Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende lenvatinib i kombination med pembrolizumab til behandling af livmoderkræft

Vers. 1.0

Bilagsoversigt

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

Eisai response to the DMC's draft assessment report for lenvatinib plus pembrolizumab (LEN+PEM) for endometrial cancer (EC)

Eisai would like to thank the DMC for their draft report and acknowledge the detailed considerations and transparent rationale regarding the DMC base case. We acknowledge that there is uncertainty within the cost-effectiveness analysis, and scenarios that could be further explored. A discussion of these scenarios and uncertainties is given below:

Patient population

The DMC report mentions that LEN+PEM is only expected to be used for a subgroup of patients with platinum free interval (PFI) < 6 months, and DNA mismatch repair-proficient (pMMR) status. This is based on the recent recommendation by the DMC of dostarlimab as a possible standard treatment for patients with DNA mismatch repair-deficient (dMMR) who have progressed during or shortly after treatment with platinum-containing chemotherapy.

It is relevant to consider that the European Commission approved the use of LEN+PEM for adult patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy in any setting (all-comers). Importantly, the LEN+PEM phase III study 309/ KN 775 was not designed or statistically powered to measure the effect of LEN+PEM in multi-level subgroups of patients, such as the PFI<6 months, pMMR/dMMR populations, which represent less than half of the total eligible patient population in study 309/KN 775. As mentioned by the DMC[1] during technical discussions, smaller sample sizes reduce the precision of the efficacy estimates. Therefore, no definite conclusions can be drawn from the efficacy estimates of these multi-level subgroups and it may not be appropriate to restrict the use of LEN+PEM to these subgroups, as patients outside these subgroups could benefit from treatment with LEN+PEM.

Furthermore, as stated in the DMC report, the analyses requested by the DMC in the ITT population revealed a trend (not statistically significant) towards an improved effect of LEN+PEM in the dMMR population in comparison to the pMMR population. This shows that there is a lack of rationale in the restriction of LEN+PEM to certain subgroups, such as the PFI<6 months, pMMR population, and supports the use of LEN+PEM in the indication approved by EMA of 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 (all-comers). This indication includes patients with both pMMR and dMMR status.

Furthermore, it is relevant to consider that the efficacy of dostarlimab was evaluated in a phase I/II study with a single treatment arm[2], while the efficacy of LEN+PEM was evaluated in a phase III randomized, controlled study (309/ KN 775), which provided robust evidence of the effect of LEN+PEM for the EMA-approved indication including both pMMR and dMMR patient populations. To date, LEN+PEM is the only approved treatment available to patients following prior treatment with a platinum-containing therapy that is supported by a robust Phase III study.

Health economic analysis

The DMC's choice of the exponential distribution for the overall survival of LEN+PEM, is associated with the worst statistical fit (highest AIC and BIC) and relies on the assumption of a constant hazard over time (i.e. the risk of death does not change over time). As stated in the DMC report, clinical experts consider that the

assumption of proportional hazards (PH) should not be assumed to hold for a significant period of time, as the mechanisms of action are different between immunotherapy and chemotherapy. If the log-normal extrapolation, which does not rely on the PH assumption, and has one of the best statistical fits, is used, the list price ICER decreases by over 100,000 DKK from 882,504 DKK to 767,768 DKK.

Assessment timeline

Eisai appreciates the DMC's extensive review of the presented evidence. However, the length of the assessment was excessively prolonged (1 year to technical validation to reach "Day 0" of the assessment period, and a total of 1 year and 4 months before a DMC decision meeting) resulting in unnecessarily delayed access to LEN+PEM for patients. Considering the significant unmet need of patients with endometrial cancer whose disease progressed on or following prior treatment with a platinum-containing therapy, the assessment process could have benefited from a single comprehensive round of technical questions and consistency in the DMC requests regarding subgroup analyses.

Summary and Results

EC is the 5th most common type of cancer among women in Denmark and the most common gynaecological cancer[3]. 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[4]. Advanced EC is considered incurable, and the prognosis for survival is less than 5 years, with a median survival of approximately 4 years for stage III and 2 years for stage IV.

LEN+PEM is the first treatment to be approved by the European Commission for adult patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy in any setting (all-comers) in 50 years, and represents an important treatment option for patients with a significant unmet need.

Results from the cost-effectiveness analysis show that LEN+PEM can be considered a cost-effective use of Danish medical resources and represents a manageable budget impact considering the significant unmet need for endometrial cancer patients with advanced or recurrent disease.

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

References

1. DMC'S questions on application, December 2022
2. Study of TSR-042, an Anti-programmed Cell Death-1 Receptor (PD-1) Monoclonal Antibody, in Participants With Advanced Solid Tumors (GARNET) (NCT02715284)
3. Dansk Gynækologisk Cancer Gruppe, D., Retningslinjer for visitation, diagnostik, behandling og kontrol af cancer corporis uteri. Kap. 1. Indledning. . 2016. p. 1-7
4. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: uterine cancer 2020 [cited 2021 27 January 2021]; Available from: https://seer.cancer.gov/statfacts/html/corp.html.

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

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

21.02.2023

DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.03.2023
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)	Nuværende SAIP (DKK)	Ny pris pr.1.4.2023 SAIP (DKK)	Rabatprocent ift. AIP
Lenvima	4 mg	30 stk.	11.931,97	[redacted]	[redacted]	[redacted]
Lenvima	10 mg	30 stk.	11.931,97	[redacted]	[redacted]	[redacted]

Lægemidlerne har været i udbud og den nye aftale gælder fra 01.04.2023 og 6 måneder frem med mulighed for 3 gange 3 måneders forlængelse.

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.	22.058,88	[redacted]	[redacted]

Aftaleforhold

Leverandøren har et identisk lægemiddel til Lenvima, der er navngivet Kisplyx (lenvatinib), med identisk indholdsstof, styrke og pakningsstørrelse. Kisplyx er vurderet af Medicinrådet til behandling af nyrekræft i november 2022. Medicinrådet anbefaler ikke Kisplyx til behandling af nyrekræft. Kisplyx indkøbes til AIP. Leverandøren differentierer priserne på de to produkter og prisen på Lenvima er den laveste.

Det er ikke muligt for leverandøren at ændre prisen før Amgros publicerer et nyt udbud med kontraktstart d. 01.10.2023. Årsagen er, at udbuddet er specielt sat sammen, da leverandøren har to lægemidler indenfor samme ATC-kode.

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 priserne for et års behandling med Lenvima i kombination med Keytruda og behandling med Jemperli.

[redacted]

Tabel 2: Sammenligning af lægemiddeludgifter

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Antal pakninger pr. år	Lægemiddeludgift pr. år (SAIP, DKK)
Lenvima	10 mg	30 stk.	20 mg dagligt PO	[redacted]	24	[redacted]
Keytruda	25 mg/ml	4 ml.	2 mg/kg IV, hver 3 uge	[redacted]	24	[redacted]
Kombination med Lenvima og Keytruda						[redacted]
Jemperli	500 mg	1 stk.	500 mg iv/3 uge i 4 cykler 1000 mg iv/6 uge efter	[redacted]	18	[redacted]

*Vægtjusteret dosis 68,9 kg

Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	https://nyemetoder.no/metoder/lenvatinib-lenvima-pembrolizumab-keytruda
Sverige	Anbefalet	https://janusinfo.se/download/18.1e732a371864ac454343cf8c/1676634100607/Keytruda-Lenvima-vid-endometriecancer-230217.pdf
England	Under vurdering	https://www.nice.org.uk/guidance/indevelopment/gid-ta10692

Konklusion

[redacted]

Application for the assessment of lenvatinib with pembrolizumab for patients with advanced or recurrent endometrial cancer who have disease progression on or following prior treatment with a platinum-containing therapy

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

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1 Basic information

Contact information	
Name	Laureanne Lorenzo
Title	Market Access Senior Manager
Phone number	+46 73 429 36 06
E-mail	laureanne_lorenzo @eisai.net

Overview of the pharmaceutical	
Proprietary name	Lenvima® Keytruda®
Generic name	Lenvatinib Pembrolizumab
Marketing authorization holder in Denmark	Eisai GmbH Merck Sharp & Dohme B.V
ATC code	L01EX08 L01XC18
Pharmacotherapeutic group	Antineoplastic agents, protein kinase inhibitors Antineoplastic agents, monoclonal antibodies
Active substance(s)	Lenvatinib Pembrolizumab
Pharmaceutical form(s)	Oral therapy IV therapy
Mechanism of action	Lenvatinib is an RTK inhibitor that selectively inhibits Vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2, and VEGFR3), as well as multiple other proangiogenic and oncogenic signalling pathways, including FGFR1, 2, 3, and 4, platelet-derived growth factor receptor alpha (PDGFRα), KIT, and RET. Pembrolizumab binds to the PD-1 receptor and blocks its interaction with the PD-L1 and PD-2 ligands, releasing PD-1-mediated inhibition of the immune response (including anti-tumour response).

Overview of the pharmaceutical	
Dosage regimen	The recommended dosage of lenvatinib is 20 mg orally once daily in combination with pembrolizumab administered as an IV infusion over 30 minutes: 200 mg every three weeks or 400 mg every 6 weeks • Until disease progression or unacceptable toxicity [1]
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Lenvima in combination with pembrolizumab is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma (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

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Other approved therapeutic indications	**Lenvatinib:**
	Lenvatinib as monotherapy for the treatment of adult patients with progressive, locally advanced, or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)
	Lenvatinib as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy, with the same price as currently approved under basic reimbursement status [2].
	Pembrolizumab**:**
	Melanoma
	Pembrolizumab as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
	Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.
	Non-small cell lung carcinoma (NSCLC)
	Pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
	Pembrolizumab, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.
	Pembrolizumab, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.
	Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.
	Classical Hodgkin lymphoma (cHL)
	Pembrolizumab as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous 3 stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.
	Urothelial carcinoma
	Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
	Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10

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Overview of the pharmaceutical	
	Head and neck squamous cell carcinoma (HNSCC) Pembrolizumab, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 Pembrolizumab as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy Renal cell carcinoma (RCC) Pembrolizumab, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults Pembrolizumab, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions Colorectal cancer Pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults Oesophageal carcinoma Pembrolizumab in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10 Triple-negative breast cancer (TNBC) Pembrolizumab in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease Endometrial carcinoma (EC) Pembrolizumab, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation [3].
Will dispensing be restricted to hospitals?	Dispensation of lenvatinib is restricted to hospitals (BEGR).
Combination therapy and/or co-medication	Yes, in combination with pembrolizumab.

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Overview of the pharmaceutical	
Packaging – types, sizes/number of units, and concentrations	Lenvima® 4mg hard capsules – Each hard capsule contains 4mg of lenvatinib (as mesylate) [4] Lenvima® 10mg hard capsules – Each hard capsule contains 10mg of lenvatinib (as mesylate) [4] Keytruda® 25mg/ml – Each pack contains 100mg of pembrolizumab [5]
Orphan drug designation	No

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2 Abbreviations

Abbreviation	Definition
AE	Adverse events
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCT	Autologous stem cell transplant
AST	Aspartate Aminotransferase
AUC	Under The Curve
BICR	Blinded Independent Central Review
BIM	Budget impact model
BP	Blood Pressure
BSA	Body surface area
CBR	Clinical Benefit Rate
CEAC	Corresponding Cost-Effectiveness Acceptability Curve
cHL	Classical Hodgkin Lymphoma
CPS	Combined Positive Score
CRC	Colorectal Cancer
CVA	Cerebrovascular Accident
DCR	Disease Control Rate
DETs	Data Extraction Tables
DGCG	Danish Gynecological Cancer Group
DKK	Danish kroner
DLT	Dose Limiting Toxicity
DMC	Danish Medicines Council
dMMR	Mismatch Repair Deficient
DOR	Duration of response
DSDR	Durable Stable Disease Rate
EBRT	External Beam Radiotherapy
EC	Endometrial Carcinoma/Cancer
EC	Endometrial Carcinoma

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Abbreviation	Definition
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization 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
FDA	Food and Drug Administration
FIGO	Federation of Gynecology and Obstetrics
HCC	Hepatocellular Carcinoma
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HRQoL	Health-related Quality of life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
INR	International Normalized Ratio
irAE	Immune-Related Adverse Events
ISPOR	Professional Society for Health Economics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intended To Treat
IUD	Intrauterine Device
IV	Intravenous
LEN	Lenvatinib
LVEF	Left Ventricular Ejection Fraction
LYs	Life Years
MAR	Missing At Random
MMI	Myometrial Invasion
MMR	Mismatch Repair
MSI-H	Metastatic Microsatellite Instability-High

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Abbreviation	Definition
MSI-L	Microsatellite Instability-Low
MSS	Microsatellite Stability
MTD	Median Treatment Duration
MUGA	Multi-Gated Radionuclide Angiography
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSCLC	Non-Small Cell Lung Carcinoma
NSCLC	The Non-Small Cell Lung Cancer
NSGO-CTU	Director, Nordic Society of Gynaecologic Oncology-Clinical Trial Unit
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PartSA	Partitioned Survival Analysis
PD	Progressed Disease
PD-1	Programmed Death Protein 1
PD-L1	Programmed Death-Ligand 1
PF	Progression-Free
PFI	Platinum Free Interval
PFS	Progression-free survival
PLD	Pegylated Liposomal Doxorubicin

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3 Tables and Figures

3.1 List of tables

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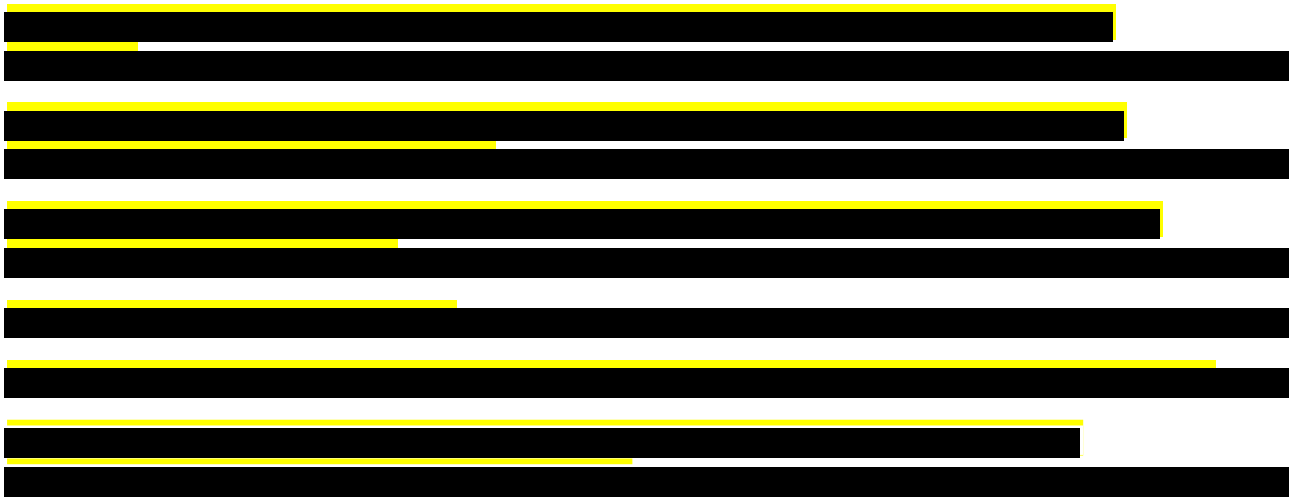
3.2 List of figures



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4 Summary

4.1 Indication

Endometrial cancer (EC) is the most common gynaecologic malignancy in developed countries and the second most common worldwide [6-8]. As the most common gynaecologic malignancy in Denmark, EC is the 5th most common type of cancer among women with an incidence of 867, and a prevalence of 9,472 in 2020 [9, 10]. The global incidence of EC is expected to increase due to risk factors including increased life expectancy/older age, exposure to excess endogenous and exogenous oestrogen levels, Lynch syndrome and obesity [11-16]. Furthermore, the global mortality rate for EC is increasing more rapidly than the incidence rate [12]. Morbidity from EC is caused by both disease-related complications (including anaemia due to vaginal bleeding, pain, weight loss and abdominal bloating) and long-term treatment-related complications (including toxic side effects of treatment and long-term genitourinary and cardiovascular outcomes [17].

EC displays tumour heterogeneity with several histological subtypes, with distinct pathogenesis and prognosis [8]. EC can broadly be classified into two subtypes: Type I that is considered to be low-risk and makes the majority (80–90%) of all EC cases and Type II that is considered to be high-risk with a poor prognosis [8, 18]. Although most women with EC are diagnosed at an early stage with cancer confined to the uterus (with a favourable 5-year survival rate of >90%), around one-third are diagnosed with advanced disease (with a poor 5-year survival rate of only 17%) [19-22]. Recurrent disease, which can be associated with lifestyle, obesity, exercise, smoking, and sexual health, occurs in up to 25% of cases and accounts for most endometrial cancer-related deaths [23].

Lenvatinib + pembrolizumab (LEN+PEM) is the first treatment to be approved by the European Commission for adult patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy in any setting (all-comers) in 50 years. This single technology assessment relates to LEN+PEM in the approved endometrial indication, with the following restriction: 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).

4.2 The pharmaceutical

LEN+PEM offers a novel therapy; 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.

4.3 The comparators

Treatment of EC may vary depending on the grade, histology, stage of the disease, and MSI/Mismatch Repair (MMR) status. For the majority of patients with low-risk EC, the mainstay of first-line treatment is curative surgery with or without radiotherapy and/or chemotherapy [24-27]. After surgery, a platinum containing regimen is recommended that aims to prolong survival by limiting further disease progression [25, 28, 29]. However, according to the 2021 ESGO/ESTRO/ESP guidelines, the Danish guidelines and clinical experts, there is no agreement on the standard treatment of patients with advanced or recurrent EC who have disease progression on or following platinum-based therapy [25, 30-33].

The 2020 ESGO/ESTRO/ESP guidelines recommend doxorubicin (DOX) and paclitaxel as the most active therapies for second-line treatment, while re-challenge with platinum containing chemotherapy, is considered as an option for patients with a long platinum-free interval [34].

The Danish Medicines Council (DMC) describes in its assessment report for dostarlimab from December 2021 [64] that the second line treatment options for EC are dependent on the duration of time passed since platinum-based treatment in first line. For patients who progress during or up to six months after treatment with first line platinum therapy, pegylated liposomal doxorubicin (PLD) is given as standard treatment. Patients who progress approximately six months or more after discontinuation of platinum treatment are considered to be platinum sensitive and can be re-treated with platinum-based chemotherapy after progression [62, 65].

Based on the available clinical guidelines, clinical expert input and consultation with DMC, the most relevant comparators in the Danish setting were therefore considered to be:

- PLD for patients that have a platinum-free interval (PFI) of less than 6 months (PFI < 6 months).
- Carboplatin in combination with paclitaxel for patients that have a PFI of 6 months or greater.

This application focuses on EC patients with advanced EC that are indicated for DOX/PLD treatment following disease progression following prior treatment with a platinum-containing therapy in less than 6 months (PFI < 6 month).

4.4 Main efficacy endpoints

The efficacy and safety of LEN+PEM in EC was investigated in the direct comparative ongoing study 309 / KN-775, a multicenter, open-label, randomized, phase 3 trial, versus DOX or paclitaxel as the treatment of physician's choice (TPC), in patients with advanced EC who were previously treated with ≥1 prior platinum-based chemotherapy regimen. LEN in combination with PEM provides a favourable risk-benefit profile with statistically significant and clinically meaningful improvements in overall survival [redacted]

Safety of the pharmaceutical

The study also demonstrates a manageable safety profile for LEN+PEM that is generally consistent with the known safety profiles of the components as monotherapies [35-41], with AEs clinically manageable by supportive medications and dose modifications. The safety profile of LEN is also consistent across different indications, including EC. The overall incidence of AEs was similar between the LEN+PEM group and the TPC group. The observed incidences of Grade 3 to 5 AEs and drug-related Grade 3 to 5 AEs were higher for LEN+PEM compared with TPC but after adjustment for exposure, the overall event rates for SAEs and drug related SAEs were similar between the treatment groups. Exposure-adjusted rates of all AEs, drug-related AEs, Grade 3 to 5 AEs, drug related Grade 3 to 5 AEs, and deaths were lower for LEN+PEM compared with TPC.

Given superior efficacy, manageable safety, and no substantial differences in HRQoL between LEN+PEM and DOX, LEN+PEM has an overall favourable risk/benefit profile compared with DOX for patients with advanced EC who have disease progression following prior platinum-based chemotherapy regimen.

4.5 Structure of the economic analysis

A cost-effectiveness model was developed using a partitioned survival analysis (PartSA) structure based on three health states, progression-free disease (PF), progressed disease (PD) and death. LEN+PEM was compared to the standard of care therapies used in Denmark with PLD as the base case comparator for the relevant population (PFI < 6 months patient population). A life-time horizon of up to 36 years was used in the base case. Deterministic sensitivity analysis, probabilistic sensitivity analysis and various scenarios were explored.

4.6 Sources of relative efficacy of the economic model

As the follow-up period for Study 309 / KN-775was shorter than the modelled time horizon, extrapolation from the observed OS, PFS and TTD data was required. A range of standard parametric distributions were explored for extrapolation of the OS, PFS and TTD endpoints with options for single or joint fits. Due to the lack of published data which would support an indirect treatment comparison of LEN+PEM to PLD in the PFI < 6 months patient population the following analyses were performed:

- Study 309 / KN-775post-hoc subgroup analysis in the LEN+PEM PFI < 6 months patient population, comparison with patients pre-assigned to DOX of TPC (assumption of PLD equivalence to DOX).

4.7 Results of the economic analysis

In the base case analysis, in the population with PFI < 6 months who were pre-assigned to DOX in Study 309, LEN+PEM is associated with incremental costs of [redacted] and incremental QALYs of [redacted], resulting in an ICER of [redacted] compared with PLD. The introduction of LEN+PEM in Denmark is associated with a total net budget impact of [redacted] in year 1 to [redacted] in year 5 resulting in a cumulative 5-year net budget impact of [redacted]

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

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

5.1 The medical condition and patient population

Endometrial cancer (EC) is the most common gynaecologic malignancy in developed countries and the second most common gynaecologic malignancy worldwide [7, 8, 42]. EC develops in the inner lining of the uterine cavity [43], 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 [11-16]. In 2030, the global incidence of EC is expected to increase to 487,316, representing a 16.8% increase from 2020 [44]. The mortality rate for EC has increased more rapidly than the incidence rate (21% increase in mortality rates from 1999 to 2016 [15]), 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 [12].

EC displays tumour heterogeneity and there are several histological subtypes, with distinct pathogenesis and prognosis [8]. 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 [8, 18].

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 [45, 46]. Both systems are based on surgical staging and include assessment of the extent of myometrial invasion (MMI) 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 [19], 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) [46, 47]. Abnormal vaginal bleeding often occurs early in the disease course, leading to most EC cases being diagnosed at an early stage [47]. 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 [48].

A deficient mismatch repair (dMMR) system is frequently associated with Type I EC [49]. 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 [50]. Deficiency in the MMR system results in the accumulation of mutations at microsatellites, resulting in microsatellite instability-high (MSI-H). This generates a high genotypic and phenotypic diversity of emerging precancerous cell clones from which carcinogenesis likely follows [50].

MSI-H tumours are found in up to 35% of patients with EC and, comprising <20% of advanced disease cases [50-53]. Non-MSI-H tumours (or proficient mismatch repair [pMMR]) consist of those with a low frequency of microsatellite instability-low (MSI-L) and those with microsatellite stability (MSS) [54].

The main risk factor for developing EC is exposure to endogenous and exogenous oestrogens [46, 55]. Other key risk factors include obesity, diabetes, age, and Lynch syndrome.

Recurrent disease, which typically becomes clinically apparent within 3 years of primary therapy [56, 57], occurs in up to 25% of cases and accounts for most EC-related deaths [58, 59]. Recurrence of EC can be associated with lifestyle, obesity, exercise, smoking, and sexual health [47]. 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 [58].

EC is the 5th most common type of cancer among women in Denmark and the most common gynaecological cancer [9]. 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 [19-22]. Advanced EC is considered incurable, and the prognosis for survival is significantly lower with a median survival of approximately 4 years for stage III and 2 years for stage IV [60].

Incidence and prevalence of EC in Denmark are presented in Table 1, based on epidemiological market research [10].

Table 1: Incidence and prevalence of EC in the past 5 years in Denmark

Year	2016	2017	2018	2019	2020
Diagnosed prevalent cases	8,683	8,884	9,088	9,271	9,472
Diagnosed incident cases	800	819	826	841	867
Advanced stage 3 and 4 incident cases	141	143	149	152	154
Advanced stage 3 incident cases	108	109	113	115	116
Advanced stage 4 incident cases	33	34	36	37	38
Recurrent incident cases	40	41	41	43	44
Recurrent early-stage low and intermediate risk	25	25	25	26	27
Recurrent early-stage high risk	15	16	16	17	17
Sum of advanced or recurrent incident cases	**181**	**184**	**190**	**195**	**198**

Source: DRG 2020 [10]

The Danish patient population expected to be candidates for treatment with lenvatinib and pembrolizumab (LEN+PEM) are patients with advanced or recurrent EC with PFI < 6 months and are not candidates for curative surgery or radiation. This population would currently be eligible for treatment with PLD.

The number of incident 1st line patients with advanced or recurrent EC is based on the DRG/Clarivate endometrial cancer epidemiology model for the years 2022 to 2026 [10] and validation by an expert clinician. Using internal forecast, a percentage of patients that are treated (80%) is applied, and it is estimated that 60% of those patients will reach 2nd line. The percentage of patients with PFI<6 months from Study 309 / KN-775[61] is then applied to this population to derive the population size for 2nd line treatable population with PFI < 6 months. Lastly, it is estimated that 80% of those patients will be eligible for systemic treatment.

Among those, based on Eisai market research, an estimated 60% would be eligible for treatment with LEN+PEM.

This results in an estimated 31 treated patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy within 6 months in 2022 (Table 2). The combination therapy is expected to be used upon reimbursement since there is currently no clear standard of care in this population.

Table 2: Estimated number of EC patients eligible for treatment

Year	Percentage of previous row	2022	2023	2024	2025	2026
1st line treatable population (advanced)		199	202	207	210	213
1st line treated population (advanced)	80%	159	162	166	168	170
2nd line treatable population (advanced)	60%	96	97	99	101	102
2nd line treatable population with PFI < 6 months	67%	64	65	67	68	69
Systemic treatment rate	80%	51	52	53	54	55
Eligible for LEN+PEM treatment	60%	31	31	32	32	33

Source: Expert clinician and DRG 2020 [10]

5.1.1 Patient population relevant for this application

Patients relevant for this application are patients with advanced EC 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.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Treatment of EC varies depending on the grade, histology, stage of the disease, and MSI/MMR status. For the majority of patients with low-risk EC, the mainstay of first-line treatment is curative aiming surgery with removal of all visible cancerous tissue (macro-radical surgery) with or without radiotherapy and/or chemotherapy [24-27]. After surgery, a combination of carboplatin and paclitaxel is recommended [25, 28, 29] with the purpose of prolonging survival by limiting further disease progression [28, 29]. The current treatment guidelines for EC include:

- The European Society for Medical Oncology (ESMO), last updated in 2013 [18]
- The joint guidelines from European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and European Society of Pathology (ESP), 2021 [34]
- National Comprehensive Cancer Network (NCCN) Uterine Neoplasms Guidelines, 2021 [47]
- Danish Gynecological Cancer Group (DGCG), 2019 [24]
- Sundhed.dk, last updated in 2015 [26]

There are, however, few approved therapy options for second line treatment of patients with advanced or recurrent EC following prior platinum-based therapy [25, 30-33]. Most recent guidelines from the Danish Gynecological Cancer Group (DGCG) and sundhed.dk [25, 26, 62] 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 this application. Please see section 11 for more details.

5.2.2 Choice of comparators

Although there is no consensus on the standard of care treatment following platinum containing therapy, the Danish Medicines Council (DMC) describes in its assessment report for dostarlimab from December 2021 [63], that the second line treatment options for EC are dependent on the duration of time passed since platinum-based treatment in first line. Patients who progress approximately six months or more after discontinuation of platinum treatment are considered to be platinum sensitive and can be re-treated with platinum-based chemotherapy after progression [34, 64]. If progression occurs during or up to six months after treatment with first line platinum therapy, pegylated liposomal doxorubicin (PLD) is given as standard.

It is however important to note that pegylated liposomal doxorubicin (Caelyx®) does not have EMA marketing authorization for EC [65] and use can be considered off-label. In spite of this, as clinicians in Denmark have several years of experience with the use of PLD for EC patients, PLD is considered standard therapy in second line treatment of EC for patients who progress during or up to six months after initial systemic therapy containing platinum [25].

Furthermore, PLD together with weekly paclitaxel are the treatments mentioned in the latest ESGO/ ESTRO/ ESP guidelines in second line EC treatment after previous use of platinum-based chemotherapy [34].

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 that have PFI < 6 months.

5.2.3 Description of comparators(s)

The efficacy and safety of LEN+PEM in EC was investigated in the direct comparative ongoing study 309 / KN-775, a multicentre, open-label, randomized, Phase 3 trial, versus doxorubicin (DOX) or paclitaxel as the treatment of physician's choice (TPC), in patients with advanced EC who were previously treated with ≥1 prior platinum-based chemotherapy regimen. There is evidence that suggests DOX and PLD are comparable with respect to efficacy and safety (described below) and therefore, evidence for the comparison of LEN+PEM and PLD were estimated from the comparison between LEN+PEM and the chemotherapy group pre-assigned to DOX in Study 309 / KN-775, with PFI < 6 months. As such, a description of both PLD (Section 5.2.3.3) and DOX (Section 5.2.3.4) will be provided in this section.

5.2.3.1 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 [66].
- In advanced and metastatic soft tissue sarcoma, there were no significant differences between DOX and PLD for PFS and OS [67].

- A meta-analysis published in 2012 demonstrated liposomal DOX and PLD have favourable toxicity profiles compared with conventional DOX [68].

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.

5.2.3.2 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 RCTs were identified [69, 70 , 71] as well as four single arm studies and one RWE study [72-76], 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 (NMA) would not yield additional comparisons of interest for the submission. For details see Appendix F – Comparative analysis of efficacy and safety.

5.2.3.3 PLD

The information in Table 3 is collected from the SmPC [65]. Information on posology is based on the DMC assessment of dostarlimab [63].

Table 3: Product characteristics for PLD

Subject	Description
Generic name (ATC-code)	Pegylated liposomal doxorubicin, L01DB01
Mode of action	The active ingredient of Caelyx®, pegylated liposomal is doxorubicin hydrochloride, a cytotoxic anthracycline antibiotic obtained from Streptomyces peucetius var. caesius. The exact mechanism of the antitumour activity of doxorubicin is not known. It is believed that inhibition of DNA, RNA and protein synthesis is responsible for the majority of the cytotoxic effects. This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix thus preventing their unwinding for replication.
Pharmaceutical form	Concentrate for solution for infusion (sterile concentrate)
Posology	40-50 mg / m^2 PLD IV every 4 weeks for up to 6-8 series [63]
Method of administration	Pegylated liposomal doxorubicin 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. Pegylated liposomal doxorubicin should only be administered under the supervision of a qualified oncologist specialised in the administration of cytotoxic agents.
Necessary monitoring, both during administration and during the treatment period	Pegylated liposomal doxorubicin should only be administered under the supervision of a qualified oncologist specialised in the administration of cytotoxic agents. It is recommended that all patients receiving pegylated liposomal doxorubicin routinely undergo frequent ECG monitoring. More specific methods for the evaluation and monitoring of cardiac functions as compared to ECG are a measurement of left ventricular ejection fraction by echocardiography or preferably by multigated angiography. These methods must be applied routinely before the initiation of pegylated liposomal doxorubicin therapy and repeated periodically during treatment. The evaluation of left ventricular function is considered to be mandatory before each additional

Subject	Description
	administration of pegylated liposomal doxorubicin that exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2. The evaluation tests and methods mentioned above concerning the monitoring of cardiac performance during anthracycline therapy are to be employed in the following order: ECG monitoring, measurement of left ventricular ejection fraction, endomyocardial biopsy.
Should the pharmaceutical 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)
Need for diagnostic or other test	Prior to pegylated liposomal doxorubicin administration, evaluate hepatic function using conventional clinical laboratory tests such as ALT/AST, alkaline phosphatase, and bilirubin.
Packaging	Type I glass vials, each with a siliconised grey bromobutyl stopper, and an aluminium seal, with a deliverable volume of 10 ml (20 mg) or 25 ml (50 mg). Caelyx pegylated liposomal is supplied as a single pack or packs of ten vials.

Abbreviation: ECG, Electrocardiogram; IV, intravenous;
Sources: [65], [63]

5.2.3.4 DOX

The information in Table 4 is collected from the EMA SmPC [77] and Danish SmPC (produktresume) [78]

Table 4: Product characteristics for DOX

Subject	Description
Generic name (ATC-code)	Doxorubicin hydrochloride, L01DB01
Mode of action	DNA intercalation (leading to an inhibition of synthesis of DNA, RNA and proteins), formation of highly reactive free-radicals and superoxides, chelation of divalent cations, the inhibition of Na-K ATPase and the binding of doxorubicin to certain constituents of cell membranes (particularly to the membrane lipids, spectrin and cardiolipin). Highest drug concentrations are attained in the lung, liver, spleen, kidney, heart, small intestine and bone-marrow. Doxorubicin does not cross the blood-brain barrier.
Pharmaceutical form	Concentrate for solution for infusion.
Posology	Due to the risk of lethal cardiomyopathy risk and benefits should be assessed for each individual patient prior to each treatment. **Monotherapy** Recommended dose 60-75 mg/m^2 body surface area every 3rd week.

Subject	Description
	Combinational therapy When doxorubicin is administrated in combination with other anti-tumorigenic drugs with overlapping toxicity doxorubicin dose must be reduced to 30-60 mg/m^2 body surface area every 3rd-4th week. **Example of combination therapy:** Doxorubicin can be administered in combination with cisplatin for treatment of advanced EC in accordance with the following treatment regimen [79]: Day 1: Doxorubicin 60mg/m2 IV push Day 1: Cisplatin 50mg/m2 IV over 60 minutes. Repeat cycle every 3 weeks for 6 cycles. OR Day 1: Doxorubicin 45mg/m2 (if prior pelvic radiation) IV push Day 1: Cisplatin 50mg/m2 IV over 60 minutes. Repeat cycle every 3 weeks for 6 cycles.
Method of administration	IV push
Necessary monitoring, both during administration and during the treatment period	Doxorubicin should be administered only under the supervision of physicians experienced in the use of cytotoxic therapy. Cardiac function should be assessed before patients undergo treatment with doxorubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of doxorubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.
Should the pharmaceutical be administered with other medicines	Can possibly be administered with other anti-tumorigenic drugs
Treatment duration / Criteria for end of treatment:	Treatment until disease progression or unacceptable toxicity (based on physician's choice). Patients can be treated every 3 weeks for 6 cycles.

Subject	Description
Need for diagnostic or other test	Before or during treatment with doxorubicin the following monitoring examinations are recommended (how often these examinations are done will depend on the general condition, the dose and the concomitant medication): • radiographs of the lungs and chest and ECG • regular monitoring of heart function (LVEF by e.g. ECG, UCG and MUGA scan) • daily inspection of the oral cavity and pharynx for mucosal changes • blood tests: haematocrit, platelets, differential white cell count, AST, ALT, LDH, bilirubin, uric acid • kidney function should also be checked before and during therapy
Packaging	5 ml vial containing 10 mg doxorubicin hydrochloride. 10 ml vial containing 20 mg doxorubicin hydrochloride. 25 ml vial containing 50 mg doxorubicin hydrochloride. 50 ml vial containing 100 mg doxorubicin hydrochloride. 100 ml vial containing 200 mg doxorubicin hydrochloride.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; ECG, Electrocardiogram; ECHO, echocardiography; LDH, Lactate dehydrogenase LVEF, Left ventrcular ejection fraction; MUGA, multi-gated radionuclide angiography, UCG, Ultrasound Cardiography

Sources: [65], [63]

5.3 The intervention

Vascular endothelial growth factor (VEGF) inhibition enhances the efficacy of programmed death protein 1 (PD-1) inhibition versus use of a single-agent PD-1 inhibitor [80-83] 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 [84, 85]. 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 [86]. LEN decreased the tumour associated macrophage (TAM) population, which is known as an immune-regulator in the tumour microenvironment. By decreasing TAMs, 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) [81].

The requested characteristics of the intervention were taken from the SmPC's for LEN [4] and PEM [5] and provided in Table 5.

Table 5: Product characteristics of LEN+PEM

Subject	Description
Generic name (ATC-code)	L01EX08, lenvatinib

Subject	Description
	L01FF02, pembrolizumab
Dosing	Lenvatinib: the recommended daily dose of lenvatinib 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.[4] Pembrolizumab: pembrolizumab is administered by IV infusion over 30 minutes. For endometrial carcinoma, the recommended dosage is 200 mg every 3 weeks or 400 mg every 6 weeks.[5]
Method of administration	Lenvatinib is for oral use Pembrolizumab is administered by IV infusion over 30 minutes
Treatment duration / Criteria for end of treatment:	Lenvatinib: [4] treatment with lenvatinib can continue for as long as the disease does not progress and the patient continues to tolerate treatment.[4] Pembrolizumab: patients should be treated with pembrolizumab until disease progression or unacceptable toxicity.[5]
Should the pharmaceutical be administered with other medicines	No
Necessary monitoring, both during administration and during the treatment period	Lenvatinib: For patients with hypertension, blood pressure should be well controlled prior to treatment, and should be regularly monitored during treatment. Cases of nephrotic syndrome have been reported in patients using lenvatinib; urine protein should be monitored regularly to avoid proteinuria. Due to hepatotoxicity, close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment; liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. To avoid cardiac dysfunction, patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary. Electrolyte abnormalities should be monitored and corrected before starting treatment and electrocardiograms and should be monitored at baseline and periodically during treatment to avoid QT/QTc interval prolongation. Thyroid function should be monitored before initiation of, and periodically throughout, treatment with lenvatinib.[4] Pembrolizumab: Patients should be monitored for signs and symptoms of immune-related: pneumonitis, colitis, changes in liver function (hepatitis), changes in renal function (nephritis), adrenal insufficiency and hypophysitis (endocrinopathies) and severe skin reactions. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes.[5]
Need for diagnostic or other test	No biomarker test or companion diagnostic is required for the use of lenvatinib + pembrolizumab.

Abbreviation: LEN, lenvatinib; IV, intravenous

There is a significant unmet medical need for patients with advanced and recurrent EC who have progressed after prior platinum treatment. Therefore, the introduction of LEN+PEM will provide an effective treatment option for patients with advanced EC who have disease progression following prior treatment with a platinum-containing therapy, particularly those within 6 months of receiving prior platinum-containing treatment (PFI < 6 months) and who are not candidates for curative surgery or radiation.

6 Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

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 [87]. Eisai and Merck Sharp & Dohme have conducted the pivotal clinical study 309/KN-755 [88] (see Section 7.1), a randomised controlled trial conducted to compare the efficacy and safety of LEN+PEM versus treatment of physician's choice (TPC) (DOX or paclitaxel). PLD is considered the standard of care in Danish clinical practice. However, as described in Section 5.2.3, there is evidence suggesting DOX and PLD are comparable with respect to efficacy and safety (described in Section 5.2.3) 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.

The evidence of the 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 < 6 months).

6.2 List of relevant studies

Table 6 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer, Makker et al., The New England Journal of Medicine, 2022 [89]	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])	NCT03517449	**Study Start Date:** June 11, 2018 **Primary Completion Date:** October 26, 2020 **Estimated Study Completion Date:** January 16, 2023	LEN + PEM vs. DOX for patients with advanced EC who have PFI < 6 months

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
	Study 309 / KN-775			

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

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

7 Efficacy and safety

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 endometrial carcinoma following at-least one prior platinum-based regimen in any setting.

7.1 Efficacy and safety of LEN+PEM compared with DOX 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)

7.1.1 Relevant studies

This section provides evidence for the efficacy and safety of LEN+PEM compared to the relevant comparator as described in Section 5.2.2: 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).

As described in Section 5.2.2, PLD is considered the relevant comparator to LEN+PEM for patients with PFI < 6 months 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 that suggests DOX and PLD are comparable with respect to efficacy and safety (described in Section 5.2.3) and therefore, evidence for the comparison of LEN+PEM and 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, as described in the following section.

The efficacy and safety of LEN+PEM have 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 description of main characteristics/methodology, population baseline characteristics, table of efficacy and safety (with definition, validity and clinical relevance) as well as safety data is available in appendices B-E.

Study 309 / KN-775is an ongoing 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, 84]. A summary of the trial details is given in Table 7.

Table 7 Summary of Study 309 / KN-775

Study name	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

Study design	Open-label, randomized, Phase 3 trial	
Sample size (n)	827	
Patient population(s)	Comparator	Intervention
	416	411
Intervention(s)	LEN 20 mg + PEM 200 mg Participants with endometrial cancer (EC) received lenvatinib (LEN) 20 mg orally, once daily, plus pembrolizumab (PEM) 200 mg intravenously, every 3 weeks 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.	
Comparator(s)	Treatment of Physician's Choice (TPC): DOX or Paclitaxel Participants with EC received either DOX 60 milligrams per square meter (mg/m^2) intravenously, every 3 weeks, 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.	
Follow-up period	As of the data cut-off date of 26th October 2020 for IA1, the median duration of follow up in the overall population (all comers and pMMR populations) was 11.4 months (range: 0.3, 26.9)	
Key eligibility criteria	Inclusion criteria	Exclusion criteria
	Adults aged ≥18 years Histologically confirmed advanced, recurrent, or metastatic EC Evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for EC. Patients 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. Measurable disease according to RECIST 1.1 and confirmed by BICR. ECOG performance status score of 0 or 1 within 7 days of the start of treatment. Adequately controlled blood pressure with or without antihypertensive medications. Have adequate organ function within 7 days prior to the start of study treatment (based on laboratory assessment).	>1 prior systemic chemotherapy regimen (other than adjuvant or neoadjuvant) for EC. Prior treatment with any treatment targeting VEGF-directed angiogenesis, any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. Patients who 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 discontinued from that treatment due to a Grade 3 or higher immune-related AE. Radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks prior to study treatment start. Prior enrollment on a clinical study evaluating LEN and PEM for EC, regardless of treatment received. Not pregnant or breast-feeding, or following contraceptive guidance if of childbearing age

Primary endpoint(s)	**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 endpoint(s)	**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 TEAEs, SAEs, and immune-related AEs. 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** 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).
Baseline characteristics	Baseline characteristics are presented in detail in Appendix C .
Predefined subgroups	No relevant subgroups analysed for this application
Used in the health economic model?	Yes

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 [87]. 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 D. In addition, validity, clinical relevance and summary of results of efficacy endpoints of interest is provided in Appendix D.

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

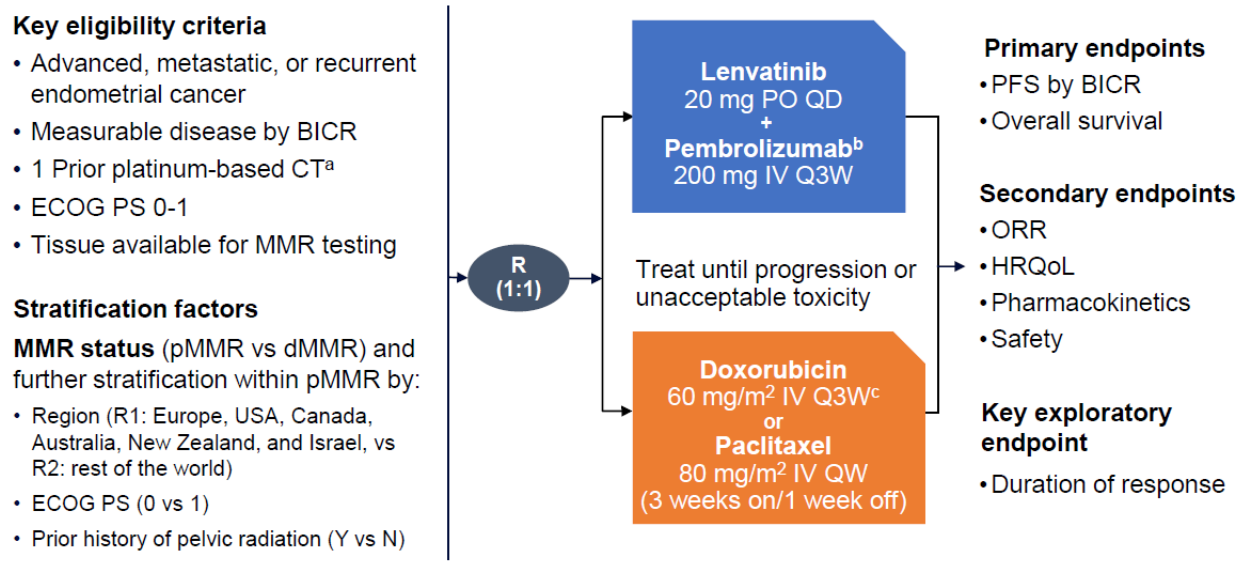
7.1.1.1 Study design

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 (treatment of physician's choice). The study then randomized (1:1) 780 eligible patients to receive either LEN+PEM or TPC (DOX or paclitaxel). As of the data cut-off date for this report, 827 participants were randomized (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 1: Study 309 / KN-775 - study design



[a]Patients may have received up to 2 prior platinum-based CT regimens if 1 is given in the neoadjuvant or adjuvant treatment setting. [b]Maximum of 35 doses. [c]Maximum cumulative dose of 500 mg/m^2.
BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; PFS, progression-free survival; pMMR, mismatch repair-proficient; ORR, objective response rate; PO, per os (by mouth); QD, once daily; Q3W, every 3 weeks; QW, once weekly.

Source: Study 309/KN775 CSR [84]

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). Following a request by the EMA for comparative results of LEN+PEM and DOX, a post-hoc subgroup analysis was conducted [90]. 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 the submission, a further subgroup was created of patients pre-assigned to DOX treatment with PFI < 6 months which will provide the clinical evidence for the population of interest in the submission. For consistancy purpose efficacy estimates (OS, PFS) for ITT population is also presented. In addition, 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 ITT population.

In the efficacy analyses for the abovementioned subgroups (pre-assigned to DOX, PFI < 6 months, n = 416) n=205 were randomized to receive LEN+PEM and n=211 patients were randomized to receive DOX. In the safety analysis set, of those subjects pre-assigned to DOX with a PFI of less than 6 months, n=204 received LEN+PEM and n=200 received DOX. 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 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 (AEs) (TEAEs) and drug-related TEAEs. A detailed description of the efficacy endpoints (Appendix D) and safety endpoints (Appendix E) are presented in the appendices.

7.1.2 Efficacy and safety comparisons – results per study

7.1.2.1 Study 309/KN-755

7.1.2.1.1 Efficacy and safety

7.1.2.1.1.1 Efficacy

Efficacy estimates (OS, PFS) (pre-assigned to doxorubicin, PFI < 6 months population)

Results for primary endpoints of PFS assessed by Blinded Independent Central Review (BICR) and OS are presented in [redacted] and Table 9 together with Kaplan Meier curves for OS (Figure 3) and PFS (Figure 2). Comparative analysis of the PFI < 6 months populations in the two treatment arms (LEN+PEM and pre-assigned to DOX) showed an improvement in PFS ([redacted]) and OS [redacted]

The median follow-up duration was [redacted] for the LEN+PEM trial arm and [redacted] in the DOX treated trial arm for the pre-assigned to DOX population.

[redacted]

	LEN + PEM [b]			DOX [b]			LEN + PEM [b] vs. DOX [b]	
	N[c]	Participants with Event n (%)	Median Timed in Months [95% CI]	N[c]	Participants with Event n (%)	Median Timed in Months [95% CI]	Hazard Ratio [95% CI]	p-value
Progression-Free Survival (BICR Primary Censoring Rule)	[redacted]							

[redacted]

Abbreviations: CI, Confidence Interval; DOX, doxorubicin; LEN, lenvatinib; PEM, pembrolizumab
Source: Study 309 / KN-775[84]

[redacted]

[redacted]

	LEN + PEM [b]			DOX [b]			LEN + PEM [b] vs. DOX [b]	
	N[c]	Participants with Event n (%)	Median Timed in Months [95% CI]	N[c]	Participants with Event n (%)	Median Timed in Months [95% CI]	Hazard Ratio [95% CI]	p-value
Overall Survival	[redacted]							

[redacted]

Abbreviations: CI, Confidence Interval; DOX, doxorubicin; LEN, lenvatinib; PEM, pembrolizumab

Source: Study 309 / KN-775[84]

[redacted]

Efficacy estimates (OS, PFS) (ITT population)

[redacted]

Treatment	N	Median OS [months] (95% CI)	Median PFS [months] (95% CI)
LEN+PEM	[redacted]		
TPC			
Pairwise comparison			
Hazard ratio (95% CI) [b]			
p-value [c]			

[redacted]

Abbreviations: CI, Confidence Interval; LEN, lenvatinib; OS, Overall Survival; PEM, pembrolizumab; PFS, Progression-free survival; TPC, Treatment of Physician's Choice

EORTC QLQ-C30 global health status score (ITT population)

Baseline global health score/quality of life scores [redacted]. Over 12 weeks of follow-up, participants receiving LEN+PEM or TPC [redacted] Within the ITT population, [redacted] were observed for those receiving LEN+PEM versus TPC: [redacted] versus [redacted] respectively. The between-group difference in least square mean score change from baseline at Week 12 was [redacted]

Empirical mean change from baseline and 95% CI for EORTC QLQ-C30 global health score/quality of life over time is provided in Figure 4

[redacted]

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	[redacted]					
TPC						

Pairwise Comparison	Difference in least square means (95% CI)[b]	p-value[b]
LEN+PEM vs. TPC	[redacted]	

[redacted]

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[84]

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[84]

7.1.2.1.1.2 Safety

Among the population group of the safety analysis set consisted of and . A total out of patients discontinued LEN+PEM due to adverse events, and out of patients discontinued DOX.

The overall incidence of treatment-emergent AEs (TEAE) and drug-related TEAEs was similar in the LEN plus PEM and DOX groups). Details regarding safety data for the LEN+PEM and DOX arm for the PFI < 6 months population is reported in Appendix E.

[redacted]

	LEN+ PEM [b] (N=204) n (%)	DOX [b] (N=200) n (%)
Any TEAEs	[redacted]	
Any Treatment-related TEAEs		
TEAEs With Worst CTCAE Grade of >=3[a]		
Treatment-related TEAEs With Worst CTCAE Grade of >=3[a]		
Any Serious TEAEs		
Any Treatment-related Serious TEAEs		
Any Fatal TEAEs		
Any Treatment-related Fatal TEAEs		
TEAEs Leading to Treatment Discontinuation		

[redacted]

Note: Non-serious adverse event up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.
MedDRA preferred term "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Data cut-off date: 26OCT2020
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; DOX, doxorubicin; LEN, lenvatinib; PEM, pembrolizumab; TEAE, treatment-emergent adverse event.
Source: Study 309 / KN-775[84]

[redacted]

	LEN+ PEM [b] (N=204)	DOX [b] (N=200)
Number of Participants exposed	[redacted]	
Total exposure person-months		
	Event Count and Rate (Event/100 person-months)[c]	
Events		
Treatment-related events		
TEAEs With Worst CTCAE Grade of >=3[a]		
Treatment-related TEAEs With Worst CTCAE Grade of >=3[a]		

	LEN+ PEM [b] (N=204)	DOX [b] (N=200)
Serious TEAEs		
Treatment-related Serious TEAEs		
Any Fatal TEAEs		
Any Treatment-related Fatal TEAEs		
TEAEs Leading to Treatment Discontinuation		

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; DOX, doxorubicin, LEN, lenvatinib; PEM, pembrolizumab; TEAE, treatment-emergent adverse event.
Source: Study 309 / KN-775[84]

7.1.3 Comparative analyses of efficacy and safety

In accordance with the DMC guidance, if a direct head-to-head study comparing the intervention in question for the submission with the comparator relevant in Danish clinical practice exists, an indirect comparative analyses is not requested [87]. As such the comparative analyses of efficacy and safety is omitted.

8 Health economic analysis

8.1 Model description

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 endometrial cancer (EC) who have disease progression following prior treatment with a platinum-containing therapy in less than 6 months (platinum free interval (PFI) < 6 months).. 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 (27).

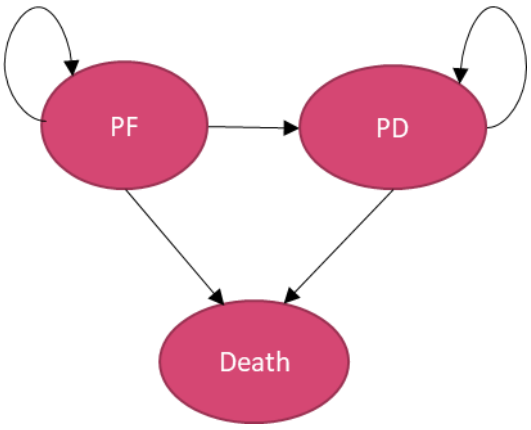
8.1.1 Model structure

The economic model is structured as a partitioned survival analysis model, with the following health states:

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

The model structure is presented in Figure 5; health state definitions are detailed in Section 8.1.1.1.

Figure 5: Model structure, partitioned survival analysis



Abbreviations: PD, progressed disease; PF, progression free.

8.1.1.1 Health states

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

In Study 309 / KN-775, OS and PFS were defined as follows:

OS was defined as the time from the date of randomization to the date of death due to any cause. Participants who were lost to follow-up and those who were alive at the date of data cut-off were censored at the date the participant was last known alive, or date of data cut-off, whichever occurred first.

PFS was defined as either:

PFS by blinded independent central review (PFS BICR; base case), defined as the time from the date of randomization to the date of the first documentation of disease progression, as determined by blinded BICR of objective radiographic disease progression per RECIST 1.1 or death due to any cause (whichever occurred first).

PFS by local investigator (PFS INV; scenario analysis), defined as the time from date of randomization to the date of the first documentation of disease progression, as determined by investigator per RECIST 1.1, or death from any cause, whichever occurred first.

PFS BICR applying alternative censoring rules (PFS BICR scenario 2 (SC2)). As per PFS BICR, this sensitivity analysis handles participants who discontinue treatment or initiate an anticancer treatment subsequent to discontinuation of study-specified treatments differently from the primary analysis (specifically, patients will be considered progressed at date of new anticancer treatment if new anti-cancer treatment is initiated, and patients will also be considered progressed if PD or death documented immediately after ≥2 consecutive missed disease assessments; both of these scenarios would be considered censoring events in the primary analysis).

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

8.1.2 Target Population

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

To align with DMC's request and Danish clinical practice, the model analysis considers patients with a PFI < 6 months who were also pre-assigned to receive DOX from Study 309 / KN-775.

8.1.3 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 AEs, subsequent treatment costs, and disease management costs. Time spent and transportation costs incurred by the patient were also included.

8.1.4 Cycle Length

A cycle length of 7 days (1 week) is used. Half-cycle correction is implemented using the life table method[1].

[1] 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.

8.1.5 Time Horizon and Discounting

The model adopts a lifetime time horizon of up to 36 years (mean age of 63.5 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. quality-adjusted life years [QALY]) outcomes were discounted at a rate of 3.5% for the first 35 years and at 2.5% for the year after in the base case in accordance with Danish guidelines [91].

8.1.6 Comparators

As per populations of interest, a comparison is presented comparing LEN+PEM with PLD in the population of patients with a PFI < 6 months and who were pre-assigned to DOX.

A summary of comparators and efficacy sources is presented in Table 14.

Table 14: Summary base case in the population of patients with a PFI < 6 months and pre-assigned to DOX

Comparator	Dose	Source of efficacy data	Source of safety data
PLD	40 mg/m^2 IV on Day 1 of each 21-day cycle	PFI <6 months *and* pre-assigned to DOX post-hoc subgroup, Study 309 / KN-775for LEN+PEM and PLD (assumed equivalent to DOX in TPC)	Pre-assigned to DOX and PFI<6 months population, 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.

8.1.7 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 26 October 2020. PLD was assumed identical to the DOX component of TPC in Study 309 / KN-775. Because patients were not randomized to DOX or paclitaxel within the TPC arm, naïve use of outcomes for patients who received DOX may provide biased estimates of efficacy; where estimates of efficacy were required (OS, PFS, and TTD), 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)
- Aes 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 Table 15 and sections 8.3, 8.4 and 8.5. Other relevant inputs were sourced from relevant HTA submissions and literature, and costs were derived from Danish sources. The cost inputs (presented in section 8.5) included drug costs, administration, subsequent treatment costs, AE and disease management costs, and non-medical direct costs (transportations costs and time spent). A full list of model inputs is presented in Appendix I – Probabilistic sensitivity analyses.

8.1.8 Model outputs

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

- Total costs
- Disaggregated costs
- Total QALYs
- Disaggregated QALYs
- Life years (Lys)
- Disaggregated Lys.

8.1.9 Mortality

Background mortality is modelled using female general population life tables for Denmark [92]. Overall survival and PFS were constrained to be greater than or equal to the age-matched general population rate.

8.1.10 Model validation

In line with the International Society for Health Economics and Outcomes Research (ISPOR) taskforce report on model transparency and validation[2] [93], 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 (HTA) agencies [94]. Data use was compared with another model in ovarian cancer to assess the face validity of the structural choices in this analysis [95], 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 (also known as verification) was conducted once by the primary modeler and once by a modeler external to the project and included: cell-by-cell checks of formulae, rebuilding of key sections of the model, logical tests, a full audit of model inputs.

An economic SLR was conducted to identify cost-effectiveness studies in the population, as an external validation approach. Cost-effectiveness for LEN and/or PEM in similar indications is limited, however, Thurgar et al [96] identified PEM to be associated with an additional 4.68 Lys and 3.80 QALYs vs chemotherapy for the treatment of US women with previously treated dMMR, MSI-H or metastatic EC [96].

Finally, an online advisory meeting was undertaken on September 22nd, 2021. Three clinical experts and three health economists attended, and topics of discussion included the plausibility of alternative extrapolations for all outcomes, the validity of alternative data sources, the validity of other key assumptions, and medical resource use. Full details are reported elsewhere [97].

[2] Note that no attempt was made to conduct a predictive validation (the fifth validation type specified in the ISPOR taskforce report).

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

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

The model inputs for clinical effect and utility values are summarized in Table 15 (further information is provided in sections 8.3 and 8.4). The clinical documentation presented in section 7.1 describes relevant efficacy measures for the treatment with LEN+PEM.

Table 15. Input data used in the model, population pre-assigned to DOX, PFI < 6 months

Name of estimates	Results from study or indirect treatment comparison (ITC)	Input value used in the model (base case)	How is the input value obtained/estimated**
LEN+PEM			
PFS	See section 8.3.2 Observed PFS Kaplan-Meier curves for LEN+PEM from Study 309/KN775	See section 8.3.2 Individual PFS curves Log-logistic distribution	Study 309/KN775 data extrapolated
OS	See section 8.3.1 and Observed OS Kaplan-Meier curves for LEN+PEM from Study 309/KN775	See section 8.3.1 Individual OS curves Log-normal distribution	Study 309/KN775 data extrapolated
TTD	See section 8.3.3 Potocol-mandated maximum number of cycles for PEM in Study 309 / KN-775	See section 8.3.3 capped at 24 months	Study 309/KN775 protocol and clinical feedback
Grade ≥3 TEAE	See section 8.4 Number of patients in Study 309/KN775 with Aes	Rate per model cycle from Study 309/KN775	Study 309/KN775
Pre-progression utility	EQ-5D-5L measured in Study 309/KN775	See section 8.5 The utility values were derived from a statistical analysis of the trial. Danish population weights applied to estimate health state utility values (refer to Appendix H – Mapping of HRQoL data)	Statistical regression analysis on Study 309/KN775 utility data
Post-progression utility			Statistical regression analysis on Study 309/KN775 utility data
PLD			
PFS by BICR	See section 8.3.2 Observed PFS Kaplan-Meier curves for DOX from Study 309/KN775	See section 8.3.2Generalised gamma distribution	Study 309/KN775 data (DOX arm) extrapolated
OS	See section 8.3.1 Observed PFS Kaplan-Meier curves for DOX from Study 309/KN775	See section 8.3.1 Gompertz distribution parameters:	Study 309/KN775 data (DOX arm) extrapolated

TTD	See section 8.3.3 Observed TTD curves for doxorubicin from Study 309/KN775	See section 8.3.3 KM data from Study 309/KN775	Study 309/KN775 observed data (DOX arm)
Grade ≥3 TRAE	See section 8.4 Number of patients in Study 309/KN775 with Aes	See section 8.4 Rate per model cycle from Study 309/KN775	Study 309/KN775 (DOX arm)
Pre-progression utility	EQ-5D-5L measured in Study 309/KN775	See section 8.5 The utility values were derived from a statistical analysis of the trial.	Statistical regression analysis on Study 309/KN775 utility data
Post-progression utility		Danish population weights applied to estimate health state utility values (refer to Appendix H – Mapping of HRQoL data)	Statistical regression analysis on Study 309/KN775 utility data

Abbreviations: DOX, doxorubicin,ITC, indirect treatment comparison; OS, overall survival; PFS by BICR, progression free survival by blinded independent central review; PLD, pegylated liposomal doxorubicin; TEAE, treatment emergent adverse events; TTD, time to discontinuation.

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

8.2.2.1 Patient population

The Danish patient population: The mean age of patients in the Danish population is slightly higher (approximately 0-3.5 years) than in Study 309 / KN-775according to clinical expert opinion.

Patient population in the clinical documentation submitted: The patient population of Study 309 / KN-775study consisted of adult patients with advanced endometrial cancer who have received prior treatment with a platinum-containing therapy. Selected baseline characteristics are presented in Table 16.

Patient population in the health economic analysis submitted: Values for age, body surface area (BSA) and weight were derived from analysis of patient-level data from Study 309 / KN-775for patients pre-assigned to doxorubicin, PFI < 6 months and are presented in Table 16.

Table 16: Patient population of Study 309 / KN-775, population pre-assigned to DOX, PFI < 6 months arm in study 309 / KN-775and Danish clinical practice.

Patient population Important baseline characteristics	Clinical documentation / (including source)	Full population of Study 309 / KN-775	Used in the model: Population Pre-assigned to DOX, PFI < 6 months, (number/value including source)	Danish clinical practice (including source)
Age (years)	Analysis of Study 309 / KN-775patient-level data	63.53 (62.91, 64.15)	63.06 (SD: 9.4)*	63.5-67 (clinical opinion)
BSA (m^2)		1.73 (1.29, 2.16)	1.70 (SD: 0.2)	Assumed to be similar to Danish population
Weight (kg)		70.51 (69.23, 71.79)	68.9 (SD: 17.4)	
Baseline EQ-5D index score		0.74 (0.73, 0.76)	0.81 (SD: 0.21)	

Note: Data cut-off date: 26OCT2020

Abbreviations: BSA, body surface area; DOX, doxorubicin

Source: Baseline and Demographic Characteristics, ITT Population For Pre-assigned to Doxorubicin, Platinum-Free Interval < 6 Months. Additional statistical analysis, Study 309 / KN-775.

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice (as defined in section 8.2): It is expected that LEN+PEM will be used as described in the SmPC.

Intervention in the clinical documentation submitted: In Study 309 / KN-775, the treatment arm LEN was administered (20 mg) orally once daily (QD) during each 21-day cycle for up to 35 cycles, and PEM (200 mg) by intravenous (IV) infusion on Day 1 of each 21-day cycle.

Intervention as in the health economic analysis submitted: The intervention considered in the cost-effectiveness analysis is LEN+PEM. LEN (20 mg) was administered orally once daily during each 21-day cycle for up to 35 cycles. PEM (200 mg) was administered by IV infusion on Day 1 of each 21-day cycle. For further details please see section 5.3.

Table 17. Intervention – LEN+PEM

Intervention	Clinical documentation (including source)		Used in the model (number / value including source)	Expected Danish clinical practice (including source if known)
	LEN+PEM	Source		
Posology	LEN 20 mg orally once daily in combination with PEM (200mg) every three weeks administered intravenously in 3-week cycles	Study 309 / KN-775	Same as clinical documentation	Expected to be used as described in SmPC
Length of treatment (time on treatment) Criteria for discontinuation	Until disease progression is radiographically documented and verified by BICR per RECIST 1.1, and only when clinically appropriate, confirmed by the site per modified RECIST 1.1 for immune-based therapeutics (iRECIST), unacceptable adverse event(s) (AEs), withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, until the participant has received 35 administrations of PEM (approximately 2 years)	Study 309/KN775	Same as clinical documentation	
The pharmaceutical's position in Danish clinical practice	NA		Following prior platinum-based therapy	Following prior platinum-based therapy

Abbreviations: AE, adverse event; BICR, blinded independent central review; LEN, Lenvatinib; PEM, pembrolizumab; NA, not applicable; RECIST, Response Evaluation Criteria in Solid Tumours; SmPC, summary of product characteristics.

8.2.2.3 Comparator

Table 18. Base case comparator – PLD for PFI < 6 months

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	NA (off-label given lack of treatment options)	40 mg/m² IV on Day 1 of each 21-day cycle up to a maximum cumulative dose of 500 mg/m² (per study 309 protocol for doxorubicin)	Following prior platinum-based therapy
Length of treatment	NA (off-label given lack of treatment options)	Until disease progression is radiographically documented and verified by BICR per RECIST 1.1, and only when clinically appropriate, confirmed by the site per modified RECIST 1.1 for immune-based therapeutics (iRECIST), unacceptable adverse event(s) (AEs), withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, until the participant has received a lifetime cumulative dose of 500 mg/m² of doxorubicin.	
The comparator's position in the Danish clinical practice	NA (off-label given lack of treatment options)	Following prior platinum-based therapy	NA (off-label given lack of treatment options)

Abbreviations: AE, adverse event; IV, intravenous; BICR, blinded independent central review; PLD, Pegylated liposomal doxorubicin, NA, not applicable; RECIST, Response Evaluation Criteria in Solid Tumours.

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation: Details about the relative efficacy outcomes are presented in section 7.

Relevance of the documentation for Danish clinical practice: The clinical documentation is relevant for the Danish population as it describes relevant efficacy measures for the proposed treatment in Denmark. Also, the relative efficacy outcomes are in line with the current clinical practice, as mentioned in section 5.

The relative efficacy outcomes in the submitted health economic analysis: The main efficacy inputs presented in the model are OS, PFS and TTD. The base case inputs were obtained through Study 309 / KN-775in a direct comparison derived from a post-hoc analysis using pre-assigned to DOX cohort with PFI < 6 months.

Table 19. Summary of Parameterization of efficacy outcomes

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Overall survival (OS)	Study 309 / KN-775	LEN+PEM: Log-normal distribution PLD: Gompertz distribution
Progression-free survival (PFS)		LEN+PEM: Log-logistic distribution TPC: Generalised gamma distribution
Time to treatment discontinuation (TTD)		PEM and PLD: KM data from Study 309/KN775 LEN: Gompertz distribution

Abbreviations: LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin, TTD, time to discontinuation.

Table 20. Summary of relevance of the relative efficacy outcomes included in the health economic model

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Overall survival (OS)	Kaplan-Meier curves	Very relevant	Very relevant
Progression-free survival (PFS)	Kaplan-Meier curves	Very relevant	Very relevant
Time to treatment discontinuation (TTD)	Kaplan-Meier curves	Relevant	Relevant

Abbreviations: LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin, TTD, time to discontinuation.

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted: Information on adverse events for LEN+PEM was obtained from Study 309 / KN-775.

Adverse reaction outcomes in the health economic analysis submitted: Modelled AEs include all those:

- Considered treatment-related in Study 309 / KN-775
- Grade 3–5, occurring in >5% of patients
- Expected to be associated with an impact on QoL and/or cost.

Modelled Grade 3-5 AEs were taken from the pre-assigned to DOX and PFI < 6 months population of Study309 / KN-775for the LEN+PEM and PLD comparison (Table 21).

Table 21. Modelled Grade 3-5 AEs from Study 309 / KN-775included in the economic model, pre-assigned to DOX and PFI<6 months population.

Grade 3–5 AE	Total number of events		Average duration per event (days)	Rate per model cycle†	
	LEN+PEM	DOX (Study 309)		LEN+PEM	PLD
Anaemia	[redacted]				
Decreased appetite					
Diarrhoea					
Febrile neutropenia					
Hypertension					
Leukopenia					
Lipase increased					
Neutropenia					
Neutrophil count decreased					
Weight decreased					
White blood cell count decrease					

Footnote: †AE rate was calculated using the total exposure time in Study 309 / KN-775of 119,296 days in the LEN+PEM arm and 53,726 days in the TPC arm to derive a rate per 7-day cycle.
Note: Database cut-off date: 26OCT2020

Abbreviations: DOX, doxorubicin; LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; PLD, pegylated liposomal doxorubicin, TTD, time to discontinuation.

Source: Grade 3-5 Treatment-related Adverse Events, APaT Population for Pre-assigned DOX Population Platinum-Free Interval < 6 Months. Post-hoc analysis.

8.3 Extrapolation of relative efficacy

As described in Section 8.1.1, 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 curves from Study 309 / KN-775for LEN+PEM. As the follow-up period for Study 309 / KN-775 was shorter than the modelled time horizon, extrapolation from the observed OS, PFS and TTD data was required.

The analysis was supplemented by clinical expert opinion (List of experts in Section 11).

A range of standard parametric distributions were explored for extrapolation of the OS, PFS and TTD endpoints:

- Exponential
- Generalised gamma
- Gompertz
- Lognormal
- Loglogistic
- Weibull

Outcomes were extrapolated for the pre-assigned to DOX and PFI<6 months subgroup in order to provide unbiased estimates of efficacy relative to DOX (which is assumed to have the same efficacy as PLD).

8.3.1 OS

[redacted] presents overall survival in the pre-assigned to DOX and PFI <6 months population.

[redacted]

The proportional hazards assumption was assessed using plots of the log-cumulative hazard. For OS in the pre-assigned to DOX and PFI < 6 months population, the plots become clearly separated over time and appear reasonably parallel. Schoenfeld residuals are shown in Appendix G – Model extrapolations. Number of risks are provided in Figure 3.

Figure 18 shows the log-cumulative hazard over time between the two arms. Global testing of the proportional hazards assumption provided a p-value of 0.6059, therefore the null hypothesis of proportional hazards could not be rejected at the 95% level of confidence.

The underlying mechanism of action for immunotherapies including PEM typically leads to effects which can be approximately divided into three stages, as described by Quinn et al [98].

- Non-separation of the Kaplan-Meier survival curves during the initial treatment phase
- Separation of the Kaplan-Meier curves as activation of the immune cells leads to a clinically measurable antitumor effect in patients receiving immunotherapy, and those receiving chemotherapy develop resistance to treatment.
- Plateauing of the tail of the immunotherapy Kaplan-Meier curve many months after the first administration and continuing long after treatment has ceased.

Clinical experts [97] confirmed the proportional hazards assumption was not likely to hold in the long-term because of differences in the mechanism of action between immunotherapy and other chemotherapies. . Based on these observations, an independent modelling approach was adopted, in which independent curves were estimated for each arm of Study 309 / KN-775.

Extrapolations based on independent statistical models are presented for OS in Figure 7 and Figure 8, and corresponding model fit diagnostics for each of the six standard parametric distributions are presented in Appendix G – Model extrapolations. AIC and BIC criteria are provided in Table 58 (OS) and Table 59 (PFS) in Appendix G – Model extrapolations of the submission.

For the pre-assigned to DOX and PFI<6 months population, the lognormal was selected for LEN+PEM on the basis of:

- Statistical fit (cf. Table 62)
- Visual inspection
- Comparison with the 2-years OS from the study (about 34.5% of patients alive from the KM curve) with the curves: the 2-years OS is 34.2% for lognormal
- External validation: whilst no suitable long-term data for this patient population was identified against which to directly compare extrapolated outcomes, the base-case extrapolations are consistent with the beliefs about expected outcomes expressed [97]. Specifically:
  - A minority of patients are assumed to long-term benefit from treatment with LEN+PEM (the model predicts 5- and 10- year survival of 11% and 3%, respectively, for patients receiving LEN+PEM).

The Gompertz model was selected for DOX, based on:

- Visual inspection
- External validation: whilst no suitable long-term data for this patient population was identified against which to directly compare extrapolated outcomes, the base-case extrapolations are consistent with the beliefs about expected outcomes expressed [97]. Specifically:
  - No survivors are expected at 5 years for DOX

The Gomperzt function was selected based on visual inspection and expected percent of patients alive at 5 years. The best statistical fit, lognormal, is presented in a scenario analysis (Table 45).

The use of different distributions for each study arm is less common than the use of the same distribution, and NICE TSD 14 suggests:

If different types of model seem appropriate for each treatment arm this should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis [99].

Immunotherapies such as PEM differ from chemotherapies in that they prime the immune system to attack tumours, rather than attempting to directly destroy cancerous cells [98]. This mechanism of action can lead to durable response and long-term remission in some patients. A review of survival modelling in economic evaluations for immunotherapies has previously reported that separation of curves and a plateauing of the tail in the long-term are typical features of survival curves when comparing immunotherapies to conventional treatments [98]. Because of these differences in mechanism of action and consequent differences in the patterns of long-term survival, we believe that the use of different distributions provides more plausible assumptions for the extrapolation of OS in the base-case (see also above for discussion).

A plot of the hazard over time is presented in Appendix G – Model extrapolations for LEN+PEM and DOX, respectively. As noted above, the hazard for LEN+PEM, as for other immunotherapies, would be expected to decline over time as some patients may be expected to achieve long-term remission; the selected lognormal distribution exhibits a declining hazard over time (see Appendix G – Model extrapolations), and therefore the use of this to inform the long-term hazard function was considered biologically plausible.

[redacted] presents the base case OS extrapolations for LEN+PEM and PLD.

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A scenario analysis is provided with the lognormal curve for both LEN+PEM and DOX OS.

8.3.2 PFS

Figure 10 presents PFS in the pre-assigned to DOX and PFI<6 months population.

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Plots of the log-cumulative hazard are presented in [redacted] for PFS BICR in the pre-assigned to DOX population of Study 309 / KN-775. Schoenfeld residuals are also shown in [redacted], and [redacted] presents the instantaneous hazards over time between the two arms. Global testing of the proportional hazards assumption provided a p-value of 0.9652, therefore the null hypothesis of proportional hazards could not be rejected at the 95% level of confidence.

Similar to OS, independent models were observed to provide better fitting extrapolations to both the DOX and LEN+PEM arms of Study 309 / KN-775. Clinical experts also confirmed that the proportional hazards assumption was not likely to hold in the long-term (see Appendix J - Key model assumptions applied in the base case for discussion). Based on these observations, an independent modelling approach was adopted, in which independent curves were estimated for each arm of Study 309 / KN-775.

Model fit diagnostics for each of the six standard parametric distributions are presented in [redacted] As described above, independent statistical models were selected to extrapolate PFS over the model horizon. The log-logistic and generalized gamma models were selected for LEN+PEM and DOX arms, respectively, based on minimization of the AIC and BIC (cf. Table 63). Extrapolations based on independent statistical models are presented in Figure 11 and Figure 12 for LEN+PEM and DOX. A plot of the hazard over time is presented in Appendix G – Model extrapolations for LEN+PEM and DOX, respectively.

As noted above, the hazard for LEN+PEM, as for other immunotherapies, would be expected to decline over time as some patients may be expected to achieve long-term remission; the selected log-logistic distribution exhibits a declining hazard over time (see Appendix G – Model extrapolations), and therefore the use of this to inform the long-term hazard function was considered biologically plausible.

PFS events include death events, and therefore, not all PFS events are associated with the costs of subsequent therapy. To estimate the number of new progression events per cycle, and to allocate the cost of post-progression therapies, the proportion of progression events is taken from Study 309 in the LEN+PEM and DOX arms and applied to the per-cycle probability of PFS (87%).

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[redacted] presents the base case PFS extrapolations for LEN+PEM and PLD.

[redacted]

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8.3.3 TTD

In the model, TTD for LEN and PEM is capped at 24 months given clinical feedback on the likely use of LEN following end of treatment with PEM, and the protocol-mandated maximum number of cycles for PEM in Study 309 / KN-775. Treatment discontinuation for DOX was observed completely during Study 309 / KN-775. The observed Kaplan-Meier data are therefore used until this timepoint, and extrapolation is therefore not required for the pre-assigned to DOX and PFI<6 months (Figure 14).

A scenario is presented where LEN discontinuation does not stop at 24 months, and here the Gompertz distribution was selected based on the lowest AIC.

In Study 309 / KN-775, a proportion of randomized patients did not start treatment in both the LEN+PEM and TPC arms. As such, TTD used in the model is applied to the proportion of patients who started treatment in all treatment arms, as shown in Table 22.

Table 22 Proportion of patients who started treatment in Study 309 / KN-775, pre-assigned to DOX population

	LEN+PEM (n, [%])	TPC (n, [%])
Started treatment	[redacted]	
Did not start treatment		

Abbreviation: DOX, doxorubicin; LEN, lenvatinib; PEM, pembrolizumab; TPC, treatment of physician's choice.

Hence, in the model the proportion of patients on treatment at any given cycle consists of the TTD curves applied to the proportion of patients who started treatment, capped by the proportion of patients in PFS. The latter reflect the assumption that patients stop treatment after progression. In addition, for LEN+PEM a stopping rule is applied in the base case, where no patients are on treatment after 24 months. A scenario analysis present the ICER without the stopping rule for LEN.

8.4 Documentation of relative safety

Modelled AEs include all those:

- Considered treatment-related in Study 309
- Grade 3–5, occurring in >5% of patients in either arm
- Expected to be associated with an impact on QoL and/or cost.

The number of events for each of the modelled AEs in each arm are presented in Table 23 for the pre-assigned to DOX and PFI<6 months population, from Study 309. The exposure adjusted AE rate observed in the LEN+PEM arm was 0.02 per 7-day cycle, compared with 0.10 per 7-day cycle for the PLD.

The weighted duration of AEs, based on the number of occurrences for each AE and the average duration per event from Study 309, was 112.70 days in the LEN+PEM arm, vs 20.18 days in the liposomal DOX arm. AEs with PLD were assumed equal to DOX in Study 309. Duration of AEs is used to derive the duration of the QoL decrement. A number of hours lost due to AEs is also included to derive productivity loss from AEs.

Costs for AEs reflect a hospitalisation based on DRG tariffs independent of the full duration of AEs.

[redacted]

Grade 3–5 AE	Total number of events		Average duration per event (days)	Rate per model cycle†	
	LEN+ PEM	DOX (Study 309)		LEN+PEM	Liposomal DOX
Anaemia	[redacted]				
Decreased appetite					
Diarrhoea					
Febrile neutropenia					
Hypertension					
Leukopenia					
Lipase increased					
Neutropenia					
Neutrophil count decreased					
Weight decreased					
White blood cell count decreased					

Abbreviations: AE, adverse event; DOX, doxorubicin; ITT, intention to treat; LEN, lenvatinib; PEM, pembrolizumab; TPC, treatment of physician's choice.

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

The health state utility values used in the model originate from Study 309 / KN-775, based on patient level data. The values were estimated with EQ-5D-5L using published tariffs for the Danish population [100].

For use within the economic model, multivariable linear mixed models were fitted to the EQ-5D index score, and covariates representing baseline EQ-5D index score, presence of Grade 3–5 AEs occurring in >5% of patients at the time of observation, treatment arm, being 'on' vs 'off' treatment, progression-status, and time before death were considered for inclusion in the model, and models were compared using the AIC and BIC diagnostic statistics, and variables which led to improvements (reductions) in these statistics retained. 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 AEs and subgroup membership).

The final statistical model of EQ-5D including PFI<6 months and pre-assigned to DOX population is presented in Table 24. The model chosen is aligned with the health states definitions, as it is the model including pre-post progression covariates with the best fits. Results suggested small decrements associated with observations post-progression (–0.037; p<0.001) and experiencing AEs at the time of observation (–0.013; p=0.136). Being on treatment (independent

of which treatment) was associated with a significant increase in EQ-5D (0.140; p<0.001). Full details are provided in Appendix H – Mapping of HRQoL data.

Table 24 EQ-5D based on PFI<6 months and pre-assigned to DOX

Parameter	Coefficient	s.e.	P>z	95% CI
Baseline EQ-5D	[redacted]			
Post-progression decrement				
AE disutility				
On treatment increment				
Constant				

Abbreviations: PFI, platinum free interval; DOX, Doxorubicin; AE, adverse event; CI, confidence interval; s.e., standard error.

However, as detailed in Appendix H – Mapping of HRQoL data, a model (model 12) which includes time-to-death covariates provided better statistical fits and was consider relevant to include as a scenario analysis.

Predictions of health states utility values, derived from applying the coefficients related to baseline EQ-5D and post-progression decrement, as well as including the constant coefficient, are presented in Table 25 below.

Table 25: Model health state utilities (predictions from the statistical model)

Health state	Utility value
Progression-free	0.652
Progressed disease	0.615

In the model, the utility calculations include all the coefficients from Table 24. The resulting combined utility value varies for each model cycle based on the proportion of patients pre/post progression, on-treatments and with AEs. An age-adjustment is also applied.

8.6 Resource use and costs

8.6.1 Drug Acquisition Costs

All 2022 pharmacy purchase prices have been fetched for the drug acquisition cost from medicinpriser.dk and is summarised in Table 26 below and includes the list of agents that are eligible for vial wastage in the submission and has been amended to note which therapies are subject to these assumptions, details of which can be found below.

Table 26. 1L Drug Acquisition Costs

Treatment	Pack #1			Pack #2			Source
	Dose	#Units per pack	Price (DKK)	Dose	#Units per pack	Price (DKK)	
PEM	100.0 mg	1	23204,61	-	-	-	Medicinpriser.dk [101]

Treatment	Pack #1			Pack #2			Source
	Dose	#Units per pack	Price (DKK)	Dose	#Units per pack	Price (DKK)	
LEN	4.0 mg	30	12551,71	10.0 mg	30	12551,71	
PLD*	20.0 mg	1	2487,31	-	-	-	

Footnote: *Method of moments used to calculate dose and associated vial wastage.
Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; PLD, pegylated liposomal doxorubicin.

Table 27 presents the dosing of each 1L treatment, to enable the calculation of drug cost per patient.

Table 27: The dosing scheme

Drug	Dependency	Dose	Administrations per cycle	Treatment cycle length (days)	Dose intensity	Source
LEN	Fixed dose per day	20.0 mg	7	7	Study 309 / KN-775(see below)	Study 309 / KN-775[84]
PEM	Fixed dose	200.0 mg	1	21	96%	Study 309 / KN-775[84]
PLD	Fixed mg/m2	40 mg	1	21	Method of moments	Study 309 / KN-775[84]

Abbreviations: LEN, lenvatinib; PEM, PEM, pembrolizumab, PLD, pegylated liposomal doxorubicin.

The acquisition cost of LEN+PEM amounted to DKK 44,453 per administration of PEM and DKK 19,254 per 30-day prescription for LEN. In the base case the cost of PEM is based on a fixed dose.

A scenario analysis is provided with a PEM dose based on weight, with 2 mg/kg every 3 weeks. In this scenario, as for any weight-based drug costs (PLD and subsequent therapies), the method of moments was used to calculate the cost of drug acquisition, where the dose intensity is based on a distribution of patients' weight.

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.

Vial wastage is applied to medicines administered intravenously based on BSA or weight. BSA and weight are reported in Table 16. The model base case assumed that vials will not be shared between patients for a conservative estimate of drug acquisition costs.

The dose intensity is calculated for each intervention in the following ways.

- PEM: a dose intensity of 96% 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 28 below [102].

Table 28: Cumulative days per dose

Daily dose (mg)	% of days
0	[redacted]
4	
8	
10	
14	
20	
40	

- 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 (Table 29). 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 [102]. This method is also used for subsequent therapies.

Table 29: Dose calculations for PLD

Total dose	Number of vials	Proportion of the cohort
20	1	[redacted]
40	2	
60	3	
80	4	
100	5	
120	6	

Using the packs characteristics, dosing schemes, and dose intensity, a cost per treatment cycle is then calculated, as shown in Table 30 (in the base case, with no vial sharing).

Table 30: Calculated 1L drug acquisition costs

Intervention	Drug	Cost per treatment cycle (DKK)
LEN + PEM	LEN	19 253.62
	PEM	44 452.60
PLD	PLD	9 720.29

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

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8.6.2 Administration Costs

The unit costs for administration were obtained from *Sundhedsdatastyrelsen DRG-ta*kster 2022 [103] and is applied to the administrations in the model. The unit cost of administration is presented in Table 31.

Table 31: Unit costs of modes of administration

Mode of administration	Unit Cost	Source
Oral chemotherapy	DKK 0	Assumption
Parenteral chemotherapy	DKK 1 921.00	DRG-takster 2022, MDC13 1-dagsgruppe, pat. mindst 7 år: 13MA98 [103]

Abbreviation: DRG, diagnosis-related group.

The mode of administration for each type of drug is presented in Table 32. The administration cost associated with LEN is DKK 0 by assumption, as it is administered orally. PEM and PLD are both delivered as parenteral chemotherapy, and each incur an administration cost of DKK 1 921 per administration. Administration costs are also subject to administration intensity in the model base case.

Table 32: Mode of administration for each drug

Cost of Administration	Mode of administration	Unit Cost	Source
LEN	Oral chemotherapy	DKK 0	Assumption
PEM	Parenteral chemotherapy	DKK 1 921.00	DRG-takster 2022, MDC13 1-dagsgruppe, pat. mindst 7 år: 13MA98 [103]
PLD	Parenteral chemotherapy	DKK 1 921.00	DRG-takster 2022, MDC13 1-dagsgruppe, pat. mindst 7 år: 13MA98 [103]

Abbreviation: DRG, diagnosis-related group; LEN, lenvatinib; PEM, pembrolizumab; PLD, pegylated liposomal doxorubicin.

8.6.3 Disease Management Costs

Healthcare resource use categories considered in the model are presented in Table 33. Rates of resource use associated with disease management were based on inputs from Danish clinical experts (see section 11 for details) [104]. The cost of each category was sourced from Sundhedsdatastyrelsen DRG-takster 2022 [103], Laboratoriemedicinsk Vejledning [105] and GP tariff costs were applied from the Honorartabel dagtid: Overenskomst om almen praksis [106]. The GP visits assumes only a consultation and does not include any additional tests. The frequency reported by KOLs and the frequency of use for each resource per model cycle is reported for both progression-free patients and progressed patients.

Table 33: Disease management costs

Type of resource	Unit cost	Frequency reported by KOLs	Frequency per model cycle in model	Reference
Consultation, oncology	DKK 1 921	PFS: 1 visit per month	Progression free: 0.229 Progressed: 0.076	DRG-takster 2022, MDC13 1-daggruppe, pat. mindst 7 på- 13MA98, Diagnosis: DC549 Livmoderkræft [103] Frequency: clinical expert input – Denmark [104]

Type of resource	Unit cost	Frequency reported by KOLs	Frequency per model cycle in model	Reference
		PD: 1 visit every 3 months		
Blood count	DKK 300	PFS: 1 visit per month PD: 1 visit per month	Progression free: 0.229 Progressed: 0	Laboratoriemedicinsk Vejledning, Combination of the following costs: Hæmoglobin;B, Erytrocytter, vol.fr.;B, Leukocytter;B, C-reaktivt protein [CRP];P, Albumin;Plv, Urat;P, Methæmoglobin;Hb(B), Trombocytter;B, Reticulocytter;B, Kreatinin;P (NPU02319, NPU01961, NPU02593, NPU19748, NPU19674, NPU03688, NPU02725, NPU03568, NPU08694, NPU04998) [105] Frequency: clinical expert input – Denmark [104]
CT scan	DKK 2411	PFS: 1 scan every 3 months PD: 1 scan every 3 months	Progression free: 0.076 Progressed: 0	DRG-takster 2022, CT-scanning, kompliceret-30PR06, Diagnosis: DC549 Livmoderkræft [103] Frequency: clinical expert input – Denmark [104]
GP visit	DKK 149	PFS: 1 visit every 2 month PD: 1 visit every 2 month	Progression free: 0.114 Progressed: 0.114	Honorartabel dagtid: Overenskomst om almen praksis, 0101 – Konsultation [106] Frequency: clinical expert input – Denmark [104]

Abbreviations: CT, computerised tomography; DRG, diagnosis-related group; GP, general practitioner PD: progressed disease; PFS: progression-free survial.

8.6.4 Subsequent Treatments

Subsequent therapy lines and proportions are presented in Table 34 and were based on Danish clinical expert inputs for each comparator as these were deemed relevant in Danish clinical practice [104]. The subsequent therapies from Study 309 / KN-775were not used in the model as they were not reflective of Danish clinical practice.

Note that the Danish clinical expert interview answers have 50% PLD and 50% paclitaxel. For the subsequent therapy costings, we use the duration of treatment from the trial. In absence of data for PLD from the trial, we used doxorubicin as a proxy for PLD. Hence the model uses 50% doxorubicin and 50% paclitaxel as subsequent treatments.

Table 34: Subsequent therapy scenario – KOL input

Subsequent therapy	2L			
	LEN+PEM	PLD	LEN+PEM	PLD

DOX	50%	50%	50%	50%
Paclitaxel	50%	50%	50%	50%

Abbreviations: DOX, doxorubicin; KOL, key opinion leader; LEN+PEM, lenvatanib and pembrolizumab; PLD, pegylated liposomal doxorubicin 2L, second-line; 3L, third-line.

The drug acquisition costs for subsequent therapy are present in Table 35 below.

Table 35: Subsequent treatment acquisition costs

Treatment	Pack #1			Pack #2			Pack #3			Source
	Strength per Unit (mg)	# Units per Pack	Price (DKK)	Strength per Unit (mg)	# Units per Pack	Price (DKK)	Strength per Unit (mg)	# Units per Pack	Price (DKK)	
Paclitaxel*	100	1	110.50	150	1	1500	300	1	201.50	Medicinpriser.dk [101]
Doxorubicin*	10	1	150	50	1	120	200	1	360	Medicinpriser.dk [101]

Footnote: *Method of moments used to calculate dose and associated vial wastage.

The duration of subsequent therapy is presented in Table 36 below.

Table 36: Subsequent treatment duration

Subsequent treatment costs	2L	3L	Source
	Duration (days)	Duration (days)	
Paclitaxel	86	71	Analysis of Study 309 patient-level data. February 2021.
Doxorubicin	70	69	Analysis of Study 309 patient-level data. February 2021.

Subsequent treatment costs for the 2L and 3L subsequent therapies are shown in Table 37 below. The costs as per treatment were calculated as the product of the per cycle drug acquisition and drug administration costs for each subsequent treatment, proportion of patients eligible to receive subsequent treatments by treatment arm, the proportions receiving each subsequent treatment by 1L treatment arm and the duration of each subsequent treatment.

Table 37: Subsequent treatment costs

Subsequent treatment costs	2L		3L	
	LEN+PEM	DOX/Comparator	LEN+PEM	DOX/Comparator
One-off cost	DKK 15,647	DKK 15,647	DKK 13,558	DKK 13,558

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; TPC, treatment of physician's choice; 2L, second line; 3L third line.

The model assumes that subsequent treatment costs are incurred at treatment progression as a one-off cost. At each cycle, the sum of incident treatment discontinuers is multiplied by the one-off subsequent treatment cost associated with LEN+PEMM or DOX. To estimate the number of new progression events per cycle, and to allocate the cost of post-progression therapies, the proportion of progression events is taken from Study 309 in the LEN+PEM and DOX arms and applied to the per-cycle probability of PFS (87%, see section 8.3.2).

8.6.5 AE costs

In order to capture the resource use associated with adverse events, the unit costs of adverse events were obtained from *Sundhedsdatastyrelsen DRG-takster 2022* [103]. The frequency of experiencing ≥ grade 3 adverse events while on treatment was obtained from Study 309 / KN-775, as described in section 8.2.2.5. All unit costs were applied to a per cycle rate of events whilst on treatment, derived from the frequency of adverse events from Study 309 / KN-775. The rate of events for PLD was assumed equal to TPC.

Table 38: Adverse event costs

Adverse event	Unit cost	Reference
Anaemia	DKK 3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD592: Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel [103]
Decreased appetite	DKK 1,954	DRG 2022, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR630: Appetitløshed [103]
Diarrhoea	DKK 6,756	DRG 2022, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS [103]
Febrile neutropenia	DKK 3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel [103]
Hypertension	DKK 1,318	DRG 2022, 05MA98: MDC05 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DI109: Essentiel hypertension [103]
Leukopenia	DKK 3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728H: Leukopeni [103]
Lipase increased	DKK 2,910	DRG 2022, 07MA98: MDC07 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR748D: Abnorm serumlipase [103]
Neutropenia	DKK 3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Neutropeni UNS [103]
Neutrophil count decreased	DKK 3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728: Anden forstyrrelse i hvide blodlegemer [103]
Weight decreased	DKK 1,954	DRG 2022, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR634: Abnormt vægttab [103]
White blood cell count decreased	DKK 3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728: Anden forstyrrelse i hvide blodlegemer [103]

Abbreviations: DRG, diagnosis-related group

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8.6.6 Non-medical direct costs

Based on the *Medicinrådet - Værdisætning af enhedsomkostninger* guidelines [107] 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 39. Patient costs used in the model

Costs	Unit Cost	Source
Transport costs		
Transportation costs – to and from treatment	DKK 140	Average transport costs, based on the guidelines by Medicinrådet Multiplied with the frequencies in each health state below [107]
Average hourly wage	DKK 181	Average transport costs, based on the guidelines by Medicinrådet Multiplied with the frequencies in each health state below [107]
Patient time spent		
Administration	3 hours	Assumption
Adverse events	4 hours	Assumption

8.7 Results

8.7.1 Base case overview

The model base case settings are presented in Table 40.

Table 40: Base case overview

Component	Base-case setting
Comparator	Liposomal doxorubicin
Type of model	Partitioned survival model
Time horizon	36 years (lifetime)
Discount rates	Years 1-35: 3.5% for costs and outcomes Year 36+: 2.5% for costs and outcomes
Treatment line	2nd line. 3rd and 4th subsequent lines are included
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L using Danish tariff.
General population utility adjustment	Applied using Danish Medicines Council. Appendiks: Aldersjustering for sundhedsrelateret livskvalitet.

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Component	Base-case setting
Included costs	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	LEN: based on dosing from Study 309 PEM: Based on Study 309 protocol Liposomal doxorubicin: based on BSA
Average time on treatment	LEN: 0.73 years, PEM: 0.73 years Liposomal doxorubicin (based on doxorubicin from Study 309): 0.20 years
Parametric function for PFS	Independent models LEN+PEM: Log logistic Liposomal doxorubicin: Generalised gamma
Parametric function for OS	Independent models LEN+PEM: Lognormal Liposomal doxorubicin: Gompertz
Parametric function for TTD	LEN: Use Kaplan-Meier within trial PEM: Use Kaplan-Meier within trial Liposomal doxorubicin: Use Kaplan-Meier within trial (assuming equal TTD as doxorubicin in Study 309)
Cap TTD with PFS	Yes
PEM stopping rule	Applied at 24 months
LEN stopping rule	Applied at 24 months
Costs excluded	Exclude: Cost of MSI test Cost of vial sharing

Abbreviations: BSA, body surface area; CARBO, carboplatin; LEN, Lenvatinib; MSI, microsatellite instability; OS, overall survival; PAC, paclitaxel; PEM, pembrolizumab; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; TPC, treatment of physician's choice; TTD, time to discontinuation.

A list of key model assumptions applied in the base case is presented in Appendix J - Key model assumptions applied in the base case.

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8.7.2 Base case results

In the population with PFI < 6 months who were pre-assigned to doxorubicin in Study 309, LEN+PEM is associated with incremental costs of DKK [redacted] and incremental QALYs of [redacted] resulting in an ICER of DKK [redacted] compared with PLD (Table [redacted]. Given that confidential discounts exist for both LEN and PEM, the true ICER value is likely to be lower than DKK [redacted]

[redacted]

Abbreviations: 2L, second line; 3L, third line; AE, adverse event; LEN, lenvatinib; MRU, medical resource use; PEM, pembrolizumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

The mean and median values for OS, PFS and TTD in the population with PFI<6 months who are pre-assigned to doxorubicin are presented in [redacted].These values are presented in the treatment engines (columns Y and AI, W and AG, S).

[redacted]

8.8 Sensitivity analyses

8.8.1 Univariate sensitivity analyses

Univariate analysis identified the ten most influential parameters (i.e., those with the greatest impact on the ICER). The input values and rationale for the ten most influence parameters examined in the univariate sensitivity analysis are reported in [redacted]. The results of the univariate analysis are presented in [redacted] and Figure 15. The four most influential parameters are those describing OS survival models for LEN+PEM and DOX; other influential parameters include the PEM administration dose intensity, and the EQ-5D model (and baseline EQ-5D itself). The economic model is sensitive to variations in the OS model, which principally affects the QALYs gained. It is of note that varying individual terms in the parametric survival models is not always strictly appropriate, as the correlation between the terms in the survival models is lost; correlation between these parameters was preserved in PSA (section 8.8.2). Given that confidential discounts exist for both LEN and PEM, the true ICER values will likely be lower than those presented below.

[redacted]

[redacted]

Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio LEN, lenvatinib; PEM, pembrolizumab; PFS, progression-free survival; PFS BICR, progression-free survival by blinded independent central review; OS, overall survival; TTD, time-to-discontinuation

[redacted]

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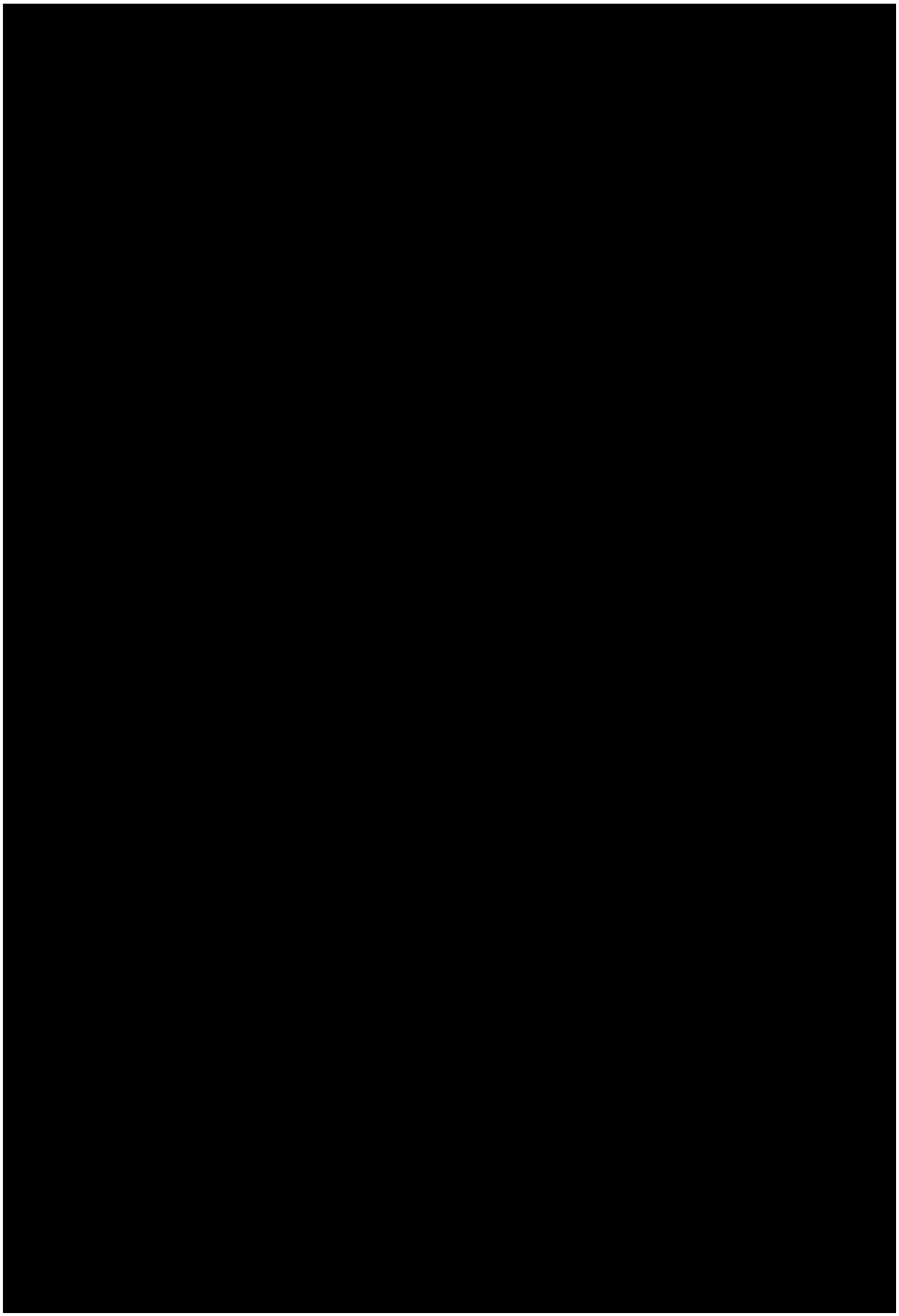
[redacted]

[redacted]

8.8.2 Probabilistic sensitivity analyses

The results of 1,000 PSA simulations were plotted on the cost-effectiveness plane (Figure 16) and a cost-effectiveness acceptability curve (CEAC) was generated (Figure 17).The average incremental costs over the simulated results were DKK [redacted] and the average incremental QALYs were [redacted] giving a probabilistic ICER of DKK [redacted] this is congruent with deterministic changes in costs and QALYs of DKK [redacted] and [redacted] respectively. [redacted]. Given that confidential discounts exist for both LEN and PEM, the true ICER values will likely be lower than those presented**, and therefore proportions of simulations below the willingness-to-**

pay thresholds is likely to be higher what is depicted in Figure 17**.**



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8.8.2.1 Scenario analysis

Scenario analyses were performed in which key structural assumptions were varied, and ICERs were reported. [redacted]. Given that confidential discounts exist for both LEN and PEM, the true ICER values will likely be lower than those presented below.

Table 45: Scenario analysis results, PFI<6 months and pre-assigned to doxorubicin

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
No cap on TTD with PFS	[redacted]			
Lognormal distribution for DOX OS				
Annual discount rate, 5%				
Annual discount rate, 0%				
Time horizon: 15 years				
Lenvatinib stopping rule at 24 months not applied				
Mean age: 67.5 (based on KOL input)				
PEM dose 2 mg/kg				
PEM dose 4 mg/kg every 6 weeks				
PLD as subsequent treatment instead of doxorubicin				

Abbreviations: AE, adverse event; ITT, intention-to-treat; KOL, key opinion leader; LEN, lenvatinib; PEM, pembrolizumab; PFS, progression-free survival; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; TTD, time to discontinuation.

[redacted]

[redacted]

9 Budget impact analysis

9.1 Patient numbers

The patient flow used to inform the population of advanced, recurrent, and metastatic EC following prior platinum-based systemic therapy is presented in Table 47. These patient numbers are based on the DRG/Clarivate endometrial cancer epidemiology model [129] and Eisai market intelligence estimates (see section 5.1). The patients included in the analysis are second-line treatable patients. Current patients are not captured in the analysis as it is not expected that patients already undergoing treatment in year one would be eligible to switch to LEN+PEM, given the aggressive nature and poor outcomes associated with EC.

The budget impact analysis (BIM) settings are the same as the health economic analysis, except for the extended societal costs that are not included in the BIM.

Table 47: Eligible population data [108]

	Year 1 - 2022	Year 2 - 2023	Year 3 - 2024	Year 4 - 2025	Year 5 - 2026
First-line treatable population (advanced)	199	202	207	210	213
First-Line treated population (advanced)	159	162	166	168	170
Second-line treatable population (advanced)	96	97	99	101	102
Pre-assigned to DOX and PFI<6 months	64	65	67	68	69
Systemic treatment rate	51	52	53	54	55
Total treated	31	31	32	32	33

9.2 Diagnosed incidence

In Year 1, the total first-line treatable population is comprised of 199 patients. The total treated patients in the model are derived from the following sub-populations, based on estimates from the DRG/Clarivate endometrial cancer epidemiology model [129] and Eisai market intelligence (Table 47):

- First-line treated population (159 in Year 1), calculated as 80% of the first-line treatable population
- Second-line treatable population (96 in Year 1), calculated as 60% of the first-line treated population
- PFI<6 months (64 in Year 1), calculated as 67% of the second-line treatable population (proportion of patients in Study 309 with PFI<6 months)
- Total treated / Second-line treated population (31 in Year 1), calculated as 80% of the pre-assigned to DOX and PFI<6 months population and assumed 60% of the eligible population for PLD/LEN+PEM

9.3 Market share

Treatment regimens were validated by Danish clinical experts to reweight 2020 market shares from Kantar Health CancerMPact report 2020 [109]. The Kantar report informs the average market shares for the most commons treatments given in second line of systemic therapy of EC in the EU5 countries (France, Germany, Italy, Spain, and UK). In the absence of Danish specific data, the available and relevant types of treatments and their estimated market shares for the Danish clinical setting were chosen according to clinical expert input, and the current shares for the remaining treatments were weighted up to 100%. The estimates for upcoming years in the scenario with LEN+PEM on the market were based on the assumptions of achieved reimbursement for LEN+PEM in December 2022 and that LEN+PEM will reach its peak sales by year four.

Table 48: Market share – if LEN+PEM is introduced

Treatment	Year 1 - 2022	Year 2 - 2023	Year 3 -2024	Year 4 - 2025	Year 5 - 2026
LEN+PEM	[redacted]				
Liposomal Doxorubicin					

Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab.

Table 49: Market share – if LEN+PEN is NOT introduced

Treatment	Year 1 - 2022	Year 2 - 2023	Year 3 -2024	Year 4 - 2025	Year 5 - 2026
LEN+PEM	[redacted]				
Liposomal Doxorubicin					

Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab.

9.4 Number of patients

Table 50: Number of patients expected to be treated over the next five-year period - if LEN+PEM is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
LEN+PEM	[redacted]				
Liposomal Doxorubicin					
Total					

Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab.

Table 51: Number of patients expected to be treated over the next five-year period - if LEN+PEM is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
LEN+PEM	[redacted]				

Liposomal Doxorubicin	[redacted]
Total	

Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab.

9.5 Expenditure per patient

Inputs on expenditure per patients are extracted from the CEM model. Per patient costs of drug acquisition, administration, subsequent therapies, adverse events, and monitoring are extracted from the CEM using 1-year, 2-year, 3-year, 4-year, and 5-year time horizons.

Costs from the CEM are applied to the number of patients getting each treatment (using the population size and market shares). Cost per patient for the first year are applied to incident patients each year. Cost for years 2 to 5 are applied to prevalent patients based on the year of entry (patients who are incident in 2022 are applied the cost of year 1 in 2022, year 2 in 2023, year 3 in 2024, year 4 in 2025 and year 5 in 2026, patients who are incident in 2023 are applied the cost of year 1 in 2023, year 2 in 2024, year 3 in 2025 and year 4 in 2026, etc..).

Table 52 presents the drug acquisition cost inputs for the BIM per patient per year for LEN+PEN and Liposomal Doxorubicin, respectively.

Table 52: Drug acquisition cost inputs per patient per year

	Year 1	Year 2	Year 3	Year 4	Year 5
LEN+PEM	[redacted]				
Liposomal Doxorubicin					

Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab.

9.6 Budget impact

The introduction of LEN+PEM in Denmark is associated total budget of DKK 4,311,257 in year 1, rising to DKK 25,513,354 in year 5 resulting in a cumulative 5-year budget of DKK 73,791,142.

The scenario where LEN+PEM is not recommended is associated with a budget of DKK 2,746,084 in year 1, rising to DKK 3,069,895 in year 5 resulting in a cumulative 5-year budget of DKK 14,713,187.

The difference between the two scenarios, which is the budget impact of recommending LEN+PEM varies from DKK 1,565,173 in year 1 to DKK 22,443,459 in year 5, with a cumulative net budget impact of DKK 59,077,955 over 5 years (Table 53).

Table 53: Expected budget impact of recommending LEN+PEM

	Year 1	Year 2	Year 3	Year 4	Year 5	
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Scenario LEN+PEM is recommended						
Drug acquisition costs	DKK 2,746,998	DKK 6,030,187	DKK 11,446,056	DKK 20,353,480	DKK 22,889,571	DKK 63,466,293
Drug administration costs	DKK 272,573	DKK 352,738	DKK 483,377	DKK 690,779	DKK 774,022	DKK 2,573,488
Subsequent therapy costs	DKK 726,109	DKK 739,442	DKK 724,668	DKK 670,810	DKK 697,135	DKK 3,558,164

Medical resource use costs	DKK 471,323	DKK 597,698	DKK 732,354	DKK 941,695	DKK 1,103,604	DKK 3,846,674
Adverse event costs	DKK 94,254	DKK 86,274	DKK 72,060	DKK 44,913	DKK 49,022	DKK 346,523
Total	DKK 4,311,257	DKK 7,806,339	DKK 13,458,515	DKK 22,701,676	DKK 25,513,354	DKK 73,791,142
Scenario LEN+PEM is NOT recommended						
Drug acquisition costs	DKK 1,215,572	DKK 1,246,097	DKK 1,282,678	DKK 1,301,746	DKK 1,320,407	DKK 6,366,501
Drug administration costs	DKK 240,231	DKK 246,264	DKK 253,493	DKK 257,261	DKK 260,949	DKK 1,258,199
Subsequent therapy costs	DKK 100,548	DKK 103,275	DKK 106,373	DKK 107,969	DKK 109,518	DKK 527,682
Medical resource use costs	DKK 2,746,084	DKK 2,889,625	DKK 2,981,168	DKK 3,026,414	DKK 3,069,895	DKK 14,713,187
Adverse event costs	DKK 1,215,572	DKK 1,246,097	DKK 1,282,678	DKK 1,301,746	DKK 1,320,407	DKK 6,366,501
Total	DKK 240,231	DKK 246,264	DKK 253,493	DKK 257,261	DKK 260,949	DKK 1,258,199
Budget Impact (Scenario with minus scenario without LEN+PEM)						
Drug acquisition costs	DKK 1,531,426	DKK 4,784,090	DKK 10,163,378	DKK 19,051,734	DKK 21,569,164	DKK 57,099,791
Drug administration costs	DKK 32,342	DKK 106,474	DKK 229,883	DKK 433,517	DKK 513,073	
Subsequent therapy costs	-DKK 15,539	-DKK 41,280	-DKK 81,670	-DKK 147,922	-DKK 133,370	-DKK 419,781
Medical resource use costs	DKK 23,238	DKK 84,431	DKK 200,068	DKK 400,989	DKK 555,089	DKK 1,263,815
Adverse event costs	-DKK 6,294	-DKK 17,001	-DKK 34,313	-DKK 63,056	-DKK 60,496	-DKK 181,160
Total budget impact	DKK 1,565,173	DKK 4,916,714	DKK 10,477,347	DKK 19,675,262	DKK 22,443,459	DKK 59,077,955

Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab

10 Discussion on the submitted documentation

The documentation submitted for this single-technology assessment stems from a comprehensive clinical development program, where the efficacy and safety of combination treatment with LEN+PEM has been evaluated in adult patients with EC. There is a significant unmet medical need for patients with advanced and recurrent EC who have progressed after prior platinum treatment.

The 309 / KN-775trial is a Phase III, multicenter, randomized, open-label study to compare the efficacy and safety of treatment with LEN+PEM in 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 who are not candidates for curative surgery or radiation. The 309 / KN-775trial presented direct head-to-head comparison of the efficacy and safety of LEN+PEM versus therapy of physician's choice (TPC) consisting of either doxorubicin or paclitaxel which were identified as the most common treatments for patients in this setting globally at the time of study design.

The DMC describes in its assessment report dostarlimab [63], the second line treatment options for EC as dependent on the duration of time passed since platinum-based treatment in first line. For patients who progress during or up to six months after treatment with first line platinum therapy, PLD is given as standard treatment. Patients who progress approximately six months or more after discontinuation of platinum treatment are considered platinum sensitive and can be re-treated with platinum-based chemotherapy after progression. Based on consultation with the DMC, these treatments are considered to represent Danish clinical practice. For the scope of the assessment, efficacy has been presented for the pre-assigned to doxorubicin PFI < 6 months subgroup from Study 309 / KN-775.

In the pre-assigned to doxorubicin and PFI < 6 months subgroup, post hoc analysis shows that treatment with LEN+PEM provides a consistent risk-benefit profile similar to the entire pre-assigned to doxorubicin population, with overall survival of additional [redacted] and [redacted] reduction in the risk of death [redacted] and progression free survival of additional [redacted] and [redacted] reduction in the risk of disease progression [redacted] in comparison to doxorubicin/PLD.

Results from the cost-effectiveness analysis show that compared to PLD, LEN+PEM can be considered a cost-effective use of Danish medical resources and represents a manageable budget impact considering the significant unmet need for endometrial cancer patients.

11 List of experts

Two clinical experts were consulted about clinical practice and model inputs for the Danish context [104]:

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

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 [15]. Eisai and Merck Sharp & Dohme have conducted the pivotal clinical study 309/KN-755 [88] (see Section 7.1), a randomised controlled trial conducted to compare the efficacy and safety of LEN+PEM versus treatment of physician's choice (TPC) (doxorubicin or paclitaxel). PLD is considered the standard of care in Danish clinical practice. However, as described in Section 5.2.3, there is evidence suggesting doxorubicin and PLD are comparable with respect to efficacy and safety (described in Section 5.2.3) 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 doxorubicin in Study 309 / KN-775, with PFI < 6 months.

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 (advanced EC who have disease progression following prior treatment with a PFI < 6 months).

Appendix B Main characteristics of included studies

Study 309 / KN-775

Table 54 Summary table study 309 / KN-775

Trial name: 309 / KN-775	
Objectives	To demonstrate that lenvatinib (LEN) plus pembrolizumab (PEM): • Prolongs progression free survival (PFS) and overall survival (OS) when compared to treatment of physician's choice.
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 endometrial 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 lenvatinib in combination with pembrolizumab versus treatment of physician's choice in patients with advanced endometrial cancer. 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 Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Cancer following prior platinum-based regimen.
Sample size (n)	**Intervention**: 411 participants **Comparator**: 416

Main inclusion and exclusion 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

Inclusion Criteria:

1. Has a histologically confirmed diagnosis of endometrial carcinoma (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 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 mismatch repair (MMR) status.
6. Has at least 1 measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and confirmed by Blinded Independent Central Review 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 pembrolizumab) or at least 180 days (for participants treated with treatment of physician's choice [TPC]) after the last dose of study treatment.

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 endometrial cancer, 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.
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 Endometrial Cancer. 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 pembrolizumab and LEN for endometrial carcinoma, 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).
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®) + pembrolizumab 200 mg (KEYTRUDA®) Participants received pembrolizumab 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 pembrolizumab group.
Comparator(s)	Active Comparator: Treatment of Physician's Choice (doxorubicin or paclitaxel) Participants received either of the following treatments: doxorubicin 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	ITT-population: The median follow-up duration was 11.4 months for ITT population and similar between treatment arms (12.2 months in the LEN plus pembrolizumab group vs 10.7 months in the TPC group).
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints

Endpoints included in this application:

Primary Outcome Measures:

- Progression Free Survival (PFS)
- Overall Survival (OS)

Secondary Outcome Measures:

- Objective Response Rate (ORR)
- Health-Related Quality of Life (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 (AE)
- Number of Participants with Serious Adverse Events (SAE)
- 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
- Model-Predicted Area Under the Concentration time Curve of Lenvatinib Based on Starting Dose from Time 0 to Infinity (AUC 0-∞)
- Model-Predicted Apparent Total Body Clearance (Cl/F) of Lenvatinib
- Model-Predicted Apparent Total Body Volume of Distribution (Vd/F) of Lenvatinib

Method of analysis

The Intention-to-Treat (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 Kaplan-Meier 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 SAEs 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)
    - 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)

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

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 55 Patient baseline and disease characteristics

Study 309 / KN-775 (Pre-assigned to doxorubicin, PFI < 6 months population)	Lenvatinib + Pembrolizumab	Doxorubicin (N=211)
Participants in population	[redacted]	
Age (Years)		
Median (range)		
<65 years		
Race		
White		
Black or African American		
Asian		
Missing		
Other		
MMR status		
pMMR		
dMMR		
ECOG		
0		
1		
History of pelvic irradiation		
Histology of initial diagnosis		
Endometrioid carcinoma		
High grade endometrioid carcinoma		

Low grade endometrioid carcinoma	[redacted]
Not specified	
Serous carcinoma	
Clear cell carcinoma	
Mixed histology	

Abbreviations: dMMR, Missmatch repair deficienct; ECOG, Eastern Cooperative Oncology Group; MMR, Missmatch repair; PFI, Platinum-free interval ; pMMR, Missmatch repair proficient

12.1 Comparability of the study populations with Danish patients eligible for treatment

The characteristics of the study population from Study 309 / KN-775are comparable to patients eligible for treatment in the Danish setting. With the exception of patients' age, which may be slightly higher in Denmark (range 63.5-67) compared to the mean age in the clinical trial (average: 63.1 years), the characteristics of the trial population were similar. A Danish cohort study reports an average age at diagnosis of EC of 65.5 years among 3638 participants [110], while Danish clinical experts interviewed for this purpose mentioned an age of 63.5-67 years. In general, endometrial cancer is rare before the age of 45 and the maximum age is around 70 years in Denmark [111].

To account for the possible difference in age, a health economic scenario analysis has been run to test how using a higher average Danish age affects the results. This resulted in an ICER similar to the base case. For further details, see section 8.

Appendix D Efficacy and safety results per study

As per the DMC guidelines [87] a list of all clinical endpoints in the included studies should be included in the submission (Table 56). However, validity, clinical relevance and efficacy results should only be included for outcome measures relevant for the submission. As such, these details for the relevant outcome measures (OS and PFS) will be described in this section.

Table 56 Definitions of all endpoints in Study 309 / KN-775

Outcome measure	Definition/Time frame
Primary outcome measures	
PFS	Time Frame: Up to approximately 27 months PFS is defined as the time from randomization to the first documented disease progression per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as determined by Blinded Independent Central Review (BICR) or death due to any cause, whichever occurred first.
OS	Time Frame: Up to approximately 43 months OS is defined as the time from date of randomization to date of death from any cause.
Secondary outcome measures	
ORR	Time Frame: Up to approximately 27 months ORR is defined as the percentage of participants who have best overall response of either CR or PR, as determined by BICR per RECIST 1.1.
HRQoL Score Using the EORTC QoL Questionnaire (QLQ-C30) Version 3.0	Time Frame: Baseline (prior to first dose of study treatment in Cycle 1 [cycle length = 21 days]) and at the end of follow-up (up to approximately 43 months) Change from baseline in HRQoL using the global score of EORTC QLQ-C30 will be determined. EORTC QLQ-C30 is a cancer specific health-related quality-of life (QoL) questionnaire, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea, and financial impact), and a global health and QoL scale. The score for each item and the overall score ranges from 0 to 100. A high overall scale and subscale scores represent improved health status. However, in case of individual symptoms, higher scores suggest increased perception of these symptoms of life.
Number of Participants With AE	Time Frame: Up to approximately 43 months The number of participants experiencing an AE will be assessed. An AE is defined as any unfavourable and unintended sign, symptom, or disease (new or worsening) temporally associated with the use of study therapy, regardless of whether or not a causal relationship with the study therapy can be determined.
Number of Participants With SAE	Time Frame: Up to approximately 43 months The number of participants experiencing an SAE will be assessed. A SAE is an AE that results in death, is life threatening, results in persistent or significant disability/incapacity, results in

Outcome measure	Definition/Time frame
	or prolongs an existing inpatient hospitalization, is a congenital anomaly/birth defect, is a cancer, is associated with an overdose, or is another important medical event.
Number of Participants With irAE	Time Frame: Up to approximately 43 months The number of participants experiencing an irAE will be assessed. An irAE is defined as any unfavourable and unintended immune-related sign, symptom, or disease (new or worsening) temporally associated with the use of study therapy, regardless of whether or not a causal relationship with the study therapy can be determined.
Number of Participants With Treatment Discontinuations Due to AEs	Time Frame: Up to approximately 43 months The number of participants who discontinue study treatment due to an AE will be assessed.

Abbreviations: AE, adverse event; BICR, Blinded Independent Central Review; EMA, European medical Agency; FDA, Food and Drug Administration; HRQoL, Health Related Quality of Life, OS, Overall survival**;** PFS, Progression- free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, Serious adverse event

Definition, validity, and clinical relevance of included outcome measures

Table 57 Definition, validity, and clinical relevance of included outcome measures in Study 309 / KN-775

Outcome measure	Definition	Validity	Clinical relevance
PFS	Time Frame: Up to approximately 27 months PFS is defined as the time from randomization to the first documented disease progression per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as determined by Blinded Independent Central Review (BICR) or death due to any cause, whichever occurred first.	The standard outcome for trials investigating cancer.	The PFS is a validated measure used in clinical trials to assess the time patients live with the disease without getting worse.
OS	Time Frame: Up to approximately 43 months OS is defined as the time from date of randomization to date of death from any cause.	The gold standard in cancer trials (FDA)(EMA) [112].	The OS is a validated measure used in clinical trials to assess the time patients remain alive on treatment.
HRQoL	Multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning.	HRQoL is a widely used and validated outcome measure [113]	HRQoL was used to measure if the treatment was associated with an improved quality of life compared to the other treatment comparators.

Abbreviations: BICR, Blinded Independent Central Review; EMA, European medical Agency; FDA, Food and Drug Administration; HRQoL, Health Related Quality of Life, RECIST, Response Evaluation Criteria in Solid Tumors; PFS, Progression- free survival; OS, Overall survival

Efficacy results: Study 309 / KN-775

Table 58 Efficacy results – Study 309 / KN-775

				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 doxorubicin, PFI < 6 months population)	LEN+PEM	[redacted]								Based on Cox regression model with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.	Study 309 / KN-775[84]
	Doxorubicin										
OS (Pre-assigned to doxorubicin, PFI < 6 months population)	LEN+PEM									Based on Cox regression model with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.	
	Doxorubicin										

Abbreviations: CI, Confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, Hazard Ratio; LEN, Lenvatinib; MMR, Missmatch repair; NA, Not applicable; OS, Overall survival; PEM, Pembrolizumab; PFI, Platinum-free interval; PFS, progression free

Appendix E Safety data for intervention and comparator(s)

Safety: Study 309 / KN-775

Table 59 Participants with grade 3-5 treatment-related adverse events by decreasing incidence, pre-assigned to doxorubicin, PFI < 6 months.

	Lenvatinib + Pembrolizumab (N=204) n (%)	Doxorubicin (N=200) n (%)
Participants in population		
with one or more adverse events		
with no adverse events		
Hypertension		
Diarrhoea		
Decreased appetite		
Weight decreased		
Asthenia		
Lipase increased		
Nausea		
Proteinuria		
Alanine aminotransferase increased		
Aspartate aminotransferase increased		
Pulmonary embolism		
Vomiting		
Anaemia		
Fatigue		
Hyponatraemia		
Mucosal inflammation		

Neutrophil count decreased	[redacted]
Platelet count decreased	
Abdominal pain	
Acute kidney injury	
Amylase increased	
Colitis	
Female genital tract fistula	
Pain in extremity	
Palmar-plantar erythrodysaesthesia syndrome	
Stomatitis	
Type 1 diabetes mellitus	
Urinary tract infection	
White blood cell count decreased	
Arthralgia	
Blood creatine phosphokinase increased	
Gamma-glutamyltransferase increased	
Hepatotoxicity	
Hyperglycaemia	
Hypothyroidism	
Immune-mediated hepatitis	
Peritonitis	
Pneumonitis	
Thrombocytopenia	
Adrenal insufficiency	
Autoimmune nephritis	
Blood alkaline phosphatase increased	
Bundle branch block left	
Cerebral haemorrhage	

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Cerebrovascular accident	[redacted]
Chronic kidney disease	
Death	
Dehydration	
Depression	
Dermatitis bullous	
Drug eruption	
Dyspepsia	
Eastern Cooperative Oncology Group performance status worsened	
Embolism	
Encephalitis autoimmune	
Erythema	
Gastritis erosive	
Gastroenteritis	
General physical health deterioration	
Haemorrhagic stroke	
Hepatic enzyme increased	
Hypertriglyceridaemia	
Hypoalbuminaemia	
Hypoglycaemia	
Hypokalaemia	
Hypomagnesaemia	
Hypophysitis	
Hypotension	
Intestinal fistula	
Large intestine perforation	
Leukocytosis	
Liver disorder	

Lower gastrointestinal perforation	[redacted]
Lymphocyte count decreased	
Lymphopenia	
Muscular dystrophy	
Myalgia	
Myositis	
Neutropenia	
Oral herpes	
Pancreatitis	
Pancreatitis acute	
Perforated ulcer	
Pneumonia	
Postoperative wound infection	
Rash maculo-papular	
Renal failure	
Respiratory failure	
Secondary hypertension	
Sialoadenitis	
Skin disorder	
Skin lesion	
Skin toxicity	
Uterine haemorrhage	
Vasculitis	
Wound infection	
Atrial fibrillation	
Blood bilirubin increased	
C-reactive protein increased	
Cardiac failure	

Dyspnoea exertional	[redacted]
Ejection fraction decreased	
Febrile bone marrow aplasia	
Febrile neutropenia	
Gastrointestinal toxicity	
Groin pain	
Haematuria	
Haemoglobin decreased	
Hepatobiliary disease	
Hypocalcaemia	
Intestinal obstruction	
Leukopenia	
Malnutrition	
Oedema peripheral	
Oesophageal candidiasis	
Oral candidiasis	
Phlebitis	
Pyelonephritis acute	
Septic shock	
Toxic cardiomyopathy	
Vascular device infection	

Table 60 Disposition of Participants pre-assigned to doxorubicin, PFI < 6 months.

	Lenvatinib + Pembrolizumab n (%)	Doxorubicin n (%)
Participants in population	[redacted]	
Status for Trial		
Discontinued		

Death	[redacted]	
Lost To Follow-Up		
Withdrawal By Subject		
Participants Ongoing		
Status for Study medication in Trial		
Started		
Completed		
Discontinued		
Adverse Event		
Clinical Progression		
Complete Response		
Non-Compliance With Study Drug		
Non-Study Anti-Cancer Therapy		
Physician Decision		
Progressive Disease		
Withdrawal By Subject		
Participants Ongoing		

Appendix F – Comparative analysis of efficacy and safety

For the comparative analysis of efficacy and safety for doxorubicin and LEN+PEM see Appendix D.

Pegylated liposomal doxorubicin

As described in Section 5.2.2, PLD is considered the most relevant comparator to LEN+PEM. Based on the DMC's recent assessment of dostarlimab, 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

Table 61: Relevant studies for doxorubicin and PLD

Intervention	RCTs, author year	Non-RCTs, author year
Doxorubicin	Subgroup of TPC treatment group, Study 309 / KN-775[1, 84] McMeekin 2015 [69] Miller 2018 ZoptEC [70 , 71]	Di Legge 2011 [75]
Liposomal doxorubicin	NA	Angioli et al., 2007 [74] Homesley 2005 [72] Julius, 2013 [76] Muggia 2002 [73]

Abbreviations: NA, Not applicable; RCT, randomized controlled trial

For doxorubicin therapy, three RCTs were identified, including Study 309 / KN-775[1, 69, 70 , 71, 84], and one single arm study [75], whilst three single arm studies and one RWE study were identified for PLD in a relevant patient population [72, 74, 76, 114]. A comparison with doxorubicin 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-775via doxorubicin to form a network for traditional network meta-analysis (NMA) 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 Kaplan-Meier curves for the survival outcomes of interest, at best only reporting median survival, with no associated variance [72-74]

Indirect comparison with the RWE study was also not considered appropriate (Julius 2013 [76]). 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.

Appendix G – Model extrapolations

Extrapolation of relative efficacy: additional graphs and tables (pre-assigned to doxorubicin and PFI<6 months population)

OS

The proportional hazards assumption was assessed using plots of the log-cumulative hazard [redacted] For OS in the pre-assigned to doxorubicin and PFI<6 months population, the plots become clearly separated over time and appear reasonably parallel beyond approximately day 100. Schoenfeld residuals are shown in [redacted] shows the Schoenfeld residuals and [redacted] the smoothed hazard estimates over time.

[redacted]

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[redacted]

Model fit diagnostics for each of the six standard parametric distributions are presented in Table 62.

Table 62: Model fit diagnostics

	N	ll0	ll	df	AIC	BIC
LEN+PEM	[redacted]					
gamma						
weibull						
gompertz						

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exponential	[redacted]								
lognormal									
loglogistic									
DOX									
gamma									
weibull									
gompertz									
exponential									
lognormal									
loglogistic									

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; df, degrees of freedom; LEN+PEM, lenvatinib plus pembrolizumab; ll, log-likelihood; N, number of patients.

A plot of the hazard over time is presented in Figure 21 and Figure 22 for LEN+PEM and DOX, respectively.

[redacted]

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PFS

Plots of the log-cumulative hazard are presented in Figure 23 for PFS BICR in the pre-assigned to doxorubicin and PFI<6 months population of Study 309 / KN-775, which is used in the model base case. Schoenfeld residuals are shown Figure 24. Figure 25 shows the instantaneous hazards over time between the two arms.

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[redacted]

Model fit diagnostics for each of the six standard parametric distributions are presented in Table 63.

Table 63: Model fit diagnostics– PFS BICR, pre-assigned to doxorubicin and PFI< 6 months population

	N	ll0	ll	df	AIC	BIC
LEN+PEM	[redacted]					
Generalized gamma						
Weibull						
Gompertz						
Exponential						
Lognormal						
Loglogistic						
DOX						
Generalized gamma						

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Weibull	[redacted]						
Gompertz							
Exponential							
Lognormal							
Loglogistic							

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; df, degrees of freedom; DOX, doxorubicin; ITT, intention-to-treat; LEN+PEM, lenvatinib plus pembrolizumab; ll, log-likelihood; N, number of patients; OS, overall survival.

A plot of the hazard over time is presented Figure 26 and Figure 27 for LEN+PEM and DOX, respectively.

[redacted]

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Appendix H – Mapping of HRQoL data

The health state utility values used in the model originate from study 309 / KN-775, based on patient level data. The values were estimated with EQ-5D-5L using published tariffs for the Danish population [100]. The models include only the population of patients with PFI<6months pre-assigned to DOX.

The EQ-5D-5L is a patient-completed HRQoL instrument evaluating five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with five levels of response.

Study 309 / KN-775includes treatments with different cycle lengths. The cycle length for LEN+PEM and TPC of doxorubicin 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 [EOT] 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 EOT visit. Completion of the EQ-5D and other HRQoL questionnaires following the EOT visit was not mandatory. In order to convert EQ-5D-5L to preference-based index scores, a tariff of general population utility weights must be applied. As preferences towards the dimensions of health reflected in the EQ-5D-5L are likely to vary between countries, tariffs are available for multiple countries. In the base case, the EQ-5D-5L using published tariffs for the Danish population [100]

For use within the economic model, multivariable linear mixed models were fitted to the EQ-5D index score, and covariates representing baseline EQ-5D index score, presence of treatment-related Grade 3–5 AEs at the time of observation, treatment arm, being 'on' vs 'off' treatment, progression-status, and time before death were considered for inclusion in the model, and models were compared using the AIC and BIC diagnostic statistics, and variables which led to improvements (reductions) in these statistics retained. 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 AEs and subgroup membership).

The time-to-death categories used were ≥ 365 days (or did not die), 183 – 364 days, 92 – 182 days, 29 – 91 days, and ≤ 28 days. These categories were selected to approximately correspond to categories used by previous analyses, modified to reflect the model cycle [3]

The use of time-to-death, in addition to pre-/post-progression status was considered on the basis that:

- EQ-5D data in study 309 / KN-775was collected beyond the end of treatment
- Analyses have previously demonstrated that use of pre-/post-progression status alone, ignoring time-to-death, may underestimate QALY gains for preventive interventions [115]
- Statistical testing of data from study 309 / KN-775demonstrated that models which included both time-to-death and pre-/post-progression status led to improved statistical goodness-of-fit (see Results below)

Mixed models assume that missing data are missing at random (MAR), and no imputation was performed [116]. Table 64 and Table 65 summarize the statistical models tested.

Table 64: Summary of tested models (models considering time-to-death and pre-post-progression)

	Model number										
Covariates	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**

Baseline EQ-5D	x	x	x	x	x	x	x	x	x	x	x	x
Time from death	x	x	x	x	x	x	x	x	x	x	x	x
On treatment		x		x	x	x	x	x	x	x	x	x
LEN+PEM (vs DOX)			x			x	x	x	x	x		
Experiencing AEs					x	x	x	x	x	x	x	x
On treatment # LEN+PEM						x	x	x	x	x		
pMMR (vs dMMR)							x					
Prior lines of therapy								x				
Hysterectomy									x			
Post-progression										x	x	x
Age											x	

Table 65: Summary of tested models (models pre-/post-progression status only)

	Model number											
Covariates	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Baseline EQ-5D	x	x	x	x	x	x	x	x	x	x	x	x
Post-progression	x	x	x	x	x	x	x	x	x	x	x	x
On treatment		x		x	x	x	x	x	x	x	x	x
LEN+PEM (vs DOX			x			x	x	x	x	x		
Experiencing AEs					x	x	x	x	x	x	x	x
On treatment # LEN+PEM						x	x	x	x	x		
pMMR (vs dMMR)							x					
Prior lines of therapy								x				
Hysterectomy									x			

Age											x	

Results

[redacted]

[redacted]

Table 66: Completion and Compliance Percentages for EQ-5D VAS by visit and by treatment (all-comer full analysis set)

EQ-5D VAS completion rate (%)	Baseline		Week 12		Week 24		Week 36	
	LENPEM	TPC	LENPEM	TPC	LENPEM	TPC	LENPEM	TPC
Completed	97.0	97.4	77.8	62.1	59.0	24.4	45.3	5.1
Compliance*	97.6	97.7	91.8	87.3	89.4	73.1	88.7	69.6

*% in those expected to complete questionnaires

[redacted]

[redacted]

Empirical mean EQ-5D index score by visit for each study arm during Year 1 is presented in Figure 29. There were no notable differences between study arms over time.

[redacted]

Mean EQ-5D index scores by model health state are presented in Table 67. As expected, the majority of observations that were available were from patients who had not experienced a PFS event and who remained on treatment [redacted]

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[redacted]

Table 67: EQ-5D by progression and on/off treatment status (PFI < 6 months and pre-assigned to DOX population)

Health state	Mean	s.e.	95% CI
Progression-free, off-treatment	[redacted]		
Progression-free, on-treatment			
Post-progression, off-treatment			
Post-progression, on-treatment			
Total			

Abbreviations: CI, confidence interval; s.e., standard error.

Table 68: EQ-5D aby time-to-death category (PFI < 6 months and pre-assigned to DOX population)

Health state	Mean	SE	95% CI
>= 365 days from death or did not die	[redacted]		
183–364 days away from death			
92–182 days away from death			
29–91 days away from death			
0–28 days away from death			

Abbreviations: CI, confidence interval; SE, standard error.

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Correlation between candidate covariates is summarised in Table 69.

Table 69 Correlation between candidate variables

	Baseline EQ-5D	Time-to-death	Post-progression	On treatment	In AEs	pMMR	Prior lines of therapy	Hysterectomy
Baseline EQ-5D	1.0000							
Time-to-death	-0.0386	1.0000						
Post-progression	0.0028	0.1299	1.0000					
On treatment	0.0154	-0.1068	-0.2619	1.0000				
In AEs	-0.0037	-0.0868	0.0167	-0.0066	1.0000			
pMMR	0.1404	0.1420	0.0258	-0.0577	0.0210	1.0000		
Prior lines of therapy	0.1182	-0.0463	-0.0237	-0.0083	-0.0872	0.0167	1.0000	
Hysterectomy	0.0222	-0.0225	0.0130	-0.0150	0.0539	0.0006	0.2339	1.0000

Abbreviations: AEs, adverse events; pMMR, mismatch repair proficient.

Models considering time-to-death

The considered statistical models of EQ-5D are presented in Table 70.

Table 70: Alternative statistical models of EQ-5D (DK index; models 1–5)

Variable	m1	m2	m3	m4	m5
Baseline EQ-5D					
0–28 days away from death					
29–91 days away from death					
92–182 days away from death					
183–364 days away from death					
On treatment (vs off treatment)					
LEN+PEM (vs DOX)					
Experiencing AEs					
Constant					
lns1_1_1					
lnsig_e					
N					

Abbreviations: AE, adverse event; LEN+PEM, lenvatinib plus pembrolizumab; DOX, doxorubicin.

Table 71: Alternative statistical models of EQ-5D (DK index; models 6–10)

Variable	m6	m7	m8	m9	m10
Baseline EQ-5D					
0–28 days away from death					
29–91 days away from death					
92–182 days away from death					
183–364 days away from death					
On treatment (vs off treatment)					
LEN+PEM (vs DOX)					
Experiencing AEs					
On treatment # LEN+PEM					
pMMR (vs dMMR)					

Prior lines of therapy: 2 (vs 1)	[redacted]
Prior lines of therapy: ≥ (3 vs 1)	
Hysterectomy	
Post-progression	
Constant	
lns1_1_1	
lnsig_e	
N	

Abbreviations: AE, adverse event; DOX, doxorubicin
mismatch repair proficient.

Table 72: Alternative statistical models of EQ-5D (DK index, models 11–12)

Variable	m11	m12
Baseline EQ-5D	[redacted]	
0–28 days away from death		
29–91 days away from death		
92–182 days away from death		
183–364 days away from death		
On treatment (vs off treatment)		
Experiencing AEs		
Post-progression		
Age		
Constant		
lns1_1_1		
lnsig_e		
N		

Abbreviations: AE, adverse event.

Model goodness-of-fit statistics for the alternative models are provided in Table 72Table 73. Models 10 and 11 provided the lowest AIC score (model 12 being third), whilst model 12 provided the lowest BIC score (model 11 being second). The difference between model 10 and model 12 was the inclusion and exclusion (in model 10 and model 12, respectively) of the LEN+PEM vs DOX covariate and interaction thereof with on-treatment status. The latter term (the interaction between being on treatment and randomized to LEN+PEM) was not statistically significant, whilst the main effect (LEN+PEM vs DOX) was borderline statistically significant. As model 12 was preferred based on the BIC score

(and was a close third based on the AIC score) and represented the more parsimonious model, without interaction terms, it was selected as the preferred model.

Table 73: EQ-5D model goodness of fit statistics

	N	ll	df	AIC	BIC
m1	[redacted]				
m2					
m3					
m4					
m5					
m6					
m7					
m8					
m9					
m10					
m11					
m12					

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; df, degrees of freedom; ll, log-likelihood.

The final statistical model of EQ-5D including time to death is presented in Table 74. Results suggested small decrements associated with observations post-progression (–0.027; p=0.003) and experiencing AEs at the time of observation (–0.012; p=0.180). Increasing proximity to death was associated with worsening EQ-5D (decrement of –0.226; p<0.001 for 0–28 days from death), with difference beyond 92 days from death not reaching statistical significance. Being on treatment (independent of which treatment) was associated with higher EQ-5D than being off treatment (0.119; p<0.001).

Table 74: EQ-5D based on time-to-death

Parameter	Coefficient	s.e.	z P>z	95% CI
Baseline EQ-5D	[redacted]			
Post-progression decrement				
AE disutility				
On treatment increment				
0–28 days away from death				
29–91 days away from death				
92–182 days away from death				
183–364 days away from death				

Constant	[redacted]

Abbreviations: AE, adverse event; CI, confidence interval; s.e., standard error.

Pre-/post-progression models

The considered statistical models of EQ-5D (using pre/post-progression status) are presented Table 70.

Table 75: Alternative statistical models of EQ-5D (DK index; models 1–5)

Variable	m13	m14	m15	m16	m17
Baseline EQ-5D	[redacted]				
Post-progression					
On treatment (vs off treatment)					
LEN+PEM (vs OX)					
Experiencing AEs					
Constant					
lns1_1_1					
lnsig_e					
N					

Abbreviations: AE, adverse event; LEN+PEM, lenvatinib plus pembrolizumab; DOX, doxorubicin.

Table 76: Alternative statistical models of EQ-5D (DK index; models 6–10)

Variable	m18	m19	m20	m21	m22
Baseline EQ-5D	[redacted]				
Post-progression					
On treatment (vs off treatment)					
LEN+PEM (vs DOX)					
Experiencing AEs					
On treatment # LEN+PEM					
pMMR (vs dMMR)					
Prior lines of therapy: 2 (vs 1)					
Prior lines of therapy: ≥ (3 vs 1)					
Hysterectomy					
Constant					
lns1_1_1					

lnsig_e	[redacted]
N	

Abbreviations: AE, adverse event; CW, crosswalk; dMMR, mismatch repair deficient; LEN+PEM, lenvatinib plus pembrolizumab; pMMR, mismatch repair proficient; DOX, doxorubicin.

Table 77: Alternative statistical models of EQ-5D (DK index, models 11–12)

Variable	m23	m24
Baseline EQ-5D	[redacted]	
Post-progression		
On treatment (vs off treatment)		
Experiencing AEs		
Age		
Constant		
lns1_1_1		
lnsig_e		
N		

Abbreviations: AE, adverse event.

Model goodness-of-fit statistics for the alternative models are provided in Table 73. RCModel 21 provided the lowest AIC score (with several other models performing similarly well), whilst model 24 provided the lowest BIC score (model 23 being second). As model 24 was preferred based on the BIC score and represented the more parsimonious model, it was selected as the preferred model.

Table 78: EQ-5D model goodness of fit statistics

	N	ll	df	AIC	BIC
m13	[redacted]				
m14					
m15					
m16					
m17					
m18					
m19					
m20					
m21					
m22					

m23	[redacted]
m24	

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; df, degrees of freedom; ll, log-likelihood.

The final statistical model of EQ-5D based on pre-/post-progression status in Table 79. Results suggested small decrements associated with observations post-progression (–0.037; p<0.001). Being on treatment (independent of which treatment) was associated with higher EQ-5D than being off treatment (0.140; p<0.001).

Table 79: EQ-5D based on pre-/post-progressions status only

Parameter	Coefficient	s.e.	z P>z	95% CI
Baseline EQ-5D	[redacted]			
On treatment increment				
AE disutility				
Post-progression decrement				
Constant				

Abbreviations: AE, adverse event; CI, confidence interval; s.e., standard error

Appendix I – Probabilistic sensitivity analyses

Table 80: Model parameters

Parameter name	Default value	Parameter distribution
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gamma, constant	6.07	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gamma, ln(sigma)	0.14	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gamma, kappa	-0.18	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - Weibull, constant	-8.29	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - Weibull, ln(p)	0.25	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gompertz, constant	-6.74	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gompertz, gamma	0.00	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - exponential, constant	-6.55	Normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - lognormal, constant	6.14	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - lognormal, ln(sigma)	0.10	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - loglogistic, constant	6.12	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - loglogistic, ln(gamma)	-0.45	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gamma, constant	5.32	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gamma, ln(sigma)	0.13	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gamma, kappa	0.11	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - Weibull, constant	-6.01	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - Weibull, ln(p)	0.05	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gompertz, constant	-5.54	Multivariate normal

PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gompertz, gamma	0.00	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - exponential, constant	-5.73	Normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - lognormal, constant	5.27	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - lognormal, ln(sigma)	0.15	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - loglogistic, constant	5.24	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - loglogistic, ln(gamma)	-0.43	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - gamma, constant	5.56	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - gamma, ln(sigma)	-0.19	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - gamma, kappa	0.30	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - Weibull, constant	-8.30	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - Weibull, ln(p)	0.36	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - gompertz, constant	-6.17	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - gompertz, gamma	0.00	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - exponential, constant	-5.81	Normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - lognormal, constant	5.45	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - lognormal, ln(sigma)	-0.13	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - loglogistic, constant	5.46	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - loglogistic, ln(gamma)	-0.68	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - gamma, constant	4.36	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - gamma, ln(sigma)	-0.36	Multivariate normal

PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - gamma, kappa	-0.48	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - Weibull, constant	-6.96	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - Weibull, ln(p)	0.36	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - gompertz, constant	-4.99	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - gompertz, gamma	0.00	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - exponential, constant	-4.84	Normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - lognormal, constant	4.52	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - lognormal, ln(sigma)	-0.34	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - loglogistic, constant	4.47	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - loglogistic, ln(gamma)	-0.88	Multivariate normal
% PFS events that are progression	0.87	Beta
Anaemia, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	4.00	Gamma
Decreased appetite, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	12.00	Gamma
Diarrhoea, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	14.00	Gamma
Hypertension, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	76.00	Gamma
Neutropenia, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	1.00	Gamma
Neutrophil count decreased, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	4.00	Gamma
Weight decreased, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	12.00	Gamma
White blood cell count decreased, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	3.00	Gamma
Anaemia, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	35.00	Gamma
Diarrhoea, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	3.00	Gamma

Febrile neutropenia, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	18.00	Gamma
Leukopenia, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	26.00	Gamma
Neutropenia, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	98.00	Gamma
Neutrophil count decreased, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	85.00	Gamma
White blood cell count decreased, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	30.00	Gamma
Anaemia, average duration per event (days) pre-assigned to dox, PFI<6 months	35	Gamma
Decreased appetite, average duration per event (days) pre-assigned to dox, PFI<6 months	0	Gamma
Diarrhoea, average duration per event (days) pre-assigned to dox, PFI<6 months	3	Gamma
Febrile neutropenia, average duration per event (days) pre-assigned to dox, PFI<6 months	18	Gamma
Hypertension, average duration per event (days) pre-assigned to dox, PFI<6 months	0	Gamma
Leukopenia, average duration per event (days) pre-assigned to dox, PFI<6 months	26	Gamma
Lipase increased, average duration per event (days) pre-assigned to dox, PFI<6 months	0	Gamma
Neutropenia, average duration per event (days) pre-assigned to dox, PFI<6 months	98	Gamma
Neutrophil count decreased, average duration per event (days) pre-assigned to dox, PFI<6 months	85	Gamma
Weight decreased, average duration per event (days) pre-assigned to dox, PFI<6 months	172.70	Gamma
White cell decreased, average duration per event (days) pre-assigned to dox, PFI<6 months	18.10	Gamma
Mean baseline EQ-5D	0.81	Normal
Baseline EQ-5D - coefficient TTD	0.64	Multivariate normal
0-29 days away from death - coefficient TTD	-0.23	Multivariate normal
30-89 days away from death - coefficient TTD	-0.09	Multivariate normal
90-179 days away from death - coefficient TTD	-0.03	Multivariate normal
180-359 days away from death - coefficient TTD	0.00	Multivariate normal
On treatment increment - coefficient TTD	0.09	Multivariate normal

AE disutility - coefficient TTD	-0.02	Multivariate normal
Post-progression decrement - coefficient TTD	-0.03	Multivariate normal
Constant HRQoL model - coefficient TTD	0.20	Multivariate normal
Weight	68.90	Normal
BSA (body surface area), m2	1.70	Normal
Pembrolizumab, admin cost	1921.00	Gamma
Pembrolizumab, administration dose intensity	0.96	Gamma
Pembrolizumab, price/pack	23204.61	Not varied
Lenvatinib, admin cost	0.00	Not varied
Lenvatinib, price/pack	12551.71	Not varied
% receiving doxorubicin	0.74	Beta
Paclitaxel, admin cost	1921.00	Gamma
Paclitaxel, dose intensity	0.99	Gamma
Paclitaxel, cost of vial size 1	110.50	Not varied
Paclitaxel, cost of vial size 2	1500.00	Not varied
Paclitaxel, cost of vial size 3	201.50	Not varied
Paclitaxel, cost of vial size 4	0	Not varied
Doxorubicin, dose intensity	0.99	Gamma
Doxorubicin, cost of vial size 1	150.00	Not varied
Doxorubicin, cost of vial size 2	120.00	Not varied
Doxorubicin, cost of vial size 3	360.00	Not varied
Liposomal doxorubicin, dose intensity	1.00	Gamma
Liposomal doxorubicin, cost of vial size 1	2487.31	Not varied
Paclitaxel/carboplatin, carboplatin, cost of vial size 1	84.00	Not varied
Paclitaxel/carboplatin, carboplatin, cost of vial size 2	203.00	Not varied
Bevacizumab, cost of vial size 1	2090.82	Not varied
Bevacizumab, cost of vial size 2	7707.76	Not varied
Gemcitabine, cost of vial size 1	1000.00	Not varied
Gemcitabine, cost of vial size 2	310.00	Not varied
Gemcitabine, cost of vial size 3	330.00	Not varied

Gemcitabine, cost of vial size 4	350.00	Not varied
Gemcitabine, cost of vial size 5	370.00	Not varied
Gemcitabine, cost of vial size 6	1200.00	Not varied
Gemcitabine, carboplatin, cost of vial size 1	84.00	Not varied
Gemcitabine, carboplatin, cost of vial size 2	203.00	Not varied
Docetaxel, cost of vial size 1	71.00	Not varied
Docetaxel, cost of vial size 2	150.00	Not varied
Docetaxel, cost of vial size 3	309.00	Not varied
Trastuzumab, cost of vial size 1	3762.73	Not varied
Trastuzumab, cost of vial size 2	10506.64	Not varied
Megestrol, cost of tablet size 1	800.02	Not varied
Nivolumab, cost of vial size 1	22567.94	Not varied
Cisplatin, cost of vial size 1	100.00	Not varied
Cisplatin + doxorubicin, cisplatin, cost of vial size 1	200.00	Not varied
Cisplatin + doxorubicin, cisplatin, cost of vial size 2	100.00	Not varied
Vinorelbine, cost of vial size 1	245.00	Not varied
Vinorelbine, cost of vial size 2	1240.00	Not varied
Topotecan, cost of vial size 1	222.00	Not varied
Topotecan, cost of vial size 2	230.00	Not varied
Cyclophosphamide, cost of vial size 1	61.50	Not varied
Cyclophosphamide, cost of vial size 2	153.75	Not varied
Cyclophosphamide, cost of vial size 3	307.50	Not varied
Oxaliplatin, cost of vial size 1	41.18	Not varied
Oxaliplatin, cost of vial size 2	68.80	Not varied
Oxaliplatin, cost of vial size 3	127.82	Not varied
Subsequent therapies - LEN+PEM - % of pts - 2L Doxorubicin	0.50	Beta
Subsequent therapies - LEN+PEM - % of pts - 2L Paclitaxel	0.50	Beta
Subsequent therapies - TPC - % of pts - 2L Doxorubicin	0.50	Beta
Subsequent therapies - TPC - % of pts - 2L Paclitaxel	0.50	Beta
Subsequent therapies - LEN+PEM - % of pts - 3L Doxorubicin	0.50	Beta
Subsequent therapies - LEN+PEM - % of pts - 3L Paclitaxel	0.50	Beta
Subsequent therapies - TPC - % of pts - 3L Doxorubicin	0.50	Beta

Subsequent therapies - TPC - % of pts - 3L Paclitaxel	0.50	Beta
Subsequent therapies - Duration 2L Doxorubicin	70.22	Gamma
Subsequent therapies - Duration 2L Paclitaxel	86.21	Gamma
Subsequent therapies - Duration 3L Doxorubicin	69.08	Gamma
Subsequent therapies - Duration 3L Paclitaxel	71.40	Gamma
% tested with MSI test	0.70	Beta
Of those tested, MSI-H and MMR	0.67	Beta
Of those tested, MMR	0.11	Beta
Mansoor - % MSS	0.70	Beta
Nicoline - % MSS	0.83	Beta
US assumption - % MSS	0.78	Beta
Mansoor - % MSI-H	0.30	Beta
Nicoline - % MSI-H	0.17	Beta
US assumption - % MSI-H	0.22	Beta
Consultation, oncology, unit cost	1921.00	Gamma
Blood count, unit cost	300.00	Gamma
CT scan, unit cost	2411.00	Gamma
GP visit, unit cost	149.09	Not varied
Nurse visit, unit cost	441.00	Not varied
Consultation, oncology, LEN+PEM, PFS	0.23	Not varied
Blood count, LEN+PEM, PFS	0.23	Not varied
CT scan, LEN+PEM, PFS	0.08	Not varied
GP visit, LEN+PEM, PFS	0.11	Not varied
Nurse visit, LEN+PEM, PFS	0.00	Not varied
Consultation, oncology, TPC, PFS	0.23	Not varied
Blood count, TPC, PFS	0.23	Not varied
CT scan, TPC, PFS	0.08	Not varied
GP visit, TPC, PFS	0.11	Not varied
Nurse visit, TPC, PFS	0.00	Not varied
Consultation, oncology, LEN+PEM, PD	0.08	Not varied
Blood count, LEN+PEM, PD	0.00	Not varied
CT scan, LEN+PEM, PD	0.00	Not varied

GP visit, LEN+PEM, PD	0.11	Not varied
Nurse visit, LEN+PEM, PD	0.00	Not varied
Consultation, oncology, PD	0.08	Not varied
Blood count, TPC, PD	0.00	Not varied
CT scan, TPC, PD	0.00	Not varied
GP visit, TPC, PD	0.11	Not varied
Nurse visit, TPC, PD	0.00	Not varied
Anaemia, unit cost	3176.00	Gamma
Decreased appetite, unit cost	1954.00	Gamma
Diarrhoea, unit cost	6756.00	Gamma
Febrile neutropenia, unit cost	3176.00	Gamma
Hypertension, unit cost	1318.00	Gamma
Leukopenia, unit cost	3176.00	Gamma
Lipase increased, unit cost	2910.00	Gamma
Neutropenia, unit cost	3176.00	Gamma
Neutrophil count decreased, unit cost	3176.00	Gamma
Weight decreased	1954.00	Gamma
White blood cell count decreased, unit cost	3176.00	Gamma
Transport costs, cost of transport to and from treatment, unit cost	140.00	Gamma
Transport costs, average hourly wage, unit cost	181.00	Gamma
Patient time spent on administration, assumed time (hours)	3.00	Gamma
Patient time spent on adverse events, assumed time (hours)	4.00	Gamma
Lenvatinib - daily dose 0, % of days	0.12	Dirichlet
Lenvatinib - daily dose 4, % of days	0.02	Dirichlet
Lenvatinib - daily dose 8, % of days	0.09	Dirichlet
Lenvatinib - daily dose 10, % of days	0.21	Dirichlet
Lenvatinib - daily dose 14, % of days	0.23	Dirichlet
Lenvatinib - daily dose 20, % of days	0.33	Dirichlet
Lenvatinib - daily dose 40, % of days	0.00	Dirichlet
BIM - first line treatable, year 1	199.00	Not varied
BIM - first line treatable, year 2	202.00	Not varied
BIM - first line treatable, year 3	207.00	Not varied

BIM - first line treatable, year 4	210.00	Not varied
BIM - first line treatable, year 5	213.00	Not varied
BIM - % treated, first-line advanced population (incident)	0.80	Not varied
BIM - % survival, first-line advanced population (incident)	0.60	Not varied
BIM - % PFI <6 months and pre-assigned to DOX	0.50	Not varied
BIM - systemic treatment rate	0.80	Not varied

Appendix J - Key model assumptions applied in the base case

Table 81: Key model assumptions

Assumption	Rationale
Independent statistical models are used in the long-term extrapolation of OS and PFS	Although the proportional hazards assumption could not be rejected for OS and PFS (Section 8.3.2) ,independent models allow for a better fitting extrapolation in the DOX and LEN+PEM arms individually. This was validated by visual inspection. Clinical experts at the September 2021 Global advisory board (8.1.10) also confirmed that due to the different mechanisms of action, the proportional hazards assumption was unlikely to hold in the long-term.
The loglogistic and lognormal distributions are used to extrapolate OS and PFS	Clinical experts at the September 2021 Global advisory board (Section 8.1.10) suggested that the log-normal and Gompertz distributions were the preferred OS distributions for LEN+PEM and TPC, respectively. In their clinical experience, they believed it unlikely that patients receiving current standard of care (as found in the TPC arm) would live beyond 5 years (as implied by most distributions), and therefore the Gompertz distribution was preferred. Conversely, the clinical experts believed that treatment with immuno-oncology treatments such as pembrolizumab would lead to long-term remission in a proportion of patients as has been shown in other indications; this fact, in combination with the visual fit to Study 309, led the clinical experts to choose the log-normal curve as preferred for LEN+PEM. Based on diagnostics presented in (Section 8.3.2), the lognormal (LEN+PEM) and loglogistic (TPC) distributions presented the lowest AIC/BIC scores for OS, and lognormal (LEN+PEM and TPC) for PFS
A stopping rule of 24 months is applied to PEM	The stopping rule at 24 months applied to PEM is consistent with the expected marketing authorisation for advanced EC following prior systemic therapy, and is consistent with existing stopping rules for PEM in other disease areas (e.g. TA428 [117])
A stopping rule of 24 months is applied to LEN	Expert clinical opinion (Section 8.1.10) suggested LEN is rarely administered once PEM is discontinued.
Vial wastage is accounted for	A conservative approach was adopted in the model base case, where it is assumed that vials will not be shared between patients. Furthermore, patient numbers for LEN+PEM are not expected

	to be large enough to allow vials to be shared between patients within the same treatment centre
HRQoL includes a decrement which reflects patients' proximity to death	In the base case, patient utility is determined by proximity to death rather than progression-based utilities (in addition to other factors described in Section 8.4)
Re-treatment with LEN+PEM is not included	LEN+PEM is not expected to be reimbursed following prior treatment with LEN+PEM (i.e. retreatment), and is therefore not included in the model base case

Abbreviations: AIC, Akaike's Information Criteria; BIC, Bayesian Information Criteria; HRQoL, health-related quality of life; LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; TPC, treatment of physician's choice.

Appendix K – Summary of Efficacy Results of Lenvatinib Plus Pembrolizumab and Pembrolizumab Monotherapy in dMMR Participants with Advanced Endometrial Carcinoma

As per the request of the DMC, below is presented the summary efficacy results of Len + Pem and Pem monotherapy in dMMR participants with advanced EC (Table 82)

Table 82 Summary of Efficacy Results of Len Plus Pem and Pem Monotherapy in dMMR Participants with Advanced EC

Parameters	Study 309/KN-775[a] Combination Therapy	Study 309/KN-775[a] TPC (Chemotherapy)	KN158 Pembrolizumab Monotherapy (data cut off date: December 6, 2018)	KN158 Pembrolizumab Monotherapy (data cut off date: October 5, 2020)
No. of participants	MSI-H/dMMR (N = 65)	MSI-H/dMMR (N = 65)	MSI-H/dMMR (N = 49)	MSI-H/dMMR (N = 79)
ORR, (%) (95% CI)	40.0 (28.0, 52.9)	12.3 (5.5, 22.8)	57.1 (42.2, 71.2)	48.1 (36.7, 59.6)
CR, n (%)	9 (13.8)	2 (3.1)	8 (16.3)	11 (13.9)
PR, n (%)	17 (26.2)	6 (9.2)	20 (40.8)	27 (34.2)
DOR (months) Median (Range: min, max)	n=26[b] NR (2.1+ - 20.4+)	n=8[b] 4.1 (1.9+ - 15.6+)	n=28[b] NR (2.9, 27.0+)	n=38[b] NR (2.9 - 49.7+)[c]
Median PFS (months) (95% CI)	10.7 (5.6, NR)	3.7 (3.1, 4.4)	25.7 (4.9, NE)	13.1 (4.3, 34.4)
Median OS (months) (95% CI)	NR (NR, NR)	8.6 (5.5, 12.9)	NR (27.2, NE)	NR (27.2, NR)
Follow-up duration (months) median (range)	13.5 (0.4, 25.1)	8.8 (1.0, 23.8)	24.4 (0.5, 34.2)	16.5 (0.5, 56.1)

Footnote: [a] Data cutoff date: 26-OCT-2020.
[b] Number of participants with responses.
[c] "+" indicates there is no progressive disease by the time of last disease assessment.
Abbreviations: CI, confidence interval; CR, complete response; dMMR, mismatch repair deficient; DOR, duration of response; max, maximum; min, minimum; MSI-H, microsatellite instability-high; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TPC, treatment of physician's choice.
Source: [118-120]Source: [118-120]

Eisai response to the DMC's draft assessment report for lenvatinib plus pembrolizumab (LEN+PEM) for endometrial cancer (EC)

Eisai would like to thank the DMC for their draft report and acknowledge the detailed considerations and transparent rationale regarding the DMC base case. We acknowledge that there is uncertainty within the cost-effectiveness analysis, and scenarios that could be further explored. A discussion of these scenarios and uncertainties is given below:

Patient population

The DMC report mentions that LEN+PEM is only expected to be used for a subgroup of patients with platinum free interval (PFI) < 6 months, and DNA mismatch repair-proficient (pMMR) status. This is based on the recent recommendation by the DMC of dostarlimab as a possible standard treatment for patients with DNA mismatch repair-deficient (dMMR) who have progressed during or shortly after treatment with platinum-containing chemotherapy.

It is relevant to consider that the European Commission approved the use of LEN+PEM for adult patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy in any setting (all-comers). Importantly, the LEN+PEM phase III study 309/ KN 775 was not designed or statistically powered to measure the effect of LEN+PEM in multi-level subgroups of patients, such as the PFI<6 months, pMMR/dMMR populations, which represent less than half of the total eligible patient population in study 309/KN 775. As mentioned by the DMC[1] during technical discussions, smaller sample sizes reduce the precision of the efficacy estimates. Therefore, no definite conclusions can be drawn from the efficacy estimates of these multi-level subgroups and it may not be appropriate to restrict the use of LEN+PEM to these subgroups, as patients outside these subgroups could benefit from treatment with LEN+PEM.

Furthermore, as stated in the DMC report, the analyses requested by the DMC in the ITT population revealed a trend (not statistically significant) towards an improved effect of LEN+PEM in the dMMR population in comparison to the pMMR population. This shows that there is a lack of rationale in the restriction of LEN+PEM to certain subgroups, such as the PFI<6 months, pMMR population, and supports the use of LEN+PEM in the indication approved by EMA of 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 (all-comers). This indication includes patients with both pMMR and dMMR status.

Furthermore, it is relevant to consider that the efficacy of dostarlimab was evaluated in a phase I/II study with a single treatment arm[2], while the efficacy of LEN+PEM was evaluated in a phase III randomized, controlled study (309/ KN 775), which provided robust evidence of the effect of LEN+PEM for the EMA-approved indication including both pMMR and dMMR patient populations. To date, LEN+PEM is the only approved treatment available to patients following prior treatment with a platinum-containing therapy that is supported by a robust Phase III study.

Health economic analysis

The DMC's choice of the exponential distribution for the overall survival of LEN+PEM, is associated with the worst statistical fit (highest AIC and BIC) and relies on the assumption of a constant hazard over time (i.e. the risk of death does not change over time). As stated in the DMC report, clinical experts consider that the

assumption of proportional hazards (PH) should not be assumed to hold for a significant period of time, as the mechanisms of action are different between immunotherapy and chemotherapy. If the log-normal extrapolation, which does not rely on the PH assumption, and has one of the best statistical fits, is used, the list price ICER decreases by over 100,000 DKK from 882,504 DKK to 767,768 DKK.

Assessment timeline

Eisai appreciates the DMC's extensive review of the presented evidence. However, the length of the assessment was excessively prolonged (1 year to technical validation to reach "Day 0" of the assessment period, and a total of 1 year and 4 months before a DMC decision meeting) resulting in unnecessarily delayed access to LEN+PEM for patients. Considering the significant unmet need of patients with endometrial cancer whose disease progressed on or following prior treatment with a platinum-containing therapy, the assessment process could have benefited from a single comprehensive round of technical questions and consistency in the DMC requests regarding subgroup analyses.

Summary and Results

EC is the 5th most common type of cancer among women in Denmark and the most common gynaecological cancer[3]. 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[4]. Advanced EC is considered incurable, and the prognosis for survival is less than 5 years, with a median survival of approximately 4 years for stage III and 2 years for stage IV.

LEN+PEM is the first treatment to be approved by the European Commission for adult patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy in any setting (all-comers) in 50 years, and represents an important treatment option for patients with a significant unmet need.

Results from the cost-effectiveness analysis show that LEN+PEM can be considered a cost-effective use of Danish medical resources and represents a manageable budget impact considering the significant unmet need for endometrial cancer patients with advanced or recurrent disease.

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

References

1. DMC'S questions on application, December 2022
2. Study of TSR-042, an Anti-programmed Cell Death-1 Receptor (PD-1) Monoclonal Antibody, in Participants With Advanced Solid Tumors (GARNET) (NCT02715284)
3. Dansk Gynækologisk Cancer Gruppe, D., Retningslinjer for visitation, diagnostik, behandling og kontrol af cancer corporis uteri. Kap. 1. Indledning. . 2016. p. 1-7
4. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer stat facts: uterine cancer 2020 [cited 2021 27 January 2021]; Available from: https://seer.cancer.gov/statfacts/html/corp.html.

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

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

21.02.2023

DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.03.2023
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)	Nuværende SAIP (DKK)	Ny pris pr.1.4.2023 SAIP (DKK)	Rabatprocent ift. AIP
Lenvima	4 mg	30 stk.	11.931,97	[redacted]	[redacted]	[redacted]
Lenvima	10 mg	30 stk.	11.931,97	[redacted]	[redacted]	[redacted]

Lægemidlerne har været i udbud og den nye aftale gælder fra 01.04.2023 og 6 måneder frem med mulighed for 3 gange 3 måneders forlængelse.

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.	22.058,88	[redacted]	[redacted]

Aftaleforhold

Leverandøren har et identisk lægemiddel til Lenvima, der er navngivet Kisplyx (lenvatinib), med identisk indholdsstof, styrke og pakningsstørrelse. Kisplyx er vurderet af Medicinrådet til behandling af nyrekræft i november 2022. Medicinrådet anbefaler ikke Kisplyx til behandling af nyrekræft. Kisplyx indkøbes til AIP. Leverandøren differentierer priserne på de to produkter og prisen på Lenvima er den laveste.

Det er ikke muligt for leverandøren at ændre prisen før Amgros publicerer et nyt udbud med kontraktstart d. 01.10.2023. Årsagen er, at udbuddet er specielt sat sammen, da leverandøren har to lægemidler indenfor samme ATC-kode.

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 priserne for et års behandling med Lenvima i kombination med Keytruda og behandling med Jemperli.

[redacted]

Tabel 2: Sammenligning af lægemiddeludgifter

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Antal pakninger pr. år	Lægemiddeludgift pr. år (SAIP, DKK)
Lenvima	10 mg	30 stk.	20 mg dagligt PO	[redacted]	24	[redacted]
Keytruda	25 mg/ml	4 ml.	2 mg/kg IV, hver 3 uge	[redacted]	24	[redacted]
Kombination med Lenvima og Keytruda						[redacted]
Jemperli	500 mg	1 stk.	500 mg iv/3 uge i 4 cykler 1000 mg iv/6 uge efter	[redacted]	18	[redacted]

*Vægtjusteret dosis 68,9 kg

Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	https://nyemetoder.no/metoder/lenvatinib-lenvima-pembrolizumab-keytruda
Sverige	Anbefalet	https://janusinfo.se/download/18.1e732a371864ac454343cf8c/1676634100607/Keytruda-Lenvima-vid-endometriecancer-230217.pdf
England	Under vurdering	https://www.nice.org.uk/guidance/indevelopment/gid-ta10692

Konklusion

[redacted]

Application for the assessment of lenvatinib with pembrolizumab for patients with advanced or recurrent endometrial cancer who have disease progression on or following prior treatment with a platinum-containing therapy

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

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1 Basic information

Contact information	
Name	Laureanne Lorenzo
Title	Market Access Senior Manager
Phone number	+46 73 429 36 06
E-mail	laureanne_lorenzo @eisai.net

Overview of the pharmaceutical	
Proprietary name	Lenvima® Keytruda®
Generic name	Lenvatinib Pembrolizumab
Marketing authorization holder in Denmark	Eisai GmbH Merck Sharp & Dohme B.V
ATC code	L01EX08 L01XC18
Pharmacotherapeutic group	Antineoplastic agents, protein kinase inhibitors Antineoplastic agents, monoclonal antibodies
Active substance(s)	Lenvatinib Pembrolizumab
Pharmaceutical form(s)	Oral therapy IV therapy
Mechanism of action	Lenvatinib is an RTK inhibitor that selectively inhibits Vascular endothelial growth factor (VEGF) receptors (VEGFR1, VEGFR2, and VEGFR3), as well as multiple other proangiogenic and oncogenic signalling pathways, including FGFR1, 2, 3, and 4, platelet-derived growth factor receptor alpha (PDGFRα), KIT, and RET. Pembrolizumab binds to the PD-1 receptor and blocks its interaction with the PD-L1 and PD-2 ligands, releasing PD-1-mediated inhibition of the immune response (including anti-tumour response).

Overview of the pharmaceutical	
Dosage regimen	The recommended dosage of lenvatinib is 20 mg orally once daily in combination with pembrolizumab administered as an IV infusion over 30 minutes: 200 mg every three weeks or 400 mg every 6 weeks • Until disease progression or unacceptable toxicity [1]
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Lenvima in combination with pembrolizumab is indicated for the treatment of adult patients with advanced or recurrent endometrial carcinoma (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

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Other approved therapeutic indications	**Lenvatinib:**
	Lenvatinib as monotherapy for the treatment of adult patients with progressive, locally advanced, or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma (DTC), refractory to radioactive iodine (RAI)
	Lenvatinib as monotherapy for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have received no prior systemic therapy, with the same price as currently approved under basic reimbursement status [2].
	Pembrolizumab**:**
	Melanoma
	Pembrolizumab as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
	Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection.
	Non-small cell lung carcinoma (NSCLC)
	Pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
	Pembrolizumab, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.
	Pembrolizumab, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.
	Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving pembrolizumab.
	Classical Hodgkin lymphoma (cHL)
	Pembrolizumab as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous 3 stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.
	Urothelial carcinoma
	Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
	Pembrolizumab as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10

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Overview of the pharmaceutical	
	Head and neck squamous cell carcinoma (HNSCC) Pembrolizumab, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 Pembrolizumab as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy Renal cell carcinoma (RCC) Pembrolizumab, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults Pembrolizumab, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions Colorectal cancer Pembrolizumab as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults Oesophageal carcinoma Pembrolizumab in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10 Triple-negative breast cancer (TNBC) Pembrolizumab in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease Endometrial carcinoma (EC) Pembrolizumab, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation [3].
Will dispensing be restricted to hospitals?	Dispensation of lenvatinib is restricted to hospitals (BEGR).
Combination therapy and/or co-medication	Yes, in combination with pembrolizumab.

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Overview of the pharmaceutical	
Packaging – types, sizes/number of units, and concentrations	Lenvima® 4mg hard capsules – Each hard capsule contains 4mg of lenvatinib (as mesylate) [4] Lenvima® 10mg hard capsules – Each hard capsule contains 10mg of lenvatinib (as mesylate) [4] Keytruda® 25mg/ml – Each pack contains 100mg of pembrolizumab [5]
Orphan drug designation	No

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2 Abbreviations

Abbreviation	Definition
AE	Adverse events
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCT	Autologous stem cell transplant
AST	Aspartate Aminotransferase
AUC	Under The Curve
BICR	Blinded Independent Central Review
BIM	Budget impact model
BP	Blood Pressure
BSA	Body surface area
CBR	Clinical Benefit Rate
CEAC	Corresponding Cost-Effectiveness Acceptability Curve
cHL	Classical Hodgkin Lymphoma
CPS	Combined Positive Score
CRC	Colorectal Cancer
CVA	Cerebrovascular Accident
DCR	Disease Control Rate
DETs	Data Extraction Tables
DGCG	Danish Gynecological Cancer Group
DKK	Danish kroner
DLT	Dose Limiting Toxicity
DMC	Danish Medicines Council
dMMR	Mismatch Repair Deficient
DOR	Duration of response
DSDR	Durable Stable Disease Rate
EBRT	External Beam Radiotherapy
EC	Endometrial Carcinoma/Cancer
EC	Endometrial Carcinoma

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Abbreviation	Definition
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization 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
FDA	Food and Drug Administration
FIGO	Federation of Gynecology and Obstetrics
HCC	Hepatocellular Carcinoma
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HRQoL	Health-related Quality of life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
INR	International Normalized Ratio
irAE	Immune-Related Adverse Events
ISPOR	Professional Society for Health Economics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intended To Treat
IUD	Intrauterine Device
IV	Intravenous
LEN	Lenvatinib
LVEF	Left Ventricular Ejection Fraction
LYs	Life Years
MAR	Missing At Random
MMI	Myometrial Invasion
MMR	Mismatch Repair
MSI-H	Metastatic Microsatellite Instability-High

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Abbreviation	Definition
MSI-L	Microsatellite Instability-Low
MSS	Microsatellite Stability
MTD	Median Treatment Duration
MUGA	Multi-Gated Radionuclide Angiography
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NSCLC	Non-Small Cell Lung Carcinoma
NSCLC	The Non-Small Cell Lung Cancer
NSGO-CTU	Director, Nordic Society of Gynaecologic Oncology-Clinical Trial Unit
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PartSA	Partitioned Survival Analysis
PD	Progressed Disease
PD-1	Programmed Death Protein 1
PD-L1	Programmed Death-Ligand 1
PF	Progression-Free
PFI	Platinum Free Interval
PFS	Progression-free survival
PLD	Pegylated Liposomal Doxorubicin

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3 Tables and Figures

3.1 List of tables

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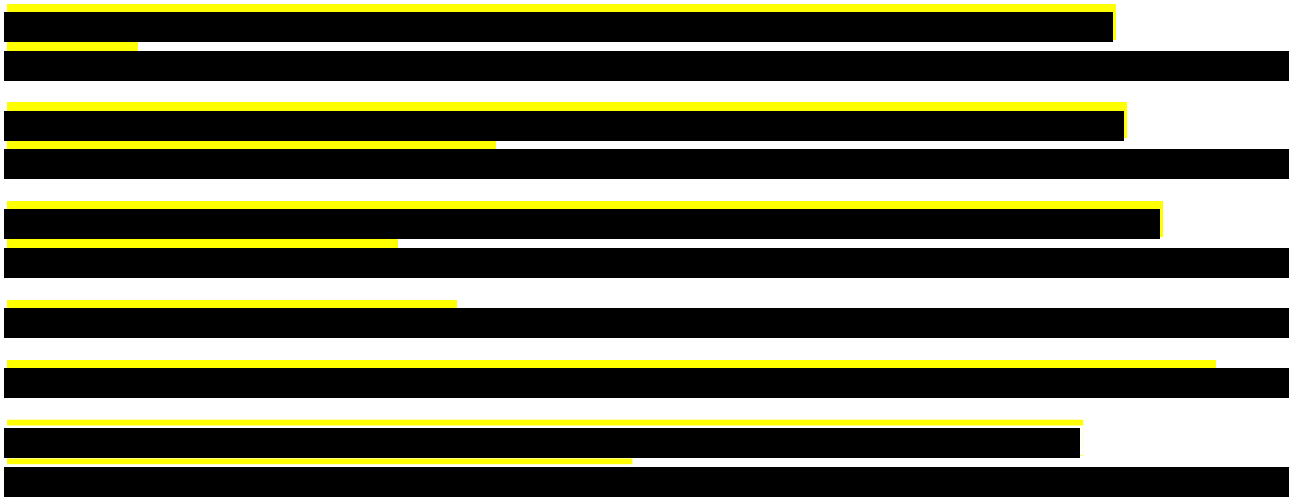
3.2 List of figures



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

4 Summary

4.1 Indication

Endometrial cancer (EC) is the most common gynaecologic malignancy in developed countries and the second most common worldwide [6-8]. As the most common gynaecologic malignancy in Denmark, EC is the 5th most common type of cancer among women with an incidence of 867, and a prevalence of 9,472 in 2020 [9, 10]. The global incidence of EC is expected to increase due to risk factors including increased life expectancy/older age, exposure to excess endogenous and exogenous oestrogen levels, Lynch syndrome and obesity [11-16]. Furthermore, the global mortality rate for EC is increasing more rapidly than the incidence rate [12]. Morbidity from EC is caused by both disease-related complications (including anaemia due to vaginal bleeding, pain, weight loss and abdominal bloating) and long-term treatment-related complications (including toxic side effects of treatment and long-term genitourinary and cardiovascular outcomes [17].

EC displays tumour heterogeneity with several histological subtypes, with distinct pathogenesis and prognosis [8]. EC can broadly be classified into two subtypes: Type I that is considered to be low-risk and makes the majority (80–90%) of all EC cases and Type II that is considered to be high-risk with a poor prognosis [8, 18]. Although most women with EC are diagnosed at an early stage with cancer confined to the uterus (with a favourable 5-year survival rate of >90%), around one-third are diagnosed with advanced disease (with a poor 5-year survival rate of only 17%) [19-22]. Recurrent disease, which can be associated with lifestyle, obesity, exercise, smoking, and sexual health, occurs in up to 25% of cases and accounts for most endometrial cancer-related deaths [23].

Lenvatinib + pembrolizumab (LEN+PEM) is the first treatment to be approved by the European Commission for adult patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy in any setting (all-comers) in 50 years. This single technology assessment relates to LEN+PEM in the approved endometrial indication, with the following restriction: 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).

4.2 The pharmaceutical

LEN+PEM offers a novel therapy; 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.

4.3 The comparators

Treatment of EC may vary depending on the grade, histology, stage of the disease, and MSI/Mismatch Repair (MMR) status. For the majority of patients with low-risk EC, the mainstay of first-line treatment is curative surgery with or without radiotherapy and/or chemotherapy [24-27]. After surgery, a platinum containing regimen is recommended that aims to prolong survival by limiting further disease progression [25, 28, 29]. However, according to the 2021 ESGO/ESTRO/ESP guidelines, the Danish guidelines and clinical experts, there is no agreement on the standard treatment of patients with advanced or recurrent EC who have disease progression on or following platinum-based therapy [25, 30-33].

The 2020 ESGO/ESTRO/ESP guidelines recommend doxorubicin (DOX) and paclitaxel as the most active therapies for second-line treatment, while re-challenge with platinum containing chemotherapy, is considered as an option for patients with a long platinum-free interval [34].

The Danish Medicines Council (DMC) describes in its assessment report for dostarlimab from December 2021 [64] that the second line treatment options for EC are dependent on the duration of time passed since platinum-based treatment in first line. For patients who progress during or up to six months after treatment with first line platinum therapy, pegylated liposomal doxorubicin (PLD) is given as standard treatment. Patients who progress approximately six months or more after discontinuation of platinum treatment are considered to be platinum sensitive and can be re-treated with platinum-based chemotherapy after progression [62, 65].

Based on the available clinical guidelines, clinical expert input and consultation with DMC, the most relevant comparators in the Danish setting were therefore considered to be:

- PLD for patients that have a platinum-free interval (PFI) of less than 6 months (PFI < 6 months).
- Carboplatin in combination with paclitaxel for patients that have a PFI of 6 months or greater.

This application focuses on EC patients with advanced EC that are indicated for DOX/PLD treatment following disease progression following prior treatment with a platinum-containing therapy in less than 6 months (PFI < 6 month).

4.4 Main efficacy endpoints

The efficacy and safety of LEN+PEM in EC was investigated in the direct comparative ongoing study 309 / KN-775, a multicenter, open-label, randomized, phase 3 trial, versus DOX or paclitaxel as the treatment of physician's choice (TPC), in patients with advanced EC who were previously treated with ≥1 prior platinum-based chemotherapy regimen. LEN in combination with PEM provides a favourable risk-benefit profile with statistically significant and clinically meaningful improvements in overall survival [redacted]

Safety of the pharmaceutical

The study also demonstrates a manageable safety profile for LEN+PEM that is generally consistent with the known safety profiles of the components as monotherapies [35-41], with AEs clinically manageable by supportive medications and dose modifications. The safety profile of LEN is also consistent across different indications, including EC. The overall incidence of AEs was similar between the LEN+PEM group and the TPC group. The observed incidences of Grade 3 to 5 AEs and drug-related Grade 3 to 5 AEs were higher for LEN+PEM compared with TPC but after adjustment for exposure, the overall event rates for SAEs and drug related SAEs were similar between the treatment groups. Exposure-adjusted rates of all AEs, drug-related AEs, Grade 3 to 5 AEs, drug related Grade 3 to 5 AEs, and deaths were lower for LEN+PEM compared with TPC.

Given superior efficacy, manageable safety, and no substantial differences in HRQoL between LEN+PEM and DOX, LEN+PEM has an overall favourable risk/benefit profile compared with DOX for patients with advanced EC who have disease progression following prior platinum-based chemotherapy regimen.

4.5 Structure of the economic analysis

A cost-effectiveness model was developed using a partitioned survival analysis (PartSA) structure based on three health states, progression-free disease (PF), progressed disease (PD) and death. LEN+PEM was compared to the standard of care therapies used in Denmark with PLD as the base case comparator for the relevant population (PFI < 6 months patient population). A life-time horizon of up to 36 years was used in the base case. Deterministic sensitivity analysis, probabilistic sensitivity analysis and various scenarios were explored.

4.6 Sources of relative efficacy of the economic model

As the follow-up period for Study 309 / KN-775was shorter than the modelled time horizon, extrapolation from the observed OS, PFS and TTD data was required. A range of standard parametric distributions were explored for extrapolation of the OS, PFS and TTD endpoints with options for single or joint fits. Due to the lack of published data which would support an indirect treatment comparison of LEN+PEM to PLD in the PFI < 6 months patient population the following analyses were performed:

- Study 309 / KN-775post-hoc subgroup analysis in the LEN+PEM PFI < 6 months patient population, comparison with patients pre-assigned to DOX of TPC (assumption of PLD equivalence to DOX).

4.7 Results of the economic analysis

In the base case analysis, in the population with PFI < 6 months who were pre-assigned to DOX in Study 309, LEN+PEM is associated with incremental costs of [redacted] and incremental QALYs of [redacted], resulting in an ICER of [redacted] compared with PLD. The introduction of LEN+PEM in Denmark is associated with a total net budget impact of [redacted] in year 1 to [redacted] in year 5 resulting in a cumulative 5-year net budget impact of [redacted]

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

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

5.1 The medical condition and patient population

Endometrial cancer (EC) is the most common gynaecologic malignancy in developed countries and the second most common gynaecologic malignancy worldwide [7, 8, 42]. EC develops in the inner lining of the uterine cavity [43], 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 [11-16]. In 2030, the global incidence of EC is expected to increase to 487,316, representing a 16.8% increase from 2020 [44]. The mortality rate for EC has increased more rapidly than the incidence rate (21% increase in mortality rates from 1999 to 2016 [15]), 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 [12].

EC displays tumour heterogeneity and there are several histological subtypes, with distinct pathogenesis and prognosis [8]. 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 [8, 18].

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 [45, 46]. Both systems are based on surgical staging and include assessment of the extent of myometrial invasion (MMI) 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 [19], 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) [46, 47]. Abnormal vaginal bleeding often occurs early in the disease course, leading to most EC cases being diagnosed at an early stage [47]. 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 [48].

A deficient mismatch repair (dMMR) system is frequently associated with Type I EC [49]. 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 [50]. Deficiency in the MMR system results in the accumulation of mutations at microsatellites, resulting in microsatellite instability-high (MSI-H). This generates a high genotypic and phenotypic diversity of emerging precancerous cell clones from which carcinogenesis likely follows [50].

MSI-H tumours are found in up to 35% of patients with EC and, comprising <20% of advanced disease cases [50-53]. Non-MSI-H tumours (or proficient mismatch repair [pMMR]) consist of those with a low frequency of microsatellite instability-low (MSI-L) and those with microsatellite stability (MSS) [54].

The main risk factor for developing EC is exposure to endogenous and exogenous oestrogens [46, 55]. Other key risk factors include obesity, diabetes, age, and Lynch syndrome.

Recurrent disease, which typically becomes clinically apparent within 3 years of primary therapy [56, 57], occurs in up to 25% of cases and accounts for most EC-related deaths [58, 59]. Recurrence of EC can be associated with lifestyle, obesity, exercise, smoking, and sexual health [47]. 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 [58].

EC is the 5th most common type of cancer among women in Denmark and the most common gynaecological cancer [9]. 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 [19-22]. Advanced EC is considered incurable, and the prognosis for survival is significantly lower with a median survival of approximately 4 years for stage III and 2 years for stage IV [60].

Incidence and prevalence of EC in Denmark are presented in Table 1, based on epidemiological market research [10].

Table 1: Incidence and prevalence of EC in the past 5 years in Denmark

Year	2016	2017	2018	2019	2020
Diagnosed prevalent cases	8,683	8,884	9,088	9,271	9,472
Diagnosed incident cases	800	819	826	841	867
Advanced stage 3 and 4 incident cases	141	143	149	152	154
Advanced stage 3 incident cases	108	109	113	115	116
Advanced stage 4 incident cases	33	34	36	37	38
Recurrent incident cases	40	41	41	43	44
Recurrent early-stage low and intermediate risk	25	25	25	26	27
Recurrent early-stage high risk	15	16	16	17	17
Sum of advanced or recurrent incident cases	**181**	**184**	**190**	**195**	**198**

Source: DRG 2020 [10]

The Danish patient population expected to be candidates for treatment with lenvatinib and pembrolizumab (LEN+PEM) are patients with advanced or recurrent EC with PFI < 6 months and are not candidates for curative surgery or radiation. This population would currently be eligible for treatment with PLD.

The number of incident 1st line patients with advanced or recurrent EC is based on the DRG/Clarivate endometrial cancer epidemiology model for the years 2022 to 2026 [10] and validation by an expert clinician. Using internal forecast, a percentage of patients that are treated (80%) is applied, and it is estimated that 60% of those patients will reach 2nd line. The percentage of patients with PFI<6 months from Study 309 / KN-775[61] is then applied to this population to derive the population size for 2nd line treatable population with PFI < 6 months. Lastly, it is estimated that 80% of those patients will be eligible for systemic treatment.

Among those, based on Eisai market research, an estimated 60% would be eligible for treatment with LEN+PEM.

This results in an estimated 31 treated patients with advanced or recurrent EC who have disease progression on or following prior treatment with a platinum-containing therapy within 6 months in 2022 (Table 2). The combination therapy is expected to be used upon reimbursement since there is currently no clear standard of care in this population.

Table 2: Estimated number of EC patients eligible for treatment

Year	Percentage of previous row	2022	2023	2024	2025	2026
1st line treatable population (advanced)		199	202	207	210	213
1st line treated population (advanced)	80%	159	162	166	168	170
2nd line treatable population (advanced)	60%	96	97	99	101	102
2nd line treatable population with PFI < 6 months	67%	64	65	67	68	69
Systemic treatment rate	80%	51	52	53	54	55
Eligible for LEN+PEM treatment	60%	31	31	32	32	33

Source: Expert clinician and DRG 2020 [10]

5.1.1 Patient population relevant for this application

Patients relevant for this application are patients with advanced EC 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.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Treatment of EC varies depending on the grade, histology, stage of the disease, and MSI/MMR status. For the majority of patients with low-risk EC, the mainstay of first-line treatment is curative aiming surgery with removal of all visible cancerous tissue (macro-radical surgery) with or without radiotherapy and/or chemotherapy [24-27]. After surgery, a combination of carboplatin and paclitaxel is recommended [25, 28, 29] with the purpose of prolonging survival by limiting further disease progression [28, 29]. The current treatment guidelines for EC include:

- The European Society for Medical Oncology (ESMO), last updated in 2013 [18]
- The joint guidelines from European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and European Society of Pathology (ESP), 2021 [34]
- National Comprehensive Cancer Network (NCCN) Uterine Neoplasms Guidelines, 2021 [47]
- Danish Gynecological Cancer Group (DGCG), 2019 [24]
- Sundhed.dk, last updated in 2015 [26]

There are, however, few approved therapy options for second line treatment of patients with advanced or recurrent EC following prior platinum-based therapy [25, 30-33]. Most recent guidelines from the Danish Gynecological Cancer Group (DGCG) and sundhed.dk [25, 26, 62] 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 this application. Please see section 11 for more details.

5.2.2 Choice of comparators

Although there is no consensus on the standard of care treatment following platinum containing therapy, the Danish Medicines Council (DMC) describes in its assessment report for dostarlimab from December 2021 [63], that the second line treatment options for EC are dependent on the duration of time passed since platinum-based treatment in first line. Patients who progress approximately six months or more after discontinuation of platinum treatment are considered to be platinum sensitive and can be re-treated with platinum-based chemotherapy after progression [34, 64]. If progression occurs during or up to six months after treatment with first line platinum therapy, pegylated liposomal doxorubicin (PLD) is given as standard.

It is however important to note that pegylated liposomal doxorubicin (Caelyx®) does not have EMA marketing authorization for EC [65] and use can be considered off-label. In spite of this, as clinicians in Denmark have several years of experience with the use of PLD for EC patients, PLD is considered standard therapy in second line treatment of EC for patients who progress during or up to six months after initial systemic therapy containing platinum [25].

Furthermore, PLD together with weekly paclitaxel are the treatments mentioned in the latest ESGO/ ESTRO/ ESP guidelines in second line EC treatment after previous use of platinum-based chemotherapy [34].

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 that have PFI < 6 months.

5.2.3 Description of comparators(s)

The efficacy and safety of LEN+PEM in EC was investigated in the direct comparative ongoing study 309 / KN-775, a multicentre, open-label, randomized, Phase 3 trial, versus doxorubicin (DOX) or paclitaxel as the treatment of physician's choice (TPC), in patients with advanced EC who were previously treated with ≥1 prior platinum-based chemotherapy regimen. There is evidence that suggests DOX and PLD are comparable with respect to efficacy and safety (described below) and therefore, evidence for the comparison of LEN+PEM and PLD were estimated from the comparison between LEN+PEM and the chemotherapy group pre-assigned to DOX in Study 309 / KN-775, with PFI < 6 months. As such, a description of both PLD (Section 5.2.3.3) and DOX (Section 5.2.3.4) will be provided in this section.

5.2.3.1 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 [66].
- In advanced and metastatic soft tissue sarcoma, there were no significant differences between DOX and PLD for PFS and OS [67].

- A meta-analysis published in 2012 demonstrated liposomal DOX and PLD have favourable toxicity profiles compared with conventional DOX [68].

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.

5.2.3.2 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 RCTs were identified [69, 70 , 71] as well as four single arm studies and one RWE study [72-76], 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 (NMA) would not yield additional comparisons of interest for the submission. For details see Appendix F – Comparative analysis of efficacy and safety.

5.2.3.3 PLD

The information in Table 3 is collected from the SmPC [65]. Information on posology is based on the DMC assessment of dostarlimab [63].

Table 3: Product characteristics for PLD

Subject	Description
Generic name (ATC-code)	Pegylated liposomal doxorubicin, L01DB01
Mode of action	The active ingredient of Caelyx®, pegylated liposomal is doxorubicin hydrochloride, a cytotoxic anthracycline antibiotic obtained from Streptomyces peucetius var. caesius. The exact mechanism of the antitumour activity of doxorubicin is not known. It is believed that inhibition of DNA, RNA and protein synthesis is responsible for the majority of the cytotoxic effects. This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix thus preventing their unwinding for replication.
Pharmaceutical form	Concentrate for solution for infusion (sterile concentrate)
Posology	40-50 mg / m^2 PLD IV every 4 weeks for up to 6-8 series [63]
Method of administration	Pegylated liposomal doxorubicin 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. Pegylated liposomal doxorubicin should only be administered under the supervision of a qualified oncologist specialised in the administration of cytotoxic agents.
Necessary monitoring, both during administration and during the treatment period	Pegylated liposomal doxorubicin should only be administered under the supervision of a qualified oncologist specialised in the administration of cytotoxic agents. It is recommended that all patients receiving pegylated liposomal doxorubicin routinely undergo frequent ECG monitoring. More specific methods for the evaluation and monitoring of cardiac functions as compared to ECG are a measurement of left ventricular ejection fraction by echocardiography or preferably by multigated angiography. These methods must be applied routinely before the initiation of pegylated liposomal doxorubicin therapy and repeated periodically during treatment. The evaluation of left ventricular function is considered to be mandatory before each additional

Subject	Description
	administration of pegylated liposomal doxorubicin that exceeds a lifetime cumulative anthracycline dose of 450 mg/m^2. The evaluation tests and methods mentioned above concerning the monitoring of cardiac performance during anthracycline therapy are to be employed in the following order: ECG monitoring, measurement of left ventricular ejection fraction, endomyocardial biopsy.
Should the pharmaceutical 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)
Need for diagnostic or other test	Prior to pegylated liposomal doxorubicin administration, evaluate hepatic function using conventional clinical laboratory tests such as ALT/AST, alkaline phosphatase, and bilirubin.
Packaging	Type I glass vials, each with a siliconised grey bromobutyl stopper, and an aluminium seal, with a deliverable volume of 10 ml (20 mg) or 25 ml (50 mg). Caelyx pegylated liposomal is supplied as a single pack or packs of ten vials.

Abbreviation: ECG, Electrocardiogram; IV, intravenous;
Sources: [65], [63]

5.2.3.4 DOX

The information in Table 4 is collected from the EMA SmPC [77] and Danish SmPC (produktresume) [78]

Table 4: Product characteristics for DOX

Subject	Description
Generic name (ATC-code)	Doxorubicin hydrochloride, L01DB01
Mode of action	DNA intercalation (leading to an inhibition of synthesis of DNA, RNA and proteins), formation of highly reactive free-radicals and superoxides, chelation of divalent cations, the inhibition of Na-K ATPase and the binding of doxorubicin to certain constituents of cell membranes (particularly to the membrane lipids, spectrin and cardiolipin). Highest drug concentrations are attained in the lung, liver, spleen, kidney, heart, small intestine and bone-marrow. Doxorubicin does not cross the blood-brain barrier.
Pharmaceutical form	Concentrate for solution for infusion.
Posology	Due to the risk of lethal cardiomyopathy risk and benefits should be assessed for each individual patient prior to each treatment. **Monotherapy** Recommended dose 60-75 mg/m^2 body surface area every 3rd week.

Subject	Description
	Combinational therapy When doxorubicin is administrated in combination with other anti-tumorigenic drugs with overlapping toxicity doxorubicin dose must be reduced to 30-60 mg/m^2 body surface area every 3rd-4th week. **Example of combination therapy:** Doxorubicin can be administered in combination with cisplatin for treatment of advanced EC in accordance with the following treatment regimen [79]: Day 1: Doxorubicin 60mg/m2 IV push Day 1: Cisplatin 50mg/m2 IV over 60 minutes. Repeat cycle every 3 weeks for 6 cycles. OR Day 1: Doxorubicin 45mg/m2 (if prior pelvic radiation) IV push Day 1: Cisplatin 50mg/m2 IV over 60 minutes. Repeat cycle every 3 weeks for 6 cycles.
Method of administration	IV push
Necessary monitoring, both during administration and during the treatment period	Doxorubicin should be administered only under the supervision of physicians experienced in the use of cytotoxic therapy. Cardiac function should be assessed before patients undergo treatment with doxorubicin and must be monitored throughout therapy to minimize the risk of incurring severe cardiac impairment. The risk may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of doxorubicin at the first sign of impaired function. The appropriate quantitative method for repeated assessment of cardiac function (evaluation of LVEF) includes multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). A baseline cardiac evaluation with an ECG and either a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiotoxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent throughout follow-up.
Should the pharmaceutical be administered with other medicines	Can possibly be administered with other anti-tumorigenic drugs
Treatment duration / Criteria for end of treatment:	Treatment until disease progression or unacceptable toxicity (based on physician's choice). Patients can be treated every 3 weeks for 6 cycles.

Subject	Description
Need for diagnostic or other test	Before or during treatment with doxorubicin the following monitoring examinations are recommended (how often these examinations are done will depend on the general condition, the dose and the concomitant medication): • radiographs of the lungs and chest and ECG • regular monitoring of heart function (LVEF by e.g. ECG, UCG and MUGA scan) • daily inspection of the oral cavity and pharynx for mucosal changes • blood tests: haematocrit, platelets, differential white cell count, AST, ALT, LDH, bilirubin, uric acid • kidney function should also be checked before and during therapy
Packaging	5 ml vial containing 10 mg doxorubicin hydrochloride. 10 ml vial containing 20 mg doxorubicin hydrochloride. 25 ml vial containing 50 mg doxorubicin hydrochloride. 50 ml vial containing 100 mg doxorubicin hydrochloride. 100 ml vial containing 200 mg doxorubicin hydrochloride.

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; ECG, Electrocardiogram; ECHO, echocardiography; LDH, Lactate dehydrogenase LVEF, Left ventrcular ejection fraction; MUGA, multi-gated radionuclide angiography, UCG, Ultrasound Cardiography

Sources: [65], [63]

5.3 The intervention

Vascular endothelial growth factor (VEGF) inhibition enhances the efficacy of programmed death protein 1 (PD-1) inhibition versus use of a single-agent PD-1 inhibitor [80-83] 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 [84, 85]. 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 [86]. LEN decreased the tumour associated macrophage (TAM) population, which is known as an immune-regulator in the tumour microenvironment. By decreasing TAMs, 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) [81].

The requested characteristics of the intervention were taken from the SmPC's for LEN [4] and PEM [5] and provided in Table 5.

Table 5: Product characteristics of LEN+PEM

Subject	Description
Generic name (ATC-code)	L01EX08, lenvatinib

Subject	Description
	L01FF02, pembrolizumab
Dosing	Lenvatinib: the recommended daily dose of lenvatinib 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.[4] Pembrolizumab: pembrolizumab is administered by IV infusion over 30 minutes. For endometrial carcinoma, the recommended dosage is 200 mg every 3 weeks or 400 mg every 6 weeks.[5]
Method of administration	Lenvatinib is for oral use Pembrolizumab is administered by IV infusion over 30 minutes
Treatment duration / Criteria for end of treatment:	Lenvatinib: [4] treatment with lenvatinib can continue for as long as the disease does not progress and the patient continues to tolerate treatment.[4] Pembrolizumab: patients should be treated with pembrolizumab until disease progression or unacceptable toxicity.[5]
Should the pharmaceutical be administered with other medicines	No
Necessary monitoring, both during administration and during the treatment period	Lenvatinib: For patients with hypertension, blood pressure should be well controlled prior to treatment, and should be regularly monitored during treatment. Cases of nephrotic syndrome have been reported in patients using lenvatinib; urine protein should be monitored regularly to avoid proteinuria. Due to hepatotoxicity, close monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment; liver function tests should be monitored before initiation of treatment, then every 2 weeks for the first 2 months and monthly thereafter during treatment. To avoid cardiac dysfunction, patients should be monitored for clinical symptoms or signs of cardiac decompensation, as dose interruptions, adjustments, or discontinuation may be necessary. Electrolyte abnormalities should be monitored and corrected before starting treatment and electrocardiograms and should be monitored at baseline and periodically during treatment to avoid QT/QTc interval prolongation. Thyroid function should be monitored before initiation of, and periodically throughout, treatment with lenvatinib.[4] Pembrolizumab: Patients should be monitored for signs and symptoms of immune-related: pneumonitis, colitis, changes in liver function (hepatitis), changes in renal function (nephritis), adrenal insufficiency and hypophysitis (endocrinopathies) and severe skin reactions. Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes.[5]
Need for diagnostic or other test	No biomarker test or companion diagnostic is required for the use of lenvatinib + pembrolizumab.

Abbreviation: LEN, lenvatinib; IV, intravenous

There is a significant unmet medical need for patients with advanced and recurrent EC who have progressed after prior platinum treatment. Therefore, the introduction of LEN+PEM will provide an effective treatment option for patients with advanced EC who have disease progression following prior treatment with a platinum-containing therapy, particularly those within 6 months of receiving prior platinum-containing treatment (PFI < 6 months) and who are not candidates for curative surgery or radiation.

6 Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

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 [87]. Eisai and Merck Sharp & Dohme have conducted the pivotal clinical study 309/KN-755 [88] (see Section 7.1), a randomised controlled trial conducted to compare the efficacy and safety of LEN+PEM versus treatment of physician's choice (TPC) (DOX or paclitaxel). PLD is considered the standard of care in Danish clinical practice. However, as described in Section 5.2.3, there is evidence suggesting DOX and PLD are comparable with respect to efficacy and safety (described in Section 5.2.3) 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.

The evidence of the 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 < 6 months).

6.2 List of relevant studies

Table 6 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer, Makker et al., The New England Journal of Medicine, 2022 [89]	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])	NCT03517449	**Study Start Date:** June 11, 2018 **Primary Completion Date:** October 26, 2020 **Estimated Study Completion Date:** January 16, 2023	LEN + PEM vs. DOX for patients with advanced EC who have PFI < 6 months

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

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of
	Study 309 / KN-775			

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

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

7 Efficacy and safety

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 endometrial carcinoma following at-least one prior platinum-based regimen in any setting.

7.1 Efficacy and safety of LEN+PEM compared with DOX 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)

7.1.1 Relevant studies

This section provides evidence for the efficacy and safety of LEN+PEM compared to the relevant comparator as described in Section 5.2.2: 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).

As described in Section 5.2.2, PLD is considered the relevant comparator to LEN+PEM for patients with PFI < 6 months 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 that suggests DOX and PLD are comparable with respect to efficacy and safety (described in Section 5.2.3) and therefore, evidence for the comparison of LEN+PEM and 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, as described in the following section.

The efficacy and safety of LEN+PEM have 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 description of main characteristics/methodology, population baseline characteristics, table of efficacy and safety (with definition, validity and clinical relevance) as well as safety data is available in appendices B-E.

Study 309 / KN-775is an ongoing 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, 84]. A summary of the trial details is given in Table 7.

Table 7 Summary of Study 309 / KN-775

Study name	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

Study design	Open-label, randomized, Phase 3 trial	
Sample size (n)	827	
Patient population(s)	Comparator	Intervention
	416	411
Intervention(s)	LEN 20 mg + PEM 200 mg Participants with endometrial cancer (EC) received lenvatinib (LEN) 20 mg orally, once daily, plus pembrolizumab (PEM) 200 mg intravenously, every 3 weeks 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.	
Comparator(s)	Treatment of Physician's Choice (TPC): DOX or Paclitaxel Participants with EC received either DOX 60 milligrams per square meter (mg/m^2) intravenously, every 3 weeks, 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.	
Follow-up period	As of the data cut-off date of 26th October 2020 for IA1, the median duration of follow up in the overall population (all comers and pMMR populations) was 11.4 months (range: 0.3, 26.9)	
Key eligibility criteria	Inclusion criteria	Exclusion criteria
	Adults aged ≥18 years Histologically confirmed advanced, recurrent, or metastatic EC Evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for EC. Patients 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. Measurable disease according to RECIST 1.1 and confirmed by BICR. ECOG performance status score of 0 or 1 within 7 days of the start of treatment. Adequately controlled blood pressure with or without antihypertensive medications. Have adequate organ function within 7 days prior to the start of study treatment (based on laboratory assessment).	>1 prior systemic chemotherapy regimen (other than adjuvant or neoadjuvant) for EC. Prior treatment with any treatment targeting VEGF-directed angiogenesis, any anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. Patients who 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 discontinued from that treatment due to a Grade 3 or higher immune-related AE. Radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks prior to study treatment start. Prior enrollment on a clinical study evaluating LEN and PEM for EC, regardless of treatment received. Not pregnant or breast-feeding, or following contraceptive guidance if of childbearing age

Primary endpoint(s)	**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 endpoint(s)	**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 TEAEs, SAEs, and immune-related AEs. 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** 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).
Baseline characteristics	Baseline characteristics are presented in detail in Appendix C .
Predefined subgroups	No relevant subgroups analysed for this application
Used in the health economic model?	Yes

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 [87]. 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 D. In addition, validity, clinical relevance and summary of results of efficacy endpoints of interest is provided in Appendix D.

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

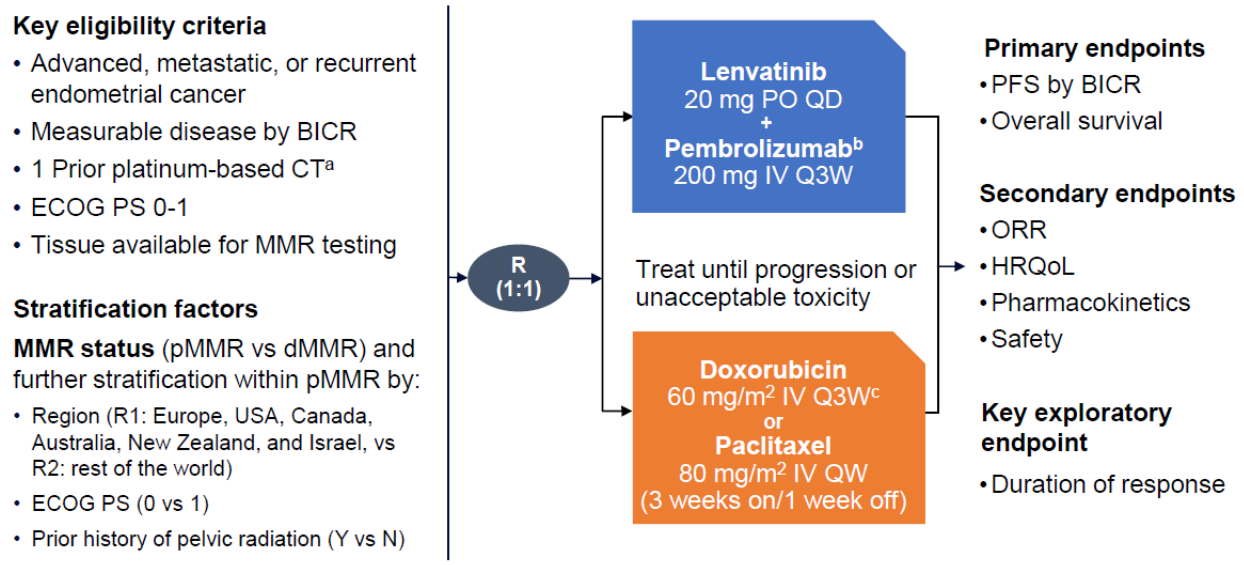
7.1.1.1 Study design

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 (treatment of physician's choice). The study then randomized (1:1) 780 eligible patients to receive either LEN+PEM or TPC (DOX or paclitaxel). As of the data cut-off date for this report, 827 participants were randomized (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 1: Study 309 / KN-775 - study design



[a]Patients may have received up to 2 prior platinum-based CT regimens if 1 is given in the neoadjuvant or adjuvant treatment setting. [b]Maximum of 35 doses. [c]Maximum cumulative dose of 500 mg/m^2.
BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; PFS, progression-free survival; pMMR, mismatch repair-proficient; ORR, objective response rate; PO, per os (by mouth); QD, once daily; Q3W, every 3 weeks; QW, once weekly.

Source: Study 309/KN775 CSR [84]

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). Following a request by the EMA for comparative results of LEN+PEM and DOX, a post-hoc subgroup analysis was conducted [90]. 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 the submission, a further subgroup was created of patients pre-assigned to DOX treatment with PFI < 6 months which will provide the clinical evidence for the population of interest in the submission. For consistancy purpose efficacy estimates (OS, PFS) for ITT population is also presented. In addition, 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 ITT population.

In the efficacy analyses for the abovementioned subgroups (pre-assigned to DOX, PFI < 6 months, n = 416) n=205 were randomized to receive LEN+PEM and n=211 patients were randomized to receive DOX. In the safety analysis set, of those subjects pre-assigned to DOX with a PFI of less than 6 months, n=204 received LEN+PEM and n=200 received DOX. 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 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 (AEs) (TEAEs) and drug-related TEAEs. A detailed description of the efficacy endpoints (Appendix D) and safety endpoints (Appendix E) are presented in the appendices.

7.1.2 Efficacy and safety comparisons – results per study

7.1.2.1 Study 309/KN-755

7.1.2.1.1 Efficacy and safety

7.1.2.1.1.1 Efficacy

Efficacy estimates (OS, PFS) (pre-assigned to doxorubicin, PFI < 6 months population)

Results for primary endpoints of PFS assessed by Blinded Independent Central Review (BICR) and OS are presented in [redacted] and Table 9 together with Kaplan Meier curves for OS (Figure 3) and PFS (Figure 2). Comparative analysis of the PFI < 6 months populations in the two treatment arms (LEN+PEM and pre-assigned to DOX) showed an improvement in PFS ([redacted]) and OS [redacted]

The median follow-up duration was [redacted] for the LEN+PEM trial arm and [redacted] in the DOX treated trial arm for the pre-assigned to DOX population.

[redacted]

	LEN + PEM [b]			DOX [b]			LEN + PEM [b] vs. DOX [b]	
	N[c]	Participants with Event n (%)	Median Timed in Months [95% CI]	N[c]	Participants with Event n (%)	Median Timed in Months [95% CI]	Hazard Ratio [95% CI]	p-value
Progression-Free Survival (BICR Primary Censoring Rule)	[redacted]							

[redacted]

Abbreviations: CI, Confidence Interval; DOX, doxorubicin; LEN, lenvatinib; PEM, pembrolizumab
Source: Study 309 / KN-775[84]

[redacted]

[redacted]

	LEN + PEM [b]			DOX [b]			LEN + PEM [b] vs. DOX [b]	
	N[c]	Participants with Event n (%)	Median Timed in Months [95% CI]	N[c]	Participants with Event n (%)	Median Timed in Months [95% CI]	Hazard Ratio [95% CI]	p-value
Overall Survival	[redacted]							

[redacted]

Abbreviations: CI, Confidence Interval; DOX, doxorubicin; LEN, lenvatinib; PEM, pembrolizumab

Source: Study 309 / KN-775[84]

[redacted]

Efficacy estimates (OS, PFS) (ITT population)

[redacted]

Treatment	N	Median OS [months] (95% CI)	Median PFS [months] (95% CI)
LEN+PEM	[redacted]		
TPC			
Pairwise comparison			
Hazard ratio (95% CI) [b]			
p-value [c]			

[redacted]

Abbreviations: CI, Confidence Interval; LEN, lenvatinib; OS, Overall Survival; PEM, pembrolizumab; PFS, Progression-free survival; TPC, Treatment of Physician's Choice

EORTC QLQ-C30 global health status score (ITT population)

Baseline global health score/quality of life scores [redacted]. Over 12 weeks of follow-up, participants receiving LEN+PEM or TPC [redacted] Within the ITT population, [redacted] were observed for those receiving LEN+PEM versus TPC: [redacted] versus [redacted] respectively. The between-group difference in least square mean score change from baseline at Week 12 was [redacted]

Empirical mean change from baseline and 95% CI for EORTC QLQ-C30 global health score/quality of life over time is provided in Figure 4

[redacted]

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	[redacted]					
TPC						

Pairwise Comparison	Difference in least square means (95% CI)[b]	p-value[b]
LEN+PEM vs. TPC	[redacted]	

[redacted]

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[84]

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[84]

7.1.2.1.1.2 Safety

Among the population group of the safety analysis set consisted of and . A total out of patients discontinued LEN+PEM due to adverse events, and out of patients discontinued DOX.

The overall incidence of treatment-emergent AEs (TEAE) and drug-related TEAEs was similar in the LEN plus PEM and DOX groups). Details regarding safety data for the LEN+PEM and DOX arm for the PFI < 6 months population is reported in Appendix E.

[redacted]

	LEN+ PEM [b] (N=204) n (%)	DOX [b] (N=200) n (%)
Any TEAEs	[redacted]	
Any Treatment-related TEAEs		
TEAEs With Worst CTCAE Grade of >=3[a]		
Treatment-related TEAEs With Worst CTCAE Grade of >=3[a]		
Any Serious TEAEs		
Any Treatment-related Serious TEAEs		
Any Fatal TEAEs		
Any Treatment-related Fatal TEAEs		
TEAEs Leading to Treatment Discontinuation		

[redacted]

Note: Non-serious adverse event up to 30 days of last dose and serious adverse events up to 120 days of last dose are included.
MedDRA preferred term "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Data cut-off date: 26OCT2020
Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; DOX, doxorubicin; LEN, lenvatinib; PEM, pembrolizumab; TEAE, treatment-emergent adverse event.
Source: Study 309 / KN-775[84]

[redacted]

	LEN+ PEM [b] (N=204)	DOX [b] (N=200)
Number of Participants exposed	[redacted]	
Total exposure person-months		
	Event Count and Rate (Event/100 person-months)[c]	
Events		
Treatment-related events		
TEAEs With Worst CTCAE Grade of >=3[a]		
Treatment-related TEAEs With Worst CTCAE Grade of >=3[a]		

	LEN+ PEM [b] (N=204)	DOX [b] (N=200)
Serious TEAEs		
Treatment-related Serious TEAEs		
Any Fatal TEAEs		
Any Treatment-related Fatal TEAEs		
TEAEs Leading to Treatment Discontinuation		

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; DOX, doxorubicin, LEN, lenvatinib; PEM, pembrolizumab; TEAE, treatment-emergent adverse event.
Source: Study 309 / KN-775[84]

7.1.3 Comparative analyses of efficacy and safety

In accordance with the DMC guidance, if a direct head-to-head study comparing the intervention in question for the submission with the comparator relevant in Danish clinical practice exists, an indirect comparative analyses is not requested [87]. As such the comparative analyses of efficacy and safety is omitted.

8 Health economic analysis

8.1 Model description

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 endometrial cancer (EC) who have disease progression following prior treatment with a platinum-containing therapy in less than 6 months (platinum free interval (PFI) < 6 months).. 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 (27).

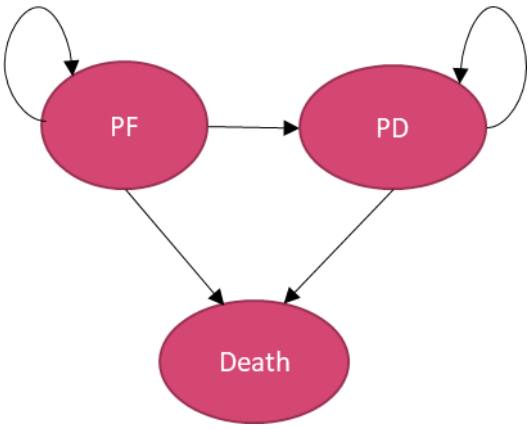
8.1.1 Model structure

The economic model is structured as a partitioned survival analysis model, with the following health states:

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

The model structure is presented in Figure 5; health state definitions are detailed in Section 8.1.1.1.

Figure 5: Model structure, partitioned survival analysis



Abbreviations: PD, progressed disease; PF, progression free.

8.1.1.1 Health states

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

In Study 309 / KN-775, OS and PFS were defined as follows:

OS was defined as the time from the date of randomization to the date of death due to any cause. Participants who were lost to follow-up and those who were alive at the date of data cut-off were censored at the date the participant was last known alive, or date of data cut-off, whichever occurred first.

PFS was defined as either:

PFS by blinded independent central review (PFS BICR; base case), defined as the time from the date of randomization to the date of the first documentation of disease progression, as determined by blinded BICR of objective radiographic disease progression per RECIST 1.1 or death due to any cause (whichever occurred first).

PFS by local investigator (PFS INV; scenario analysis), defined as the time from date of randomization to the date of the first documentation of disease progression, as determined by investigator per RECIST 1.1, or death from any cause, whichever occurred first.

PFS BICR applying alternative censoring rules (PFS BICR scenario 2 (SC2)). As per PFS BICR, this sensitivity analysis handles participants who discontinue treatment or initiate an anticancer treatment subsequent to discontinuation of study-specified treatments differently from the primary analysis (specifically, patients will be considered progressed at date of new anticancer treatment if new anti-cancer treatment is initiated, and patients will also be considered progressed if PD or death documented immediately after ≥2 consecutive missed disease assessments; both of these scenarios would be considered censoring events in the primary analysis).

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

8.1.2 Target Population

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

To align with DMC's request and Danish clinical practice, the model analysis considers patients with a PFI < 6 months who were also pre-assigned to receive DOX from Study 309 / KN-775.

8.1.3 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 AEs, subsequent treatment costs, and disease management costs. Time spent and transportation costs incurred by the patient were also included.

8.1.4 Cycle Length

A cycle length of 7 days (1 week) is used. Half-cycle correction is implemented using the life table method[1].

[1] 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.

8.1.5 Time Horizon and Discounting

The model adopts a lifetime time horizon of up to 36 years (mean age of 63.5 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. quality-adjusted life years [QALY]) outcomes were discounted at a rate of 3.5% for the first 35 years and at 2.5% for the year after in the base case in accordance with Danish guidelines [91].

8.1.6 Comparators

As per populations of interest, a comparison is presented comparing LEN+PEM with PLD in the population of patients with a PFI < 6 months and who were pre-assigned to DOX.

A summary of comparators and efficacy sources is presented in Table 14.

Table 14: Summary base case in the population of patients with a PFI < 6 months and pre-assigned to DOX

Comparator	Dose	Source of efficacy data	Source of safety data
PLD	40 mg/m^2 IV on Day 1 of each 21-day cycle	PFI <6 months *and* pre-assigned to DOX post-hoc subgroup, Study 309 / KN-775for LEN+PEM and PLD (assumed equivalent to DOX in TPC)	Pre-assigned to DOX and PFI<6 months population, 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.

8.1.7 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 26 October 2020. PLD was assumed identical to the DOX component of TPC in Study 309 / KN-775. Because patients were not randomized to DOX or paclitaxel within the TPC arm, naïve use of outcomes for patients who received DOX may provide biased estimates of efficacy; where estimates of efficacy were required (OS, PFS, and TTD), 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)
- Aes 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 Table 15 and sections 8.3, 8.4 and 8.5. Other relevant inputs were sourced from relevant HTA submissions and literature, and costs were derived from Danish sources. The cost inputs (presented in section 8.5) included drug costs, administration, subsequent treatment costs, AE and disease management costs, and non-medical direct costs (transportations costs and time spent). A full list of model inputs is presented in Appendix I – Probabilistic sensitivity analyses.

8.1.8 Model outputs

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

- Total costs
- Disaggregated costs
- Total QALYs
- Disaggregated QALYs
- Life years (Lys)
- Disaggregated Lys.

8.1.9 Mortality

Background mortality is modelled using female general population life tables for Denmark [92]. Overall survival and PFS were constrained to be greater than or equal to the age-matched general population rate.

8.1.10 Model validation

In line with the International Society for Health Economics and Outcomes Research (ISPOR) taskforce report on model transparency and validation[2] [93], 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 (HTA) agencies [94]. Data use was compared with another model in ovarian cancer to assess the face validity of the structural choices in this analysis [95], 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 (also known as verification) was conducted once by the primary modeler and once by a modeler external to the project and included: cell-by-cell checks of formulae, rebuilding of key sections of the model, logical tests, a full audit of model inputs.

An economic SLR was conducted to identify cost-effectiveness studies in the population, as an external validation approach. Cost-effectiveness for LEN and/or PEM in similar indications is limited, however, Thurgar et al [96] identified PEM to be associated with an additional 4.68 Lys and 3.80 QALYs vs chemotherapy for the treatment of US women with previously treated dMMR, MSI-H or metastatic EC [96].

Finally, an online advisory meeting was undertaken on September 22nd, 2021. Three clinical experts and three health economists attended, and topics of discussion included the plausibility of alternative extrapolations for all outcomes, the validity of alternative data sources, the validity of other key assumptions, and medical resource use. Full details are reported elsewhere [97].

[2] Note that no attempt was made to conduct a predictive validation (the fifth validation type specified in the ISPOR taskforce report).

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

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

The model inputs for clinical effect and utility values are summarized in Table 15 (further information is provided in sections 8.3 and 8.4). The clinical documentation presented in section 7.1 describes relevant efficacy measures for the treatment with LEN+PEM.

Table 15. Input data used in the model, population pre-assigned to DOX, PFI < 6 months

Name of estimates	Results from study or indirect treatment comparison (ITC)	Input value used in the model (base case)	How is the input value obtained/estimated**
LEN+PEM			
PFS	See section 8.3.2 Observed PFS Kaplan-Meier curves for LEN+PEM from Study 309/KN775	See section 8.3.2 Individual PFS curves Log-logistic distribution	Study 309/KN775 data extrapolated
OS	See section 8.3.1 and Observed OS Kaplan-Meier curves for LEN+PEM from Study 309/KN775	See section 8.3.1 Individual OS curves Log-normal distribution	Study 309/KN775 data extrapolated
TTD	See section 8.3.3 Potocol-mandated maximum number of cycles for PEM in Study 309 / KN-775	See section 8.3.3 capped at 24 months	Study 309/KN775 protocol and clinical feedback
Grade ≥3 TEAE	See section 8.4 Number of patients in Study 309/KN775 with Aes	Rate per model cycle from Study 309/KN775	Study 309/KN775
Pre-progression utility	EQ-5D-5L measured in Study 309/KN775	See section 8.5 The utility values were derived from a statistical analysis of the trial. Danish population weights applied to estimate health state utility values (refer to Appendix H – Mapping of HRQoL data)	Statistical regression analysis on Study 309/KN775 utility data
Post-progression utility			Statistical regression analysis on Study 309/KN775 utility data
PLD			
PFS by BICR	See section 8.3.2 Observed PFS Kaplan-Meier curves for DOX from Study 309/KN775	See section 8.3.2Generalised gamma distribution	Study 309/KN775 data (DOX arm) extrapolated
OS	See section 8.3.1 Observed PFS Kaplan-Meier curves for DOX from Study 309/KN775	See section 8.3.1 Gompertz distribution parameters:	Study 309/KN775 data (DOX arm) extrapolated

TTD	See section 8.3.3 Observed TTD curves for doxorubicin from Study 309/KN775	See section 8.3.3 KM data from Study 309/KN775	Study 309/KN775 observed data (DOX arm)
Grade ≥3 TRAE	See section 8.4 Number of patients in Study 309/KN775 with Aes	See section 8.4 Rate per model cycle from Study 309/KN775	Study 309/KN775 (DOX arm)
Pre-progression utility	EQ-5D-5L measured in Study 309/KN775	See section 8.5 The utility values were derived from a statistical analysis of the trial.	Statistical regression analysis on Study 309/KN775 utility data
Post-progression utility		Danish population weights applied to estimate health state utility values (refer to Appendix H – Mapping of HRQoL data)	Statistical regression analysis on Study 309/KN775 utility data

Abbreviations: DOX, doxorubicin,ITC, indirect treatment comparison; OS, overall survival; PFS by BICR, progression free survival by blinded independent central review; PLD, pegylated liposomal doxorubicin; TEAE, treatment emergent adverse events; TTD, time to discontinuation.

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

8.2.2.1 Patient population

The Danish patient population: The mean age of patients in the Danish population is slightly higher (approximately 0-3.5 years) than in Study 309 / KN-775according to clinical expert opinion.

Patient population in the clinical documentation submitted: The patient population of Study 309 / KN-775study consisted of adult patients with advanced endometrial cancer who have received prior treatment with a platinum-containing therapy. Selected baseline characteristics are presented in Table 16.

Patient population in the health economic analysis submitted: Values for age, body surface area (BSA) and weight were derived from analysis of patient-level data from Study 309 / KN-775for patients pre-assigned to doxorubicin, PFI < 6 months and are presented in Table 16.

Table 16: Patient population of Study 309 / KN-775, population pre-assigned to DOX, PFI < 6 months arm in study 309 / KN-775and Danish clinical practice.

Patient population Important baseline characteristics	Clinical documentation / (including source)	Full population of Study 309 / KN-775	Used in the model: Population Pre-assigned to DOX, PFI < 6 months, (number/value including source)	Danish clinical practice (including source)
Age (years)	Analysis of Study 309 / KN-775patient-level data	63.53 (62.91, 64.15)	63.06 (SD: 9.4)*	63.5-67 (clinical opinion)
BSA (m^2)		1.73 (1.29, 2.16)	1.70 (SD: 0.2)	Assumed to be similar to Danish population
Weight (kg)		70.51 (69.23, 71.79)	68.9 (SD: 17.4)	
Baseline EQ-5D index score		0.74 (0.73, 0.76)	0.81 (SD: 0.21)	

Note: Data cut-off date: 26OCT2020

Abbreviations: BSA, body surface area; DOX, doxorubicin

Source: Baseline and Demographic Characteristics, ITT Population For Pre-assigned to Doxorubicin, Platinum-Free Interval < 6 Months. Additional statistical analysis, Study 309 / KN-775.

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice (as defined in section 8.2): It is expected that LEN+PEM will be used as described in the SmPC.

Intervention in the clinical documentation submitted: In Study 309 / KN-775, the treatment arm LEN was administered (20 mg) orally once daily (QD) during each 21-day cycle for up to 35 cycles, and PEM (200 mg) by intravenous (IV) infusion on Day 1 of each 21-day cycle.

Intervention as in the health economic analysis submitted: The intervention considered in the cost-effectiveness analysis is LEN+PEM. LEN (20 mg) was administered orally once daily during each 21-day cycle for up to 35 cycles. PEM (200 mg) was administered by IV infusion on Day 1 of each 21-day cycle. For further details please see section 5.3.

Table 17. Intervention – LEN+PEM

Intervention	Clinical documentation (including source)		Used in the model (number / value including source)	Expected Danish clinical practice (including source if known)
	LEN+PEM	Source		
Posology	LEN 20 mg orally once daily in combination with PEM (200mg) every three weeks administered intravenously in 3-week cycles	Study 309 / KN-775	Same as clinical documentation	Expected to be used as described in SmPC
Length of treatment (time on treatment) Criteria for discontinuation	Until disease progression is radiographically documented and verified by BICR per RECIST 1.1, and only when clinically appropriate, confirmed by the site per modified RECIST 1.1 for immune-based therapeutics (iRECIST), unacceptable adverse event(s) (AEs), withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, until the participant has received 35 administrations of PEM (approximately 2 years)	Study 309/KN775	Same as clinical documentation	
The pharmaceutical's position in Danish clinical practice	NA		Following prior platinum-based therapy	Following prior platinum-based therapy

Abbreviations: AE, adverse event; BICR, blinded independent central review; LEN, Lenvatinib; PEM, pembrolizumab; NA, not applicable; RECIST, Response Evaluation Criteria in Solid Tumours; SmPC, summary of product characteristics.

8.2.2.3 Comparator

Table 18. Base case comparator – PLD for PFI < 6 months

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	NA (off-label given lack of treatment options)	40 mg/m² IV on Day 1 of each 21-day cycle up to a maximum cumulative dose of 500 mg/m² (per study 309 protocol for doxorubicin)	Following prior platinum-based therapy
Length of treatment	NA (off-label given lack of treatment options)	Until disease progression is radiographically documented and verified by BICR per RECIST 1.1, and only when clinically appropriate, confirmed by the site per modified RECIST 1.1 for immune-based therapeutics (iRECIST), unacceptable adverse event(s) (AEs), withdrawal of consent, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the participant, noncompliance with study treatment or procedure requirements or administrative reasons requiring cessation of treatment, until the participant has received a lifetime cumulative dose of 500 mg/m² of doxorubicin.	
The comparator's position in the Danish clinical practice	NA (off-label given lack of treatment options)	Following prior platinum-based therapy	NA (off-label given lack of treatment options)

Abbreviations: AE, adverse event; IV, intravenous; BICR, blinded independent central review; PLD, Pegylated liposomal doxorubicin, NA, not applicable; RECIST, Response Evaluation Criteria in Solid Tumours.

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation: Details about the relative efficacy outcomes are presented in section 7.

Relevance of the documentation for Danish clinical practice: The clinical documentation is relevant for the Danish population as it describes relevant efficacy measures for the proposed treatment in Denmark. Also, the relative efficacy outcomes are in line with the current clinical practice, as mentioned in section 5.

The relative efficacy outcomes in the submitted health economic analysis: The main efficacy inputs presented in the model are OS, PFS and TTD. The base case inputs were obtained through Study 309 / KN-775in a direct comparison derived from a post-hoc analysis using pre-assigned to DOX cohort with PFI < 6 months.

Table 19. Summary of Parameterization of efficacy outcomes

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Overall survival (OS)	Study 309 / KN-775	LEN+PEM: Log-normal distribution PLD: Gompertz distribution
Progression-free survival (PFS)		LEN+PEM: Log-logistic distribution TPC: Generalised gamma distribution
Time to treatment discontinuation (TTD)		PEM and PLD: KM data from Study 309/KN775 LEN: Gompertz distribution

Abbreviations: LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin, TTD, time to discontinuation.

Table 20. Summary of relevance of the relative efficacy outcomes included in the health economic model

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Overall survival (OS)	Kaplan-Meier curves	Very relevant	Very relevant
Progression-free survival (PFS)	Kaplan-Meier curves	Very relevant	Very relevant
Time to treatment discontinuation (TTD)	Kaplan-Meier curves	Relevant	Relevant

Abbreviations: LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin, TTD, time to discontinuation.

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted: Information on adverse events for LEN+PEM was obtained from Study 309 / KN-775.

Adverse reaction outcomes in the health economic analysis submitted: Modelled AEs include all those:

- Considered treatment-related in Study 309 / KN-775
- Grade 3–5, occurring in >5% of patients
- Expected to be associated with an impact on QoL and/or cost.

Modelled Grade 3-5 AEs were taken from the pre-assigned to DOX and PFI < 6 months population of Study309 / KN-775for the LEN+PEM and PLD comparison (Table 21).

Table 21. Modelled Grade 3-5 AEs from Study 309 / KN-775included in the economic model, pre-assigned to DOX and PFI<6 months population.

Grade 3–5 AE	Total number of events		Average duration per event (days)	Rate per model cycle†	
	LEN+PEM	DOX (Study 309)		LEN+PEM	PLD
Anaemia	[redacted]				
Decreased appetite					
Diarrhoea					
Febrile neutropenia					
Hypertension					
Leukopenia					
Lipase increased					
Neutropenia					
Neutrophil count decreased					
Weight decreased					
White blood cell count decrease					

Footnote: †AE rate was calculated using the total exposure time in Study 309 / KN-775of 119,296 days in the LEN+PEM arm and 53,726 days in the TPC arm to derive a rate per 7-day cycle.
Note: Database cut-off date: 26OCT2020

Abbreviations: DOX, doxorubicin; LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; PLD, pegylated liposomal doxorubicin, TTD, time to discontinuation.

Source: Grade 3-5 Treatment-related Adverse Events, APaT Population for Pre-assigned DOX Population Platinum-Free Interval < 6 Months. Post-hoc analysis.

8.3 Extrapolation of relative efficacy

As described in Section 8.1.1, 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 curves from Study 309 / KN-775for LEN+PEM. As the follow-up period for Study 309 / KN-775 was shorter than the modelled time horizon, extrapolation from the observed OS, PFS and TTD data was required.

The analysis was supplemented by clinical expert opinion (List of experts in Section 11).

A range of standard parametric distributions were explored for extrapolation of the OS, PFS and TTD endpoints:

- Exponential
- Generalised gamma
- Gompertz
- Lognormal
- Loglogistic
- Weibull

Outcomes were extrapolated for the pre-assigned to DOX and PFI<6 months subgroup in order to provide unbiased estimates of efficacy relative to DOX (which is assumed to have the same efficacy as PLD).

8.3.1 OS

[redacted] presents overall survival in the pre-assigned to DOX and PFI <6 months population.

[redacted]

The proportional hazards assumption was assessed using plots of the log-cumulative hazard. For OS in the pre-assigned to DOX and PFI < 6 months population, the plots become clearly separated over time and appear reasonably parallel. Schoenfeld residuals are shown in Appendix G – Model extrapolations. Number of risks are provided in Figure 3.

Figure 18 shows the log-cumulative hazard over time between the two arms. Global testing of the proportional hazards assumption provided a p-value of 0.6059, therefore the null hypothesis of proportional hazards could not be rejected at the 95% level of confidence.

The underlying mechanism of action for immunotherapies including PEM typically leads to effects which can be approximately divided into three stages, as described by Quinn et al [98].

- Non-separation of the Kaplan-Meier survival curves during the initial treatment phase
- Separation of the Kaplan-Meier curves as activation of the immune cells leads to a clinically measurable antitumor effect in patients receiving immunotherapy, and those receiving chemotherapy develop resistance to treatment.
- Plateauing of the tail of the immunotherapy Kaplan-Meier curve many months after the first administration and continuing long after treatment has ceased.

Clinical experts [97] confirmed the proportional hazards assumption was not likely to hold in the long-term because of differences in the mechanism of action between immunotherapy and other chemotherapies. . Based on these observations, an independent modelling approach was adopted, in which independent curves were estimated for each arm of Study 309 / KN-775.

Extrapolations based on independent statistical models are presented for OS in Figure 7 and Figure 8, and corresponding model fit diagnostics for each of the six standard parametric distributions are presented in Appendix G – Model extrapolations. AIC and BIC criteria are provided in Table 58 (OS) and Table 59 (PFS) in Appendix G – Model extrapolations of the submission.

For the pre-assigned to DOX and PFI<6 months population, the lognormal was selected for LEN+PEM on the basis of:

- Statistical fit (cf. Table 62)
- Visual inspection
- Comparison with the 2-years OS from the study (about 34.5% of patients alive from the KM curve) with the curves: the 2-years OS is 34.2% for lognormal
- External validation: whilst no suitable long-term data for this patient population was identified against which to directly compare extrapolated outcomes, the base-case extrapolations are consistent with the beliefs about expected outcomes expressed [97]. Specifically:
  - A minority of patients are assumed to long-term benefit from treatment with LEN+PEM (the model predicts 5- and 10- year survival of 11% and 3%, respectively, for patients receiving LEN+PEM).

The Gompertz model was selected for DOX, based on:

- Visual inspection
- External validation: whilst no suitable long-term data for this patient population was identified against which to directly compare extrapolated outcomes, the base-case extrapolations are consistent with the beliefs about expected outcomes expressed [97]. Specifically:
  - No survivors are expected at 5 years for DOX

The Gomperzt function was selected based on visual inspection and expected percent of patients alive at 5 years. The best statistical fit, lognormal, is presented in a scenario analysis (Table 45).

The use of different distributions for each study arm is less common than the use of the same distribution, and NICE TSD 14 suggests:

If different types of model seem appropriate for each treatment arm this should be justified using clinical expert judgement, biological plausibility, and robust statistical analysis [99].

Immunotherapies such as PEM differ from chemotherapies in that they prime the immune system to attack tumours, rather than attempting to directly destroy cancerous cells [98]. This mechanism of action can lead to durable response and long-term remission in some patients. A review of survival modelling in economic evaluations for immunotherapies has previously reported that separation of curves and a plateauing of the tail in the long-term are typical features of survival curves when comparing immunotherapies to conventional treatments [98]. Because of these differences in mechanism of action and consequent differences in the patterns of long-term survival, we believe that the use of different distributions provides more plausible assumptions for the extrapolation of OS in the base-case (see also above for discussion).

A plot of the hazard over time is presented in Appendix G – Model extrapolations for LEN+PEM and DOX, respectively. As noted above, the hazard for LEN+PEM, as for other immunotherapies, would be expected to decline over time as some patients may be expected to achieve long-term remission; the selected lognormal distribution exhibits a declining hazard over time (see Appendix G – Model extrapolations), and therefore the use of this to inform the long-term hazard function was considered biologically plausible.

[redacted] presents the base case OS extrapolations for LEN+PEM and PLD.

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A scenario analysis is provided with the lognormal curve for both LEN+PEM and DOX OS.

8.3.2 PFS

Figure 10 presents PFS in the pre-assigned to DOX and PFI<6 months population.

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Plots of the log-cumulative hazard are presented in [redacted] for PFS BICR in the pre-assigned to DOX population of Study 309 / KN-775. Schoenfeld residuals are also shown in [redacted], and [redacted] presents the instantaneous hazards over time between the two arms. Global testing of the proportional hazards assumption provided a p-value of 0.9652, therefore the null hypothesis of proportional hazards could not be rejected at the 95% level of confidence.

Similar to OS, independent models were observed to provide better fitting extrapolations to both the DOX and LEN+PEM arms of Study 309 / KN-775. Clinical experts also confirmed that the proportional hazards assumption was not likely to hold in the long-term (see Appendix J - Key model assumptions applied in the base case for discussion). Based on these observations, an independent modelling approach was adopted, in which independent curves were estimated for each arm of Study 309 / KN-775.

Model fit diagnostics for each of the six standard parametric distributions are presented in [redacted] As described above, independent statistical models were selected to extrapolate PFS over the model horizon. The log-logistic and generalized gamma models were selected for LEN+PEM and DOX arms, respectively, based on minimization of the AIC and BIC (cf. Table 63). Extrapolations based on independent statistical models are presented in Figure 11 and Figure 12 for LEN+PEM and DOX. A plot of the hazard over time is presented in Appendix G – Model extrapolations for LEN+PEM and DOX, respectively.

As noted above, the hazard for LEN+PEM, as for other immunotherapies, would be expected to decline over time as some patients may be expected to achieve long-term remission; the selected log-logistic distribution exhibits a declining hazard over time (see Appendix G – Model extrapolations), and therefore the use of this to inform the long-term hazard function was considered biologically plausible.

PFS events include death events, and therefore, not all PFS events are associated with the costs of subsequent therapy. To estimate the number of new progression events per cycle, and to allocate the cost of post-progression therapies, the proportion of progression events is taken from Study 309 in the LEN+PEM and DOX arms and applied to the per-cycle probability of PFS (87%).

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[redacted] presents the base case PFS extrapolations for LEN+PEM and PLD.

[redacted]

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8.3.3 TTD

In the model, TTD for LEN and PEM is capped at 24 months given clinical feedback on the likely use of LEN following end of treatment with PEM, and the protocol-mandated maximum number of cycles for PEM in Study 309 / KN-775. Treatment discontinuation for DOX was observed completely during Study 309 / KN-775. The observed Kaplan-Meier data are therefore used until this timepoint, and extrapolation is therefore not required for the pre-assigned to DOX and PFI<6 months (Figure 14).

A scenario is presented where LEN discontinuation does not stop at 24 months, and here the Gompertz distribution was selected based on the lowest AIC.

In Study 309 / KN-775, a proportion of randomized patients did not start treatment in both the LEN+PEM and TPC arms. As such, TTD used in the model is applied to the proportion of patients who started treatment in all treatment arms, as shown in Table 22.

Table 22 Proportion of patients who started treatment in Study 309 / KN-775, pre-assigned to DOX population

	LEN+PEM (n, [%])	TPC (n, [%])
Started treatment	[redacted]	
Did not start treatment		

Abbreviation: DOX, doxorubicin; LEN, lenvatinib; PEM, pembrolizumab; TPC, treatment of physician's choice.

Hence, in the model the proportion of patients on treatment at any given cycle consists of the TTD curves applied to the proportion of patients who started treatment, capped by the proportion of patients in PFS. The latter reflect the assumption that patients stop treatment after progression. In addition, for LEN+PEM a stopping rule is applied in the base case, where no patients are on treatment after 24 months. A scenario analysis present the ICER without the stopping rule for LEN.

8.4 Documentation of relative safety

Modelled AEs include all those:

- Considered treatment-related in Study 309
- Grade 3–5, occurring in >5% of patients in either arm
- Expected to be associated with an impact on QoL and/or cost.

The number of events for each of the modelled AEs in each arm are presented in Table 23 for the pre-assigned to DOX and PFI<6 months population, from Study 309. The exposure adjusted AE rate observed in the LEN+PEM arm was 0.02 per 7-day cycle, compared with 0.10 per 7-day cycle for the PLD.

The weighted duration of AEs, based on the number of occurrences for each AE and the average duration per event from Study 309, was 112.70 days in the LEN+PEM arm, vs 20.18 days in the liposomal DOX arm. AEs with PLD were assumed equal to DOX in Study 309. Duration of AEs is used to derive the duration of the QoL decrement. A number of hours lost due to AEs is also included to derive productivity loss from AEs.

Costs for AEs reflect a hospitalisation based on DRG tariffs independent of the full duration of AEs.

[redacted]

Grade 3–5 AE	Total number of events		Average duration per event (days)	Rate per model cycle†	
	LEN+ PEM	DOX (Study 309)		LEN+PEM	Liposomal DOX
Anaemia	[redacted]				
Decreased appetite					
Diarrhoea					
Febrile neutropenia					
Hypertension					
Leukopenia					
Lipase increased					
Neutropenia					
Neutrophil count decreased					
Weight decreased					
White blood cell count decreased					

Abbreviations: AE, adverse event; DOX, doxorubicin; ITT, intention to treat; LEN, lenvatinib; PEM, pembrolizumab; TPC, treatment of physician's choice.

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

The health state utility values used in the model originate from Study 309 / KN-775, based on patient level data. The values were estimated with EQ-5D-5L using published tariffs for the Danish population [100].

For use within the economic model, multivariable linear mixed models were fitted to the EQ-5D index score, and covariates representing baseline EQ-5D index score, presence of Grade 3–5 AEs occurring in >5% of patients at the time of observation, treatment arm, being 'on' vs 'off' treatment, progression-status, and time before death were considered for inclusion in the model, and models were compared using the AIC and BIC diagnostic statistics, and variables which led to improvements (reductions) in these statistics retained. 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 AEs and subgroup membership).

The final statistical model of EQ-5D including PFI<6 months and pre-assigned to DOX population is presented in Table 24. The model chosen is aligned with the health states definitions, as it is the model including pre-post progression covariates with the best fits. Results suggested small decrements associated with observations post-progression (–0.037; p<0.001) and experiencing AEs at the time of observation (–0.013; p=0.136). Being on treatment (independent

of which treatment) was associated with a significant increase in EQ-5D (0.140; p<0.001). Full details are provided in Appendix H – Mapping of HRQoL data.

Table 24 EQ-5D based on PFI<6 months and pre-assigned to DOX

Parameter	Coefficient	s.e.	P>z	95% CI
Baseline EQ-5D	[redacted]			
Post-progression decrement				
AE disutility				
On treatment increment				
Constant				

Abbreviations: PFI, platinum free interval; DOX, Doxorubicin; AE, adverse event; CI, confidence interval; s.e., standard error.

However, as detailed in Appendix H – Mapping of HRQoL data, a model (model 12) which includes time-to-death covariates provided better statistical fits and was consider relevant to include as a scenario analysis.

Predictions of health states utility values, derived from applying the coefficients related to baseline EQ-5D and post-progression decrement, as well as including the constant coefficient, are presented in Table 25 below.

Table 25: Model health state utilities (predictions from the statistical model)

Health state	Utility value
Progression-free	0.652
Progressed disease	0.615

In the model, the utility calculations include all the coefficients from Table 24. The resulting combined utility value varies for each model cycle based on the proportion of patients pre/post progression, on-treatments and with AEs. An age-adjustment is also applied.

8.6 Resource use and costs

8.6.1 Drug Acquisition Costs

All 2022 pharmacy purchase prices have been fetched for the drug acquisition cost from medicinpriser.dk and is summarised in Table 26 below and includes the list of agents that are eligible for vial wastage in the submission and has been amended to note which therapies are subject to these assumptions, details of which can be found below.

Table 26. 1L Drug Acquisition Costs

Treatment	Pack #1			Pack #2			Source
	Dose	#Units per pack	Price (DKK)	Dose	#Units per pack	Price (DKK)	
PEM	100.0 mg	1	23204,61	-	-	-	Medicinpriser.dk [101]

Treatment	Pack #1			Pack #2			Source
	Dose	#Units per pack	Price (DKK)	Dose	#Units per pack	Price (DKK)	
LEN	4.0 mg	30	12551,71	10.0 mg	30	12551,71	
PLD*	20.0 mg	1	2487,31	-	-	-	

Footnote: *Method of moments used to calculate dose and associated vial wastage.
Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; PLD, pegylated liposomal doxorubicin.

Table 27 presents the dosing of each 1L treatment, to enable the calculation of drug cost per patient.

Table 27: The dosing scheme

Drug	Dependency	Dose	Administrations per cycle	Treatment cycle length (days)	Dose intensity	Source
LEN	Fixed dose per day	20.0 mg	7	7	Study 309 / KN-775(see below)	Study 309 / KN-775[84]
PEM	Fixed dose	200.0 mg	1	21	96%	Study 309 / KN-775[84]
PLD	Fixed mg/m2	40 mg	1	21	Method of moments	Study 309 / KN-775[84]

Abbreviations: LEN, lenvatinib; PEM, PEM, pembrolizumab, PLD, pegylated liposomal doxorubicin.

The acquisition cost of LEN+PEM amounted to DKK 44,453 per administration of PEM and DKK 19,254 per 30-day prescription for LEN. In the base case the cost of PEM is based on a fixed dose.

A scenario analysis is provided with a PEM dose based on weight, with 2 mg/kg every 3 weeks. In this scenario, as for any weight-based drug costs (PLD and subsequent therapies), the method of moments was used to calculate the cost of drug acquisition, where the dose intensity is based on a distribution of patients' weight.

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.

Vial wastage is applied to medicines administered intravenously based on BSA or weight. BSA and weight are reported in Table 16. The model base case assumed that vials will not be shared between patients for a conservative estimate of drug acquisition costs.

The dose intensity is calculated for each intervention in the following ways.

- PEM: a dose intensity of 96% 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 28 below [102].

Table 28: Cumulative days per dose

Daily dose (mg)	% of days
0	[redacted]
4	
8	
10	
14	
20	
40	

- 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 (Table 29). 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 [102]. This method is also used for subsequent therapies.

Table 29: Dose calculations for PLD

Total dose	Number of vials	Proportion of the cohort
20	1	[redacted]
40	2	
60	3	
80	4	
100	5	
120	6	

Using the packs characteristics, dosing schemes, and dose intensity, a cost per treatment cycle is then calculated, as shown in Table 30 (in the base case, with no vial sharing).

Table 30: Calculated 1L drug acquisition costs

Intervention	Drug	Cost per treatment cycle (DKK)
LEN + PEM	LEN	19 253.62
	PEM	44 452.60
PLD	PLD	9 720.29

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

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8.6.2 Administration Costs

The unit costs for administration were obtained from *Sundhedsdatastyrelsen DRG-ta*kster 2022 [103] and is applied to the administrations in the model. The unit cost of administration is presented in Table 31.

Table 31: Unit costs of modes of administration

Mode of administration	Unit Cost	Source
Oral chemotherapy	DKK 0	Assumption
Parenteral chemotherapy	DKK 1 921.00	DRG-takster 2022, MDC13 1-dagsgruppe, pat. mindst 7 år: 13MA98 [103]

Abbreviation: DRG, diagnosis-related group.

The mode of administration for each type of drug is presented in Table 32. The administration cost associated with LEN is DKK 0 by assumption, as it is administered orally. PEM and PLD are both delivered as parenteral chemotherapy, and each incur an administration cost of DKK 1 921 per administration. Administration costs are also subject to administration intensity in the model base case.

Table 32: Mode of administration for each drug

Cost of Administration	Mode of administration	Unit Cost	Source
LEN	Oral chemotherapy	DKK 0	Assumption
PEM	Parenteral chemotherapy	DKK 1 921.00	DRG-takster 2022, MDC13 1-dagsgruppe, pat. mindst 7 år: 13MA98 [103]
PLD	Parenteral chemotherapy	DKK 1 921.00	DRG-takster 2022, MDC13 1-dagsgruppe, pat. mindst 7 år: 13MA98 [103]

Abbreviation: DRG, diagnosis-related group; LEN, lenvatinib; PEM, pembrolizumab; PLD, pegylated liposomal doxorubicin.

8.6.3 Disease Management Costs

Healthcare resource use categories considered in the model are presented in Table 33. Rates of resource use associated with disease management were based on inputs from Danish clinical experts (see section 11 for details) [104]. The cost of each category was sourced from Sundhedsdatastyrelsen DRG-takster 2022 [103], Laboratoriemedicinsk Vejledning [105] and GP tariff costs were applied from the Honorartabel dagtid: Overenskomst om almen praksis [106]. The GP visits assumes only a consultation and does not include any additional tests. The frequency reported by KOLs and the frequency of use for each resource per model cycle is reported for both progression-free patients and progressed patients.

Table 33: Disease management costs

Type of resource	Unit cost	Frequency reported by KOLs	Frequency per model cycle in model	Reference
Consultation, oncology	DKK 1 921	PFS: 1 visit per month	Progression free: 0.229 Progressed: 0.076	DRG-takster 2022, MDC13 1-daggruppe, pat. mindst 7 på- 13MA98, Diagnosis: DC549 Livmoderkræft [103] Frequency: clinical expert input – Denmark [104]

Type of resource	Unit cost	Frequency reported by KOLs	Frequency per model cycle in model	Reference
		PD: 1 visit every 3 months		
Blood count	DKK 300	PFS: 1 visit per month PD: 1 visit per month	Progression free: 0.229 Progressed: 0	Laboratoriemedicinsk Vejledning, Combination of the following costs: Hæmoglobin;B, Erytrocytter, vol.fr.;B, Leukocytter;B, C-reaktivt protein [CRP];P, Albumin;Plv, Urat;P, Methæmoglobin;Hb(B), Trombocytter;B, Reticulocytter;B, Kreatinin;P (NPU02319, NPU01961, NPU02593, NPU19748, NPU19674, NPU03688, NPU02725, NPU03568, NPU08694, NPU04998) [105] Frequency: clinical expert input – Denmark [104]
CT scan	DKK 2411	PFS: 1 scan every 3 months PD: 1 scan every 3 months	Progression free: 0.076 Progressed: 0	DRG-takster 2022, CT-scanning, kompliceret-30PR06, Diagnosis: DC549 Livmoderkræft [103] Frequency: clinical expert input – Denmark [104]
GP visit	DKK 149	PFS: 1 visit every 2 month PD: 1 visit every 2 month	Progression free: 0.114 Progressed: 0.114	Honorartabel dagtid: Overenskomst om almen praksis, 0101 – Konsultation [106] Frequency: clinical expert input – Denmark [104]

Abbreviations: CT, computerised tomography; DRG, diagnosis-related group; GP, general practitioner PD: progressed disease; PFS: progression-free survial.

8.6.4 Subsequent Treatments

Subsequent therapy lines and proportions are presented in Table 34 and were based on Danish clinical expert inputs for each comparator as these were deemed relevant in Danish clinical practice [104]. The subsequent therapies from Study 309 / KN-775were not used in the model as they were not reflective of Danish clinical practice.

Note that the Danish clinical expert interview answers have 50% PLD and 50% paclitaxel. For the subsequent therapy costings, we use the duration of treatment from the trial. In absence of data for PLD from the trial, we used doxorubicin as a proxy for PLD. Hence the model uses 50% doxorubicin and 50% paclitaxel as subsequent treatments.

Table 34: Subsequent therapy scenario – KOL input

Subsequent therapy	2L			
	LEN+PEM	PLD	LEN+PEM	PLD

DOX	50%	50%	50%	50%
Paclitaxel	50%	50%	50%	50%

Abbreviations: DOX, doxorubicin; KOL, key opinion leader; LEN+PEM, lenvatanib and pembrolizumab; PLD, pegylated liposomal doxorubicin 2L, second-line; 3L, third-line.

The drug acquisition costs for subsequent therapy are present in Table 35 below.

Table 35: Subsequent treatment acquisition costs

Treatment	Pack #1			Pack #2			Pack #3			Source
	Strength per Unit (mg)	# Units per Pack	Price (DKK)	Strength per Unit (mg)	# Units per Pack	Price (DKK)	Strength per Unit (mg)	# Units per Pack	Price (DKK)	
Paclitaxel*	100	1	110.50	150	1	1500	300	1	201.50	Medicinpriser.dk [101]
Doxorubicin*	10	1	150	50	1	120	200	1	360	Medicinpriser.dk [101]

Footnote: *Method of moments used to calculate dose and associated vial wastage.

The duration of subsequent therapy is presented in Table 36 below.

Table 36: Subsequent treatment duration

Subsequent treatment costs	2L	3L	Source
	Duration (days)	Duration (days)	
Paclitaxel	86	71	Analysis of Study 309 patient-level data. February 2021.
Doxorubicin	70	69	Analysis of Study 309 patient-level data. February 2021.

Subsequent treatment costs for the 2L and 3L subsequent therapies are shown in Table 37 below. The costs as per treatment were calculated as the product of the per cycle drug acquisition and drug administration costs for each subsequent treatment, proportion of patients eligible to receive subsequent treatments by treatment arm, the proportions receiving each subsequent treatment by 1L treatment arm and the duration of each subsequent treatment.

Table 37: Subsequent treatment costs

Subsequent treatment costs	2L		3L	
	LEN+PEM	DOX/Comparator	LEN+PEM	DOX/Comparator
One-off cost	DKK 15,647	DKK 15,647	DKK 13,558	DKK 13,558

Abbreviations: LEN, lenvatinib; PEM, pembrolizumab; TPC, treatment of physician's choice; 2L, second line; 3L third line.

The model assumes that subsequent treatment costs are incurred at treatment progression as a one-off cost. At each cycle, the sum of incident treatment discontinuers is multiplied by the one-off subsequent treatment cost associated with LEN+PEMM or DOX. To estimate the number of new progression events per cycle, and to allocate the cost of post-progression therapies, the proportion of progression events is taken from Study 309 in the LEN+PEM and DOX arms and applied to the per-cycle probability of PFS (87%, see section 8.3.2).

8.6.5 AE costs

In order to capture the resource use associated with adverse events, the unit costs of adverse events were obtained from *Sundhedsdatastyrelsen DRG-takster 2022* [103]. The frequency of experiencing ≥ grade 3 adverse events while on treatment was obtained from Study 309 / KN-775, as described in section 8.2.2.5. All unit costs were applied to a per cycle rate of events whilst on treatment, derived from the frequency of adverse events from Study 309 / KN-775. The rate of events for PLD was assumed equal to TPC.

Table 38: Adverse event costs

Adverse event	Unit cost	Reference
Anaemia	DKK 3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD592: Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel [103]
Decreased appetite	DKK 1,954	DRG 2022, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR630: Appetitløshed [103]
Diarrhoea	DKK 6,756	DRG 2022, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag., Diagnosis: DK529B: Ikke-infektiøs diaré UNS [103]
Febrile neutropenia	DKK 3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel [103]
Hypertension	DKK 1,318	DRG 2022, 05MA98: MDC05 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DI109: Essentiel hypertension [103]
Leukopenia	DKK 3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728H: Leukopeni [103]
Lipase increased	DKK 2,910	DRG 2022, 07MA98: MDC07 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR748D: Abnorm serumlipase [103]
Neutropenia	DKK 3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Neutropeni UNS [103]
Neutrophil count decreased	DKK 3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728: Anden forstyrrelse i hvide blodlegemer [103]
Weight decreased	DKK 1,954	DRG 2022, 10MA98: MDC10 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DR634: Abnormt vægttab [103]
White blood cell count decreased	DKK 3,176	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD728: Anden forstyrrelse i hvide blodlegemer [103]

Abbreviations: DRG, diagnosis-related group

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8.6.6 Non-medical direct costs

Based on the *Medicinrådet - Værdisætning af enhedsomkostninger* guidelines [107] 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 39. Patient costs used in the model

Costs	Unit Cost	Source
Transport costs		
Transportation costs – to and from treatment	DKK 140	Average transport costs, based on the guidelines by Medicinrådet Multiplied with the frequencies in each health state below [107]
Average hourly wage	DKK 181	Average transport costs, based on the guidelines by Medicinrådet Multiplied with the frequencies in each health state below [107]
Patient time spent		
Administration	3 hours	Assumption
Adverse events	4 hours	Assumption

8.7 Results

8.7.1 Base case overview

The model base case settings are presented in Table 40.

Table 40: Base case overview

Component	Base-case setting
Comparator	Liposomal doxorubicin
Type of model	Partitioned survival model
Time horizon	36 years (lifetime)
Discount rates	Years 1-35: 3.5% for costs and outcomes Year 36+: 2.5% for costs and outcomes
Treatment line	2nd line. 3rd and 4th subsequent lines are included
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L using Danish tariff.
General population utility adjustment	Applied using Danish Medicines Council. Appendiks: Aldersjustering for sundhedsrelateret livskvalitet.

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Component	Base-case setting
Included costs	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	LEN: based on dosing from Study 309 PEM: Based on Study 309 protocol Liposomal doxorubicin: based on BSA
Average time on treatment	LEN: 0.73 years, PEM: 0.73 years Liposomal doxorubicin (based on doxorubicin from Study 309): 0.20 years
Parametric function for PFS	Independent models LEN+PEM: Log logistic Liposomal doxorubicin: Generalised gamma
Parametric function for OS	Independent models LEN+PEM: Lognormal Liposomal doxorubicin: Gompertz
Parametric function for TTD	LEN: Use Kaplan-Meier within trial PEM: Use Kaplan-Meier within trial Liposomal doxorubicin: Use Kaplan-Meier within trial (assuming equal TTD as doxorubicin in Study 309)
Cap TTD with PFS	Yes
PEM stopping rule	Applied at 24 months
LEN stopping rule	Applied at 24 months
Costs excluded	Exclude: Cost of MSI test Cost of vial sharing

Abbreviations: BSA, body surface area; CARBO, carboplatin; LEN, Lenvatinib; MSI, microsatellite instability; OS, overall survival; PAC, paclitaxel; PEM, pembrolizumab; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; TPC, treatment of physician's choice; TTD, time to discontinuation.

A list of key model assumptions applied in the base case is presented in Appendix J - Key model assumptions applied in the base case.

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8.7.2 Base case results

In the population with PFI < 6 months who were pre-assigned to doxorubicin in Study 309, LEN+PEM is associated with incremental costs of DKK [redacted] and incremental QALYs of [redacted] resulting in an ICER of DKK [redacted] compared with PLD (Table [redacted]. Given that confidential discounts exist for both LEN and PEM, the true ICER value is likely to be lower than DKK [redacted]

[redacted]

Abbreviations: 2L, second line; 3L, third line; AE, adverse event; LEN, lenvatinib; MRU, medical resource use; PEM, pembrolizumab; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

The mean and median values for OS, PFS and TTD in the population with PFI<6 months who are pre-assigned to doxorubicin are presented in [redacted].These values are presented in the treatment engines (columns Y and AI, W and AG, S).

[redacted]

8.8 Sensitivity analyses

8.8.1 Univariate sensitivity analyses

Univariate analysis identified the ten most influential parameters (i.e., those with the greatest impact on the ICER). The input values and rationale for the ten most influence parameters examined in the univariate sensitivity analysis are reported in [redacted]. The results of the univariate analysis are presented in [redacted] and Figure 15. The four most influential parameters are those describing OS survival models for LEN+PEM and DOX; other influential parameters include the PEM administration dose intensity, and the EQ-5D model (and baseline EQ-5D itself). The economic model is sensitive to variations in the OS model, which principally affects the QALYs gained. It is of note that varying individual terms in the parametric survival models is not always strictly appropriate, as the correlation between the terms in the survival models is lost; correlation between these parameters was preserved in PSA (section 8.8.2). Given that confidential discounts exist for both LEN and PEM, the true ICER values will likely be lower than those presented below.

[redacted]

[redacted]

Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio LEN, lenvatinib; PEM, pembrolizumab; PFS, progression-free survival; PFS BICR, progression-free survival by blinded independent central review; OS, overall survival; TTD, time-to-discontinuation

[redacted]

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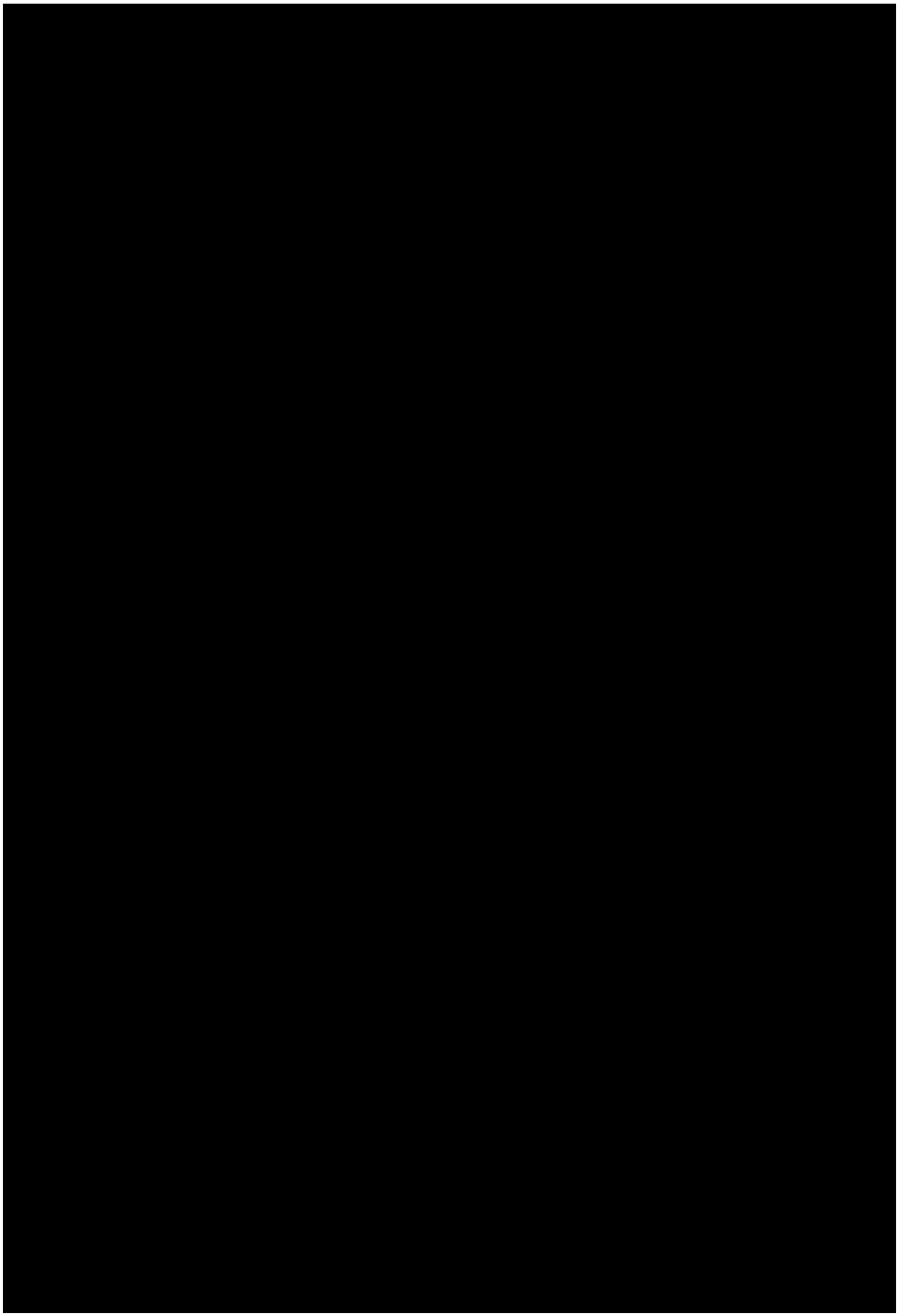
[redacted]

[redacted]

8.8.2 Probabilistic sensitivity analyses

The results of 1,000 PSA simulations were plotted on the cost-effectiveness plane (Figure 16) and a cost-effectiveness acceptability curve (CEAC) was generated (Figure 17).The average incremental costs over the simulated results were DKK [redacted] and the average incremental QALYs were [redacted] giving a probabilistic ICER of DKK [redacted] this is congruent with deterministic changes in costs and QALYs of DKK [redacted] and [redacted] respectively. [redacted]. Given that confidential discounts exist for both LEN and PEM, the true ICER values will likely be lower than those presented**, and therefore proportions of simulations below the willingness-to-**

pay thresholds is likely to be higher what is depicted in Figure 17**.**



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8.8.2.1 Scenario analysis

Scenario analyses were performed in which key structural assumptions were varied, and ICERs were reported. [redacted]. Given that confidential discounts exist for both LEN and PEM, the true ICER values will likely be lower than those presented below.

Table 45: Scenario analysis results, PFI<6 months and pre-assigned to doxorubicin

Scenario	Incremental costs	Incremental QALYs	ICER	% change from base-case ICER
No cap on TTD with PFS	[redacted]			
Lognormal distribution for DOX OS				
Annual discount rate, 5%				
Annual discount rate, 0%				
Time horizon: 15 years				
Lenvatinib stopping rule at 24 months not applied				
Mean age: 67.5 (based on KOL input)				
PEM dose 2 mg/kg				
PEM dose 4 mg/kg every 6 weeks				
PLD as subsequent treatment instead of doxorubicin				

Abbreviations: AE, adverse event; ITT, intention-to-treat; KOL, key opinion leader; LEN, lenvatinib; PEM, pembrolizumab; PFS, progression-free survival; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; TTD, time to discontinuation.

[redacted]

[redacted]

9 Budget impact analysis

9.1 Patient numbers

The patient flow used to inform the population of advanced, recurrent, and metastatic EC following prior platinum-based systemic therapy is presented in Table 47. These patient numbers are based on the DRG/Clarivate endometrial cancer epidemiology model [129] and Eisai market intelligence estimates (see section 5.1). The patients included in the analysis are second-line treatable patients. Current patients are not captured in the analysis as it is not expected that patients already undergoing treatment in year one would be eligible to switch to LEN+PEM, given the aggressive nature and poor outcomes associated with EC.

The budget impact analysis (BIM) settings are the same as the health economic analysis, except for the extended societal costs that are not included in the BIM.

Table 47: Eligible population data [108]

	Year 1 - 2022	Year 2 - 2023	Year 3 - 2024	Year 4 - 2025	Year 5 - 2026
First-line treatable population (advanced)	199	202	207	210	213
First-Line treated population (advanced)	159	162	166	168	170
Second-line treatable population (advanced)	96	97	99	101	102
Pre-assigned to DOX and PFI<6 months	64	65	67	68	69
Systemic treatment rate	51	52	53	54	55
Total treated	31	31	32	32	33

9.2 Diagnosed incidence

In Year 1, the total first-line treatable population is comprised of 199 patients. The total treated patients in the model are derived from the following sub-populations, based on estimates from the DRG/Clarivate endometrial cancer epidemiology model [129] and Eisai market intelligence (Table 47):

- First-line treated population (159 in Year 1), calculated as 80% of the first-line treatable population
- Second-line treatable population (96 in Year 1), calculated as 60% of the first-line treated population
- PFI<6 months (64 in Year 1), calculated as 67% of the second-line treatable population (proportion of patients in Study 309 with PFI<6 months)
- Total treated / Second-line treated population (31 in Year 1), calculated as 80% of the pre-assigned to DOX and PFI<6 months population and assumed 60% of the eligible population for PLD/LEN+PEM

9.3 Market share

Treatment regimens were validated by Danish clinical experts to reweight 2020 market shares from Kantar Health CancerMPact report 2020 [109]. The Kantar report informs the average market shares for the most commons treatments given in second line of systemic therapy of EC in the EU5 countries (France, Germany, Italy, Spain, and UK). In the absence of Danish specific data, the available and relevant types of treatments and their estimated market shares for the Danish clinical setting were chosen according to clinical expert input, and the current shares for the remaining treatments were weighted up to 100%. The estimates for upcoming years in the scenario with LEN+PEM on the market were based on the assumptions of achieved reimbursement for LEN+PEM in December 2022 and that LEN+PEM will reach its peak sales by year four.

Table 48: Market share – if LEN+PEM is introduced

Treatment	Year 1 - 2022	Year 2 - 2023	Year 3 -2024	Year 4 - 2025	Year 5 - 2026
LEN+PEM	[redacted]				
Liposomal Doxorubicin					

Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab.

Table 49: Market share – if LEN+PEN is NOT introduced

Treatment	Year 1 - 2022	Year 2 - 2023	Year 3 -2024	Year 4 - 2025	Year 5 - 2026
LEN+PEM	[redacted]				
Liposomal Doxorubicin					

Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab.

9.4 Number of patients

Table 50: Number of patients expected to be treated over the next five-year period - if LEN+PEM is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
LEN+PEM	[redacted]				
Liposomal Doxorubicin					
Total					

Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab.

Table 51: Number of patients expected to be treated over the next five-year period - if LEN+PEM is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
LEN+PEM	[redacted]				

Liposomal Doxorubicin	[redacted]
Total	

Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab.

9.5 Expenditure per patient

Inputs on expenditure per patients are extracted from the CEM model. Per patient costs of drug acquisition, administration, subsequent therapies, adverse events, and monitoring are extracted from the CEM using 1-year, 2-year, 3-year, 4-year, and 5-year time horizons.

Costs from the CEM are applied to the number of patients getting each treatment (using the population size and market shares). Cost per patient for the first year are applied to incident patients each year. Cost for years 2 to 5 are applied to prevalent patients based on the year of entry (patients who are incident in 2022 are applied the cost of year 1 in 2022, year 2 in 2023, year 3 in 2024, year 4 in 2025 and year 5 in 2026, patients who are incident in 2023 are applied the cost of year 1 in 2023, year 2 in 2024, year 3 in 2025 and year 4 in 2026, etc..).

Table 52 presents the drug acquisition cost inputs for the BIM per patient per year for LEN+PEN and Liposomal Doxorubicin, respectively.

Table 52: Drug acquisition cost inputs per patient per year

	Year 1	Year 2	Year 3	Year 4	Year 5
LEN+PEM	[redacted]				
Liposomal Doxorubicin					

Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab.

9.6 Budget impact

The introduction of LEN+PEM in Denmark is associated total budget of DKK 4,311,257 in year 1, rising to DKK 25,513,354 in year 5 resulting in a cumulative 5-year budget of DKK 73,791,142.

The scenario where LEN+PEM is not recommended is associated with a budget of DKK 2,746,084 in year 1, rising to DKK 3,069,895 in year 5 resulting in a cumulative 5-year budget of DKK 14,713,187.

The difference between the two scenarios, which is the budget impact of recommending LEN+PEM varies from DKK 1,565,173 in year 1 to DKK 22,443,459 in year 5, with a cumulative net budget impact of DKK 59,077,955 over 5 years (Table 53).

Table 53: Expected budget impact of recommending LEN+PEM

	Year 1	Year 2	Year 3	Year 4	Year 5	
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Scenario LEN+PEM is recommended						
Drug acquisition costs	DKK 2,746,998	DKK 6,030,187	DKK 11,446,056	DKK 20,353,480	DKK 22,889,571	DKK 63,466,293
Drug administration costs	DKK 272,573	DKK 352,738	DKK 483,377	DKK 690,779	DKK 774,022	DKK 2,573,488
Subsequent therapy costs	DKK 726,109	DKK 739,442	DKK 724,668	DKK 670,810	DKK 697,135	DKK 3,558,164

Medical resource use costs	DKK 471,323	DKK 597,698	DKK 732,354	DKK 941,695	DKK 1,103,604	DKK 3,846,674
Adverse event costs	DKK 94,254	DKK 86,274	DKK 72,060	DKK 44,913	DKK 49,022	DKK 346,523
Total	DKK 4,311,257	DKK 7,806,339	DKK 13,458,515	DKK 22,701,676	DKK 25,513,354	DKK 73,791,142
Scenario LEN+PEM is NOT recommended						
Drug acquisition costs	DKK 1,215,572	DKK 1,246,097	DKK 1,282,678	DKK 1,301,746	DKK 1,320,407	DKK 6,366,501
Drug administration costs	DKK 240,231	DKK 246,264	DKK 253,493	DKK 257,261	DKK 260,949	DKK 1,258,199
Subsequent therapy costs	DKK 100,548	DKK 103,275	DKK 106,373	DKK 107,969	DKK 109,518	DKK 527,682
Medical resource use costs	DKK 2,746,084	DKK 2,889,625	DKK 2,981,168	DKK 3,026,414	DKK 3,069,895	DKK 14,713,187
Adverse event costs	DKK 1,215,572	DKK 1,246,097	DKK 1,282,678	DKK 1,301,746	DKK 1,320,407	DKK 6,366,501
Total	DKK 240,231	DKK 246,264	DKK 253,493	DKK 257,261	DKK 260,949	DKK 1,258,199
Budget Impact (Scenario with minus scenario without LEN+PEM)						
Drug acquisition costs	DKK 1,531,426	DKK 4,784,090	DKK 10,163,378	DKK 19,051,734	DKK 21,569,164	DKK 57,099,791
Drug administration costs	DKK 32,342	DKK 106,474	DKK 229,883	DKK 433,517	DKK 513,073	
Subsequent therapy costs	-DKK 15,539	-DKK 41,280	-DKK 81,670	-DKK 147,922	-DKK 133,370	-DKK 419,781
Medical resource use costs	DKK 23,238	DKK 84,431	DKK 200,068	DKK 400,989	DKK 555,089	DKK 1,263,815
Adverse event costs	-DKK 6,294	-DKK 17,001	-DKK 34,313	-DKK 63,056	-DKK 60,496	-DKK 181,160
Total budget impact	DKK 1,565,173	DKK 4,916,714	DKK 10,477,347	DKK 19,675,262	DKK 22,443,459	DKK 59,077,955

Abbreviations: LEN+PEM, lenvatinib plus pembrolizumab

10 Discussion on the submitted documentation

The documentation submitted for this single-technology assessment stems from a comprehensive clinical development program, where the efficacy and safety of combination treatment with LEN+PEM has been evaluated in adult patients with EC. There is a significant unmet medical need for patients with advanced and recurrent EC who have progressed after prior platinum treatment.

The 309 / KN-775trial is a Phase III, multicenter, randomized, open-label study to compare the efficacy and safety of treatment with LEN+PEM in 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 who are not candidates for curative surgery or radiation. The 309 / KN-775trial presented direct head-to-head comparison of the efficacy and safety of LEN+PEM versus therapy of physician's choice (TPC) consisting of either doxorubicin or paclitaxel which were identified as the most common treatments for patients in this setting globally at the time of study design.

The DMC describes in its assessment report dostarlimab [63], the second line treatment options for EC as dependent on the duration of time passed since platinum-based treatment in first line. For patients who progress during or up to six months after treatment with first line platinum therapy, PLD is given as standard treatment. Patients who progress approximately six months or more after discontinuation of platinum treatment are considered platinum sensitive and can be re-treated with platinum-based chemotherapy after progression. Based on consultation with the DMC, these treatments are considered to represent Danish clinical practice. For the scope of the assessment, efficacy has been presented for the pre-assigned to doxorubicin PFI < 6 months subgroup from Study 309 / KN-775.

In the pre-assigned to doxorubicin and PFI < 6 months subgroup, post hoc analysis shows that treatment with LEN+PEM provides a consistent risk-benefit profile similar to the entire pre-assigned to doxorubicin population, with overall survival of additional [redacted] and [redacted] reduction in the risk of death [redacted] and progression free survival of additional [redacted] and [redacted] reduction in the risk of disease progression [redacted] in comparison to doxorubicin/PLD.

Results from the cost-effectiveness analysis show that compared to PLD, LEN+PEM can be considered a cost-effective use of Danish medical resources and represents a manageable budget impact considering the significant unmet need for endometrial cancer patients.

11 List of experts

Two clinical experts were consulted about clinical practice and model inputs for the Danish context [104]:

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

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 [15]. Eisai and Merck Sharp & Dohme have conducted the pivotal clinical study 309/KN-755 [88] (see Section 7.1), a randomised controlled trial conducted to compare the efficacy and safety of LEN+PEM versus treatment of physician's choice (TPC) (doxorubicin or paclitaxel). PLD is considered the standard of care in Danish clinical practice. However, as described in Section 5.2.3, there is evidence suggesting doxorubicin and PLD are comparable with respect to efficacy and safety (described in Section 5.2.3) 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 doxorubicin in Study 309 / KN-775, with PFI < 6 months.

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 (advanced EC who have disease progression following prior treatment with a PFI < 6 months).

Appendix B Main characteristics of included studies

Study 309 / KN-775

Table 54 Summary table study 309 / KN-775

Trial name: 309 / KN-775	
Objectives	To demonstrate that lenvatinib (LEN) plus pembrolizumab (PEM): • Prolongs progression free survival (PFS) and overall survival (OS) when compared to treatment of physician's choice.
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 endometrial 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 lenvatinib in combination with pembrolizumab versus treatment of physician's choice in patients with advanced endometrial cancer. 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 Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Cancer following prior platinum-based regimen.
Sample size (n)	**Intervention**: 411 participants **Comparator**: 416

Main inclusion and exclusion 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

Inclusion Criteria:

1. Has a histologically confirmed diagnosis of endometrial carcinoma (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 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 mismatch repair (MMR) status.
6. Has at least 1 measurable target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and confirmed by Blinded Independent Central Review 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 pembrolizumab) or at least 180 days (for participants treated with treatment of physician's choice [TPC]) after the last dose of study treatment.

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 endometrial cancer, 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.
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 Endometrial Cancer. 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 pembrolizumab and LEN for endometrial carcinoma, 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).
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®) + pembrolizumab 200 mg (KEYTRUDA®) Participants received pembrolizumab 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 pembrolizumab group.
Comparator(s)	Active Comparator: Treatment of Physician's Choice (doxorubicin or paclitaxel) Participants received either of the following treatments: doxorubicin 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	ITT-population: The median follow-up duration was 11.4 months for ITT population and similar between treatment arms (12.2 months in the LEN plus pembrolizumab group vs 10.7 months in the TPC group).
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints

Endpoints included in this application:

Primary Outcome Measures:

- Progression Free Survival (PFS)
- Overall Survival (OS)

Secondary Outcome Measures:

- Objective Response Rate (ORR)
- Health-Related Quality of Life (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 (AE)
- Number of Participants with Serious Adverse Events (SAE)
- 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
- Model-Predicted Area Under the Concentration time Curve of Lenvatinib Based on Starting Dose from Time 0 to Infinity (AUC 0-∞)
- Model-Predicted Apparent Total Body Clearance (Cl/F) of Lenvatinib
- Model-Predicted Apparent Total Body Volume of Distribution (Vd/F) of Lenvatinib

Method of analysis

The Intention-to-Treat (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 Kaplan-Meier 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 SAEs 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)
    - 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)

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

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 55 Patient baseline and disease characteristics

Study 309 / KN-775 (Pre-assigned to doxorubicin, PFI < 6 months population)	Lenvatinib + Pembrolizumab	Doxorubicin (N=211)
Participants in population	[redacted]	
Age (Years)		
Median (range)		
<65 years		
Race		
White		
Black or African American		
Asian		
Missing		
Other		
MMR status		
pMMR		
dMMR		
ECOG		
0		
1		
History of pelvic irradiation		
Histology of initial diagnosis		
Endometrioid carcinoma		
High grade endometrioid carcinoma		

Low grade endometrioid carcinoma	[redacted]
Not specified	
Serous carcinoma	
Clear cell carcinoma	
Mixed histology	

Abbreviations: dMMR, Missmatch repair deficienct; ECOG, Eastern Cooperative Oncology Group; MMR, Missmatch repair; PFI, Platinum-free interval ; pMMR, Missmatch repair proficient

12.1 Comparability of the study populations with Danish patients eligible for treatment

The characteristics of the study population from Study 309 / KN-775are comparable to patients eligible for treatment in the Danish setting. With the exception of patients' age, which may be slightly higher in Denmark (range 63.5-67) compared to the mean age in the clinical trial (average: 63.1 years), the characteristics of the trial population were similar. A Danish cohort study reports an average age at diagnosis of EC of 65.5 years among 3638 participants [110], while Danish clinical experts interviewed for this purpose mentioned an age of 63.5-67 years. In general, endometrial cancer is rare before the age of 45 and the maximum age is around 70 years in Denmark [111].

To account for the possible difference in age, a health economic scenario analysis has been run to test how using a higher average Danish age affects the results. This resulted in an ICER similar to the base case. For further details, see section 8.

Appendix D Efficacy and safety results per study

As per the DMC guidelines [87] a list of all clinical endpoints in the included studies should be included in the submission (Table 56). However, validity, clinical relevance and efficacy results should only be included for outcome measures relevant for the submission. As such, these details for the relevant outcome measures (OS and PFS) will be described in this section.

Table 56 Definitions of all endpoints in Study 309 / KN-775

Outcome measure	Definition/Time frame
Primary outcome measures	
PFS	Time Frame: Up to approximately 27 months PFS is defined as the time from randomization to the first documented disease progression per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as determined by Blinded Independent Central Review (BICR) or death due to any cause, whichever occurred first.
OS	Time Frame: Up to approximately 43 months OS is defined as the time from date of randomization to date of death from any cause.
Secondary outcome measures	
ORR	Time Frame: Up to approximately 27 months ORR is defined as the percentage of participants who have best overall response of either CR or PR, as determined by BICR per RECIST 1.1.
HRQoL Score Using the EORTC QoL Questionnaire (QLQ-C30) Version 3.0	Time Frame: Baseline (prior to first dose of study treatment in Cycle 1 [cycle length = 21 days]) and at the end of follow-up (up to approximately 43 months) Change from baseline in HRQoL using the global score of EORTC QLQ-C30 will be determined. EORTC QLQ-C30 is a cancer specific health-related quality-of life (QoL) questionnaire, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea, and financial impact), and a global health and QoL scale. The score for each item and the overall score ranges from 0 to 100. A high overall scale and subscale scores represent improved health status. However, in case of individual symptoms, higher scores suggest increased perception of these symptoms of life.
Number of Participants With AE	Time Frame: Up to approximately 43 months The number of participants experiencing an AE will be assessed. An AE is defined as any unfavourable and unintended sign, symptom, or disease (new or worsening) temporally associated with the use of study therapy, regardless of whether or not a causal relationship with the study therapy can be determined.
Number of Participants With SAE	Time Frame: Up to approximately 43 months The number of participants experiencing an SAE will be assessed. A SAE is an AE that results in death, is life threatening, results in persistent or significant disability/incapacity, results in

Outcome measure	Definition/Time frame
	or prolongs an existing inpatient hospitalization, is a congenital anomaly/birth defect, is a cancer, is associated with an overdose, or is another important medical event.
Number of Participants With irAE	Time Frame: Up to approximately 43 months The number of participants experiencing an irAE will be assessed. An irAE is defined as any unfavourable and unintended immune-related sign, symptom, or disease (new or worsening) temporally associated with the use of study therapy, regardless of whether or not a causal relationship with the study therapy can be determined.
Number of Participants With Treatment Discontinuations Due to AEs	Time Frame: Up to approximately 43 months The number of participants who discontinue study treatment due to an AE will be assessed.

Abbreviations: AE, adverse event; BICR, Blinded Independent Central Review; EMA, European medical Agency; FDA, Food and Drug Administration; HRQoL, Health Related Quality of Life, OS, Overall survival**;** PFS, Progression- free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, Serious adverse event

Definition, validity, and clinical relevance of included outcome measures

Table 57 Definition, validity, and clinical relevance of included outcome measures in Study 309 / KN-775

Outcome measure	Definition	Validity	Clinical relevance
PFS	Time Frame: Up to approximately 27 months PFS is defined as the time from randomization to the first documented disease progression per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as determined by Blinded Independent Central Review (BICR) or death due to any cause, whichever occurred first.	The standard outcome for trials investigating cancer.	The PFS is a validated measure used in clinical trials to assess the time patients live with the disease without getting worse.
OS	Time Frame: Up to approximately 43 months OS is defined as the time from date of randomization to date of death from any cause.	The gold standard in cancer trials (FDA)(EMA) [112].	The OS is a validated measure used in clinical trials to assess the time patients remain alive on treatment.
HRQoL	Multi-dimensional concept that includes domains related to physical, mental, emotional, and social functioning.	HRQoL is a widely used and validated outcome measure [113]	HRQoL was used to measure if the treatment was associated with an improved quality of life compared to the other treatment comparators.

Abbreviations: BICR, Blinded Independent Central Review; EMA, European medical Agency; FDA, Food and Drug Administration; HRQoL, Health Related Quality of Life, RECIST, Response Evaluation Criteria in Solid Tumors; PFS, Progression- free survival; OS, Overall survival

Efficacy results: Study 309 / KN-775

Table 58 Efficacy results – Study 309 / KN-775

				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 doxorubicin, PFI < 6 months population)	LEN+PEM	[redacted]								Based on Cox regression model with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.	Study 309 / KN-775[84]
	Doxorubicin										
OS (Pre-assigned to doxorubicin, PFI < 6 months population)	LEN+PEM									Based on Cox regression model with treatment as a covariate stratified by MMR status, ECOG performance status, geographic region, and prior history of pelvic radiation.	
	Doxorubicin										

Abbreviations: CI, Confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, Hazard Ratio; LEN, Lenvatinib; MMR, Missmatch repair; NA, Not applicable; OS, Overall survival; PEM, Pembrolizumab; PFI, Platinum-free interval; PFS, progression free

Appendix E Safety data for intervention and comparator(s)

Safety: Study 309 / KN-775

Table 59 Participants with grade 3-5 treatment-related adverse events by decreasing incidence, pre-assigned to doxorubicin, PFI < 6 months.

	Lenvatinib + Pembrolizumab (N=204) n (%)	Doxorubicin (N=200) n (%)
Participants in population		
with one or more adverse events		
with no adverse events		
Hypertension		
Diarrhoea		
Decreased appetite		
Weight decreased		
Asthenia		
Lipase increased		
Nausea		
Proteinuria		
Alanine aminotransferase increased		
Aspartate aminotransferase increased		
Pulmonary embolism		
Vomiting		
Anaemia		
Fatigue		
Hyponatraemia		
Mucosal inflammation		

Neutrophil count decreased	[redacted]
Platelet count decreased	
Abdominal pain	
Acute kidney injury	
Amylase increased	
Colitis	
Female genital tract fistula	
Pain in extremity	
Palmar-plantar erythrodysaesthesia syndrome	
Stomatitis	
Type 1 diabetes mellitus	
Urinary tract infection	
White blood cell count decreased	
Arthralgia	
Blood creatine phosphokinase increased	
Gamma-glutamyltransferase increased	
Hepatotoxicity	
Hyperglycaemia	
Hypothyroidism	
Immune-mediated hepatitis	
Peritonitis	
Pneumonitis	
Thrombocytopenia	
Adrenal insufficiency	
Autoimmune nephritis	
Blood alkaline phosphatase increased	
Bundle branch block left	
Cerebral haemorrhage	

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Cerebrovascular accident	[redacted]
Chronic kidney disease	
Death	
Dehydration	
Depression	
Dermatitis bullous	
Drug eruption	
Dyspepsia	
Eastern Cooperative Oncology Group performance status worsened	
Embolism	
Encephalitis autoimmune	
Erythema	
Gastritis erosive	
Gastroenteritis	
General physical health deterioration	
Haemorrhagic stroke	
Hepatic enzyme increased	
Hypertriglyceridaemia	
Hypoalbuminaemia	
Hypoglycaemia	
Hypokalaemia	
Hypomagnesaemia	
Hypophysitis	
Hypotension	
Intestinal fistula	
Large intestine perforation	
Leukocytosis	
Liver disorder	

Lower gastrointestinal perforation	[redacted]
Lymphocyte count decreased	
Lymphopenia	
Muscular dystrophy	
Myalgia	
Myositis	
Neutropenia	
Oral herpes	
Pancreatitis	
Pancreatitis acute	
Perforated ulcer	
Pneumonia	
Postoperative wound infection	
Rash maculo-papular	
Renal failure	
Respiratory failure	
Secondary hypertension	
Sialoadenitis	
Skin disorder	
Skin lesion	
Skin toxicity	
Uterine haemorrhage	
Vasculitis	
Wound infection	
Atrial fibrillation	
Blood bilirubin increased	
C-reactive protein increased	
Cardiac failure	

Dyspnoea exertional	[redacted]
Ejection fraction decreased	
Febrile bone marrow aplasia	
Febrile neutropenia	
Gastrointestinal toxicity	
Groin pain	
Haematuria	
Haemoglobin decreased	
Hepatobiliary disease	
Hypocalcaemia	
Intestinal obstruction	
Leukopenia	
Malnutrition	
Oedema peripheral	
Oesophageal candidiasis	
Oral candidiasis	
Phlebitis	
Pyelonephritis acute	
Septic shock	
Toxic cardiomyopathy	
Vascular device infection	

Table 60 Disposition of Participants pre-assigned to doxorubicin, PFI < 6 months.

	Lenvatinib + Pembrolizumab n (%)	Doxorubicin n (%)
Participants in population	[redacted]	
Status for Trial		
Discontinued		

Death	[redacted]	
Lost To Follow-Up		
Withdrawal By Subject		
Participants Ongoing		
Status for Study medication in Trial		
Started		
Completed		
Discontinued		
Adverse Event		
Clinical Progression		
Complete Response		
Non-Compliance With Study Drug		
Non-Study Anti-Cancer Therapy		
Physician Decision		
Progressive Disease		
Withdrawal By Subject		
Participants Ongoing		

Appendix F – Comparative analysis of efficacy and safety

For the comparative analysis of efficacy and safety for doxorubicin and LEN+PEM see Appendix D.

Pegylated liposomal doxorubicin

As described in Section 5.2.2, PLD is considered the most relevant comparator to LEN+PEM. Based on the DMC's recent assessment of dostarlimab, 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

Table 61: Relevant studies for doxorubicin and PLD

Intervention	RCTs, author year	Non-RCTs, author year
Doxorubicin	Subgroup of TPC treatment group, Study 309 / KN-775[1, 84] McMeekin 2015 [69] Miller 2018 ZoptEC [70 , 71]	Di Legge 2011 [75]
Liposomal doxorubicin	NA	Angioli et al., 2007 [74] Homesley 2005 [72] Julius, 2013 [76] Muggia 2002 [73]

Abbreviations: NA, Not applicable; RCT, randomized controlled trial

For doxorubicin therapy, three RCTs were identified, including Study 309 / KN-775[1, 69, 70 , 71, 84], and one single arm study [75], whilst three single arm studies and one RWE study were identified for PLD in a relevant patient population [72, 74, 76, 114]. A comparison with doxorubicin 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-775via doxorubicin to form a network for traditional network meta-analysis (NMA) 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 Kaplan-Meier curves for the survival outcomes of interest, at best only reporting median survival, with no associated variance [72-74]

Indirect comparison with the RWE study was also not considered appropriate (Julius 2013 [76]). 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.

Appendix G – Model extrapolations

Extrapolation of relative efficacy: additional graphs and tables (pre-assigned to doxorubicin and PFI<6 months population)

OS

The proportional hazards assumption was assessed using plots of the log-cumulative hazard [redacted] For OS in the pre-assigned to doxorubicin and PFI<6 months population, the plots become clearly separated over time and appear reasonably parallel beyond approximately day 100. Schoenfeld residuals are shown in [redacted] shows the Schoenfeld residuals and [redacted] the smoothed hazard estimates over time.

[redacted]

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[redacted]

Model fit diagnostics for each of the six standard parametric distributions are presented in Table 62.

Table 62: Model fit diagnostics

	N	ll0	ll	df	AIC	BIC
LEN+PEM	[redacted]					
gamma						
weibull						
gompertz						

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exponential	[redacted]								
lognormal									
loglogistic									
DOX									
gamma									
weibull									
gompertz									
exponential									
lognormal									
loglogistic									

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; df, degrees of freedom; LEN+PEM, lenvatinib plus pembrolizumab; ll, log-likelihood; N, number of patients.

A plot of the hazard over time is presented in Figure 21 and Figure 22 for LEN+PEM and DOX, respectively.

[redacted]

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PFS

Plots of the log-cumulative hazard are presented in Figure 23 for PFS BICR in the pre-assigned to doxorubicin and PFI<6 months population of Study 309 / KN-775, which is used in the model base case. Schoenfeld residuals are shown Figure 24. Figure 25 shows the instantaneous hazards over time between the two arms.

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[redacted]

Model fit diagnostics for each of the six standard parametric distributions are presented in Table 63.

Table 63: Model fit diagnostics– PFS BICR, pre-assigned to doxorubicin and PFI< 6 months population

	N	ll0	ll	df	AIC	BIC
LEN+PEM	[redacted]					
Generalized gamma						
Weibull						
Gompertz						
Exponential						
Lognormal						
Loglogistic						
DOX						
Generalized gamma						

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Weibull	[redacted]						
Gompertz							
Exponential							
Lognormal							
Loglogistic							

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; df, degrees of freedom; DOX, doxorubicin; ITT, intention-to-treat; LEN+PEM, lenvatinib plus pembrolizumab; ll, log-likelihood; N, number of patients; OS, overall survival.

A plot of the hazard over time is presented Figure 26 and Figure 27 for LEN+PEM and DOX, respectively.

[redacted]

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Appendix H – Mapping of HRQoL data

The health state utility values used in the model originate from study 309 / KN-775, based on patient level data. The values were estimated with EQ-5D-5L using published tariffs for the Danish population [100]. The models include only the population of patients with PFI<6months pre-assigned to DOX.

The EQ-5D-5L is a patient-completed HRQoL instrument evaluating five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with five levels of response.

Study 309 / KN-775includes treatments with different cycle lengths. The cycle length for LEN+PEM and TPC of doxorubicin 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 [EOT] 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 EOT visit. Completion of the EQ-5D and other HRQoL questionnaires following the EOT visit was not mandatory. In order to convert EQ-5D-5L to preference-based index scores, a tariff of general population utility weights must be applied. As preferences towards the dimensions of health reflected in the EQ-5D-5L are likely to vary between countries, tariffs are available for multiple countries. In the base case, the EQ-5D-5L using published tariffs for the Danish population [100]

For use within the economic model, multivariable linear mixed models were fitted to the EQ-5D index score, and covariates representing baseline EQ-5D index score, presence of treatment-related Grade 3–5 AEs at the time of observation, treatment arm, being 'on' vs 'off' treatment, progression-status, and time before death were considered for inclusion in the model, and models were compared using the AIC and BIC diagnostic statistics, and variables which led to improvements (reductions) in these statistics retained. 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 AEs and subgroup membership).

The time-to-death categories used were ≥ 365 days (or did not die), 183 – 364 days, 92 – 182 days, 29 – 91 days, and ≤ 28 days. These categories were selected to approximately correspond to categories used by previous analyses, modified to reflect the model cycle [3]

The use of time-to-death, in addition to pre-/post-progression status was considered on the basis that:

- EQ-5D data in study 309 / KN-775was collected beyond the end of treatment
- Analyses have previously demonstrated that use of pre-/post-progression status alone, ignoring time-to-death, may underestimate QALY gains for preventive interventions [115]
- Statistical testing of data from study 309 / KN-775demonstrated that models which included both time-to-death and pre-/post-progression status led to improved statistical goodness-of-fit (see Results below)

Mixed models assume that missing data are missing at random (MAR), and no imputation was performed [116]. Table 64 and Table 65 summarize the statistical models tested.

Table 64: Summary of tested models (models considering time-to-death and pre-post-progression)

	Model number										
Covariates	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**

Baseline EQ-5D	x	x	x	x	x	x	x	x	x	x	x	x
Time from death	x	x	x	x	x	x	x	x	x	x	x	x
On treatment		x		x	x	x	x	x	x	x	x	x
LEN+PEM (vs DOX)			x			x	x	x	x	x		
Experiencing AEs					x	x	x	x	x	x	x	x
On treatment # LEN+PEM						x	x	x	x	x		
pMMR (vs dMMR)							x					
Prior lines of therapy								x				
Hysterectomy									x			
Post-progression										x	x	x
Age											x	

Table 65: Summary of tested models (models pre-/post-progression status only)

	Model number											
Covariates	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Baseline EQ-5D	x	x	x	x	x	x	x	x	x	x	x	x
Post-progression	x	x	x	x	x	x	x	x	x	x	x	x
On treatment		x		x	x	x	x	x	x	x	x	x
LEN+PEM (vs DOX			x			x	x	x	x	x		
Experiencing AEs					x	x	x	x	x	x	x	x
On treatment # LEN+PEM						x	x	x	x	x		
pMMR (vs dMMR)							x					
Prior lines of therapy								x				
Hysterectomy									x			

Age											x	

Results

[redacted]

[redacted]

Table 66: Completion and Compliance Percentages for EQ-5D VAS by visit and by treatment (all-comer full analysis set)

EQ-5D VAS completion rate (%)	Baseline		Week 12		Week 24		Week 36	
	LENPEM	TPC	LENPEM	TPC	LENPEM	TPC	LENPEM	TPC
Completed	97.0	97.4	77.8	62.1	59.0	24.4	45.3	5.1
Compliance*	97.6	97.7	91.8	87.3	89.4	73.1	88.7	69.6

*% in those expected to complete questionnaires

[redacted]

[redacted]

Empirical mean EQ-5D index score by visit for each study arm during Year 1 is presented in Figure 29. There were no notable differences between study arms over time.

[redacted]

Mean EQ-5D index scores by model health state are presented in Table 67. As expected, the majority of observations that were available were from patients who had not experienced a PFS event and who remained on treatment [redacted]

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[redacted]

Table 67: EQ-5D by progression and on/off treatment status (PFI < 6 months and pre-assigned to DOX population)

Health state	Mean	s.e.	95% CI
Progression-free, off-treatment	[redacted]		
Progression-free, on-treatment			
Post-progression, off-treatment			
Post-progression, on-treatment			
Total			

Abbreviations: CI, confidence interval; s.e., standard error.

Table 68: EQ-5D aby time-to-death category (PFI < 6 months and pre-assigned to DOX population)

Health state	Mean	SE	95% CI
>= 365 days from death or did not die	[redacted]		
183–364 days away from death			
92–182 days away from death			
29–91 days away from death			
0–28 days away from death			

Abbreviations: CI, confidence interval; SE, standard error.

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Correlation between candidate covariates is summarised in Table 69.

Table 69 Correlation between candidate variables

	Baseline EQ-5D	Time-to-death	Post-progression	On treatment	In AEs	pMMR	Prior lines of therapy	Hysterectomy
Baseline EQ-5D	1.0000							
Time-to-death	-0.0386	1.0000						
Post-progression	0.0028	0.1299	1.0000					
On treatment	0.0154	-0.1068	-0.2619	1.0000				
In AEs	-0.0037	-0.0868	0.0167	-0.0066	1.0000			
pMMR	0.1404	0.1420	0.0258	-0.0577	0.0210	1.0000		
Prior lines of therapy	0.1182	-0.0463	-0.0237	-0.0083	-0.0872	0.0167	1.0000	
Hysterectomy	0.0222	-0.0225	0.0130	-0.0150	0.0539	0.0006	0.2339	1.0000

Abbreviations: AEs, adverse events; pMMR, mismatch repair proficient.

Models considering time-to-death

The considered statistical models of EQ-5D are presented in Table 70.

Table 70: Alternative statistical models of EQ-5D (DK index; models 1–5)

Variable	m1	m2	m3	m4	m5
Baseline EQ-5D					
0–28 days away from death					
29–91 days away from death					
92–182 days away from death					
183–364 days away from death					
On treatment (vs off treatment)					
LEN+PEM (vs DOX)					
Experiencing AEs					
Constant					
lns1_1_1					
lnsig_e					
N					

Abbreviations: AE, adverse event; LEN+PEM, lenvatinib plus pembrolizumab; DOX, doxorubicin.

Table 71: Alternative statistical models of EQ-5D (DK index; models 6–10)

Variable	m6	m7	m8	m9	m10
Baseline EQ-5D					
0–28 days away from death					
29–91 days away from death					
92–182 days away from death					
183–364 days away from death					
On treatment (vs off treatment)					
LEN+PEM (vs DOX)					
Experiencing AEs					
On treatment # LEN+PEM					
pMMR (vs dMMR)					

Prior lines of therapy: 2 (vs 1)	[redacted]
Prior lines of therapy: ≥ (3 vs 1)	
Hysterectomy	
Post-progression	
Constant	
lns1_1_1	
lnsig_e	
N	

Abbreviations: AE, adverse event; DOX, doxorubicin
mismatch repair proficient.

Table 72: Alternative statistical models of EQ-5D (DK index, models 11–12)

Variable	m11	m12
Baseline EQ-5D	[redacted]	
0–28 days away from death		
29–91 days away from death		
92–182 days away from death		
183–364 days away from death		
On treatment (vs off treatment)		
Experiencing AEs		
Post-progression		
Age		
Constant		
lns1_1_1		
lnsig_e		
N		

Abbreviations: AE, adverse event.

Model goodness-of-fit statistics for the alternative models are provided in Table 72Table 73. Models 10 and 11 provided the lowest AIC score (model 12 being third), whilst model 12 provided the lowest BIC score (model 11 being second). The difference between model 10 and model 12 was the inclusion and exclusion (in model 10 and model 12, respectively) of the LEN+PEM vs DOX covariate and interaction thereof with on-treatment status. The latter term (the interaction between being on treatment and randomized to LEN+PEM) was not statistically significant, whilst the main effect (LEN+PEM vs DOX) was borderline statistically significant. As model 12 was preferred based on the BIC score

(and was a close third based on the AIC score) and represented the more parsimonious model, without interaction terms, it was selected as the preferred model.

Table 73: EQ-5D model goodness of fit statistics

	N	ll	df	AIC	BIC
m1	[redacted]				
m2					
m3					
m4					
m5					
m6					
m7					
m8					
m9					
m10					
m11					
m12					

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; df, degrees of freedom; ll, log-likelihood.

The final statistical model of EQ-5D including time to death is presented in Table 74. Results suggested small decrements associated with observations post-progression (–0.027; p=0.003) and experiencing AEs at the time of observation (–0.012; p=0.180). Increasing proximity to death was associated with worsening EQ-5D (decrement of –0.226; p<0.001 for 0–28 days from death), with difference beyond 92 days from death not reaching statistical significance. Being on treatment (independent of which treatment) was associated with higher EQ-5D than being off treatment (0.119; p<0.001).

Table 74: EQ-5D based on time-to-death

Parameter	Coefficient	s.e.	z P>z	95% CI
Baseline EQ-5D	[redacted]			
Post-progression decrement				
AE disutility				
On treatment increment				
0–28 days away from death				
29–91 days away from death				
92–182 days away from death				
183–364 days away from death				

Constant	[redacted]

Abbreviations: AE, adverse event; CI, confidence interval; s.e., standard error.

Pre-/post-progression models

The considered statistical models of EQ-5D (using pre/post-progression status) are presented Table 70.

Table 75: Alternative statistical models of EQ-5D (DK index; models 1–5)

Variable	m13	m14	m15	m16	m17
Baseline EQ-5D	[redacted]				
Post-progression					
On treatment (vs off treatment)					
LEN+PEM (vs OX)					
Experiencing AEs					
Constant					
lns1_1_1					
lnsig_e					
N					

Abbreviations: AE, adverse event; LEN+PEM, lenvatinib plus pembrolizumab; DOX, doxorubicin.

Table 76: Alternative statistical models of EQ-5D (DK index; models 6–10)

Variable	m18	m19	m20	m21	m22
Baseline EQ-5D	[redacted]				
Post-progression					
On treatment (vs off treatment)					
LEN+PEM (vs DOX)					
Experiencing AEs					
On treatment # LEN+PEM					
pMMR (vs dMMR)					
Prior lines of therapy: 2 (vs 1)					
Prior lines of therapy: ≥ (3 vs 1)					
Hysterectomy					
Constant					
lns1_1_1					

lnsig_e	[redacted]
N	

Abbreviations: AE, adverse event; CW, crosswalk; dMMR, mismatch repair deficient; LEN+PEM, lenvatinib plus pembrolizumab; pMMR, mismatch repair proficient; DOX, doxorubicin.

Table 77: Alternative statistical models of EQ-5D (DK index, models 11–12)

Variable	m23	m24
Baseline EQ-5D	[redacted]	
Post-progression		
On treatment (vs off treatment)		
Experiencing AEs		
Age		
Constant		
lns1_1_1		
lnsig_e		
N		

Abbreviations: AE, adverse event.

Model goodness-of-fit statistics for the alternative models are provided in Table 73. RCModel 21 provided the lowest AIC score (with several other models performing similarly well), whilst model 24 provided the lowest BIC score (model 23 being second). As model 24 was preferred based on the BIC score and represented the more parsimonious model, it was selected as the preferred model.

Table 78: EQ-5D model goodness of fit statistics

	N	ll	df	AIC	BIC
m13	[redacted]				
m14					
m15					
m16					
m17					
m18					
m19					
m20					
m21					
m22					

m23	[redacted]
m24	

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; df, degrees of freedom; ll, log-likelihood.

The final statistical model of EQ-5D based on pre-/post-progression status in Table 79. Results suggested small decrements associated with observations post-progression (–0.037; p<0.001). Being on treatment (independent of which treatment) was associated with higher EQ-5D than being off treatment (0.140; p<0.001).

Table 79: EQ-5D based on pre-/post-progressions status only

Parameter	Coefficient	s.e.	z P>z	95% CI
Baseline EQ-5D	[redacted]			
On treatment increment				
AE disutility				
Post-progression decrement				
Constant				

Abbreviations: AE, adverse event; CI, confidence interval; s.e., standard error

Appendix I – Probabilistic sensitivity analyses

Table 80: Model parameters

Parameter name	Default value	Parameter distribution
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gamma, constant	6.07	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gamma, ln(sigma)	0.14	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gamma, kappa	-0.18	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - Weibull, constant	-8.29	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - Weibull, ln(p)	0.25	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gompertz, constant	-6.74	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gompertz, gamma	0.00	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - exponential, constant	-6.55	Normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - lognormal, constant	6.14	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - lognormal, ln(sigma)	0.10	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - loglogistic, constant	6.12	Multivariate normal
OS - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - loglogistic, ln(gamma)	-0.45	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gamma, constant	5.32	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gamma, ln(sigma)	0.13	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gamma, kappa	0.11	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - Weibull, constant	-6.01	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - Weibull, ln(p)	0.05	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gompertz, constant	-5.54	Multivariate normal

PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - gompertz, gamma	0.00	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - exponential, constant	-5.73	Normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - lognormal, constant	5.27	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - lognormal, ln(sigma)	0.15	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - loglogistic, constant	5.24	Multivariate normal
PFS BICR - LEN+PEM - pre-assigned to doxorubicin and PFI<6 months - loglogistic, ln(gamma)	-0.43	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - gamma, constant	5.56	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - gamma, ln(sigma)	-0.19	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - gamma, kappa	0.30	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - Weibull, constant	-8.30	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - Weibull, ln(p)	0.36	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - gompertz, constant	-6.17	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - gompertz, gamma	0.00	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - exponential, constant	-5.81	Normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - lognormal, constant	5.45	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - lognormal, ln(sigma)	-0.13	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - loglogistic, constant	5.46	Multivariate normal
OS - TPC - pre-assigned to doxorubicin and PFI<6 months - loglogistic, ln(gamma)	-0.68	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - gamma, constant	4.36	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - gamma, ln(sigma)	-0.36	Multivariate normal

PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - gamma, kappa	-0.48	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - Weibull, constant	-6.96	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - Weibull, ln(p)	0.36	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - gompertz, constant	-4.99	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - gompertz, gamma	0.00	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - exponential, constant	-4.84	Normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - lognormal, constant	4.52	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - lognormal, ln(sigma)	-0.34	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - loglogistic, constant	4.47	Multivariate normal
PFS BICR - TPC - pre-assigned to doxorubicin and PFI<6 months - loglogistic, ln(gamma)	-0.88	Multivariate normal
% PFS events that are progression	0.87	Beta
Anaemia, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	4.00	Gamma
Decreased appetite, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	12.00	Gamma
Diarrhoea, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	14.00	Gamma
Hypertension, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	76.00	Gamma
Neutropenia, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	1.00	Gamma
Neutrophil count decreased, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	4.00	Gamma
Weight decreased, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	12.00	Gamma
White blood cell count decreased, number of events, LEN+PEM, Pre-assigned to DOX, PFI<6 months population	3.00	Gamma
Anaemia, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	35.00	Gamma
Diarrhoea, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	3.00	Gamma

Febrile neutropenia, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	18.00	Gamma
Leukopenia, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	26.00	Gamma
Neutropenia, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	98.00	Gamma
Neutrophil count decreased, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	85.00	Gamma
White blood cell count decreased, number of events, DOX, Pre-assigned to DOX, PFI<6 months population	30.00	Gamma
Anaemia, average duration per event (days) pre-assigned to dox, PFI<6 months	35	Gamma
Decreased appetite, average duration per event (days) pre-assigned to dox, PFI<6 months	0	Gamma
Diarrhoea, average duration per event (days) pre-assigned to dox, PFI<6 months	3	Gamma
Febrile neutropenia, average duration per event (days) pre-assigned to dox, PFI<6 months	18	Gamma
Hypertension, average duration per event (days) pre-assigned to dox, PFI<6 months	0	Gamma
Leukopenia, average duration per event (days) pre-assigned to dox, PFI<6 months	26	Gamma
Lipase increased, average duration per event (days) pre-assigned to dox, PFI<6 months	0	Gamma
Neutropenia, average duration per event (days) pre-assigned to dox, PFI<6 months	98	Gamma
Neutrophil count decreased, average duration per event (days) pre-assigned to dox, PFI<6 months	85	Gamma
Weight decreased, average duration per event (days) pre-assigned to dox, PFI<6 months	172.70	Gamma
White cell decreased, average duration per event (days) pre-assigned to dox, PFI<6 months	18.10	Gamma
Mean baseline EQ-5D	0.81	Normal
Baseline EQ-5D - coefficient TTD	0.64	Multivariate normal
0-29 days away from death - coefficient TTD	-0.23	Multivariate normal
30-89 days away from death - coefficient TTD	-0.09	Multivariate normal
90-179 days away from death - coefficient TTD	-0.03	Multivariate normal
180-359 days away from death - coefficient TTD	0.00	Multivariate normal
On treatment increment - coefficient TTD	0.09	Multivariate normal

AE disutility - coefficient TTD	-0.02	Multivariate normal
Post-progression decrement - coefficient TTD	-0.03	Multivariate normal
Constant HRQoL model - coefficient TTD	0.20	Multivariate normal
Weight	68.90	Normal
BSA (body surface area), m2	1.70	Normal
Pembrolizumab, admin cost	1921.00	Gamma
Pembrolizumab, administration dose intensity	0.96	Gamma
Pembrolizumab, price/pack	23204.61	Not varied
Lenvatinib, admin cost	0.00	Not varied
Lenvatinib, price/pack	12551.71	Not varied
% receiving doxorubicin	0.74	Beta
Paclitaxel, admin cost	1921.00	Gamma
Paclitaxel, dose intensity	0.99	Gamma
Paclitaxel, cost of vial size 1	110.50	Not varied
Paclitaxel, cost of vial size 2	1500.00	Not varied
Paclitaxel, cost of vial size 3	201.50	Not varied
Paclitaxel, cost of vial size 4	0	Not varied
Doxorubicin, dose intensity	0.99	Gamma
Doxorubicin, cost of vial size 1	150.00	Not varied
Doxorubicin, cost of vial size 2	120.00	Not varied
Doxorubicin, cost of vial size 3	360.00	Not varied
Liposomal doxorubicin, dose intensity	1.00	Gamma
Liposomal doxorubicin, cost of vial size 1	2487.31	Not varied
Paclitaxel/carboplatin, carboplatin, cost of vial size 1	84.00	Not varied
Paclitaxel/carboplatin, carboplatin, cost of vial size 2	203.00	Not varied
Bevacizumab, cost of vial size 1	2090.82	Not varied
Bevacizumab, cost of vial size 2	7707.76	Not varied
Gemcitabine, cost of vial size 1	1000.00	Not varied
Gemcitabine, cost of vial size 2	310.00	Not varied
Gemcitabine, cost of vial size 3	330.00	Not varied

Gemcitabine, cost of vial size 4	350.00	Not varied
Gemcitabine, cost of vial size 5	370.00	Not varied
Gemcitabine, cost of vial size 6	1200.00	Not varied
Gemcitabine, carboplatin, cost of vial size 1	84.00	Not varied
Gemcitabine, carboplatin, cost of vial size 2	203.00	Not varied
Docetaxel, cost of vial size 1	71.00	Not varied
Docetaxel, cost of vial size 2	150.00	Not varied
Docetaxel, cost of vial size 3	309.00	Not varied
Trastuzumab, cost of vial size 1	3762.73	Not varied
Trastuzumab, cost of vial size 2	10506.64	Not varied
Megestrol, cost of tablet size 1	800.02	Not varied
Nivolumab, cost of vial size 1	22567.94	Not varied
Cisplatin, cost of vial size 1	100.00	Not varied
Cisplatin + doxorubicin, cisplatin, cost of vial size 1	200.00	Not varied
Cisplatin + doxorubicin, cisplatin, cost of vial size 2	100.00	Not varied
Vinorelbine, cost of vial size 1	245.00	Not varied
Vinorelbine, cost of vial size 2	1240.00	Not varied
Topotecan, cost of vial size 1	222.00	Not varied
Topotecan, cost of vial size 2	230.00	Not varied
Cyclophosphamide, cost of vial size 1	61.50	Not varied
Cyclophosphamide, cost of vial size 2	153.75	Not varied
Cyclophosphamide, cost of vial size 3	307.50	Not varied
Oxaliplatin, cost of vial size 1	41.18	Not varied
Oxaliplatin, cost of vial size 2	68.80	Not varied
Oxaliplatin, cost of vial size 3	127.82	Not varied
Subsequent therapies - LEN+PEM - % of pts - 2L Doxorubicin	0.50	Beta
Subsequent therapies - LEN+PEM - % of pts - 2L Paclitaxel	0.50	Beta
Subsequent therapies - TPC - % of pts - 2L Doxorubicin	0.50	Beta
Subsequent therapies - TPC - % of pts - 2L Paclitaxel	0.50	Beta
Subsequent therapies - LEN+PEM - % of pts - 3L Doxorubicin	0.50	Beta
Subsequent therapies - LEN+PEM - % of pts - 3L Paclitaxel	0.50	Beta
Subsequent therapies - TPC - % of pts - 3L Doxorubicin	0.50	Beta

Subsequent therapies - TPC - % of pts - 3L Paclitaxel	0.50	Beta
Subsequent therapies - Duration 2L Doxorubicin	70.22	Gamma
Subsequent therapies - Duration 2L Paclitaxel	86.21	Gamma
Subsequent therapies - Duration 3L Doxorubicin	69.08	Gamma
Subsequent therapies - Duration 3L Paclitaxel	71.40	Gamma
% tested with MSI test	0.70	Beta
Of those tested, MSI-H and MMR	0.67	Beta
Of those tested, MMR	0.11	Beta
Mansoor - % MSS	0.70	Beta
Nicoline - % MSS	0.83	Beta
US assumption - % MSS	0.78	Beta
Mansoor - % MSI-H	0.30	Beta
Nicoline - % MSI-H	0.17	Beta
US assumption - % MSI-H	0.22	Beta
Consultation, oncology, unit cost	1921.00	Gamma
Blood count, unit cost	300.00	Gamma
CT scan, unit cost	2411.00	Gamma
GP visit, unit cost	149.09	Not varied
Nurse visit, unit cost	441.00	Not varied
Consultation, oncology, LEN+PEM, PFS	0.23	Not varied
Blood count, LEN+PEM, PFS	0.23	Not varied
CT scan, LEN+PEM, PFS	0.08	Not varied
GP visit, LEN+PEM, PFS	0.11	Not varied
Nurse visit, LEN+PEM, PFS	0.00	Not varied
Consultation, oncology, TPC, PFS	0.23	Not varied
Blood count, TPC, PFS	0.23	Not varied
CT scan, TPC, PFS	0.08	Not varied
GP visit, TPC, PFS	0.11	Not varied
Nurse visit, TPC, PFS	0.00	Not varied
Consultation, oncology, LEN+PEM, PD	0.08	Not varied
Blood count, LEN+PEM, PD	0.00	Not varied
CT scan, LEN+PEM, PD	0.00	Not varied

GP visit, LEN+PEM, PD	0.11	Not varied
Nurse visit, LEN+PEM, PD	0.00	Not varied
Consultation, oncology, PD	0.08	Not varied
Blood count, TPC, PD	0.00	Not varied
CT scan, TPC, PD	0.00	Not varied
GP visit, TPC, PD	0.11	Not varied
Nurse visit, TPC, PD	0.00	Not varied
Anaemia, unit cost	3176.00	Gamma
Decreased appetite, unit cost	1954.00	Gamma
Diarrhoea, unit cost	6756.00	Gamma
Febrile neutropenia, unit cost	3176.00	Gamma
Hypertension, unit cost	1318.00	Gamma
Leukopenia, unit cost	3176.00	Gamma
Lipase increased, unit cost	2910.00	Gamma
Neutropenia, unit cost	3176.00	Gamma
Neutrophil count decreased, unit cost	3176.00	Gamma
Weight decreased	1954.00	Gamma
White blood cell count decreased, unit cost	3176.00	Gamma
Transport costs, cost of transport to and from treatment, unit cost	140.00	Gamma
Transport costs, average hourly wage, unit cost	181.00	Gamma
Patient time spent on administration, assumed time (hours)	3.00	Gamma
Patient time spent on adverse events, assumed time (hours)	4.00	Gamma
Lenvatinib - daily dose 0, % of days	0.12	Dirichlet
Lenvatinib - daily dose 4, % of days	0.02	Dirichlet
Lenvatinib - daily dose 8, % of days	0.09	Dirichlet
Lenvatinib - daily dose 10, % of days	0.21	Dirichlet
Lenvatinib - daily dose 14, % of days	0.23	Dirichlet
Lenvatinib - daily dose 20, % of days	0.33	Dirichlet
Lenvatinib - daily dose 40, % of days	0.00	Dirichlet
BIM - first line treatable, year 1	199.00	Not varied
BIM - first line treatable, year 2	202.00	Not varied
BIM - first line treatable, year 3	207.00	Not varied

BIM - first line treatable, year 4	210.00	Not varied
BIM - first line treatable, year 5	213.00	Not varied
BIM - % treated, first-line advanced population (incident)	0.80	Not varied
BIM - % survival, first-line advanced population (incident)	0.60	Not varied
BIM - % PFI <6 months and pre-assigned to DOX	0.50	Not varied
BIM - systemic treatment rate	0.80	Not varied

Appendix J - Key model assumptions applied in the base case

Table 81: Key model assumptions

Assumption	Rationale
Independent statistical models are used in the long-term extrapolation of OS and PFS	Although the proportional hazards assumption could not be rejected for OS and PFS (Section 8.3.2) ,independent models allow for a better fitting extrapolation in the DOX and LEN+PEM arms individually. This was validated by visual inspection. Clinical experts at the September 2021 Global advisory board (8.1.10) also confirmed that due to the different mechanisms of action, the proportional hazards assumption was unlikely to hold in the long-term.
The loglogistic and lognormal distributions are used to extrapolate OS and PFS	Clinical experts at the September 2021 Global advisory board (Section 8.1.10) suggested that the log-normal and Gompertz distributions were the preferred OS distributions for LEN+PEM and TPC, respectively. In their clinical experience, they believed it unlikely that patients receiving current standard of care (as found in the TPC arm) would live beyond 5 years (as implied by most distributions), and therefore the Gompertz distribution was preferred. Conversely, the clinical experts believed that treatment with immuno-oncology treatments such as pembrolizumab would lead to long-term remission in a proportion of patients as has been shown in other indications; this fact, in combination with the visual fit to Study 309, led the clinical experts to choose the log-normal curve as preferred for LEN+PEM. Based on diagnostics presented in (Section 8.3.2), the lognormal (LEN+PEM) and loglogistic (TPC) distributions presented the lowest AIC/BIC scores for OS, and lognormal (LEN+PEM and TPC) for PFS
A stopping rule of 24 months is applied to PEM	The stopping rule at 24 months applied to PEM is consistent with the expected marketing authorisation for advanced EC following prior systemic therapy, and is consistent with existing stopping rules for PEM in other disease areas (e.g. TA428 [117])
A stopping rule of 24 months is applied to LEN	Expert clinical opinion (Section 8.1.10) suggested LEN is rarely administered once PEM is discontinued.
Vial wastage is accounted for	A conservative approach was adopted in the model base case, where it is assumed that vials will not be shared between patients. Furthermore, patient numbers for LEN+PEM are not expected

	to be large enough to allow vials to be shared between patients within the same treatment centre
HRQoL includes a decrement which reflects patients' proximity to death	In the base case, patient utility is determined by proximity to death rather than progression-based utilities (in addition to other factors described in Section 8.4)
Re-treatment with LEN+PEM is not included	LEN+PEM is not expected to be reimbursed following prior treatment with LEN+PEM (i.e. retreatment), and is therefore not included in the model base case

Abbreviations: AIC, Akaike's Information Criteria; BIC, Bayesian Information Criteria; HRQoL, health-related quality of life; LEN, lenvatinib; OS, overall survival; PEM, pembrolizumab; PFS, progression-free survival; TPC, treatment of physician's choice.

Appendix K – Summary of Efficacy Results of Lenvatinib Plus Pembrolizumab and Pembrolizumab Monotherapy in dMMR Participants with Advanced Endometrial Carcinoma

As per the request of the DMC, below is presented the summary efficacy results of Len + Pem and Pem monotherapy in dMMR participants with advanced EC (Table 82)

Table 82 Summary of Efficacy Results of Len Plus Pem and Pem Monotherapy in dMMR Participants with Advanced EC

Parameters	Study 309/KN-775[a] Combination Therapy	Study 309/KN-775[a] TPC (Chemotherapy)	KN158 Pembrolizumab Monotherapy (data cut off date: December 6, 2018)	KN158 Pembrolizumab Monotherapy (data cut off date: October 5, 2020)
No. of participants	MSI-H/dMMR (N = 65)	MSI-H/dMMR (N = 65)	MSI-H/dMMR (N = 49)	MSI-H/dMMR (N = 79)
ORR, (%) (95% CI)	40.0 (28.0, 52.9)	12.3 (5.5, 22.8)	57.1 (42.2, 71.2)	48.1 (36.7, 59.6)
CR, n (%)	9 (13.8)	2 (3.1)	8 (16.3)	11 (13.9)
PR, n (%)	17 (26.2)	6 (9.2)	20 (40.8)	27 (34.2)
DOR (months) Median (Range: min, max)	n=26[b] NR (2.1+ - 20.4+)	n=8[b] 4.1 (1.9+ - 15.6+)	n=28[b] NR (2.9, 27.0+)	n=38[b] NR (2.9 - 49.7+)[c]
Median PFS (months) (95% CI)	10.7 (5.6, NR)	3.7 (3.1, 4.4)	25.7 (4.9, NE)	13.1 (4.3, 34.4)
Median OS (months) (95% CI)	NR (NR, NR)	8.6 (5.5, 12.9)	NR (27.2, NE)	NR (27.2, NR)
Follow-up duration (months) median (range)	13.5 (0.4, 25.1)	8.8 (1.0, 23.8)	24.4 (0.5, 34.2)	16.5 (0.5, 56.1)

Footnote: [a] Data cutoff date: 26-OCT-2020.
[b] Number of participants with responses.
[c] "+" indicates there is no progressive disease by the time of last disease assessment.
Abbreviations: CI, confidence interval; CR, complete response; dMMR, mismatch repair deficient; DOR, duration of response; max, maximum; min, minimum; MSI-H, microsatellite instability-high; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TPC, treatment of physician's choice.
Source: [118-120]Source: [118-120]