Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende lenvatinib i kombination med pembrolizumab til behandling af lokalavanceret, recidiverende eller metastatisk pMMR kræft i livmoderslimhinden

Patienter, som har sygdomsprogression med eller efter tidligere platinholdig behandling, og som ikke er kandidater til kurativt intenderet behandling

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. lenvatinib i kombination med pembrolizumab
2. Amgros' forhandlingsnotat vedr. lenvatinib i kombination med pembrolizumab
3. Ansøgning vedr. lenvatinib i kombination med pembrolizumab

March 27, 2025

Eisai comments on the Danish Medicines Council (DMC) assessment report of lenvatinib plus pembrolizumab (LEN+PEM) for patients with advanced or recurrent endometrial cancer who have disease progression following prior treatment with a platinum-containing therapy of less than 6 months (PFI < 6 months) and proficient mismatch repair (pMMR) status.

Eisai would like to thank the DMC and acknowledge the significant work that the DMC has done during the assessment of lenvatinib in combination with pembrolizumab. We are aligned with the DMC's methodology in many of the key aspects of this assessment. At the same time, we would like to clarify and address the following points:

Cost-effectiveness (CE) analysis:

Use of Kaplan-Meier (KM) data

Regarding survival data modelling, it seems logical that utilization of the observed KM data should be prioritized during the observation period. The KM curves represent actual patient outcomes showing the true survival benefit of LEN+PEM, including the immunotherapy-typical plateau phase indicating durable responses. While fewer patients contribute at later timepoints, this data reflects real outcomes rather than projections/estimates. Notably, the parametric models chosen by the DMC may introduce systematic bias by underestimating LEN+PEM overall survival (OS) from year 2 onwards while simultaneously overestimating comparator group OS from year 1.75 onwards.

Proportional hazard of PFS

Regarding the proportional hazards assumption, there seem to be inconsistencies in the DMC assessment. While the DMC rejects proportional hazards for progression-free survival (PFS) based on log-cumulative hazard plots showing crossings at approximately 1.2 on the log scale, the DMC accepts proportional hazards for OS despite crossings at 1.6 on the log scale. We agree with the DMC's assessment that OS holds proportional hazards despite early crossings, therefore it seems logical that this same principle should also apply to PFS. Although with a visual inspection of the residual plot the hazard ratio might not appear perfectly constant, the Schoenfeld residual test for PFS yields a p-value of 0.362 (and 0.858 for OS), which is not statistically significant and therefore fails to reject the proportional hazards assumption. Crossing points at around 1 on the log scale only refer to very early treatment phases, which do not necessarily invalidate proportional hazards for the clinically relevant treatment period. These considerations would support maintaining the proportional hazards assumption for PFS modelling, and ensure consistency with the approach already used for OS.

Impact on the CE results

Overall, the DMC's modelling assumptions regarding not using KM data, differential proportional hazards application, among others reduced the QALY difference between interventions from 0.73 to 0.5, a significant 32% reduction that is not fully supported with evidence and consistent methodologies.

Market uptake

Eisai would like to clarify the market uptake assumptions cited in the DMC report. The statement that Eisai "assumes a market uptake for years 1, 2, 3 and 4-5 of 9%, 25%, 50% and 91%, respectively" does not reflect our submitted analysis. In the budget impact calculations, a more gradual adoption pattern was used, with specific market uptake percentages: Year 1: 25%, Year 2: 40%, Year 3: 60%, Year 4: 70%, and Year 5: 80%. These values demonstrate a measured and more realistic approach to market penetration, beginning at 25% in the first year and incrementally growing to 80% by year 5.

Impact on the budget impact results

Eisai's estimate of eligible patients differs significantly from DMC's 50 patients (30 in second-line and 20 in third-line) shown in the treatment flowchart. This difference potentially arises from the use of the DRG/Clarivate epidemiology model. Eisai calculates that only 60% of first-line patients reach second-line treatment, with 67% having PFI <6 months and 80% remaining eligible for systemic therapy.

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19.03.2025
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	Revurdering, april 2025
Leverandør	Eisai
Lægemiddel	Lenvima (lenvatinib) i kombination med Keytruda (pembrolizumab)
Ansøgt indikation	Behandling af voksne patienter med fremskreden eller recidiverende endometriekarcinom (EC), som har sygdomsprogression med eller efter tidligere behandling med en hvilken som helst anden behandling, som indeholder platin, og som ikke er kandidater til kurativ operation eller strålebehandling.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende pris på Lenvima (lenvatinib):

Tabel 1: Aftalepris Lenvima

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Aftalepris SAIP (DKK)	Rabatprocent ift. AIP
Lenvima	4 mg	30 stk.	11.669,47	[redacted]	[redacted]
Lenvima	10 mg	30 stk.	11.669,47	[redacted]	[redacted]

Amgros har følgende pris på Keytruda (pembrolizumab):

Tabel 2: Aftalepris Keytruda

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Keytruda	25 mg/ml	4 ml.	21.573,58	[redacted]	[redacted]

Aftaleforhold

Der er en aftale på Lenvatinib (begge lægemidler) indtil 31.11.2025, med mulighed for 6 måneders forlængelse.

Leverandøren har et yderligere lægemiddel, som er identisk med Lenvima: Kisplyx (lenvatinib). Kisplyx og Lenvima er identisk mht. indholdsstof, styrke og pakningsstørrelse, men er godkendt til forskellige indikationer. Kisplyx i kombination med Keytruda, er vurderet af Medicinrådet til behandling af nyrekræft og blev delvist anbefalet i januar 2025.

[redacted]

Konkurrencesituationen

Jemperli (dostarlimab) blev anbefalet af Medicinrådet i november 2022 til behandling af patienter med livmoderkræft og dMMR/MSI-H status. Tabel 3 nedenfor, viser lægemiddeludgifterne for et års behandling med Lenvima i kombination med Keytruda og for Jemperli.

Tabel 3: Sammenligning af lægemiddeludgifter

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddel-udgift pr. år (SAIP, DKK)	Total behandlings pris
Lenvima	10 mh (30 stk)	20 mg dagligt oralt	[redacted]	[redacted]	[redacted]
Keytruda	25 mg/ml (4 ml)	2 mg/kg i.v., hver 3. uge	[redacted]	[redacted]	
Lenvima	10 mg (30 stk.) 4 mg (30 stk.)	14 mg dagligt*	[redacted]	[redacted]	[redacted]
Keytruda	25 mg/ml (4 ml.)	2 mg/kg i.v., hver 3. uge	[redacted]	[redacted]	
Jemperli	500 mg (1 stk.)	500 mg i.v. hver 3. uge i 4 cykler og derefter 1.000 mg i.v. hver 6.uge	[redacted]	[redacted]	[redacted]

* Dosisjusteret fra 20 mg dagligt til 14 mg dagligt
** Vægtjusteret dosis 68,9 kg

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling

Opsummering

[redacted]

Application for the re-assessment of lenvatinib plus pembrolizumab (LEN+PEM) for patients with advanced or recurrent endometrial cancer who have disease progression following prior treatment with a platinum-containing therapy of less than 6 months (PFI < 6 months) and proficient mismatch repair (pMMR) status

Contact information

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Abbreviations

Abbreviation	Definition
1L	1st line
2L	2nd line
AIC	Akaike information criterion
AJCC	American Joint Committee on Cancer
BIC	Bayesian information criterion
BICR	Blinded Independent Central Review
BSA	Body surface area
CTCAE	Common Terminology Criteria for Adverse Events
DGCG	Danish Gynaecological Cancer Group
DMC	Danish Medicines Council
dMMR	Deficient mismatch repair
DOX	Doxorubicin
DRG	Diagnosis-related groups
EC	Endometrial cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire
ESGO	European Society of Gynaecological Oncology
ESMO	European Society for Medical Oncology
ESP	European Society of Pathology
ESTRO	European Society for Radiotherapy and Oncology
FIGO	International Federation of Gynaecology and Obstetrics
HRQoL	Health-related quality of life

HSUVs	Health state utility values
ICER	Incremental cost-effectiveness ratio
ISPOR	International Society for Health Economics and Outcomes Research
ITT	Intention-to-Treat
KM	Kaplan-Meier
LEN	Lenvatinib
MMR	Mismatch repair
MSI	Microsatellite instability
MSI-H	Microsatellite instability-high
MSI-L	Microsatellite instability-low
NA	Not applicable
NCCN	National Comprehensive Cancer Network
OS	Overall survival
OWSA	One-way sensitivity analysis
PartSA	Partitioned survival analysis
PD	Progressed disease
PD-L1	Programmed death-ligand 1
PEM	Pembrolizumab
PF	Progression-free disease
PFI	Platinum free interval
PFS	Progression-free survival
PLD	Pegylated liposomal doxorubicin
pMMR	Proficient mismatch repair
Q3W	Every 3 weeks
QALY	Quality-adjusted life years
RCT	Randomized controlled trial
RWE	Real-world evidence
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
SEs	Standard errors
SLR	Systematic literature review
TEAEs	Treatment-emergent adverse events
TNM	Tumour-Node-Metastasis
ToT	Time on treatment
TPC	Treatment of physician choice
TTD	Time to discontinuation
VEGF	Vascular Endothelial Growth Factor

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Lenvima® (lenvatinib) Keytruda® (pembrolizumab)
Generic name	Lenvatinib (LEN) Pembrolizumab (PEM)
Therapeutic indication as defined by EMA	Indicated for the treatment of adult patients with advanced or recurrent endometrial cancer (EC) who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation.
Marketing authorization holder in Denmark	Eisai GmbH Merck Sharp & Dohme B.V.
ATC code	L01EX08, LEN L01FF02, PEM
Combination therapy and/or co-medication	Yes
Date of EC approval	29/11/2021
Has the medicine received a conditional marketing authorization?	NA
Accelerated assessment in the European Medicines Agency (EMA)	NA
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	LEN: 1) differentiated thyroid carcinoma; 2) hepatocellular carcinoma PEM: 1) melanoma; 2) non-small cell lung cancer; 3) classical Hodgkin lymphoma; 4) urothelial cancer; 5) head and neck squamous cell carcinoma; 6) renal cell carcinoma; 7) oesophageal cancer; 8) gastric and gastro-oesophageal junction adenocarcinoma; 9) triple negative breast cancer; 10) cervical cancer; 11) biliary tract cancer; 12) microsatellite instability high

Overview of the medicine		
	(MSI-H) or mismatch repair deficient (dMMR) colorectal cancer; 13) MHI-H or dMMR gastric cancer.	
Other indications that have been evaluated by the DMC (yes/no)	Lenvatinib (Kisplyx) in comb. with pembrolizumab (Keytruda)	Adults with advanced renal cell carcinoma (No)
	Lenvatinib (Lenvima)	Liver cancer (Yes)
	Pembrolizumab (Keytruda)	1st line treatment of patients with MSI-h/dMMR metastatic colorectal cancer (Yes)
	Pembrolizumab (Keytruda)	Adjuvant treatment of high-risk stage II melanoma (No)
	Pembrolizumab (Keytruda)	Kidney cancer (No)
	Pembrolizumab (Keytruda)	Head and neck cancer, first-line treatment (Yes)
	Pembrolizumab (Keytruda)	Breast cancer, adjuvant treatment (Yes)
	Pembrolizumab (Keytruda) in combination with chemotherapy	(Neo)adjuvant treatment of early triple-negative breast cancer (No)
	Pembrolizumab (Keytruda) in combination with chemotherapy	Cervical cancer (Yes)
	Pembrolizumab (Keytruda) in combination with chemotherapy	Non-squamous non-small cell lung cancer with PD-L1 expression < 1% (Yes)
	Pembrolizumab (Keytruda) in combination with chemotherapy	Non-squamous non-small cell lung cancer (No)
	Pembrolizumab (Keytruda) in combination with chemotherapy	Squamous cell non-small cell lung cancer (No)
	Pembrolizumab (Keytruda) in combination with paclitaxel, nab-paclitaxel, or gemcitabine + carboplatin	Locally advanced or metastatic triple-negative breast cancer (Yes)
Dispensing group	LEN: BEGR PEM: BEGR	
Packaging – types, sizes/number of units and concentrations	Capsules, hard. 1 capsule contains 4 mg or 10 mg of LEN. Concentrate for solution for infusion. 1 ml contains 25 mg PEM.	

2. Summary table

Provide the summary in the table below, maximum 2 pages.

Summary	
Therapeutic indication relevant for the assessment	LEN in combination with PEM is indicated for the treatment of adult patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and are not candidates for curative surgery or radiation. The scope of this application is restricted to the patients with advanced EC who have disease progression following prior treatment with a platinum-containing therapy in less than 6 months (platinum free interval (PFI) < 6 months) and whose tumour is categorized as having a functional mismatch repair pathway (proficient mismatch repair (pMMR)).
Dosage regiment and administration	The recommended dosage of LEN is 20 mg orally once daily in combination with PEM administered as an IV infusion over 30 minutes: 200 mg every three weeks or 400 mg every 6 weeks Until disease progression or unacceptable toxicity (1)
Choice of comparator	Efficacy: Treatment of physician choice (TPC): Pre-assigned to Doxorubicin (DOX) component Economic evaluation: Pegylated liposomal doxorubicin (PLD)
Prognosis with current treatment (comparator)	EC displays tumour heterogeneity and there are several histological subtypes, with distinct pathogenesis and prognosis (2). EC can broadly be classified into two subtypes: Type I and Type II, with most cases (80–90%) considered to be Type I. In general, Type I EC is considered to be low-risk, while Type II EC is considered to be high-risk with a poor prognosis (2, 3).
Type of evidence for the clinical evaluation	Head-to-head study of LEN+PEM vs TPC (pre assigned to DOX) with efficacy assumed equal to PLD
Most important efficacy endpoints (Difference/gain compared to comparator)	OS PFS
Most important serious adverse events for the intervention and comparator	Intervention: Hypertension (67) Comparator: Neutropenia (67)
Impact on health-related quality of life (HRQoL)	Clinical documentation: Trial-based EQ-5D-5L DK tariffs Health economic model: Greater QALYs for LEN+PEM

Summary	
Type of economic analysis that is submitted	Cost-utility Partitioned survival model
Data sources used to model the clinical effects	Study 309/N-775 (NCT03517449)
Data sources used to model the HRQoL	EQ-5D-5L measures from Study 309/N-775 (NCT03517449)
Life years gained	1.00 year
Quality-adjusted life years (QALYs) gained	0.73 QALY
Incremental costs	**DKK 534,934**
ICER (DKK/QALY)	**DKK 735,863**
Uncertainty associated with the ICER estimate	The most significant parameter that affects the ICER is the cost of liposomal doxorubicin (comparator component)
Number of eligible patients in Denmark	39 eligible patients in Year 1
Budget impact (in year 5)	**DKK 4,564,929**

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

EC is the most common gynaecologic malignancy in developed countries and the second most common gynaecologic malignancy worldwide (2, 4, 5). EC develops in the inner lining of the uterine cavity (6), with malignant cancer cells forming in the tissues of the endometrium. EC is one of the few cancers with increasing global incidence due to modifiable and non-modifiable risk factors (7-12). In 2030, the global incidence of EC is expected to increase to 487,316, representing a 16.8% increase from 2020 (13). The mortality rate for EC has increased more rapidly than the incidence rate (21% increase in

mortality rates from 1999 to 2016 (11)), which may be attributed to an increased rate of advanced-stage cancers, high-risk histology (e.g., serous carcinomas), and patients being diagnosed at an older age (8).

EC displays tumour heterogeneity and there are several histological subtypes, with distinct pathogenesis and prognosis (2). EC can broadly be classified into two subtypes: Type I and Type II, with most cases (80–90%) considered to be Type I. In general, Type I EC is considered to be low risk, while Type II EC is considered to be high-risk with a poor prognosis (2, 3).

The 2009 International Federation of Gynecology and Obstetrics (FIGO) and the American Joint Committee on Cancer (AJCC) TNM (Tumor-Node-Metastasis) staging systems are the most-adopted classifications for staging EC (14, 15). Both systems are based on surgical staging and include assessment of the extent of myometrial invasion and local and distant metastatic disease. The majority of women with EC are diagnosed at an early stage with cancer confined to the uterus, although around one-third are diagnosed with advanced disease. US Surveillance, Epidemiology, and End Results (SEER) data indicate that 67% of women have localized disease at diagnosis; approximately 20% will have regional spread to pelvic lymph nodes, and 9% will have distant metastases (16), suggesting that ~29% of women are diagnosed at an advanced stage.

Reported in about 90% of patients, abnormal vaginal bleeding is the most common symptom of EC, especially in the postmenopausal period, and is sometimes associated with vaginal discharge and pyometra (infection of the uterus) (15, 17). Abnormal vaginal bleeding often occurs early in the disease course, leading to most EC cases being diagnosed at an early stage (17). Symptoms of patients with advanced disease may be similar to those of advanced ovarian cancer, and may include abdominal or pelvic pain, abdominal distension, early satiety, or change in bowel or bladder function (18).

A dMMR system is frequently associated with Type I EC (19). The mismatch repair (MMR) system is responsible for the recognition and repair of base mismatches that occur during DNA replication, particularly at repetitive DNA stretches, such as microsatellites (20). Deficiency in the MMR system results in the accumulation of mutations at microsatellites, resulting in MSI-H. This generates a high genotypic and phenotypic diversity of emerging precancerous cell clones from which carcinogenesis likely follows (20).

MSI-H tumours are found in up to 35% of patients with EC and, comprising <20% of advanced disease cases (20-23). Non-MSI-H tumours (or pMMR) consist of those with a low frequency of microsatellite instability-low (MSI-L) and those with microsatellite stability (24).

The main risk factor for developing EC is exposure to endogenous and exogenous oestrogens (15, 25). Other key risk factors include obesity, diabetes, age, and Lynch syndrome.

Recurrent disease, which typically becomes clinically apparent within 3 years of primary therapy (26, 27), occurs in up to 25% of cases and accounts for most EC-related deaths (28, 29). Recurrence of EC can be associated with lifestyle, obesity, exercise, smoking, and sexual health (17). Factors associated with a risk of poor prognosis and recurrence in

patients with localized, stage I–III EC following primary surgical treatment include: age ≥60 years; histologic type II (serous carcinomas, clear cell carcinomas, and carcinosarcomas); higher grade (3 versus 1 or 2) and stage (II and III versus I) and lymphovascular invasion (28).

Uterine cancer is the 5th most common type of cancer among women in Denmark and the most common gynaecological cancer (30). Although most women with EC are diagnosed at an early stage with cancer confined to the uterus, around one-third are diagnosed with advanced disease (16, 31-33). Advanced EC is considered incurable, and the prognosis for survival is poor, with a median survival of approximately 4 years for stage III and 2 years for stage IV (34).

3.2 Patient population

As per request from the DMC (Danish Medicines Council), the relevant patient population for this resubmission is: adults with advanced EC, pMMR status, who have disease progression within 6 months following prior treatment with a platinum-containing therapy (PFI < 6 months) and are not candidates for curative surgery or radiation.

The number of incident 1st line (1L) patients with advanced or recurrent EC is based on the Diagnosis-related groups (DRG)/Clarivate endometrial cancer epidemiology model for the years 2022 to 2026 (35). Using Eisai market research estimates, a percentage of patients that are treated (80%) is applied, and it is estimated that 60% of those patients will reach 2nd line (2L). The percentage of patients with PFI<6 months (67%) from Study 309 / KN-775(36) is then applied to this population to derive the population size for 2L population with PFI < 6 months. It is then estimated that 80% of these patients will be eligible for systemic treatment. Lastly, in accordance with the DMC report on dostarlimab (37) in which 22-30% of patients are considered dMMR, it was assumed that 78-70% (74% as an average) are pMMR (see Table 2).

This results in an estimated 23 treated patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy within 6 months, and pMMR status in 2024. The combination therapy is expected to be used upon reimbursement since there is currently no clear standard of care in this population.

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Diagnosed prevalent cases	9,271	9,409	9,602	9,793	9,980
Diagnosed incident cases	841	843	854	865	876
Advanced stage 3 and 4 incident cases	152	152	153	156	158
Advanced stage 3 incident cases	115	114	115	117	119

Advanced stage 4 incident cases	37	38	38	39	39
Recurrent incident cases	43	42	43	44	45
Recurrent early-stage low and intermediate risk	26	26	27	27	28
Recurrent early-stage high risk	17	16	16	17	17
Sum of advanced or recurrent incident cases	**195**	194	196	200	203

Table 2 Estimated number of patients eligible for treatment

Year	Percentage of previous row	2024	2025	2026	2027	2028
1L treatable population (advanced)		205	208	211	214	216
1L line treated population (advanced)	80%	164	166	169	171	173
2L treatable population (advanced)	60%	98	100	101	103	104
2L treatable population with PFI < 6 months	67%	66	67	68	69	69
Systemic treatment rate	80%	53	54	54	55	56
pMMR proportion	74%	39	40	40	41	41

Notes: Data based on Clarivate dashboard (35), increased number or eligible patients due to population growth

3.3 Current treatment options

Treatment of EC varies depending on the grade, histology, stage of the disease, and microsatellite instability (MSI)/MMR status. For the majority of patients with low-risk EC, the mainstay of 1L treatment is curative aiming surgery with removal of all visible cancerous tissue (macro-radical surgery) with or without radiotherapy and/or chemotherapy (38-41). After surgery, a combination of carboplatin and paclitaxel is recommended (39, 42, 43) with the purpose of prolonging survival by limiting further disease progression (42, 43). The current treatment guidelines for EC include:

- The European Society for Medical Oncology (ESMO), last updated in 2013 (3)
- The joint guidelines from European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP), 2021 (44)
- National Comprehensive Cancer Network (NCCN) Uterine Neoplasms Guidelines, 2021 (17)
- Danish Gynecological Cancer Group (DGCG), 2019 (38)
- Sundhed.dk, last updated in 2022 (40)

There are, however, few approved therapy options for 2L treatment of patients with advanced or recurrent EC following prior platinum-based therapy (39, 45-48). The most recent guidelines from the DGCG and sundhed.dk (39, 40) offer no harmonized recommendations for standard of care at this stage of the disease. This is also confirmed by two clinical experts that Eisai consulted in preparations of the previous submission (49).

3.4 The intervention

LEN+PEM offers a novel treatment option; the combined attributes of the multitargeted tyrosine kinase inhibitor, LEN and the immune checkpoint (PD-1) inhibitor, PEM, work to decrease the suppressive tumour microenvironment and enhance anti-tumour activity. The mode of actions of each agent are complementary, targeting different parts of the immune response. As LEN inhibits the kinase activities of Vascular Endothelial Growth Factor (VEGF) and fibroblast growth factor receptors resulting in decreased angiogenesis, immunosuppressive effects, and tumour cell proliferation, PEM binds to the PD-1 receptor on immune cells to block PD-L1 and PD-L2 inhibition of the immune system and restore T-cell anti-tumour immune activity.

VEGF inhibition enhances the efficacy of PD-1 inhibition versus use of a single-agent PD-1 inhibitor (50-53) and it demonstrated that combining a PD-1 inhibitor (i.e., PEM) with simultaneous inhibition of angiogenesis and VEGF-mediated immune suppression (i.e., LEN) may be an effective anti-tumour strategy (54, 55). The combination of LEN and anti-PD-1 has shown increased anti-tumour activity than either single treatment in an in vivo study in syngeneic mouse tumour models (56). LEN decreased the tumour associated macrophage population, which is known as an immune-regulator in the tumour microenvironment. By decreasing tumour associated macrophages, expression levels of cytokines and immune-regulating receptors were changed to increase immune activation. The immune-modulating effect of LEN may result in a potent combination effect with PD-1/ Programmed death-ligand 1 (PD-L1) signal inhibitors. The effect of combining LEN with anti-PD-1/PD-L1 monoclonal antibodies has been investigated in the Computed tomography (CT26) colorectal cancer syngeneic model (anti-PD-L1 mAb) as well as the LL/2 lung cancer syngeneic model (anti-PD1 mAb) (51).

The requested characteristics of the intervention were taken from the SmPC's for LEN (57) and PEM (58).

Overview of intervention	
Therapeutic indication relevant for the assessment	The scope of this application is restricted to the patients with advanced EC who have disease progression within 6 months of having completed or discontinued prior treatment with a platinum-containing therapy (PFI < 6 months) and whose tumour is categorized as having a functional mismatch repair pathway (pMMR).
Method of administration	LEN is for oral use PEM is administered by IV infusion over 30 minutes
Dosing	LEN: the recommended daily dose is 20 mg (two 10 mg capsules) once daily. The daily dose is to be modified as needed according to the dose/toxicity management plan (57). PEM: administered by IV infusion over 30 minutes. For EC, the recommended dosage is 200 mg Q3W or 400 mg every 6 weeks (58).
Dosing in the health economic model (including relative dose intensity)	LEN: the recommended daily dose is 20 mg (two 10 mg capsules) once daily (57). RDI: 100% PEM: administered by IV infusion over 30 minutes. For EC, the recommended dosage is 200 mg Q3W or 400 mg every 6 weeks (58). RDI: 95% based on Study 309
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	LEN: treatment with LEN can continue for as long as the disease does not progress and the patient continues to tolerate treatment (57). PEM: patients should be treated with PEM until disease progression or unacceptable toxicity for a maximum of 24 months (58).
Necessary monitoring, both during administration and during the treatment period	LEN: For patients with hypertension, blood pressure should be well controlled prior to treatment and should be regularly monitored during treatment. Cases of nephrotic syndrome have been reported in patients using LEN; urine protein should be monitored regularly to avoid proteinuria. Due to hepatotoxicity, close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment; liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. To avoid cardiac dysfunction, patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be

Overview of intervention		
	necessary. Electrolyte abnormalities should be monitored and corrected before starting treatment and electrocardiograms and should be monitored at baseline and periodically during treatment to avoid QT/QTc interval prolongation. Thyroid function should be monitored before initiation of, and periodically throughout, treatment with LEN (57). PEM: Patients should be monitored for signs and symptoms of immune-related: pneumonitis, colitis, changes in liver function (hepatitis), changes in renal function (nephritis), adrenal insufficiency and hypophysitis (endocrinopathies) and severe skin reactions. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes (58).	
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No biomarker test or companion diagnostic is required for the use of LEN+PEM.	
Package size(s)	LEN	
	30 stk. 4 mg	VNR: 049075
	30 stk. 10 mg	VNR: 387479
	PEM	
	4 ml x 25 mg/ml	VNR: 585389

3.4.1 The intervention in relation to Danish clinical practice

As confirmed by the DMC in its previous assessment of LEN+PEM, PLD is considered the standard of care in Danish clinical practice (59). However, as described in Section 3.5.1.1, there is evidence suggesting that DOX and PLD are comparable with respect to efficacy and safety. Therefore, following the rationale of the previous submission, evidence for the comparison of LEN+PEM and standard of care in Danish clinical practice (PLD) were drawn from a comparison between LEN+PEM and the chemotherapy group pre-assigned to DOX in Study 309 / KN-775, with PFI < 6 months, and pMMR status.

3.5 Choice of comparator(s)

Although there is no consensus on the standard of care treatment following platinum containing therapy, the DMC describes in its assessment report for dostarlimab from December 2021, the more recent 2024 assessment (37, 60) and in the previous assessment of LEN+PEM (59), that the 2L treatment options for EC are dependent on the duration of time that has passed since platinum-based treatment in 1L. Patients who

progress approximately 6 months or more after discontinuation of platinum treatment are considered platinum sensitive and can be re-treated with platinum-based chemotherapy after progression (44, 61). If progression occurs during or up to 6 months after treatment with 1L platinum therapy, PLD is given as standard therapy.

It is however important to note that PLD (Caelyx®) does not have EMA marketing authorization for EC (62) and its use can be considered off-label. Inspite of this, clinicians in Denmark have several years of experience with the use of PLD for EC patients and PLD is considered standard therapy in the 2L treatment of EC for patients who progress during or up to 6 months after initial systemic therapy containing platinum (39).

Furthermore, PLD together with weekly paclitaxel are the treatments mentioned in the latest ESGO/ ESTRO/ ESP guidelines in 2L EC treatment after previous use of platinum-based chemotherapy (44).

Therefore, based on the available clinical guidelines, clinical expert input and consultation with DMC, the most relevant comparator in the Danish setting is considered to be: PLD for patients with PFI < 6 months and pMMR status.

Overview of comparator	
Generic name	Pegylated liposomal doxorubicin (PLD) (Caelyx®)
ATC code	L01DB01
Mechanism of action	PLD hydrochloride, a cytotoxic anthracycline antibiotic obtained from Streptomyces peucetius var. caesius.
Method of administration	PLD is administered intravenously at a dose of 40 mg/m^2 once every 4 weeks for as long as the disease does not progress, and the patient continues to tolerate treatment. PLD should only be administered under the supervision of a qualified oncologist specialised in the administration of cytotoxic agents.
Dosing	40-50 mg/m^2 PLD IV every 4 weeks for up to 6-8 series (60)
Dosing in the health economic model (including relative dose intensity)	40 mg/m^2 PLD IV every 4 weeks (60); RDI: 100%
Should the medicine be administered with other medicines?	Can possibly be administered with other anti-tumorigenic drugs.
Treatment duration/ criteria for end of treatment	Every 4 weeks for up to 6-8 series (~6-8 months) Treatment until disease progression or unacceptable toxicity (based on physician's choice).

Overview of comparator		
Need for diagnostics or other tests (i.e. companion diagnostics)	Prior to PLD administration, evaluate hepatic function using conventional clinical laboratory tests such as ALT/AST, alkaline phosphatase, and bilirubin.	
Package size(s)	Caelyx pegylated liposomal	
	10ml x 2mg/ml	VNR: 479471

Sources: (62), (60)

3.5.1.1 Assessment of equivalence between DOX and PLD

Given the paucity of data for PLD in this indication, an assumption was made that the efficacy and safety of PLD is similar to that of DOX. The following data were identified in a focused review of the relevant literature to support this assumption:

- A Phase III trial in metastatic breast cancer showed PLD had comparable efficacy to DOX (PFS and OS) with significantly improved safety profile (63).
- In advanced and metastatic soft tissue sarcoma, there were no significant differences between DOX and PLD for PFS and OS (64).
- A meta-analysis published in 2012 demonstrated liposomal DOX and PLD have favourable toxicity profiles compared with conventional DOX (65).

In conclusion, PLD and DOX showed similar efficacy (PFS and OS). However, differences were observed in the safety profile of the two drugs. In lieu of data for PLD for the indication of interest, and in accordance with Danish clinical practice and previous DMC assessment, PLD was considered as the base case comparator in the economic analysis using the pre-assigned to DOX group in patients with PFI <6 months. The 'pre-assigned to DOX' group is the subgroup of patients who were reported to be eligible for DOX treatment prior to randomization,

3.5.1.2 Evaluation of indirect comparison of LEN+PEM vs PLD

Additional evidence to support the comparison between LEN+PEM and PLD were explored. For both DOX and PLD, although two randomized controlled trials (RCTs) were identified (66, 67 , 68) as well as four single arm studies and one real-world evidence (RWE) study (69-73), an ITC was deemed not possible as it was considered not feasible to form an appropriate network. In addition, connecting the RCT studies with Study 309 / KN-775 via DOX to form a network for traditional network meta-analysis would not yield additional comparisons of interest for the submission.

3.6 Cost-effectiveness of the comparator(s)

As outlined in section 3.5, based on the available clinical guidelines, clinical expert input, and consultation with DMC, the most relevant comparator in the Danish setting is PLD for patients with PFI < 6 months and pMMR status.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

OS and PFS are the relevant outcomes in this application. These outcomes have been previously deemed relevant by the DMC to assess the efficacy of LEN+PEM in patients with advanced or recurrent EC. The efficacy outcomes are defined in Table 3.

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Duration of progression-free survival (PFS)	Data cut off: 01/03/2022	PFS, defined as the time from date of randomization to the date of the first documentation of disease progression, as determined by Blinded Independent Central Review (BICR) per RECIST 1.1, or death from any cause, whichever occurs first	Per RECIST v1.1 by BICR. Kaplan-Meier (KM) estimates were used for analysis
Duration of Overall survival (OS)	Data cut off: 01/03/2022	OS, defined as the time from date of randomization to date of death from any cause	KM estimates were used for analysis

* Time point for data collection used in analysis

3.7.1.1.1 Validity of outcomes

OS is considered an important clinical endpoint in clinical trials within oncology. For many years it has been considered the gold-standard endpoint for establishing clinical benefit. However, using OS can be associated with certain limitations as it may be affected by subsequent therapy (74). PFS is also a commonly used endpoint within oncology trials. It is used to assess the time during which patients are alive without progressive disease. PFS is not affected by the impact of subsequent treatment in the same manner as OS, and therefore serves as a relevant supplement to OS (74)

4. Health economic analysis

4.1 Model structure

A cost-effectiveness model was developed in Microsoft Excel® to assess the cost effectiveness of LEN+PEM in the treatment of patients with advanced, recurrent or

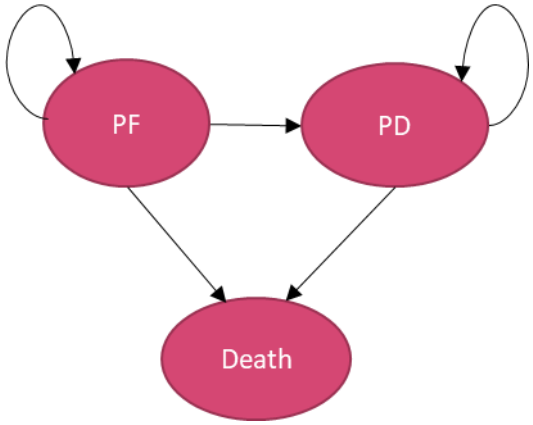
metastatic EC who have disease progression following prior treatment with a platinum-containing therapy in less than 6 months (PFI < 6 months), and pMMR status. The economic model is structured as a partitioned survival analysis (PartSA) model. PartSA models have previously been used in the modelling of LEN+PEM and other treatments for EC and are commonly used and accepted in oncology (25, 26). PartSA models are often used because the endpoints and survival curves reported (e.g., PFS and OS) can be directly used to model state membership. The main limitation of this approach is the lack of dependence between endpoints, reducing the validity of extrapolations and sensitivity analyses. For instance, adjusting the PFS curve has no effect on OS, which is biologically implausible (41).

The economic model is structured as a PartSA model, with the following health states:

- Progression-free disease (PF)
- Progressed disease (PD)
- Death

The model structure is presented in Figure 1 and health state definitions are detailed below in section 4.1.1.

Figure 1 Model structure, partitioned survival analysis



Abbreviations: PD, progressed disease; PF, progression free

4.1.1 Health states

The proportion of patients in the PF, PD, and death health states at each cycle in the model were defined by the OS and PFS KM curves from Study 309 / KN-775 for LEN+PEM and TPC.

Time to discontinuation (TTD) informed by the patient-level data is used to calculate time on treatment (ToT) for LEN+PEM (independently for LEN and for PEM), and for TPC. TTD from the TPC arm in Study 309 / KN-775 is also used to model ToT for PLD, in the absence of treatment duration data specific to these treatments.

4.1.2 Target Population

The population evaluated in Study 309 / KN-775 and the approved EMA marketing authorization is individuals with advanced, recurrent, or metastatic EC who have disease progression following prior platinum-based chemotherapy.

To align with DMC's request and Danish clinical practice, the model-based analysis considered patients with a PFI < 6 months and with pMMR status (Study 309 / KN-775).

4.1.3 Perspective

This analysis used the limited societal perspective in Denmark and considered all relevant treatment related costs, including drug costs, drug administration costs, management of adverse events, subsequent treatment costs, and disease management costs. Time spent and transportation costs incurred by the patient were also included.

4.1.4 Cycle Length

A cycle length of 7 days (1 week) is used. Half-cycle correction is implemented using the life table method (the time in a given cycle is estimated by taking the average of the number of people at the start and end of the cycle).

4.1.5 Time Horizon and Discounting

The model adopts a lifetime time horizon of up to 36 years (mean age of 63.29 years, from Study 309 / KN-775) and assumes patients can live to a maximum of 100 years old, to capture differences in outcomes over the lifetime of the individual. Cost and health-related (i.e., QALY) outcomes were discounted at a rate of 3.5% in accordance with Danish guidelines (75).

4.1.6 Comparators

As per populations of interest, a comparison is presented comparing LEN+PEM with TPC in the population of patients pre-assigned to DOX, PFI < 6 months, and pMMR status. A summary of the comparator is presented in Table 4.

Table 4: Summary base case in the population of patients pre-assigned to DOX, PFI < 6 months, and pMMR status

Comparator	Dose	Source of efficacy data	Source of safety data
TPC (DOX component)	60 mg/m^2 IV on Day 1 of each 21-day cycle	pre-assigned to DOX, PFI < 6 months, and pMMR status post-hoc subgroup, Study 309 / KN-775 for LEN+PEM and PLD (assumed equivalent to DOX in TPC)	pMMR *and* PFI <6 months *and* pre-assigned to DOX post-hoc subgroup, Study 309 / KN-775

Abbreviations: DOX, doxorubicin; ITT, intention to treat; IV, intravenous; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; TPC, treatment of physician's choice.

4.1.7 Model inputs

The model inputs were based on Danish sources where possible. The principal source of data informing the economic evaluations is patient-level data from Study 309 / KN-775. The database cut-off date was the 1st of March 2022.

Given that prior to randomization, investigators must have selected and recorded the TPC option in the event the participant was assigned to that arm, a naïve use of outcomes for patients who received DOX may provide biased estimates of efficacy. Thus, where estimates of efficacy were required (OS, PFS, and ToT), these were therefore taken from the subgroup of patients who were reported to be eligible for DOX treatment prior to randomization, the 'pre-assigned to DOX' population. Different types of patient-level data were accessed to inform:

- Extrapolation of OS, PFS, and TTD (trial data)
- Duration, efficacy, and administration of LEN+PEM and PLD (trial data)
- Mortality (Danish clinical data)
- Adverse events and their duration, frequency, and management (trial data and Danish clinical expert input)
- Quality of life (trial data)

The efficacy inputs are further presented in Section 6. Other relevant inputs were sourced from relevant health technology assessment submissions and literature, and costs were derived from Danish sources. The cost inputs (presented in section 11) included drug costs, administration costs, subsequent treatment costs, adverse events and disease management costs, and non-medical direct costs (transportations costs and time).

4.1.8 Model outputs

The primary outcome of interest of the model-based analysis is the incremental cost-effectiveness ratio (ICER) expressed as the cost per QALY gained. Additional outcomes reported (discounted and undiscounted) are:

- Total costs
- Disaggregated costs
- Total QALYs
- Disaggregated QALYs
- Life years
- Disaggregated life years

4.1.9 Mortality

Background mortality is modelled using only the female general population life tables for Denmark, provided in the mandatory DMC General Mortality excel sheet (75). OS and PFS were constrained to be smaller than or equal to the age-matched general population rate.

4.1.10 Model validation

In line with the International Society for Health Economics and Outcomes Research (ISPOR) taskforce report on model transparency and validation (76), the following types

of validation were conducted: face validation, internal validation, cross validation, and external validation.

No interviews were needed to validate structural model choices, as there is extensive case precedence of partitioned survival modelling in oncology, as well as guidance produced by health technology assessment agencies (77). Data use was compared with another model in ovarian cancer to assess the face validity of the structural choices in this analysis (78), and other published cost-effectiveness appraisals of LEN and PEM, identified through a targeted literature search. Given the lack of outcomes data in the literature for advanced EC, extensive validation of model results with observational or real-world evidence was not possible

Internal validation (verification) was conducted once by the primary modeler and once by a modeler external to the project.

Cost-effectiveness for LEN and/or PEM in similar indications is limited. However, Ralph et al. (2024) (79) recently assessed LEN+PEM for advanced EC in Sweden. Their findings suggest that the treatment would be considered cost-effective compared to chemotherapy, with incremental costs of SEK 1,187,073 and incremental QALYs of 1.49 in the all-comers population. The subgroup analysis for pMMR patients also led to an ICER that fell below the cost-effectiveness threshold of SEK 1,000,000 per QALY gained (i.e., SEK 958,306). In addition, Thurgar et al (80) identified PEM to be associated with an additional 4.68 life years and 3.80 QALYs vs chemotherapy for the treatment of US women with previously treated dMMR, MSI-H or metastatic EC (80).

4.2 Model features

Table 5 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with EC who have experienced disease progression following treatment with platinum-based therapy (PFI < 6 months, preassigned to DOX, and pMMR status)	NA
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (63 years - up to age 100)	To capture all health benefits and costs in line with DMC guidelines Based on mean age at beginning of Study 309 (63.3 years) Validated by Danish clinical expert
Model structure	Partitioned Survival Model	Commonly used oncology model structure

Model features	Description	Justification
Cycle length	7 days	Commonly used approach in partitioned survival models
Half-cycle correction	Yes	Commonly used approach in partitioned survival models
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	LEN+PEM	NA
Comparator(s)	Efficacy: TPC (DOX component) Economic evaluation: PLD	Validated by DMC in previous submission (49)
Outcomes	OS, PFS, QALYs, ICER	Commonly used outcomes in cost-effectiveness analyses

5. Overview of literature

In accordance with the DMC guidance, if a head-to-head study with a comparator relevant to Danish clinical practice exists, the literature search can be omitted (81). Eisai and Merck Sharp & Dohme have conducted the pivotal clinical study, Study 309/KN-755 (82), a randomised controlled trial conducted to compare the efficacy and safety of LEN+PEM versus TPC (DOX or paclitaxel). PLD is considered the standard of care in Danish clinical practice. However, as described in Section 3.5.1.1, there is evidence suggesting DOX and PLD are comparable with respect to efficacy and safety and therefore, evidence for the comparison of LEN+PEM and standard of care in Danish clinical practice (PLD) were drawn from a comparison between LEN+PEM and the chemotherapy group pre-assigned to DOX in Study 309 / KN-775, with PFI < 6 months, and pMMR status.

The evidence of the Study 309/KN-755 trial was therefore considered to provide the best possible basis to inform the comparison of LEN+PEM with the relevant comparator in Danish clinical practice (PLD) for the relevant patient group (advanced EC who have disease progression following prior treatment with a PFI within 6 months and pMMR status).

5.1 Literature used for the clinical assessment

Table 6 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer, Makker et al., The New England Journal of Medicine, 2022 (83)	Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer (MK-3475-775/E7080-G000-309 Per Merck Standard Convention [KEYNOTE-775]) **Study 309 / KN-775**	NCT03517449	**Study Start Date:** June 11, 2018 **Primary Completion Date:** October 26, 2020 **Estimated Study Completion Date:** October 07, 2024	LEN + PEM vs. TPC for patients with advanced EC, pre-assigned to DOX, PFI < 6 months and pMMR status
Lenvatinib Plus Pembrolizumab in Previously Treated Advanced Endometrial Cancer: Updated Efficacy and Safety From the Randomized Phase III Study 309/KEYNOTE-775 (84)	Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer (MK-3475-775/E7080-G000-309 Per Merck Standard Convention [KEYNOTE-775]) **Study 309 / KN-775**	NCT03517449	**Study Start Date:** June 11, 2018 **Primary Completion Date:** October 26, 2020 **Estimated Study Completion Date:** October 07, 2024	LEN + PEM vs. TPC for patients with advanced EC, pre-assigned to DOX, PFI < 6 months and pMMR status

Abbreviations: DOX, doxorubicin; LEN, lenvatinib; NA, Not applicable; PEM, pembrolizumab; PFI, Platinum-free interval

For detailed information about included studies, refer to Appendix A.

5.2 Literature used for the assessment of health-related quality of life

No systematic literature review (SLR) was conducted to identify HRQoL data. HRQoL and health state utility values (HSUVs) for this submission were solely obtained from Study 309 (head-to-head) as described in Section 10.

Table 7 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
NA	NA	NA

5.3 Literature used for inputs for the health economic model

No SLR was conducted to identify inputs for the health economic model.

Table 8 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
NA	NA	NA	NA

6. Efficacy

The efficacy and safety of LEN+PEM has been evaluated in the pivotal Phase 3 study (Study 309/KN-755). LEN+PEM was evaluated in comparison to TPC (DOX or paclitaxel) for patients with advanced EC following at-least one prior platinum-based regimen in any setting.

6.1 Efficacy for patients with advanced or recurrent endometrial cancer who have disease progression following prior treatment with a platinum-containing therapy of less than 6 months (PFI < 6 months) and pMMR status

6.1.1 Relevant studies

This section provides evidence for the efficacy of LEN+PEM compared to the relevant comparator as described in Section 3.5: PLD for patients with advanced EC who have disease progression following prior treatment with a platinum-containing therapy in less than 6 months (PFI < 6 months) and pMMR status.As described in Section 3.5 PLD is considered the relevant comparator to LEN+PEM for patients with PFI < 6 months and pMMR status in Denmark and was therefore chosen as the base case comparator for this population in the health economic analysis. No head-to-head RCT data are available for this comparison and the possibility of an indirect comparison was explored but deemed not appropriate based on the available data. Moreover, there is evidence (see Section 3.5.1.1) that suggests DOX and PLD are comparable with respect to efficacy and safety. Evidence for the comparison of LEN+PEM and PLD were drawn from a comparison between LEN+PEM and the chemotherapy group (TPC) pre-assigned to DOX, with PFI < 6 months, and pMMR status of Study 309 / KN-775.

The efficacy of LEN+PEM has been evaluated in a comprehensive clinical trial programme. The results of the 309/KN-755 trial constitute the primary source of clinical evidence for this submission. A summary of methodology for 309/KN-755 is provided, along with supporting efficacy and safety data. Full in-detail descriptions of main characteristics/methodology, population baseline characteristics, efficacy data (with definitions, validity, and clinical relevance) as well as safety data are available in Section 9. Study 309 / KN-775 is a multicenter, open-label, randomized, Phase 3 trial to compare the efficacy and safety of LEN+PEM versus TPC (DOX or paclitaxel) in patients with advanced EC that was previously treated with prior platinum-based chemotherapy regimen (1, 54). A summary of the trial details is given in Table 9.

Table 9 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
A multicentre, open-label, randomized, Phase 3 trial to compare the efficacy and safety of Lenvatinib plus Pembrolizumab versus treatment of physician's choice in patients with advanced Endometrial Cancer NCT03517449	multicentre, open-label, randomized, Phase 3 trial	Completion expected: October 07, 2024	Patients with advanced Endometrial Cancer	LEN 20 mg + PEM 200 mg Participants with EC received LEN 20 mg orally, once daily, plus PEM 200 mg intravenously, Q3W in each 21-day cycle. Participants continued to receive treatment until disease progression, development of unacceptable toxicity, withdrawal of consent, completion of 35 treatments (approximately 2 years) with PEM, or sponsor termination of the study.	TPC: DOX or Paclitaxel Participants with EC received either DOX 60 milligrams per square meter (mg/m^2) intravenously, Q3W, in each 21-day treatment cycle, or paclitaxel 80 mg/m^2 intravenously, weekly (3 weeks on/1 week off), in each 28-day treatment cycle. Participants continued to receive treatment until a lifetime cumulative dose of 500 mg/m^2 DOX, a maximum dose of paclitaxel per standard of care, or until disease progression, development of unacceptable toxicity, withdrawal of consent, or sponsor termination of the study.	As of the data cut-off date of 1st March 2022, the median duration of follow up in the population relevant for this assessment (pre-assigned to DOX, PFI < 6 months, and pMMR status) was 14.9 months in the intervention arm and 8.6 in the comparator arm. **Dual primary endpoints** PFS, defined as the time from date of randomization to the date of the first documentation of disease progression, as determined by BICR per RECIST 1.1, or death from any cause, whichever occurs first. OS, defined as the time from date of randomization to date of death from any cause **Secondary endpoints** **Efficacy:** ORR, defined as the proportion of patients who have either CR or PR, as determined by BICR per RECIST 1.1 **Safety:** Incidence of treatment-emergent adverse events (TEAEs), serious adverse

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						events, and immune-related adverse events. Proportion of participants discontinuing study treatment due to TEAEs. Time to treatment failure due to toxicity, defined as the time from the date of randomization to the date that a participant discontinues study treatment due to TEAEs. **HRQoL:** assessed using the global health score of the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30).

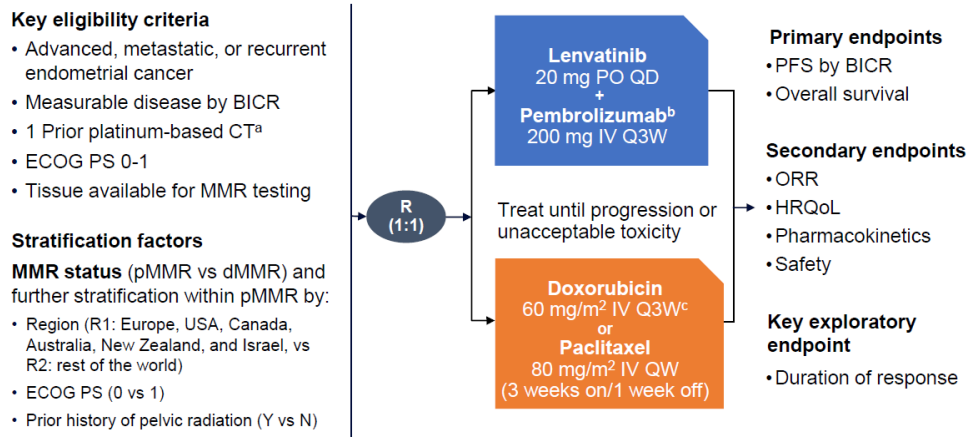
Note: As per the DMC method guideline a full list of efficacy endpoints should be included. However, the submission should only include documentation of relevant efficacy endpoint results (81). Relevant efficacy endpoints used in the submission are OS, PFS and safety data. A list of the definition of all efficacy endpoints is presented in Appendix B. In addition, validity, clinical relevance and summary of results of efficacy endpoints of interest is provided in Appendix B.

Abbreviations: AE, adverse event; BICR, Blinded Independent Central Review; CR, Complete response; EC, endometrial cancer; ECOG, Eastern cooperative oncology group; EMA; European medical agency; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire; HRQoL, Health Related Quality of Life; LEN, lenvatinib; MMR, Miss match repair; OS, Overall survival; PEM; pembrolizumab; PFS, Progression- free survival; PR, Partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, Serious adverse event; TEAE, Treatment emergent adverse events; TPC, Treatment of Physician's Choice; VEGF, Vascular endothelial growth factor

As per the clinical study protocol, prior to randomization, investigators must have selected and recorded the TPC option in the event the participant was assigned to the TPC arm. Assignment to the specific TPC option was assessed prospectively per investigator's survey. The study then randomized (1:1) 827 eligible patients to receive either LEN+PEM or TPC (DOX or paclitaxel), 411 to LEN plus PEM group, 416 to TPC group:

- LEN 20 mg (orally once daily) plus PEM 200 mg IV every 3 weeks (Q3W)
- TPC consisting of either DOX 60 mg/m^2 (by IV bolus injection, 1-hour infusion, or per institutional guidelines) Q3W, or paclitaxel 80 mg/m^2 (by 1-hour IV infusion or per institutional guidelines) given weekly, 3 weeks on/1 week off

Figure 2 Study 309 / KN-775 - study design



Source: Study 309/KN775 CSR (54)

In the following sections, efficacy and safety results will be presented for Study 309 / KN-775 based primarily on the post-hoc subgroup analysis subjects pre-assigned to DOX, PFI < 6 months, and pMMR status. As per the Study 309 / KN-775 trial design, all subjects were assigned to receive treatment with either DOX or paclitaxel before being randomized to receive either LEN and PEM or TPC. As mentioned previously in this submission, a further subgroup was created of patients pre-assigned to DOX treatment with PFI < 6 months, and pMMR status which will provide the clinical evidence for the population of interest in the submission. For consistency purposes efficacy estimates (OS, PFS) for the Intention-to-Treat (ITT) population are also presented. In addition, the analysis of change from baseline in European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) global health status is presented for the ITT population.

In the efficacy analyses for the abovementioned subgroups (pre-assigned to DOX, PFI < 6 months, pMMR status, n=329) n=160 patients were randomized to receive LEN+PEM and n=169 patients were randomized to receive TPC. Note that Study 309/KEYNOTE-775 was not designed or powered to evaluate efficacy against each of the individual chemotherapy choices, or formally compare efficacy between the two chemotherapies administered,

especially when the comparison is made in the even smaller PFI < 6 months and pMMR status subgroup. In addition, there may be underlying patient or disease characteristics that leads to bias in the selection by an investigator for paclitaxel or DOX, so that the comparison is most appropriate when accounting for the pre-randomization selected chemotherapy.

The efficacy endpoints results presented are PFS and OS. The safety endpoints presented are treatment-emergent adverse events (TEAEs).

6.1.2 Comparability of studies

NA. Only one study included

6.1.2.1 Comparability of patients across studies

NA. Only one study included

Table 10 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	[Study name]		[Study name]		[Study name]	
	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]
Age	NA	NA	NA	NA	NA	NA
Gender	NA	NA	NA	NA	NA	NA
[characteristic]	NA	NA	NA	NA	NA	NA

6.1.3 Comparability of the study population with Danish patients eligible for treatment

The Danish patient population

The mean age of patients in the Danish population is slightly older (approximately 0-3.5 years) than in Study 309 / KN-775 according to clinical expert opinion and as reported in the previous submission (49)

The patient population in the health economic analysis submitted

Values for age, body surface area (BSA), and weight were derived from the analysis of patient-level data of Study 309 / KN-775 for the sub-population relevant for this submission. Additional baseline characteristic for the population relevant for this submission are presented in 0.

Table 11 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)[a]
Age	63.5-67 (clinical opinion)	63.29 (SD: 9.07)
Gender	Female	Female
Patient weight (kg)	Assumed to be similar	69.3 (17.54)
BSA (m^2)	Assumed to be similar	1.7 (0.24)

Notes:
a) Baseline and demographic characteristics from additional statistical analysis of Study 309 / KN-775 (March 2022 data cut-off).
Abbreviations: BSA, body surface area

6.1.4 Efficacy – results per Study 309/KN-755

6.1.4.1.1 Efficacy estimates for OS and PFS (pre-assigned to DOX, PFI < 6 months, pMMR status)

Results for primary endpoints of PFS assessed by BICR and OS are presented in Table 12 and Table 13 together with KM curves for OS (Figure 4) and PFS (Figure 3). Comparative analysis of the PFI < 6 months and pMMR status populations in the two treatment arms, LEN+PEM and TPC (pre-assigned to DOX) showed an improvement in both PFS (HR 0.458, p-value < 0.001) and OS (HR 0.518, p-value < 0.001)

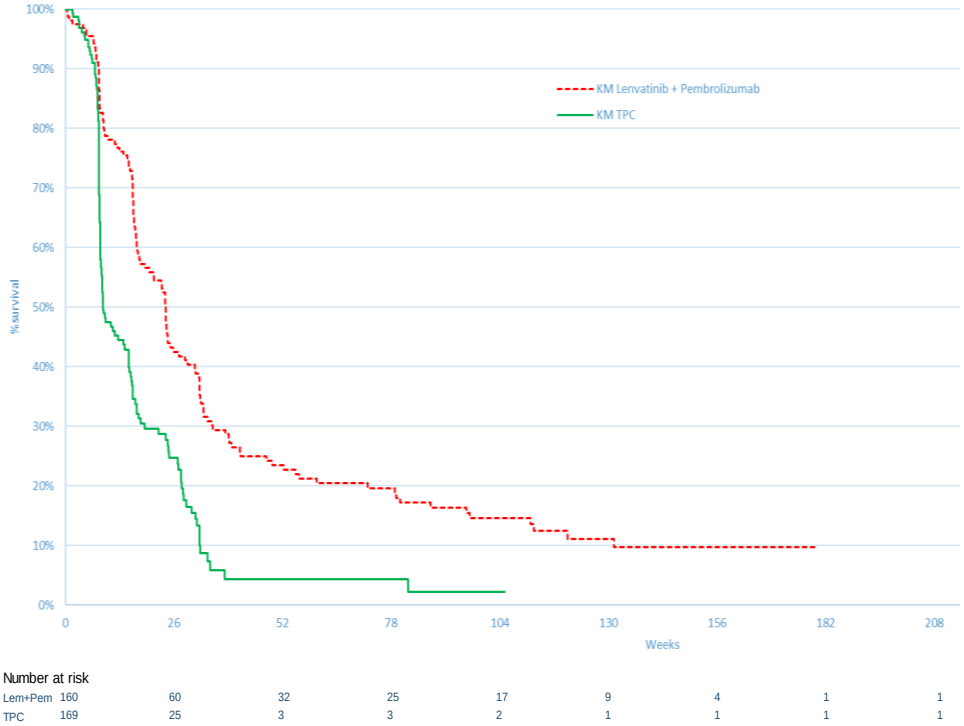
The median follow-up duration for OS was 61.21 weeks for the LEN+PEM trial arm and 32.42 weeks in the TPC (pre-assigned to DOX) arm.

Table 12: Analysis of progression-free survival (BICR) in the population relevant for this submission

	LEN+PEM			TPC (pre-assigned to DOX)			Intervention vs comparator	
	N	Participants with Event n (%)	Median weeks [95% CI]	N	articipants vith Event n (%)	Median weeks [95% CI]	HR [95% CI]	p-value
Progression free survival	160	127 (79%)	24.1 [17.6; 28.7]	169	126 (75%)	9 [8.57;17.9]	0.458 [0.352; 0.595]	<0.001

Database Cut-off Date: 1st of March 2022
Note: Values derived from product-limit (Kaplan-Meier) method for censored data. Based on Cox regression model with treatment as a covariate
*Event refers to progression or death
Abbreviations: CI, Confidence Interval; TPC, treatment of physician's choice; LEN, lenvatinib; PEM, pembrolizumab
Source: Study 309 / KN-775(54)

Figure 3 Kaplan-Meier plot of progression free survival in pre-assigned to DOX, PFI < 6 months, pMMR population



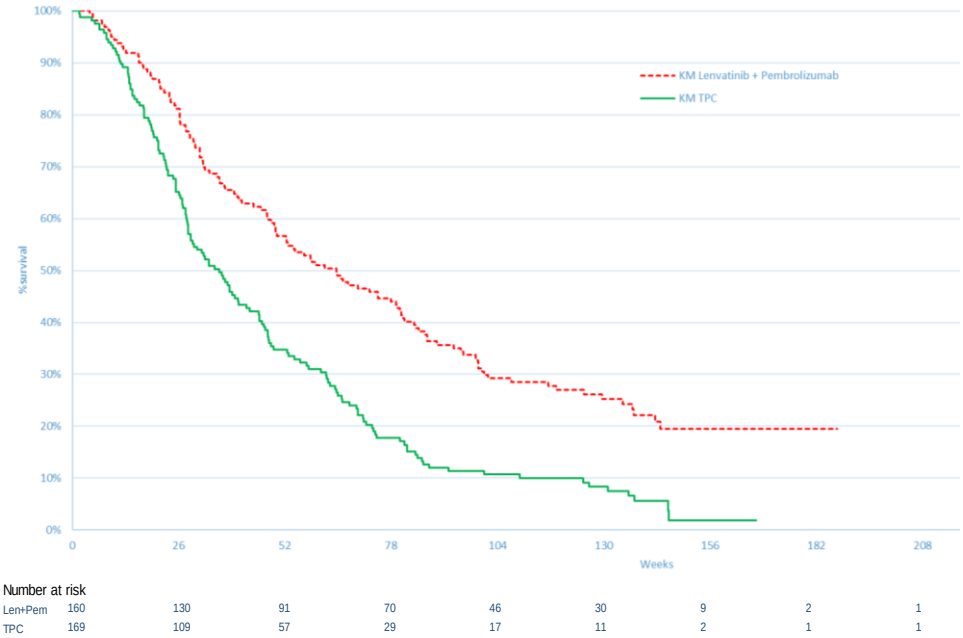
Abbreviations: CI, confidence interval; Len+Pem, lenvatinib + pembrolizumab; PFI, platinum free interval; TPC, treatment of physician's choice; DOX, doxorucibin

Table 13: Analysis of OS in the population relevant for this submission

	LEN+PEM			TPC (pre-assigned to DOX)			Intervention vs comparator	
	N	Participants with Event* n (%)	Median weeks [95% CI]	N	Participants with Event n (%)	Median weeks [95% CI]	HR [95% CI]	p-value
OS	160	122 (76%)	64.57 [50.1; 80.6]	169	152 (90%)	36 [28.4; 45.6]	0.518 [0.406; 0.660]	<0.001

Database Cut-off Date: 1st of March 2022
Note: Values derived from product-limit (Kaplan-Meier) method for censored data. Based on Cox regression model with treatment as a covariate
*Event refers to death
Abbreviations: CI, Confidence Interval; DOX, doxorubicin; LEN, lenvatinib; PEM, pembrolizumab
Source: Study 309 / KN-775(54)

Figure 4 Kaplan-Meier plot of overall survival in pre-assigned to DOX, PFI < 6 months, pMMR status population



Abbreviations: CI, confidence interval; Len+Pem, lenvatinib + pembrolizumab; PFI, platinum free interval; TPC, treatment of physician's choice; DOX, doxorucibin

6.1.4.1.2 Efficacy estimates for OS and PFS (ITT population)

Consistent with the pre-assigned to DOX, PFI< 6 months, pMMR status population, treatment with LEN+PEM also resulted in improved OS in the ITT population (HR: 0.62, p-value <0.001) and PFS (HR: 0.56, p-value <0.001) (Table 10)

Table 14 Analysis of OS and PFS in the ITT population

Treatment	N	Median OS, months (95% CI)	Median PFS, months (95% CI)
LEN+PEM	411	18.3 (15.2, 20.5)	7.2 (5.7, 7.6)
TPC	416	11.4 (10.5, 12.9)	3.8 (3.6, 4.2)
Pairwise comparison			
Hazard ratio (95% CI)		0.62 (0.51, 0.75)	0.56 (0.47, 0.66)
p-value		< 0.001	< 0.001

Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
One-sided p-value based on log-rank test stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
Abbreviations: CI, Confidence Interval; LEN, lenvatinib; OS, Overall Survival; PEM, pembrolizumab; PFS, Progression-free survival; TPC, Treatment of Physician's Choice

7. Comparative analyses of efficacy

The head-to-head Study 309 / KN-755 trial was used as main source for analysis. Therefore, a comparative analysis is not applicable (NA). Results from the head-to-head comparison are presented in Table 15.

7.1.1 Differences in definitions of outcomes between studies

NA

7.1.2 Method of synthesis

NA

7.1.3 Results from the comparative analysis

NA

Table 15 Results from the comparative analysis of LEN+PEM vs TPC (pre-assigned to DOX, PFI < 6 months, pMMR status)

Outcome measure	Len+Pem (N=160)	TPC (pre-assigned to DOX) (N=169)	Result
OS	Median: 64.6 weeks (95 % CI: 50.1; 80.6)	Median: 36 weeks (95 % CI: 28.4; 45.6)	Difference:28.6 weeks HR: 0.518 (95 % CI: 0.406; 0.660)
PFS	Median: 24.1 weeks (95 % CI: 17.6; 28.7)	Median: 9 weeks (95 % CI: 8.57;17.9)	Difference: 15.1 weeks HR: 0.458 (95 % CI:0.352; 0.595)

Notes: Only head-to-head Study 309 / KN-775 was used to inform the table

Abbreviations: OS, overall survival; PFS, progression free survival; HR, hazard ratio; CI, confidence interval; LEN+PEM, lenvatinib + pembrolizumab; TPC, treatment of physician choice; DOX, doxorucibin; pMMR, proficient mismatch repair

7.1.4 Efficacy – results per [outcome measure]

NA

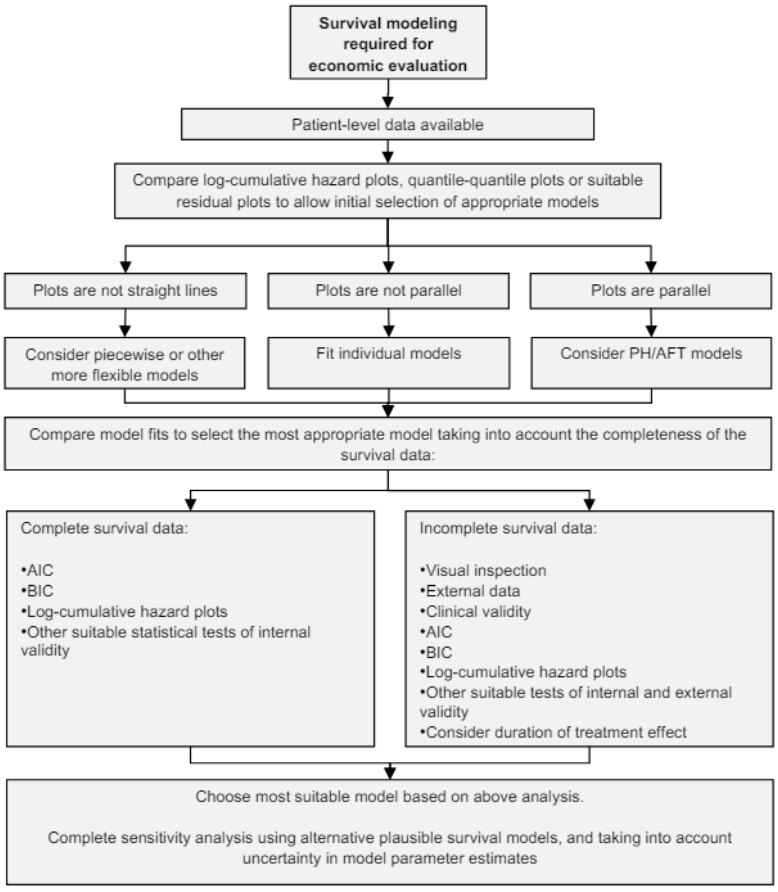
8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

Study 309/KN-775 was directly used as head-to-head evidence to compare the clinical efficacy of LEN+PEM vs TPC (pre-assigned to DOX, PFI < 6 months, pMMR status).

The PFS, OS, and ToT endpoints presented in this section, for patients treated with either LEN+PEM or TPC (pre-assigned to DOX), were derived from patient-level data from the 1st of March 2022 data cut of Study 309/N-775. Extrapolation methodologies and survival models were chosen based on guidelines presented in the NICE DSU technical support document 14, as seen in Figure 5. All information presented in this section refers to the sub-population relevant for this submission (pre-assigned to DOX, PFI < 6 months, pMMR status).

Figure 5 Survival model selection process algorithm



8.1.1 Extrapolation of efficacy data

For PFS and OS, parametric curves could be fitted both independently (i.e., separate models for the LEN+PEM arm and TPC (pre-assigned to DOX) arm), and jointly (dependent curves fitted to both LEN+PEM and TPC (pre-assigned to DOX) arms, with the calculation of a treatment arm coefficient to capture differences between the two).

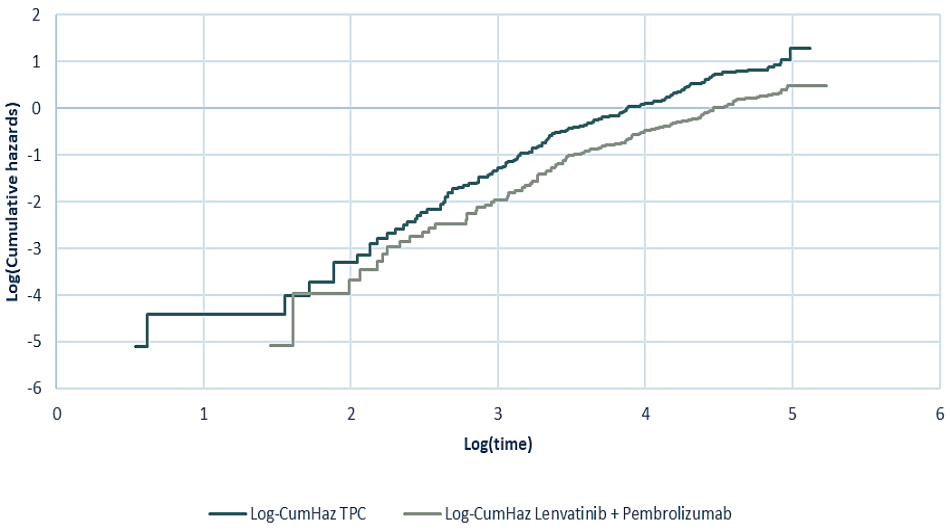
Each approach has its advantages: the jointly fitted estimates draw on a greater pool of evidence, informed by approximately twice the number of observations, but assumes proportional hazards between the two arms. Independent curve fitting avoids the undue influence of the comparator arm on estimates, and does not rely on the proportional hazard's assumption, but incurs greater uncertainty associated with sample size. Proportional hazards assessments (log (cumulative hazards) versus log (time)) were conducted for the subpopulation population of interest. Seven parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) were fitted to data for each endpoint. Appropriate curve selection was determined according to statistical (Akaike information criterion (AIC) and Bayesian information criterion (BIC)), visual goodness of fit, and the clinical plausibility of the extrapolations.

8.1.1.1 Extrapolation of overall survival

Based on the visual assessment of the of the log cumulative hazards over time (Figure 6) in which LEN+PEM and TPC (pre-assigned to DOX) lines are parallel, the proportional hazard assumption for OS is not violated in the defined sub-population. This is further confirmed by the plot of Schoenfeld residuals (Figure 7), and the p-value of the test associated with them (p=0.86). Therefore, the base-case analysis fitted joint models to extrapolate OS.

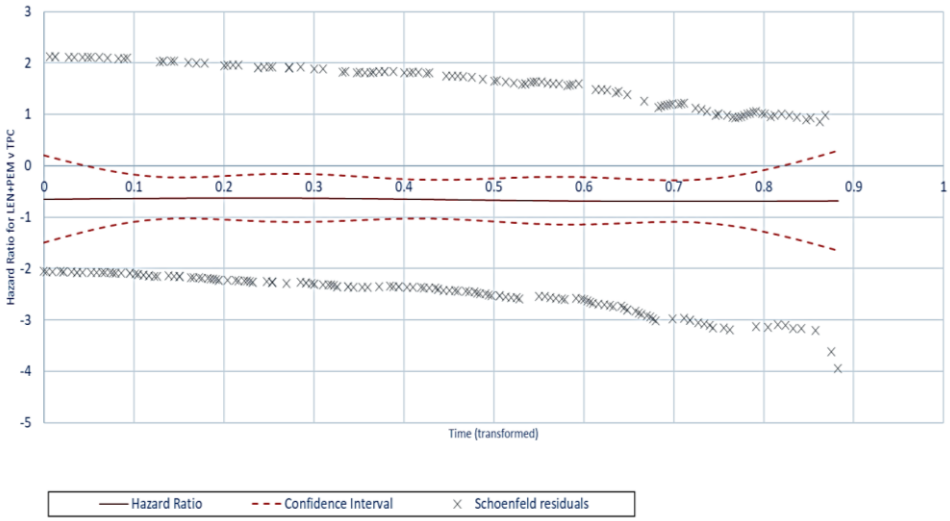
Table 17 summarises assumptions and extrapolation methods for OS. Scenario analyses explored other plausible models.

Figure 6 Log cumulative hazard over log time for LEN+PEM and TPC (pre-assigned to DOX) for OS



Abbreviations: TPC, treatment of physician choice; CumHaz, cumulative hazard**;** OS, overall survival; LEN+PEM, lenvatinib + pembrolizumab; TPC, treatment of physician choice; DOX, doxorucibin

Figure 7 Schoenfeld residuals plot for overall survival



Curve selection was based on visual assessment and statistical fit of the models. Specifically, we selected the log-normal joint model (treatment effect), which presented the lowest AIC and BIC values (Table 16)

Table 16 AIC and BIC for joint models of OS

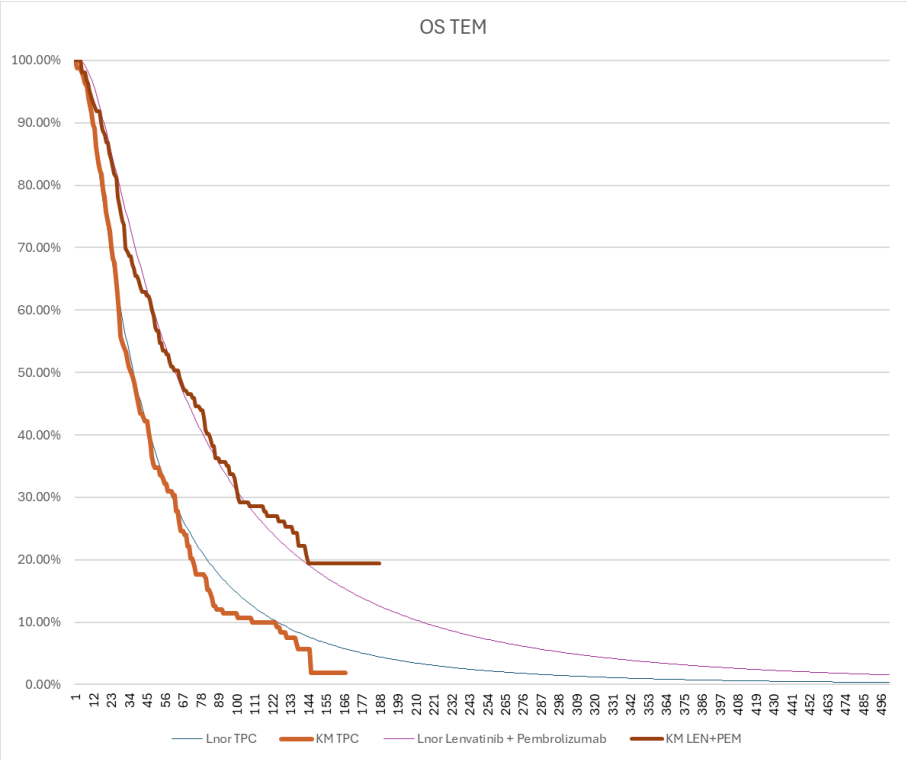
Distribution	AIC	BIC
Exponential	2856.7	2864.3
Weibull	2842.3	2853.7
Gompertz	2856.9	2868.3
Log-normal	**2825.8**	**2837.2**
Log-logistic	2826.2	2837.6
Generalized gamma	2826.3	2841.5
Gamma	2835.8	2847.2

Table 17 Summary of assumptions associated with extrapolation of overall survival

Method/approach	Description/assumption
Data input	Study 309/KN-775 (pre-assigned to DOX, PFI < 6 months, pMMR status)
Model	Joint model
Assumption of proportional hazards between intervention and comparator	PH is not violated

Method/approach	Description/assumption
Function with best AIC fit	Joint model: Log normal
Function with best BIC fit	Joint model: Log normal
Function with best visual fit	Joint model: Log normal
Function with best fit according to evaluation of smoothed hazard assumptions	Joint model: Log normal
Validation of selected extrapolated curves (external evidence)	NA. Not conducted
Function with the best fit according to external evidence	NA. Not conducted
Selected parametric function in base case analysis	Joint model: Log normal
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 8 Base case curves for the extrapolation of OS



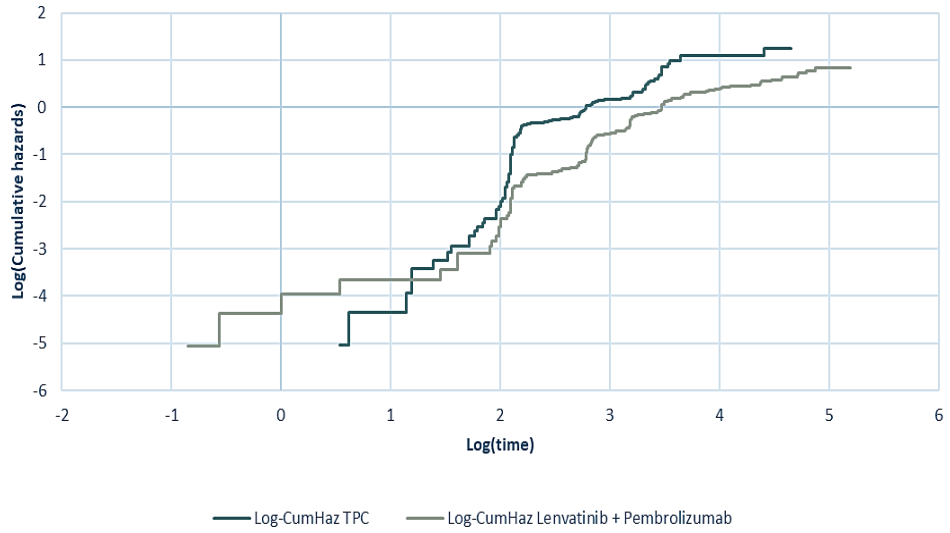
Abbreviations: OS, overall survival; TPC, treatment of physician choice

8.1.1.2 Extrapolation of progression free survival

Based on the visual assessment of the of the log cumulative hazards over time (

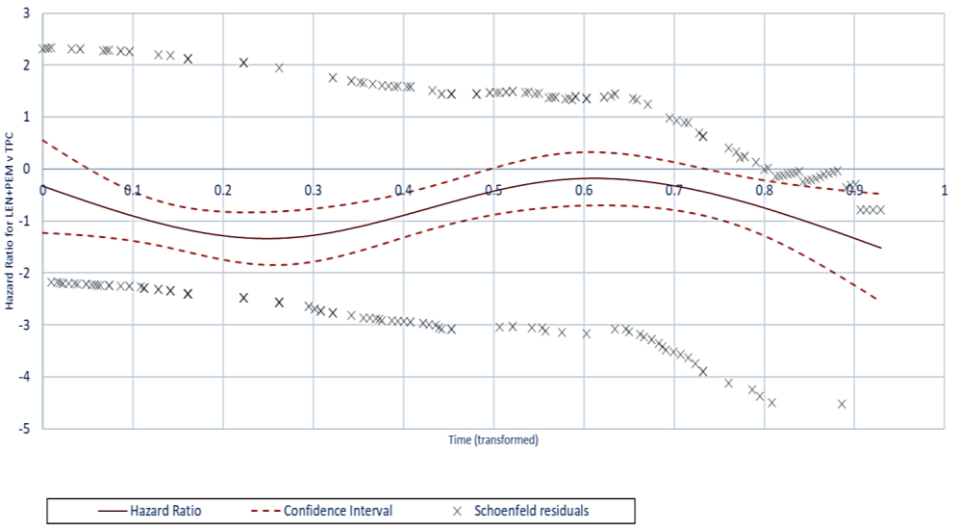
Figure 9) in which LEN+PEM and TPC (pre-assigned to DOX) lines quickly become parallel, the proportional hazard assumption for PFS is not violated in the defined sub-population. This is further confirmed by the plot of Schoenfeld residuals (Figure 10) and the p-value of the test associated with them (p=0.36). Therefore, the base-case analysis fitted joint parametric models to extrapolate progression free survival. Table 19 summarises assumptions and extrapolation methods for PFS. Scenario analyses explored other plausible models.

Figure 9 Log cumulative hazard over log time for LEN+PEM and TPC (pre-assigned to DOX) for PFS



Abbreviations: TPC, treatment of physician choice; CumHaz, cumulative hazard**;** PFS, progression free survival; LEN+PEM, lenvatinib + pembrolizumab; TPC, treatment of physician choice; DOX, doxorucibin

Figure 10 Schoenfeld residuals plot for progression free survival



Curve selection was based on visual assessment and statistical fit of the models. Specifically, we selected the log-logistic joint model (treatment effect), which presented the lowest AIC and BIC values (Table 18)

Table 18 AIC and BIC for dependent fits of PFS

Distribution	AIC	BIC
Exponential	2206.3	2213.9
Weibull	2204.0	2215.4
Gompertz	2197.3	2208.7

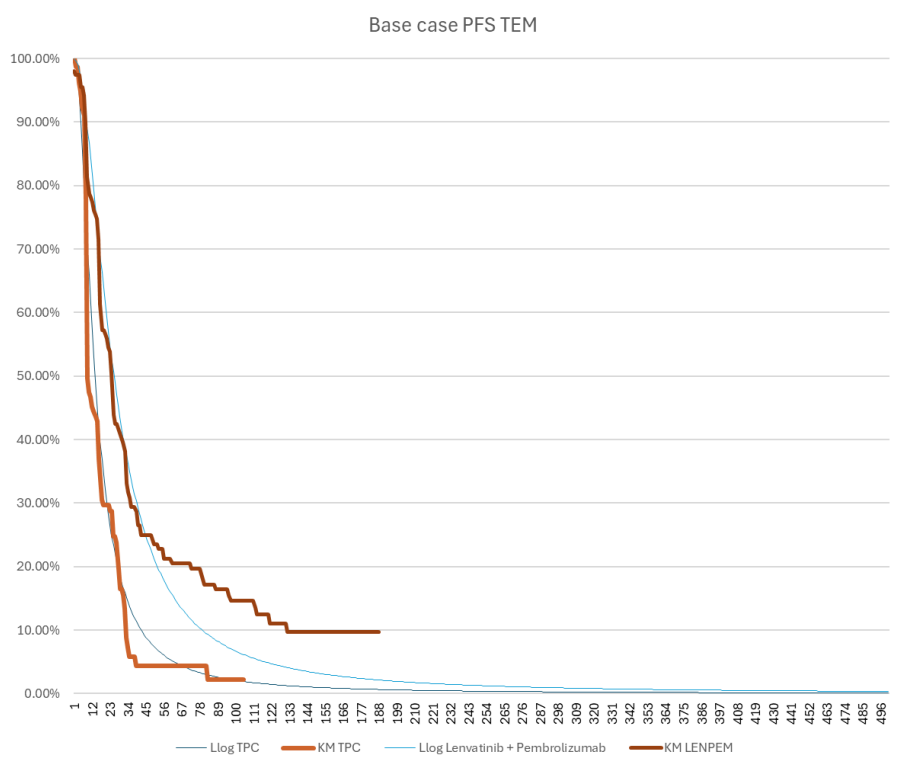
Log-normal	2156.0	2167.4
Log-logistic	**2137.8**	**2149.2**
Generalized gamma	NA*	NA*
Gamma	2195.2	2206.6

Abbreviations: PFS, progression free survival; AIC, akaike information criterion; BIC, bayesian information criterion
Notes: *Generalised gamma model did not converge.

Table 19 Summary of assumptions associated with extrapolation of progression free survival

Method/approach	Description/assumption
Data input	Study 309/KN-775 (pre-assigned to DOX, PFI < 6 months, pMMR status)
Model	Joint model
Assumption of proportional hazards between intervention and comparator	PH is not violated
Function with best AIC fit	Joint model: Log logistic
Function with best BIC fit	Joint model: Log logistic
Function with best visual fit	Joint model: Log logistic
Function with best fit according to evaluation of smoothed hazard assumptions	Joint model: Log logistic
Validation of selected extrapolated curves (external evidence)	NA. Not conducted
Function with the best fit according to external evidence	NA. Not conducted
Selected parametric function in base case analysis	Joint model: Log logistic
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 11 Base case curves for the extrapolation of PFS



Abbreviations: TPC, treatment of physician choice

8.1.1.3 Extrapolation of time on treatment

ToT was extrapolated independently for LEN, PEM, and TPC (pre-assigned to DOX) to capture each of the different treatment durations.

In the base-case, ToT was informed with KM and extrapolated thereafter. Results that relied on ToT based on parametric distributions only were addressed in a separate scenario analysis.

Time on treatment LEN:

Curve selection was based on a visual assessment and the statistical fit of the independent models. Specifically, we selected the Gompertz distribution, which presented the lowest AIC and BIC values (Table 20).

Table 20 AIC and BIC for independent fits of LEN ToT

Distribution	AIC	BIC
Exponential	1386.5	1389.6
Weibull	1382.3	1388.4
Gompertz	**1373.6**	**1379.8**
Log-normal	1390.7	1396.8

Log-logistic	1378.0	1384.1
Generalized gamma	1381.4	1390.7
Gamma	1384.4	1390.6

Abbreviations: ToT, time on treatment; AIC, akaike information criterion; BIC, bayesian information criterion

Table 21 Summary of assumptions associated with extrapolation of LEN ToT

Method/approach	Description/assumption
Data input	Study 309/KN-775 (pre-assigned to DOX, PFI < 6 months, pMMR status)
Model	Independent model
Assumption of proportional hazards between intervention and comparator	NA
Function with best AIC fit	Independent model: Gompertz
Function with best BIC fit	Independent model: Gompertz
Function with best visual fit	Independent model: Gompertz
Function with best fit according to evaluation of smoothed hazard assumptions	NA
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	NA
Selected parametric function in base case analysis	Independent model: Gompertz
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	NA
Assumptions of waning effect	NA
Assumptions of cure point	NA

Figure 12 Base case curves for the extrapolation of LEN ToT

Abbreviations: LEN, lenvatinib; ToT, time on treatment

Time on treatment PEM:

Given that KM data was available for the first 24 months, after which a stopping rule was implemented, ToT for PEM in the base-case was not extrapolated. Nonetheless, Table 22 presents AIC and BIC of the independent models extrapolated for PEM.

Table 22 AIC and BIC for independent fits of PEM ToT

Distribution	AIC	BIC
Exponential	1470.1	1473.2
Weibull	1472.1	1478.3
Gompertz	1468.9	1475.0
Log-normal	1541.2	1547.3
Log-logistic	1510.0	1516.1
Generalized gamma	**1466.1**	**1475.3**
Gamma	1471.8	1477.9

Abbreviations: ToT, time on treatment; AIC, akaike information criterion; BIC, bayesian information criterion

Time on treatment TPC (pre-assigned to DOX):

Curve selection was based on a visual assessment and the statistical fit of the independent models. Specifically, we selected the Generalized gamma distribution, which presented the lowest AIC and BIC value. Table 23 presents AIC and BIC of the independent models extrapolated for TPC (pre-assigned to DOX).

Table 23 AIC and BIC for independent models of ToT (pre-assigned to DOX)

Distribution	AIC	BIC
Exponential	1087.7	1090.8
Weibull	1078.2	1084.3
Gompertz	1058.0	1064.1
Log-normal	1160.0	1166.2
Log-logistic	1125.5	1131.6
Generalized gamma	**1047.0**	**1056.3**
Gamma	1085.0	1091.2

Abbreviations: ToT, time on treatment; AIC, akaike information criterion; BIC, bayesian information criterion

8.1.2 Calculation of transition probabilities

NA. Partitioned survival model was used.

8.2 Presentation of efficacy data from additional documentation

NA. Additional documentation of efficacy data was not used.

8.3 Modelling effects of subsequent treatments

NA. No effects were modelled for remaining subsequent treatments.

8.4 Other assumptions regarding efficacy in the model

In the cost-effectiveness model, ToT for PEM was capped with a stopping rule of 24 months following EMA guidelines (58) and reflecting Study 309/KN-775 protocol (1).

8.5 Overview of modelled average treatment length and time in model health state

Table 24 Estimates in the model for OS

	Modelled average OS (reference in Excel)	Modelled median OS (reference in Excel)	Observed median from relevant study
LEN+PEM	[redacted]	[redacted]	[redacted]
TPC (pre-assigned to DOX)	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival; LEN, lenvatinib; PEM, pembrolizumab; TPC, treatment of physician choice

Table 25 Estimates in the model for PFS

	Modelled average PFS (reference in Excel)	Modelled median PFS (reference in Excel)	Observed median from relevant study
LEN+PEM	[redacted]	[redacted]	[redacted]
TPC (pre-assigned to DOX)	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression free survival; LEN, lenvatinib; PEM, pembrolizumab; TPC, treatment of physician choice

Table 26 Overview of modelled average treatment length, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [years]
LEN	[redacted]
PEM	[redacted]
TPC (pre-assigned to DOX)	[redacted]

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; TPC , treatment of physician choice

9. Safety

9.1 Safety data from the clinical documentation

Among the sub-population group of patients pre-assigned to DOX, PFI < 6 months, and pMMR status, the safety analysis set consisted of n=160 subjects for LEN+PEM and n=160 subjects for TPC (pre-assigned to DOX). A total of 26 (16.3%) out of 160 patients discontinued LEN+PEM due to adverse events, and 15 (9.4%) out of 160 patients discontinued DOX.

The overall incidence of TEAEs and drug-related TEAEs was similar in the LEN+PEM and TPC (pre-assigned to DOX) groups, with the LEN+PEM group reporting more cases of Hypertension.

Table 27 Overview of safety events

	LEN+PEM (N=160, post-hoc analysis of Study 309)	TPC (pre-assigned to DOX) (N=160, post-hoc analysis of Study 309)
Number of adverse events, n	3703	1845
Number and proportion of patients with ≥1 adverse events, n (%)	159 (99.4)	160 (100)
Number of serious adverse events, n	144	99
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	83 (51.9)	60 (37.5)
Number of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 events*, n	453	447
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	115 (71.9)	118 (73.8)
Number of adverse reactions, n	NA	NA
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NA	NA

	LEN+PEM (N=160, post-hoc analysis of Study 309)	TPC (pre-assigned to DOX) (N=160, post-hoc analysis of Study 309)
Number and proportion of patients who had a dose reduction, n (%)	NA	NA
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	142 (88.8)	119 (74.4)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	26 (16.3)	15 (9.4)

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; TPC , treatment of physician choice

Notes:
Grades are based on NCI CTCAE version 4.03.
For Lenvatinib + Pembrolizumab, the discontinuation of Pembrolizumab and Lenvatinib.
Non-serious adverse events up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.
MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" which are not related to the study drug are excluded.

Table 28 Serious adverse events

Adverse events	LEN+PEM (N=160)	TPC (pre-assigned to DOX) (N=160)	
Any serious TEAEs, n(%)	83 (52%)	60 (37.5%)	Post-hoc analysis of Study 309
Any treatment related TEAEs, n (%)	48 (30%)	31 (19.4%)	Post-hoc analysis of Study 309
Any fatal TEAEs, n (%)	7 (4.3%)	10 (6.3%)	Post-hoc analysis of Study 309
Any treatment related fatal TEAEs, n (%)	0	4 (2.5%)	Post-hoc analysis of Study 309

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; TPC , treatment of physician choice; TEAE, treatment emergent adverse event

Table 29 Adverse events used in the health economic model

Adverse events	LEN+PEM (N=160)	TPC (pre-assigned to DOX) (N=160)	
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source
Appetite decreased	9.00	0.00	Post-hoc analysis of Study 309
Anaemia	3.00	28.00	Post-hoc analysis of Study 309
Diarrhoea	11.00	3.00	Post-hoc analysis of Study 309
Febrile neutropenia	0.00	15.00	Post-hoc analysis of Study 309
Leukopenia	0.00	22.00	Post-hoc analysis of Study 309
Lipase increased	10.00	0.00	Post-hoc analysis of Study 309
Neutropenia	1.00	82.00	Post-hoc analysis of Study 309
Neutrophil count decreased	4.00	78.00	Post-hoc analysis of Study 309
Hypertension	62.00	0.00	Post-hoc analysis of Study 309
Weight decreased	0.00	0.00	Post-hoc analysis of Study 309
White blood cell count decreased	2.00	28.00	Post-hoc analysis of Study 309
Exposure time in days	52,788	17,047	Post-hoc analysis of Study 309

Notes: Grade3-5 Treatment-Emergent Related Adverse Events (Including Multiple Occurrences of Events) (Incidence >=5% in Unique Subjects in One or More Treatment Groups) in Pre-Assigned Doxorubicin Participants for pMMR Participants and PFI < 6 months.

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; TPC , treatment of physician choice

9.2 Safety data from external literature applied in the health economic model

NA. No external safety data used in the model.

Table 30 Adverse events that appear in more than >10% of patient in one or more treatment groups

Adverse events	LEN+PEM (N=160)		TPC (pre-assigned to DOX) (N=160)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	159 (99.4)	NA	160 (100.0)	NA
Hypertension	106 (66.3)	NA	2 (1.3)	NA
Hypothyroidism	91 (56.9)	NA	2 (1.3)	NA
Nausea	80 (50.0)	NA	85 (53.1)	NA
Diarrhoea	79 (49.4)	NA	29 (18.1)	NA
Decreased appetite	69 (43.1)	NA	46 (28.8)	NA
Vomiting	61 (38.1)	NA	40 (25.0)	NA
Arthralgia	53 (33.1)	NA	10 (6.3)	NA
Fatigue	53 (33.1)	NA	43 (26.9)	NA
Proteinuria	52 (32.5)	NA	5 (3.1)	NA
Constipation	47 (29.4)	NA	38 (23.8)	NA
Urinary tract infection	47 (29.4)	NA	13 (8.1)	NA
Weight decreased	46 (28.8)	NA	8 (5.0)	NA
Asthenia	45 (28.1)	NA	47 (29.4)	NA
Abdominal pain	43 (26.9)	NA	23 (14.4)	NA
Anaemia	43 (26.9)	NA	89 (55.6)	NA
Headache	43 (26.9)	NA	15 (9.4)	NA
Alanine aminotransferase increased	38 (23.8)	NA	9 (5.6)	NA
Aspartate aminotransferase increased	36 (22.5)	NA	10 (6.3)	NA

Adverse events	LEN+PEM (N=160)		TPC (pre-assigned to DOX) (N=160)	
Palmar-plantar erythrodysaesthesia syndrome	33 (20.6)	NA	2 (1.3)	NA
Pyrexia	32 (20.0)	NA	9 (5.6)	NA
Stomatitis	31 (19.4)	NA	18 (11.3)	NA
Dysphonia	30 (18.8)	NA	1 (0.6)	NA
Hypomagnesaemia	30 (18.8)	NA	13 (8.1)	NA
Cough	25 (15.6)	NA	17 (10.6)	NA
Platelet count decreased	24 (15.0)	NA	13 (8.1)	NA
Blood alkaline phosphatase increased	23 (14.4)	NA	10 (6.3)	NA
Blood thyroid stimulating hormone increased	23 (14.4)	NA	0 (0.0)	NA
Oedema peripheral	23 (14.4)	NA	10 (6.3)	NA
Rash	23 (14.4)	NA	1 (0.6)	NA
Abdominal pain upper	22 (13.8)	NA	14 (8.8)	NA
Mucosal inflammation	22 (13.8)	NA	19 (11.9)	NA
Pain in extremity	22 (13.8)	NA	8 (5.0)	NA
Dyspnoea	20 (12.5)	NA	21 (13.1)	NA
Hypertriglyceridaemia	20 (12.5)	NA	4 (2.5)	NA
Hypokalaemia	20 (12.5)	NA	10 (6.3)	NA
Lipase increased	20 (12.5)	NA	3 (1.9)	NA
Dizziness	19 (11.9)	NA	10 (6.3)	NA
Hyponatraemia	19 (11.9)	NA	7 (4.4)	NA

Adverse events	LEN+PEM (N=160)		TPC (pre-assigned to DOX) (N=160)	
Myalgia	19 (11.9)	NA	8 (5.0)	NA
Blood cholesterol increased	18 (11.3)	NA	2 (1.3)	NA
Back pain	17 (10.6)	NA	11 (6.9)	NA
Blood creatinine increased	17 (10.6)	NA	4 (2.5)	NA
Thrombocytopenia	17 (10.6)	NA	15 (9.4)	NA
Amylase increased	16 (10.0)	NA	2 (1.3)	NA
Dry mouth	16 (10.0)	NA	5 (3.1)	NA
Dysgeusia	16 (10.0)	NA	11 (6.9)	NA
Hyperglycaemia	16 (10.0)	NA	6 (3.8)	NA
Neutropenia	14 (8.8)	NA	70 (43.8)	NA
Leukopenia	11 (6.9)	NA	26 (16.3)	NA
Neutrophil count decreased	9 (5.6)	NA	46 (28.8)	NA
White blood cell count decreased	7 (4.4)	NA	29 (18.1)	NA
Alopecia	6 (3.8)	NA	42 (26.3)	NA

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; TPC , treatment of physician choice

Notes: The type of information requested for this table, on serious adverse events, was not available for this post-hoc subgroup. Therefore we present adverse events with incidence >10% as a proxy.

10. Documentation of health-related quality of life (HRQoL)

Table 31 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	Study 309/KN-775 NCT03517449	Estimation of PF and PD utilities

Abbreviations: PF; progression free; PD, progressed disease

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

In Study 309/KN-755, HRQoL was assessed with the patient reported outcomes instruments EORTC QLQ-C30, EORTC QLQ-EN24, and EuroQoL EQ-5D-5L. The QoL score of EORTC QLQ-30 was a secondary endpoint, whereas EORTC QLQ-C30 physical functioning score, EORTC QLQ EN24 urological symptoms score, and EuroQoL EQ-5D-5L VAS score were exploratory endpoints.

For the estimation of HSUVs used in the cost-effectiveness analysis (section 10.2), a post-hoc analysis was carried out. The analysis considered the sub-population relevant for this submission (pre-assigned to DOX, PFI < 6 months, and pMMR status). However, data on patient reported outcomes from the trial clinical study report, such as completion rates, were only available for the ITT and pMMR groups. For these reasons, section 10.1 reports data (from the clinical study report) for the pMMR population only.

10.1.2 Data collection

Study 309 includes treatments with different cycle lengths. The cycle length for LEN+PEM and TPC of DOX is 21 days while the cycle length for TPC of paclitaxel is 28 days. Per the schedule of assessments, EQ-5D was collected at Cycle 1 Day 1, on Day 1 of each subsequent cycle, and at the time of discontinuation (End of Treatment visit).

The questionnaire was performed prior to dosing and before other assessments and procedures. Participants were asked to complete the EQ-5D-5L either every 21 or 28 days, depending on the cycle length of assigned treatment, until the End of Treatment visit. Completion of the EQ-5D and other HRQoL questionnaires following the End of treatment visit was not mandatory.

Table 32 Pattern of missing data and completion for LEN+PEM (pMMR only)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	329	2 (0.6)	327	319 (97.6)
Week 3	329	5 (1.5)	324	304 (93.8)
Week 6	329	18 (5.5)	311	288 (92.6)
Week 9	329	36 (10.9)	293	278 (94.9)
Week 12	329	50 (15.2)	279	256 (91.8)
Week 15	329	66 (20.1)	263	239 (90.9)
Week 18	329	79 (24.0)	250	234 (93.6)
Week 21	329	85 (25.8)	244	217 (88.9)
Week 24	329	110 (33.4)	219	195 (89.0)
Week 27	329	125 (38.0)	204	179 (87.7)
Week 30	329	139 (42.2)	190	173 (91.1)
Week 33	329	154 (46.8)	175	153 (87.4)
Week 36	329	161 (48.9)	168	149 (88.7)
Week 39	329	173 (52.6)	156	137 (87.8)
Week 42	329	188 (57.1)	141	125 (88.7)
Week 45	329	199 (60.5)	130	118 (90.8)
Week 48	329	201 (61.1)	128	112 (87.5)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 51	329	205 (62.3)	124	109 (87.9)
Week 54	329	207 (62.9)	122	104 (85.2)
Week 57	329	216 (65.7	113	99 (87.6)
Week 60	329	225 (68.4)	104	91 (87.5)
Week 63	329	236 (71.7)	93	83 (89.2)
Week 66	329	232 (70.5)	97	80 (82.5)
Week 69	329	243 (73.9)	86	77 (89.5)
Week 72	329	244 (74.2)	85	75 (88.2)
Week 75	329	251 (76.3)	78	71 (91.0)
Week 78	329	250 (76.0)	79	69 (87.3)
Week 81	329	256 (77.8)	73	64 (87.7)
Week 84	329	259 (78.7)	70	60 (85.7)
Week 87	329	267 (81.2)	62	55 (88.7)
Week 90	329	269 (81.8)	60	54 (90.0)
Week 93	329	265 (80.5)	64	59 (92.2)
Week 96	329	273 (83.0)	56	50 (89.3)
Week 99	329	271 (82.4)	58	50 (86.2)
Week 102	329	272 (82.7)	57	48 (84.2)
Week 105	329	282 (85.7)	47	41 (87.2)
Week 108	329	277 (84.2)	52	41 (78.8)
Week 111	329	283 (86.0)	46	39 (84.8)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 114	329	292 (88.8)	37	29 (78.4)
Week 117 (last)	329	289 (87.8)	40	31 (77.5)

Abbreviations: LEN, lenvatinib; PEM, Pembrolizumab; pMMR, proficient mismatch repair

Table 33 Pattern of missing data and completion for TPC (pMMR only)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	311	1 (0.3)	310	303 (97.7)
Week 3	311	1 (0.3)	310	280 (90.3)
Week 6	311	13 (4.2)	298	207 (69.5)
Week 9	311	34 (10.9)	277	247 (89.2)
Week 12	311	90 (28.9)	221	193 (87.3)
Week 15	311	108 (34.7)	203	152 (74.9)
Week 18	311	137 (44.1)	174	123 (70.7)
Week 21	311	162 (52.1)	149	115 (77.2)
Week 24	311	200 (64.3)	111	76 (68.5)
Week 27	311	224 (72.0)	87	53 (60.9)
Week 30	311	263 (84.6)	48	25 (52.1)
Week 33	311	263 (84.6)	48	24 (50.0)
Week 36	311	281 (90.4)	30	16 (53.3)
Week 39	311	288 (92.6)	23	14 (60.9)

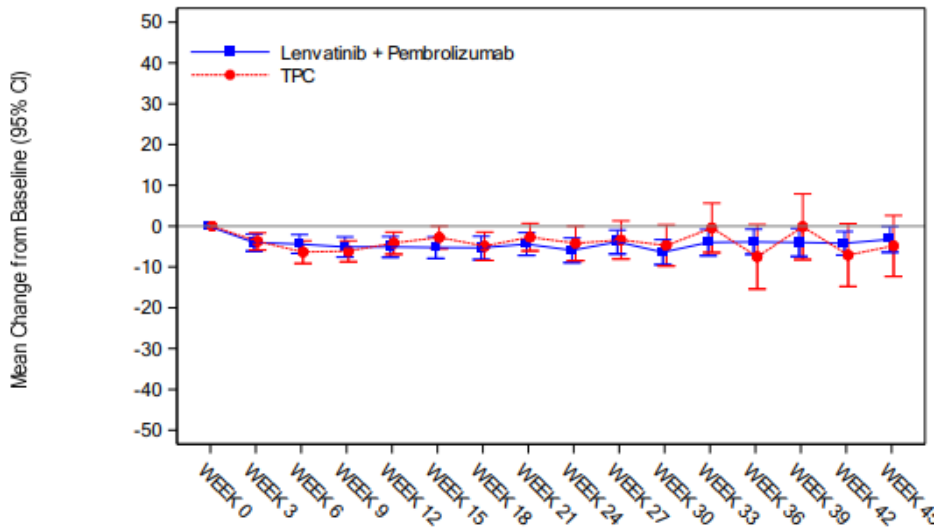
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 42	311	296 (95.2)	15	12 (80.0)
Week 45	311	294 (94.5)	17	13 (76.5)
Week 48	311	303 (97.4)	8	7 (87.5)
Week 51	311	295 (94.9)	16	14 (87.5)
Week 54	311	301 (96.8)	10	10 (100.0)
Week 57	311	299 (96.1)	12	11 (91.7)
Week 60	311	302 (97.1)	9	9 (100.0)
Week 63	311	301 (96.8)	10	8 (80.0)
Week 66	311	302 (97.1)	9	7 (77.8)
Week 69	311	300 (96.5)	11	7 (63.6)
Week 72	311	305 (98.1)	6	5 (83.3)
Week 75	311	306 (98.4)	5	5 (100.0)
Week 78	311	309 (99.4)	2	1 (50.0)
Week 81	311	305 (98.1)	6	6 (100.0)
Week 84	311	306 (98.4)	5	5 (100.0)
Week 87	311	308 (99.0)	3	3 (100.0)
Week 90	311	306 (98.4)	5	5 (100.0)
Week 93	311	305 (98.1)	6	5 (83.3)
Week 96	311	307 (98.7)	4	3 (75.0)
Week 99	311	307 (98.7)	4	3 (75.0)
Week 102	311	308 (99.0)	3	3 (100.0)
Week 105	311	308 (99.0)	3	3 (100.0)
Week 108	311	308 (99.0)	3	3 (100.0)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 111	311	309 (99.4)	2	2 (100.0)
Week 114	311	310 (99.7)	1	1 (100.0)
Week 117 (last)	311	309 (99.4)	2	2 (100.0)

Abbreviations: TPC, treatment of physician's choice; pMMR, proficient mismatch repair

10.1.3 HRQoL results (pMMR only)

Figure 13 Mean change from baseline and 95% CI for EQ-5D VAS score over time (pMMR only)



Number of Participants

Lenvatinib + Pembrolizumab	319	297	281	272	251	234	229	212	193	178	172	152	148	136	123	117
TPC	303	275	203	241	189	150	122	114	75	52	25	24	16	14	12	13

Table 34 HRQoL EQ-5D-5L VAS scores summary statistics (pMMR)

	Intervention LEN+PEM		Comparator TPC		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	319	74.08 (18.33)	303	74.13 (18.61)	NA

	Intervention LEN+PEM		Comparator TPC		Intervention vs. comparator
Week 12	256	70.23 (18.63)	193	70.90 (19.77)	NA
					Difference in LS means*
Change from Baseline to Week 12.	-5.35 (-7.58; -3.11)		-7.41 (-9.85; -4.69)		2.06 (-1.08, 5.20) P = 0.1981

Abbreviations: pMMR, proficient mismatch repair; LEN, lenvatinib; PEM, Pembrolizumab; TPC, treatment of physician's choice; LS, least squares; cLDA, constrained longitudinal data analysis models

Note: *Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

The HSUVs used in the model originate from a post-hoc sub-group analysis of study 309 / KN-775, based on patient level data. The values were estimated with the EQ-5D-5L instrument using published tariffs for the Danish population (85).

For use within the economic model, a multivariable linear mixed model was fitted to the EQ-5D index score, and covariates representing baseline EQ-5D index score, presence of Grade 3–5 As occurring in >5% of patients at the time of observation, treatment arm, being 'on' vs 'off' treatment, and progression-status were included in the model. The list of candidate covariates themselves was not selected systematically and was based on covariates which define health states (e.g., post-progression status, on vs off treatment) or other features of the model (such as adverse events).

The final statistical model for utilities in the pre-assigned to DOX, PFI<6 months, and pMMR (as described in section 3.4.1) population is presented in Table 35. Results suggested small decrements associated with observations post-progression ([redacted]; p<0.001) and experiencing adverse events at the time of observation ([redacted]; p<0.001). Being on treatment (independent of which treatment) was associated with a significant increase in EQ-5D ([redacted]; p<0.001).

The mixed-effects utility model was then used to derive specific HSUVs corresponding to the progression-free (PF) and progressed disease (PD) states. To achieve this, we computed the estimated marginal means (EMMs) for the predefined factors included in the linear model. EMMs, also referred to as least-squares means, represent the expected means for each level of a factor, adjusted for the effects of other variables in the model. By estimating these marginal means, we obtained HSUVs that reflect the relative

contribution of the variables while accounting for the influence of baseline covariates and random effects in the model. This approach ensures that the derived HSUVs are both robust and appropriately adjusted for patient-level variability.

Using estimated marginal means from a mixed-effects model provides a superior approach to simply computing subgroup averages because EMMs adjust for covariates, imbalances in sample sizes, and incorporate random effects to account for individual variability. Such approached provided statistically robust and clinically meaningful estimates (aligned, for example, with the previous submission), ensuring that the derived HSUVs reflected the true underlying relationships in the data while, at the same time, avoiding the oversimplification inherent of a simple averages approach.

Table 35 Mixed effects utility model with Danish tariff

Coefficient	Estimate	Standard error (SE)	p-value
Intercept	[redacted]	[redacted]	[redacted]
Post progression decrement	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]
Adverse event decrement	[redacted]	[redacted]	[redacted]
On treatment	[redacted]	[redacted]	[redacted]

Mathematically, the estimated HSUVs for the PF and PD states were computed as:

$$\text{Utility} = \beta_0 + \beta_1(\text{PROGRESSION2}) + \beta_2(\text{BASELINE}) + \beta_3(\text{ADVERSE}) + \beta_4(\text{ONTX}) + u\_i + \varepsilon$$

Where:

- β_0 is the intercept
- β_1, β_2, β_3, β_4 are the fixed effect coefficients
- PROGRESSION2 is the disease state (0 = progression-free, 1 = progressed)
- BASELINE is the patient's baseline utility value
- ADVERSE indicates presence of adverse events (0 = no, 1 = yes)
- ONTX indicates if patient is on treatment (0 = no, 1 = yes)
- u_i is the random effect for patient i
- ε is the residual error term

Specifically, for each level of interest (i.e., pre progression / post progression) we computed the values, from patient level data, adjusting for all the covariates in the regression model. After that, the average values over the combinations of variables were used in the cost-effectiveness model. A detailed overview of the calculations is provided below:

Reference Grid Values:

- BASELINE = [redacted]
- ADVERSE = {Without AE, With AE}
- ONTX = {Off treatment, On treatment}
- PROGRESSION2 = {Pre, Post}

Model Coefficients:

- Intercept = [redacted]
- PROGRESSION2 (Post) = [redacted]
- BASELINE = [redacted]
- ADVERSE (With AE) = [redacted]
- ONTX (On treatment) = [redacted]

Calculation for each factor combination

Progression Free state:

1. Without AE, Off treatment:

Utility_PF_1 = [redacted] + 0(Pre) + [redacted] ([redacted]) + 0(Without AE) + 0(Off treatment)

= [redacted] + [redacted] = [redacted]

2. With AE, Off treatment:

Utility_PF_2 = [redacted] + 0 + [redacted] ([redacted]) + ([redacted]) + 0

= [redacted] - [redacted] = [redacted]

3. Without AE, On treatment:

Utility_PF_3 = [redacted] + 0 + [redacted] ([redacted]) + 0 + [redacted]

= [redacted] + [redacted] = [redacted]

4. With AE, On treatment:

Utility_PF_4 = [redacted] + 0 + [redacted] ([redacted]) + [redacted]) + [redacted]

= [redacted] + [redacted] = [redacted]

Progression free utility = Average (Utility_PF_1, Utility_PF_2, Utility_PF_3, Utility_PF_4)
= ([redacted] + [redacted] + [redacted] + [redacted])/4 = [redacted]

Progressed Disease state:

(Same calculations as above but we add [redacted] for PROGRESSION2 (Post))

1. Without AE, Off treatment: [redacted]

2. With AE, Off treatment: [redacted]

3. Without AE, On treatment: [redacted]

4. With AE, On treatment: [redacted]

Progressed disease utility = ([redacted] + [redacted] + [redacted] + [redacted])/4 = [redacted]

Mapping

NA. No mapping was needed.

10.2.2 Disutility calculation

Disutilities associated with adverse events (grade 3+ and occurring in >5%), are included in the mixed-effects regression model used in the estimation of HSUVs for the pre- and post-progression states. To avoid double counting, single disutilities associated with adverse events were not accounted for in the cost-effectiveness model.

10.2.3 HSUV results

Table 36 Overview of HSUVs

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
PF	[redacted] ([redacted]; [redacted])	EQ-5D-5L	DK	Estimate is based on data from both trial arms.
PD	[redacted] ([redacted]; [redacted])	EQ-5D-5L	DK	Estimate is based on data from both trial arms.

Abbreviations: HSUV, health state utility value; DK, denmark; CI, confidence interval

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

NA. Utilities are based entirely on Study 309/KN-775.

11. Resource use and associated costs

11.1 Medicine costs - intervention and comparator

All pharmacy purchase prices for 2024 have been derived from the drug acquisition cost from medicinpriser.dk and are summarised in Table 24 below. The indicated price per pack of LEN is the current list price. Please note that there is an agreed confidential discount with Amgros.

As previously mentioned in section 3.5, in Denmark, PLD is used for the treatment of advanced or recurrent EC. In the cost effectiveness model, it is possible to decide whether to use PLD (Caelyx®) prices as a reference (aligning with Danish clinical practice) or DOX prices (aligning with the TPC trial arm). Therefore, the base case presents results of LEN+PEM against PLD (Caelyx®) with the DOX price being accounted for in a scenario analysis.

Table 37 Medicine costs used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Pack size	Price per pack (DKK)
LEN	20 mg	See below	Daily	No	30 units	[redacted]
PEM	200 mg	95.3%	Once per 3 weeks cycle	No	100 mg	21,574
PLD	20 mg	See below	Once per 3 weeks cycle	No	20 mg	3,700
***Doxorucibin**	60 mg/m^2	98.9%	Once per 3 weeks cycle	No	200 mg	350

Abbreviations: LEN, lenvatinib; PEM, Pembrolizumab; PLD, pegylated liposomal doxorubicin

Notes:* Not used in the basecase

In the model, the cost of PEM is applied to the proportion of patients on PEM treatment once every 21 days (200 mg unit dose), as per the trial protocol. Although LEN is administered once per day (20 mg unit dose [subject to further adjustment for dose intensity]), the cost of LEN is applied to the proportion of patients on LEN treatment once every 30 days.

The acquisition costs of PEM, which accounted for multiple packages and relative dose intensity, amounted to DKK 41,117 per administration. Acquisition costs of LEN amounted to DKK [redacted] per 30-day prescription. In the base case the cost of PEM is based on a fixed dose.

The acquisition costs in the TPC (pre-assigned to DOX) arm were driven by the PLD cost per pack (DKK 3,700), which led to a cost per administration of DKK 15,210.

The model base-case assumed that vials will not be shared between patients for a conservative approach towards drug acquisition costs. The relative dose intensities for each treatment are:

- PEM: a dose intensity of [redacted] % is applied, from Study 309 / KN-775
- LEN: treatment dosing is subject to an observed estimate of dose intensity, for LEN this was calculated based on the cumulative days per LEN dose from Study 309 / KN-775, presented in Table 38 below.

- PLD: the method of moments was used to calculate the proportion of patients using different dosage, where the dose intensity is based on a distribution of patients' weight. The fitted-distribution approach involves fitting the normal distribution to the cumulative density of patient weight or BSA. Distribution parameters were estimated using a method of moments technique (86). This method is also used for subsequent therapies

Table 38: LEN cumulative days per dose

Daily dose (mg)	% of days
0	[redacted]
4	[redacted]
8	[redacted]
10	[redacted]
14	[redacted]
20	[redacted]
28	[redacted]

Abbreviations: LEN, lenvatinib

Table 39 shows a summary of the cost per treatment cycle of each arm using the packs characteristics, dosing schemes, and dose intensity (with no vial sharing).

Table 39: Calculated drug acquisition costs

Intervention	Drug	Cost per treatment cycle (DKK)
LEN + PEM	LEN	[redacted]
	PEM	41,117
PLD	PLD	15,210

Abbreviations: LEN, lenvatinib; PEM, Pembrolizumab; PLD, pegylated liposomal doxorubicin

11.2 Medicine costs – co-administration

NA

11.3 Administration costs

Administration cost of LEN+PEM was solely driven by PEM (DKK 1,314) assuming that LEN is provided concomitantly to PEM. Administration cost of PLD was set equal to the administration of PEM (DKK 1,314)

Table 40 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV infusion	Every 3rd week for PEM and PLD regimens	1,314	13MA98	DRG 2024

Abbreviations: PEM, Pembrolizumab; PLD, pegylated liposomal doxorubicin

11.4 Disease management costs

Healthcare resource use categories considered in the model are presented in Table 42, with DRG codes sourced from the Danish Health Data Authority's Interactive DRG website (interaktivdrg.sundhedsdata.dk). The general practitioner visit cost assumes only a consultation and does not include any additional tests.

Two clinical experts were consulted about clinical practice and the frequency of each event associated with disease management (87). The frequency reported by clinical experts and the frequency of use for each resource per model cycle is reported for both PF patients and progressed patients in Table 42.

Table 41 Disease management costs used in the model

Activity	Unit cost [DKK]	DRG code	Reference
Consultation (oncology)	816	Specialist consultation	https://medicinraadet-classic.azureedge.net/media/lemjycrd/vaerdisaetning-af-enhedsomkostninger-vers-1-8.pdf
Blood count	1,314	13MA98	Diagnosis: DC549M Procedure: ZZ0149W
CT scan	2,021	30PR07	Diagnosis: DC549M Procedure: UXCD15
General practitioner visit	156	consultation	https://medicinraadet-classic.azureedge.net/media/lemjycrd/vaerdisaetning-af-enhedsomkostninger-vers-1-8.pdf
Nurse Visit	462	Assumed as 1 hour of nurse time	https://medicinraadet-classic.azureedge.net/media/lemjycrd/vaerdisaetning-af-enhedsomkostninger-vers-1-8.pdf

Table 42 Disease management frequencies

Activity	PF		PD	
	LEN+PEM	TPC (pre-assigned to DOX)	LEN+PEM	TPC (pre-assigned to DOX)
Consultation (oncology)	0.23	0.23	0.08	0.08
Blood count	0.23	0.23	0.00	0.00
CT scan	0.11	0.11	0.00	0.00
General practitioner visit	0.11	0.11	0.11	0.11
Nurse Visit	0.00	0.00	0.00	0.00

Abbreviations: LEN, lenvatinib; PEM, Pembrolizumab; TPC, treatment of physician's choice
Source: Clinical experts (87)

11.5 Costs associated with management of adverse events

Costs associated with management of adverse events are based on DRG codes. In accordance with DMC guidelines, the secondary diagnosis used in the Interactive DRG was "DC549 Livmoderkræft". Costs are not applied one-time, rather are applied in the model based on estimated per cycle rate of events whilst on treatment taken from Study 309/KN-775.

Table 43 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Appetite decreased	10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR630: Appetitløshed	DKK 1,847
Anaemia	16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD592: Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel	DKK 2,111
Colitis	06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DA099: Gastroenteritis eller colitis af ikke specificeret årsag	DKK 7,818
Diarrhoea	06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS	DKK 7,818

	DRG code	Unit cost/DRG tariff
Febrile neutropenia	16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DT888N Neutropen feber ved cytostatisk behandling	DKK 2,111
Leukopenia	16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Leukocytopeni	DKK 2,111
Lipase increased	07MA98: MDC07 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR748D: Abnorm serumlipase	DKK 1,947
Neutropenia	16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Neutropeni UNS	DKK 2,111
Neutrophil count decreased	16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728: Anden forstyrrelse i hvide blodlegemer	DKK 2,111
Hypertension	05MA98: MDC05 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DI109: Essentiel hypertension	DKK 1,183
Transaminases increased	23MA03: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR740B: Transaminaseforhøjelse i serum	DKK 5,103
Weight decreased	10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR634: Abnormt vægttab	DKK 1,847
White blood cell count decreased	16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728 Anden forstyrrelse i hvide blodlegemer	DKK 2,111

11.6 Subsequent treatment costs

Subsequent therapy lines and proportions are presented in Table 45 and were based on Danish clinical expert inputs for each comparator as these were deemed relevant in Danish clinical practice (87). The original subsequent therapies proportions from Study 309 / KN-775 were not used in the model as they were not reflective of Danish clinical practice.

Danish clinical experts provided input that 50% PLD and 50% paclitaxel were relevant for subsequent therapy (49). To calculate the subsequent therapy costs, of the therapies deemed relevant (i.e., PLD and paclitaxel) we used the duration of treatment from the available trial data. However, in the absence of data for PLD from the trial, we used DOX as a proxy for PLD.

Table 44 Medicine costs of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Pack size	Price per pack (DKK)
PLD	40 mg/m2	100%	Once per 4 weeks cycle	No	20 mg	3,700
Paclitaxel	80 mg/m2	100%	Weekly 3 weeks on/1 week off	No	300 mg	202

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; TPC, treatment of physician's choice; PLD, pegylated liposomal doxorubicin

Table 45 Proportions of subsequent therapies by treatment arm

Subsequent therapy	LEN+PEM	TPC (pre-assigned to DOX)
PLD	50%	50%
Paclitaxel	50%	50%

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; TPC, treatment of physician's choice; PLD, pegylated liposomal doxorubicin

Table 46 Duration of subsequent treatment

Subsequent therapy	LEN+PEM	TPC (pre-assigned to DOX)
Paclitaxel	88.93 days	88.93 days
PLD*	83.63 days	83.63 days

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; TPC, treatment of physician's choice; PLD, pegylated liposomal doxorubicin.

*Duration based on analysis of Study 309 patient-level data. July 2022 (Using duration of DOX as a proxy for PLD.

Subsequent treatment costs used in the model are shown in Table 47 below. The cost per subsequent treatment was calculated as the product of the per cycle drug acquisition cost, drug administration cost for each subsequent treatment, the average number of subsequent treatment lines per patient (1.64 in LEN+PEM and 1.56 in TPC), the proportions receiving each subsequent treatment (50% PLD and 50% for both LEN+PEN and TPC), the duration of each subsequent treatment, and he proportion of PFS events that resulted in a subsequent treatment (52% in LEN+PEM and 69% in TPC).

Table 47 Modelled subsequent treatment cost

	LEN+PEM	TPC (pre-assigned to DOX)

One-off cost	DKK 10,773	DKK 10,203

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; TPC, treatment of physician's choice

11.7 Patient costs

Based on the *Medicinrådet - Værdisætning af enhedsomkostninge*r guidelines (88) by the DMC, the average transport costs is included in the health economic analysis. The model allows the inclusion of non-medical direct costs, which includes both transportation costs and patient time spent and is multiplied with the frequencies in each health state.

Table 48 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Patient Time Cost per Hour	DKK 188 (https://medicinraadet-classic.azureedge.net/media/lemjycrd/vaerdisaetning-af-enhedsomkostninger-vers-1-8.pdf)
Travel cost per Visit	DKK 140 (https://medicinraadet-classic.azureedge.net/media/lemjycrd/vaerdisaetning-af-enhedsomkostninger-vers-1-8.pdf)
Patient time Per IV administration	Assumed 3 hours
Patient time Per monitoring visit	Assumed 1 hour
Average Progression-Free hours per cycle – LEN+PEM	Assumed 0.46
Average Progression-Free hours per cycle – TPC	Assumed 0.46
Average Progressed Disease hours per cycle – LEN+PEM	Assumed 0.19
Average Progressed Disease hours per cycle – TPC	Assumed 0.19

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Costs for MSI testing were included in the base-case and assumed as a one-off cost (DKK 785), only applied to the LEN+PEM group. The cost was based on the cost of an immunohistochemistry test (89) and an assumed proportion of 70% that would get tested.

12. Results

12.1 Base case overview

Table 49 Base case overview

Feature	Description
Comparator	PLD
Type of model	Partitioned survival model
Time horizon	37 years (lifetime)
Treatment line	Subsequent lines are included
Measurement and valuation of health effects	Utilities estimated with HRQoL measured with EQ-5D-5L using Danish tariff
Costs included	Drug acquisition costs Drug administration costs Subsequent therapy costs Adverse event costs Medical resource use costs End of life costs Transportation and wage lost (restricted societal perspective)
Dosage of medicine	LEN: based on dosing from Study 309 PEM: Based on Study 309 protocol PLD: Based on previous LEN+PEM submission(59)
Average ToT	LEN: [redacted] years, PEM: [redacted] years TPC: (based on DOX from Study 309): [redacted] years
Parametric function for PFS	Joint model: Log-logistic
Parametric function for OS	Joint model: Log-normal
Inclusion of waste	Yes, no assumption on vial sharing in base-case

Feature	Description
Average time in model health state	
PF (LEN+PEM)	[redacted]
PD (LEN+PEM)	[redacted]
PF (TPC pre-assigned to DOX)	[redacted]
PD (TPC pre-assigned to DOX)	[redacted]

12.1.1 Base case results

Table 50 presents the discounted base case results for the treatment of advanced EC, following treatment with platinum-based chemotherapy, with LEN+PEM vs TPC (pre-assigned to DOX) in the PFI<6 months, pMMR status population. The comparison indicates a net QALY gain of 0.73 at an incremental cost of DKK 534,934. Results indicate that LEN+PEM is more effective but also more costly than TPC (pre-assigned to DOX), with an overall ICER of DKK 735,863 per QALY.

Table 50 Base case results, discounted estimates

	LEN+PEM	TPC (pre-assigned to DOX)	Difference
Acquisition costs	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]
Medical resource use costs	[redacted]	[redacted]	[redacted]
Subsequent therapies costs	[redacted]	[redacted]	[redacted]
Limited Societal costs (Patient Time and Transportation)	[redacted]	[redacted]	[redacted]
MSI testing cost	[redacted]	[redacted]	[redacted]
Adverse event costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life years gained (PF)	[redacted]	[redacted]	[redacted]
Life years gained (PD)	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	**1.00**

	LEN+PEM	TPC (pre-assigned to DOX)	Difference
QALYs (state A)	[redacted]	[redacted]	[redacted]
QALYs (state B)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	**0.73**
Incremental costs per life year gained		**DKK 536,236**	
Incremental cost per QALY gained (ICER)		**DKK 735,863**	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

A one-way sensitivity analysis (OWSA) was performed to identify key model drivers based on their relative influence on results. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using SEs when available or using SEs estimated based on ±15% variation around the mean where measures of variance around the base case values were not available. Pairwise one way sensitivity analyses were performed separately for each comparator and are reported for the 10 most influential parameters on the ICER.

OWSA results for LEN+PEM versus TPC (pre-assigned to DOX) are presented in Figure 14 and Table 51. The OWSA showed that the parameters with the greatest influence on the ICER were the BSA and the dose intensity of DOX/PLD. Overall, the analysis illustrates robustness to univariant analyses.

Table 51 One-way sensitivity analyses results

Parameter	ICER at lower value of parameter	ICER at upper value of parameter	% change at lower value of parameter	% change at upper value of parameter
Utility PF	[redacted]	[redacted]	[redacted]	[redacted]
BSA (body surface area), m2	[redacted]	[redacted]	[redacted]	[redacted]
Utility PD	[redacted]	[redacted]	[redacted]	[redacted]
Blood count, LEN+PEM, PFS	[redacted]	[redacted]	[redacted]	[redacted]
Liposomal doxorubicin, dose per day	[redacted]	[redacted]	[redacted]	[redacted]
CT scan, LEN+PEM, PFS	[redacted]	[redacted]	[redacted]	[redacted]
Consultation, oncology, LEN+PEM, PFS	[redacted]	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]	[redacted]
Blood count, TPC, PFS	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]

Figure 14 One-way sensitivity analysis

12.2.1.1 Scenario analyses

Scenario analyses were performed to test the impact of change in key inputs and assumptions on the cost-effectiveness estimates. Table 52 lists the scenarios conducted around the base case analysis presented above. These scenarios included alternative discount rates, extrapolations of OS, PFS, ToT, changes to costs, and other assumptions.

To assess the impact of discounting, more extreme values have been selected and presented in scenarios. Furthermore, alternative models for the extrapolation of OS, PFS, and ToT were explored based on clinical plausibility, AIC/BIC fit, and visual goodness-of-fit curves.

The results of the scenario analyses (Table 52) illustrate the robustness of the analysis with ICER results varying from DKK 474,261 to DKK 775,798 per QALY.

Table 52 Scenario analyses for the health economic model

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
Base-case	[redacted]	[redacted]	DKK 735,863	0%
Discount rates = 1.5%	[redacted]	[redacted]	DKK 703,530	-4%
Discount rates = 6.0%	[redacted]	[redacted]	DKK 775,798	5%
Parametric curves for ToT instead of KM	[redacted]	[redacted]	DKK 717,521	-2%
50% discount on pembrolizumab	[redacted]	[redacted]	DKK 517,862	-30%
PFS modelled independently	[redacted]	[redacted]	DKK 746,231	1%

Healthcare perspective only	[redacted]	[redacted]	DKK 726,867	-1%
60% discount on pembrolizumab	[redacted]	[redacted]	DKK 474,261	-36%

Notes: *patient time and transport costs excluded

12.2.2 Probabilistic sensitivity analyses

A probabilistic analysis was conducted to account for the joint uncertainty of the underlying parameter estimates. The choice of distribution (beta, gamma, log-normal, normal and Dirichlet) applied to parameters was selected based on recommendations outlined in Briggs et al. 2008 (90). SEs were taken directly from source data if reported or calculated from published standard deviations (SD) sample size and/ or 95% confidence interval data. If none were reported SE is estimated as 20% of the default value. The probabilistic base case was run with 1000 iterations following a visual assessment to ensure adequate convergence of incremental costs estimates (

Figure 17) and of incremental QALYs (Figure 18). Indeed, after around 500 simulations incremental costs have a variation of less than DKK 20. While, after 700 simulations incremental QALYs have a variation of less than 0.0001.

The probabilistic results (ICER: DKK 724,850/QALY gained) align well with deterministic results (ICER: DKK 735,863/QALY gained). The scatterplot of all the PSA iterations is presented in Figure 15, while Figure 16 presents the cost-effectiveness acceptability curves. The scatterplot confirms that LEN+PEM is more efficacious but also more expensive compared to TPC (pre-assigned to DOX)

Figure 15 Cost-effectiveness scatterplot

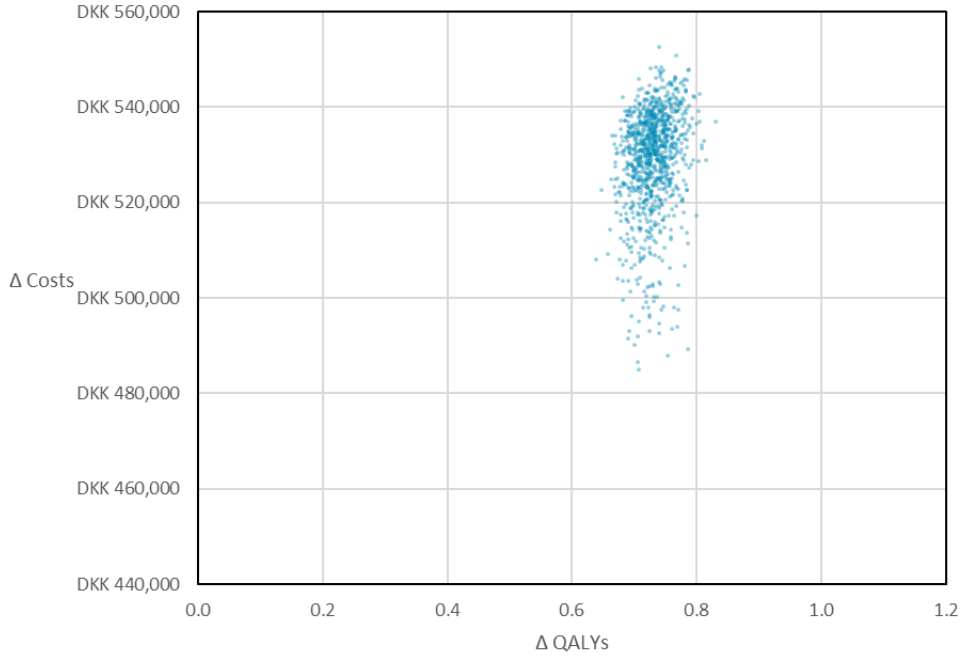


Figure 16 Cost-effectiveness acceptability curves for LEN+PEM and TPC

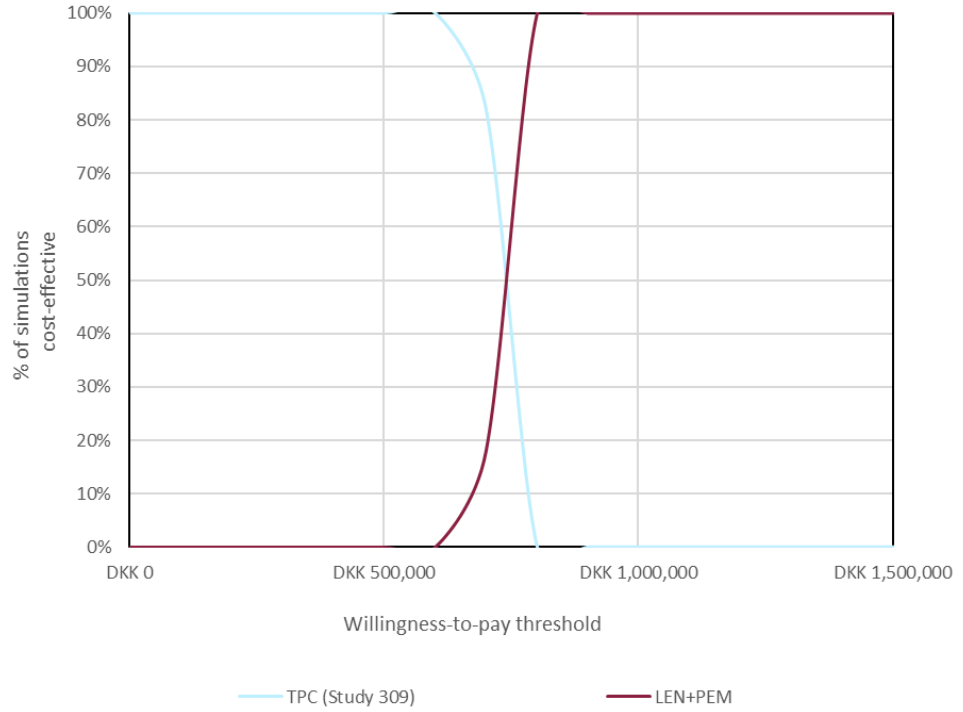


Figure 17 Incremental cost convergence over number of simulations

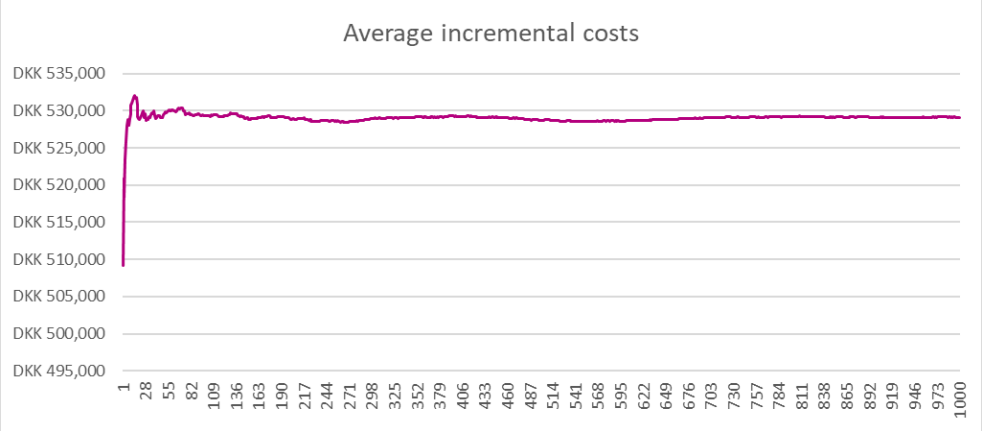
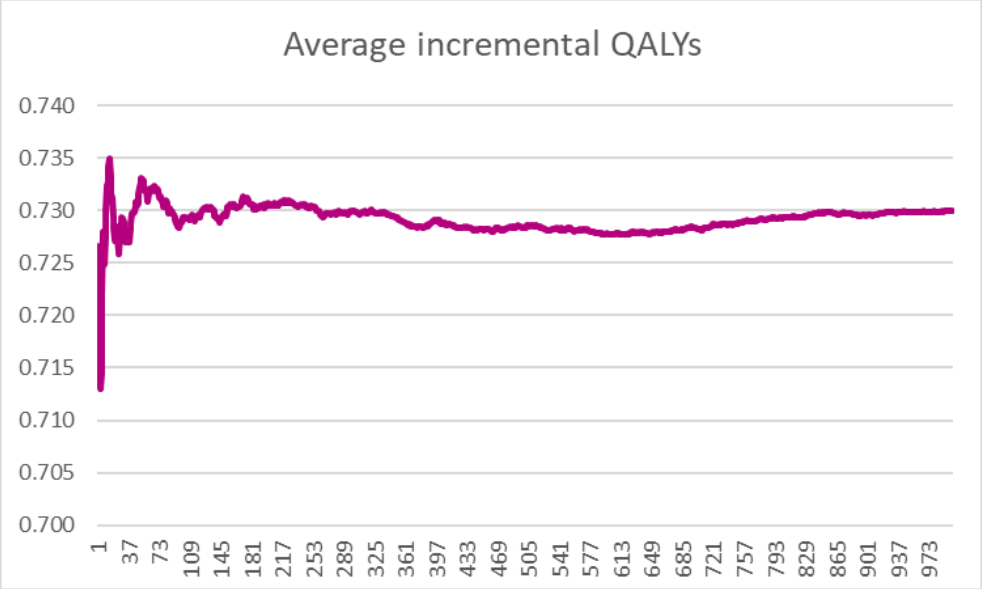


Figure 18 Incremental QALYs convergence over number of simulations



13. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending LEN+PEM in Denmark. The budget impact analysis has been embedded within the cost-effectiveness model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the populations in the cost per patient model. The costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included as per the guidelines by the DMC.

The analysis is developed by comparing the costs for the Danish regions per year over five years in the scenario where LEN+PEM is recommended as a standard treatment and the scenario where LEN+PEM is not recommended as a standard treatment. The total budget impact per year is the difference between the two scenarios.

Number of patients (including assumptions of market share)

In accordance with previous submissions to the DMC, Eisai has estimated that each year, approximately 53 patients receive systemic oncological treatment for newly diagnosed advanced EC, of these, 39 would also be part of the pMMR subgroup (and PFI) (see Table 2). In case LEN+PEM were to be introduced, Eisai assumes that 25% will receive LEN+PEM in the first year. The share is assumed to incrementally grow up to approximately 80% in year 5.

Number of patients (including assumptions of market share)

Table 53 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
	Recommendation				
LEN+PEM	10	26	50	79	112
TPC (DOX)	30	54	70	82	90
	Non-recommendation				
LEN+PEM	0	0	0	0	0
TPC (DOX)	39	79	119	160	201

Notes: Numbers in this table are presented with zero decimal points. In the excel model numbers are not rounded.

Budget impact

Table 54 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	**DKK 4,564,929**

14. List of experts

Two clinical experts were consulted about clinical practice and model inputs for the Danish context

Mansoor Raza Mirza, MD. Chief Oncologist, Dept. of Oncology, Rigshospitalet, Copenhagen University Hospital, Denmark. Medical Director, Nordic Society of Gynaecologic Oncology-Clinical Trial Unit (NSGO-CTU). Vice-Chairman, Society of Gynaecologic Oncology (DGCG)

Nicoline Raaschou-Jensen, MD. Departmental physician, Dept. of Oncology, Herlev Hospital

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Appendix A. Main characteristics of studies included

Table 55 Main characteristic of studies included

Trial name: Study 309 / KN-775		**NCT03517449**
Objective	To demonstrate that LEN plus PEM: • Prolongs progression free survival (PFS) and OS when compared to TPC.	
Publications – title, author, journal, year	Colombo N, Lorusso D, Casado A, et al. Outcomes by histology and prior therapy with Lenvatinib plus Pembrolizumab vs treatment of physician's choice in patients with advanced Evascundometrial Cancer (Study 309/KEYNOTE-775). Presented at: European Society for Medical Oncology (ESMO) Congress 2021; September 16-21, 2021. Abstract 726MO. Makker V, Colombo N, Casado Herráez A, et al. A multicenter, open-label, randomized, phase III study to compare the efficacy and safety of LEN in combination with PEM versus treatment of physician's choice in patients with advanced EC. Gynecol Oncol. 2021;162 (suppl 1):S4 https://doi.ssorg/10.1016/S0090-8258(21)00657-0	
Study type and design	A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of LEN in Combination with PEM Versus TPC in Participants with Advanced EC following prior platinum-based regimen.	
Sample size (n)	**Intervention:** 411 participants **Comparator**: 416	
Main inclusion criteria	Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
	Sexes Eligible for Study:	Female
	Gender Based Eligibility:	Yes
	Accepts Healthy Volunteers:	No
	<u>Inclusion Criteria:</u> 1. Has a histologically confirmed diagnosis of EC 2. Documented evidence of advanced, recurrent or metastatic EC. 3. Has radiographic evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for EC. Participants may have received up to 1 additional line of	

Trial name: Study 309 / KN-775	NCT03517449
	platinum-based chemotherapy if given in the neoadjuvant or adjuvant treatment setting. 4. Note: There is no restriction regarding prior hormonal therapy. 5. Has historical or fresh tumour biopsy specimen for determination of MMR status. 6. Has at least 1 measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and confirmed by BICR. 7. Has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 7 days of starting study treatment. 8. Is not pregnant, breastfeeding, and agrees to use a highly effective method of contraception during the treatment period and for at least 120 days (for participants treated with LEN plus PEM) or at least 180 days (for participants treated with TPC) after the last dose of study treatment.
Main exclusion criteria	Exclusion Criteria: 1. Has carcinosarcoma (malignant mixed Mullerian tumour), endometrial leiomyosarcoma and endometrial stromal sarcomas. 2. Has unstable central nervous system metastases. 3. Has active malignancy (except for EC, definitively treated in-situ carcinomas [e.g. breast, cervix, bladder], or basal or squamous cell carcinoma of the skin) within 24 months of study start. 4. Has gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of LEN. 5. Has a pre-existing greater than or equal (>=) Grade 3 gastrointestinal or non-gastrointestinal fistula. 6. Has radiographic evidence of major blood vessel invasion/infiltration. 7. Has clinically significant haemoptysis or tumour bleeding within 2 weeks prior to the first dose of study treatment. 8. Has a history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, myocardial infarction, cerebrovascular accident (CVA) stroke, or cardiac arrhythmia associated with hemodynamic instability within 12 months of the first dose of study treatment. 9. Has an active infection requiring systemic treatment. 10. Has not recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy. 11. Is positive for Human Immunodeficiency Virus.

Trial name: Study 309 / KN-775	NCT03517449
	12. Has active Hepatitis B or C. 13. Has a history of (non-infectious) pneumonitis that required treatment with steroids, or has current pneumonitis. 14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study. 15. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to study start -Has an active autoimmune disease (with the exception of psoriasis) that has required systemic treatment in the past 2 years. 16. Is pregnant or breastfeeding. 17. Has had an allogenic tissue/solid organ transplant. 18. Has received >1 prior systemic chemotherapy regimen (other than adjuvant or neoadjuvant) for EC. Participants may receive up to 2 regimens of platinum-based chemotherapy in total, as long as one is given in the neoadjuvant or adjuvant treatment setting. 19. Has received prior anticancer treatment within 28 days of study start. All acute toxicities related to prior treatments must be resolved to Grade ≤1, except for alopecia and Grade ≤2 peripheral neuropathy. 20. Has received prior treatment with any treatment targeting VEGF-directed angiogenesis, any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. 21. Has received prior treatment with an agent directed to a stimulatory or co-inhibitory T-cell receptor other than an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, and who has discontinued from that treatment due to a Grade 3 or higher immune-related adverse event. 22. Has received prior radiation therapy within 21 days of study start with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks of study start. Participants must have recovered from all radiation-related toxicities and/or complications prior to randomization. 23. Has received a live vaccine within 30 days of study start. 24. Has a known intolerance to study treatment (or any of the excipients). 25. Prior enrolment on a clinical study evaluating PEM and LEN for EC, regardless of treatment received. 26. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks of study start. 27. Participants with urine protein ≥1 gram (g)/24 hour. 28. Prolongation of corrected QT interval to >480 milliseconds (ms).

Trial name: Study 309 / KN-775	NCT03517449
	29. Left ventricular ejection fraction (LVEF) below the institutional normal range as determined by multigated acquisition scan (MUGA) or echocardiogram (ECHO).
Intervention	LEN 20 mg (LENVIMA®) + PEM 200 mg (KEYTRUDA®) Participants received PEM 200 mg administered by intravenous (IV) infusion on Day 1 of each 21-day cycle plus LEN 20 mg administered orally (PO) once daily (QD) during each 21-day cycle for up to 35 cycles. 411 participants in LEN plus PEM group.
Comparator(s)	Active Comparator: TPC (DOX or paclitaxel, TPC) Participants received either of the following treatments: DOX 60 milligram per square meter (mg/m^2) administered by IV on Day 1 of each 21-day cycle for up to a maximum cumulative dose of 500 mg/m^2 OR paclitaxel 80 mg/m^2 administered by IV on a 28-day cycle: 3 weeks receiving paclitaxel once a week and 1 week not receiving paclitaxel. 416 participants in TPC group.
Follow-up time	March 2022
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary Outcome Measures: • Progression Free Survival (PFS) • OS Secondary Outcome Measures: • Objective Response Rate (ORR) • HRQoL Score Using the European Organization for Research and Treatment (EORTC) Quality of Life (QoL) Questionnaire (QLQ-C30) Version 3.0 • Number of Participants with Adverse Events • Number of Participants with Serious Adverse Events • Number of Participants with Immune-related Adverse Events (irAE) • Number of Participants with Treatment Discontinuations Due to AEs Other endpoints: • Time to Treatment Failure (TTF) Due to Treatment Emergent AEs

Trial name: Study 309 / KN-775	NCT03517449
	• Model-Predicted Area Under the Concentration time Curve of LEN Based on Starting Dose from Time 0 to Infinity (AUC 0-∞) • Model-Predicted Apparent Total Body Clearance (Cl/F) of LEN • Model-Predicted Apparent Total Body Volume of Distribution (Vd/F) of LEN
Method of analysis	The ITT population served as the population for the primary efficacy analyses. All randomized participants were included in this population. Participants were analysed in the treatment group to which they were randomized. The non-parametric KM method was used to estimate the PFS curve and survival curves respectively and the treatment differences in PFS and OS were assessed by the stratified log-rank test. Stratified Miettinen and Nurminen's method was used for comparison of the ORR between two treatment groups. The total family-wise error rate (Type-I error) among theprimary PFS and OS analyses, ORR analysis for all-comer participants is strongly controlled at one-sided 0.025 level. The safety analyses were conducted using all subjects as treated population, which included all randomized subjects who received at least 1 dose of study treatment. The analysis of safety results will follow a tiered approach. The tiers differed with respect to the analyses that was being performed including methods of statistical inferential test and descriptive statistics.

Subgroup analyses	Efficacy and safety were analysed by subgroups as follows:
	• For PFS, OS, and ORR, the following subgroups will be summarized
	  ○ Age (<65 years, ≥65 years)
	  ○ Age (<65 years, ≥65 to <75 years, ≥75 to <85 years, ≥85 years)
	  ○ Race (White, Asian, other)
	  ○ ECOG performance status (0, 1)
	  ○ Region (Region 1: Europe, US, Canada, Australia, New Zealand, and Israel or Region 2: rest of the world)
	  ○ Prior history of pelvic radiation (yes, no)
	  ○ Histology (endometrioid, non-endometrioid)
	  ○ Prior lines of therapy (1, 2, ≥3)
	  ○ MMR status (pMMR, dMMR)
	• For safety endpoints, all TEAEs, TEAEs of CTCAE Grades 3–5, and treatment-emergent serious adverse events the following subgroups will be summarized
	  ○ Age (<65 years, ≥65 years)
	  ○ Age (<65 years, ≥65 to <75 years, ≥75 to <85 years, ≥85 years)
	  ○ Race (White, Asian, other)

Trial name: Study 309 / KN-775	NCT03517449
	○ ECOG performance status (0, 1) ○ Region (Region 1: Europe, US, Canada, Australia, New Zealand, and Israel or Region 2: rest of the world) ○ Region (US, ex-US) ○ Region (EU, ex-EU) ○ Renal function category (CrCl <60 mL/min, ≥60mL/min) ○ Hepatic function category (normal, abnormal) ○ MME status (pMMR, dMMR)
Other relevant information	

Abbreviations: AE, adverse event; BICR, Blinded Independent Central Review; CR, Complete response; EC, endometrial cancer; ECHO, echocardiography; ECOG, Eastern cooperative oncology group; EMA; European medical agency; HRQoL, Health Related Quality of Life; irAE, Immune-related Adverse Events; ITT, intention to treat; IV, Intraveous; LVEF, left ventrcular ejection; MMR, Miss match repair; MUGA, multi-gated radionuclide angiography; OS, Overall survival; PFS, Progression- free survival; PO, orally; ORR, Objective response rate; PR, Partial response; QD, Once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, Serious adverse event; TEAE, Treatment emergent adverse events; TPC, Treatment of Physician's Choice; TTF, Time to treatment failure; VEGF, Vascular endothelial growth factor

Table 56 Baseline characteristics for the pre-assigned to DOX, PFI < 6 months, pMMR status population

	Lenvatinib+ Pembrolizumab (N=160)	Doxorubicin (N=169)	Total (N=329)
Sex, n (%)			
Female	160 (100.0)	169 (100.0)	329 (100.0)
Age (Years)			
<65	83 (51.9)	83 (49.1)	166 (50.5)
>=65	77 (48.1)	86 (50.9)	163 (49.5)
n	160	169	329
Mean (SD)	62.6 (9.06)	64.0 (9.04)	63.3 (9.07)
Median	64.0	65.0	64.0
Q1, Q3	57.0,70.0	59.0,70.0	58.0,70.0
Min, Max	30.0,79.0	37.0,86.0	30.0,86.0

Race, n (%)			
American Indian Or Alaska Native	1 (0.6)	4 (2.4)	5 (1.5)
Asian	34 (21.3)	32 (18.9)	66 (20.1)
Black Or African American	6 (3.8)	4 (2.4)	10 (3.0)
Multiple	1 (0.6)	6 (3.6)	7 (2.1)
American Indian Or Alaska Native Black Or African American	0 (0.0)	1 (0.6)	1 (0.3)
American Indian Or Alaska Native White	1 (0.6)	3 (1.8)	4 (1.2)
Black Or African American White	0 (0.0)	2 (1.2)	2 (0.6)
Native Hawaiian Or Other Pacific Islander	1 (0.6)	0 (0.0)	1 (0.3)
White	103 (64.4)	100 (59.2)	203 (61.7)
Missing	14 (8.8)	23 (13.6)	37 (11.2)
Ethnicity, n (%)			
Hispanic Or Latino	19 (11.9)	28 (16.6)	47 (14.3)
Not Hispanic Or Latino	123 (76.9)	114 (67.5)	237 (72.0)
Not Reported	16 (10.0)	21 (12.4)	37 (11.2)
Unknown	2 (1.3)	6 (3.6)	8 (2.4)
Age (Years) Group, n (%)			
<75	151 (94.4)	151 (89.3)	302 (91.8)
>=75	9 (5.6)	18 (10.7)	27 (8.2)
Age (Years), n (%)			
<65	83 (51.9)	83 (49.1)	166 (50.5)
65 - 74	68 (42.5)	68 (40.2)	136 (41.3)
75 - 84	9 (5.6)	17 (10.1)	26 (7.9)
85+	0 (0.0)	1 (0.6)	1 (0.3)
Age (Years) at Initial Diagnosis, n (%)			
<65	99 (61.9)	99 (58.6)	198 (60.2)
>=65	61 (38.1)	70 (41.4)	131 (39.8)
Age (Years) at Initial Diagnosis			

n	160	169	329
Mean (SD)	60.8 (9.30)	62.3 (9.10)	61.6 (9.21)
Median	62.4	63.3	63.0
Q1, Q3	55.8,67.2	57.0,68.1	56.1,67.7
Min, Max	29.8,78.8	35.0,84.0	29.8,84.0
Region, n (%)[a]			
Region 1	93 (58.1)	98 (58.0)	191 (58.1)
Region 2	67 (41.9)	71 (42.0)	138 (41.9)
MMR Status, n (%)			
pMMR	160 (100.0)	169 (100.0)	329 (100.0)
dMMR	0 (0.0)	0 (0.0)	0 (0.0)
ECOG, n (%)			
0	95 (59.4)	94 (55.6)	189 (57.4)
1	65 (40.6)	75 (44.4)	140 (42.6)
3	0 (0.0)	0 (0.0)	0 (0.0)
Prior History of Pelvic Radiation, n (%)			
Yes	59 (36.9)	72 (42.6)	131 (39.8)
No	101 (63.1)	97 (57.4)	198 (60.2)
Elapsed Time (Years) from Initial Diagnosis			
n	160	169	329
Mean (SD)	2.2 (2.83)	2.2 (1.88)	2.2 (2.39)
Median	1.2	1.5	1.3
Q1, Q3	0.8,2.6	0.9,2.8	0.8,2.7
Min, Max	0.3,21.3	0.4,10.9	0.3,21.3
Histology Initial Diagnosis, n (%)			
Clear Cell Carcinoma	16 (10.0)	9 (5.3)	25 (7.6)
Endometrioid Carcinoma	23 (14.4)	30 (17.8)	53 (16.1)

Endometrioid Carcinoma With Squamous Differentiation	4 (2.5)	4 (2.4)	8 (2.4)
High Grade Endometrioid Carcinoma	35 (21.9)	38 (22.5)	73 (22.2)
High Grade Mucinous Carcinoma	0 (0.0)	0 (0.0)	0 (0.0)
High Grade Serous	28 (17.5)	27 (16.0)	55 (16.7)
Low Grade Endometrioid Carcinoma	23 (14.4)	18 (10.7)	41 (12.5)
Low Grade Mucinous Carcinoma	1 (0.6)	0 (0.0)	1 (0.3)
Mixed	9 (5.6)	7 (4.1)	16 (4.9)
Neuroendocrine	2 (1.3)	0 (0.0)	2 (0.6)
Serous Carcinoma	15 (9.4)	28 (16.6)	43 (13.1)
Unclassified	0 (0.0)	2 (1.2)	2 (0.6)
Undifferentiated Histology	3 (1.9)	2 (1.2)	5 (1.5)
Other	1 (0.6)	4 (2.4)	5 (1.5)
FIGO Stage at Initial Diagnosis, n (%)			
I	3 (1.9)	2 (1.2)	5 (1.5)
IA	22 (13.8)	21 (12.4)	43 (13.1)
IB	16 (10.0)	22 (13.0)	38 (11.6)
II	8 (5.0)	11 (6.5)	19 (5.8)
III	3 (1.9)	4 (2.4)	7 (2.1)
IIIA	7 (4.4)	16 (9.5)	23 (7.0)
IIIB	6 (3.8)	2 (1.2)	8 (2.4)
IIIC	8 (5.0)	11 (6.5)	19 (5.8)
IIIC1	7 (4.4)	10 (5.9)	17 (5.2)
IIIC2	8 (5.0)	13 (7.7)	21 (6.4)
IV	13 (8.1)	13 (7.7)	26 (7.9)
IVA	2 (1.3)	2 (1.2)	4 (1.2)
IVB	57 (35.6)	42 (24.9)	99 (30.1)
Brain - Primary Lesion or Metastasis at Study Enrollment[c], n (%)			
Yes	1 (0.6)	1 (0.6)	2 (0.6)

No	159 (99.4)	168 (99.4)	327 (99.4)
Bone - Primary Lesion or Metastasis at Study Enrollment[c], n (%)			
Yes	18 (11.3)	17 (10.1)	35 (10.6)
No	142 (88.8)	152 (89.9)	294 (89.4)
Liver - Primary Lesion or Metastasis at Study Enrollments[c], n (%)			
Yes	48 (30.0)	52 (30.8)	100 (30.4)
No	112 (70.0)	117 (69.2)	229 (69.6)
Lung - Primary Lesion or Metastasis at Study Enrollments[c], n (%)			
Yes	62 (38.8)	63 (37.3)	125 (38.0)
No	98 (61.3)	106 (62.7)	204 (62.0)
Intra-abdominal - Primary Lesion or Metastasis at Study Enrollments[b] [c], n (%)			
Yes	82 (51.3)	80 (47.3)	162 (49.2)
No	78 (48.8)	89 (52.7)	167 (50.8)
Lymph node - Primary Lesion or Metastasis at Study Enrollments [c], n (%)			
Yes	101 (63.1)	104 (61.5)	205 (62.3)
No	59 (36.9)	65 (38.5)	124 (37.7)
Brain - Primary Lesion or Metastasis at Initial Diagnosis[c], n (%)			
Yes	0 (0.0)	0 (0.0)	0 (0.0)
No	160 (100.0)	169 (100.0)	329 (100.0)
Bone - Primary Lesion or Metastasis at Initial Diagnosis[c], n (%)			
Yes	8 (5.0)	4 (2.4)	12 (3.6)
No	152 (95.0)	165 (97.6)	317 (96.4)
Liver - Primary Lesion or Metastasis at Initial Diagnosis[c], n (%)			
Yes	8 (5.0)	6 (3.6)	14 (4.3)
No	152 (95.0)	163 (96.4)	315 (95.7)
Lung - Primary Lesion or Metastasis at Initial Diagnosis[c], n (%)			
Yes	18 (11.3)	8 (4.7)	26 (7.9)
No	142 (88.8)	161 (95.3)	303 (92.1)

Intra-abdominal - Primary Lesion or Metastasis at Initial Diagnosis[b] [c], n (%)			
Yes	51 (31.9)	43 (25.4)	94 (28.6)
No	109 (68.1)	126 (74.6)	235 (71.4)
Lymph node - Primary Lesion or Metastasis at Initial Diagnosis[c], n (%)			
Yes	59 (36.9)	59 (34.9)	118 (35.9)
No	101 (63.1)	110 (65.1)	211 (64.1)
Baseline Weight (kg)			
n	160	169	329
Mean (SD)	70.6 (17.74)	68.0 (17.30)	69.3 (17.54)
Median	67.7	64.0	66.0
Q1, Q3	58.0,79.9	55.1,78.3	56.0,79.0
Min, Max	36.1,127.8	41.0,130.3	36.1,130.3
BSA (m^2)			
n	159	160	319
Mean (SD)	1.8 (0.25)	1.7 (0.22)	1.7 (0.24)
Median	1.7	1.7	1.7
Q1, Q3	1.6,1.9	1.5,1.9	1.6,1.9
Min, Max	1.3,3.0	1.3,2.4	1.3,3.0

Notes:

Data cutoff date March 2022

a: Region 1: Europe, USA, Canada, Australia, New Zealand, Isreal; Region 2: Rest of World

b: Includes reported locations of colon, abdominal cavity, omentum, small intestine, peritoneal cavity, and peritoneum. Does not include lymph nodes or other organs.

c: Lesion location as determined by investigator review.

Appendix B. Efficacy results per study

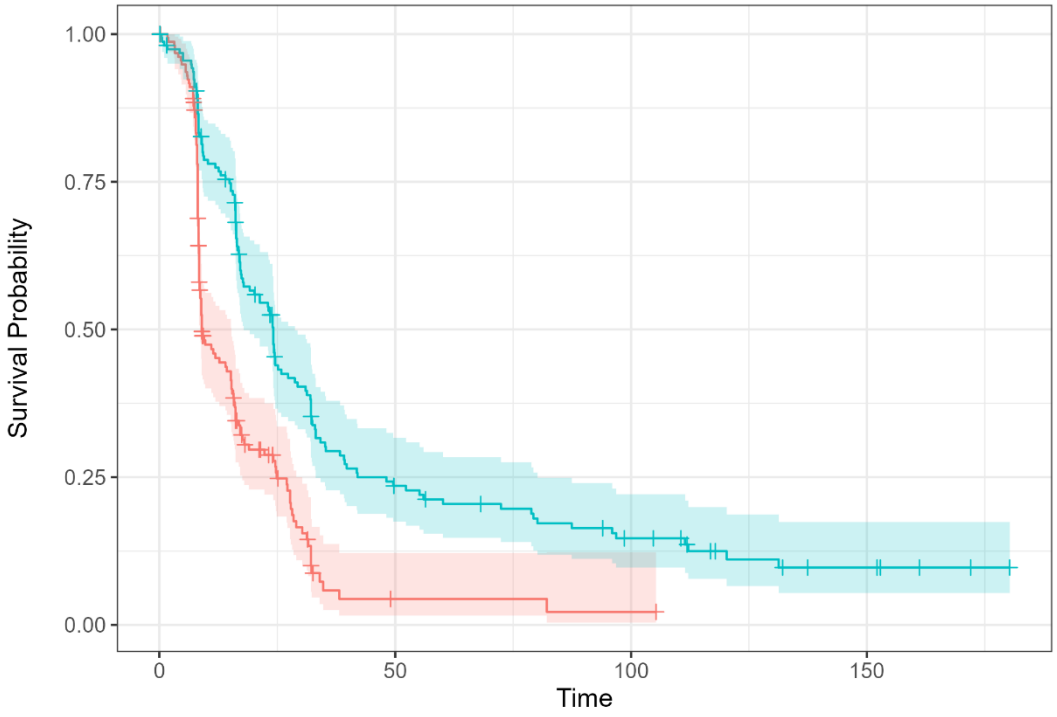
Results per study

Table 57 Results per study

Results of Study 302/KN-755 (NCT03517449)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
PFS (pre-assigned to DOX, PFI < 6 months population, pMMR status)	LEN+PEM	160	24.1 weeks [17.6; 28.7]	15.1	NA	NA	HR: 0.458	[0.352; 0.595]	< 0.001	Based on Cox regression model with treatment as a covariate	Post hoc analysis
	TPC	169	9 weeks [8.57;17.9]								
OS (pre-assigned to DOX, PFI < 6 months population, pMMR status)	LEN+PEM	160	64.57 [50.1; 80.6]	28.57	NA	NA	HR: 0.518	[0.406; 0.660]	< 0.001	Based on Cox regression model with treatment as a covariate	Post hoc analysis
	TPC	169	36 [28.4; 45.6]								

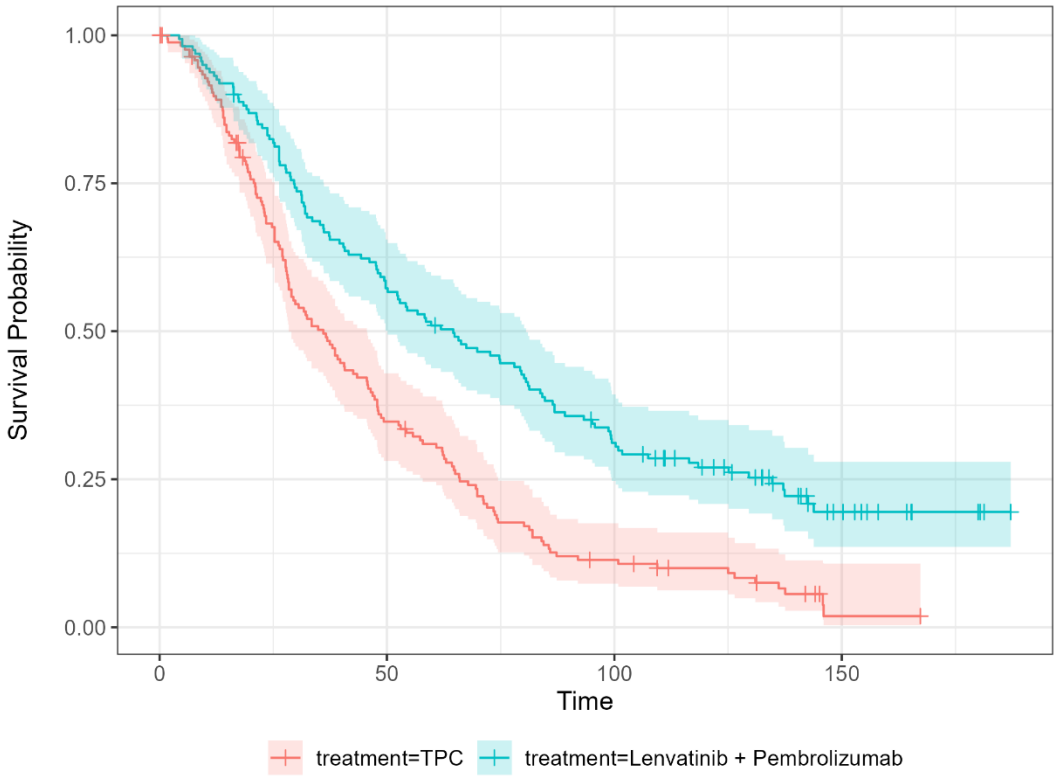
Abbreviations: CI, Confidence interval; HR, Hazard Ratio; LEN, Lenvatinib; pMMR, proficient Missmatch repair; NA, Not applicable; OS, Overall survival; PEM, Pembrolizumab; PFI, Platinum-free interval; PFS, progression free

Figure 19 Kaplan-Meier plot of PFS for the pre-assigned to DOX, PFI < 6 months, pMMR status population



treatment=TPC				
At Risk	169	2	1	0
Events	0	125	126	126
treatment=Lenvatinib + Pembrolizumab				
At Risk	160	31	16	5
Events	0	112	123	127

Figure 20 Kaplan-Meier plot of PFS for the pre-assigned to DOX, PFI < 6 months, pMMR status population



treatment=TPC				
At Risk	169	56	17	1
Events	0	106	143	152
treatment=Lenvatinib + Pembrolizumab				
At Risk	160	91	48	12
Events	0	68	109	122

Appendix C. Comparative analysis of efficacy

PLD is considered the most relevant comparator to LEN+PEM. Based on the DMC's previous assessment report (59), the population and comparators of interest are based on PFI: If the patient has a platinum-free interval of less than 6 months PLD is the most appropriate comparator

For doxorubicin therapy, three RCTs were identified, including Study 309 / KN-775(1, 54, 66, 67 , 68), and one single arm study (72), whilst three single arm studies and one RWE study were identified for PLD in a relevant patient population (69, 71, 73, 91). A comparison with DOX may be obtained directly from the individual patient level data from in the TPC group of Study 309 / KN-775. In addition, connecting the RCT studies with Study 309 / KN-775 via DOX to form a network for traditional network meta-analysis would not yield additional comparisons of interest for the submission. A treatment comparison between LEN+PEM and PLD was not possible: The three single arm studies did not report KM curves for the survival outcomes of interest, at best only reporting median survival, with no associated variance (69-71). Indirect comparison with the RWE study was also not considered appropriate (Julius 2013 (73)). A comparison between LEN+PEM and PLD would have to be unanchored (no common comparator across studies), and for such analyses, it is widely recommended that all prognostic factors and effect modifying factors are adjusted for. However, this would not be possible from the Julius 2013 dataset as insufficient characteristics are reported and thus any comparison could be significantly biased, with no data to indicate the likely direction of bias.

Table 58 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Example: median OS	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA	NA	NA
Insert outcome 4	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table 59 Relevant studies for DOX and PLD

Intervention	RCTs, author year	Non-RCTs, author year
DOX	Subgroup of TPC treatment group, Study 309 / KN-775(1, 54) McMeekin 2015 (66) Miller 2018 ZoptEC (67 , 68)	Di Legge 2011 (72)

PLD	NA	Angioli et al., 2007 (71) Homesley 2005 (69) Julius, 2013 (73) Muggia 2002 (70)

Appendix D. Extrapolation

D.1 Extrapolation of overall survival

D.1.1 Data input

OS was based on Study 309/KN-755 and was extrapolated beyond the follow-up of the study to assess the cost-effectiveness of LEN+PEM vs TPC over a lifetime horizon.

D.1.2 Model

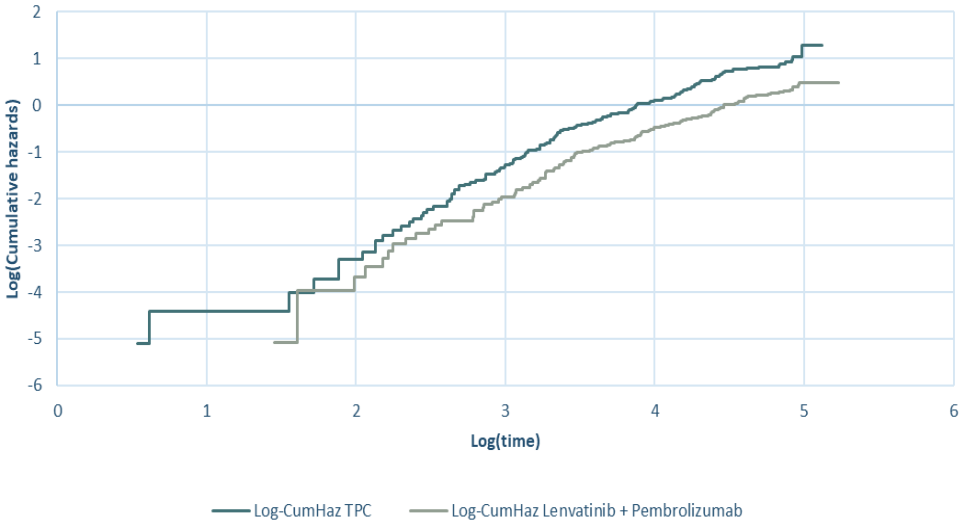
Standard parametric models were used to extrapolate OS from Study 309/KN-755 data, the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma

D.1.3 Proportional hazards

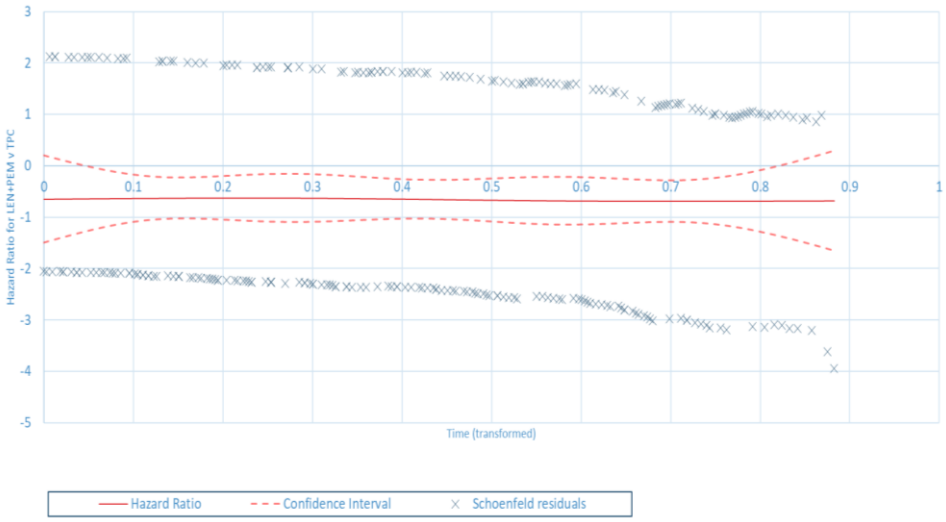
To assess proportional hazards (PH) two plots are presented, see cumulative hazards in Figure 21 and Schoenfeld residuals plot in Figure 22. From the figures, PH was not violated and we fitted dependent curves for OS.

Figure 21 Log cumulative hazard over log time for LEN+PEM and TPC for OS



Abbreviations: TPC, treatment of physician choice; CumHaz, cumulative hazard

Figure 22 Schoenfeld residuals plot for overall survival



D.1.4 Evaluation of statistical fit (AIC and BIC) - dependent

Distribution	AIC	BIC
Exponential	2856.7	2864.3
Weibull	2842.3	2853.7
Gompertz	2856.9	2868.3
Log-normal	2825.8	2837.2
Log-logistic	2826.2	2837.6
Generalized gamma	2826.3	2841.5
Gamma	2835.8	2847.2

D.1.5 LEN+PEM Evaluation of statistical fit (AIC and BIC) – independent fits

Distribution	AIC	BIC
Exponential	1357.4	1360.4
Weibull	1355.8	1362.0
Gompertz	1359.3	1365.5
Log-normal	1344.5	1350.6
Log-logistic	1346.5	1352.6
Generalized gamma	1346.3	1355.6
Gamma	1353.6	1359.8

D.1.6 TPC Evaluation of statistical fit (AIC and BIC) – independent fits

Distribution	AIC	BIC
Exponential	1499.4	1502.5
Weibull	1487.4	1493.7
Gompertz	1498.2	1504.4
Log-normal	1479.1	1485.4
Log-logistic	1477.2	1483.4
Generalized gamma	1479.0	1488.4
Gamma	1482.5	1488.8

D.1.7 Evaluation of visual fit

Figure 23 Extrapolation of OS LEN+PEM dependent models

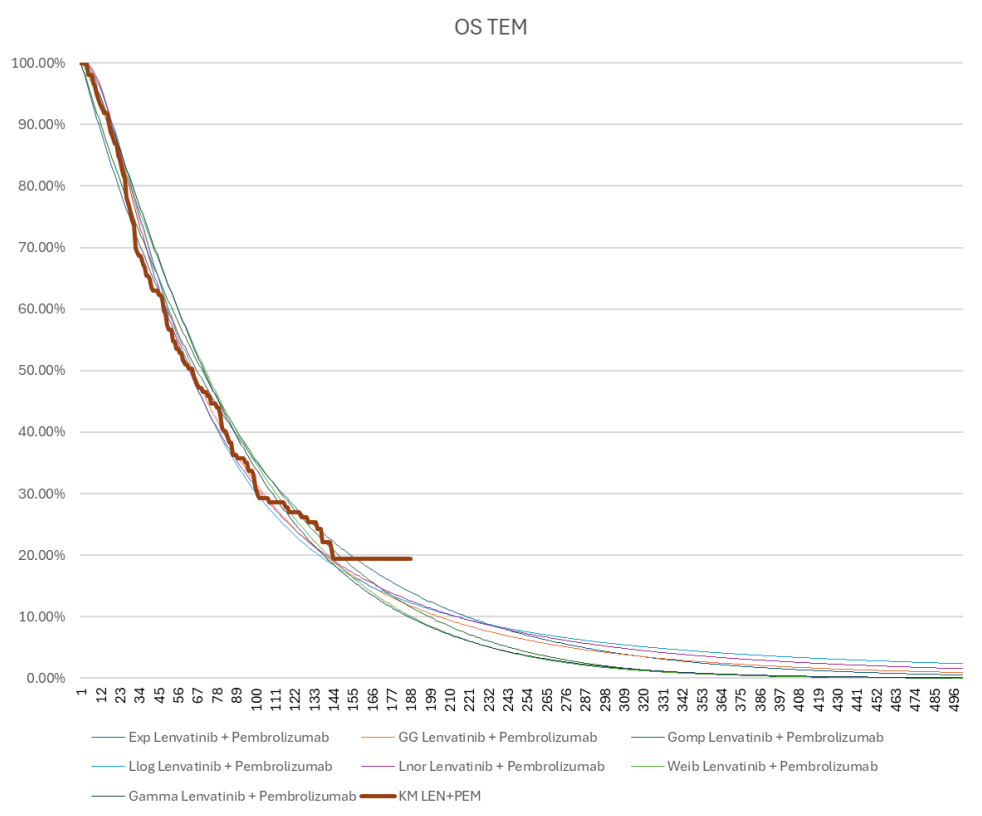
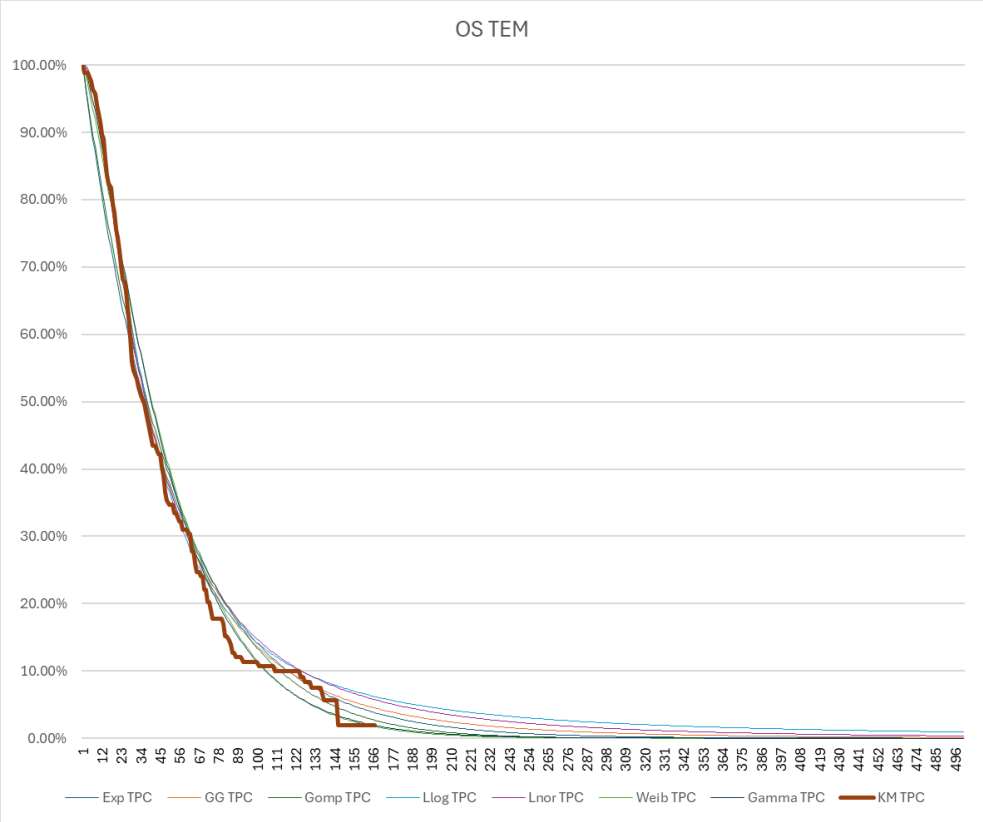


Figure 24 Extrapolation of OS TPC dependent models



D.1.8 Evaluation of hazard functions

Figure 25 Hazard profiles LEN+PEM OS – Dependent models

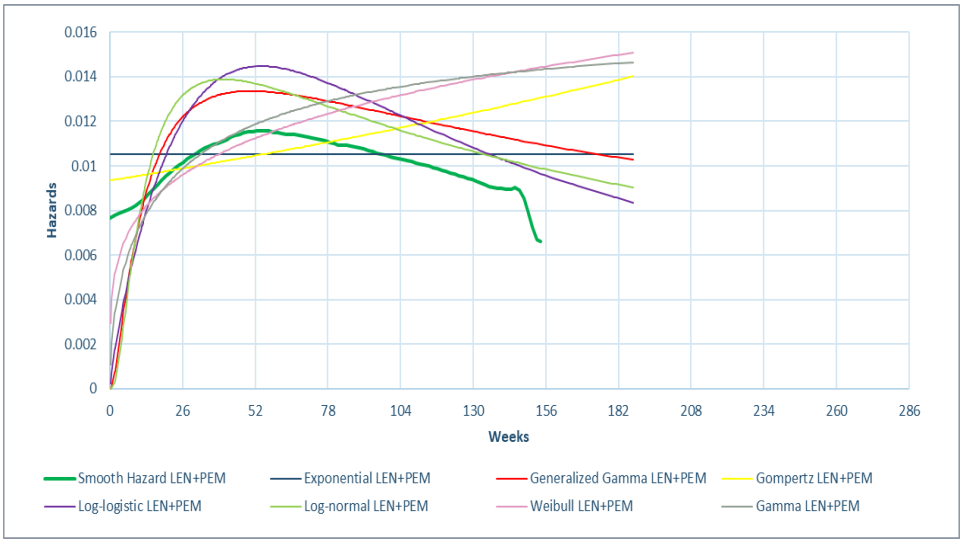


Figure 26 Hazard profiles TPC OS - Dependent models

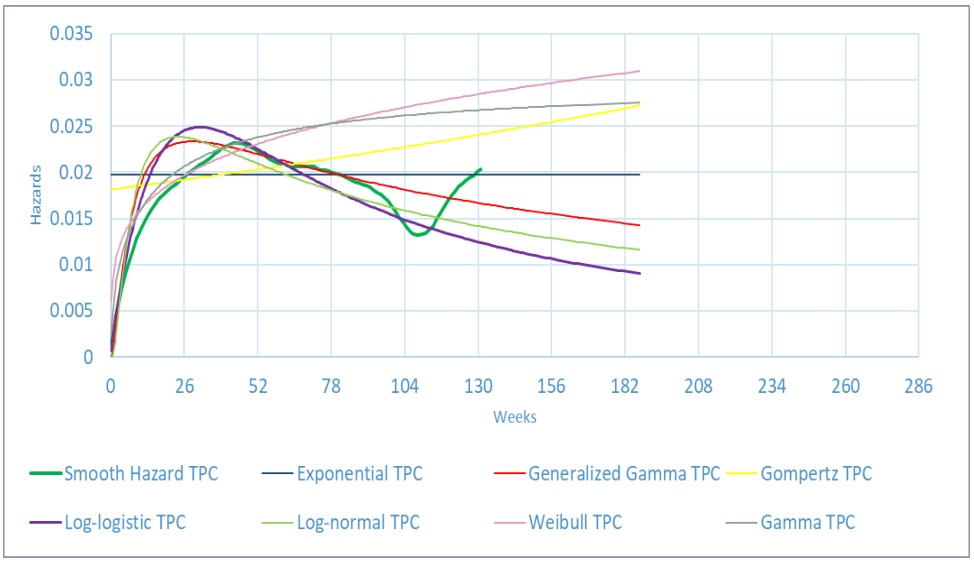


Figure 27 Hazard profiles LEN+PEM OS - Independent models

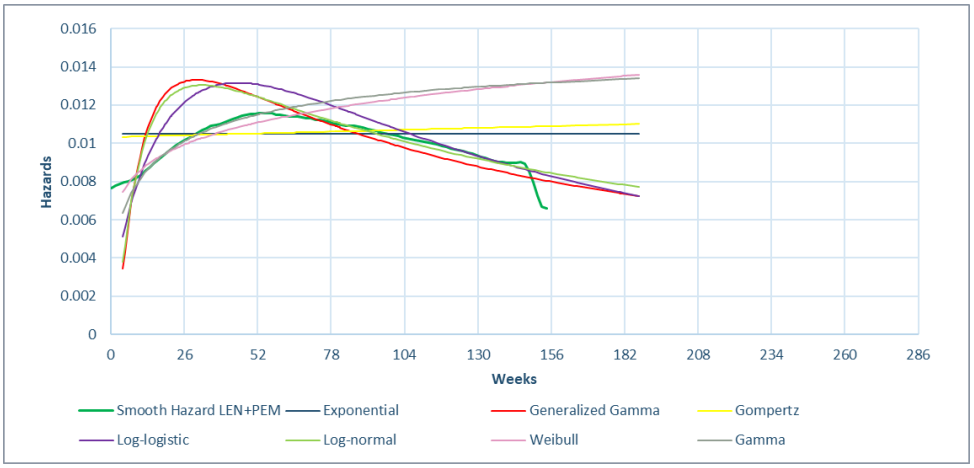
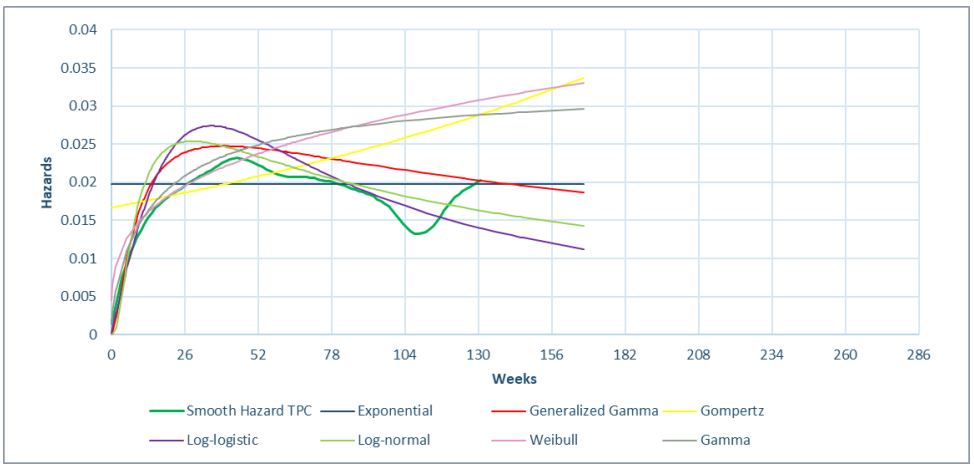


Figure 28 Hazard profiles TPC OS - Independent models



D.1.9 Validation and discussion of extrapolated curves

Evaluation of the hazards for LEN+PEM demonstrated an increasing and then decreasing hazard which matched the Hazard profile of the log logistic distribution.

For TPC a similar trend is observed with the respective dependent extrapolation of the log normal distribution providing an overall good fit. The dependent lognormal model was selected for LEN+PEM and for TPC due to the overall best fit.

D.1.10 Adjustment of background mortality

Yes, based on Danish life tables

D.1.11 Adjustment for treatment switching/cross-over

NA

D.1.12 Waning effect

No waning in the base case, assumed continuation of hazards

D.1.13 Cure-point

No cure point.

D.2 Extrapolation of progression free survival

D.2.1 Data input

PFS was based on Study 309/KN-755 and was extrapolated beyond the follow-up of the study to assess the cost-effectiveness of LEN+PEM vs TPC over a lifetime horizon.

D.2.2 Model

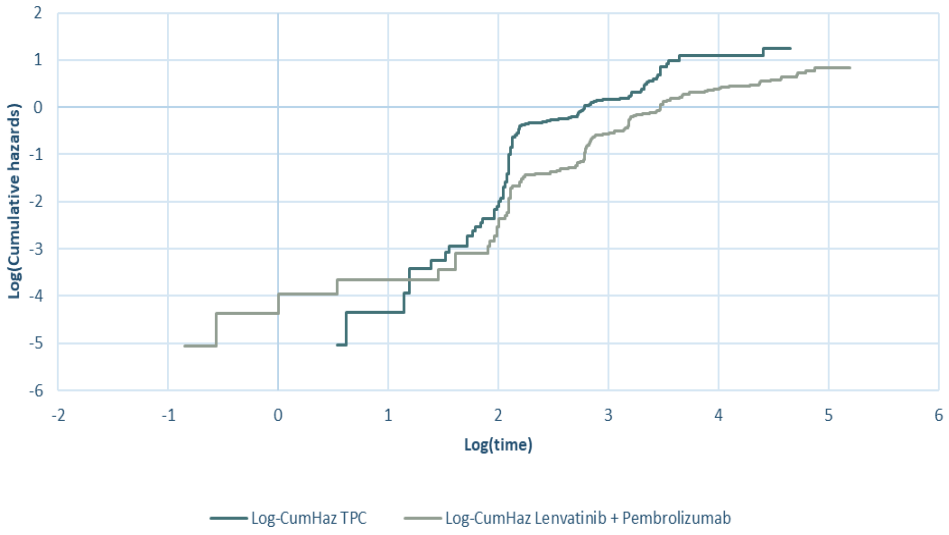
Standard parametric models were used to extrapolate PFS from Study 309/KN-755 data, the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma

D.2.3 Proportional hazards

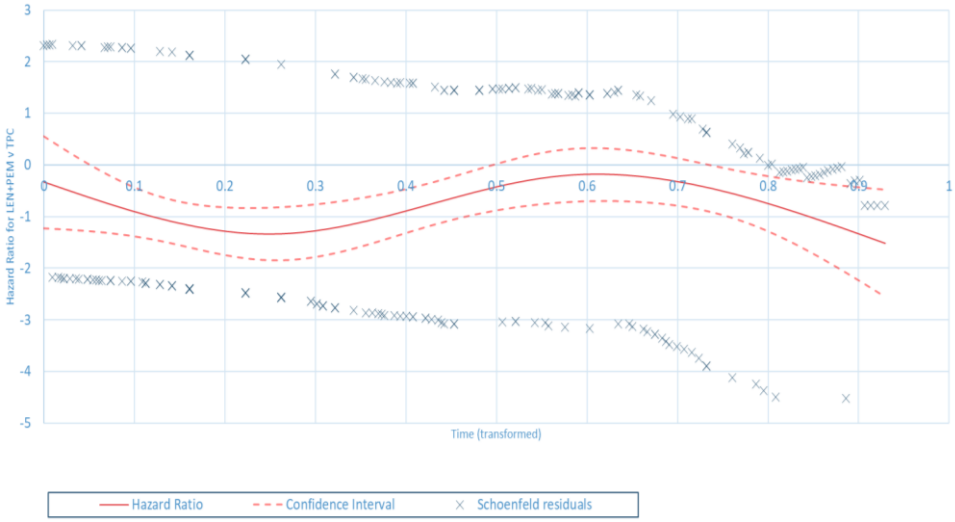
To assess proportional hazards two plots are presented, see cumulative hazards in Figure 29 and Schoenfeld residuals plot in Figure 30. From the figures PH was not violated and we fitted dependent curves for PFS.

Figure 29 Log cumulative hazard over log time for LEN+PEM and Soc for PFS



Abbreviations: TPC, treatment of physician choice; CumHaz, cumulative hazard

Figure 30 Schoenfeld residuals plot for PFS



D.2.4 Evaluation of statistical fit (AIC and BIC)

Distribution	AIC	BIC
Exponential	2206.3	2213.9
Weibull	2204.0	2215.4
Gompertz	2197.3	2208.7
Log-normal	2156.0	2167.4
Log-logistic	2137.8	2149.2
Generalized gamma	NA*	NA*
Gamma	2195.2	2206.6

D.2.5 LEN+PEM Evaluation of statistical fit (AIC and BIC) – independent fits

Distribution	AIC	BIC
Exponential	1220.6	1223.7
Weibull	1221.7	1227.9
Gompertz	1207.9	1214.0
Log-normal	1200.4	1206.5
Log-logistic	1192.0	1198.2
Generalized gamma	1202.3	1211.6
Gamma	1222.6	1228.7

D.2.6 TPC Evaluation of statistical fit (AIC and BIC) – independent fits

Distribution	AIC	BIC
Exponential	985.7	988.8

Weibull	970.0	976.3
Gompertz	987.4	993.7
Log-normal	930.8	937.0
Log-logistic	930.8	937.1
Generalized gamma	927.8	937.1
Gamma	956.1	962.4

D.2.7 Evaluation of visual fit

Figure 31 Extrapolation of PFS LEN+PEM dependent models

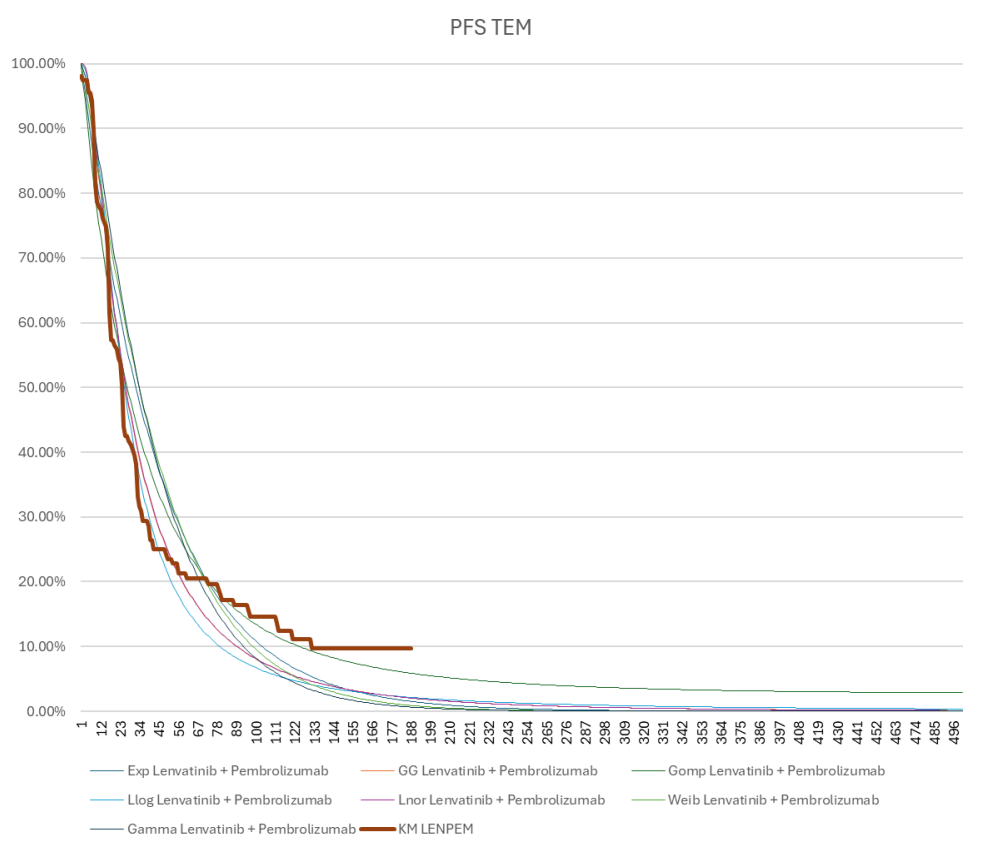
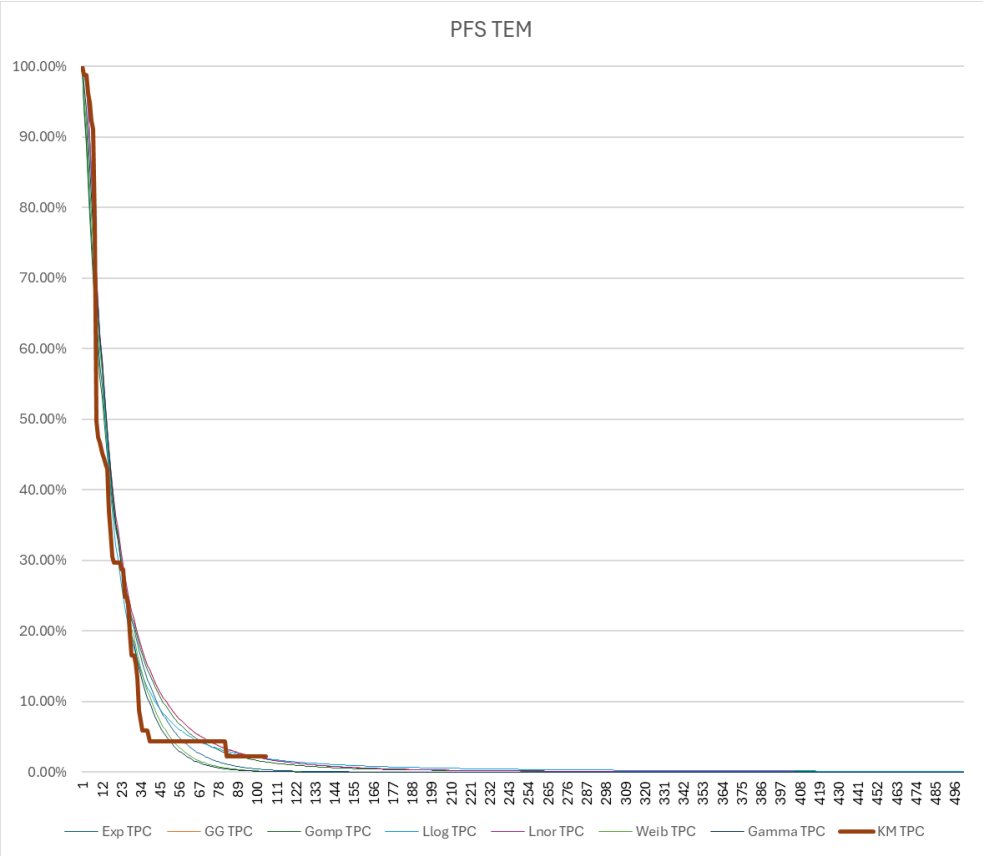


Figure 32 Extrapolation of PFS TPC dependent models



D.2.8 Evaluation of hazard functions

Figure 33 Hazard profiles LEN+PEM PFS

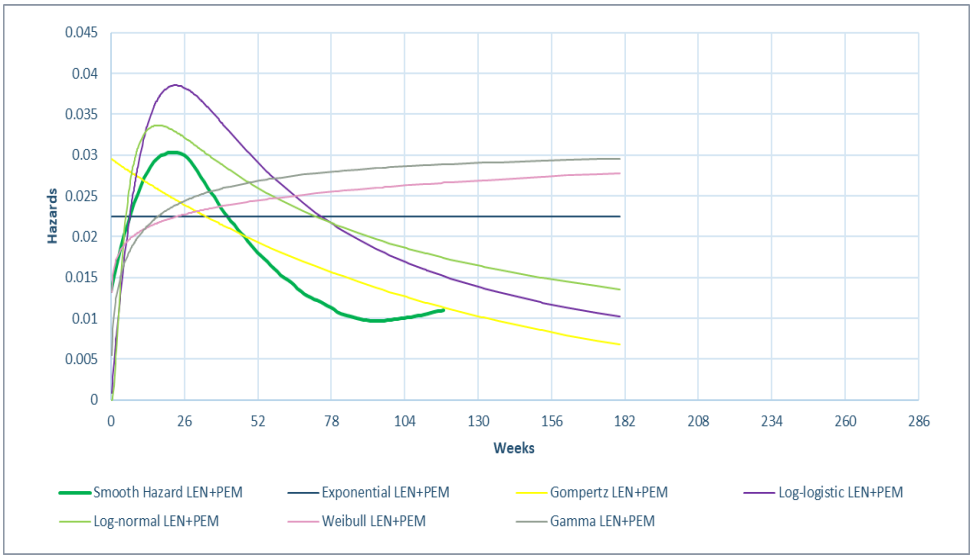


Figure 34 Hazard profiles TPC PFS

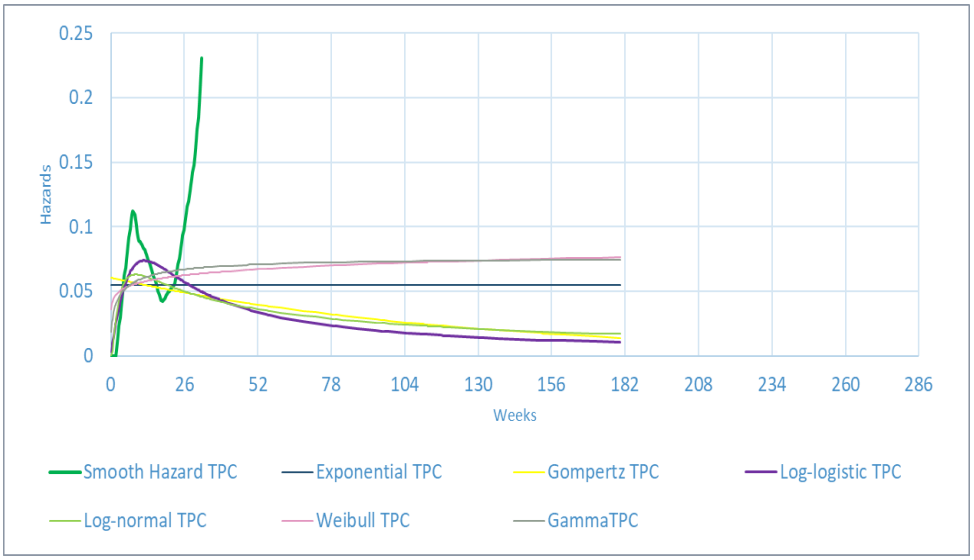


Figure 35 Hazard profiles LEN+PEM PFS - Independent models

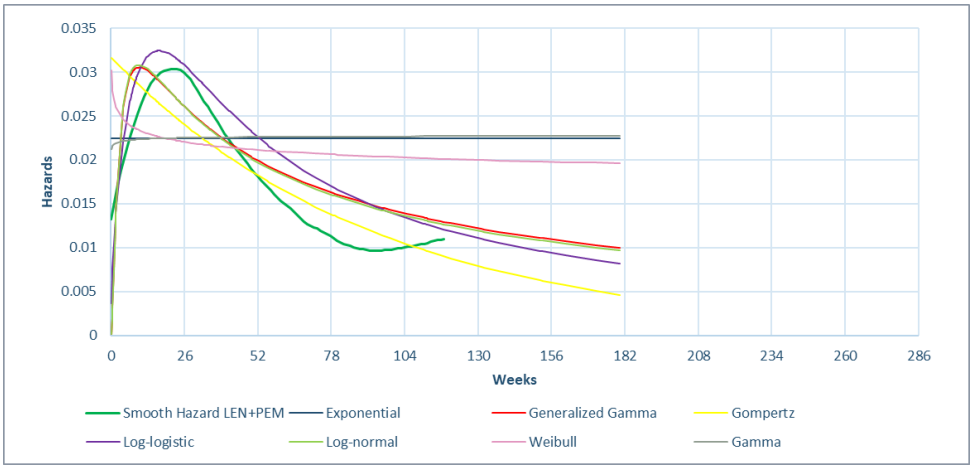
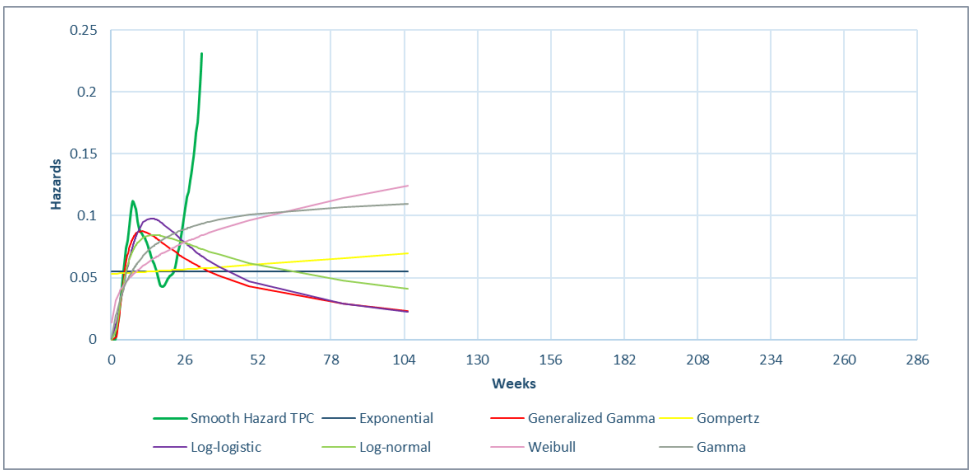


Figure 36 Hazard profiles TPC PFS - Independent models



D.2.9 Validation and discussion of extrapolated curves

Evaluation of the hazards for LEN+PEM demonstrated an increasing and then decreasing hazard which matched the Hazard profile of the log logistic distribution.

For TPC a similar trend is observed with the respective dependent extrapolation of the log logistic distribution providing an overall good fit. The dependent loglogistic model was selected for LEN+PEM and for TPC due to the overall best fit.

D.2.10 Adjustment of background mortality

Yes, based on Danish life tables

D.2.11 Adjustment for treatment switching/cross-over

NA

D.2.12 Waning effect

No waning in the base case, assumed continuation of hazards

D.2.13 Cure-point

No cure point.

D.3 Extrapolation of time on treatment

D.3.1 Data input

ToT was based on Study 309/KN-755 and was extrapolated beyond the follow-up of the study to assess the cost-effectiveness of LEN+PEM vs TPC over a lifetime horizon. Extrapolation of ToT was carried out separately for LEN, PEM, and TPC.

D.3.2 Model

Standard parametric models were used to extrapolate ToT from Study 309/KN-755 data, the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma

D.3.3 Proportional hazards

NA. Since treatments were modelled separately no assessment of proportional hazards was needed.

D.3.4 Evaluation of statistical fit (AIC and BIC)

Table 60 AIC and BIC for independent fits of LEN ToT

Distribution	AIC	BIC
Exponential	1386.5	1389.6
Weibull	1382.3	1388.4
Gompertz	**1373.6**	**1379.8**
Log-normal	1390.7	1396.8
Log-logistic	1378.0	1384.1
Generalized gamma	1381.4	1390.7
Gamma	1384.4	1390.6

Table 61 AIC and BIC for independent fits of PEM ToT

Distribution	AIC	BIC
Exponential	1470.1	1473.2
Weibull	1472.1	1478.3
Gompertz	1468.9	1475.0
Log-normal	1541.2	1547.3
Log-logistic	1510.0	1516.1
Generalized gamma	**1466.1**	**1475.3**

Gamma	1471.8	1477.9

Table 62 AIC and BIC for independent fits of TPC ToT

Distribution	AIC	BIC
Exponential	1087.7	1090.8
Weibull	1078.2	1084.3
Gompertz	1058.0	1064.1
Log-normal	1160.0	1166.2
Log-logistic	1125.5	1131.6
Generalized gamma	**1047.0**	**1056.3**
Gamma	1085.0	1091.2

D.3.5 Evaluation of visual fit

Figure 37 Extrapolation of ToT LEN

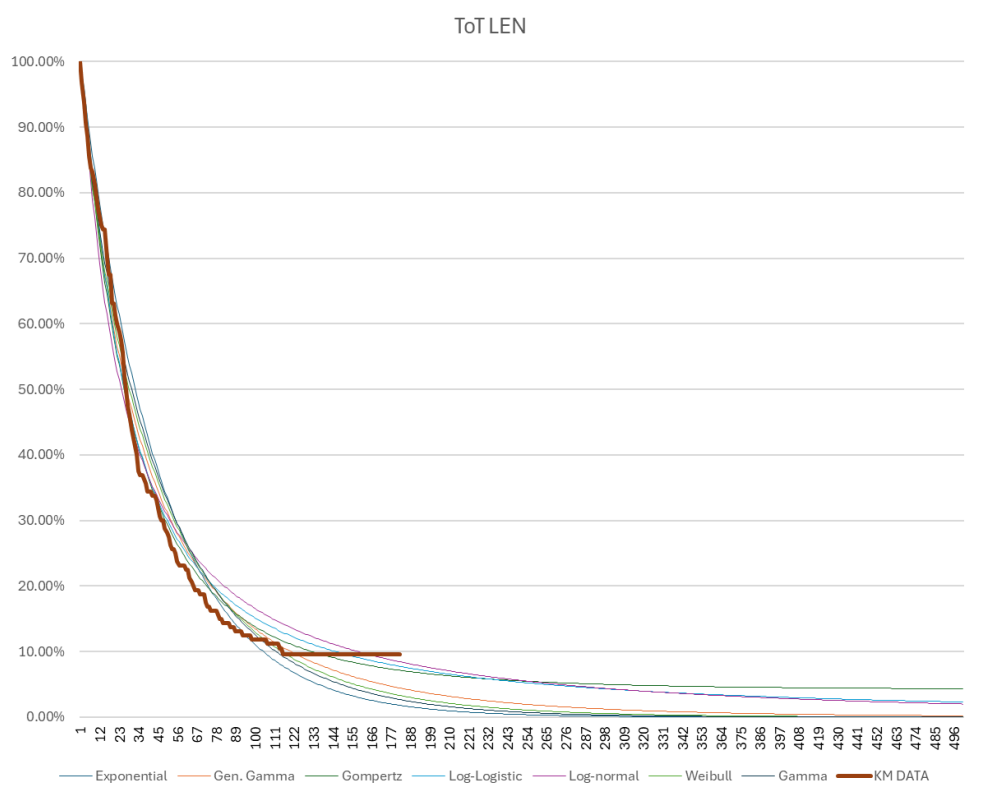


Figure 38 Extrapolation of ToT PEM

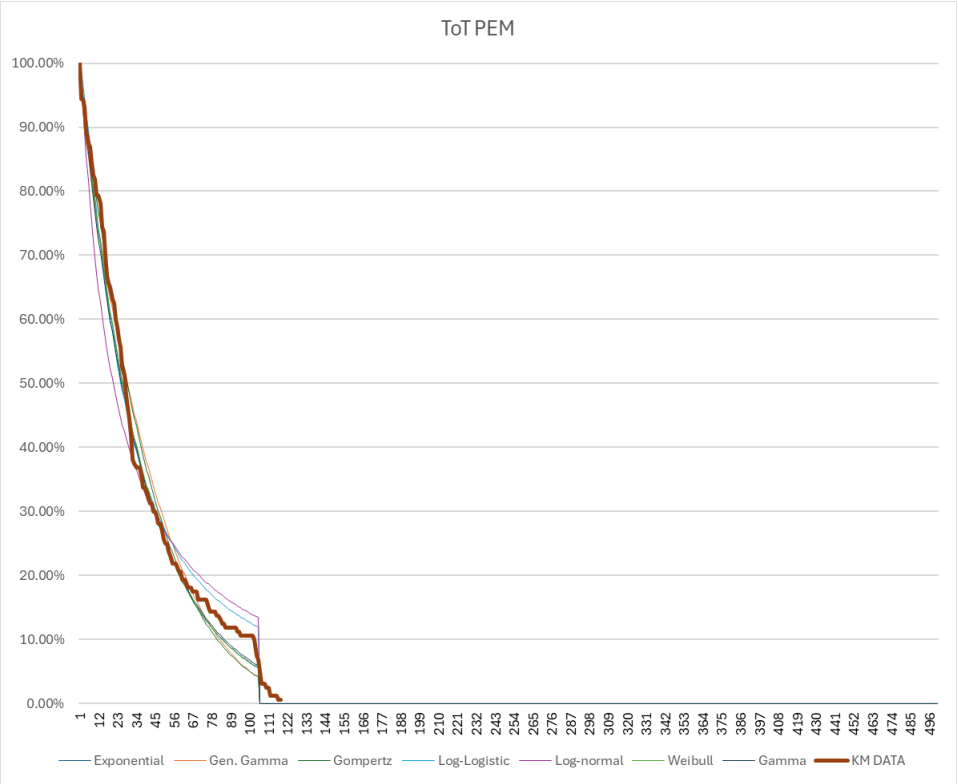
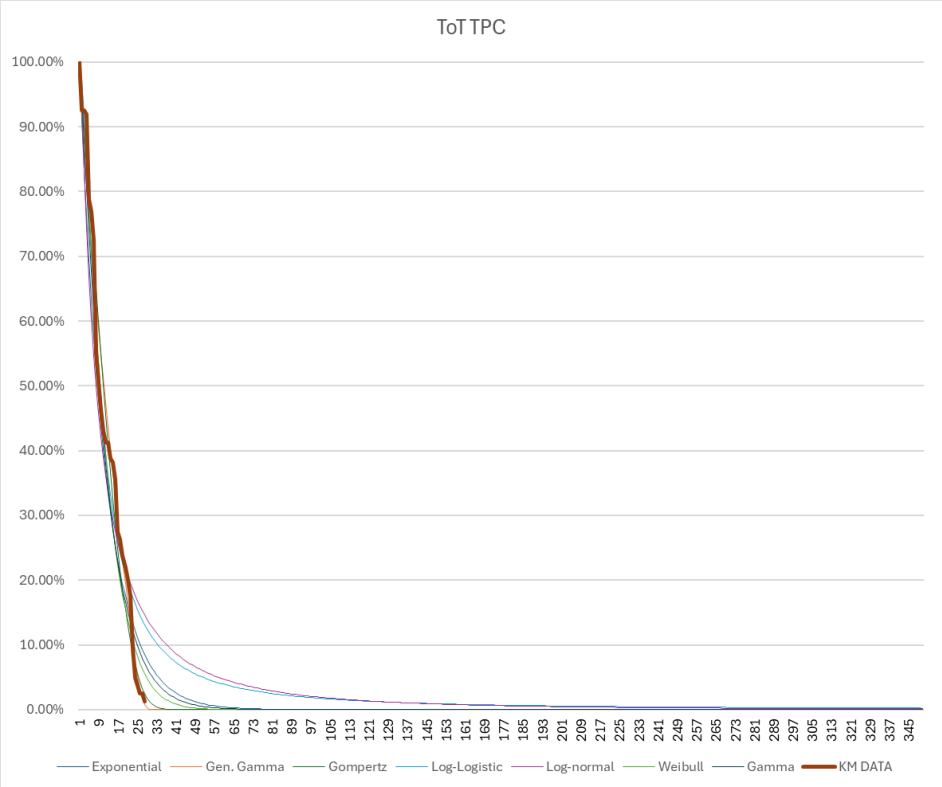
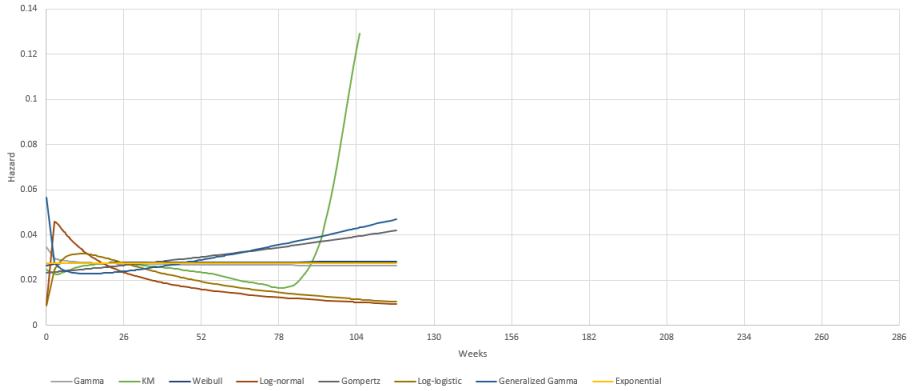


Figure 39 Extrapolation of ToT TPC



D.3.6 Evaluation of hazard functions

Figure 40 Hazard profile LEN



D.3.7 Validation and discussion of extrapolated curves

No hazard profiles for TPC and PEM are presented since these are modelled using complete KM data.

D.3.8 Adjustment of background mortality

Yes, based on Danish life tables

D.3.9 Adjustment for treatment switching/cross-over

NA

D.3.10 Waning effect

No waning in the base case, assumed continuation of hazards

D.3.11 Cure-point

No cure point.

Appendix E. Serious adverse events

NA. All relevant information has been presented in Section 9.

Appendix F. Health-related quality of life

Additional HRQoL for the ITT and pMMR populations is presented in this appendix, specifically the global health status score of the EORTC instrument.

F.1 EORTC QLQ-C30 global health status score (ITT-pMMR population)

Baseline global health score/quality of life scores were similar between the LEN+PEM group and TPC group in the ITT population. Over 12 weeks of follow-up, participants receiving LEN+PEM or TPC had decreases in global health score/quality of life score (Table 63). Within the ITT population, directionally smaller decreases were observed for those receiving LEN+PEM versus TPC: -5.97 (95% CI: -8.36%, -3.58%) versus -6.98 (95% CI: -9.63%, -4.33%), respectively. The between-group difference in least square mean score change from baseline at Week 12 was 1.01 points (95% CI: -2.28%, 4.31%).

Empirical mean change from baseline and 95% CI for EORTC QLQ-C30 global health score/quality of life over time is provided in Figure 41

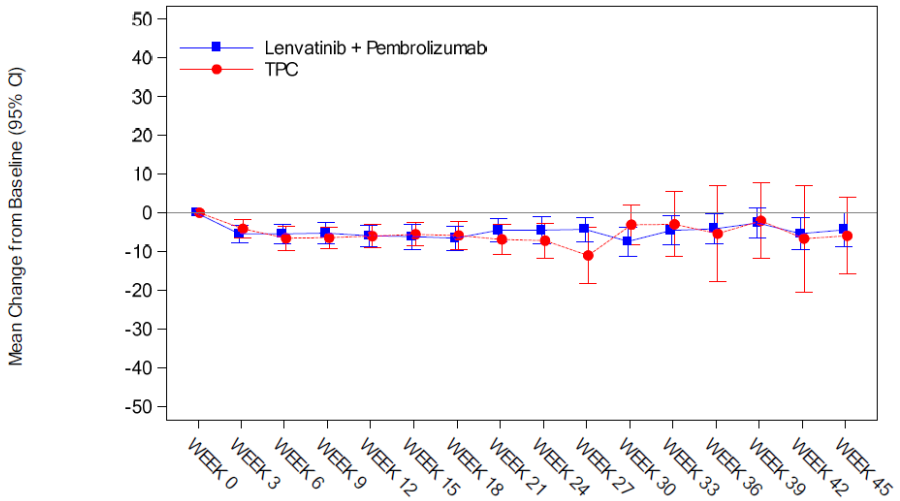
Table 63 Analysis of change from baseline in EORTC QLQ-C30 global health status to week 12; Population ITT[a]

Treatment	Baseline		Week 12		Change from baseline to week 12	
	N	Mean (SD)	N	Mean (SD)	N	Least square mean (95% CI)[b]
LEN+PEM	370	65.74 (21.87)	310	60.56 (21.35)	386	-5.97 (-8.36, -3.58)
TPC	351	65.69 (22.71)	227	62.70 (21.08)	363	-6.98 (-9.63, -4.33)
Pairwise Comparison					**Difference in least square means (95% CI)[b]**	**p-value[b]**
LEN+PEM vs. TPC					1.01 (-2.28, 4.31)	0.5460

b: Based on a cLDA model with the patient reported outcome scores as the response variable with covariates for treatment by study visit interaction, stratification factors MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.
For baseline and Week 12, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

Abbreviations: CI, Confidence Interval; ECOG, Eastern Cooperative Oncology Group; ITT, Intention to treat; LEN, lenvatinib; PEM, pembrolizumab; SD, Standard Deviation; TPC, Treatment of Physician's Choice
Source: Study 309 / KN-775(54)

Figure 41 Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time; Population ITT[a]

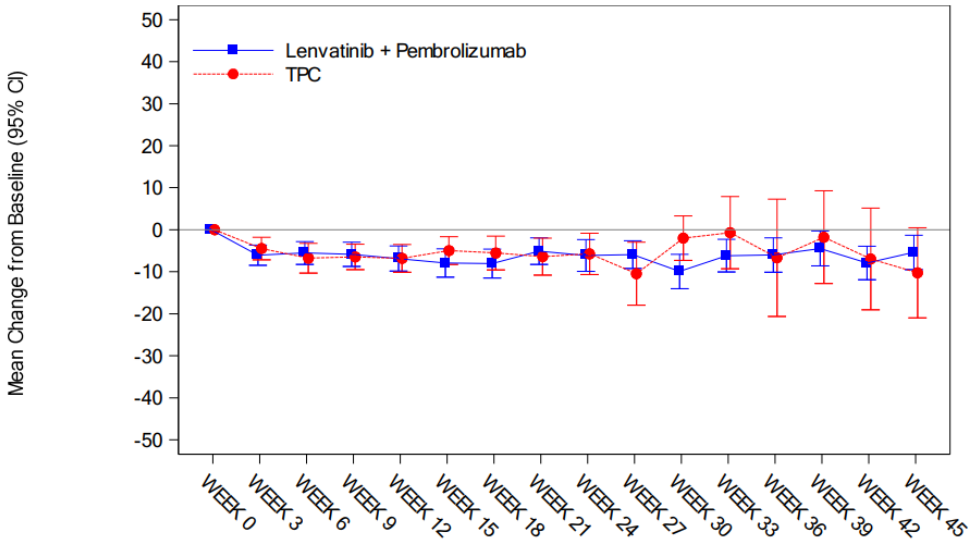


Number of Participants

Lenvatinib + Pembrolizumab	370	341	325	319	298	273	266	247	226	216	208	185	180	169	148	131
TPC	351	317	233	282	221	172	138	132	88	59	27	28	17	16	10	14

Abbreviations: CI, Confidence Interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; ITT, Intention to treat; TPC, Treatment of Physician's Choice
Source: Study 309 / KN-775(54)

Figure 42 Empirical Mean Change from Baseline and 95% CI for the EORTC QLQ-C30 Global Health Status/QoL Over Time; pMMR population



Number of Participants

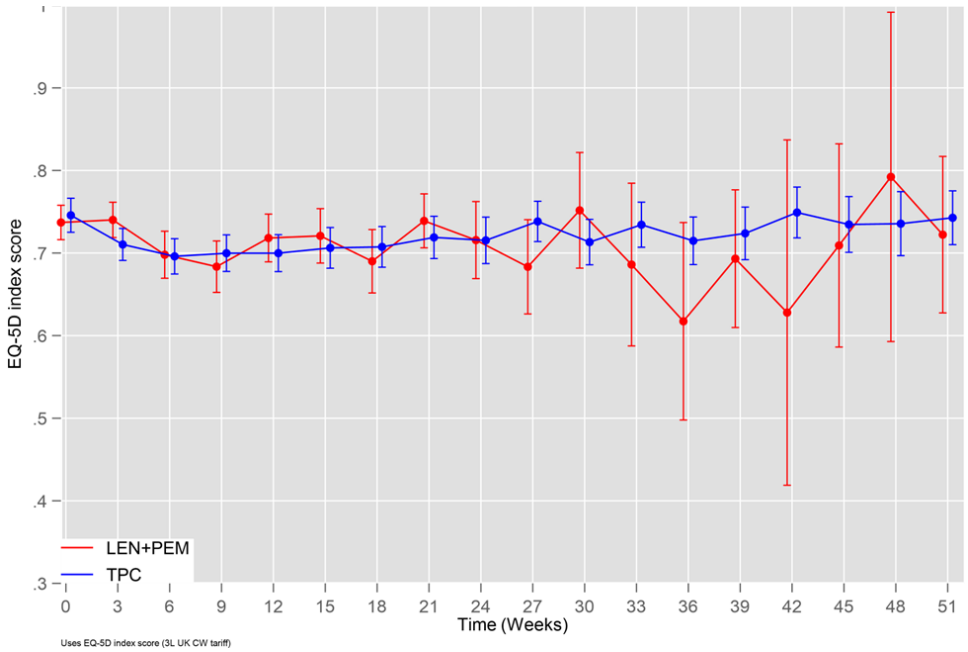
Lenvatinib + Pembrolizumab	316	292	278	268	249	232	226	211	192	175	169	150	146	135	122	116
TPC	298	269	197	238	186	146	119	111	74	51	25	24	15	14	12	13

Abbreviations: CI, Confidence Interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; ITT, Intention to treat; TPC, Treatment of Physician's Choice

Source: Study 309 / KN-775(54)

F.2 EQ-5D index score (ITT)

Figure 43 Empirical mean EQ-5D index score and 95% confidence interval by visit and study arm; ITT population



Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab; TPC, treatment of physician's choice.

Appendix G. Probabilistic sensitivity analyses

Table 64. Overview of parameters in the PSA

Parameter name	Current value	Lower value of parameter	Upper value of parameter	Parameter distribution
Age	63.28875	62.90766	64.154	Normal
Appetite decreased, pMMR, number of events, LEN+PEM	19	16.15	21.85	Normal
Anaemia, pMMR, number of events, LEN+PEM	8	6.8	9.2	Normal
Colitis, pMMR, number of events, LEN+PEM	7	5.95	8.05	Normal
Diarrhoea, pMMR, number of events, LEN+PEM	27	22.95	31.05	Normal
Febrile neutropenia, pMMR, number of events, LEN+PEM	1	0.85	1.15	Normal
Lipase increased, pMMR, number of events, LEN+PEM	23	19.55	26.45	Normal
Neutropenia, pMMR, number of events, LEN+PEM	5	4.25	5.75	Normal
Neutrophil count decreased, pMMR, number of events, LEN+PEM	7	5.95	8.05	Normal
Hypertension, pMMR, number of events, LEN+PEM	172	146.2	197.8	Normal
Transaminases increased, pMMR, number of events, LEN+PEM	1	0.85	1.15	Normal
Weight decreased, pMMR, number of events, LEN+PEM	20	17	23	Normal
White blood cell count decreased, pMMR, number of events, LEN+PEM	3	2.55	3.45	Normal
Anaemia, pMMR, number of events, TPC	43	36.55	49.45	Normal
Diarrhoea, pMMR, number of events, TPC	3	2.55	3.45	Normal
Febrile neutropenia, pMMR, number of events, TPC	18	15.3	20.7	Normal
Leukopenia, pMMR, number of events, TPC	30	25.5	34.5	Normal
Lipase increased, pMMR, number of events, TPC	2	1.7	2.3	Normal
Neutropenia, pMMR, number of events, TPC	112	95.2	128.8	Normal
Neutrophil count decreased, pMMR, number of events, TPC	162	137.7	186.3	Normal
Hypertension, pMMR, number of events, TPC	1	0.85	1.15	Normal

White blood cell count decreased, pMMR, number of events, TPC	73	62.05	83.95	Normal
Appetite decreased, pMMR, average duration per event (days)	96.99 9933 07	36.15035	157.8495	Normal
Anaemia, pMMR, average duration per event (days)	75.21 4297 7	32.73823	117.6904	Normal
Colitis, pMMR, average duration per event (days)	81.49 9452 59	0	570.6934	Normal
Diarrhoea, pMMR, average duration per event (days)	32.13 0705 22	13.39857	50.86284	Normal
Febrile neutropenia, pMMR, average duration per event (days)	4.079 8611 09	3.045107	5.114615	Normal
Leukopenia, pMMR, average duration per event (days)	11.83 3279 93	0	31.48217	Normal
Lipase increased, pMMR, average duration per event (days)	86.71 4055 2	37.63618	135.7919	Normal
Neutropenia, pMMR, average duration per event (days)	24.66 6699 36	5.748843	43.58456	Normal
Neutrophil count decreased, pMMR, average duration per event (days)	17.25 8063 1	9.277811	25.23832	Normal
Hypertension, pMMR, average duration per event (days)	74.77 0773 42	45.75321	103.7883	Normal
Weight decreased, pMMR, average duration per event (days)	272.5 6737 68	126.7096	418.4251	Normal
White blood cell count decreased, pMMR, average duration per event (days)	39.99 9833 48	30.91412	49.08555	Normal
Appetite decreased, pre-assigned to doxorubicin, number of events, LEN+PEM	9	7.65	10.35	Normal
Anaemia, pre-assigned to doxorubicin, number of events, LEN+PEM	3	2.55	3.45	Normal
Diarrhoea, pre-assigned to doxorubicin, number of events, LEN+PEM	11	9.35	12.65	Normal
Lipase increased, pre-assigned to doxorubicin, number of events, LEN+PEM	10	8.5	11.5	Normal
Neutropenia, pre-assigned to doxorubicin, number of events, LEN+PEM	1	0.85	1.15	Normal

Neutrophil count decreased, pre-assigned to doxorubicin, number of events, LEN+PEM	4	3.4	4.6	Normal
Hypertension, pre-assigned to doxorubicin, number of events, LEN+PEM	62	52.7	71.3	Normal
White blood cell count decreased, pre-assigned to doxorubicin, number of events, LEN+PEM	2	1.7	2.3	Normal
Anaemia, pre-assigned to doxorubicin, number of events, TPC	28	23.8	32.2	Normal
Diarrhoea, pre-assigned to doxorubicin, number of events, TPC	3	2.55	3.45	Normal
Febrile neutropenia, pre-assigned to doxorubicin, number of events, TPC	15	12.75	17.25	Normal
Leukopenia, pre-assigned to doxorubicin, number of events, TPC	22	18.7	25.3	Normal
Neutropenia, pre-assigned to doxorubicin, number of events, TPC	82	69.7	94.3	Normal
Neutrophil count decreased, pre-assigned to doxorubicin, number of events, TPC	78	66.3	89.7	Normal
Appetite decreased, pre-assigned to doxorubicin, average duration per event (days)	96.99 9933 07	82.44994	111.5499	Normal
Anaemia, pre-assigned to doxorubicin, average duration per event (days)	75.21 4297 7	63.93215	86.49644	Normal
Colitis, pre-assigned to doxorubicin, average duration per event (days)	81.49 9452 59	69.27453	93.72437	Normal
Diarrhoea, pre-assigned to doxorubicin, average duration per event (days)	32.13 0705 22	27.3111	36.95031	Normal
Febrile neutropenia, pre-assigned to doxorubicin, average duration per event (days)	4.079 8611 09	3.467882	4.69184	Normal
Leukopenia, pre-assigned to doxorubicin, average duration per event (days)	11.83 3279 93	10.05829	13.60827	Normal
Lipase increased, pre-assigned to doxorubicin, average duration per event (days)	86.71 4055 2	73.70695	99.72116	Normal
Neutropenia, pre-assigned to doxorubicin, average duration per event (days)	24.66 6699 36	20.96669	28.3667	Normal
Neutrophil count decreased, pre-assigned to doxorubicin, average duration per event (days)	17.25 8063 1	14.66935	19.84677	Normal
Hypertension, pre-assigned to doxorubicin, average duration per event (days)	74.77 0773 42	63.55516	85.98639	Normal

Weight decreased, pre-assigned to doxorubicin, average duration per event (days)	272.5 6737 68	231.6823	313.4525	Normal
White blood cell count decreased, pre-assigned to doxorubicin, average duration per event (days)	39.99 9833 48	33.99986	45.99981	Normal
Mean baseline EQ-5D (pMMR)	0.758 1589	0.74282	0.773498	Beta
Weight	69.3	68.02525	70.57475	Normal
BSA (body surface area), m2	1.726 289	1.288045	2.164533	Normal
Mean serum ccreatinine (mg/dL)	0.791 636	0.7761	0.807172	Normal
Pembrolizumab, administration dose intensity	0.952 9453 62	0.949082	0.958611	Normal
Paclitaxel, dose intensity	0.947 0960 18	0.805032	1	Normal
Doxorubicin, dose (mg/m2)	60	51	69	Normal
Liposomal doxorubicin, dose per day	40	34	46	Gamma
Subsequent therapies - LEN+PEM - % of pts - all lines Doxorubicin (ITT)	0.5	0.444783	0.555217	Beta
Subsequent therapies - LEN+PEM - % of pts - all lines Paclitaxel (ITT)	0.5	0.444783	0.555217	Beta
Subsequent therapies - TPC - % of pts - all lines Doxorubicin (ITT)	0.5	0.451303	0.548697	Beta
Subsequent therapies - TPC - % of pts - all lines Paclitaxel (ITT)	0.5	0.451303	0.548697	Beta
% tested with MSI test	0.7	0.595	0.805	Beta
Of those tested, MSI-H and MMR	0.67	0.5695	0.7705	Beta
Of those tested, MSI-H	0.22	0.187	0.253	Beta
Of those tested, MMR	0.11	0.0935	0.1265	Beta
Consultation, oncology, LEN+PEM, PFS	0.229 9794 66	0.195483	0.264476	Beta
Blood count, LEN+PEM, PFS	0.229 9794 66	0.195483	0.264476	Beta
CT scan, LEN+PEM, PFS	0.114 9897 33	0.097741	0.132238	Beta
GP visit, LEN+PEM, PFS	0.114 9897 33	0.097741	0.132238	Beta

Consultation, oncology, TPC, PFS	0.229979466	0.195483	0.264476	Beta
Blood count, TPC, PFS	0.229979466	0.195483	0.264476	Beta
CT scan, TPC, PFS	0.114989733	0.097741	0.132238	Beta
GP visit, TPC, PFS	0.114989733	0.097741	0.132238	Beta
Consultation, oncology, LEN+PEM, PD	0.076659822	0.065161	0.088159	Beta
GP visit, LEN+PEM, PD	0.114989733	0.097741	0.132238	Beta
Consultation, oncology, PD	0.076659822	0.065161	0.088159	Beta
GP visit, TPC, PD	0.114989733	0.097741	0.132238	Beta
Lenvatinib - daily dose 0, % of days	0.111268716	0.106207	0.116331	Dirichlet
Lenvatinib - daily dose 4, % of days	0.047266314	0.042025	0.052507	Dirichlet
Lenvatinib - daily dose 8, % of days	0.114683478	0.109631	0.119736	Dirichlet
Lenvatinib - daily dose 10, % of days	0.235498518	0.230804	0.240193	Dirichlet
Lenvatinib - daily dose 14, % of days	0.224045933	0.219316	0.228776	Dirichlet
Lenvatinib - daily dose 20, % of days	0.267222035	0.262626	0.271818	Dirichlet
Lenvatinib - daily dose 28, % of days	7.50497E-06	0	0.005377	Dirichlet
Lenvatinib - daily dose 40, % of days	7.50497E-06	0	0.005377	Dirichlet
OS JOINT	1			Normal
OS SEPARATE	1			Normal

PFS JOINT	1			Normal
PFS SEPARATE	1			Normal
TOT LEN	1			Normal
TOT PEM	1			Normal
TOT TPC	1			Normal
Utility PF	0.743194	0.7235	0.7629	Beta
Utility PD	0.6991482	0.6787	0.7196	Beta

Appendix H. Literature searches for the clinical assessment

In accordance with the DMC guidance, if a head-to-head study with a comparator relevant in Danish clinical practice exists, the systematic literature search can be omitted. As such all tables in this section have been left empty.

Eisai and Merck Sharp & Dohme have conducted the pivotal clinical study 309/KN-755 (82) a randomised controlled trial conducted to compare the efficacy and safety of LEN+PEM versus TPC (DOX or paclitaxel). PLD is considered the standard of care in Danish clinical practice. However, as described in Section 3.5.1.1, there is evidence suggesting DOX and PLD are comparable with respect to efficacy and safety and therefore, evidence for the comparison of LEN+PEM and standard of care in Danish clinical practice (PLD) were drawn from a comparison between LEN+PEM and the chemotherapy group pre-assigned to DOX in Study 309 / KN-775, with PFI < 6 months, and pMMR status.

The evidence of the 309/KN-755 trial was therefore considered sufficient to inform the comparison of LEN+PEM with the relevant comparator in Danish clinical practice (PLD) for the relevant patient group.

H.1 Efficacy and safety of the intervention and comparator(s)

Table 65 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
NA	NA	NA	dd.mm.yyyy
NA	NA	NA	dd.mm.yyyy
NA	NA	NA	dd.mm.yyyy

Abbreviations:

Table 66 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NA	NA	NA	dd.mm.yyyy
NA	NA	NA	dd.mm.yyyy

Abbreviations:

Table 67 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA	NA	NA	NA	dd.mm.yyyy
NA	NA	NA	NA	dd.mm.yyyy

H.1.1 Search strategies

NA

Table 68 of search strategy table for [name of database]

No.	Query	Results
#1	NA	NA
#2	NA	NA
#3	NA	NA
#4	NA	NA

H.1.2 Systematic selection of studies

NA

Table 69 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	NA	NA
Intervention	NA	NA
Comparators	NA	NA
Outcomes	NA	NA
Study design/publication type	NA	NA
Language restrictions	NA	NA

Table 70 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	NA	NA	NA	NA	NA	NA
Study 2	NA	NA	NA	NA	NA	NA

H.1.3 Quality assessment

NA

H.1.4 Unpublished data

NA

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

NA. See Appendix H for justification.

Table 71 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	NA	NA	dd.mm.yyyy
Medline	NA	NA	dd.mm.yyyy
Specific health economics databases[1]	NA	NA	dd.mm.yyyy

Abbreviations:

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

Table 72 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NA	NA	NA	dd.mm.yyyy
NA	NA	NA	dd.mm.yyyy

Table 73 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA	NA	NA	NA	dd.mm.yyyy
NA	NA	NA	NA	dd.mm.yyyy

I.1.1 Search strategies

NA

Table 74 Search strategy for [name of database]

No.	Query	Results
#1	NA	NA
#2	NA	NA

NA

I.1.2 Quality assessment and generalizability of estimates

NA

I.1.3 Unpublished data

NA

Appendix J. Literature searches for input to the health economic model

NA. See Appendix H for justification

J.1 External literature for input to the health economic model

NA.

J.1.1 Ex. Systematic search for […]

NA.

Table 75 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
NA	NA	NA	NA
NA	NA	NA	NA
NA	NA	NA	NA

Abbreviations:

NA.

J.1.2 Ex. Targeted literature search for [estimates]

NA.

Table 76 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
NA	NA	NA	NA
NA	NA	NA	NA

Abbreviations:

[Describe the selection process and criteria for inclusion or exclusion.]

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.

NA.

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