the function of these anti-tumour T-cells which have become ineffective or suppressed. Therefore, the efficacy of PD-L1 inhibition relies on a pre-existing immune response.[82]

### 5.4.4 Description of how the introduction of Cabo/Nivo can potentially change clinical practice

The introduction of Cabo/Nivo will provide a new treatment option for the general patient population of ccmRCC patients with IMDC intermediate/poor risk disease, i.e., Ipi/Nivo eligible patients, and for a subgroup of patients with IMDC intermediate/poor risk disease who are ineligible for Ipi/Nivo treatment. Both of these patient populations have a significant unmet need for an effective, tolerable new option which improves OS, delays disease progression and improves disease control, while maintaining or improving patients' QoL. Figure 4 illustrates how the introduction of Cabo/Nivo will change the current 1L treatment algorithm for ccmRCC patients with IMDC intermediate/poor risk:

**Figure 4: Comparison of current 1L line treatment algorithm and 1L treatment algorithm after introduction of Cabo/Nivo.**




# 6. Literature search and identification of efficacy and safety studies

## 6.1 Identification and selection of relevant studies

The randomized, phase III, open-label trial CheckMate 9ER compared Cabo/Nivo with sunitinib as 1L therapy in patients with aRCC. This head-to-head study is the only relevant direct comparison of Cabo/Nivo available and serves as the basis for the evidence for Cabo/Nivo in 1L aRCC included in this application and the CE model.

In the DMC methodological guidelines, it is stated that if one or several studies have already directly compared the new pharmaceutical with the relevant comparator(s), the systematic search for documentation of the effect and safety can be omitted. Therefore, with this head-to-head study available, no systemic literature search (SLR) was performed to inform the comparison of Cabo/Nivo with **sunitinib**. The acceptability of this approach is supported by results from a SLR within the therapeutic area (but with a broader scope) conducted by IPSEN in 2021 (based on an update of previous SLRs conducted), which did not identify additional information to inform the direct comparison of Cabo/Nivo vs. sunitinib [93].

For the comparison between Cabo/Nivo and **Ipi/Nivo**, there are no trials available that provide a direct comparison between these treatments. Accordingly, a systematic literature search was undertaken to inform this treatment comparison. Appendix A describes the methodology and outcome of this literature search in more detail.

The objective of the SLR was to identify trials evaluating treatment outcomes, including clinical efficacy and safety, of Cabo/Nivo versus the comparator Ipi/Nivo for the treatment of aRCC. The above-mentioned SLR [93] was used as a basis for the literature search undertaken to inform the comparison of Cabo/Nivo versus Ipi/Nivo in the current DMC application. This review had a broader scope and also included a search for studies of other therapies within aRCC that could be of potential relevance in other markets. Since these treatments are not used in Danish clinical practice, any articles on other interventions than Cabo/Nivo or Ipi/Nivo were considered irrelevant for the purpose of the current DMC application and were therefore excluded from the literature review. For the purpose of this DMC submission, a complementary PUBMED search was also performed in order to identify any recent full-text publications reporting results from phase III studies of Cabo/Nivo or Ipi/Nivo in the treatment of aRCC. Relevant new conference materials were also identified by searching the websites of recent important scientific conferences of relevance for RCC (ASCO Annual Meeting 2022, ASCO Genitourinary Cancers Symposium 2022, ESMO Congress 2022, and European Association of Urology (EAU) Congress 2022). In addition, the websites of International Kidney Cancer Symposium (IKCS) 2021 and ESMO Immuno-Oncology Virtual Congress 2021 were searched. Furthermore, updated versions of EMA's European Public Assessment Report (EPAR)/Summary of Product Characteristics (SmPC) for Cabometyx (cabozantinib), Yervoy (ipilimumab) and Opdivo (nivolumab) were searched for, and if available, consulted.

## 6.2 List of relevant studies

After the selection process, a total of 13 citations describing two studies (Table 7) were included in the application. Main study characteristics of the included studies are detailed in Appendix B.

**Table 7: Relevant studies included in the assessment**

| Trial name | NCT number | Dates of study (start and expected completion date) | Reference (title, author, journal, year) | Rationale for inclusion |
|---|---|---|---|---|
| **CheckMate 9ER**<br>A Study of Nivolumab Combined with Cabozantinib Compared to Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma | NCT03141177 | July 11, 2017 - May 14, 2024 | Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. Motzer RJ et al, Lancet Oncol, 2022. [35] | Latest data presented for outcomes relevant for this assessment |
| | | | Assessment report Cabometyx EMEA/H/C/004163/II/0017. EMA, 2021. [32] | Includes data not reported in other non-confidential sources |
| | | | Addendum Clinical Study Report for Study CA2099ER-OS: A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Cabozantinib versus Sunitinib in Participants with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma. Bristol Myers Squibb, 2021 [36] | Includes data not reported elsewhere |
| | | | Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. Choueiri et al. New England Journal of Medicine, 2021. [34] | Original publication; included to show consistency of original data and most updated data |
| | | | Final Clinical Study Report for Study CA2099ER: Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Cabozantinib versus Sunitinib in Participants with Previously Untreated Advanced or Metastatic Renal Cell Carcinoma. Bristol Myers Squibb, 2020. [33] | Includes original data not reported elsewhere (included to show consistency of original data and most updated data) |
| | | | Assessment report Cabometyx (SmPC). EMA, 2022. [2] | Updated SmPC |
| | | | Health-related quality of life in previously untreated patients with advanced renal cell carcinoma: CheckMate 9ER updated results. Cella et al, Journal of Clinical Oncology, 2022. [43] | Latest data presented for outcomes relevant for this assessment |

| Trial name | NCT number | Dates of study (start and expected completion date) | Reference (title, author, journal, year) | Rationale for inclusion |
|---|---|---|---|---|
| **CheckMate 214**<br>Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma | NCT02231749 | Oct 16, 2014 – Jan 10, 2023 | Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. Cancer. Motzer RJ, et al. Cancer, 2022. [45] | Latest data presented for outcomes relevant for this assessment |
| | | | 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 et al., ESMO open, 2020. [104] | Data reported for 24-month PFS and OS rates |
| | | | https://clinicaltrials.gov/ct2/show/study/NCT02231749. Bristol Myers Squibb, 2021. [105] | N/A |
| | | | Assessment report Ipilimumab (SmPC). EMA, 2022. [90] | Updated SmPC |
| | | | Assessment report Nivolumab (SmPC). EMA, 2022. [1] | Updated SmPC includes data not reported elsewhere |
| | | | Health-related quality of life in previously untreated patients with advanced renal cell carcinoma in CheckMate 214: 5-year follow-up results. Cella et al, Journal of Clinical Oncology, 2022. [106] | Latest data presented for outcomes relevant for this assessment |

# 7. Efficacy and safety

## 7.1 Efficacy and safety of cabozantinib + nivolumab compared to sunitinib for patients with previously untreated advanced or metastatic renal cell carcinoma

### 7.1.1 Relevant studies

#### 7.1.1.1 CheckMate 9ER

CheckMate 9ER (study CA2099ER, NCT03141177) is a robust, large (n=651), phase III randomised control trial (RCT) designed to compare the efficacy and safety of Cabo/Nivo (doublet regimen, Arm A) vs. sunitinib (Arm C) in participants with previously untreated (1L) aRCC or mRCC with a clear-cell component. Overall, 651 patients were assigned to receive Cabo/Nivo (323 patients) or sunitinib (328 patients). Patients underwent randomization in a 1:1 ratio and were stratified according to IMDC prognostic risk score, geographic region (United States and Europe vs. the rest of the world), and tumour expression of the PD-1 ligand PD-L1 (≥1% vs.<1% or indeterminate). To represent the typical frequency of the favourable risk group in real-world mRCC, enrolment of participants with favourable risk was capped at approximately 25%. The overall population was representative of the general patient population with aRCC, with IMDC favourable, intermediate, and poor risk distribution of 22.9%, 58.2% and 18.9%, respectively. [33, 34, 100] The study characteristics

are summarized in Table 8 below. For detailed study characteristics, including methods of analysis, see Appendix B. For baseline characteristics of patients included in the study see Appendix C.

**Table 8: Study characteristics of CheckMate 9ER**

| Study/Phase/Status | CheckMate 9ER/Phase 3/ongoing |
|---|---|
| **Study design** | Phase 3, multicentre, randomised, open-label study.<br>Subjects were randomised 1:1 between cabozantinib + nivolumab (Arm A) and sunitinib (Arm C).[a] Randomisation was stratified by IMDC prognostic score (0 [favourable risk] vs. 1-2 [intermediate risk] vs. 3-6 [poor risk]), PD-L1 tumour expression (≥ 1% vs. < 1% or indeterminate), and Region (US/Canada/Western Europe/Northern Europe vs. rest of the world [ROW]). [34] |
| **Treatment** | Arm A: nivolumab 240 mg flat dose IV Q2W + cabozantinib 40 mg PO QD (nivolumab treatment until progressive disease (PD) or unacceptable toxicity with maximum treatment of 2 years and cabozantinib treatment until PD or unacceptable toxicity) or<br>Arm C: sunitinib 50 mg PO QD for 4 weeks, followed by 2 weeks off-treatment, per cycle until PD or unacceptable toxicity. [34] |
| **Study population** | Subjects (≥18 years) with no prior systemic therapy for advanced or metastatic RCC. Subjects were required to have histologically confirmed advanced or metastatic RCC (with a clear-cell component, including participants who may also have sarcomatoid features). Advanced or metastatic RCC subjects across all IMDC risk groups (favourable, intermediate, and poor risk categories) were included in the study. [34] |
| **Number of subjects** | All Randomised, N = 651[b]. |
| **Treatment** | Arm A (N = 323): nivolumab 240 mg flat dose IV Q2W + cabozantinib 40 mg PO QD.<br>Arm C (N = 328): sunitinib 50 mg PO QD for 4 weeks on treatment then 2 weeks off, continuously.<br>Treatment was given until toxicity or disease progression. [34] |
| **Primary objectives** | To compare PFS per BICR of cabozantinib combined with nivolumab vs. sunitinib in all randomized participants. [34] |
| **Secondary objectives** | OS, ORR, DoR, TTR and Safety. [34] |
| **Explorative endpoint** | HRQoL was assessed using the FKSI-19 and EQ-5D-3L instruments. Both measures were completed on Day 1 of each treatment cycle prior to any study-related procedures. [34] |
| **Follow-up time** | Data with follow-up of 32.9 months are reported in Motzer et. al., 2022. [35] |

*BICR: blinded independent central review; CSR: clinical study report; EMA: European Medicines Agency; EPAR: European Public Assessment Report; IV: intravenous(ly); DoR: duration of response; FKSI: Functional Assessment of Cancer Therapy - Kidney Symptom Index; HRQoL: Health related quality of life; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; ORR: objective response rate; OS: overall survival; PD-L1: programmed death ligand 1; PFS: progression-free survival; PO: by mouth; Q2W: every 2 weeks; ROW: rest of world; TTR, time to response.*

*[a]Enrolment to Arm B (nivolumab + ipilimumab + cabozantinib) was stopped after the implementation of a trial protocol amendment. Subjects continued 1:1 randomization of nivolumab + cabozantinib arm (Arm A) and sunitinib arm (Arm C). Subjects previously randomized to Arm B continued with Arm B treatment and continued with the study, per protocol. However, results from Arm B are not included in the application.*

*[b]Overall 701 participants were randomized in Study CheckMate 9ER; 651 in Arm A and C and 50 in Arm B.*

### 7.1.2 Efficacy and safety CheckMate 9ER

Study results for all patients in the IMDC intermediate/poor prognostic risk subgroups will be used to represent the DK Cabo/Nivo target population and thus be the main focus in this submission. As the DMC treatment guidelines and drug recommendation do not differentiate between patients with intermediate and poor prognostic risk, respectively, the descriptive results section below will focus on results for the pooled intermediate/poor prognostic risk group to the extent possible. To demonstrate consistency with efficacy results for the overall study population, results for the intention-to-treat (ITT) population are also described in the following sections and in Appendix D, Section 16.2. For some endpoints, results are not available at the intermediate/poor subgroup level and are therefore only described and presented based on the overall study population.

#### 7.1.2.1 Efficacy outcomes

**Primary:**

- To compare progression-free survival (PFS) per blinded independent central review (BICR) of Cabo/Nivo with sunitinib in all randomized participants.

**Secondary:**

- To compare OS of Cabo/Nivo with sunitinib in all randomized participants.
- To compare the ORR per BICR, and also best objective response (BOR), duration of response (DOR) and time to response (TTR) observed with Cabo/Nivo vs. sunitinib in all randomized participants.
- To assess overall safety and tolerability in all treated participants.

**Exploratory:**

- To explore potential predictive biomarkers of clinical response to Cabo/Nivo.
- To evaluate health-related (HR)QoL using the Functional Assessment of Cancer Therapy-Kidney Symptom Index-19 and EuroQol Health Questionnaire Instrument (EQ-5D-3L) instruments.
- To characterize the pharmacokinetics (PK) of Cabo/Nivo and explore exposure response relationships, if applicable
- To characterize the immunogenicity of nivolumab.
- To assess PFS after next line of treatment (PFS-2) in each arm.

Survival outcomes are the most persuasive endpoints of an oncology clinical trial [107-109] and favourable effects on OS are considered clinically meaningful and reliable.[107, 109] Prolonged PFS is also considered to be of benefit to the patient and has been strongly correlated with positive treatment effects on OS.[110, 111] Furthermore, ORR is considered to be a convincing measure of anti-tumour activity, and can be measured earlier than survival outcomes.[107, 109, 112] The endpoints ORR, DOR and TTR and safety are acknowledged by the European Committee for Medicinal Products for Human Use (CHMP) and the US Food and Drug Administration (FDA) as the standard outcomes for oncology trials.[107-109]

#### 7.1.2.2 Assessment of safety

The assessment of safety was based on the incidence of AEs, serious AEs (SAEs), AEs leading to discontinuation, AEs leading to dose modification, select AEs, immune-mediated AE (IMAEs), other events of special interest (OESI), events to monitor (ETMs) for cabozantinib, and deaths. The use of immune-modulating concomitant medication was also summarized. In addition, clinical laboratory tests were analysed. AEs were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, version 4.0. [32]

Available safety data for cabozantinib and nivolumab monotherapies in RCC were compared to data from the CheckMate 9ER study to contextualize the contribution of each drug to the safety profile of the Cabo/Nivo combination.

#### 7.1.2.3 Efficacy results

Efficacy outcomes according to key disease and demographic characteristics at baseline were evaluated by means of prespecified supportive subgroup analyses. Detailed information on efficacy is provided in Appendix D.

The overall efficacy results include the primary and secondary endpoints in all randomised subjects (ITT population) and all predefined stratification subgroups (including IMDC favourable, intermediate, and poor risk). Results from three different CheckMate 9ER data-cuts have currently been published in a peer-reviewed journal and/or the EPAR for Cabometyx:

- For all primary and secondary study endpoints the clinical cut-off (last patient last visit) was 12 February, 2020 and DBL was 30 March, 2020. The minimum and median follow-up for OS were approximately 10.6 and 18.1 months, respectively. [34]
- Extended follow-up at DBL 10 September, 2020, with approximately 5.5 months additional follow-up. The minimum and median follow-up for OS were approximately 16.0 and 23.5 months, respectively. Results from this DBL were confirmative.
- Extended follow-up at DBL at 24 June, 2021, with approximately 14.5 months additional follow-up. The minimum and median follow-up for OS were approximately 25.4 and 32.9 months, respectively. [35]. Results from this DBL were confirmative.

Results from the first DBL March 30, 2020 and DBL with longest follow-up (DBL June 24, 2021) are presented in this application. The results from the first DBL serve to demonstrate that results with longer follow-up confirm those from the original analyses.

##### 7.1.2.3.1 Efficacy results in the population with IMDC intermediate/poor prognosis

**Primary endpoint**

Progression-free survival: PFS was defined as "the time between the date of randomization and the first date of documented progression per Response Evaluation Criteria in Solid Tumours (RECIST) v.1.1 based on BICR, or death due to any cause, whichever occurs first".

At DBL June 24, 2021, Cabo/Nivo demonstrated an improvement in PFS per BICR compared with sunitinib in all randomized subjects with IMDC intermediate/poor prognostic risk, confirming the results from DBL March 30, 2020. The Kaplan-Meier (KM) plots for PFS per BICR in the intermediate/poor risk subgroup are shown in Figure 5. [36, 113]

**DBL March 30, 2020 (median follow-up: 18.1 months)**

- Median PFS was longer with Cabo/Nivo compared with sunitinib: 16.6 (95% CI: 11.2, 22.9) vs. 7.1 (95% CI: 5.7, 8.9) months, respectively. [Cabometyx EPAR table 18 [32], [113]]
- Relative difference in effect: HR = 0.48 (95% CI: 0.37, 0.61) [Cabometyx EPAR table 18 [32], [114]]
- [redacted]

**DBL June 24, 2021 (median follow-up: 32.9 months)**

- Median PFS was longer with Cabo/Nivo compared with sunitinib [redacted]
- Relative difference in effect: [redacted]
- Absolute difference in effect: [redacted]
- Both the 12-month and 24-month PFS rates were higher for Cabo/Nivo compared with sunitinib: 12-month rates were [redacted] respectively, with an absolute difference in effect o [redacted]; 24-month PFS rates were [redacted] for Cabo/Nivo vs. [redacted] for sunitinib, with an absolute difference in effect magnitude [redacted]

[redacted]

**Secondary endpoints**

Overall survival: OS was defined as "the time from randomization to death from any cause". At both DBL 30 March, 2020 and DBL June 24, 2021, Cabo/Nivo demonstrated improvement in patients' OS vs. sunitinib. KM plots for OS in the IMDC intermediate/poor risk subgroup are shown in Figure 6.

**DBL March 30, 2020 (median follow-up: 18.1 months)**

- Median OS was not reached in either treatment arms. [Cabometyx EPAR table 18 [32], [116]]
- A total [redacted] deaths had occurred [redacted] [Cabometyx EPAR table 18 [32], [116]]
- Relative difference in effect: HR=0.56, 95% CI: 0.40, 0.79, [redacted] [Cabometyx EPAR table [32], [116]]

**DBL June 24, 2021 (median follow-up: 32.9 months)**

- Median OS was reached in the sunitinib treatment group at 29.0 months and at 37.6 months in the Cabo/Nivo arm. [37]
- A total of 231 deaths had occurred (100 in the Cabo/Nivo arm, 131 in the sunitinib arm). [37]
- Relative difference in effect: HR=0.66, 95% CI: 0.50, 0.85, p=0.002 [37]
- Absolute difference in effect was [redacted]
- Both the 12-month and 24-month rates OS rates were higher for Cabo/Nivo compared with sunitinib: 12-month rates were [redacted], respectively, with an absolute difference in effect of [redacted] 24-month OS rates were [redacted] for sunitinib with an absolute difference in effect o [redacted]

When interpreting the OS results from the DBL June 24, 2021, it is important to note that [redacted] Nevertheless, even with a median follow-up for OS of 32.9 months, the combination of Cabo/Nivo continued to provide improved survival versus sunitinib, and the results from the third data cut continue to support Cabo/Nivo as a first-line treatment option for patients with aRCC.

[redacted]

Objective response rate: ORR was defined as "the proportion of randomised patients who achieve a BOR of complete response (CR) or partial response (PR) per RECIST v.1.1 between randomisation and the date of objectively documented progression per RECIST v.1.1. or the date of subsequent therapy, whichever occurs first". [redacted]

**DBL March 30, 2020 (median follow-up: 18.1 months)**

- ORR was 52.2% (95% CI: 45.8, 58.6) vs. 23.0% (95% CI: 18.0, 28.7), for Cabo/Nivo vs. sunitinib, respectively. [Cabometyx EPAR table 18 [32], [120]]

- Relative difference in effect: OR: [redacted] [Cabometyx EPAR table 18 [32], [121]]
- Absolute difference in effect: 29.0% [redacted]

**DBL June 24, 2021 (median follow-up: 32.9 months)**

- ORR was 52.6% [redacted] vs. 23.8% [redacted] for Cabo/Nivo vs. sunitinib, respectively. [36]
- Relative difference in effect: OR: [redacted]
- Absolute difference in effect: [redacted]

**Table 9: Confirmed Best Overall Response (BICR) – CheckMate 9ER, All intermediate/poor risk subjects, DBL March 30, 2020 & DBL June 24, 2021**

| Subjects in IMDC intermediate/poor prognostic risk group | Cabo/Nivo N=249 | Sunitinib N=256 | Cabo/Nivo N=249 | Sunitinib N=256 |
|---|---|---|---|---|
| | DBL March 30, 2020[1] | | DBL June 24, 2021[2] | |
| **Confirmed BOR[a] per BICR, n (%)** | | | | |
| **Complete response** | 21 (8.4) | 9 (3.5) | 30 (12.0) | 9 (3.5) |
| **Partial response** | 109 (43.8) | 50 (19.5) | 101 (40.6) | 52 (20.3) |
| **Stable disease** | [redacted] | [redacted] | 82 (32.9) | 105 (41.0) |
| **Progressive disease** | 16 (6.4) | 43 (16.8) | 18 (7.2) | 43 (16.8) |
| **UTD (unable to determine)** | [redacted] | [redacted] | 18 (7.2) | 46 (18.0) |
| **Objective response rate per BICR (95% CI)** | [redacted] (52.2%) (45.8, 58.6) | [redacted] (23.0%) (18.0, 28.7) | 131 (52.6%) [redacted] | 61 (23.8%) [redacted] |

*BICR: blinded independent central review; BOR: best overall response; CI: confidence interval; IMDC: International Metastatic RCC Database Consortium RECIST: Response Evaluation Criteria In Solid Tumours.*
*aBOR is defined as the best response recorded between randomisation and objectively documented progression per RECIST 1.1 or subsequent therapy (including tumour-directed radiotherapy and tumour-directed surgery), whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment.*
*Sources: [1] [32, 120] [2] Calculated from Motzer 2022 suppl table S4 [35] [3] [36]*

Duration of response: DOR was defined as "the time between the date of the first confirmed documented response CR or PR to the date of first documented tumour progression (per RECIST 1.1) as assessed by BICR or death due to any cause, whichever occurs first".

Time to response: TTR was defined as "the time from randomization to the date of the first confirmed documented response (CR or PR), as assessed by BICR". DOR and TTR were evaluated for responders (CR or PR) only.

[redacted]. KM plots for DOR in the IMDC intermediate/poor risk subgroup, DBL march 30, 2020 and DBL June 24, 2021 is shown in Figure 7. Of note, [redacted] For the DOR and TTR endpoints, it was not considered reasonable to calculate 95% CIs or p-values for the absolute differences in effect nor any relative differences in effect between the treatment arms in

CheckMate 9ER. TTR and DOR estimates are limited to responders only and no formal statistical comparative analyses of these measures were included in the statistical analysis plan for the CheckMate 9ER trial.

**DBL March 30, 2020 (median follow-up: 18.1 months)**

- Median DOR was [redacted] for Cabo/Nivo vs. sunitinib, respectively, with the absolute difference in effect being [redacted]
- Median TTR was [redacted] for Cabo/Nivo vs. sunitinib, respectively, with the absolute difference in effect being [redacted]

**DBL June 24, 2021 (median follow-up: 32.9 months)**

- Median DOR was [redacted] for Cabo/Nivo vs. sunitinib, respectively, with the absolute difference in effect being [redacted]
- Median TTR was [redacted] for Cabo/Nivo vs. sunitinib, respectively, with the absolute difference in effect being [redacted]

[redacted]

#### 7.1.2.3.2 Efficacy results, ITT population

Detailed information on efficacy is provided in Appendix D.

**Primary Objective**

PFS: In all randomized subjects (ITT population), Cabo/Nivo demonstrated a statistically significant improvement in PFS as assessed by BICR and censoring for subsequent therapy (primary definition) compared with sunitinib. The Cabo/Nivo therapy doubled PFS compared to the sunitinib arm, and the risk of progression or death was reduced by 44-49%. The benefit observed at the June 24, 2021 DBL was consistent with that observed at the first data cut-off date (30 March, 2020). Also in the updated efficacy data from DBL June, 24, 2021, PFS benefit was observed regardless of baseline IMDC prognostic score and tumour PD-L1 expression status. KM plots of PFS per BICR in the ITT population at DBL March 2020

and DBL June 24, 2021 are shown in Figure 8 and Figure 9, respectively. The KM analysis also showed an early separation of the PFS curves, demonstrating the early benefit of Cabo/Nivo over sunitinib.

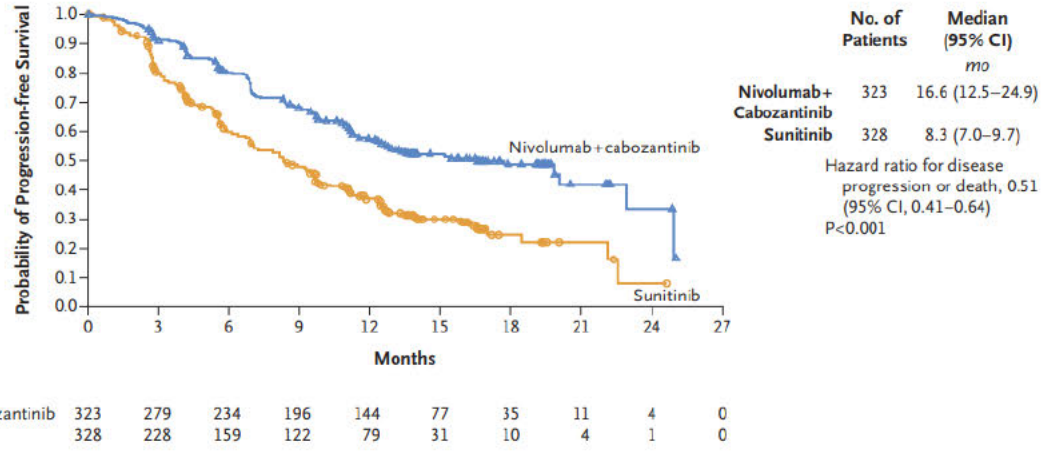
**DBL March 30, 2020 (median follow up: 18.1 months)**

- A total of 335 events had occurred, 144 (44.6%) in the Cabo/Nivo arm and 191 (58.2%) in the sunitinib arm. [Cabometyx EPAR, table 17 [32]]
- The median PFS for Cabo/Nivo vs. sunitinib was: 16.6 (95% CI: 12.5, 24.9) vs. 8.3 (95% CI: 7.0, 9.7) months, respectively. [Cabometyx EPAR, table 13 [32], [34]]
- Relative difference in effect: HR = 0.51 (95% CI: 0.41, 0.64), p<0.0001. [Cabometyx EPAR, table 13 [32], [34]]
- Absolute difference in effect: [redacted]

**DBL June 24, 2021 (median follow up: 32.9 months)**

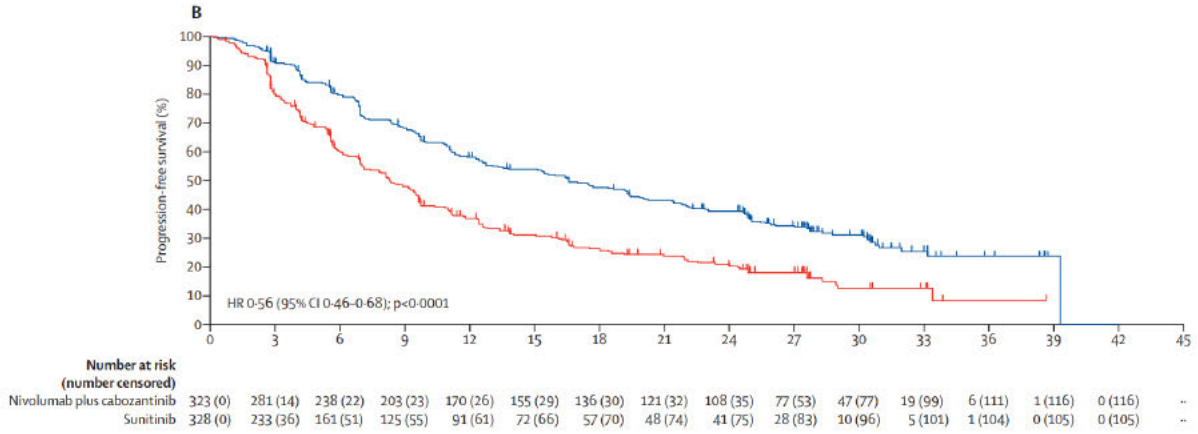
- A total of 430 events had occurred, 207 (64.1%) in the Cabo/Nivo arm and 223 (68.0%) in the sunitinib arm [35]
- The median PFS for Cabo/Nivo vs. sunitinib was: 16.6 (95% CI: 12.8, 19.8) vs. 8.3 (95% CI: 7.0, 9.7) months, respectively. [35]
- Relative difference in effect: HR = 0.56 (95% CI: 0.46, 0.68), p<0.0001. [35]
- Absolute difference in effect: [redacted]
- Both the 12-month and 24-month PFS rates were higher for Cabo/Nivo compared with sunitinib: 12-month PFS rates were [redacted] with an absolute difference in effect of [redacted] 24-months PFS rates were 39.5% (95% CI: 33.9, 45.1) for Cabo/Nivo vs. 20.9% (95% CI: 16.0, 26.3) for sunitinib [35] with an absolute difference in effect of [redacted]

**Figure 8: Kaplan-Meier plot of progression-free survival per BICR (primary definition) – CheckMate 9ER, All randomised patients, DBL March 30, 2020**




*Source: [34]*

**Figure 9. Kaplan-Meier plot of progression-free survival per BICR (primary definition) – CheckMate 9ER, All randomised patients, DBL June 24, 2021**




*Source: [35]*

**Secondary objectives**

Overall survival: In all randomized subjects (ITT population), Cabo/Nivo demonstrated significant improvement in patients' OS vs. sunitinib. The benefit observed at the June 24, 2021 DBL was consistent with that observed at the first data cut-off date (30 March, 2020). Figure 10 and Figure 11 show the KM plots of OS in the ITT population at DBL March 2020 and DBL June 24, 2021, respectively.

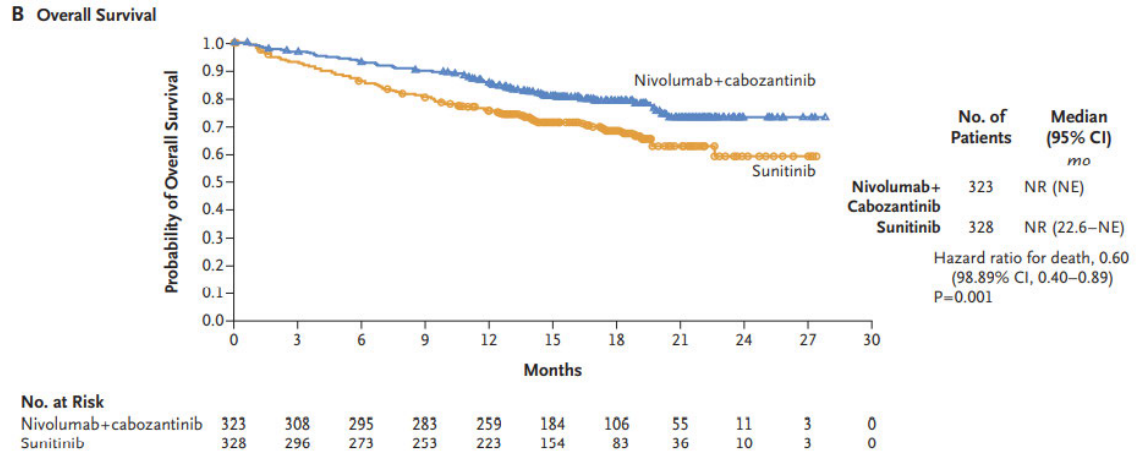
**DBL March 30, 2020 (median follow up: 18.1 months)**

- Median OS was not reached in either treatment group. [Cabometyx EPAR, table 13 [32], [34]]
- A total of 166 deaths had occurred (67 in the Cabo/Nivo arm, 99 in the sunitinib arm). [Cabometyx EPAR, table 13 [32], [34]]
- Relative difference in effect: HR = 0.60 (95% CI: 0.40, 0.89), p = 0.0010. [34]

**DBL June 24, 2021 (median follow up: 32.9 months)**

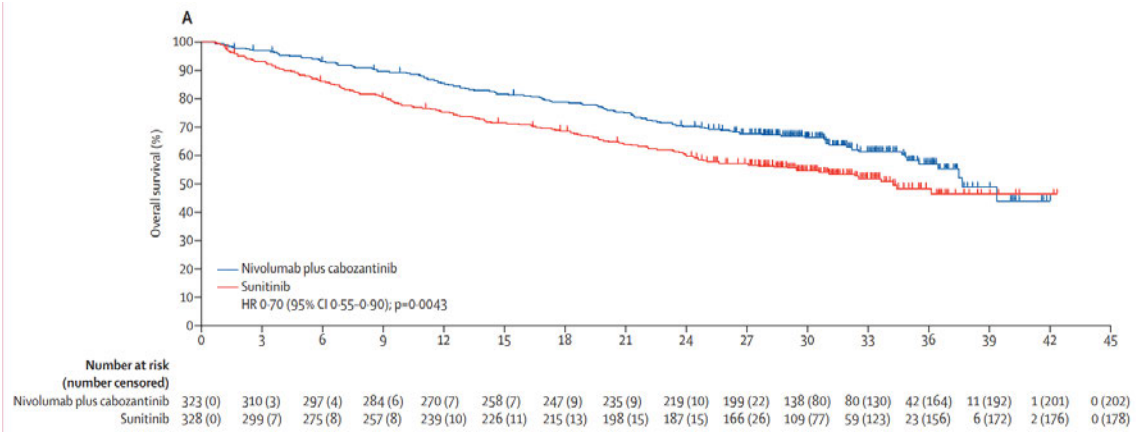
- A total of 271 deaths had occurred (121 in the Cabo/Nivo arm, 150 in the sunitinib arm) [35].
- Median OS was reached at 37.7 months (95% CI: 35.5, NE) in the Cabo/Nivo treatment group and at 34.3 months (95% CI: 29.0, NE) in the sunitinib treatment group [35], with an absolute difference of [redacted]
- Relative difference in effect: HR = 0.70 (95% CI: 0.55, 0.90), p = 0.0043. [35]
- Both 12-month and 24-month OS rates were higher for Cabo/Nivo compared with sunitinib: [redacted] with an absolute difference in effect of [redacted]; 24-month OS rates were 70% (95% CI: 65, 75) for Cabo/Nivo vs. 60% (95% CI: 55, 66) for sunitinib [35], and the absolute difference in effect was [redacted]

**Figure 10: Kaplan-Meier plot of overall survival – CheckMate 9ER, All randomised patients, DBL March 30, 2020**




*Source: [34]*

**Figure 11: Kaplan-Meier plot of overall survival – CheckMate 9ER, All randomised patients, DBL June 24, 2021**




*Source: [35]*

Objective response rate: In the ITT population, BICR-assessed confirmed ORR at DBL March 30, 2020, was statistically significantly higher with Cabo/Nivo than with sunitinib, and a greater proportion of subjects in the Cabo/Nivo arm had a CR (8.0% vs. 4.6%) or PR (47.7% vs. 22.6%). Further, the rate of progressive disease was more than twice lower in the Cabo/Nivo arm (5.6% vs. 13.7%). [34]

The results from DBL March 30, 2020 were confirmed at DBL June 24, 2021; the proportion of patients with a confirmed objective response was higher in the Cabo/Nivo group than in the sunitinib group and importantly, more patients also had a complete response with Cabo/Nivo than with sunitinib at this DBL. The rate of progressive disease continued to be more than twice lower in the Cabo/Nivo arm (6% vs. 14%) [35]. Results on confirmed best overall response per RECIST for the ITT population at DBL March 30, 2020 and DBL June 24, 2021 are presented in Table 10.

**DBL March 30, 2020 (median follow up: 18.1 months)**

- BICR-assessed ORR was 55.7% (95% CI: 50.1, 61.2) vs. 27.1% (95% CI: 22.4, 32.3) for Cabo/Nivo vs. sunitinib respectively [Cabometyx EPAR, table 13 [32], [34]]
- Relative difference in effect: OR: 3.52 (95% CI: 2.5, 4.95), [redacted]. [Cabometyx EPAR, table 13 [32], [129]]
- Absolute difference in effect: 28.6% (95% CI: 21.7, 35.6), p<0.0001. [Cabometyx EPAR, table 13 [32], [129]]

**DBL June 24, 2021 (median follow up: 32.9 months)**

- BICR-assessed ORR was 56% (95% CI: 50, 61) vs. 28% (95% CI: 24, 34) for Cabo/Nivo vs. sunitinib, respectively. [35]
- Relative difference in effect: OR: [redacted]
- Absolute difference in effect [redacted]

**Table 10: Confirmed Best Overall Response (BICR) - CheckMate 9ER, All randomised patients, DBL March 30, 2020 vs. DBL June 24, 2021**

| Subjects in ITT population | Cabo/Nivo N=323 | Sunitinib N=328 | Cabo/Nivo N=323 | Sunitinib N=328 |
|---|---|---|---|---|
| | DBL March 30, 2020 | | DBL June 24, 2021 | |
| **Confirmed BOR[a] per BICR, n (%)** | | | | |
| **Complete response** | 26 (8.0) | 15 (4.6) | 40 (12) | 17 (5) |
| **Partial response** | 154 (47.7) | 74 (22.6) | 140 (43) | 76 (23) |
| **Stable disease** | 104 (32.2) | 138 (42.1) | 105 (33) | 134 (41) |
| **Progressive disease** | 18 (5.6) | 45 (13.7) | 20 (6) | 45 (14) |
| **UTD (unable to determine)** | 21 (6.5) | 55 (16.8) | 18 (6) | 55 (17) |

*BICR: blinded independent central review; BOR: best overall response; CMH: Cochran-Mantel-Haenszel; CI: confidence interval; CR: complete response; IMDC: International Metastatic RCC Database Consortium; IRT: interactive response technology; ITT: intent to treat; ORR: objective response rate; PR: partial response: RECIST: Response Evaluation Criteria In Solid Tumours.*
*BOR is defined as the best response recorded between randomisation and objectively documented progression per RECIST 1.1 or subsequent therapy (including tumour-directed radiotherapy and tumour-directed surgery), whichever occurs first. For participants without document progression or subsequent therapy, all available response designations will contribute to the BOR assessment.*
*Sources: Cabometyx EPAR, table 17 [32], [35]*

Duration of response and time to response: In all randomized subjects, median DOR was longer with Cabo/Nivo compared to sunitinib, and 88 (49%) of 180 versus 42 (45%) of 93 responses were ongoing at DBL. BICR-assessed median TTR was shorter with Cabo/Nivo than with sunitinib, confirming the results from DBL march 30, 2020. Figure 12 and Figure 13 shows the KM plots of DOR in the ITT population at DBL March 2020 and DBL June 24, 2021, respectively. [35]

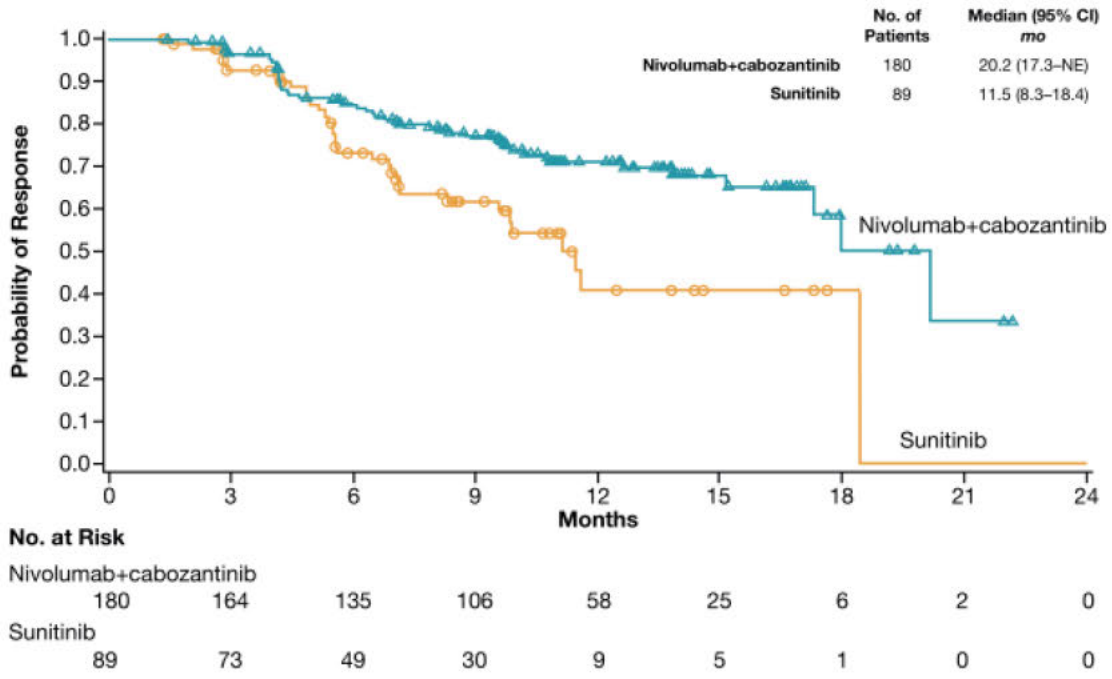
**DBL March 30, 2020 (median follow-up: 18.1 months)**

- Median DOR was 20.2 [redacted] vs. 11.5 [redacted] for Cabo/Nivo vs. sunitinib, respectively, with the absolute difference in effect being [redacted]
- Median TTR was 2.8 [redacted] vs. 4.2 [redacted] months for Cabo/Nivo vs. sunitinib, respectively, with the absolute difference in effect being [redacted] [Cabometyx EPAR, page 127 [32]]

**DBL June 24, 2021 (median follow-up: 32.9 months)**

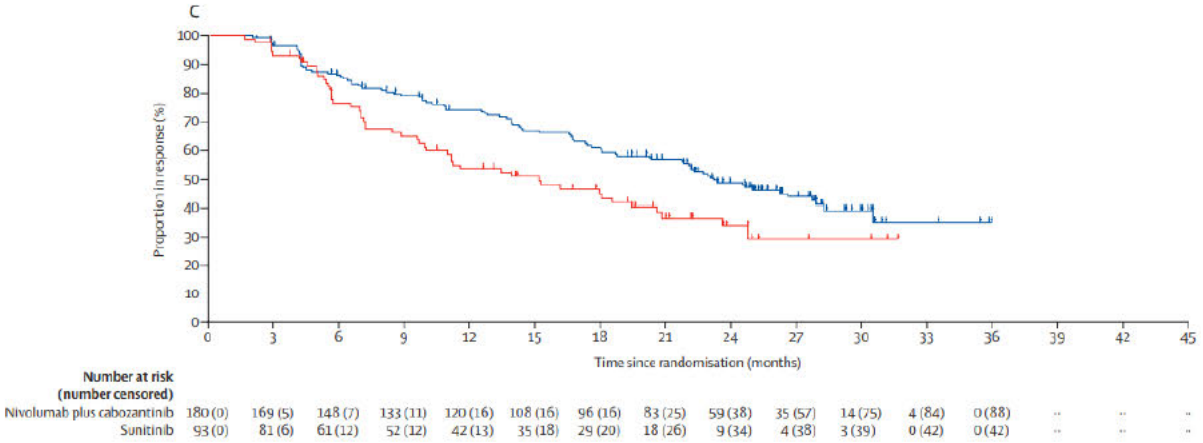
- Median DOR was 23.1 (95% CI: 20.2, 27.9) vs. 15.1 (95% CI: 9.9, 20.5) months for Cabo/Nivo vs. sunitinib, respectively, with the absolute difference in effect being [redacted]
- Median TTR was 2.8 (IQR: 2.8, 4.2) vs. 4.2 (IQR: 2.8, 7.1) months for Cabo/Nivo vs. sunitinib, respectively, with the absolute difference in effect being [redacted]

**Figure 12: Kaplan-Meier Plot of duration of response per BICR – CheckMate 9ER, All randomized patients, DBL March 30, 2021**




*Abbreviations: NE, not estimable. Source: [34]*

**Figure 13: Kaplan-Meier Plot of duration of response per BICR – CheckMate 9ER, All randomized patients, DBL June 24, 2021**




*Source: [35]*

**Exploratory endpoints**

The publication by Cella *et al.* describes the patient-reported outcome (PRO) results from CheckMate 9ER at the DBL Sep 10, 2020. [41] In addition, updated PRO results from the DBL June 24, 2020 were presented at the 2022 ASCO Genitourinary Cancers Symposium. [42] Disease-related symptoms were evaluated using the 19-item Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI-19), and global health status was assessed with the three-level EQ-5D (EQ-5D-3L) visual analogue scale (VAS) and UK utility index. The study reported on the FKSI-19 total score (19 items; score range 0–76) and related scales: the FKSI-19 disease-related symptoms version 1 (nine items; score range 0–36), FKSI-19 disease-related symptoms physical (12 items; score range 0–48), FKSI-19 functional wellbeing (three items; score range 0–12), and the single-item GP5 (FKSI-19 item 16; score range 0–4), which assesses bother associated with the side-effects of treatment. The EQ-5D-3L descriptive system includes five items that assess current problems related to mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. All PRO analyses were done in the ITT population and these exploratory analyses were not performed in any subgroups. Both the FKSI-19 and EQ-5D-3L measures were completed on Day 1 of each treatment cycle prior to any study-related procedures, every 2 weeks after baseline in the Cabo/Nivo arm and every 6 weeks after baseline in the sunitinib arm. Completion rates for PRO instruments were defined as the proportion of patients who completed evaluable forms (i.e., >50% of the items completed according to the scoring algorithms for FKSI-19 and all five items of the descriptive system or the VAS for EQ-5D-3L) among those who were expected to complete them (i.e., who were alive and still on study), according to the schedule of assessments (Figure 14). [41]

Overall, at the most recent data cut (DBL 24 June, 2020), for both treatment arms the percentage of patients completing the FKSI-19 and EQ-5D-3L instruments at baseline were high (>90%). The completion rates declined over time, but remained high in both treatment arms through week 115 (> 75% except for week 109, where it was 73% in the sunitinib arm). For the DBL Sept 10, 2020, completion of PRO assessments, including numbers of patients with data and patients available to be assessed, is shown in Figure 15. For the DBL Sept 10, 2020 and the DBL June 24, 2021, the number of patients included in the different PRO analyses are available in Table A 22 and Table A 23, respectively.

The observed decrease in the proportion of patients who completed PRO assessment is likely due to patients' treatment discontinuation. Patients could discontinue therapy due to progression, death or other reasons defined in the study protocol. Thereafter, PRO assessment was not collected for these patients.

Longitudinal change from baseline in PRO scores was evaluated with a mixed-model repeated measures (MMRM) analysis, which assumed that missing observations were missing at random. In addition, a prespecified sensitivity analysis using a pattern mixture model (PMM) with sequential modelling with multiple imputation and delta adjustment was done (ie, assuming missing not at random). Analyses included all visits with at least ten patients in each group. Follow-up visits and unscheduled visits were excluded from MMRM analyses. The dependent variable was changed from baseline for each PRO score. The model included the treatment group, timepoint (study week), and randomisation factors (IMDC prognostic score, PD-L1 tumour expression, and region) as fixed-effect categorical factors, the baseline PRO score as a continuous parameter, and the interactions between baseline and timepoint and between treatment and timepoint. An unstructured covariance matrix was first used for model fitting and, upon a failure of the iterative procedure to converge, a heterogeneous Toeplitz covariance structure was used. Effect sizes, expressed as Hedges' g with 95% CIs, were also calculated.

Time to first deterioration and time to confirmed deterioration were assessed for FKSI-19 and EQ-5D-3L. Time to first deterioration was defined as the time from randomisation to the first date that a patient had a change from baseline meeting or exceeding the prespecified primary meaningful change threshold for the scale. Time to confirmed deterioration was defined as the time from randomisation to the date of first deterioration in PRO scores that was either confirmed at the next consecutive scheduled visit common for both groups (at least 6 weeks apart), or followed by dropout, resulting in missing data. Patients with no baseline assessment were censored at the randomisation date. Patients without an assessment after baseline were censored at the date of the baseline assessment. Patients who did

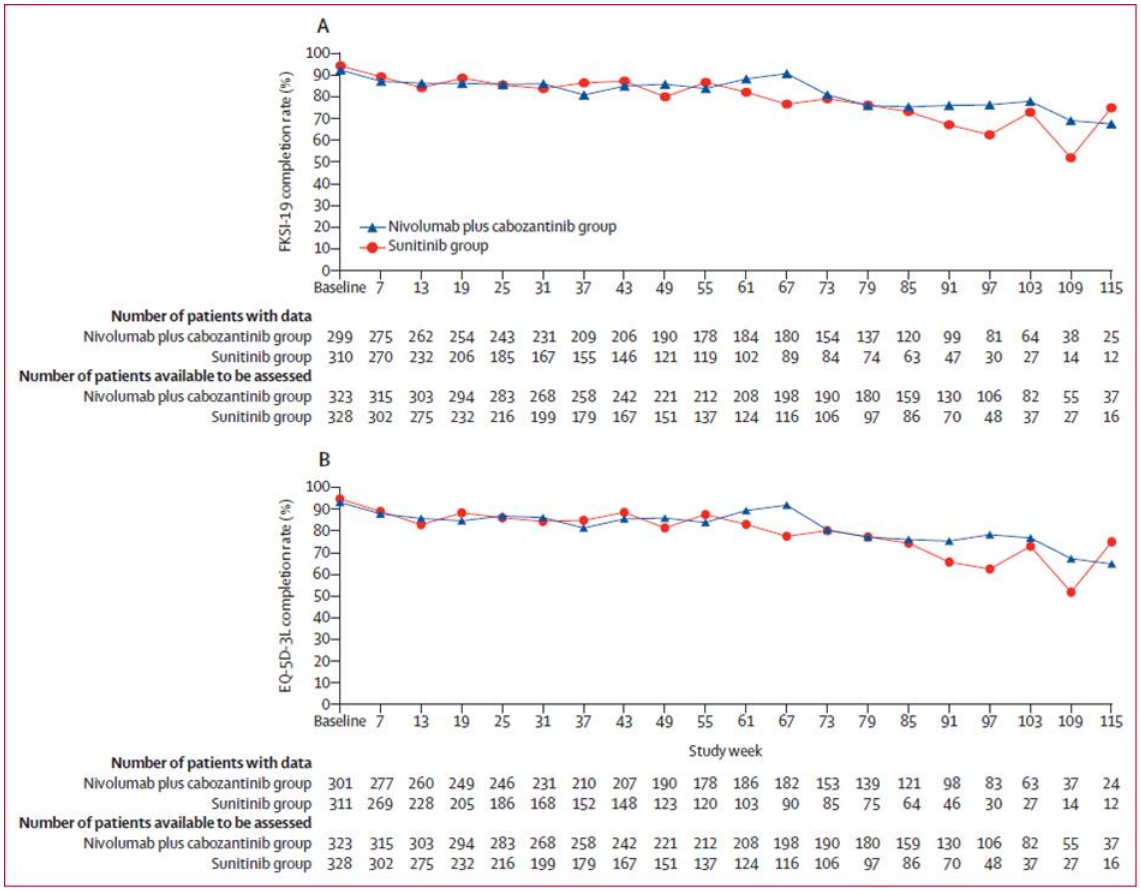
not experience deterioration before the time of the data cut-off or patients whose baseline scores did not allow for further deterioration were censored at the date of the last available PRO assessment (i.e., date of the last non-missing value). Death or progression were not considered deterioration events. The Kaplan-Meier product limit method was used for the time-to-deterioration analyses. Inferences for time-to-event endpoints were assessed by a log-rank test stratified by the factors at randomisation. HRs and associated 95% CIs were ascertained with a stratified Cox proportional hazards model, using the same stratification factors as above. [41]

**Figure 14: Study visits and PRO frequency of collection**

| 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* | FU1† | FU2† | Survival FU‡ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab + cabozantinib | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | ✓ | | | |
| *PRO collection* | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | X | X | X |
| Sunitinib | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ | | | ✓ | | | |
| *PRO collection* | X | | | | | | X | | | | | | X | | | | | | X | | | | | | X | X | X | X |

*FU=follow-up. PRO=patient-reported outcome. Orange columns indicate assessment points common to treatment arms that were used in analysis. Check marks indicate clinic visits; × indicates PRO collection. *After week 25, cycles continued until disease progression or unacceptable toxicity (nivolumab for a maximum of 2 years); PRO collection for nivolumab plus cabozantinib occurred every 2 weeks thereafter, and for sunitinib every 6 weeks thereafter. †Follow-up visit 1 had to occur 30 days (±7 days) from the last dose of study drug or could be performed on the date of discontinuation if that date was greater than 42 days from last dose. Follow-up visit 2 had to occur ~100 days (±7 days) from last dose of study drug. Both FU visits were conducted in person. ‡Survival follow-up visits had to occur every 3 months from follow-up visit 2; only the three-level version of the EQ-5D (EQ-5D-3L) was administered at these visits.*
*Source: [41]*

**Figure 15: Completion of patient-reported outcome assessments (A) FKSI-19. (B) EQ-5D-3L (DBL Sept 10, 2020)**




*Abbreviations: FKSI-19, 19-item Functional Assessment of Cancer Therapy-Kidney Symptom Index; EQ-5D, EuroQol Health Questionnaire Instrument.*
*Source: [41]*

**DBL Sep 10, 2020 (median follow up: 23.5 months)**

The overall difference in mean score change from baseline until week 115 was nominally significant in favour of Cabo/Nivo vs. sunitnib for FKSI-19 total score, FKSI-19 disease-related symptoms version 1, EQ-5D-3L VAS as well as for EQ-5D-3L UK utility index [41]:

- FKSI-19 total score (LS mean change from baseline) was -0.64 (SE: 0.46) in the Cabo/Nivo arm compared to -3.02 (SE: 0.53) in the sunitinib arm. Change from baseline in PRO scores indicated that Cabo/Nivo was associated with more favourable outcomes vs. sunitinib, with a treatment difference of 2.38 (95% CI: 1.20, 3.56), nominal p<0.0001. [41]
- FKSI-19 disease-related symptoms ver. 1 (LS mean change from baseline) was 0.76 (SE: 0.19) and -0.57 (SE: 0.22) for Cabo/Nivo and sunitinib, respectively. The treatment difference was 1.33 (95% CI:8.84, 1.83), nominal p<0.0001. [41]
- EQ-5D-3L VAS (LS mean change from baseline) was 2.23 for Cabo/Nivo vs. -1.25 for sunitinib, with a treatment difference of 3.48 (95% CI: 1.58, 5.39), nominal p=0.0004. [41]
- EQ-5D-3L UK utility index (LS mean change from baseline) was -0.02 and -0.06 for Cabo/Nivo and sunitinib, respectively, with a treatment difference of 0.04 (95% CI: 0.01, 0.07), nominal p=0.0036. [41]

In the time-to-deterioration analyses for FKSI-19 total score, patients in the Cabo/Nivo group had a longer median time to confirmed deterioration in FKSI-19 total score than did patients in the sunitinib group [41]:

- FKSI-19 total score (time to confirmed deterioration event) was 19.38 (95% CI: 12.48-NE) months and 6.97 (95% CI:4.50, 10.09) months for Cabo/Nivo and sunitinib, respectively. The treatment difference was 12.41, and confirmed deterioration event HR was 0.63 (95% CI: 0.50, 0.80), nominal p=0.0001. [41]
- FKSI-19 disease-related symptoms version 1 (time to confirmed deterioration event) was not reached in the Cabo/Nivo arm, and 15.28 (months 95% CI: 10.12, NE) in the sunitinib arm. HR was 0.65 (95% CI: 0.49, 0.86), p= 0.0020. [41]

Further, patients receiving Cabo/Nivo had a significantly longer median time to confirmed deterioration in EQ-5D-3L VAS score than in the sunitinib group [41]:

- EQ-5D VAS score (time to confirmed deterioration event) was not reached in the Cabo/Nivo arm, and 18.04 (95% CI: 11.17, NE) in the sunitinib arm. HR: 0.73 (95% CI:0. 56, 0.96), p=0.022 [41]
- EQ-5D-3L UK utility index (time to confirmed deterioration event) was 22.14 (95% CI: 13.83, NE) and 12.58 (95% CI: 10.41, 19.32) in the Cabo/Nivo arm, and in the sunitinib arm respectively, with a treatment difference of 9.56 months. HR: 0.78 (95% CI: 0.62, 1.00), p=0.047. [41]

Moreover, Cella *et al.* [41] also reported responses to the FKSI-19 GP5 item 16, which assesses bother associated with the side-effects of treatment, where 80% of the patients in the Cabo/Nivo group and 78% in the sunitinib group reported "not at all" in response to the item. The number of patients who felt "quite a bit" or "very much" bothered by side-effects of treatment throughout the first year of the study when toxicity is most evident was in favour of Cabo/Nivo, with a smaller proportion of patients Cabo/Nivo reporting that they were bothered by treatment side-effects than those receiving sunitinib. Overall, at all timepoints the proportion of patients who reported little to no bother was greater with Cabo/Nivo than with sunitinib. [41]

**DBL June 24, 2021 (median follow-up: 32.9 months)**

Overall, the results from DBL June 24, 2021 with median follow-up of 32.9 months confirmed the results from the DBL Sept 10, 2020 published by Cella *et al.* [41]

- FKSI-19 total score (LS mean change from baseline) was -0.47 in the Cabo/Nivo arm compared to -2.84 in the sunitinib arm. Change from baseline in PRO scores indicated that Cabo/Nivo was associated with more favourable outcomes vs. sunitinib, with a treatment difference of 2.37 (95% CI: 1.19, 3.54), nominal p<0.0001. [42, 43]
- FKSI-19 disease-related symptoms ver. 1 (LS mean change from baseline) was 0.71 and -0.46 for Cabo/Nivo and sunitinib, respectively. The treatment difference was 1.17 (95% CI: 0.68, 1.66), nominal p<0.0001. [42, 43]
- EQ-5D-3L VAS (LS mean change from baseline) was 2.73 for Cabo/Nivo vs. -0.95 for sunitinib, with a treatment difference of 3.68 (95% CI: 1.83, 5.54), nominal p=0.0001. [42, 43]
- EQ-5D-3L UK utility index (LS mean change from baseline) was -0.01 and -0.06 for Cabo/Nivo and sunitinib, respectively, with a treatment difference of 0.05 (95% CI: N/A), nominal p=0.001. [42]

In the time-to-deterioration analyses for FKSI-19 total score, patients in the Cabo/Nivo group had a longer median time to confirmed deterioration in FKSI-19 total score than did patients in the sunitinib group:

- FKSI-19 total score (time to confirmed deterioration event) was 18.23 (95% CI: N/A) months and 6.97 (95% CI: N/A) months for Cabo/Nivo and sunitinib, respectively. The treatment difference was 11.26, and confirmed deterioration event HR was 0.66 (95% CI: 0.52, 0.84), nominal p=0.0005. [42]
- FKSI-19 disease-related symptoms version 1 (time to confirmed deterioration event) was not reached in the Cabo/Nivo arm, and 15.28 (95% CI: N/A) months in the sunitinib arm. HR was 0.65 (95% CI: 0.5, 0.86), p=0.0020. [42]

Further, median time to confirmed deterioration in EQ-5D-3L VAS score was longer in patients receiving Cabo/Nivo than in the sunitinib group:

- EQ-5D VAS score (time to confirmed deterioration event) was 34.56 (95% CI: N/A) months in the Cabo/Nivo arm, and 17.74 (95% CI: N/A) months in the sunitinib arm. The treatment difference was 16.82 months and HR was 0.74 (95% CI: 0.58, 0.95), p=0.0183 [42]
- EQ-5D-3L UK utility index (time to confirmed deterioration event) was 19.35 (95% CI: N/A) and 12.58 (95% CI: N/A) in the Cabo/Nivo arm, and in the sunitinib arm respectively, with a treatment difference of 6.77 months. HR: 0.81 (95% CI: 0.64, 1.02), p=0.0747 [42].

A breakdown of responses to the FKSI-19 GP5 item 16 was reported [42, 43], showing that fewer patients in the Cabo/Nivo arm reported to be bothered by side effects compared with patients in the sunitinib arm. Based on weighted generalized estimating equations, patients in the Cabo/Nivo arm were 48% less likely to be notably bothered by side effects than patients in sunitinib arm (OR: 0.52 [95% CI: 0.35, 0.77]) [42, 43]

Overall, changes from baseline through week 151 favored Cabo/Nivo with nominal significant differences between treatments observed for all the scores reported here (FKSI-19 total score and DRS, EQ-5D-3L VAS and UK utility index) . Similarly, decreased risk of deterioration was observed with Cabo/Nivo vs. sunitinib for all the scores reported here except EQ-5D-3L UK utility index, irrespective of the deterioration definition used, first (TTFD), confirmed (TTCD) or definitive (TTDD) deterioration. In conclusion, at nearly 3 years of follow-up, patients continued to report improved HRQoL with Cabo/Nivo compared with sunitinib and were also less likely to be notably bothered by treatment side effects than patients in the sunitinib arm [42, 43] These results further support the treatment benefit of Cabo/Nivo over sunitinib monotherapy.

**Minimal clinically important differences**

In the protocol for the mRCC treatment guideline issued by DMC, there are minimal clinically important differences (MCIDs) set for OS, PFS, quality of life, SAEs and ORR. The MCIDs for median PFS and OS are set at a difference of 3 months. [28] A comparison of the MCIDs set by the DMC and results from Cabo/Nivo vs. sunitinib (CheckMate 9ER) is presented in Table 11. Median OS was not reached at DBL March 30, 2020, meaning that absolute differences between the two treatment groups cannot be calculated. However, at DBL June 24, 2021, the median OS was reached in both treatment arms and both in the IMDC intermediate/poor risk subgroup and ITT population. At this DBL, absolute differences of [redacted] respectively, were observed. [redacted]. The MCID for ORR is set to 10% points, which is indeed surpassed for Cabo/Nivo vs. sunitinib, with an absolute difference of 29.0% points at DBL March 30, 2020 and [redacted] at DBL June 24, 2021 in the intermediate/poor subgroup. Absolute differences in ORR in the ITT population at DBL March 30, 2020 and DBL June 24, 2021 were 28.6% points and [redacted] respectively . In terms of quality of life, even though not reaching the MCID of 5 points, the change from baseline in PRO scores indicated that Cabo/Nivo was associated with more favourable outcomes vs. sunitinib; FSK-19 and EQ-5D VAS score (mean change from baseline) with treatment differences of 2.37 points and 3.68, respectively (DBL June 24, 2021). Taken together, the treatment differences between Cabo/Nivo and sunitinib reported in the CheckMate 9ER study highlights the promising efficacy of Cabo/Nivo.

**Table 11: MCID according to DMC and efficacy outcome of CheckMate 9ER, Cabo/Nivo vs. Sunitinib**

| Efficacy outcome | DMC MCID | Intermediate/poor 18.5 months follow-up | Intermediate/poor 32.9 months follow-up | ITT population 18.5 months follow-up | ITT population 32.9 months follow-up |
|---|---|---|---|---|---|
| **Median OS** | 3 months difference | Median OS not reached | [redacted] 37.6 vs. 29.0) HR: 0.66 , p=0.002 [37, 117] | Median OS not reached | [redacted] (37.7 vs. 34.3) HR: 0.70, p= 0.0043 [35, 127] |

| | | | | | |
|---|---|---|---|---|---|
| **Median PFS** | 3 months difference | [redacted] (16.6 vs. 7.1 months) HR: 0.48 [33, 114] | [redacted] | [redacted] (16.6 vs. 8.3 months), HR: 0.51, p<0.0001 [32];[34];[124] | [redacted] (16.6 vs. 8.3 months), HR: 0.56, p<0.0001 [35, 125] |
| **QoL (FKSI-19)** | Difference of 5 points | NA | NA | Mean change from baseline; 1.33 treatment difference [41]* | Mean change from baseline; 2.37 treatment difference [42, 43] |
| **QoL (EQ-5D VAS score)** | Difference of 5 points | NA | NA | Mean change from baseline; 3.48 treatment difference [41]* | Mean change from baseline; 3.68 treatment difference [42, 43] |
| **ORR, proportion of patients reaching ORR** | Absolute difference of 10% points | 29.0% point difference (52.2% vs. 23.0%) [33, 121] | [redacted] (52.6% vs. 23.8%) [36, 39] | 28.6% point difference (55.7% vs. 27.1%) [32, 34] | [redacted] (56% vs. 28%) [35, 36] |
| **SAE, proportion of patients with AE grade 3-4** | Absolute difference of 10% points | NA | NA | [redacted] (70.3% vs. 65.3%) [32] | [redacted] |

**HRQoL results with 18.5 months follow-up do exist, but have only been presented as abstract/poster, and therefore the published HRQoL results with 23.5 months follow-up (DBL Sept 10, 2020) are included in the dossier and in this table for reference instead.*

#### 7.1.2.4 Safety results

Detailed safety information is provided in Appendix E.

The safety data presented here, in support of the new indication, are derived from 320 subjects treated with Cabo/Nivo in the ongoing CheckMate 9ER study. The data are based on DBL 30 March, 2020 with minimum 10.6 months of follow-up for OS. Updated safety data were published at DBL June 24, 2021, and are presented separately, as indicated in Appendix E.

Briefly, safety results from 320 subjects treated in the 1L setting with Cabo/Nivo in the CheckMate 9ER study were used to characterize the safety profile of the Cabo/Nivo combination regimen in aRCC. The 640 patients who received at least 1 dose of study treatment constitute the safety population (320 cabozantinib, 320 sunitinib). Analyses of all-cause AEs were conducted using the 30-day safety window and repeated using the 100-day safety window for drug-related AEs. Deaths were summarised within 30 days and 100 days of the last dose received. Safety was analysed at the time of primary endpoint analysis and summarised through the DBL 30 March, 2020. [33]

**DBL March 30, 2020**

At DBL March 30, 2020, a total of 67 (20.9%) subjects in the Cabo/Nivo arm and 99 (30.9%) subjects in the sunitinib arm had died during the study. The primary reason for death was disease progression for 51 subjects treated with Cabo/Nivo (15.9% of the total number of Cabo/Nivo subjects in the safety population, n=320) and 74 subjects treated with sunitinib (23.1% of the total sunitinib subjects in the safety population, n=320). The number of deaths attributed to study drug toxicity was low for both Cabo/Nivo and sunitinib arms (1 subject with small intestine perforation for Cabo/Nivo vs. 2 subjects for sunitinib: one due to respiratory distress and one due to pneumonia. [33]

The overall incidence of AEs was similar in both arms, while exposure to Cabo/Nivo was 50% longer than exposure to sunitinib. When incidence was exposure-adjusted, the overall rate of AEs was lower in patients treated with Cabo/Nivo as compared to sunitinib (1,705.2 events per 100 person-years vs. 1,852.6 events per 100 person-years, respectively). [33]

All-causality grade 3-4 AEs were reported in 70.3% of the Cabo/Nivo treated subjects and 65.3% in the sunitinib treated subjects [32]. Drug-related grade 3-4 AEs were reported in 60.6% and 50.6% of subjects treated with Cabo/Nivo and sunitinib respectively. [32] All-causality AEs leading to discontinuation of any study drug were reported in 19.7% and 16.9% of subjects, and drug-related AEs leading to discontinuation of any study drug were reported in 15.3% and 8.8% of subjects treated with Cabo/Nivo and sunitinib, respectively. [32] The most commonly reported all-causality AEs of any grade were diarrhea (63.8% for Cabo/Nivo vs. 47.2% for sunitinib), Palmar-plantar erythrodysaesthesia syndrome (PPES) (40.0% vs. 40.6%), and hypertension (34.7% vs. 37.2%) in both treatment groups. [34]

**DBL June 24, 2021**

At DBL June 24, 2021, a total of 121 (37.5%) subjects in the Cabo/Nivo arm and 150 (45.7%) subjects in the sunitinib arm had died during the study. [35]

All-causality grade 3-4 AEs had occurred in [redacted] of the 320 patients receiving Cabo/Nivo and in [redacted] of the 320 patients receiving sunitinib, with an estimated absolute difference of [redacted] comparing Cabo/Nivo and sunitinib. [redacted]

Overall, [redacted] of the patients in the combination group discontinued at least one of the trial drugs owing to all-causality AE, and [redacted] in the sunitinib group. The estimated absolute difference in effect was [redacted] comparing Cabo/Nivo and sunitinib. [40]

Since the primary analysis (DBL March 30, 2020), no new deaths that investigators considered to be related to treatment occurred with Cabo/Nivo; one additional death that was considered to be related to treatment occurred with sunitinib (sudden death).

Safety data specifically for patients with intermediate/poor risk have not been published, and therefore the safety data reported here reflect that of the overall safety population. However, when comparing unpublished safety subgroup analyses for patients with favourable risk with patients with intermediate/poor risk, no large differences in all-causality (any grade, grade 3-4) AEs, SAEs and AEs leading to discontinuation were observed between subjects with IMDC favourable risk vs. the subgroup with intermediate/poor risk for the Cabo/Nivo arm, [32] supporting that the safety data presented for the overall safety population here is representative for patients with intermediate/poor risk. The DMC expert committee on kidney cancer has also confirmed in relation to previous assessments of new drugs within aRCC that occurrence of AEs is not correlated with prognostic group [132]. Furthermore, the vast majority of the patients included in the CheckMate 9ER study had intermediate/poor risk (77.6%).[34]

#### 7.1.2.5 Conclusion

Cabo/Nivo showed significant benefits over sunitinib with respect to PFS, OS, and HRQoL in patients with previously untreated aRCC. The positive results of CheckMate 9ER prompted the inclusion of Cabo/Nivo in the ESMO guidelines as a 1L therapy in aRCC.[44] Cabozantinib monotherapy is approved for 1L therapy of IMDC intermediate/poor risk aRCC patients by EMA (and is the first-choice for 2L treatment of aRCC in Denmark, which further supports the clinical value of cabozantinib in RCC).

Overall, with extended follow-up and results available from the pre-planned final overall survival analysis per protocol of the CheckMate 9ER trial, Cabo/Nivo has been demonstrated to offer significant and clinically meaningful benefits for 1L aRCC patients as shown by the superior efficacy and QoL profile combined with a manageable safety profile.

## 7.2 Efficacy and safety of ipilimumab+ nivolumab compared to sunitinib for patients with previously untreated advanced or metastatic renal cell carcinoma

### 7.2.1 Relevant studies

#### 7.2.1.1 CheckMate 214

CheckMate 214 (NCT02231749) is a global, open-label, randomized, phase III trial designed to compare the efficacy and safety of Ipi/Nivo vs. sunitinib in patients with previously untreated advanced or metastatic renal-cell carcinoma with a clear-cell component. In total, 1,096 patients were randomized (in a 1.1 ratio) to Ipi/Nivo (ITT patients, n = 550; intermediate/poor risk patients, n = 425; favourable-risk patients, n = 125) or sunitinib (ITT patients, n = 546; intermediate/poor risk patients, n = 422; favourable-risk patients, n = 124). Overall, 547 patients in the Ipi/Nivo arm and 535 in the sunitinib arm received treatment and were included in the safety analyses. [133] The study characteristics are summarized in Table 12 below. For detailed study characteristics, including methods of analysis see Appendix B. For baseline characteristics of patients included in the study see Appendix C.

**Table 12: Study characteristics of CheckMate 214**

| Study/Phase/Status | CheckMate 214/Phase 3/ongoing |
|---|---|
| **Study design** | Phase 3, randomised, open-label study of nivolumab plus ipilimumab followed by nivolumab monotherapy versus sunitinib monotherapy in patients with previously untreated advanced or metastatic RCC with a clear-cell component. Randomization (in a 1:1 ratio) was performed with a block size of 4 with stratification according to IMDC risk score (0 [favourable] vs. 1 or 2 [intermediate] vs. 3 to 6 [poor risk]) and geographic region (United States vs. Canada and Europe vs. the rest of the world). [133] |
| **Treatment** | 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. [N=550]<br>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. [N=546]<br>[133] |
| **Study population** | Subjects (≥1 8 years) with no prior systemic therapy for advanced RCC. Subjects were required to have histologically confirmed advanced or metastatic RCC with a clear-cell component. [133] |
| **Number of subjects** | All Randomised, N = 1,096 |
| **Primary objectives** | ORR per IRRC, OS and PFS in IMDC intermediate/poor risk participants |
| **Secondary objectives** | The efficacy measures for primary endpoint were also secondary endpoints in ITT patients |

| Study/Phase/Status | CheckMate 214/Phase 3/ongoing |
|---|---|
| **Explorative endpoint** | To evaluate health-related (HR)QoL using the FKSI-19, FACT-G and EQ-5D-3L instruments in ITT and intermediate/poor risk patients. To evaluate same efficacy measures as for primary endpoint in favourable-risk patients. [106] |
| **Follow-up time** | Minimum follow-up of 5 years/median follow-up of 67.7 months [45] |

*FKSI: Functional Assessment of Cancer Therapy - Kidney Symptom Index; HRQoL: Health related quality of life; IMDC: International Metastatic Renal Cell Carcinoma Database Consortium; IRRC: independent radiology review committee; ORR: objective response rate; OS: overall survival; PFS: progression-free survival*

## 7.2.2 Efficacy and Safety CheckMate 214

### 7.2.2.1 Efficacy outcomes

The purpose of the CheckMate 214 trial was to compare ORR, PFS and OS of nivolumab combined with ipilimumab to sunitinib monotherapy in patients with previously untreated aRCC. Co-primary trial-endpoints were OS, PFS per independent radiology review committee (IRRC) and ORR per IRRC (with DOR), OS and (PFS) in IMDC intermediate-risk/poor-risk patients. These efficacy measures were also secondary endpoints in ITT patients and exploratory endpoints in favourable-risk patients. HRQoL was another exploratory endpoint and was evaluated using the FKSI-19, Functional Assessment of Cancer Therapy-General (FACT-G) and EQ-5D-3L instruments. HRQoL was assessed in ITT and intermediate/poor risk patients. [45, 106].

For the assessment of Cabo/Nivo vs. Ipi/Nivo, the intermediate/poor risk population is the relevant one and also reflects the EMA indication for Ipi/Nivo in 1L aRCC, why only results for the co-primary endpoints of the CheckMate 214 trial are presented here. Data from the most recent data cut and longest available follow-up (DBL Feb 24, 2021 with median follow-up of 67.7 months for most endpoints) are presented in this application [45, 106]. Detailed information on efficacy is provided in Appendix D.

### 7.2.2.2 Assessment of safety

The assessment of safety was based on the incidence of treatment-related AEs, treatment-related select AEs, treatment-related AEs leading to discontinuation, and corticosteroid use for treatment-related select AEs. AEs were graded according to the NCI Common Terminology Criteria for Adverse Events v4.0. 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). Treatment related AEs occurring between the first dose and 30 days after last dose of study therapy were reported. [47].

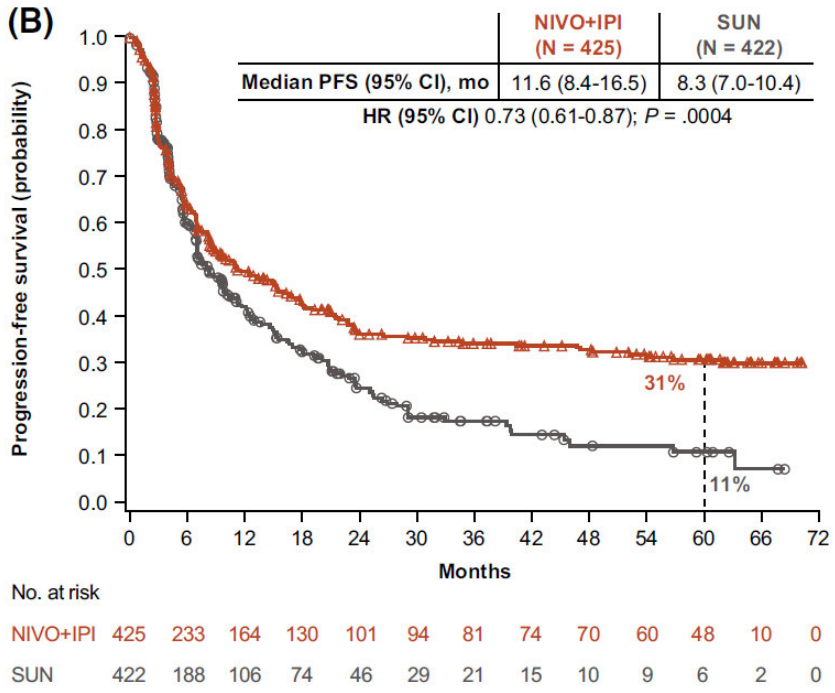
### 7.2.2.3 Efficacy results in IMDC intermediate/poor risk population

Progression-free survival: PFS was defined as the "time between the date of randomization 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". At DBL Feb 24, 2021, Ipi/Nivo demonstrated improvement in PFS per IRRC compared with sunitinib in all randomized subjects with IMDC intermediate/poor prognostic risk. The KM plot for PFS per IRRC in the intermediate/poor risk subgroup is shown in Figure 16. [45]

Median PFS was longer with Ipi/Nivo compared with sunitinib: 11.6 (95% CI: 8.4, 16.5) vs. 8.3 (95% CI: 7.0, 10.4) months, respectively. Relative difference in effect: HR = 0.73 (95% CI: 0.0.61, 0.87), p=0.0004. [45] Absolute difference in effect: 3.3 months.

Both the 12-month and 24-month PFS rates were higher for Ipi/Nivo compared with sunitinib: 12-month rates were 41% vs. 36%, respectively [47], and the 24-month PFS rates were 36.4% for Ipi/Nivo vs. 25.1% for sunitinib. [104]

**Figure 16: Kaplan-Meier plot of progression-free survival per IRRC – CheckMate 214, All intermediate/poor risk subjects, DBL Feb 24, 2021**



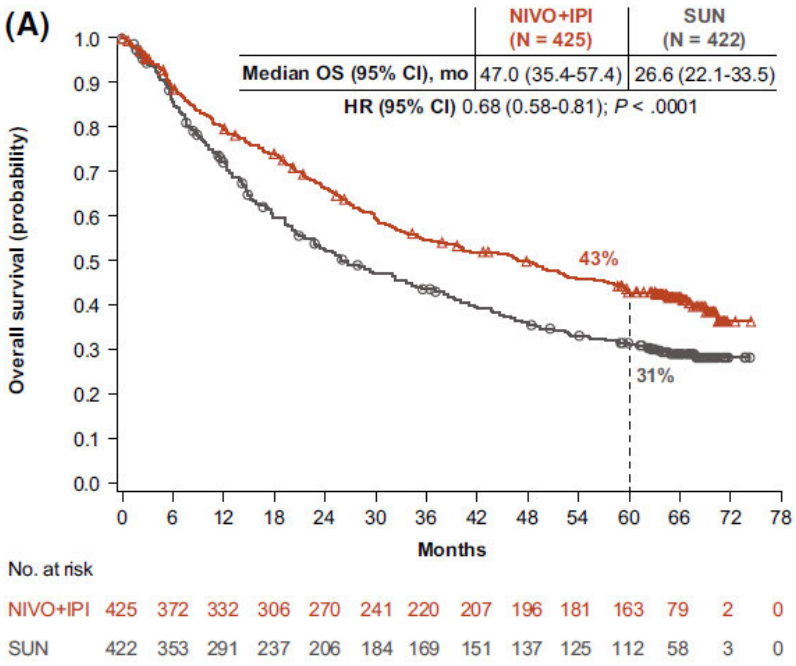

*Source: [45]*

Overall survival: OS was defined as the ”time from randomization to the date of death from any cause”. At DBL Feb 24, 2021, Ipi/Nivo demonstrated improvement in patients’ OS vs. sunitinib. KM plot for OS in the IMDC intermediate/poor risk subgroup is shown in Figure 17.

Median OS was 47.0 (95% CI: 35.4, 57.4) months in the Ipi/Nivo arm compared to 26.6 (95% CI: 22.1, 33.5) months in the sunitinib arm, HR=0.68 (95% CI: 0.58, 0.81), p<0.0001 [45]; [Nivolumab SmPC, table 27 [1]]. A total of 524 deaths had occurred (242 in the Ipi/Nivo arm, 282 in the sunitinib arm). [[45]; Nivolumab SmPC, table 27 [1]]

Both the 12-month and 24 month OS rates were higher for Ipi/Nivo compared with sunitinib: 12-month rates were 80% vs. 72%, respectively [47], and the 24-month OS rates were 66.3% for Ipi/Nivo vs. 52.4% for Sunitinib. [Nivolumab SmPC, table 27 [1]]

**Figure 17: Kaplan-Meier plot of overall survival – CheckMate 214, All intermediate/poor risk subjects, DBL Feb 24, 2021**




*Source: [45]*

Objective response rate (with DOR): ORR was defined as "proportion of randomized subjects who achieved a best response of CR or PRs using the RECIST v1.1 criteria based on IRRC assessment". In all randomized subjects with IMDC intermediate/poor risk, IRRC-assessed ORR was higher with Ipi/Nivo than with sunitinib, as shown in Table 13 below. The median TTR was shorter and DOR longer with Ipi/Nivo versus sunitinib. As for CheckMate 9ER, it was not considered reasonable to calculate 95% CIs or p-values for the absolute differences in effect nor any relative differences in effect between the treatment arms that were not already published from the CheckMate 214 trial.

- ORR was 42.1% (95% CI: 37.4, 47.0) vs. 26.8% (95% CI: 22.6, 31.3), for Ipi/Nivo vs. sunitinib, respectively. [45]
- Relative difference in effect: OR: 1.99 (95% CI: 1.37, 2.29), p<0.0001. [45]
- Absolute difference in effect: 16.2% (95% CI: 10.0, 22.5), p: NA. [Nivolumab SmPC, table 27 [1]]
- Median TTR was 2.8 (IQR: 2.6, 3.8) months for Ipi/Nivo and 3.1 (IQR: 2.8, 5.4) months for sunitinib, with an absolute difference in effect of -0.3 months
- Median DOR was not reached (95% CI: 50.9, NE) for Ipi/Nivo and 19.7 (95% CI: 15.4, 25.1) months for sunitinib
- Relative difference in effect: HR: 0.46 (95% CI: 0.31, 0.66), p<0.0001

**Table 13: Best Overall Response per IRRC Using RECIST v1.1 – CheckMate 214, All intermediate/poor risk subjects, DBL February 24, 2021**

| Subjects in IMDC intermediate/poor prognostic risk group | Ipi/Nivo N=425 | Sunitinib N=422 |
|---|---|---|
| | DBL February 24, 2021 | |
| **Best overall response, n (%)** | | |
| **Complete response** | 48 (11.3) | 9 (2.1) |
| **Partial response** | 131 (30.8) | 104 (24.6) |
| **Stable disease** | 131 (30.8) | 187 (44.3) |
| **Progressive disease** | 82 (19.3) | 71 (16.8) |
| **UTD (unable to determine)** | 32 (7.5) | 48 (11.4) |
| **Not reported** | 1 (0.2) | 3 (0.7) |
| **Confirmed objective response rate per IRRC (95% CI)** | 42.1% (37.4, 47.0) | 26.8% (22.6, 31.3) |

*IRRC: independent radiologic review committee; BOR: best overall response; CI: confidence interval; IMDC: International Metastatic RCC Database Consortium RECIST: Response Evaluation Criteria In Solid Tumours.*
*aBOR is defined as the best response recorded between randomisation and objectively documented progression per RECIST 1.1 or subsequent therapy (including tumour-directed radiotherapy and tumour-directed surgery), whichever occurs first. For participants without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment.*
*Source: [45]*

### Health-related quality of life

At the 2022 ASCO Genitourinary Cancers Symposium, updated PRO results from CheckMate 214 (DBL February 24, 2021) were presented [134]. HRQoL was assessed using 3 PRO instruments: the FKSI-19, EQ-5D-3L, and the Functional FACT-G. All PRO analyses were done for the intermediate/poor risk patients and all randomized patients. The PRO instruments were administered at baseline, on day 1 of weeks 1 and 4 of the first 2 cycles, on day 1 of weeks 1 and 5 of the next 2 cycles, and on day 1 of week 1 of subsequent cycles. Completion rates for PRO instruments were defined as the proportion of patients who completed evaluable forms (i.e., >50% of the items completed according to the scoring algorithms for FKSI-19 and all five items of the descriptive system or the VAS for EQ-5D-3L) among those who were expected to complete them (i.e., who were alive and still on study) [134].

Overall, for both treatment arms, the percentage of patients completing the 3 instruments at baseline was high and above 95%. The completion rates remained above 75% for the duration of the study. Baseline PRO scores were comparable between treatment arms.

Longitudinal changes from baseline in PRO scores were evaluated with a MMRM with baseline score and stratification factors as covariates, and included all available assessments during treatment through week 235 (approx. 4.5 years). Given the large number of visits, the MMRM was parameterized to include random effects for patients and study days. Confirmed deterioration was defined as a first clinically meaningful deterioration in the PRO score that was also followed by meaningful deterioration at the next consecutive visit or dropout, resulting in missing data. Clinically meaningful deterioration was determined using prespecified threshold values based on score changes from baseline considered to be clinically meaningful in previous literature. Time to confirmed deterioration was analysed using a stratified log-rank test and stratified Cox regression model.

Results for selected PRO measures (FKSI-19 total score, FKSI-19 DRS, EQ-5D-3L VAS and EQ-5D-3L Utility Index) are summarized in Table 14, Figure 18 and Figure 19. In both all randomized patients and in intermediate/poor risk patients specifically, significant differences between Ipi/Nivo and sunitinib treatment arms were observed for overall changes from baseline through 59 months for all outcomes as shown in Table 14. Descriptive plots of mean change from baseline

in FKSI-19 total score and DRS further illustrate these between-group differences (Figure 18 and Figure 19). Moreover, patients in the Ipi/Nivo arm were less likely to be bothered by side effects compared with the sunitinib arm, both for all randomized and intermediate/poor risk populations.

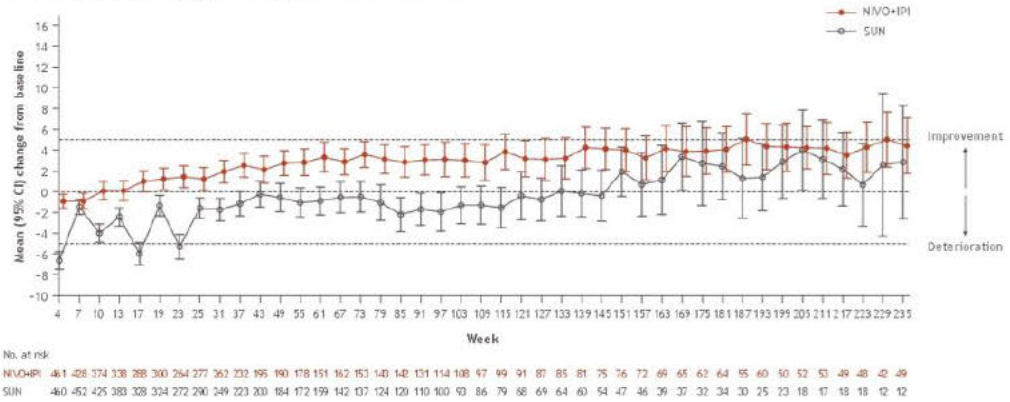
**Table 14: Overall changes from baseline through the study in PRO scores (MMRM analysis)**

| Scores | All-randomized population | | | Intermediate/poor-risk population | | |
|---|---|---|---|---|---|---|
| | LS Mean (SE), Ipi/Nivo | LS Mean (SE), Sunitinib | LS Mean (95% CI) for treatment differences, Ipi/Nivo vs. sunitinib | LS Mean (SE), Ipi/Nivo | LS Mean (SE), Sunitinib | LS Mean (95% CI) for treatment differences, Ipi/Nivo vs. sunitinib |
| **FKSI-19** | | | | | | |
| **Total Score** | 0.45 (0.37) | -2.53 (0.38) | 2.98 (2.04-3.92) | 0.96 (0.43) | -2.43 (0.46) | 3.39 (2.31-4.47) |
| **DRS** | -0.17 (0.16) | -0.93 (0.16) | 0.76 (0.36-1.16) | -0.03 (0.19) | -0.90 (0.20) | 0.87 (0.40-1.33) |
| **EQ5D-3L** | | | | | | |
| **VAS** | 2.82 (0.79) | 0.39 (0.81) | 2.44 (0.42-4.46) | 2.92 (0.93) | -0.38 (1.02) | 3.29 (0.96-5.63) |
| **UK Utility Score** | 0.01 (0.01) | -0.03 (0.01) | 0.04 (0.03-0.06) | 0.01 (0.01) | -0.04 (0.01) | 0.05 (0.03-0.07) |

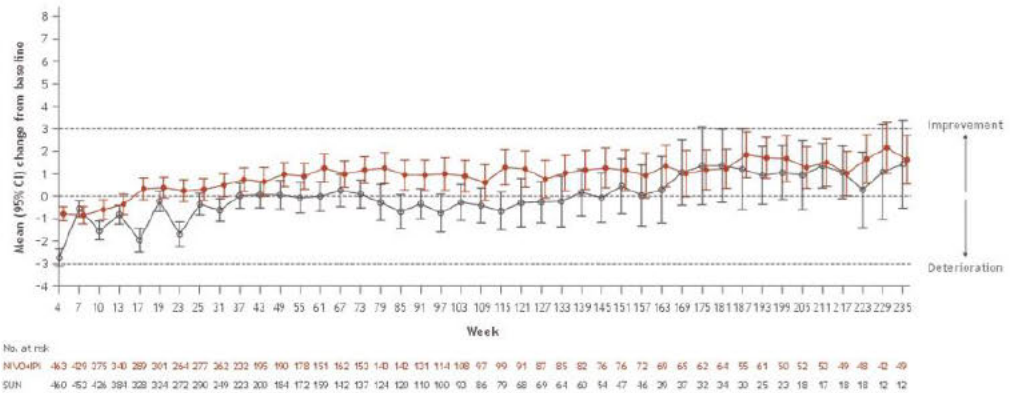
*Source: [134]*

**Figure 18: FKSI-19 mean change from baseline, CheckMate 24, All-randomized population**

A. All-randomized population, FKSI-19 total score

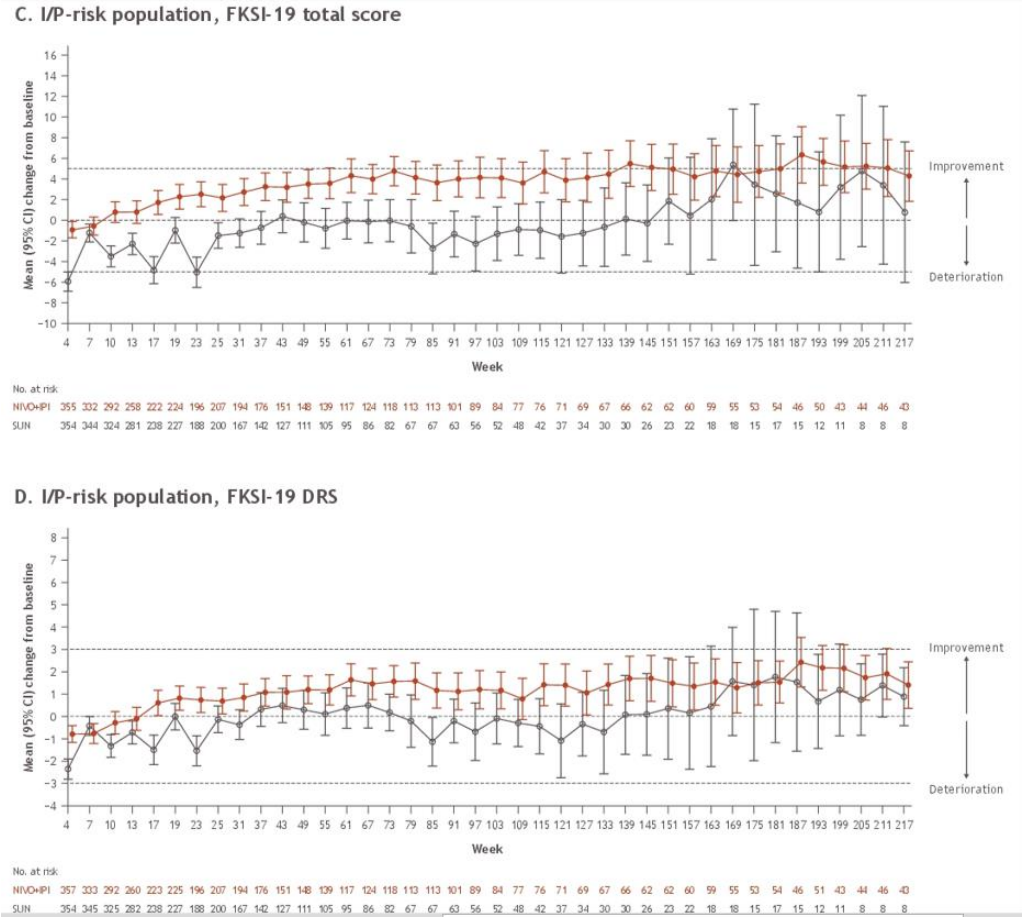



B. All-randomized population, FKSI-19 DRS




*Source: [134]*

**Figure 19: FKSI-19 mean change from baseline, Checkmate 214, Intermediate/poor risk population**




*Source: [134]*

Moreover, patients treated with Ipi/Nivo had a significantly longer median time to confirmed deterioriation vs. sunitinib for all FKSI-19 scores in both the all randomized population and the intermediate/poor-risk population ($P < 0.05$). [134]:

For the all randomized population:

- FKSI-19 total score (time to confirmed deterioration event) was 16.62 (95% CI: N/A) months and 5.13 (95% CI: N/A) months for Ipi/Nivo and sunitinib, respectively. The treatment difference was 11.49, and confirmed deterioration event HR was 0.64 (95% CI: 0.54, 0.76), nominal p<0.0001. [134]
- FKSI-19 disease-related symptoms version 1 (time to confirmed deterioration event) was 17.74 (95% CI: N/A) months for Ipi/Nivo, and 7.95 (95% CI: N/A) in the sunitinib arm. HR was 0.74 (95% CI: 0.62, 0.88), p=0.00070. [134]
- EQ-5D VAS score (time to confirmed deterioration event) was 21.42 (95% CI: N/A) months in the Ipi/Nivo arm, and 13.14 (95% CI: N/A) months in the sunitinib arm. The treatment difference was 8.28 and HR was 0.83 (95% CI: 0.70, 0.98), p=0.0266 [134]
- EQ-5D-3L UK utility index (time to confirmed deterioration event) was 23.85 (95% CI: N/A) and 10.51 (95% CI: N/A) in the Ipi/Nivo arm, and in the sunitinib arm respectively, with a treatment difference of 13.34 months. HR: 0.73 (95% CI: 0.62, 0.86), p=0.0002.

For the intermediate/poor-risk population:

- FKSI-19 total score (time to confirmed deterioration event) was 17.87 (95% CI: N/A) months and 5.26 (95% CI: N/A) months for Ipi/Nivo and sunitinib, respectively. The treatment difference was 12.61, and confirmed deterioration event HR was 0.62 (95% CI: 0.51, 0.75), nominal p<0.0001. [134]
- FKSI-19 disease-related symptoms version 1 (time to confirmed deterioration event) was 19.88 (95% CI:N/A) months for Ipi/Nivo, and 7.33 (95% CI: N/A) in the sunitinib arm. The treatment difference was 12.5, and HR was 0.72 (95% CI: 0.59, 0.88), p=0.0010. [134]
- EQ-5D VAS score (time to confirmed deterioration event) was 18.92 (95% CI: N/A) months in the Ipi/Nivo arm, and 13.14 (95% CI: N/A) months in the sunitinib arm. The treatment difference was 5.78 and HR was 0.85 (95% CI: 0.70, 1.03), p=0.0935 [134]
- EQ-5D-3L UK utility index (time to confirmed deterioration event) was 22.93 (95% CI: N/A) and 9.46 (95% CI: N/A) in the Ipi/Nivo arm, and in the sunitinib arm respectively, with a treatment difference of 13.47 months. HR: 0.69 (95% CI: 0.57, 0.83), p=0.0001. [134]

**Transferability of HRQoL results in ITT and intermediate/poor-risk population**

In the CheckMate 9ER trial, the HRQoL findings consistently favoured Cabo/Nivo over sunitinib throughout the trial, further supporting the treatment benefit of Cabo/Nivo over sunitinib monotherapy. In this trial, HRQoL analyses were not performed in any subgroups. In contrast, in the CheckMate 214 trial, HRQoL analyses were performed in both the ITT and IMDC intermediate/poor-risk populations. In both of these populations, Ipi/Nivo demonstrated HRQoL benefits vs. sunitinib with significant differences in PRO scores between the treatment arms. When comparing the ITT population data to the intermediate/poor risk population data, it is clear that for all the PRO scores presented, the treatment differences between Ipi/Nivo vs. sunitinib were greater in the intermediate/poor risk subpopulation as compared to the ITT population, i.e. even more clearly in favor of Ipi/Nivo vs. sunitinib. Even though differences in study design, populations etc. do exist between the CheckMate 9ER and CheckMate 214 trials, sunitinib is the comparator and nivolumab constitutes part of the combination intervention regimen in both trials. Based on this, it is reasonable to expect that the overall trend between ITT vs. intermediate/poor risk population data observed in the CheckMate 214 trial would be similar in CheckMate 9ER. Therefore, even though HRQoL data from CheckMate 214 and CheckMate 9ER can only be compared at ITT population level, as data are not available for any subpopulations in the CheckMate 9ER trial, it should be expected that the use of PRO data for the ITT population rather than the intermediate/poor population to assess the clinical benefit of Cabo/Nivo in terms of HRQoL would lead to conservative conclusions, especially in the comparison of Cabo/Nivo. sunitinib.

#### 7.2.2.4 Safety results

Detailed safety information is provided in Appendix E.

The safety data presented here are derived from subjects treated with Ipi/Nivo in the ongoing CheckMate 214 study. The data are based on DBL 24 February, 2021 with minimum of 5 years of follow-up for OS.

Briefly, safety results from 547 subjects treated in the 1L setting with Ipi/Nivo in the CheckMate 214 study were used to characterize the safety profile of the Ipi/Nivo combination regimen in aRCC. The 1,082 patients who received at least 1 dose of study treatment constitute the safety population (547 Ipi/nivo, 535 sunitinib). Analyses of all-cause AEs were conducted using the 30-day safety window [45]. Treatment-related deaths were reported in 8 patients in the Ipi/Nivo arm and in 5 patients in the sunitinib arm. One death assigned to the sunitinib arm occurred in a patient after crossover from sunitinib to Ipi/Nivo.

All-causality AEs of any grade were reported in 99% of subjects in the Ipi/Nivo arm and 100% of subjects in the sunitinib arm. Treatment-related AEs of any grade were reported in 94% (Ipi/Nivo) and 98% (sunitinib) of subjects. All-causality grade 3-4 AEs were reported in 68% of subjects in the Ipi/Nivo arm and 78% of subjects in the sunitinib arm [45], with an estimated absolute difference of -10.0% (95% CI: -15.3%, -4.7%; p=0.0002), and RR: 0.87 (95% CI: 0.81-0.94;

p<0.0001) comparing Ipi/Nivo and sunitinib. Drug-related grade 3-4 AEs were reported in 48% (Ipi/Nivo) and 64% (sunitinib) of subjects [45], with an estimated absolute difference of -16.0% (95% CI: -21.8%, -10.2%; p<0.0001), and RR: 0.75 (95% CI: 0.67-0.83; p<0.0001). Information on all-causality AEs leading to discontinuation of any study drug were not reported, but drug-related AEs leading to discontinuation of any study drug were reported in 127 patients (23%) and 70 patients (13%) treated with Ipi/Nivo and sunitinib, respectively [45], with an estimated absolute difference of 10.0% (95% CI: 5.5%, 14.5%; p<0.0001), and RR: 1.77 (95% CI: 1.36-2.32; p<0.0001). The most commonly reported treatment-related AE of any grade were fatigue (38% for Ipi/Nivo vs. 50% for sunitinib), pruritus (31% for Ipi/Nivo vs. 9% for sunitinib) and diarrhea (28% for Ipi/Nivo vs. 53% for sunitinib). The three most common treatment-related select AEs (potentially immune-mediated) were skin related (reported in 51% of Ipi/Nivo subjects and in 58% of the sunitinib subjects); endocrine related (reported in 33% of the Ipi/Nivo subjects and 31% in the sunitinib subjects) and gastrointestinal related (reported in 30% of the Ipi/Nivo subjects and 53% in the sunitinib subjects). In total, 162 of 547 patients (30%) treated with ipi/Nivo received corticosteroids (≥40 mg prednisone daily or equivalent (PDE)) to manage any-grade, treatment-related, select AEs, as reported within 30 days of the last dose of Ipi/Nivo; 108 patients (20%) received ≥40 mg PDE continuously for ≥2 weeks, and 56 (10%) received ≥40 mg PDE continuously for ≥30 days. [45]

#### 7.2.2.5 Conclusion

In summary, Ipi/Nivo showed significant benefits over sunitinib with respect to PFS, OS, ORR and HRQoL in patients with previously untreated aRCC. However, it should be noted that within 1L aRCC and based on the CheckMate 214 results, Ipi/Nivo is only indicated for treatment of patients with IMDC intermediate/poor risk disease.

## 7.3 Comparative analyses of efficacy and safety of cabozantinib + nivolumab versus ipilimumab + nivolumab

There is no head-to-head study comparing Cabo/Nivo and Ipi/Nivo in the treatment of aRCC. An indirect treatment comparison (ITC) was therefore undertaken to explore the relative treatment efficacy and safety of these treatments.

Formal ITCs were performed for efficacy (median PFS, 12-month and 24-month PFS rates, median OS, 12-month and 24-month OS rates, ORR) and safety endpoints, while TTR and DOR as well as QoL endpoints were compared descriptively. For the TTR and DOR endpoints, as described previously, it was not considered reasonable to calculate 95% CIs or p-values for the absolute differences in effect for the CheckMate 214 or CheckMate 9ER study nor any relative differences in effect between the treatment arms in the CheckMate 9ER study. A formal ITC of TTR and DOR was therefore not performed for Cabo/Nivo vs. Ipi/Nivo. For the QoL endpoints, it was not deemed appropriate to compare these results using formal statistical methods due to differences in the timing of QoL outcome collection in the CheckMate 9ER and CheckMate 214 trials. In CheckMate 9ER, QOL outcomes were collected on day 1 of each treatment cycle, every 2 weeks after baseline in the Cabo/Nivo arm and every 6 weeks after baseline in the sunitinib arm. In the sunitinib arm, the collection therefore occurred after the 2-week treatment-free period. In CheckMate 214, QoL collection occurred on week 1 and week 4 of the first two 6-week cycles, week 1 and week 5 of the next two cycles, week 1 of the subsequent cycles, and at the first two follow-up visits (the first at 30 days after last dose or on the date of discontinuation and the second 84 days after the first follow-up visit). The fact that the QoL outcomes were collected only after the 2-week treatment-free period in the sunitinib arm in the CheckMate 9ER trial may have led to an underestimation of the impact of AEs related to sunitinib treatment on the observed QoL as patients in the sunitinib arm would less likely to be affected by AEs at the time of QoL collection. Looking at the overall pattern in the QoL data in the sunitinib arm in the first period of the two trials, this also clearly reflects the difference in QoL collection: in the sunitinib arm of the CheckMate 214 trial, the mean change from baseline estimates fluctuates, but such a fluctuation is not observed in the sunitinib arm of the CheckMate 9ER trial. As this difference will influence the overall relative QoL

results of Cabo/Nivo vs. Sunitinib and Ipi/Nivo vs. Sunitinib, any formal ITC of Cabo/Nivo vs. Ipi/Nivo were considered to be inappropriately biased by this difference.

### 7.3.1 Method of synthesis

An ITC using the Bucher methodology was performed, computing absolute and relative differences based on aggregated data from the CheckMate 9ER and CheckMate 214 trials, which shared sunitinib as the common comparator.

Details of the comparative analysis are provided in Appendix F.

Briefly, absolute differences between Cabo/Nivo vs. Ipi/Nivo were computed as diff(Cabo/Nivo vs. Ipi/Nivo) = abs(diff(Cabo/Nivo vs. Sunitinib) – diff(Ipi/Nivo vs. Sunitinib)). The variance of absolute difference between Cabo/Nivo vs. Ipi/Nivo was computed as var(diff(Cabo/Nivo vs. Ipi/Nivo)) = var(diff(Cabo/Nivo vs. Sunitinib))+ var(diff(Ipi/Nivo vs. Sunitinib)). Finally, the 95% CIs of the absolute difference in treatments of Cabo/Nivo and Ipi/Nivo were obtained by diff(Cabo/Nivo vs. Ipi/Nivo) ± $1.96\sqrt{Var(diff(Cabo/Nivo\ vs.\ Ipi/Nivo))}$.

The relative differences between Cabo/Nivo vs. Ipi/Nivo were computed using the estimated relative differences of θAB and θAC for comparisons of A vs. B (sunitinib vs Cabo/Nivo) and A vs. C (sunitinib vs Ipi/Nivo), respectively. The effect for the comparison B vs. C (Cabo/Nivo vs Ipi/Nivo) was estimated as θBC= exp(lnθAB-lnθAC), and var(lnθBC) = var(lnθAB) + var(lnθAC). The 95% confidence interval for θBC was obtained as exp(logθBC±1.96√(var(lnθBC)).

Efficacy outcomes were analysed based on data for the intermediate/poor prognostic risk subpopulation as this reflects the EMA indication for Ipi/Nivo and the indication for Cabo/Nivo relevant for this assessment, while safety outcomes were analysed based on overall safety population data. All indirect comparisons were based on the most recent data available for each endpoint. For CheckMate 9ER, this represents the DBL 24 June 2021. For CheckMate 214, data were based on DBL 24 Feb 2021 for median OS and 24-month OS rate, median PFS, ORR and all safety endpoints, DBL 25 Feb 2020 for the 24-month PFS rate, while 12-month OS and PFS rates were based on the DBL 6 Aug 2018.

### 7.3.2 Results from the comparative analysis

Detailed results tables for the comparative analyses are provided in Appendix F, and summarized below.

#### 7.3.2.1 Progression free survival

The analyses indicated that median PFS was significantly superior with Cabo/Nivo compared with Ipi/Nivo.

The estimated absolute difference in median PFS between Cabo/Nivo and Ipi/Nivo was [redacted] vs. 3.3 months longer than sunitinib). The HRs for median PFS in the trials were [redacted] for Cabo/Nivo versus sunitinib, and 0.73 (95% CI: 0.61, 0.87) for Ipi/Nivo versus sunitinib, for patients with intermediate/poor prognostic risk. The ITC based on these data indicated that median PFS was significantly increased for Cabo/Nivo compared to Ipi/Nivo, with a relative difference estimated to [redacted]

For PFS rates at 12 and 24 months, absolute differences between Cabo/Nivo and Ipi/Nivo were estimated, and the PFS rates relative to sunitinib were numerically higher for Cabo/Nivo than for Ipi/Nivo at both time points [redacted]

#### 7.3.2.2 Overall survival

The estimated absolute difference in median OS between Cabo/Nivo and Ipi/Nivo was [redacted] vs. 20.3 months longer than sunitinib). For median OS, the HRs in the trials were 0.66 (95% CI: 0.50, 0.85) for Cabo/Nivo versus sunitinib, and HR 0.68 (95% CI: 0.58, 0.81) for Ipi/Nivo versus sunitinib, for patients with intermediate/poor prognostic risk. The ITC based on these data indicated no significant difference in OS between Cabo/Nivo and Ipi/Nivo: [redacted]

For OS rates at 12 and 24 months, absolute differences between Cabo/Nivo and Ipi/Nivo were estimated, and the OS rates relative to sunitinib were numerically higher for Cabo/Nivo than for Ipi/Nivo at both time points: [redacted]

#### 7.3.2.3 Objective response rate, time to response and duration of response

The analyses indicated that ORR was significantly superior with Cabo/Nivo compared with Ipi/Nivo.

The estimated absolute difference in ORR between Cabo/Nivo and Ipi/Nivo was [redacted] vs. 15% higher than sunitinib; [redacted]. For ORR, the ORs in the trials were [redacted] for Cabo/Nivo versus sunitinib, and 1.99 (95% CI: 1.37, 2.29) for Ipi/Nivo versus sunitinib, for patients with intermediate/poor prognostic risk. The ITC based on these data indicated that ORR was significantly better for Cabo/Nivo compared to Ipi/Nivo, with a relative difference estimated to [redacted]

The estimated absolute difference in median TTR between Cabo/Nivo and sunitinib was [redacted] while it was -0.3 months between Ipi/Nivo. For median DOR, the absolute difference between Cabo/Nivo and sunitinib was [redacted] while it was not estimable for Ipi/Nivo vs. Sunitinib based on currently available data, as median DOR has not yet been reached for patients with intermediate/poor prognostic risk in the CheckMate 214 trial. However, [redacted]

#### 7.3.2.4 Safety

Safety data were described for the overall safety population in the respective trial, and accordingly the comparative analysis was based on data for this population. The ITC indicated that Cabo/Nivo was associated with higher AE rates than Ipi/Nivo, but that differences in discontinuation due to TRAE were not statistically significant.

For grade 3-4 all-causality AE rates, the estimated absolute difference between Cabo/Nivo and Ipi/Nivo [redacted] vs. -10.0% difference to sunitinib; [redacted] The relative difference to sunitinib was [redacted] for Cabo/Nivo and RR 0.87 (95% CI: 0.81, 0.94) for Ipi/Nivo. The ITC based on these data indicated that grade 3-4 all-causality AE rates were significantly higher with Cabo/Nivo than with Ipi/Nivo, with a relative difference estimated to [redacted]

For grade 3-4 TRAE rates, the estimated absolute difference between Cabo/Nivo and Ipi/Nivo was [redacted] vs. -16.0% difference to sunitinib; [redacted] The relative difference to sunitinib was [redacted] for Cabo/Nivo and RR 0.75 (95% CI: 0.67, 0.83) for Ipi/Nivo. The ITC based on these data indicated that grade 3-4 TRAE rates were significantly higher with Cabo/Nivo than with Ipi/Nivo, with a relative difference estimated to [redacted]

For discontinuation due to TRAE (any grade) rates, the estimated absolute difference between Cabo/Nivo and Ipi/Nivo was [redacted] vs. 10.0% difference to sunitinib; [redacted] The relative differences to sunitinib were [redacted] for Cabo/Nivo and RR 1.8 (95% CI: 1.4, 2.3) for Ipi/Nivo. The ITC based on these data indicated no statistically significant difference in discontinuation rates due to TRAE between Cabo/Nivo and Ipi/Nivo: [redacted]

Therefore, even though Cabo/Nivo may be associated with higher overall grade 3-4 AE rates than Ipi/Nivo, importantly, the ITC results indicate that this difference does not imply a significantly increased risk for experiencing AEs leading to discontinuation with Cabo/Nivo. One possible explanation for this could be that the AEs experienced with Cabo/Nivo are more manageable in clinical practice compared to the AEs experienced with Ipi/Nivo.

#### 7.3.2.5 Quality of life

For **FKSI-19 total score**, LS mean change from BL was significantly better with Cabo/Nivo as compared with sunitinib, with an absolute difference in effect of 2.37 (-0.47 vs. -2.84; 95% CI: 1.19-3.54; p<0.0001); and significantly better with Ipi/Nivo as compared with sunitinib, with an absolute difference in effect of 2.98 (0.45 vs. -2.53; 95% CI: 2.04-3.92; p<0.05). Confirmed time to deterioration was 11.3 months longer and significantly better with Cabo/Nivo than with sunitinib (18.23 vs. 6.97 months; HR 0.66, 95% CI: 0.52-0.84; p<0.0005); while it was 11.5 months longer and significantly better with Ipi/Nivo than with sunitinib (16.62 vs. 5.13 months; HR 0.64, 95% CI: 0.54-0.76; p<0.0001).

For **FKSI-19 DRS**, LS mean change from BL was significantly better with Cabo/Nivo as compared with sunitinib, with an absolute difference in effect of 1.17 (0.71 vs. -0.46; 95% CI: 0.68-1.66; p<0.0001); and significantly better with Ipi/Nivo as compared with sunitinib, with an absolute difference in effect of 0.76 (-0.17 vs. -0.93; 95% CI: 0.36-1.16; p<0.05). Confirmed time to deterioration was significantly longer with Cabo/Nivo than with sunitinib (not reached at a median follow-up of 32.9 months vs. 15.28 months; HR 0.65, 95% CI: 0.50-0.86; p<0.0020); while it was 9.8 months longer and significantly better with Ipi/Nivo than with sunitinib (17.74 vs. 7.95 months; HR 0.74, 95% CI: 0.62-0.88; p=0.0007).

For **EQ-5D-3L VAS**, LS mean change from BL was significantly better with Cabo/Nivo as compared with sunitinib, with an absolute difference in effect of 3.68 (2.73 vs. -0.95; 95% CI: 1.83-5.54; p=0.0001); and significantly better with Ipi/Nivo as compared with sunitinib, with an absolute difference in effect of 2.44 (2.82 vs. 0.39; 95% CI: 0.42-4.46; p<0.05). Confirmed time to deterioration was 16.8 months longer and significantly better with Cabo/Nivo than with sunitinib (34.56 vs. 17.74 months; HR 0.74, 95% CI: 0.58, 0.95; p<0.018); while it was 8.3 months longer and significantly better with Ipi/Nivo than with sunitinib (21.42 vs 13.14 months; HR 0.83, 95% CI: 0.70-0.98; p<0.027).

For **EQ-5D-3L UK Index**, LS mean change from BL was significantly better with Cabo/Nivo as compared with sunitinib, with an absolute difference in effect of 0.05 (-0.01 vs. -0.06; 95% CI not reported; p=0.001); and significantly better with Ipi/Nivo as compared with sunitinib, with an absolute difference in effect of 0.04 (0.01 vs. -0.03; 95% CI: 0.03-0.06; p<0.05). Confirmed time to deterioration was 6.8 months longer with Cabo/Nivo than with sunitinib (19.35 vs. 12.58 months; HR 0.81, 95% CI: 0.64-1.02; p=0.075); while it was 13.3 months longer and significantly better with Ipi/Nivo than with sunitinib (23.85 vs. 10.51 months; HR 0.73, 95% CI: 0.62-0.86; p=0.0002).

**Overall**, these results indicate that Cabo/Nivo as well as Ipi/Nivo have superior positive effects on QoL as compared with sunitinib, while the descriptive comparison doesn't indicate any clear trends towards superiority for either of Cabo/Nivo or Ipi/Nivo in a comparison between these treatments: similar results were reported for FKSI-19 total score outcomes in both trials; superiority for Cabo/Nivo could be suggested for FKSI-19 DRS and EQ-5D-3L VAS outcomes; while a minor advantage for Ipi/Nivo could be suggested for the EQ-5D-3L UK Index outcomes.

#### 7.3.2.6 Conclusion of indirect treatment comparison

The ITC indicates that Cabo/Nivo is statistically significantly superior to Ipi/Nivo in terms of PFS and ORR, while no significant differences in OS were indicated. The ITC indicated statistically significantly better results for Ipi/Nivo on some of the safety outcomes, but importantly not for the treatment-related discontinuation rate. For TTR, DOR and QoL outcomes, no formal ITC was performed. In terms of TTR, the descriptive analysis indicated an advantage for Cabo/Nivo, but for DOR and QoL, the descriptive analysis did not indicate a conclusive advantage for either of the treatments.

# 8. Health economic analysis

This health economic (HE) analysis evaluated the cost-effectiveness (CE) of Cabo/Nivo as a first-line treatment for aRCC in the Danish clinical setting. The CE model focused on treatment-naïve aRCC patients with intermediate or poor prognostic risk by the IMDC criteria. The CE versus two comparators were assessed: sunitinib and Ipi/Nivo. The clinical efficacy data used in the model were based on data from the CheckMate 9ER study (in the comparison vs. sunitinib) or informed by results from a FP NMA conducted by IPSEN (in the comparison vs. Ipi/Nivo).

The HE analysis follows the standard analysis depicted in the DMC guidelines [135]. The analysis uses a cost-utility analysis (CUA), where patients are followed over a lifetime horizon upon 1L treatment with either the intervention (Cabo/Nivo) or the comparator (sunitinib or Ipi/Nivo). A CUA model was considered to provide the best means of capturing all relevant treatment costs incurred as well as the life years and QALYs gained from the treatment.

## 8.1 Model

### 8.1.1 Model structure

The CE model was developed in Microsoft Excel® using a partitioned survival model structure in both a deterministic and probabilistic (Monte Carlo simulation) framework. Partitioned survival models have been used in the CE analyses for prior health technology assessments (HTAs) of first-line treatments for aRCC and are often used in oncology CE models. They are considered to be one of the standard methods for population-based cancer patient survival analysis. The model has been adapted to the Danish settings in order to reflect the Danish clinical practice for the management of RCC, the Danish target patient population, the Danish guidelines for HE models, and the Danish relevant unit costs.

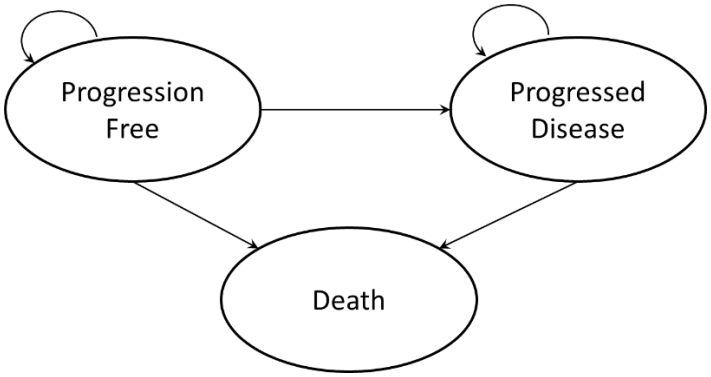
The model was developed with a maximum of a lifetime horizon, suitable to capture the life expectancy of the cohort. The impact of the time horizon on the economic results was further explored in a sensitivity analysis.

The partitioned survival approach estimates proportions in each health state based on parametric survival curves fitted to clinical trial data on PFS and OS over time. The structure of the model has been chosen based on previously identified models for aRCC and mRCC treatment (e.g. TA645 [56]) and is in line with that of models previously submitted and approved during relevant DK HTA processes [92, 95, 136]. It contains the three most relevant, mutually exclusive, health states from a patient, clinician and healthcare system perspective:

- Progression-free (PF) – during this stage it was assumed that patients' tumours are expected to be in a stable or responding state and not actively progressing. Patients in this stage were assumed to incur costs associated with first-line treatment (drug and administration costs), costs associated with medical management of the condition (regular follow-up visits, blood tests, and CT scans), and grade 3/4 AE. Patients also experienced a higher utility weighting associated with non-progressing disease.
- Progressed disease (PD) – when a patient transitioned into the PD health state, first-line treatment was considered to be terminated, and second-line treatment had the possibility to be initiated within a certain number of weeks. Patients continued to incur potential costs associated with medical management of the condition, as well as costs associated with second-line treatment (drug and administration costs) and palliative care. Patients with PD experienced a lower utility weighting.
- Death – this was treated as an absorbing health state.

The circles below represent health states, and the arrows represent transition between states (Figure 20). At any point in time, a patient was assumed to be in one of the states. Patients moved between states at the end of each model cycle to model the health states of a cohort of patients. All patients entered the model in the PF state where it was assumed that they were treated with the first-line treatment.

**Figure 20: Structure of economic model**




Patients remained in the PF state until they experienced disease progression or died. Once patients entered the PD state, first-line treatment was discontinued, and some patients were treated with subsequent treatment for second-line medication. The outcome of treatment following progression with alternative targeted therapy was captured in the relevant clinical trials. This means that the KM curves for OS used in the model include impact of subsequent therapy for patients. Patients remained in the PD state until death.

The structure (see Figure 20) was designed to capture disease progression, including PFS, the primary endpoint in the CheckMate 9ER trial. The division into states in the model structure allows to reflect the way RCC patients are treated, as described earlier. Therefore, it also enables the analysis to capture all relevant costs and outcomes associated with each treatment option and health state.

The model structure is appropriate to simulate differences in HRQoL experienced by patients during different health states (PF and PD), and the utility decrement for experiencing AE.

### 8.1.2 Cycle length

A cycle length of 7 days (one week) was applied for the first two years in the model, and after that 6-month cycles were used. The shorter model cycles at the beginning of the model were better suited to treatment schedules of different first-line treatment options, and the longer model cycles later on helped to make the model calculations more efficient in this lifetime model. This structure was regarded as appropriate for capturing the health effects and costs in patients with aRCC and mRCC.

### 8.1.3 Half-cycle correction

Half-cycle correction is applied in the base case analysis. Implementation of half-cycle correction can compensate for the over-estimation of outcomes that tends to happen in standard analysis because clinical parameters in a model are captured at the start of each cycle.

### 8.1.4 Time horizon

A lifetime time horizon (up to 50 years) has been chosen to capture the life expectancy of the cohort.

***Justification for choice of time horizon***

The time horizon for the analysis should be long enough to include all significant differences in health benefits and costs between the alternatives [135]. When assessing the length of the time horizon, the patients' life expectancy with currently existing treatments should be considered. The average OS observed before entry of new therapies, and

specifically the combination therapies of which Cabo/Nivo is one, to the market would be of limited relevance when assessing the length of time horizon used in the present health economic evaluation.

The main benefits of novel combination therapies in aRCC are improved disease response rates and indeed also longer survival. For example, OS at 5 years was reported to be 43% in patients with intermediate/poor risk based on long-term data for Ipi/Nivo combination therapy [132].

The improvement in OS observed with novel combination therapies seems to be true especially for patients who have achieved deep/complete responses, even if their therapy has been discontinued e.g., due to treatment-related AEs. This has been seen very clearly in the first combination phase III trial CheckMate 214, where extensive follow-up data is already available. In CheckMate 214, Ipi/Nivo is used as an induction therapy. After this induction phase, the treatment continues as nivolumab monotherapy. In the analysis with a minimum follow up of 5 years, it can be seen that with this continuing nivolumab treatment, or even after discontinuing the treatment entirely either after a 2-year cap or due to adverse events, patients stay "in response" much longer than what is seen with sunitinib. Nivolumab is the PD-1 component also of the Checkmate 9ER study, making a similar expectation regarding long responders/survivors logical.

Based on the above, it is reasonable that the lifespan for aRCC patients is longer when modelling for treatment with novel combination therapies in aRCC. This is also supported by the DMC mRCC treatment guideline stating that the prognosis for ccRCC patients has improved considerably across prognostic groups during the last 15 years [28]. Using shorter time horizons in the health economic evaluation would therefore cause a significant risk of not including all essential costs and health effects. Some patients must be expected to have very long survival times and would continue to incur disease-related costs and/or health effects after the end of an analysis with a restricted time horizon. This would be non-compliant with general health economic methodological practice, and with DMC's methodological guidelines on health economic evaluations.

### 8.1.5 Discount rates

In the CUA model, costs and outcomes are discounted with annual discount rates (Table 15) that corresponds to the current socio-economic discount rate from the Danish Ministry of Finance [137].

**Table 15: Annual discount rates applied in the model**

| Time period | Annual discount rate, costs | Annual discount rate, outcomes |
|---|---|---|
| **0-35 years** | 3.5% | 3.5% |
| **36-70 years** | 2.5% | 2.5% |
| **>70 years** | 1.5% | 1.5% |

### 8.1.6 Model validation

[redacted]

[redacted]

### 8.1.7 Key assumptions

Key assumptions in the base case analysis are summarized in Table 17.

**Table 17: Key model assumptions**

| Domain | Assumption | Justification |
|---|---|---|
| **Effectiveness (Cabo/Nivo versus sunitinib)** | | |
| | [redacted] | Direct head-to-head comparisons are the preferred source according to DMC guidelines [135]. [redacted] |
| | [redacted] | [redacted] |

| Domain | Assumption | Justification |
|---|---|---|
| **Effectiveness (Cabo/Nivo versus Ipi/Nivo)** | | |
| | The efficacy inputs are based on a FP NMA carried out by IPSEN to compare the efficacy of first-Line treatments in patients with aRCC, in terms of PFS and OS. | In the absence of direct head-to-head comparisons, indirect treatment comparisons are advised according to DMC guidelines, including NMA [135].<br>The choice of using an FP NMA approach rather than a constant HR in the health economic model was based on the conclusion that the proportional hazards assumption was violated for both PFS and OS in the CheckMate 214 study. When the proportional hazard assumption is violated, applying the same HR over the entire time horizon in a health economic model does not reproduce accurately the relative efficacy of Ipi/Nivo over time. In this situation, the use of alternative methods with time-varying models are recommended to compare survival in economic analyses, both in the recent National Institute for Health and Care Excellence (NICE) manual for health technology evaluations and in the DMC's guidance document for survival extrapolations in health economic evaluations. Overall, using the fractional polynomial NMA approach gives more robust estimates of relative efficacy over time than using a constant HR. |
| | [redacted] | The evaluation of best fit was made based on the results of Deviance Information Criterion (DIC) statistics and long-term clinical plausibility. |
| **Quality of life** | | |
| | Quality of life is dependent on disease progression status and toxicity of treatments. | Standard assumption in oncology models. |
| | Utilities were estimated from patient-level data from the CheckMate 9ER study for all comparators. All treatments were assumed to have health state-specific utilities with reductions associated with AEs experienced by patients. | By sourcing all utilities from one source, it is avoided to combine several sources/methods of preference elicitation together. |
| **Resource use and costs** | | |
| | Treatment duration is characterised by the PFS curve for Cabo/Nivo, sunitinib and Ipi/Nivo, respectively. | In clinical practice, discontinuation of first-line treatment is anticipated upon disease progression. |
| | Wastage of IV drugs is included in the base case analysis. | It is anticipated that vial sharing will not occur in practice, and hence drug wastage was assumed. |
| | Management of grade 3 and 4 AEs is associated with resource use. | Standard assumption. |

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

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

The pivotal study to inform the economic model was the CheckMate 9ER study, which provides a head-to-head comparison of Cabo/Nivo and sunitinib treatment of aRCC.

For the CE analysis comparing Cabo/Nivo and sunitinib, the OS and PFS data from the CheckMate 9ER study were used to calculate the proportion of patients in each treatment arm in each health state at any time point after starting treatment, and OS and PFS curve fitting was performed to generate survival curves to the partioned survival model. For the CE model, the survival analysis and curve fitting were done on patient-level data for the study subpopulation of patients at intermediate/poor prognostic risk specifically. Patient-level data from the CheckMate 9ER trial were also used to inform the CE model with input data regarding AE rates and duration as well as utility input values.

For the CE analysis comparing Cabo/Nivo and Ipi/Nivo, OS and PFS curves were estimated based on an indirect treatment comparison using an FP-NMA model informed by the data for the subpopulation of patients at intermediate or poor prognostic risk in the CheckMate 9ER and CheckMate 214 studies. AE rates for Ipi/Nivo were sourced from the CheckMate 214 study.

**Table 18: Input data used in the model**

| Name of estimates | Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population) | Input value used in the model | How is the input value obtained/estimated |
|---|---|---|---|
| **Progression-free survival curve** | Cabo/Nivo vs. sunitinib: CheckMate 9ER, subpopulation of patients at intermediate or poor prognostic risk.<br><br>Cabo/Nivo vs. Ipi/Nivo: ITC: FP NMA model, subpopulation of patients at intermediate/poor prognostic risk. | See sections 8.3.1.1; 8.3.1.2 | Cabo/Nivo vs. sunitinib: extrapolation curves were fitted onto PFS and OS KM data for the CheckMate 9ER study subpopulation of patients at intermediate/poor prognostic risk.<br><br>Cabo/Nivo vs. Ipi/Nivo: an FP NMA was carried out to compare the efficacy of these treatments in terms of PFS and OS. Best fitting models were selected based on statistical fit and long-term clinical plausibility. |
| **Overall survival curve** | Cabo/Nivo vs. sunitinib: CheckMate 9ER, subpopulation of patients at intermediate/poor prognostic risk.<br><br>Cabo/Nivo vs. Ipi/Nivo: ITC: FP NMA model, subpopulation of patients at intermediate/poor prognostic risk. | See sections 8.3.1.1; 8.3.1.2 | |
| **Adverse reactions (occurrence)** | CheckMate 9ER, ITT (Cabo/Nivo, sunitinib)<br><br>CheckMate 214, ITT (Ipi/Nivo) | See section 8.2.2.5 | Observed rates of Treatment Emergent AE (TEAE) of grade 3 or 4. |
| **Adverse reactions (duration and average number of episodes)** | CheckMate 9ER, ITT. | See section 8.2.2.5 | Duration of AE: the average duration of all grade 3-4 AEs found among patients in the study.<br><br>Average number of episodes of AE per patient: for each patient, the average number of episodes of AEs was calculated by dividing the total number of AE (grade 3 or 4) episodes by the number of AEs; then taking the average value among all patients across the two treatment groups. |

| Name of estimates | Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population) | Input value used in the model | How is the input value obtained/estimated |
|---|---|---|---|
| **Health state utility values** | CheckMate 9ER, subpopulation of patients at intermediate/poor prognostic risk. | [redacted]<br>[redacted]<br>See section 8.4.2 | Patient-reported QoL data were collected using EQ-5D-3L. Data from both treatment arms were combined and stratified by health state. The responses were mapped to EQ-5D-5L using Danish preference weights. |
| **Adverse reactions (utility loss)** | CheckMate 9ER, subpopulation of patients at intermediate/poor prognostic risk. | [redacted]<br>See section 8.4.2 | Patient-reported QoL data were collected using EQ-5D-3L for patients with and without an AE. Data from both treatment arms were combined. The responses were mapped to EQ-5D-5L using Danish preference weights.<br>The difference between the average utility value reported by patients with and without an AE were used as a common disutility for all AEs in the model. |
| **Background mortality** | Danish general population [139] | n/a | Danish life tables were applied. |

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

### 8.2.2.1 Patient population

**The Danish patient population:**

As described above (Section 5.2), the patient population expected to use Cabo/Nivo in Denmark is restricted to the following two clinically relevant target populations covered in the current application:

1. IMDC intermediate/poor prognostic risk patients who are eligible for Ipi/Nivo treatment
2. IMDC intermediate/poor prognostic risk patients who are ineligible for Ipi/Nivo treatment but eligible for Cabo/Nivo treatment

**Patient population in the clinical documentation submitted:**

The clinical documentation describes the head-to-head studies between Cabo/Nivo and sunitinib in the CheckMate 9ER study, and between Cabo/Nivo and Ipi/Nivo in the CheckMate 214 study. The study populations included subjects (≥18 years) with no prior systemic therapy for aRCC or mRCC. Subjects were required to have histologically confirmed aRCC or mRCC (with a clear-cell component, including participants who may also have sarcomatoid features). aRCC or mRCC subjects across all IMDC risk groups (favourable, intermediate and poor risk categories) were included in the study.

The clinical documentation further presents results for the IMDC intermediate/poor risk subpopulation. It is assumed that the treatment outcomes are not affected by the Ipi/Nivo ineligibility restriction, and hence that the study data are representative for both targeted patient populations.

**Patient population in the health economic analysis submitted:**

The HE model evaluates the CE of Cabo/Nivo as a 1L treatment for aRCC. In the base case analysis, the model population reflects the IMDC intermediate/poor risk subpopulation in the CheckMate 9ER study. Relevant patient characteristics are presented in Table 19.

**Table 19: Patient population**

| Patient population<br><br>Important baseline characteristics | Clinical documentation/indirect comparison etc. (including source) | Used in the model (number/value including source) | Danish clinical practice (including source) |
|---|---|---|---|
| **Gender distribution, % male** | 73.9% (N=651) [33] | 73.9% | 71.7% (based on most recent data for all newly diagnosed kidney cancer patients included in DaRenCaData) [5] |
| **Baseline age, mean (SD) years** | [redacted] | [redacted] | 68 years (based on most recent data for all newly diagnosed kidney cancer patients included in DaRenCaData) [5] |
| **Baseline weight, mean (SE) kg** | [redacted] | [redacted] | 80 kg [29] |

The mean age at baseline was slightly lower in the CheckMate 9ER trial as compared with the mean age of all newly diagnosed Danish kidney cancer patients included in DaRenCaData. Meanwhile, the difference was much smaller than the full age range of subjects in the trial (28-90 years at baseline), and the age of the Danish patient population was well represented within this age range. The relative treatment efficacy results from the trial were therefore considered relevant for Danish patient population and were applied in the CE analysis.

#### 8.2.2.2 Intervention

**Intervention as expected in Danish clinical practice (as defined in section 2.2)**:

It is anticipated that the Danish clinical practice will reflect the posology recommended in the Cabometyx SmPC [2].

**Intervention in the clinical documentation submitted**:

The clinical documentation describes the head-to-head study between Cabo/Nivo and sunitinib in the CheckMate 9ER study. In the intervention arm (study arm A, N=323), subjects received nivolumab 240 mg flat dose IV every 2 weeks and cabozantinib 40 mg PO once daily. Nivolumab treatment was continued until PD or unacceptable toxicity, with maximum treatment of 2 years. Cabozantinib treatment was continued until PD or unacceptable toxicity.

**Intervention as in the health economic analysis submitted**:

The HE model evaluates Cabo/Nivo as intervention, in the 1L of treatment. The posology applied (Table 20) reflects the study protocol. In the model, drug consumption is further adjusted by dose intensity, assuming that relative dose intensity is a function of dose reduction and treatment interruption. The relative dose intensities applied in the model

were based on CheckMate 9ER data and the actual doses received in this trial. As such, the relative dose intensity is associated with the clinical efficacy data resulting from the trial.

As cabozantinib has the same price for each dose (60, 40 and 20 mg), dose reduction does not impact the treatment cost. [redacted]

**Table 20: Intervention**

| Intervention (Cabo/Nivo) | Clinical documentation (including source) | Used in the model (number/value including source) | Expected Danish clinical practice (including source if known) |
|---|---|---|---|
| **Dose [32]** | Cabo: 20-60 mg once daily<br>Nivo: 240 mg every 2nd week | Cabo: 40 mg per administration[2]<br>Nivo: 240 mg per administration | Cabo: 20-60 mg once daily<br>Nivo: 240 mg every 2nd week |
| **Administration frequency [32]** | Cabo: Once daily<br>Nivo: Every 2nd week | Cabo: 30.4 per month<br>Nivo: 2.2 per month | Cabo: Once daily<br>Nivo: Every 2nd week |
| **Length of treatment (time on treatment) (mean/median)** | [redacted] | [redacted] | Cabo: until disease progression or unacceptable toxicity.<br>Nivo: until disease progression or unacceptable toxicity, with maximum treatment of 2 years. |
| **Criteria for discontinuation [32]** | Cabo: progressive disease or unacceptable toxicity.<br>Nivo: progressive disease or unacceptable toxicity, with maximum treatment of 2 years. | Progression to the 'Progressed disease' state. | Cabo: progressive disease or unacceptable toxicity.<br>Nivo: progressive disease or unacceptable toxicity, with maximum treatment of 2 years. |

| Intervention (Cabo/Nivo) | Clinical documentation (including source) | Used in the model (number/value including source) | Expected Danish clinical practice (including source if known) |
|---|---|---|---|
| **The pharmaceutical's position in Danish clinical practice** | 1L | 1L | 1L |
| **Dose intensity[1] [141]** | [redacted] | [redacted] | [redacted] |

[redacted]

[2] *As cabozantinib has the same price for each dose (60, 40 and 20 mg), dose reduction does not impact the treatment cost.*

#### 8.2.2.3 Comparators

**The current Danish clinical practice (as described in section 5)**:

In Denmark, the treatment choice for patients with mRCC is guided by "Baggrund for Medicinrådets behandlingsvejledning vedrørende lægemidler til metastatisk nyrekræft" and "Medicinrådets lægemiddel-rekommandation og behandlingsvejledning vedrørende lægemidler til metastatisk nyrekræft" published by the DMC in June 2022 [28, 93]. In the treatment guideline and drug recommendation [28, 93], the choice of first line medical treatment is based on the patient's prognosis using the IMDC prognostic stratification tool [143], as well as the patient's general condition and comorbidities. [29, 93]

It is anticipated that the Danish clinical practice reflects the posology recommended in the Sutent [23], Yervoy [90], and Opdivo [1] SmPCs, respectively.

**Comparator(s) in the clinical documentation submitted:**

The clinical documentation describes the head-to-head study between Cabo/Nivo and sunitinib in the CheckMate 9ER study. In the comparator arm (study arm B, N=328), subjects received sunitinib 50 mg PO once daily for 4 weeks, followed by 2 weeks off-treatment per cycle until PD or unacceptable toxicity.

For Ipi/Nivo, the clinical documentation describes the head-to-head study between Ipi/Nivo and sunitinib in the CheckMate 214 study.

**Comparator(s) in the health economic analysis submitted:**

In the first base case analysis, the HE model evaluates sunitinib as comparator, in the 1L of treatment. The posology applied (Table 21) reflects the study protocol from the CheckMate 9ER trial. In the model, drug consumption is further adjusted by dose intensity, assuming that relative dose intensity is a function of dose reduction and treatment interruption. [redacted]

In the second base case analysis, the HE model evaluates Ipi/Nivo as comparator, in the 1L of treatment. The posology applied (Table 22) reflects the study protocol from the CheckMate 214 study.

Table 21: Comparator: sunitinib

| Comparator (sunitinib) | Clinical documentation (including source) | Used in the model (number/value including source) | Expected Danish clinical practice (including source) |
|---|---|---|---|
| **Dose [32]** | 50 mg per administration | 50 mg per administration | 50 mg per administration |
| **Administration frequency [32]** | Cycles of 4 weeks with once daily administrations, followed by 2 weeks off-treatment. | 20.3 per month | Cycles of 4 weeks with once daily administrations, followed by 2 weeks off-treatment. |
| **Length of treatment (time on treatment) (mean/median)** | [redacted] | [redacted] | Until disease progression or unacceptable toxicity. |
| **Criteria for discontinuation [32]** | Progressive disease or unacceptable toxicity. | Progression to the 'Progressed disease' state. | Progressive disease or unacceptable toxicity. |
| **The pharmaceutical's position in Danish clinical practice** | 1L | 1L | 1L |
| **Dose intensity [141]** | [redacted] | [redacted] | [redacted] |

Table 22: Comparator: Ipi/Nivo

| Comparator (Ipi/Nivo) | Clinical documentation (including source) | Used in the model (number/value including source) | Expected Danish clinical practice (including source) |
|---|---|---|---|
| **Dose [105]** | Ipi: 1 mg/kg first 4 administrations<br>Nivo: 3 mg/kg first 4 administrations; then 240 mg every 2nd week | Ipi: 100 mg first 4 administrations (wastage included)<br>Nivo: 300 mg first 4 administrations (wastage included); then 240 mg every 2nd week | Ipi: 1 mg/kg first 4 administrations<br>Nivo: 3 mg/kg first 4 administrations; then 240 mg every 2nd week |
| **Administration frequency [105]** | Ipi: Every 3rd week for 4 administrations.<br>Nivo: Every 3rd week for 4 administrations, thereafter every 2nd week. | Ipi: Every 3rd week for 4 administrations.<br>Nivo: Every 3rd week for 4 administrations, thereafter every 2nd week. | Ipi: Every 3rd week for 4 administrations.<br>Nivo: Every 3rd week for 4 administrations, thereafter every 2nd week. |

| Comparator (Ipi/Nivo) | Clinical documentation (including source) | Used in the model (number/value including source) | Expected Danish clinical practice (including source) |
|---|---|---|---|
| **Length of treatment (time on treatment) (mean/median)** | Ipi/Nivo arm (ITT population): median 7.9 months (IQR: 2.1, 21.8 months)[1] [45] | [redacted] | Ipi: until disease progression or unacceptable toxicity, with maximum treatment of 4 doses (12 weeks).<br>Nivo: until disease progression or unacceptable toxicity. |
| **Criteria for discontinuation [105]** | Ipi: progressive disease or unacceptable toxicity, with maximum treatment of 4 doses (12 weeks).<br>Nivo: progressive disease or unacceptable toxicity. | Progression to the 'Progressed disease' state. | Ipi: progressive disease or unacceptable toxicity, with maximum treatment of 4 doses (12 weeks).<br>Nivo: progressive disease or unacceptable toxicity. |
| **The pharmaceutical's position in Danish clinical practice** | 1L | 1L | 1L |
| **Dose intensity** | [redacted] | [redacted] | [redacted] |

[1]*Length of treatment not reported separately for ipilimumab and nivolumab;* [redacted]
*Abbreviations: ITT, intention-to-treat; IQR, interquartile range.*

#### 8.2.2.4 Relative efficacy outcomes

**The relative efficacy outcomes in the submitted clinical documentation:**

The CheckMate 9ER trial reported PFS and OS for subjects treated with Cabo/Nivo or sunitinib, respectively. Data were reported for the ITT population as well as for subpopulations stratified by IMDC prognostic risk. HRs were calculated based on the PFS and OS data (Table 23). The primary efficacy endpoint was PFS. The primary definition of PFS (PFS truncated at subsequent therapy, which included anti-cancer therapy, radiotherapy, or surgery) was defined as the time between randomisation to the date of first documented tumour progression, based on BICR assessments per RECIST v1.1 criteria, or death due to any cause, whichever occurred first. [32] The secondary efficacy endpoint was OS, defined as the time from randomisation to death from any cause. [32]

The CheckMate 214 trial reported PFS and OS for subjects treated with Ipi/Nivo or sunitinib, respectively. Data were reported for the ITT population as well as for the IMDC intermediate/poor subpopulation.

**Relevance of the documentation for Danish clinical practice:**

PFS and OS are well-established relevant outcomes in oncology and have been evaluated as critical endpoints in previous DMC assessments within aRCC. [92, 95, 136]

As discussed previously, the anticipated patient population in Denmark is restricted to IMDC intermediate/poor prognostic risk patients who are either (1) eligible for Ipi/Nivo treatment, or (2) ineligible for Ipi/Nivo treatment but eligible for Cabo/Nivo treatment. Therefore, the relative efficacy outcomes reported in the trial subpopulation of

patients at intermediate/poor prognostic risk were considered to be more relevant for the Danish clinical practice, as compared with the ITT population.

**The relative efficacy outcomes in the submitted health economic analysis:**

For the comparison between Cabo/Nivo and sunitinib, extrapolation curves were fitted onto PFS and OS KM data for the CheckMate 9ER study subpopulation of patients at intermediate/poor prognostic risk, as described in section 8.3.1.1. The median PFS and OS generated in the CE model by applying the selected extrapolation curves are presented in Table 23.

For the comparison between Cabo/Nivo and Ipi/Nivo, extrapolation curves were estimated using an FP NMA model comparing the efficacy of these treatments in the subpopulation of patients at intermediate/poor prognostic risk in terms of PFS and OS, as described in section 8.3.1.2. Best fitting models were selected based on statistical fit and long-term clinical plausibility. The median PFS and OS generated in the CE model by applying the selected best-fit FP NMA models are presented in Table 24.

**Table 23: Summary of text regarding *value* of clinical efficacy outcomes *(Cabo/Nivo vs. sunitinib)***

| Clinical efficacy outcome | Clinical documentation<br>IMDC intermediate/poor prognostic subpopulation (CheckMate 9ER: DBL June, 2021) | Used in the model (value) |
|---|---|---|
| **Primary endpoint in the study:**<br>**Progression-free survival (PFS)** | [redacted] | [redacted] |
| **Secondary endpoint:**<br>**Overall survival (OS)** | At the database lock date, median OS was:<br>Cabo/Nivo: 37.6 months (95% CI: 32.5-NR)<br>Sunitinib: 29.0 months (95% CI: 23.8-36.2)<br>At that time, a total of 231 deaths had occurred (100/249 [40.2%] in the Cabo/Nivo arm, 131/256 [51.2%] in the sunitinib arm) after a median follow-up of 32.9 months.<br>Cabo/Nivo demonstrated to significantly improve patients' OS with a reduced risk of death by 34% (HR = 0.66; 95% CI: 0.50-0.85; p=0.002).<br>[37] | [redacted] |

*Abbreviations: NR, not reached*

**Table 24: Summary of text regarding *value* of clinical efficacy outcomes *(Cabo/Nivo vs. Ipi/Nivo)***

| Clinical efficacy outcome | Clinical documentation<br><br>IMDC intermediate/poor prognostic subpopulation (CheckMate 9ER: DBL 24 June, 2021; CheckMate 214; DBL 24 Feb, 2021) | Used in the model (value) |
|---|---|---|
| **Primary endpoint in the study:**<br><br>**Progression-free survival (PFS)** | [redacted]<br><br>Ipi/Nivo: 11.6 months (95% CI: 8.4-16.5) [45]<br><br>[redacted] | [redacted] |
| **Secondary endpoint:**<br><br>**Overall survival (OS)** | At the database lock dates, median OS was:<br><br>Cabo/Nivo: 37.6 months (95% CI: 32.5-NR) [36]<br><br>Ipi/Nivo: 47.0 months (95% CI: 35.4-57.4) [45]<br><br>[redacted] | [redacted] |

*Abbreviations: FP NMA, fractional polynomial network meta-analysis*

As seen in Table 23, the PFS outputs from the model for the Cabo/Nivo vs. sunitinib comparison align well with the observed PFS in the CheckMate 9ER trial, although the model slightly underestimates the median PFS in the Cabo/Nivo arm, as compared with the trial observation, and slightly overestimates the median PFS in the sunitinib arm.

For OS, the model estimates longer median survival with Cabo/Nivo as compared with observed median OS in the trial. One underlying reason to this is the apparent drop in OS in the end of the KM curve for Cabo/Nivo (Figure 6, DBL June 24, 2021) which is an artefact due to censoring of patients. The median OS is therefore expected to increase with longer follow-up. The parametric curves do not reflect this drop currently observed in the KM curve, which leads to the apparent overestimation vs. the current trial data.

It can be noted that the modelled median OS as presented in Table 23 is not a model input that is applied in the model. Instead, it is the median OS generated by the best-fit OS extrapolation curve. Although the selected base case [redacted] distribution generated a median OS deviating from that observed in the clinical trial for the Cabo/Nivo arm, the selected curve is the one with the best statistical fit, meaning it is the curve with the best fit to the observed data for the entire duration of the follow up period. The application of a function does not allow the exact reproduction of the shape of the KM curve, as we obtain a smooth curve. This can lead to slight differences when we look at a specific time point. That is the case here, when looking just at the median, but that does not necessarily mean that the rest of the curve is not accurate. [redacted]

[redacted]

**Table 25: Summary of text regarding *relevance* of clinical efficacy outcomes**

| Clinical efficacy outcome | Clinical documentation (measurement method) | Relevance of outcome for Danish clinical practice | Relevance of measurement method for Danish clinical practice |
|---|---|---|---|
| **Primary endpoint in the study:**<br><br>**Progression-free survival (PFS)** | The primary efficacy endpoint was PFS. The primary definition of PFS (PFS truncated at subsequent therapy, which included anti-cancer therapy, radiotherapy, or surgery) was defined as the time between randomisation to the date of first documented tumour progression, based on BICR assessments per RECIST v1.1 criteria, or death due to any cause, whichever occurred first. [32] | PFS is a well-established relevant outcome in oncology and has been evaluated as a critical endpoint in previous DMC assessments within aRCC. [92, 95, 136] | RECIST is a set of criteria used to determine treatment response in clinical trials. E.g., for a valid response, you need a reduction in target tumour dimensions of over 30 %. For this, you need to use a computed tomography (CT) scan. In clinical practice, CT is also used, but not the RECIST criteria, since 1) it is not common practice and 2) whether the patient responds is more complex than just precise reduction of target tumour mass. One way of making the RECIST outcomes more relevant to real life is to check if the "investigator assessed" outcomes of the trial are well in line with the BICR (whom only look at the scans, never met the patients). In the 9ER trial, concordance between BICR and investigator PFS assessments was high [32]. PFS as measured by BICR and per RECIST v1.1 criteria is therefore relevant for 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 |
|---|---|---|---|
| **Secondary endpoint:**<br>**Overall survival (OS)** | Overall survival was defined as the time from randomisation to death from any cause. [32] | Overall survival is a well-established relevant outcome in oncology and has been evaluated as a critical endpoint in previous DMC assessments within aRCC. [92, 95, 136] | Relevant |

#### 8.2.2.5 Adverse reaction outcomes

**Adverse reaction outcomes in the clinical documentation submitted:**

Safety data collected in the CheckMate 9ER trial included observed rates per treatment arm, average duration, and average number of episodes of Treatment Emergent AEs (TEAE) of grade 3 or 4 (Table 26). The data describes the full study safety population.

Safety data collected from the CheckMate 214 trial, of relevance to the HE analysis, included observed AE rates among all randomised subjects in the Ipi/Nivo treatment arm.

**Adverse reaction outcomes in the health economic analysis submitted:** The most frequent (≥ 5%) grade 3 and 4 TEAEs (all-cause) experienced by Cabo/Nivo, sunitinib or Ipi/Nivo treated patients in the respective trials were included in the CE analysis.

The average duration of all grade 3-4 AEs found among patients in the CheckMate 9ER study was applied for all AEs.

The average number of episodes of AEs per patient was calculated as follows: for each patient in the CheckMate 9ER study, the average number of episodes of AEs was calculated by dividing the total number of AE (grade 3 or 4) episodes by the number of distinct AEs; then taking the average value among all patients across the two treatment groups [145].

The use of average values for duration and number of episodes across all AEs was a pragmatic approach to reduce possible errors due to large uncertainty in the estimation of individually rare AEs. Grouping all grade 3/4 AEs together decreases the possibility of having a strong impact of individual outliers based on very few observations and thus decreases the overall variance.

[redacted]

An analysis was conducted to explore the potential differences in AE duration across arms in CheckMate 9ER. [redacted]. An analysis was also conducted to explore the potential difference of number of average episodes per patient per AE between treatments, [redacted]

Table 26: Adverse reaction outcomes

| Adverse reaction outcome | Clinical documentation | | | Used in the model (numerical value) | | |
|---|---|---|---|---|---|---|
| Average duration of adverse events[1] | [redacted] | | | [redacted] | | |
| Average number of episodes per patient[1] | [redacted] | | | [redacted] | | |
| Adverse event rates, per treatment arm (showing AEs with ≥5% occurrence) | Cabo/Nivo[2] | Sunitinib[2] | Ipi/Nivo[3] | Cabo/Nivo | Sunitinib | Ipi/Nivo |
| Hypertension | [redacted] | [redacted] | 0.7% | [redacted] | [redacted] | 0.7% |
| Hyponatremia | [redacted] | [redacted] | N/R | [redacted] | [redacted] | 0.0% |
| Diarrhoea (Diarrhea) | [redacted] | [redacted] | 3.8% | [redacted] | [redacted] | 3.8% |
| Palmar-plantar erythrodysaesthesia syndrome | [redacted] | [redacted] | 0.0% | [redacted] | [redacted] | 0.0% |
| Increased lipase | [redacted] | [redacted] | 10.2% | [redacted] | [redacted] | 10.2% |
| Hypophosphataemia | [redacted] | [redacted] | N/R | [redacted] | [redacted] | 0.0% |
| Alanine aminotransferase increased | [redacted] | [redacted] | N/R | [redacted] | [redacted] | 0.0% |
| Anaemia | [redacted] | [redacted] | 0.4% | [redacted] | [redacted] | 0.4% |
| Fatigue | [redacted] | [redacted] | 4.2% | [redacted] | [redacted] | 4.2% |
| Increased amylase | [redacted] | [redacted] | N/R | [redacted] | [redacted] | 0.0% |
| Pulmonary embolism | [redacted] | [redacted] | N/R | [redacted] | [redacted] | 0.0% |
| Decreased neutrophil count | [redacted] | [redacted] | N/R | [redacted] | [redacted] | 0.0% |
| Thrombocytopenia | [redacted] | [redacted] | 0.0% | [redacted] | [redacted] | 0.0% |

*Source: [1] [145] [2] [36], [3] [133] N/R: adverse events with <15% occurance in both treatment arms were not reported.*

## 8.3 Extrapolation of relative efficacy

### 8.3.1 Time to event data – summarized:

For full methods and results, please see Appendix G.

#### 8.3.1.1 Cabo/Nivo versus sunitinib

In summary, individual patient-level survival data for PFS and OS from the CheckMate 9ER trial was extrapolated beyond the trial period by fitting the data to parametric survival models and selecting the best-fit models. The best-fitted parametric survival models were selected based on standard goodness-of-fit statistics (Akaike Information Criterion [AIC], AIC corrected for small sample size [AICc] and Bayesian Information Criterion [BIC]). In addition, the different

parametric survival curve types were assessed for clinical plausibility. Data for the IMDC intermediate/poor prognostic risk subpopulation was used. [redacted]

#### 8.3.1.1.1 Overall survival

[redacted]. No corrections have been made for treatment switch or cross over, as cross over between groups was not permitted [34].

#### 8.3.1.1.2 Progression-free survival

[redacted] No corrections have been made for treatment switch or cross over, as cross over between groups was not permitted [34].

#### 8.3.1.1.3 Overall survival and progression-free survival curves applied in the health economic model – Cabo/Nivo versus sunitinib

The resulting OS and PFS curves applied in the base case analysis for the comparison between Cabo/Nivo and sunitinib are shown in Figure 22. A tabular presentation of the proportion of patients in each state at various time points is provided in Table 27.



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#### 8.3.1.2 Cabo/Nivo versus Ipi/Nivo

For the purpose of the health economic analysis, and in the absence of direct trial-based comparisons of Cabo/Nivo with Ipi/Nivo, a fractional polynomial network meta-analysis (NMA) was carried out to compare the efficacy of these first line treatments in patients with aRCC, in terms of PFS and OS. Details are provided in Appendix G.

The choice of using a fractional polynomial NMA approach rather than a constant HR in the health economic model was based on the conclusion of the proportional hazards tests for the CheckMate 214 study. In this trial, the proportional hazards assumption was violated for both PFS and OS. When the proportional hazard assumption is violated, applying the same HR over the entire time horizon in a health economic model does not reproduce accurately the relative efficacy of Ipi/Nivo over time. In this situation, the use of alternative methods with time-varying models are recommended to compare survival in economic analyses, both in the recent National Institute for Health and Care Excellence (NICE) manual for health technology evaluations [148] and in the DMC's guidance document for survival extrapolations in health economic evaluations [149]. Overall, using the fractional polynomial NMA approach gives more robust estimates of relative efficacy over time than using a constant HR.

In the case of Ipi/Nivo, there is a large variation of HR over time compared with sunitinib when comparing the KM curves (see Figure 16 above). Before 6 months, the HR for PFS is around 1 and then the curves start separating and the Ipi/Nivo curve is flattening, describing less risk of progression compared to sunitinib, which significantly decreases the HR. However, during the first approx. 6 months of treatment, there is no relative PFS benefit of Ipi/Nivo vs. TKI monotherapy with sunitinib. This situation is very different from the one with Cabo/Nivo treatment where an early separation of the Cabo/Nivo and sunitinib PFS curves is clearly observed, beginning already after 1 month of treatment (see Figure 5 above).

For the Bayesian fractional polynomial NMA conducted, 1st order and 2nd order fractional polynomials with powers P and (P1, P2) were fitted to OS and PFS along with the fixed effects and random effects with heterogeneity for the intercept and the coefficients of all powers, i.e. 2 parameters for 1st order FP models and 3 parameters for 2nd order FP models. This approach does not rely on the proportional hazards assumption and as a result, the model is more closely fitted to available survival data. Also, the parametrization of hazard rate with a 2nd order polynomial has a lot of flexibility which is especially beneficial for the PFS fitting. The results used in the health economic evaluation are for random effects models.

[redacted]

##### 8.3.1.2.1 Overall survival and progression-free survival curves applied in the health economic model – Cabo/Nivo versus Ipi/Nivo

Model fit was assessed based on DIC and long-term clinical plausibility. [redacted]

The resulting OS and PFS curves applied in the base case analysis for the comparison between Cabo/Nivo and Ipi/Nivo are shown in Figure 23. A tabular presentation of the proportion of patients in each state at various time points is provided in Table 28.

[redacted]

Out of the OS models tested in the NMA, most models generated clinically implausible long-term outcomes, and were therefore excluded from further analyses (see details on clinical plausibility assessment in Appendix G). In addition to the base case model, four other models were considered to have overall reasonable long-term clinical plausibility based

on visual inspection of the curves. However, for three of these models a benefit for Ipi/Nivo compared to Cabo/Nivo for OS in the long term would be assumed, and there is no evidence available to justify this long-term benefit. Therefore, only the remaining model (P= -1) which assumed similar relative efficacy for Cabo/Nivo and Ipi/Nivo in the long term was considered relevant to include in sensitivity analyses (section 8.6.4.1).

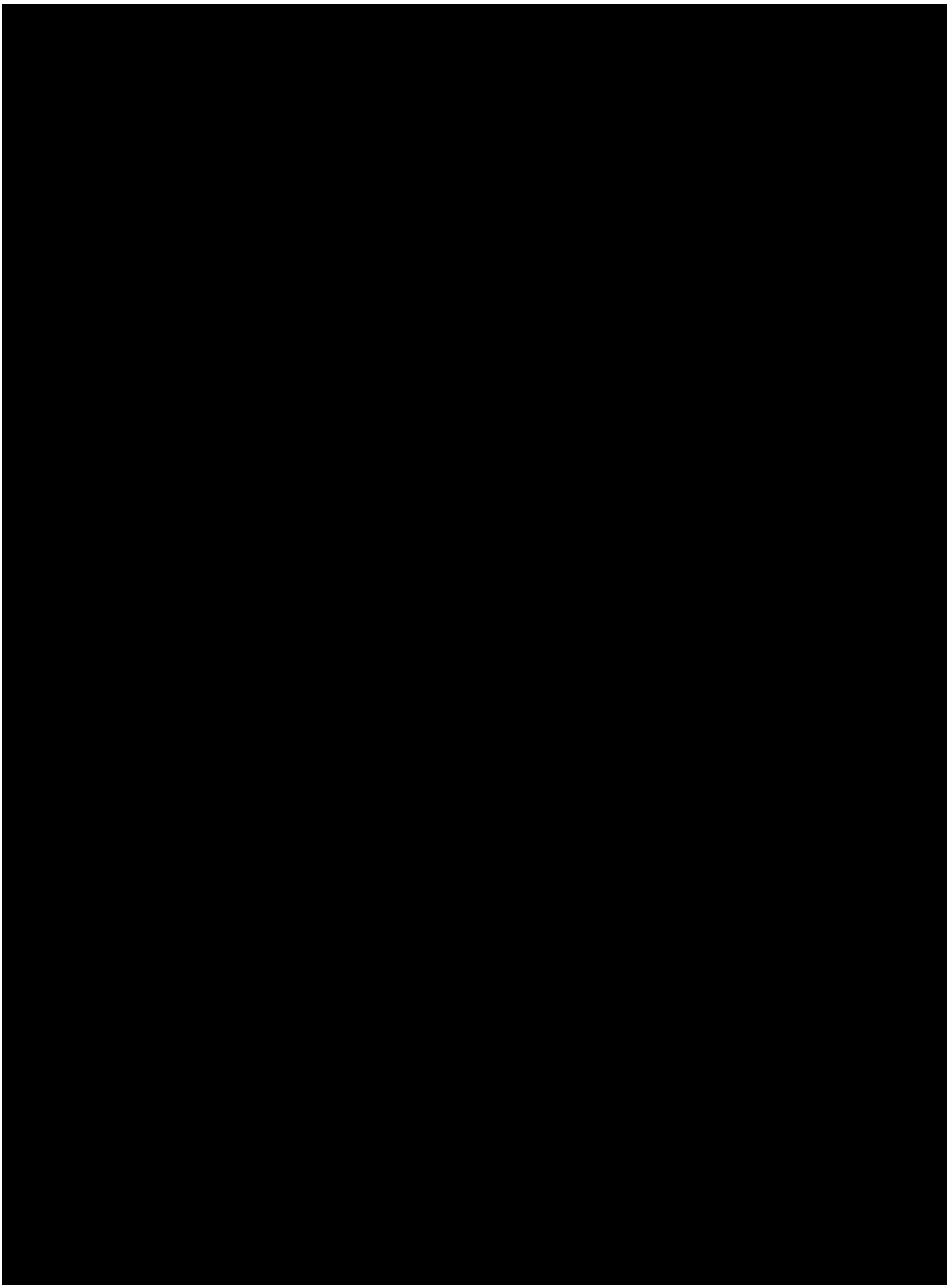
## 8.4 Documentation of health-related quality of life (HRQoL)

### 8.4.1 Overview of health state utility values (HSUV)

HRQoL data were collected in the CheckMate 9ER trial, for the relevant health states and AEs (Table 29). Thus, these trial data were used to inform the model with all necessary HRQoL inputs. The CheckMate 9ER trial recorded data on QoL using the generic EQ-5D-3L questionnaire. To generate the health state utility values (HSUVs) applied in the model, the data was mapped to EQ-5D-5L, and the Danish preference weights were applied (Table 30), as described in Appendix I.

Since the necessary HRQoL data were available from the trial, no literature search was undertaken.

[redacted]





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[redacted]

### 8.4.2 Health state utility values used in the health economic model

The selection of HSUVs used in the model is justified as follows:

- **HSUVs <u>for PF and PD:</u>**
  Patient-reported QoL data were collected in the CheckMate 9ER trial using EQ-5D-3L. Separate data were available by prognosis. According to guidelines from the DMC, the responses were mapped to EQ-5D-5L using Danish preference weights, providing a highly relevant data source for evaluating CE in a Danish setting.
- **HSUVs <u>for adverse reactions:</u>**
  Patient-reported QoL data was collected in the CheckMate 9ER trial using EQ-5D-3L for patients with and without an AE. According to guidelines from the DMC, the responses were mapped to EQ-5D-5L using Danish preference weights, providing a highly relevant data source for evaluating CE in a Danish setting. The difference between the two utility values was used as a common disutility for all AEs in the model.

Age adjustment of all utilities were applied in the HE model using a multiplicative approach. The adjustment index provided on the DMC website was used.

[redacted]

**Table 31: Summary of the HSUVs used in the model**

| | HSUV | 95% C.I. | Source (literature search, study, ITC, etc.) |
|---|---|---|---|
| **Health state** | | | |
| **Progression free - intermediate and poor risk patients** | [redacted] | [redacted] | Mapped from EQ-5D-3L in study [151] |
| **Progressed disease - intermediate and poor risk patients** | [redacted] | [redacted] | Mapped from EQ-5D-3L in study [151] |
| **Adverse reaction** | | | |
| **Any adverse event (disutility)** | [redacted] | [redacted] | Mapped from EQ-5D-3L in study [151] |

The QoL data is derived from a clinical study (CheckMate 9ER) where treatment with the intervention is directly compared to one of the relevant comparators in the CE analysis (sunitinib). The data was adapted to fit a Danish setting according to guidelines provided by the DMC. EQ-5D-3L was used, requiring mapping to 5L and Danish preference weights. For the HE analysis this provides highly relevant and valid inputs to utility and QALY calculations. The QoL utility values for progression free and progressed disease health states, and for having an AE, were considered relevant also for patients treated with Ipi/Nivo since these health states utility values were treatment independent. It was found that the most suitable source to estimate utilities was the patient-level EQ-5D data from the CheckMate 9ER trial for all comparators in the model to avoid combining several sources and methods of preference elicitation together. Moreover, the use of patient-level CheckMate 9ER EQ-5D data and a mean disutility value made it possible to calculate disutility values for AEs included for comparators outside the CheckMate 9ER trial.

Mapping exercises will always introduce uncertainty, but the methods used have been published and validated and follow the recommendations and guidelines from the DMC.

The use of a mean value for disutility across all AEs was a practical choice to reduce possible errors due to large uncertainty in the estimation of disutility of individually rare AEs and to have a standardized disutility value for all grade 3/4 AEs. Grouping all grade 3/4 AEs together decreases the possibility of having a strong impact of individual outliers based on very few observations and thus decreases the overall variance (at the expense at gaining additional resolution by assigning each grade 3/4 event its own disutility value).

***EQ-5D response rates***

Furthermore, the EQ-5D response rates in the CheckMate 9ER trial were high which supports the validity of the measurements:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

## 8.5 Resource use and costs

Costs for the Danish setting were applied in the model.

The model included the following cost categories:

- Drug and treatment costs
- First-line treatment costs
- Second-line treatment costs
- Health care costs, by health state
- PF state costs
- PD state costs
- End-of-life costs
- AE-management costs

In the model, the primary treatment cost information for the different treatment regimens was centered around cost per administration and cost per month. The cost of a single drug administration was determined based on dose size and

dose intensity data. Using the number of monthly administrations, the monthly cost of each drug was calculated. When appropriate, stopping rules and drug administration costs were considered.

### 8.5.1 Cost A - Drug costs, 1L treatment

#### 8.5.1.1 Resource use for cost A

**Dose per administration:** The proposed posology for **Cabo/Nivo** is either 240 mg nivolumab intravenous (IV) every 2 weeks (Q2W) or 480 mg IV every 4 weeks (Q4W) in combination with 40 mg cabozantinib administered orally once daily (QD) (see SmPC section 4.2 [2]).

Cabozantinib is available in three strengths: 60 mg, 40 mg, and 20 mg per tablet. Flat pricing is applied, so that all strengths carry the same cost per tablet. The relevant resource use per administration in the model was therefore 1 tablet per administration, irrespective of strength applied.

Nivolumab is available as 40 mg, 100 mg, and 240 mg vials, which are priced at an equal price per mg. To take a conservative approach, the Q2W dose was applied in the model, as this generated more intravenous administration events and thus higher administration costs for the intervention arm, as compared with the Q4W dose. Hence, it was assumed that one 240 mg vial would be consumed per administration.

For **sunitinib**, the recommended posology is 50 mg once daily in treatment cycles of 4 weeks on treatment and 2 weeks off treatment [23]. Sunitinib is available in three strengths: 50 mg, 25 mg, and 12.5 mg. The recommended dose is 50 mg daily. Hence, it was assumed in the model that one tablet of 50 mg would be used per administration.

The proposed posology for **Ipi/Nivo** in the treatment of RCC is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks in an initial phase of 4 doses. This is then followed by a maintenance phase in which nivolumab monotherapy is administered intravenously at either 240 mg Q2W, or at 480 mg Q4W [1].

In alignment with the Cabo/Nivo arm, the Q2W dose and 240 mg vial is applied in the maintenance phase in the model. In the initial phase, the 100 mg vial generated least wastage and was thus applied in the model.

Ipilimumab is available as 50 mg and 200 mg vials, which are priced at an approximately equal price per mg. The 50 mg vial was considered most relevant to apply in the model as this generated least wastage.

**Dose intensity:** Drug costs were further adjusted by the dose intensity. It was assumed that relative dose intensity is a function of dose reductions and treatment interruptions, which impacted the treatment cost as this was associated with cost savings. The assumptions applied in the model are presented in Table 33 for Cabo/Nivo and sunitinib, and Table 34 for Ipi/Nivo. For cabozantinib, flat pricing with the same price for each dose (60, 40 and 20 mg) has been applied. Thus, dose reductions within these dose ranges do not impact the treatment cost. However, the posology for cabozantinib in combination with nivolumab allows for a dose reduction to 10 mg per day, administered as 20 mg orally every second day [23]. The cost-saving effect associated with this dosing schedule was included in the dose intensity calculation. [redacted]

The dose intensities for Cabo/Nivo and sunitinib were based on data from CheckMate 9ER [141] and defined/calculated as follows:

- [redacted]

[redacted]

- [redacted]

[redacted]

**Stopping rule:** Nivolumab used in combination with cabozantinib can be used for a maximum treatment period of 24 months [23], therefore this stopping rule was included in the model: no nivolumab treatment costs were applied for time points beyond 24 months from baseline. The stopping rule was not applied for nivolumab as 2L treatment.

Nivolumab used in combination with ipilimumab should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient [1]. No stopping rule was thus applied. Treatment with ipilimumab, in combination with nivolumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient, up to a maximum of 4 doses (12 weeks) [90].

**Wastage:** The assumption applied to the base case was that vial sharing would not occur in practice in the administration of IV drugs, i.e., nivolumab and ipilimumab. The cost of wastage was thus included in the analysis.

#### 8.5.1.2 Unit cost(s) for cost A

The drug unit costs are specified in Table 33 and Table 34. The model uses AIP prices, collected from medicinpriser.dk on November 19, 2022 [97].

#### 8.5.1.3 Value used in the model for cost A

Table 33 summarizes the elements used to calculate the drug costs per month for Cabo/Nivo and sunitinib as 1L treatments. Table 34 summarizes the elements used to calculate the drug costs per administration for Ipi/Nivo as 1L treatment, in the initial 12-week and the maintenance phases, respectively.

**Table 33: 1L treatment pharmaceutical costs used in the model: Cabo/Nivo and sunitinib**

| Cost item | Dose per administration | Monthly administrations | Dose intensity | Pack size | Unit cost, DKK [1] | Cost per month, DKK |
|---|---|---|---|---|---|---|
| **Intervention** | | | | | | |
| **Cabozantinib** | 40 mg [2] | 30.4<br>*Every day [2]* | [redacted] | 30 x 40 mg | 49,400.00 | [redacted] |
| **Nivolumab** | 240 mg [2] | 2.2<br>*Every 2nd week [2]* | [redacted] | 1 x 240 mg vial | 21,453.65 | [redacted] |
| **Comparator: sunitinib** | | | | | | |
| **Sunitinib** | 50 mg [23] | 20.3<br>*Alternating 4w on daily treatment/2w off treatment [23]* | [redacted] | 30 x 50 mg | 1,800.00 | [redacted] |

[1] *AIP costs applied. Source: medicinpriser.dk, as of Nov 19, 2022.*

Table 34: 1L treatment pharmaceutical costs used in the model: Ipi/Nivo

| Cost item | Pack size | Unit cost, DKK [1] | Dose per administration | Packs per administrations | Dose intensity | Cost per administration, DKK | Frequency of administrations |
|---|---|---|---|---|---|---|---|
| **Initial phase (Week 0-12)** | | | | | | | |
| **Ipilimumab** | 1 x 50 mg | 25,012.19 | 1 mg/kg [2] | 2 [2] | [redacted] | 50,024 | Every 3rd week [2] |
| **Nivolumab** | 1 x 100 mg vial | 8.939.02 | 3 mg/kg [2] | 3 [2] | [redacted] | 26,817 | Every 3rd week [2] |
| **Maintenance phase (Week 12 and onwards)** | | | | | | | |
| **Nivolumab** | 1 x 240 mg vial | 21,453.65 | 240 mg [2] | 1 | [redacted] | 21,454 | Every 2nd week [2] |

[1] *AIP costs applied. Source: medicinpriser.dk, as of Nov 19, 2022.*
[2] *Based on average weight of* [redacted] *(Table 19) and including wastage.*

## 8.5.2 Cost B - Drug administration costs, 1L treatment

### 8.5.2.1 Resource use for cost B

No administration costs were assumed for the orally administered treatments: cabozantinib and sunitinib.

Nivolumab and ipilimumab are administered intravenously in the hospital setting and accordingly an administration cost was applied for each administration.

### 8.5.2.2 Unit cost(s) for cost B

A cost of DKK 2,038 per intravenous administration was applied in the model (DRG 11MA98, 2022 [156]).

### 8.5.2.3 Value used in the model for cost B

The elements used to calculate the administration costs per month for Cabo/Nivo, sunitinib, and Ipi/Nivo as 1L treatments are summarized in Table 35 and Table 36.

Table 35: 1L treatment administration costs used in the model: Cabo/Nivo and sunitinib

| Cost item | Type of administration | Monthly administrations | Unit cost, DKK | Cost per month, DKK |
|---|---|---|---|---|
| **Intervention** | | | | |
| **Cabozantinib** | Oral | N/A | N/A | 0 |
| **Nivolumab** | IV injection | 2.2<br>*Every 2nd week [2]* | 2,038<br>*DRG 11MA98 [156]* | 4,431 |
| **Comparator** | | | | |
| **Sunitinib** | Oral | N/A | N/A | 0 |

Table 36: 1L treatment administration costs used in the model: Ipi/Nivo

| Cost item | Type of administration | Monthly administrations | Unit cost, DKK | Cost per month, DKK |
|---|---|---|---|---|
| **Initial phase (Week 0-12)** | | | | |
| **Ipilimumab** | IV injection | 1.4<br>*Every 3rd week [2]* | 2,038<br>*DRG 11MA98 [156]* | 2,954 |
| **Nivolumab** | IV injection | 1.4<br>*Every 3rd week [2]* | 2,038<br>*DRG 11MA98 [156]* | 2,954 |
| **Maintenance phase (Week 12 and onwards)** | | | | |
| **Nivolumab** | IV injection | 2.2<br>*Every 2nd week [2]* | 2,038<br>*DRG 11MA98 [156]* | 4,431 |

### 8.5.3 Cost C - Drug costs, 2L treatment

#### 8.5.3.1 Resource use for cost C

Following initial treatment discontinuation, patients are administered with subsequent lines of treatment. The model includes treatments which were reported to be used as 2L treatments by patients in the IMDC intermediate/poor prognostic risk subpopulation in the Checkmate 9ER study (Cabo/Nivo; sunitinib) or in the CheckMate 214 study (Ipi/Nivo), and are available in Denmark. Potential 2L treatments thus include: axitinib, cabozantinib, nivolumab, pazopanib, everolimus, sorafenib, and sunitinib. Based on clinical expert input [89], re-treatment with sunitinib, cabometyx or nivolumab was not possible in the respective treatment arm in the model. The distribution of and duration of subsequent treatments according to initial treatment are shown in Table 37. Dose, administration frequency and relative dose intensity for each 2L treatment are provided according to initial treatment in Table 38.

Table 37: Distribution and duration of 2L treatments applied in the model

| Cost item | % of patients using, following 1L treatment with Cabo/Nivo[1] | % of patients using, following 1L treatment with sunitinib[1] | % of patients using, following 1L treatment with Ipi/Nivo[2] | Mean duration of 2L treatment, weeks | Source, mean duration |
|---|---|---|---|---|---|
| **Axitinib** | [redacted] | [redacted] | 35.3% (79/224) | 31.5 | Axitinib NICE technology appraisal [157].<br>Mean treatment duration= 220.8 days, for all population. |
| **Cabozantinib** | [redacted] | [redacted] | 31.3% (70/224) | [redacted] | [redacted] |
| **Everolimus** | [redacted] | [redacted] | 20.1% (45/224) | [redacted] | [redacted] |
| **Nivolumab** | [redacted] | [redacted] | N/A | 23.9 | Opdivo SmPC [1].<br>In the randomised phase 3 study of nivolumab as monotherapy vs. everolimus (CA209025), median duration of treatment was 5.5 months. |

| Cost item | % of patients using, following 1L treatment with Cabo/Nivo[1] | % of patients using, following 1L treatment with sunitinib[1] | % of patients using, following 1L treatment with Ipi/Nivo[2] | Mean duration of 2L treatment, weeks | Source, mean duration |
|---|---|---|---|---|---|
| Pazopanib | [redacted] | [redacted] | 35.3% (79/224) | [redacted] | [redacted] |
| Sorafenib | [redacted] | [redacted] | 5.4% (12/224) | 25.8 | Axitinib NICE technology appraisal [157].<br>Mean treatment duration = 180.7 days, for all population. |
| Sunitinib | [redacted] | [redacted] | 47.3% (106/224) | [redacted] | [redacted] |

*Source* [redacted] *[2] CheckMate 214, Intermediate/Poor Risk patients [45]*

#### 8.5.3.2 Unit cost(s) for cost C

The drug unit costs are specified in Table 38. The model uses AIP prices, collected from medicinpriser.dk on Nov 19, 2022.

#### 8.5.3.3 Value used in the model for cost C

Table 38 summarizes the elements used to calculate the drug costs per month for 2L treatments in the model.

The average cost per patient for an entire 2L treatment period was applied when patients transition to the PD state in the model.

**Table 38: 2L treatment pharmaceutical costs used in the model**

| 1L treatment with Cabo/Nivo | | | | | | |
|---|---|---|---|---|---|---|
| **Cost item** | **Dose per administration, mg** | **Monthly administrations** | **Dose intensity** | **Pack size** | **Unit cost, DKK [2]** | **Cost per month, DKK** |
| **Axitinib** | 5 [161] | 60.9<br>*Twice daily* [161] | 100%[1] | 56 x 5 mg | 26,002.58 | 28,266 |
| **Everolimus** | 10 [162] | 30.4<br>*Once Daily* [163] | 100%[1] | 30 x 10 mg | 19,584.00 | 19,869 |
| **Pazopanib** | 800 [25] | 30.4<br>*Once daily* [25] | 86%<br>Pazopanib NICE technical appraisal [164] | 60 x 400 mg | 18,470.43 | 16,116 |
| **Sorafenib** | 400 [165] | 60.9<br>*Twice daily* [165] | 100%[1] | 112 x 200 mg | 20,111.98 | 21,862 |
| **Sunitinib** | 50 [23] | 20.3<br>*Alternating 4w on daily treatment/2w off treatment* [23] | [redacted] | 30 x 50 mg | 1,800.00 | [redacted] |

| 1L treatment with sunitinib | | | | | | |
|---|---|---|---|---|---|---|
| **Cost item** | **Dose per administration, mg** | **Monthly administrations** | **Dose intensity** | **Pack size** | **Unit cost, DKK [2]** | **Cost per month, DKK** |
| **Axitinib** | 5 [161] | 60.9<br>*Twice daily* [161] | 100%[1] | 56 x 5 mg | 26,002.58 | 28,266 |
| **Cabozantinib** | 60 [2] | 30.4<br>*Once daily* [2] | [redacted] | 30 x 60 mg | 49,400.00 | [redacted] |
| **Everolimus** | 10 [162] | 30.4<br>*Once Daily* [163] | 100%[1] | 30 x 10 mg | 19,584.00 | 19,869 |
| **Nivolumab** | 240 [1] | 2.2<br>*Every 2nd week* [1] | 100%[1] | 1 x 240 mg | 21,453.65 | 46,642 |
| **Pazopanib** | 800 [25] | 30.4<br>*Once daily* [25] | 86%<br>Pazopanib NICE technical appraisal [164] | 60 x 400 mg | 18,470.43 | 16,116 |
| **Sorafenib** | 400 [165] | 60.9<br>*Twice daily* [165] | 100%[1] | 112 x 200 mg | 20,111.98 | 21,862 |

| 1L treatment with Ipi/Nivo | | | | | | |
|---|---|---|---|---|---|---|
| **Cost item** | **Dose per administration, mg** | **Monthly administrations** | **Dose intensity** | **Pack size** | **Unit cost, DKK [2]** | **Cost per month, DKK** |
| **Axitinib** | 5 [161] | 60.9<br>*Twice daily* [161] | 100%[1] | 56 x 5 mg | 26,002.58 | 28,266 |
| **Cabozantinib** | 60 [2] | 30.4<br>*Once daily* [2] | [redacted] | 30 x 60 mg | 49,400.00 | [redacted] |
| **Everolimus** | 10 [162] | 30.4<br>*Once Daily* [163] | 100%[1] | 30 x 10 mg | 19,584.00 | 19,869 |
| **Pazopanib** | 800 [25] | 30.4<br>*Once daily* [25] | 86%<br>Pazopanib NICE technical appraisal [164] | 60 x 400 mg | 18,470.43 | 16,116 |
| **Sorafenib** | 400 [165] | 60.9<br>*Twice daily* [165] | 100%[1] | 112 x 200 mg | 20,111.98 | 21,862 |
| **Sunitinib** | 50 [23] | 20.3<br>*Alternating 4w on daily treatment/2w off treatment* [23] | [redacted] | 30 x 50 mg | 1,800 | [redacted] |

[1] *Assumption (no data available).*
[2] *AIP costs applied. Source: medicinpriser,dk, as of Nov 19, 2022.*

### 8.5.4 Cost D - Drug administration costs, 2L treatment

#### 8.5.4.1 Resource use for cost D

Nivolumab is administered intravenously in the hospital setting, and accordingly an administration cost was applied for each administration.

The remaining 2L treatments are orally administrated, and thus not associated with an administration cost.

#### 8.5.4.2 Unit cost(s) for cost D

A cost of DKK 2,038 per intravenous administration was applied in the model (DRG 11MA98, 2022 [156]).

#### 8.5.4.3 Value used in the model for cost D

Table 39 summarizes the elements used to calculate the administration costs per month for the 2L treatments.

**Table 39: 2L treatment administration costs used in the model**

| Cost item | Type of administration | Monthly administrations | Unit cost, DKK | Cost per month, DKK |
|---|---|---|---|---|
| **Axitinib** | Oral | N/A | N/A | 0 |
| **Cabozantinib** | Oral | N/A | N/A | 0 |
| **Everolimus** | Oral | N/A | N/A | 0 |
| **Nivolumab** | IV injection | 2.2<br>*Every 2nd week [1]* | 2,038<br>*DRG 11MA98 [156]* | 4,431 |
| **Pazopanib** | Oral | N/A | N/A | 0 |
| **Sorafenib** | Oral | N/A | N/A | 0 |
| **Sunitinib** | Oral | N/A | N/A | 0 |

### 8.5.5 Cost E - Hospital costs by health state

#### 8.5.5.1 Resource use for cost E

Prior to therapy initiation it was assumed that patients required a first outpatient consultation appointment. Thereafter, follow-up outpatient visits to a medical oncologist every 8$^{th}$ week, nurse visits and blood tests every 4$^{th}$ week, and CT scans every 12$^{th}$ week were assumed for the PF health state (Table 40). The health care resource use estimates in the PF state were in accordance with clinical expert estimates presented in the Amgros report for the previous appraisal of axitinib/avelumab as treatment for RCC. [95] In the PD health state, patients were assumed to require follow-up outpatient visits to a medical oncologist, nurse visits and blood tests and CT scans with the same frequencies as in the PF health state.

Furthermore, an end-of-life cost was applied when patients transition to the death state in the model.

#### 8.5.5.2 Unit cost(s) for cost E

Hospital resources were costed using DRG costs for 2022 [156] and are presented in Table 40.

The DRG cost for cancer-related hospitalization was used as a source for the end-of-life health care costs including hospice and palliative care, and it was assumed that this was generally covered within the trim point for the DRG, i.e., 11 days for DRG group 11 (renal and urinary disease).

#### 8.5.5.3 Value used in the model for cost E

Table 40 summarizes the elements used to calculate the hospital costs per month for the model health states.

**Table 40: Hospital costs used in the model**

| Costs | Resource use | | | Unit cost, DKK | Cost per month, by health state | | |
|---|---|---|---|---|---|---|---|
| | Progression-free | Progressed | Death | | Progression-free | Progressed | Death |
| **Outpatient visit, first visit** | 1.0; one-off cost in 1$^{st}$ cycle | - | - | DKK 2,038 per visit<br>DRG 11MA98 [156] | 2,038 | 0 | 0 |

| Costs | Resource use | | | Unit cost, DKK | Cost per month, by health state | | |
|---|---|---|---|---|---|---|---|
| | Progression-free | Progressed | Death | | Progression-free | Progressed | Death |
| **Doctor visits, follow-up** | 0.54 per month (1/8 weeks) | 0.54 per month (1/8 weeks) | - | DKK 2,038 per visit DRG 11MA98 [156] | 1,108 | 1,108 | 0 |
| **Nurse visits, follow-up** | 1.09 per month (1/4 weeks) | 1.09 per month (1/4 weeks) | - | DKK 2,038 per visit DRG 11MA98 [156] | 2,215 | 2,215 | 0 |
| **CT scan** | 0.36 per month (1/12 weeks) | 0.36 per month (1/12 weeks) | - | DKK 1,979 per scan DRG 30PR07 [156] | 717 | 717 | 0 |
| **End-of-life cost** | - | - | 1.0; one-off | DKK 34,436 per death DRG 11MA04 [156] | 0 | 0 | 34,436 |

### 8.5.6 Cost F - Adverse event costs

#### 8.5.6.1 Resource use for cost F

AE costs were included in the model by including AEs as one-off events during the first cycle.

An AE was defined as any new, untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation participant to whom a study drug was administered and that did not necessarily have a causal relationship with this treatment. The model included grade 3 and 4 treatment-emergent (all-cause) AEs, experienced by ≥5% of treated patients (Table 26) in the CheckMate 9ER [36] or CheckMate 214 [133] trials.

It was further assumed that [redacted] occurred per patient and AE, on average. This assumption was derived based on patient-level analysis of CheckMate 9ER trial data, as the average value among all patients across the two treatment groups [145].

#### 8.5.6.2 Unit cost(s) for cost F

AEs were costed using DRG costs for 2022 [156] and are presented in Table 41.

#### 8.5.6.3 Value used in the model for cost F

Table 41 summarizes the elements used to calculate the AE costs applied in the model for Cabo/Nivo, sunitinib and Ipi/Nivo treated patients, respectively.

**Table 41: Adverse events, costs and frequency by event**

| Adverse event | Cost per event | | AE rates | | | Episodes per patient[3] | Average AE cost per patient, cycle 1, DKK | | |
|---|---|---|---|---|---|---|---|---|---|
| | DRG [156] | DKK | Cabo/ Nivo[1] | Suni-tinib[1] | Ipi/Nivo[2] | | Cabo/Nivo | Sunitinib | Ipi/Nivo |
| **All events / Total** | | **N/A** | **N/A** | **N/A** | **N/A** | [redacted] | **8,758.40** | **6,733.43** | **645.36** |
| **Alanine aminotransferase increased** | 07MA98 | 2,910 | [redacted] | [redacted] | 0.0% | [redacted] | 238.16 | 94.51 | - |
| **Anaemia (Anemia)** | 16PR02 | 4,223 | [redacted] | [redacted] | 0.4% | [redacted] | 120.69 | 323.67 | 20.06 |
| **Decreased neutrophil count** | 05MA98 | 2,067 | [redacted] | [redacted] | 0.0% | [redacted] | 8.06 | 142.31 | - |
| **Diarrhoea (Diarrhea)** | 06MA98 | 2,358 | [redacted] | [redacted] | 3.8% | [redacted] | 269.56 | 143.97 | 117.60 |
| **Fatigue** | 08MA98 | 1,645 | [redacted] | [redacted] | 4.2% | [redacted] | 73.46 | 119.67 | 89.85 |
| **Hypertension** | 05MA11 | 16,630 | [redacted] | [redacted] | 0.7% | [redacted] | 3,240.50 | 2,835.43 | 157.98 |
| **Hyponatremia** | 10MA98 | 1,954 | [redacted] | [redacted] | 0.0% | [redacted] | 237.97 | 159.92 | - |
| **Hypophosphataemia** | 10MA98 | 1,954 | [redacted] | [redacted] | 0.0% | [redacted] | 167.53 | 31.73 | - |
| **Increased amylase** | 10MA98 | 1,954 | [redacted] | [redacted] | 0.0% | [redacted] | 134.53 | 63.46 | - |
| **Increased lipase** | 10MA98 | 1,954 | [redacted] | [redacted] | 10.2% | [redacted] | 190.38 | 126.92 | 259.87 |
| **Palmar-plantar erythrodysaesthesia syndrome** | 09MA03 | 19,518 | [redacted] | [redacted] | 0.0% | [redacted] | 1,977.69 | 2,053.75 | - |
| **Pulmonary embolism** | 04MA04 | 30,269 | [redacted] | [redacted] | 0.0% | [redacted] | 2,084.02 | 511.17 | - |
| **Thrombocytopenia** | 10MA98 | 1,954 | [redacted] | [redacted] | 0.0% | [redacted] | 15.86 | 126.92 | - |

[1] *Based on patient-level analysis of CheckMate 9ER trial data [36]*
[2] *Motzer 2018 [133]*
[3] *Based on patient-level analysis of CheckMate 9ER trial data [145].*

### 8.5.7 Cost G - Patient time and transportation costs

#### 8.5.7.1 Resource use for cost G

It was estimated that each hospital visit and examination was associated with one transport event, and an average of 30 minutes of the patient's time spent on the treatment. IV injections were estimated to take 30 minutes of the patient's time (Table 42). These estimates were in line with the estimates applied in the Amgros report for the previous appraisal of axitinib/avelumab as treatment for RCC [95].

#### 8.5.7.2 Unit cost(s) for cost G

As instructed in the DMC guidelines [30], the costs applied in the model were DKK 140 for each transport event, and DKK 181 per hour for patients' time spent on treatment (Table 42).

Table 42: Patient costs used in the model

| Costs | Number of units | Cost per unit | DKK per event |
|---|---|---|---|
| **Patient time spent on treatment, per IV injection** | 30 min | DKK 181 per hour | DKK 90.50 |
| **Patient time spent on hospital visits, per visit** | 30 min | DKK 181 per hour | DKK 90.50 |
| **Patient time spent on CT scans, per event** | 30 min | DKK 181 per hour | DKK 90.50 |
| **Patient transport cost per IV injection/hospital visit/CT scan** | 1 | DKK 140 per visit | DKK 140.00 |

#### 8.5.7.3 Value used in the model for cost G

Table 43 summarizes the elements used to calculate the patient costs per month, for the model health states and for IV administration of nivolumab and ipilimumab, respectively.

Table 43: Patient costs per month and health state

| Costs | Number of events per month | | | Patient cost per month | | |
|---|---|---|---|---|---|---|
| | IV injection | Hospital visits | CT scans | Time cost | Transport cost | Total cost |
| **Progression-free** | - | 1.63 | 0.36 | DKK 180.36 | DKK 279.00 | DKK 459.36 |
| **Progressed** | - | 1.63 | 0.36 | DKK 180.36 | DKK 279.00 | DKK 459.36 |
| **Ipilimumab treatment, initial phase** | 1.4 | - | - | DKK 131.17 | DKK 202.91 | DKK 334.08 |
| **Nivolumab treatment, initial phase** | 1.4 | - | - | DKK 131.17 | DKK 202.91 | DKK 334.08 |
| **Nivolumab treatment, maintenance phase** | 2.2 | - | - | DKK 196.75 | DKK 304.37 | DKK 501.12 |

### 8.5.8 Cost H - Municipality costs

No municipal costs were assumed.

## 8.6 Results

### 8.6.1 Base case overview

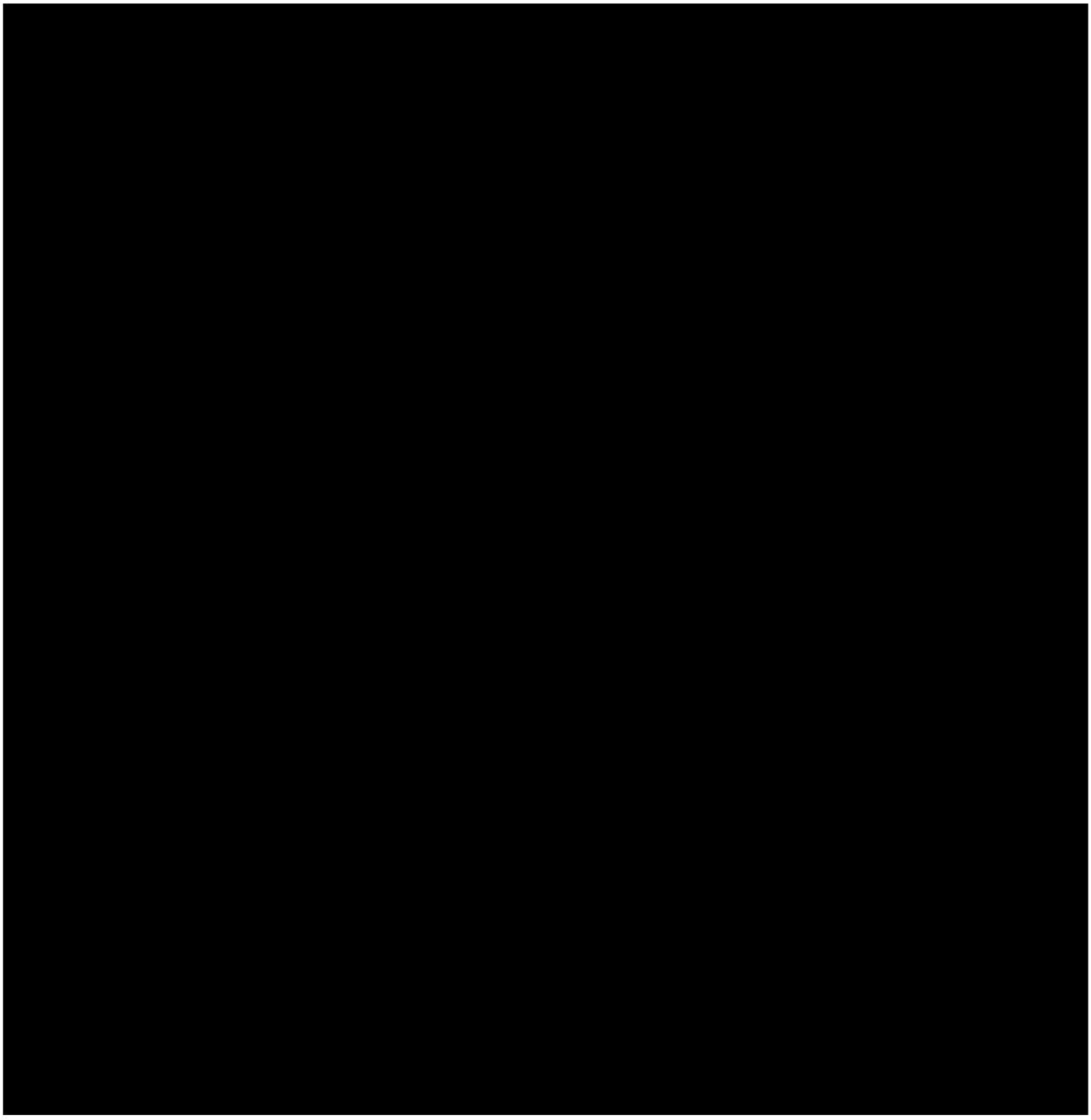
**Table 44: Base case overview**

| | |
|---|---|
| Population | Patients with aRCC with IMDC intermediate/poor prognostic risk |
| Comparators | (1) Sunitinib<br>(2) Ipi/Nivo |
| Type of model | Partitioned survival model |
| Time horizon | Lifetime (50 years) |
| Treatment line | 1st line treatment is evaluated.<br>Subsequent treatment lines were included in the analysis. |
| Measurement and valuation of health effects | Health-related quality of life measured with EQ-5D-3L in the CheckMate 9ER study [34]. Danish population weights were used to estimate health-state utility values. |
| Included costs | 1L treatment costs, including administration costs<br>Hospital costs<br>Costs of adverse events<br>2L treatment costs, including administration costs<br>Patient costs |
| Dosage of pharmaceutical | Fixed dose for cabozantinib, sunitinib, nivolumab in combination with cabozantinib, and nivolumab during Ipi/Nivo maintenance phase.<br>Weight-based dose for ipilimumab and nivolumab during Ipi/Nivo initial treatment phase. |
| Parametric function for PFS | [redacted]<br>(2) NMA-based fractional polynomial fit |
| Parametric function for OS | [redacted]<br>(2) NMA-based fractional polynomial fit |

### 8.6.2 Base case results: Cabo/Nivo versus sunitinib

Table 45 shows the deterministic results of the base case analysis. The CE base case analysis comparing Cabo/Nivo with sunitinib in the IMDC intermediate/poor prognostic risk patient subpopulation indicated that treatment with Cabo/Nivo is expected to generate [redacted] with Cabo/Nivo as compared with sunitinib treatment over a lifetime horizon.

[redacted]





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### 8.6.3 Base case results: Cabo/Nivo versus Ipi/Nivo

Table 46 shows the deterministic results of the base case analysis. The CE base case analysis comparing Cabo/Nivo with Ipi/Nivo in the IMDC intermediate/poor prognostic risk patient subpopulation indicated that treatment with Cabo/Nivo is expected to generate 0.161 life years (4.417 vs. 4.256) and 0.125 incremental QALYs (3.613 vs. 3.488) as compared with Ipi/Nivo, [redacted] The additional total cost with Cabo/Nivo treatment was DKK 182,483 per patient [redacted] which generated an ICER of **DKK 1,461,841 per QALY** gained with Cabo/Nivo as compared with Ipi/Nivo treatment over a lifetime horizon.

[redacted]

**Table 46: Base case results for the comparison between Cabo/Nivo and Ipi/Nivo in the intermediate/poor prognostic risk subpopulation**

| Per patient | Cabo/Nivo | Ipi/Nivo | Difference |
|---|---|---|---|
| **Life years gained** | | | |
| Total life years gained | 4.417 | 4.256 | 0.161 |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| **QALYs** | | | |
| Total QALYs | 3.613 | 3.488 | 0.125 |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| **Costs** | | | |
| [redacted] | [redacted] | [redacted] | 182,483 |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |

| Per patient | Cabo/Nivo | Ipi/Nivo | Difference |
|---|---|---|---|
| **Incremental results** | **Cabo/Nivo vs. Ipi/Nivo** | | |
| ICER (per QALY) | 1,461,841 | | |

### 8.6.4 Sensitivity analyses

One-way sensitivity analyses, scenario analyses and probabilistic scenario analyses (PSA) were performed, as described hereunder.

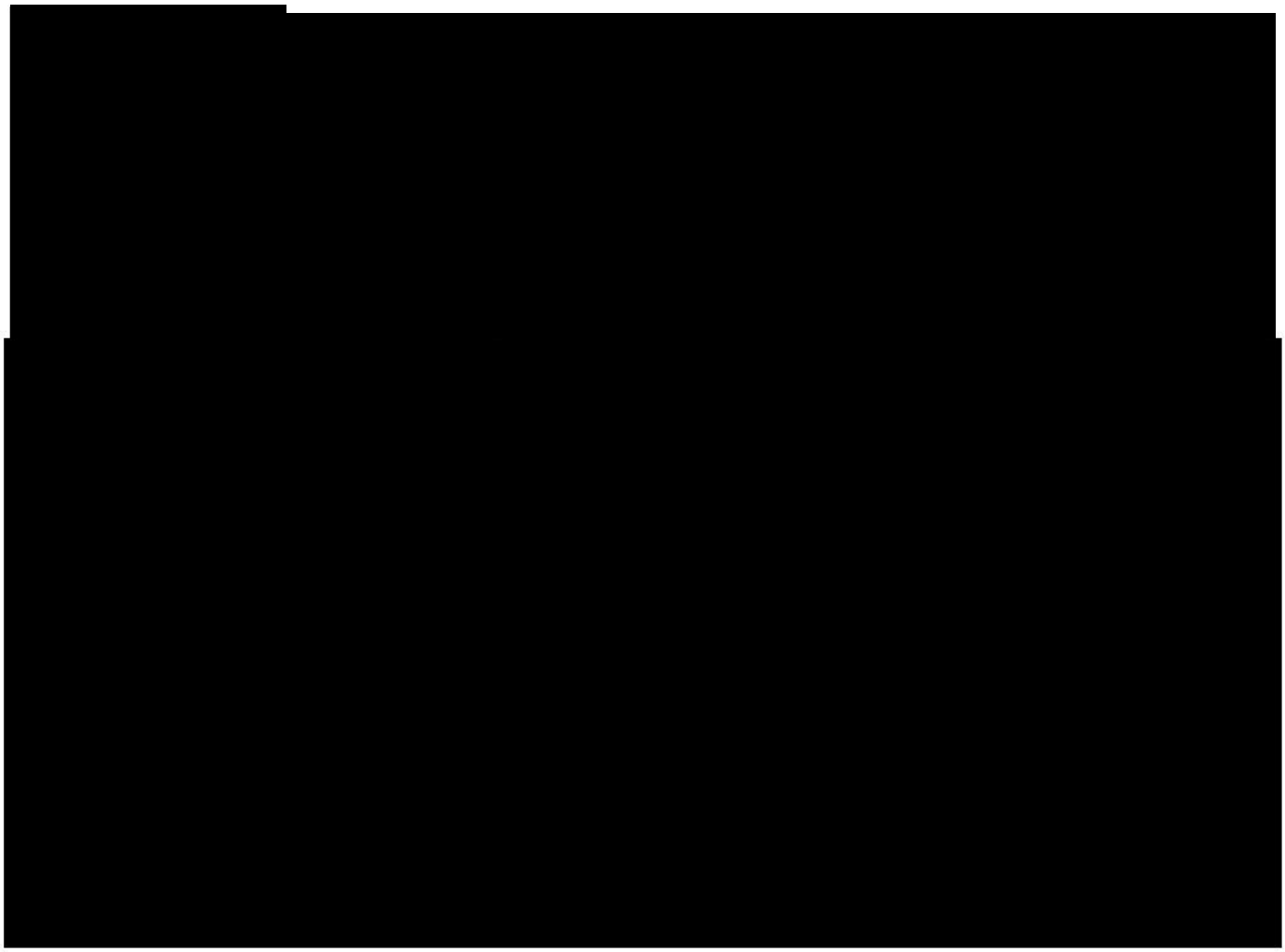
#### 8.6.4.1 Deterministic sensitivity analyses

***One-way sensitivity analyses***

To assess the robustness of the model results, OWSA were conducted by varying one model input at a time, for both comparisons. The results, shown in Table 47/Figure 24, and

Table 48/Figure 25, respectively, indicate that the results were robust for variation of most parameters.

[redacted]





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[redacted]

***Scenario analyses***

In addition to the OWSA described above, a number of scenario analyses were performed to assess the effect of changing modelling assumptions:

- **Shorter time horizons:** The base case analysis was based on a lifetime horizon. Shorter time horizons of 5, 10 and 20 years were assessed in scenario analyses.
- **Choice of extrapolation model:** The best fit curves were applied in the base case analysis. Scenario analyses were used to assess the impact of applying the other tested parametric functions for PFS and OS extrapolation, respectively.
- **Varying annual discount rates:** Undiscounted analyses were performed, either for both cost and effects or for effects only.
- **Health state utility value source:** The health state utilities derived directly from the study, based on EQ-5D-3L and the Canadian tariff, were applied in a scenario analysis. Another scenario analysis assessed the impact of applying health state utility values reported from all trial patients, rather than the base case utility values based on the data reported by IMDC intermediate/poor prognostic risk patients specifically.

***Cabo/Nivo versus sunitinib***

[redacted]

[redacted]

| Scenario name | Base case | Scenario input | Cabo/ Nivo QALY | Cabo/ Nivo cost | Sunitinib QALY | Sunitinib cost | Incr QALY | Incr Cost | ICER |
|---|---|---|---|---|---|---|---|---|---|
| **Base case** | | | | | | | | | |
| Time horizon | Lifetime | 20 years | | | | | | | |
| | | 10 years | | | | | | | |
| | | 5 years | | | | | | | |
| PFS extrapolation model | | | | | | | | | |
| OS extrapolation model | | | | | | | | | |
| Undiscounted results | 3.5%<br>2.5%<br>1.5% | - 0%<br>- | | | | | | | |
| 0% annual discount rates on effects | 3.5%<br>2.5%<br>1.5% | - 0%<br>- | | | | | | | |
| Health state utility values from trial (EQ-5D-3L, Canadian tariff, all subjects) | | | | | | | | | |
| Health state utility values from whole study population (EQ-5D-5L, Danish tariff) | | | | | | | | | |
| Half cycle correction applied | Yes | No | | | | | | | |

The requested analysis of the relation between ICER and the drug price of the intervention is shown in Figure 26.

[redacted]

***Cabo/Nivo versus Ipi/Nivo***

[redacted]

| Scenario name | Base case | Scenario input | Cabo/ Nivo QALY | Cabo/ Nivo cost | Ipi/Nivo QALY | Ipi/Nivo cost | Incr QALY | Incr Cost | ICER |
|---|---|---|---|---|---|---|---|---|---|
| **Base case** | | [redacted] | | | | | | | |
| Time horizon | Lifetime | | | | | | | | |
| PFS extrapolation model | | [redacted] | | | | | | | |

| | | | |
|---|---|---|---|
| [redacted] | | | |
| OS extrapolation model | [redacted] | | |
| OS extrapolation model & shorter time horizon | | | |
| Undiscounted results | 3.5% - 2.5% - 1.5% | 0% | [redacted] |
| 0% annual discount rates on effects | 3.5% - 2.5% - 1.5% | 0% | |
| Health state utility values from trial (EQ-5D-3L, Canadian tariff, all subjects) | [redacted] | | |
| Health state utility values from whole study population (EQ-5D-5L, Danish tariff) | [redacted] | | |
| Half cycle correction applied | Yes | No | [redacted] |

The requested analysis of the relation between ICER and the drug price of the intervention is shown in

Figure 27 [redacted]

[redacted]

#### 8.6.4.2 Probabilistic sensitivity analyses

Probabilistic sensitivity analyses were performed applying the parameter distributions presented in Appendix J. The PSA was run with 2,000 simulations.

***Cabo/Nivo versus sunitinib***

The resulting cost and QALY increments for Cabo/Nivo vs. sunitinib treatment in IMDC intermediate/poor prognostic risk patients are presented in the CE plane in Figure 28.

The CE acceptability curve for the PSA is presented in Figure 29, displaying the probability that the intervention has the greatest net monetary benefit at increasing values of WTP.

[redacted]

[redacted]

***Cabo/Nivo versus Ipi/Nivo***

The resulting cost and QALY increments for Cabo/Nivo vs. Ipi/Nivo treatment in IMDC intermediate/poor prognostic risk patients are presented in the CE plane in Figure 30.

The CE acceptability curve for the PSA is presented in Figure 31, displaying the probability that the intervention has the greatest net monetary benefit at increasing values of WTP.

[redacted]

# 9. Budget impact analysis

## 9.1 Number of patients

According to the DMC treatment guidelines, 210 ccmRCC patients with IMDC intermediate/poor risk receive 1L treatment each year. [28, 29] About 20% of these patients (i.e., 42 patients per year) are estimated to be ineligible for Ipi/Nivo treatment based on DK clinical expert input collected by IPSEN during the application process and by Amgros during previous assessment processes of new drugs used for renal cancer.[31, 92] Of the Ipi/Nivo ineligible patients, about 20% are estimated to be eligible for Cabo/Nivo as an alternative treatment option. [31] As described in section 5.2.1, Cabo/Nivo would also be a relevant alternative treatment option for the 168 (80%) of the 210 ccmRCC patients with IMDC intermediate/poor risk who would be expected to be Ipi/Nivo eligible. The two Cabo/Nivo target populations combined corresponds to 176 patients annually and approximately 84% of the total population of IMDC intermediate/poor risk patients receiving 1L treatment (see also Table 3, section 5.2).

Table 51 summarizes the number of patients in Denmark who are expected to receive Cabo/Nivo treatment in the next 5 years. The numbers are based on assumptions of a [redacted] Cabo/Nivo market share in the Ipi/Nivo eligible patient population and a [redacted] Cabo/Nivo market share in the Ipi/Nivo ineligible + Cabo/Nivo eligible patient population, combined with an assumption of a gradual market uptake. In the first year after introduction, it is assumed that 50% of the total number of expected patients based on the market share assumptions actually receive Cabo/Nivo. After the first year, all expected Cabo/Nivo patients are assumed to receive the treatment.

[redacted]

| | 2023 | 2024 | 2025 | 2026 | 2027 |
|---|---|---|---|---|---|
| Cabo/Nivo | [redacted] | | | | |
| Ipi/Nivo | | | | | |
| Sunitinib | | | | | |
| Total number of patients | 176 | 352 | 528 | 704 | 880 |

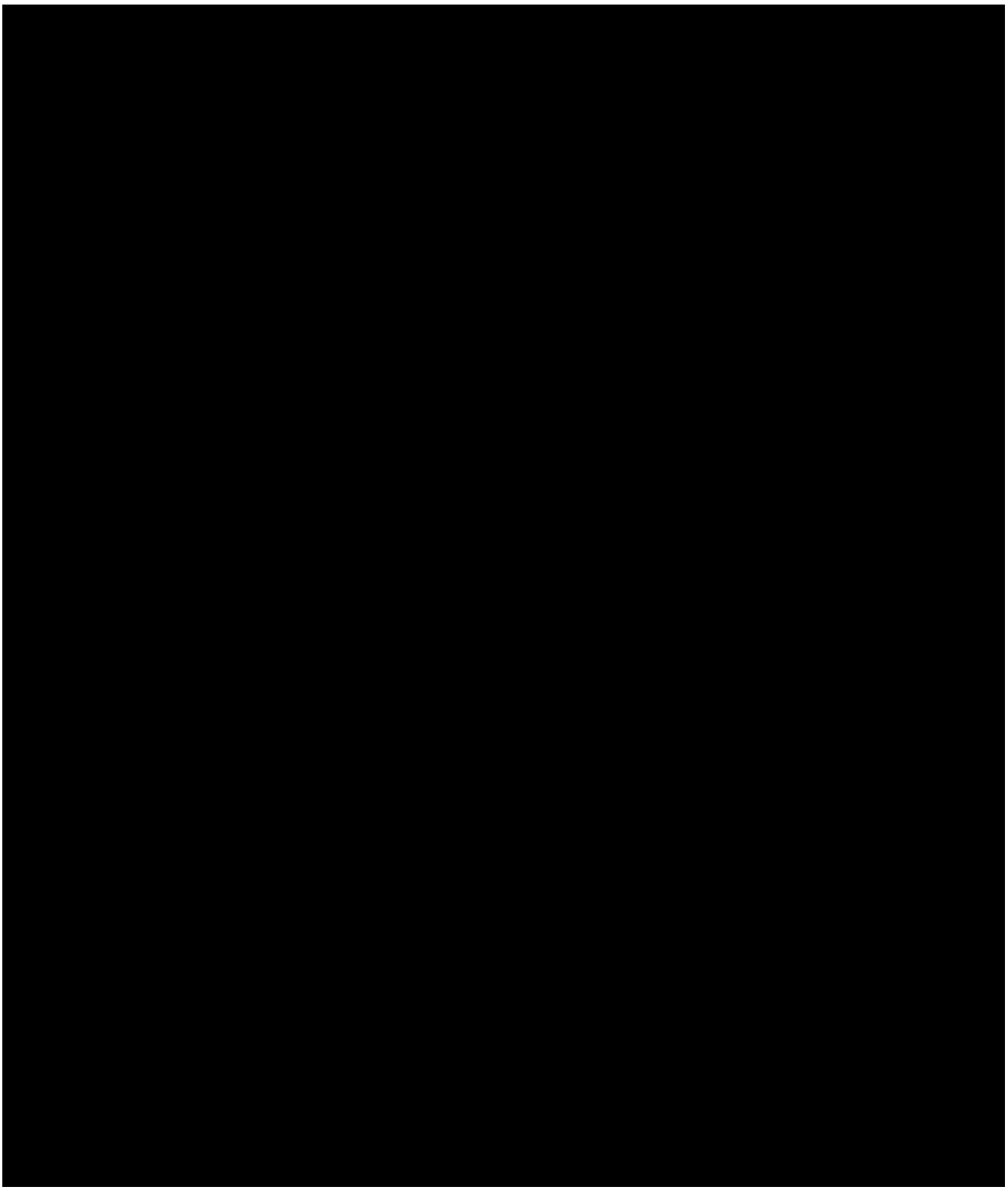
[redacted]

| | 2023 | 2024 | 2025 | 2026 | 2027 |
|---|---|---|---|---|---|
| Cabo/Nivo | [redacted] | | | | |
| Ipi/Nivo | | | | | |
| Sunitinib | | | | | |
| Total number of patients | 176 | 352 | 528 | 704 | 880 |

## 9.2 Expenditure per patient

Annual treatment (incl. administration costs) are given in Table 53, together with costs for AE management and hospital costs. These costs were extracted directly from the model and reflect the average cost per patient per year over a 5-year period.

[redacted]



## 9.3 Budget impact

The resulting estimated budget impact over the next 5 years if Cabo/Nivo is or is not recommended for the full indication proposed is presented in Table 55, showing that the added annual expenditure 5 years forward would be [redacted] if recommending Cabo/Nivo for the full indication proposed.



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### 9.3.1 Alternative scenarios

Scenario 1: In the case where Cabo/Nivo is recommended only for patient population 1, i.e Ipi/Nivo eligible patients, the number of patients expected to be treated with Cabo/Nivo over the next 5 years is presented in Table 56 below. The resulting estimated budget impact over the next 5 years if Cabo/Nivo is or is not recommended for this indication would be the added annual expenditure 5 years forward of [redacted] if recommending Cabo/Nivo for this indication.

**Table 56: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced – scenario 1**

| | 2023 | 2024 | 2025 | 2026 | 2027 |
|---|---|---|---|---|---|
| **Cabo/Nivo** | | | | | |
| **Ipi/Nivo** | | | | | |
| **Total number of patients** | | | | | |

Scenario 2: In the case where Cabo/Nivo is recommended only for patient population 2, i.e Ipi/nivo ineligible patients, the number of patients expected to be treated with Cabo/Nivo over the next 5 years is presented in Table 58 below. The resulting estimated budget impact over the next 5 years if Cabo/Nivo is or is not recommended for the current indication is presented in Table 59, showing that the added annual expenditure 5 years forward would be [redacted] if recommending Cabo/Nivo for the current indication.

**Table 58: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced – scenario 2**

| | 2023 | 2024 | 2025 | 2026 | 2027 |
|---|---|---|---|---|---|
| **Cabo/Nivo** | | | | | |
| **Sunitinib** | | | | | |
| **Total number of patients** | | | | | |

# 10. Discussion on the submitted documentation

In a very recent review published in July 2022, the combination of Cabo/Nivo was determined to offer the most significant net health benefit of any 1L treatment within aRCC, scoring higher (50.8) than both Axi/Pembro (48.7), Ipi/Nivo (41.9), Lenva/Pembro (35.2) and Axi/Ave (22.4) [88]. In Denmark, the two patient populations expected to use Cabo/Nivo are (1) patients with IMDC intermediate/poor prognostic risk who are eligible for Ipi/Nivo treatment and (2) patients with IMDC intermediate/poor prognostic risk who are ineligible for Ipi/Nivo treatment but eligible for Cabo/Nivo treatment. In the first of these populations, current standard treatment is combination treatment with Ipi/Nivo, while current standard treatment in the second of these populations is TKI monotherapy with sunitinib.

The results of the CE analyses comparing Cabo/Nivo with Ipi/Nivo and sunitinib, respectively, indicate that by delaying the progression of the disease and extending survival, Cabo/Nivo is a superior treatment option to both comparators. Better clinical outcomes with Cabo/Nivo in terms of improved survival as well as improved HRQoL to the patients generated a higher number of QALYs, with a larger difference demonstrated in the comparison with sunitinib. The base case CE analysis and scenario analyses demonstrated that Cabo/Nivo overall is a cost-effective treatment option for both populations.

For the comparison to sunitinib, the evaluation benefits from being informed by head-to-head clinical trial data from the robust, randomized phase III controlled trial CheckMate 9ER. The CheckMate 9ER study design allowed to conduct detailed analyses of subgroups relevant in the Danish setting, and the baseline characteristics of the patients included in CheckMate 9ER are generally representative of the Danish aRCC patient population. One limitation of the clinical documentation submitted is that the CheckMate 9ER trial did not exclusively include patients reflecting the Ipi/Nivo Danish patients populations expected to be eligible for treatment with Cabo/Nivo, as the trial included patients with both IMDC favourable, intermediate and poor prognostic risk. In general, the inclusion of such a broad patient population reflecting the real-life aRCC patient population is a considerable strength of the CheckMate 9ER trial. Though the study design did allow to conduct detailed analyses of subgroups, due to sample size considerations and the fact that Ipi/Nivo ineligibility can have various causes, it was necessary to use data from the subgroup including all patients with IMDC intermediate and poor risk to represent data for both of the Danish Cabo/Nivo target populations.

For the comparison to Ipi/Nivo, a weakness in relation to this was clearly that head-to-head trial data do not exist for the comparison of Cabo/Nivo to Ipi/Nivo. Cross-trial comparisons will always be difficult as varying study designs, methodology and patients populations limit the ability to draw conclusions of comparative efficacy and safety. However, the overall similarity of study designs and key baseline characteristics of the patients in the CheckMate 9ER and CheckMate 214 trials allowed indirect comparisons of Cabo/Nivo and Ipi/Nivo for most of the relevant clinical trial endpoints in this application. In the clinical sections of the dossier, the indirect comparison was conducted using the Bucher method. Despite having its limitations, this approach was considered to be acceptable and has also been used to generate indirect evidence vs. Ipi/Nivo in previous DMC assessments of other TKI/CPI combinations used in 1L aRCC. In the health economic model, the indirect evidence vs. Ipi/Nivo used was based on a FP NMA comparing PFS and OS. This decision followed the NICE and DMC recommendations to use alternative methods with time-varying models for survival extrapolations in health economic evaluations when HRs cannot be demonstrated to be constant over time. Overall, using the fractional polynomial NMA approach in the health economic model has resulted in more robust estimates of relative efficacy over time than using a constant HR.

The extrapolation of survival data beyond the trial period is a well-known source of uncertainty in health economic analyses. The CheckMate 9ER trial provided published clinical data for a median follow-up period of 32.9 months at the latest DBL date (June 2021). At this time point, [redacted] The fitting of the extrapolated PFS and OS curves was made according to the best standards and statistical methods. Sensitivity analyses were conducted using alternative parametric survival functions than those identified as the best fits to investigate the influence of uncertainties on the overall cost-effectiveness results.

# 11. List of experts

[redacted]



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