Medicinrådet

Bilag til Medicinrådets anbefaling vedr. durvalumab, dostarlimab og pembrolizumab i kombination med kemoterapi til behandling af avanceret eller tilbagevendende dMMR eller pMMR kræft i livmoderslimhinden (endometrie-cancer)

Vers. 1.0

Bilagsoversigt

1. Ansøgers (AstraZeneca) notat til Rådet vedr. durvalumab
2. Ansøgers (GSK) notat til Rådet vedr. dostarlimab
3. Ansøgers (MSD) notat til Rådet vedr. pembrolizumab
4. Forhandlingsnotat fra Amgros vedr. durvalumab, dostarlimab og pembrolizumab
5. Ansøgers endelige ansøgning vedr. durvalumab
6. Ansøgers endelige ansøgning vedr. dostarlimab
7. Ansøgers endelige ansøgning vedr. pembrolizumab

Til Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

14.04.2025

Note on the Medicines Council's draft assessment of durvalumab plus platinum-based chemotherapy followed by maintenance durvalumab in primary advanced or recurrent mismatch repair deficient (dMMR) endometrial cancer

AstraZeneca appreciates the opportunity to comment on the draft assessment report submitted for review. We believe the assessment addresses the relevant aspects and, therefore, have no additional comments. We would like to thank the secretariat's role in facilitating this process and the communication around this and look forward to the Council's decision in May.

Kind regards,
Sara Vinther

Market Access Manager
AstraZeneca A/S

11.04.2025

Til Medicinrådet

Hermed GSKs tilbagemelding på Medicinrådets udkast til vurdering af dostarlimab i kombination med carboplatin og paclitaxel til patienter med pMMR endometriecancer

Vi takker for muligheden for at kommentere på Medicinrådets vurdering af dostarlimab i kombination med carboplatin og paclitaxel til behandling af patienter med pMMR endometriecancer. Vi ønsker hermed at udtrykke vores accept af vurderingsrapporten.

Det er glædeligt at se, at I anerkender, at behandlingen med dostarlimab i kombination med carboplatin og paclitaxel har vist sig at forlænge progressionsfri overlevelse (PFS) samt den samlede overlevelse (OS) hos patienter med avanceret eller tilbagevendende pMMR endometriecancer sammenlignet med placebo i kombination med kemoterapi. Vi værdsætter også, at patienternes helbredsrelaterede livskvalitet ikke blev væsentligt påvirket negativt af behandlingen, og at dostarlimab + kemoterapi er blevet vurderet som klinisk ligeværdig med pembrolizumab + carboplatin og paclitaxel.

[redacted]

Sammenfattende støtter vi Medicinrådets vurdering af dostarlimab i kombination med carboplatin og paclitaxel som en værdifuld behandlingsmulighed for patienter med pMMR endometriecancer og ser frem til, at denne behandling kan implementeres i dansk klinisk praksis på et fornuftigt økonomisk fundament.

På vegne af GSK,

Christina Lotzkat Matzen, Market Access Manager

Den 11. april 2025

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Til: Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

Notat vedr. Medicinrådets vurdering af pembrolizumab i kombination med kemoterapi til behandling af avanceret eller tilbagevendende endometriecancer.

MSD Danmark vil hermed takke for, at Medicinrådet endnu engang har formået at optimere en proces, og for den kondenserede vurderingsrapport, der indeholder alle relevante lægemidler og oplysninger. Og for at sekretariatet har holdt os fint orienteret om processen undervejs.

Vi noterer os, at Medicinrådet vurderer, at pembrolizumab i kombination med kemoterapi ser ud til at have samme effekt som dostarlimab i kombination med kemoterapi til patienter med både dMMR og pMMR. Vi mener, at det i den sammenhæng er en meget vigtig nuance, at de tilsyneladende ensartede effekter er opnået efter temmelig forskellige lægemiddel-eksponeringer: [redacted]. Patienter behandlet med dostarlimab havde en median behandlingsvarighed på 43 uger (dMMR + pMMR), svarende til ca. 14 serier dostarlimab[2]. Forskellen skyldes, at i pembrolizumab-studiet (NRG-GY018) kunne patienterne modtage behandling til progression eller max 20 serier i alt (svarende til 2 år), og i RUBY-1 til progression eller i max. tre år.

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[1] MSD data-on-file
[2] Powell MA, Bjørge L, Willmont L, et al. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin–paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. Ann Oncol. 2024;35(8):728-738. doi:10.1016/j.annonc.2024.05.546

Medicinrådet begrænser typisk sine anbefalinger af immunterapier til max. 2 år, hvorfor regionernes pris-/omkostningssammenligninger også typisk regner med denne behandlingsvarighed. Her ser vi en risiko for, at beregningerne bliver meget usikre, og ikke afspejler de omkostninger, der reelt ville være forbundet med at opnå de effektstørrelser, som er rapporteret fra de to studier.

Medicinrådets kliniske ligestillinger er i denne – og mange andre sager – baseret på indirekte evidens, og indebærer derfor en del usikkerhed. Man kan sige, at lægemidlerne er lige gode indenfor en vis klinisk margin. Derfor vil vi opfordre til, at der tages højde for usikkerhederne i de økonomiske sammenligninger og i sådanne situationer også ligestiller klinisk ligeværdige lægemidler indenfor en vis økonomisk margin, for på den måde at opnå proportionalitet mellem den kliniske og den økonomiske sammenligning.

Venlig hilsen

Simon Leth
Chef for sundhedsøkonomi, MSD Danmark

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10.04.2025

DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	23.04.2025
Leverandør	AstraZeneca, GlaxoSmithKline (GSK), MSD
Lægemiddel	Jemperli (dostarlimab), Imfinzi (durvalumab), Keytruda (pembrolizumab),
Ansøgt indikation	Imfinzi, Jemperli og Keytruda i kombination med kemoterapi til behandling af avanceret eller tilbagevendende mis-match-repair deficient (dMMR) eller mismatch-repair proficient (pMMR) kræft i livmoderslimhinden (endometriecancer)
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse - fast track

Prisinformation

Amgros har følgende priser på lægemidlerne:

Tabel 1: Priser

Lægemiddel	Styrke og pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Jemperli (dostarlimab)	500 mg, 1 stk.	42.427,75	[redacted]	[redacted]
Keytruda (pembolizumab)	25 mg/ml, 4 ml	21.573,58	[redacted]	[redacted]
Imfinzi (durvalumab)	50 mg, 10 ml	17.307,33	[redacted]	[redacted]

Aftaleforhold

Amgros har aftaler med alle tre leverandører, da alle tre lægemidler indgår i udbuddet for immunterapier. Der er mulighed for prisregulering i disse aftaler. Baseret på de kommende indikationer, som bliver ansøgt til vurdering i Medicinrådet, planlægges, hvornår der skal åbnes for en prisregulering.

Konkurrencesituationen

Medicinrådets vurdering omfatter de tre lægemidler, Imfinzi, Jemperli og Keytruda i kombination med kemoterapi. De vurderes enten til patienter med dMMR endometriecancer (Imfinzi og Keytruda) eller pMMR endometriecancer (Jemperli og Keytruda).

Tabel 2: Sammenligning af lægemiddeludgifter (uden kemoterapi) pr. patient.

Lægemiddel	Styrke og pakningstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Jemperli Opstartsår	500 mg, 1 stk.	500 mg i.v. hver 3. uge i 6 serier og herefter 1.000 mg i.v. hver 6. uge	[redacted]	[redacted]
Jemperli Vedligeholdelsesår	500 mg, 1 stk.	1.000 mg i.v. hver 6 uge	[redacted]	[redacted]
Keytruda	20 mg/ml, 4 ml	2 mg/kg i.v. hver 3. uge eller 4 mg/kg hver 6.uge	[redacted]	[redacted]
Imfinzi Opstartsår	50 mg/ml	1.120 mg i.v. hver 3. uge de første 6 cykler. Derefter 1.500 mg i.v. hver 4 uge	[redacted]	[redacted]
Imfinzi Vedligeholdelsesår	50 mg/ml	1.500 mg i.v. hver 4. uge	[redacted]	[redacted]

*Patientvægt 68,9 kg

Opsummering:

Der kan muligvis komme bedre priser i forbindelsen med en kommende prisregulering baseret på ansøgning til disse indikationer samt de andre indikationer, som også er ansøgt i Medicinrådet. Tidspunktet for prisreguleringen er endnu ikke fastlagt.

Application for the assessment of durvalumab plus platinum-based chemotherapy followed by maintenance durvalumab in primary advanced or recurrent mismatch repair deficient (dMMR) endometrial cancer

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

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Tables and Figures

Abbreviations

AE	Adverse event
AUC	Area under the concentration–time curve
BICR	Blinded Independent Central Review
CI	Confidence interval
CP	Carboplatin-paclitaxel
CTCAE v4.03	Common Terminology Criteria for Adverse Events version 4.03
DCO	Data cut off
DGCG	Danish Gynaecological Cancer Group
DMC	Danish Medicines Council
dMMR	Mismatch repair deficient
EC	Endometrial cancer
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EORTC-QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
FIGO	International Federation of Gynaecology and Obstetrics
HR	Hazard Ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
IA	Interim analysis
IVRS	Interactive Voice Response System
ITT	Intention-to-treat

KM	Kaplan Meier
MMR	Mismatch repair
MSI-H	Microsatellite instability high
pMMR	Mismatch repair proficient
OS	Overall survival

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Imfinzi
Generic name	Durvalumab
Therapeutic indication as defined by EMA	Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with: • Durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) • Durvalumab in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR).
Marketing authorization holder in Denmark	AstraZeneca AB SE-151 85 Södertälje Sverige
ATC code	L01FF03
Combination therapy and/or co-medication	Platinum-based chemotherapy Carboplatin and paclitaxel
Date of EC approval	August 14th 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	**Non-Small Cell Lung Cancer (NSCLC)** Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy (see section 5.1). Durvalumab in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations. **Small Cell Lung Cancer (SCLC)**

Overview of the medicine	
	Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC). **Biliary Tract Cancer (BTC)** Durvalumab in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC). **Hepatocellular Carcinoma (HCC)** Durvalumab as monotherapy is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC). Durvalumab in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).
Other indications that have been evaluated by the DMC (yes/no)	Recommendations on: **Non-Small Cell Lung Cancer (NSCLC)** Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy (see section 5.1). **Biliary Tract Cancer (BTC)** Durvalumab in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC). **Small Cell Lung Cancer (SCLC)** Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC). **Hepatocellular Carcinoma (HCC)** Durvalumab as monotherapy is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC). Durvalumab in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).
Joint Nordic assessment (JNHB)	Would not be suitable for JNHB assessment as already nationally recommended in Norway and Sweden under the PD-(L)1 simplification or general recommendation. Not yet nationally recommended/funded in Finland.
Dispensing group	BEGR

Overview of the medicine	
Packaging – types, sizes/number of units and concentrations	Vial of 2,4 ml and 10 ml. 50 mg/ml

2. Summary table

Summary	
Indication relevant for the assessment	Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with: • Durvalumab as monotherapy in endometrial cancer that is dMMR This application focuses on Durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR). Durvalumab in combination with carboplatin and paclitaxel also received approval where maintenance treatment constitutes durvalumab in combination with olaparib for endometrial cancer that is mismatch repair proficient (pMMR). As the pMMR population will fit into the standard process with a cost effectiveness analysis, this will be handled in a separate assessment. Both the dMMR and pMMR subgroups were included in the DUO-E study.
Dosage regiment and administration	1120 mg IV every 3rd week (+ standard of care every 3rd week) in the chemotherapy phase. 1500 mg every 4th week in the maintenance phase.
Choice of comparator	Carboplatin plus paclitaxel Dosage: Carboplatin AUC 5 mg/mL/min Paclitaxel 175 mg/m^2 Q3W for 6 cycles Carboplatin plus paclitaxel is the comparator in DUO-E, the key study for this indication, and is a standard of care for first-line advanced or recurrent endometrial cancer in Denmark. Dostarlimab was recommended in Denmark for advanced or recurrent endometrial cancer that is dMMR/MSI-H in late August 2024. Durvalumab is considered to have similar efficacy to dostarlimab within this indication, which is supported by an indirect comparison shown in section 7. 500 mg Q3W for 4 cycles, then 1000mg Q6W thereafter.

Summary	
Prognosis with current treatment	A range of treatment options may be considered for patients with advanced or recurrent EC. These include radiotherapy (RT), systemic therapies (such as chemotherapy), hormonal therapy in some cases or immunotherapy. Of these treatments, platinum-based chemotherapy with carboplatin in combination with paclitaxel is currently considered the standard of care (SoC) first-line (1L) treatment for advanced and recurrent EC. (1, 2) Evidence for the safety and efficacy of this regimen in the advanced and recurrent EC setting was demonstrated in the GOG-209 trial, which demonstrated that paclitaxel and carboplatin were associated with non-inferior efficacy, but a more favourable HRQoL and toxicity profile, compared to paclitaxel, doxorubicin and cisplatin (TAP) (3) . Despite the availability of these 1L therapies, approximately half the patients experience disease progression within one year of initiating therapy with carboplatin and paclitaxel, and further platinum-based chemotherapy (4) is often only considered for patients who are sensitive to platinum-based therapy (relapsed more than six months since their last platinum-based regimen). (1, 2) In addition, the absence of a maintenance regimen following 1L therapy often results in a limited treatment response, leading to disease progression and the need for further therapy in the second-line (2L) setting. (1, 2) Considering this, there is a substantial unmet need for a novel, highly effective and well-tolerated 1L therapy for EC that enhances progression free survival (PFS) and overall survival (OS) and thereby reduces the clinical, humanistic and economic burden of primary advanced and recurrent EC. For patients with first-line advanced or recurrent EC, median overall survival was approx. 3 years (3, 5) . For deficient mismatch repair (dMMR) patients*, evidence from trials shows a median survival of 2-2.5 years (6, 7) .This is confirmed in the DUO-E trial with the control arm demonstrating median OS of 23.7 months (16.9-NR) (8). **Various genomic alterations have been reported to contribute to an increased risk of EC. (9) As such, molecular classification of EC now represents a key stage of EC diagnosis and clinical decision-making, including determination of a patient's mismatch repair (MMR) status. Determination of MMR status divides patients into proficient MMR (pMMR) and deficient MMR (dMMR) EC and is currently considered an important prognostic factor. (1, 2, 9, 10)*
Type of evidence for the clinical evaluation	Head-to-head study (NCT04269200). DUO-E is a pivotal, Phase III, randomised, multicentre, double-blind, placebo-controlled study of first-line platinum-based

Summary	
	chemotherapy in combination with durvalumab, followed by maintenance durvalumab with or without olaparib in patients with newly diagnosed advanced or recurrent endometrial cancer. All patients had to have evidence of histologically confirmed, advanced (Stage III or IV) or recurrent high-grade epithelial endometrial cancer including carcinosarcomas. The NCT number of the trial: NCT04269200. (8) Pre-planned subgroup analyses were performed by MMR status given recent data in the disease setting, and randomization was stratified by MMR status. The MMR system is a cellular system that, among other things, repairs errors in the DNA strands (11). This application covers only the treatment with durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab, in the deficient MMR (dMMR) population. Consistent with the results of RUBY Part 1 and NRG-GY018 within the same population as DUO-E, the results from DUO-E for each treatment arm vs SoC showed a lower risk of disease progression (as assessed by the investigator) or death, irrespective of MMR status with the greatest benefit of durvalumab as monotherapy seen in the dMMR population. (8, 12, 13)
Most important efficacy endpoints (Difference/gain compared to comparator)	Durvalumab compared to CP: Subgroup analyses by MMR status showed that in the dMMR population, a clinically meaningful PFS benefit was observed for durvalumab + CP versus Placebo + CP (HR, 0.42; 95% CI, 0.22, 0.80), with approximately 68% of patients in the dMMR population remaining progression-free at 18 months compared with approximately 32% in the placebo + CP treated population. (8) In support of the PFS findings, a significant improvement in OS was observed for the durvalumab + CP arm compared with the placebo + CP arm in the dMMR population (HR 0.34; 95% CI 0.13, 0.79). (14) Durvalumab compared to dostarlimab: The anchored ITC results compared to dostarlimab + CP, without adjustment for differences in the trial populations except for MSI-H status, suggest that there is no significant difference between treatments in terms of PFS [redacted]

Summary	
Most important serious adverse events for the intervention and comparator	Serious adverse events in the durvalumab treatment arm in DUO-E occurred in 31.1% of patients. Serious adverse events in the dostarlimab treatment arm (dMMR/MSI-H) in RUBY occurred in 37.8% of patients.
Impact on health-related quality of life	Clinical documentation: EQ-5D-5L 
Type of economic analysis that is submitted	NA
Data sources used to model the clinical effects	NA
Data sources used to model the health-related quality of life	NA
Life years gained	NA
QALYs gained	NA
Incremental costs	NA
ICER (DKK/QALY)	NA
Uncertainty associated with the ICER estimate	NA
Number of eligible patients in Denmark	The DUO-E study excluded early-stage patients. Only patients with evidence of histologically confirmed, advanced (Stage III or IV) or recurrent high-grade epithelial endometrial cancer including carcinosarcomas were enrolled. (8) Therefore, only stage I & II patients, who later recur would be eligible for the intervention. In a large National cohort study Øtoft et al 2019 and Øtoft et al 2020 investigated recurrence patterns in Stage I & II endometrial cancer patients and demonstrated a total recurrence rate for Stage I & II patients of 9.7 % and 23.6 % respectively. (15, 16) With an average annual incidence of stage I & II endometrial cancer patients of 397 and 31 in Denmark (17), AstraZeneca estimates that 39 stage I and 7 stage II patients will experience a recurrence and become eligible for the intervention.

Summary	
	In addition, 91 stage III & IV patients meet the DUO-E eligibility criteria resulting in an estimated annual patient pool of 137 patients with advanced (Stage III or IV) or recurrent epithelial endometrial cancer. (17) Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by treatment with Durvalumab as monotherapy in endometrial cancer that is dMMR According to the literature, 22-30% of endometrial cancer cases have dMMR, regardless of disease stage (18, 19), and this prevalence has been used in previously assessment of dostarlimab. Applying this prevalence to the estimated patient pool of 137 results in an estimated 30 – 41 dMMR advanced (Stage III or IV) or recurrent epithelial endometrial cancer patients
Budget impact (in year 5)	NA

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

3.1 The medical condition

Uterine cancer is the 5th most common form of cancer amongst women in Denmark and the most frequent form of gynaecological cancer. The most common form of uterine cancer is cancer of the lining of the uterus (endometrial cancer) (20)

Approximately 21–25% of patients with EC are diagnosed at Stages III–IV.(21, 22) Corresponding numbers from DGCD Annual Report 2021/2022 demonstrates that 15.8% - 19.4% of endometrial carcinoma patients with known stage are diagnosed with stage III/IV disease (17). In addition, between 15.5%–17.1% of women with EC experience recurrent disease, the majority of whom have advanced disease (Stage III–IV). (23, 24) Specifically for Stage I dMMR Endometrial cancer patients Lindemann et al 2024 demonstrated 20% recurrence rate. (25)

Both advanced and recurrent EC are associated with significant morbidity and mortality, such that only 17–22% of patients with Stage IV EC survive longer than 5 years. (26-29)

Moreover, the health-related quality of life (HRQoL) impact of EC is often most pronounced in patients with advanced and recurrent disease due to the poor prognosis, debilitating symptoms and deteriorations in physical functioning during later disease stages compared to early stage EC. (29, 30)

Patients with advanced and recurrent EC often report that their EC has a profound negative impact on their health-related quality of life (HRQoL), primarily driven by the life-limiting impacts of treatment and the psychological burden attributed to living with a life-threatening disease with a bleak prognosis.(4, 29-33)

The pathophysiology of EC is complex. Key risk factors include obesity, older age and increased exposure to oestrogen (e.g. diabetes and post-menopausal hormone therapies). (34-36) Various genomic alterations have also been reported to contribute to an increased risk of EC.(34) As such, molecular classification of EC now represents a key stage of EC diagnosis and clinical decision-making, including determination of a patient's mismatch repair (MMR) status. Determination of MMR status divides patients into MMR proficient (pMMR) and MMR deficient (dMMR) EC and is currently considered an important prognostic factor. (1, 34, 37, 38)

Deficient mismatch repair (dMMR) is a condition associated with endometrial cancer where the DNA mismatch repair system is not functioning properly specifically in microsatellite regions. MSI-H is one of the consequences of dMMR and refers to the accumulation of mutations in these regions (39). dMMR in endometrial cancer is often due to mutations in one of the mismatch repair genes, such as MLH1, MSH2, MSH6, and PMS2. These mutations can be sporadic or hereditary. (40)

Endometrial cancers with dMMR tend to have a distinct clinical behavior. They are often associated with a higher tumor mutation burden and recent data suggest MMR status to predict response to immune checkpoint inhibitors (8, 13)

3.2 Patient population

Around 800 women are diagnosed with uterine cancer every year in Denmark, with the most frequent form (> 90%) being cancer of the uterine lining (EC). The disease typically affects older women (median age 63 years), and there are almost 11,000 patients currently living after receiving the diagnosis. (20, 41)

The majority of endometrial carcinoma patients are diagnosed at an early stage (Stage I or II) ranging between 69 % and 74% in the years 2019/20 to 2021/22 in Denmark. A relatively better prognosis is associated with earlier stages with reported 5-year survival rates for Stage I & II corpus cancer (carcinoma) patients of 86 % (95% CI: 84 – 87) and 75 % (95% CI: 68 – 80) respectively. In contrast, Stage III & IV corpus cancer (carcinoma) patients demonstrate survival rates of 48% (95% CI: 43 – 54) and 30% (95% CI: 20 - 41) respectively. (17)

The DUO-E study excluded early-stage patients. Only patients with evidence of histologically confirmed, advanced (Stage III or IV) or recurrent high-grade epithelial

endometrial cancer including carcinosarcomas were enrolled (8). Therefore, only stage I & II patients, who later recur would be eligible for the intervention.

In a large National cohort study Øtoft et al 2019 and Øtoft et al 2020 investigated recurrence patterns in Stage I & II endometrial cancer patients and demonstrated a total recurrence rate for Stage I & II patients of 9.7 % and 23.6 % respectively. (15, 16)

With an average annual incidence of stage I & II endometrial cancer patients of 397 and 31 in Denmark (17) AstraZeneca estimates that 39 stage I and 7 stage II patients will experience a recurrence and become eligible for the intervention.

In addition, 91 stage III & IV patients meet the DUO-E eligibility criteria resulting in an estimated annual patient pool of 137 patients with advanced (Stage III or IV) or recurrent epithelial endometrial cancer. (17)

Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by treatment with Durvalumab as monotherapy in endometrial cancer that is dMMR

According to the literature, 22-30% of endometrial cancer cases have dMMR, regardless of disease stage (18, 19), and this prevalence has been used in previously assessment of dostarlimab. Applying this prevalence to the estimated patient pool of 137 results in an estimated 30 – 41 dMMR advanced (Stage III or IV) or recurrent epithelial endometrial cancer patients.

In Table 1 the incidence and prevalence of endometrial cancer is presented. The subgroup of the population relevant to this application is the dMMR population. There is no official data on the incidence and prevalence of the dMMR populations, however Table 2 present estimated numbers of patients eligible for treatment with durvalumab plus carboplatin and paclitaxel which is in line with previous Danish Medicines Council (DMC) assessment of the specific subgroup. The estimated number of new patients is 30 per year. Thus, in year 2 and the coming years this will sum up to 60 patients per year in line with the treatment cap of two years the DMC have set for dostarlimab in this indication.

Table 1 Incidence of endometrioid carcinoma and prevalence of corpus cancer in the past 5 years. The Incidence is adapted from (17) while the prevalence is adapted from (41)

Year	2017/18	2018/19	2019/20	2020/21	2021/22
Incidence of endometrioid carcinoma in Denmark	638	653	601	642	537
Year	**2018**	**2019**	**2020**	**2021**	**2022**
Total Prevalence Corpus Cancer in Denmark	380,4	384.6	387.6	388.6	388.5

Year	2017/18	2018/19	2019/20	2020/21	2021/22
(Proportion per 100.000, Females)					

Table 2 Estimated number of patients eligible for treatment. From (42)

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	30	60	60	60	60

3.3 Current treatment options

The treatment of endometrial cancer is described in clinical guidelines from the Danish Gynaecological Cancer Group (DGCG)(43). Most patients with early-stage endometrial cancer are treated with curative surgery (44, 45). The treatment algorithm hereafter for primary advanced or recurrent endometrial cancer is illustrated in Figure 1 Overview of treatment algorithm for patients with primary advanced or recurrent endometrial cancer including suggestion of where durvalumab fits in (yellow). Figure 1 .

According to the guideline from DGCG, advanced and recurrent endometrial cancer can be treated with surgery and/or radiotherapy, supplemented with carboplatin and paclitaxel (CP) for up to 6 cycles or Dostarlimab plus CP, depending on the MMR status(44). The aim of the treatment is to prolong survival by limiting further disease progression. The DGCG guidelines were updated in October 2023 to include dostarlimab as a 1st line treatment, depending on MMR status, in combination with carboplatin and paclitaxel. Until then the standard treatment choice for patients with primary disseminated endometrial cancer was carboplatin plus paclitaxel (43).

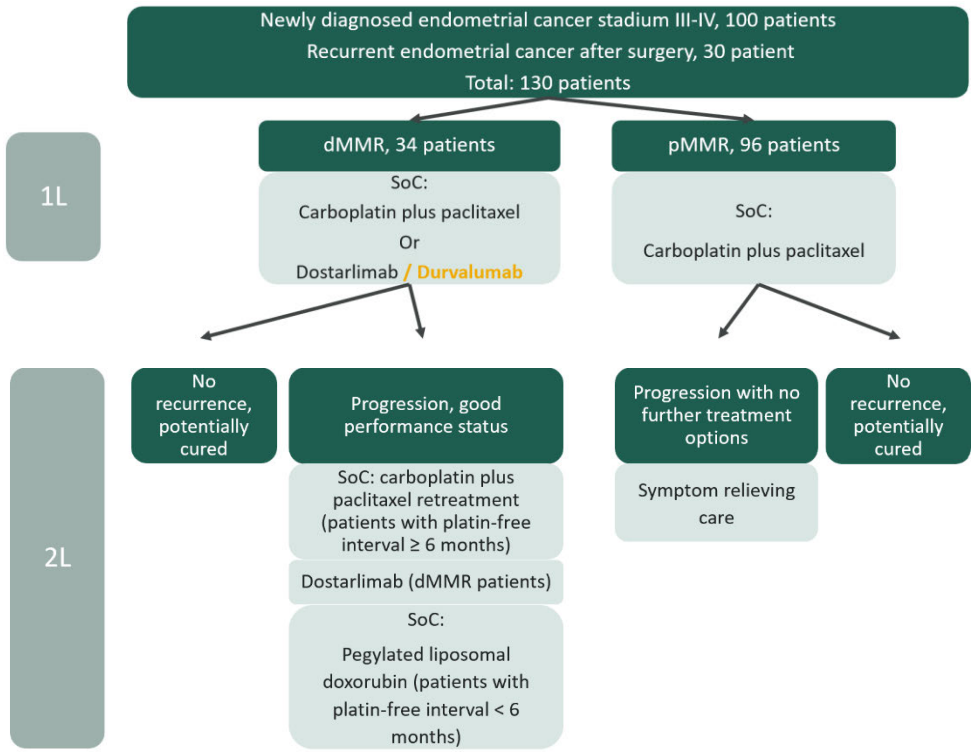


Figure 1 Overview of treatment algorithm for patients with primary advanced or recurrent endometrial cancer including suggestion of where durvalumab fits in (yellow). Source: Created by AstraZeneca based on DGCG updated guidelines (44)

If patients progress with a good performance status, it is expected that they will receive retreatment with CP for patients with a platinum-free interval ≥6 months and pegylated liposomal doxorubicin for patients with a platinum-free interval <6 months. Remaining (patients without good performance score) will receive symptom-relieving care.

3.4 The intervention

Durvalumab is a high-affinity, human, recombinant monoclonal antibody of the immunoglobulin G (IgG) 1 kappa subclass that selectively blocks the interaction of PD-L1 with PD-1 and CD80 on immune cells. (46) *In vivo*, studies demonstrate that durvalumab inhibits tumour growth in co-engrafted human tumour and immune cell xenograft mouse models via a T-cell-dependent mechanism. Based on these data, durvalumab, by binding to PD-L1, is expected to stimulate the patient's anti-tumour response.(46) Moreover, durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity on effector T-cells following the expression of PD-L1 on activated T-cells, thus preventing T-cell depletion. (47, 48)

Table 3. Overview of intervention

Overview of intervention	
Indication relevant for the assessment	Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with: • Durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR) • Durvalumab in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR). This application focuses on Durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR). Additional analyses of clinical outcome in relevant molecular subgroups in the pMMR population are being investigated, and we are planning on submitting a request for assessment separately for the pMMR population, as this will fit into the standard process with a cost effectiveness analysis. This is despite of these two subgroups are both presented in the DUO-E study.
ATMP	NA
Method of administration	Intravenous use. It is to be administered as an intravenous infusion solution over 1 hour
Dosing	1,120 mg intravenously once every 3 weeks for six cycles, followed by maintenance durvalumab 1,500 mg intravenously once every 4 weeks
Dosing in the health economic model (including relative dose intensity)	NA
Should the medicine be administered with other medicines?	Given in combination with carboplatin (AUC 5) and paclitaxel (175 mg/m^2) for 6 cycles (see Table 4)
Treatment duration / criteria for end of treatment	The expert committee for gynaecologic cancers in DMC state that unless there is a compelling clinical reason to continue beyond 24 months, patients with dMMR would be stopped at 24 months. (42) The expectation is that this capping of treatment will be applied for durvalumab 1L dMMR as well.
Necessary monitoring, both during administration and during the treatment period	No

Overview of intervention	
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	dMMR test is needed. These tests are already standard of care in Danish clinical practice.
Package size(s)	2.4 mL of concentrate in vial containing 120 mg durvalumab. Pack size of 1 vial. 10 mL of concentrate in a vial containing 500 mg durvalumab. Pack size of 1 vial.

3.4.1 The intervention in relation to Danish clinical practice

As investigated in the DUO-E trial, durvalumab is an add on to existing standard treatment (carboplatin and paclitaxel for 6 cycles) for patients with dMMR EC in the 1L setting. DMC recommended dostarlimab in late August 2024 in the 1L setting. (20) Durvalumab is expected to have the same placement in guidelines if recommended by DMC.

The biomarker testing of dMMR is being performed at the time of diagnosis in Danish clinical practice (20).

3.5 Choice of comparator(s)

As an established standard of care for patients with first line primary advanced or recurrent endometrial cancer (regardless of MMR status), carboplatin in combination with paclitaxel is considered a relevant comparator for Imfinzi in combination with carboplatin and paclitaxel for dMMR patients. As another PD-(L)1 inhibitor, recently recommended for use in the same setting for patients with dMMR/MSI-H, dostarlimab is considered to be a relevant comparator. Both head-to-head data versus carboplatin plus paclitaxel and an indirect treatment comparison (ITC) versus dostarlimab will be presented.

Table 4. Overview of carboplatin + paclitaxel

Overview of comparator	
Generic name	Carboplatin + paclitaxel
ATC code	L01XA02 / L01CD01

Overview of comparator	
Mechanism of action	Carboplatin interferes with DNA intra-strand and inter-strand crosslinks in cells exposed to the drug. DNA reactivity has been correlated with cytotoxicity. Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability inhibits the normal dynamic reorganisation of the microtubule network, which is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.
Method of administration	Intravenous infusion
Dosing	Carboplatin AUC 5 mg/mL/min + paclitaxel 175 mg/m2 Q3W
Dosing in the health economic model (including relative dose intensity)	NA
Should the medicine be administered with other medicines?	Carboplatin No concomitant medicines or premedication specified in the SmPC Paclitaxel Due to the risk of hypersensitivity reactions, all patients must be premedicated with glucocorticoid (e.g., dexamethasone 20 mg PO), antihistamine (e.g., diphenhydramine 50 mg IV) and H2-receptor antagonist (e.g., cimetidine 300 mg IV or ranitidine 50 mg IV).
Treatment duration/ criteria for end of treatment	Up to 6 cycles
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Carboplatin (1-pack concentrate for solution for infusion): • 150 mg (10 mg/ml x 15 ml) • 450 mg (10 mg/ml x 45 ml) Paclitaxel (1-pack concentrate for solution for infusion): • 100 mg (6 mg/ml x 16,7 ml) • 150 mg (6 mg/ml x 25 ml) • 300 mg (6 mg/ml x 50 ml)

Table 5. Overview of dostarlimab

Overview of comparator	
Generic name	Dostarlimab
ATC code	L01FF07
Mechanism of action	Dostarlimab is a humanised mAb of the IgG4 isotype that binds to PD-1 receptors and blocks the interactions of binding with its ligands PD-L1 and PD-L2. The inhibition of PD-1 pathway-mediated immune response results in reactivation of T-cell function such as proliferation, cytokine production, and cytotoxic activity. Dostarlimab potentiates T-cell responses, including anti-tumour immuno responses through blockade of PD-1 binding to PD-L1 and PD-L2. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.
Method of administration	Intravenous infusion
Dosing	500 mg Q3W for 6 cycles, followed by 1000 mg Q6W thereafter
Dosing in the health economic model (including relative dose intensity)	NA
Should the medicine be administered with other medicines?	Given in combination with carboplatin (AUC 5) and paclitaxel (175 mg/m^2) for 6 cycles (see Table 4)
Treatment duration/ criteria for end of treatment	Administration of dostarlimab should continue until disease progression or unacceptable toxicity, or for a duration of up to 3 years. DMC recommends that dostarlimab is given for a maximum of 24 months from the first dose.
Need for diagnostics or other tests (i.e. companion diagnostics)	dMMR or MSI-H is needed. These tests are already standard of care in Danish clinical practice.
Package size(s)	1-pack concentration for solution for infusion: 500 mg (50 mg/ml x 10 ml)

3.6 Cost-effectiveness of the comparator(s)

Carboplatin + paclitaxel are two generic compounds that have been used to treat endometrial and ovarian cancer for over two decades. Carboplatin + paclitaxel has therefore not been evaluated by DMC, however it has been used as a comparator in the assessment of dostarlimab in both first- and second-line endometrial cancer and is also a

current standard of care. The cost-effectiveness of dostarlimab in combination with carboplatin and paclitaxel for advanced or recurrent dMMR/MSI-H endometrial cancer was assessed by DMC and received a positive recommendation.(42)

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 6 presents the outcome measures included in the present application and the definitions and method of measurement for each outcome. The rationale for including each outcome and the validity of the outcomes is presented later in this section.

Table 6 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression-free survival (PFS), dMMR population	Median duration of follow-up for PFS in censored patients with dMMR was 10.2 months for the control arm and 15.5 months for the durvalumab plus CP arm	Time from randomization to date of objective disease progression or death, regardless of patient withdrawal or whether a patient received another anticancer therapy prior to progression	Investigator-assessed using RECIST 1.1.
Overall survival (OS), dMMR population	Median duration of follow-up for OS in censored patients with dMMR was 18.4 months for the control arm and 19.1 for the durvalumab plus CP arm	OS is defined as the time from randomization to death from any cause.	Time measured from randomization until death from any cause.

* Time point for data collection used in analysis (follow up time for time-to-event measures)

The dual primary endpoints (PFS for durvalumab + CP vs. placebo + CP) were assessed according to RECIST 1.1 guidelines, assessed by the investigator, as this was a double-blind study, but had a sensitivity analysis with Blinded Independent Central Review (BICR) assessments to ascertain bias.

Tumour assessments were performed at baseline, every 9 weeks (±1 week) for 18 weeks, and every 12 weeks (±1 week) thereafter until objective radiologic disease progression. Following disease progression, patients were followed as per local clinical guidelines, but scheduled for assessment every 12 weeks for second progression (PFS2) and every 2 months for survival. Preferred assessment methods included CT or MRI scans of the chest, abdomen and pelvis, or any other areas of disease involvement, based on the signs and symptoms of individual patients.

Safety monitoring for the occurrence and severity of adverse events (AEs) and severe adverse events (SAEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE; version 5.0) and monitored throughout treatment and for 30 calendar days after the last dose of olaparib and 90 calendar days after the last dose of durvalumab, whichever was later. Any events that occurred in patients who discontinued from study treatment were flagged in the data listings. Additionally, a separate data listing of AEs occurring more than 30 calendar days after discontinuation of olaparib or 90 days after the discontinuation of durvalumab, whichever was later, were produced. These events were not included in AE data.

Validity of outcomes

PFS and OS are generally considered the gold standard measures of efficacy in oncology clinical trials and are required by regulatory authorities for the approval of new cancer treatments. PFS and OS as endpoints in trials are easily and precisely measured and based on objective and quantitative assessment. Thus, it is included as efficacy outcomes in the present application. The primary evaluation of PFS, as determined by the Investigator, was performed per RECIST v.1.1, which represents standardized World Health Organization response criteria, and are well-established criteria for patients with solid tumours (49).

In previous DMC assessments, OS and PFS were used as efficacy endpoints. It is described by DMC that the overall survival and progression-free disease measures are critical for assessing the value of the medicine to patients, because improved OS with the least toxicity is the optimal measure for cancer treatment and PFS reflects the burden and duration of the disease.

4. Health economic analysis

This application follows the 14-week process track and health economic evaluation is not submitted as a part of the application. Thus, this section should be disregarded.

4.1 Model structure

NA

4.2 Model features

NA

Table 7 Features of the economic model

Model features	Description	Justification
NA		

5. Overview of literature

The literature used in the present application is presented in this section. Since the DUO-E trial is a head-to-head study comparing durvalumab with carboplatin plus paclitaxel both in terms of efficacy, safety and health-related quality of life, no literature search was needed for this comparison. The DUO-E trial is described in more details in Appendix A. However, to identify literature on the efficacy of dostarlimab in combination with carboplatin and paclitaxel, insights were taken from a systematic literature review (SLR) of clinical studies in advanced or recurrent endometrial cancer.

5.1 Literature used for the clinical assessment

An SLR was performed with the objective of identifying clinical trial evidence of efficacy, health-related quality of life (HRQoL)/utility and safety data of first line and second line treatments for the management of patients with endometrial cancer. This was adapted to be relevant to the decision problem in Denmark. A summary of the PICO framework for study selection for the Danish application is outlined in Table 8, with full reporting in Appendix H. Searches were conducted in MEDLINE, Embase, the Cochrane Library, and the Database of Abstracts of Reviews of Effects (DARE), as well as selected conference proceedings (ESMO, ESMO Gynaecological Cancers Congress, ASCO Annual Meeting, SGO Annual Meeting, and IGCS Annual Meeting). Whilst the global SLR had a broad scope, only studies evaluating the efficacy of dostarlimab + CP (or those required to close a network of evidence between durvalumab + CP and dostarlimab + CP) were considered relevant for this application. Therefore, of the 90 unique studies identified in the SLR, only one (RUBY; NCT03981796) was considered relevant, in addition to DUO-E.

Table 8 PICO framework

Domain	Inclusion Criteria	Exclusion Criteria
Population	• Adult women (≥18 years) with histologically confirmed diagnosis of epithelial endometrial carcinoma (newly diagnosed stage III/IV disease or recurrent disease) with any histologic subtypes (i.e. including carcinosarcomas), except sarcomas • Patients treated in the first- or second- line setting; either (1) naïve to first-line systemic anti-cancer treatment or (2) with one prior chemotherapy regimen	• Children or adolescents (<18 years of age) • Patients without endometrial carcinoma • Patients with sarcoma histology • Patients with any other stage of endometrial cancer (stage I/II)
Intervention	• Durvalumab in combination with platinum-based chemotherapy • Dostarlimab in combination with platinum-based chemotherapy	Non-systemic anti-cancer treatments (e.g., surgery or radiotherapy)
Comparator	Any or none	N/A

Domain	Inclusion Criteria	Exclusion Criteria
Outcomes	**Efficacy outcomes** • Overall survival • Progression-free survival • Progression-free survival 2 • Disease response, including objective response rate • Duration of response • Time to subsequent therapy **Safety/tolerability outcomes** • Adverse events (any grade or grade 3 and above) • Time to treatment discontinuation • Discontinuation or patient withdrawals due to adverse events • Mortality **HRQoL outcomes, from generic or disease specific measures** • Utility values (e.g. EQ-5D-5L, EQ-5D-3L, SF-6D) • Health-related quality of life values (EORTC QLQ-C30, EORTC QLQ-EN24/Endometrial, SF-36, FACT-G, EQ-5D VAS)	• Any other outcome • Studies where outcomes are not reported separately for the population of interest
Study design	• RCTs of any design (open label/double/single blind, parallel/cross-over) • Interventional, non-RCTs: • Non-randomised comparative studies • Single-arm trials • Other interventional, prospective studies	Any other study design: • Observational studies (cross-sectional, retrospective, prospective cohort studies) • Registry/database studies • Case-control studies • Secondary research articles (narrative reviews, editorials, commentaries)
Language	Articles with at least the abstract in the English language	Articles without an abstract or full-text in the English language
Other	• Studies in humans • Conference abstracts published in or after 2021	• Animal/in vitro studies

Domain	Inclusion Criteria	Exclusion Criteria
		• Conference abstracts published before 2021

Table 9 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Shannon N. Westin et al., Durvalumab Plus Carboplatin / Paclitaxel followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial. JCO 42, 283-299(2024). DOI:10.1200/JCO.23.02132 (8)	DUO-E	NCT04269200	Start: 05/05/2020 Estimated primary completion: 08/07/2024 Estimated study completion: 14/08/2027 Data cut-off 12/04/2023 [redacted]	Durvalumab plus CP vs. placebo plus CP as First-Line Treatment for Advanced Endometrial Cancer
Baurain et al., Durvalumab + carboplatin/paclitaxel follwoed bu durvalumab +/- Olaparib as first-line treatment for endometrial cancer: overall survival and additional secondary efficacy endpoints by mismatch repair status in the DUO-E/GOG-3041/ENGOT-EN10 trial. Presented at SGO Congress 2024. March. San Diego, CA. (7)	DUO-E	NCT04269200	Start: 05/05/2020 Estimated primary completion: 08/07/2024 Estimated study completion: 14/08/2027 Data cut-off 12/04/2023	Durvalumab plus CP vs. placebo plus CP as First-Line Treatment for Advanced Endometrial Cancer

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Data on file: Unpublished data 2024: durvalumab +/- Olaparib clinical study report (50)	DUO-E	NCT04269200	Start: 05/05/2020 Estimated primary completion: 08/07/2024 Estimated study completion: 14/08/2027 Data cut-off 12/04/2023	Durvalumab plus CP vs. placebo plus CP as First-Line Treatment for Advanced Endometrial Cancer
Van Nieuwenhuysen E, Moore K, Tillmanns T, Haygood C, Chambers SK, et al. Durvalumab plus carboplatin/paclitaxel followed by durvalumab with/without olaparib for endometrial cancer: mismatch repair deficient and/or microsatellite instability-high subpopulation efficacy analyses from the DUO-E trial. Presented at IGCS 2024 Annual Global Meeting. 2024, October 16-18. Dublin, IE. (51)	DUO-E	NCT04269200	Start: 05/05/2020 Estimated primary completion: 08/07/2024 Estimated study completion: 14/08/2027 Data cut-off 12/04/2023	ITC versus dostarlimab
Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novak Z, et al.	RUBY/ ENGOT-EN6-NSGO/GOG-3031	NCT03981796	Start: 15/07/2019	ITC versus dostarlimab

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023;388:2145-58. (13)			Estimated primary complete: 26/11/2026 Estimated study completion: 26/11/2026 Data cut-off: 28/09/2022	

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

Health related quality of life data presented is based on data from the DUO-E trial. As no published data on relevant domains of HRQoL (e.g., EQ-5D-5L) were identified for dostarlimab in the SLR, no other studies are utilized besides DUO-E.

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

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

5.3 Literature used for inputs for the health economic model

This application follows the 14-week process track and health economic evaluation is not submitted as a part of the application. Thus, this section should be disregarded.

Table 11 Relevant literature used for input to the health economic model

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

6. Efficacy

6.1 Efficacy of durvalumab plus carboplatin and paclitaxel compared to carboplatin and paclitaxel for primary advanced or recurrent dMMR endometrial cancer

6.1.1 Relevant studies

In adult patients with recurrent or advanced dMMR endometrial cancer, the efficacy of durvalumab has been assessed in the DUO-E trial where durvalumab plus CP was compared head-to-head with placebo plus CP. As the study is a head-to-head study, no additional studies were used in the comparison of durvalumab and CP. Table 12 presents and overview of DUO-E, and additional information can be found in Appendix A.

DUO-E is a Phase III double-blind clinical trial that aimed to investigate the safety and efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab or maintenance durvalumab in combination with olaparib as a 1L therapy in patients with newly diagnosed advanced or recurrent EC. Randomization of patients to each study arm was based on the following stratification factors:

- MMR status (dMMR vs. pMMR)
- Disease status (recurrent vs. newly diagnosed)
- Geographic region (Asia vs. rest of the world)

DUO-E includes two durvalumab treatment arms; one with and one without the addition of olaparib in the maintenance treatment. The applied population in the present application is limited to the subgroup of dMMR population and only includes the arm treating with durvalumab plus CP. Efficacy results are presented for the dMMR population and ITT population when relevant (eg. Safety data and Quality of life endpoints).

Table 12 Overview of study design for studies included in the comparison

Trial name, NCT-number, (8)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
DUO-E, NCT04269200 (8)	Phase III double-blind clinical trial	The study is ongoing with a median follow-up of 15.4 months for PFS censored patients in the durvalumab plus CP arm and 12.6 in the placebo plus CP arm in the first data-cut.	Adult female patients (≥18 year of age) with a histologically confirmed diagnosis of newly diagnosed Stage III, newly diagnosed Stage IV, or recurrent epithelial EC (excluding sarcomas), and naïve to 1L systemic anti-cancer treatment (prior adjuvant chemotherapy was allowed if ≥12 months from last treatment to relapse for those with recurrent disease)	Durvalumab 1,120 mg (IV) Q3W in combination with platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of six cycles (minimum of four cycles), followed by maintenance durvalumab 1,500 mg (IV) Q4W in combination with placebo tablets (matched to olaparib) BID in the maintenance phase for patients without objective disease progression	Placebo durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of six cycles (minimum of four cycles), followed by maintenance placebo (matched to durvalumab) Q4W and placebo tablets (matched to olaparib) BID in the maintenance phase for patients without objective disease progression	**Primary endpoint:** Investigator-assessed PFS **Secondary endpoints:** OS Time to second progression or death (PFS2) Objective response rate (ORR) Duration of response Time to first subsequent therapy or death (TFST) Time to second subsequent therapy or death (TSST) Time to treatment discontinuation or death (TDT) Safety and tolerability

6.1.2 Comparability of studies

Not applicable due to head-to-head study.

6.1.2.1 Comparability of patients across studies

As the comparison between durvalumab plus CP vs placebo plus CP is based on a direct comparative analysis with data from the head-to-head study DUO-E, it is only baseline characteristics from the DUO-E trial are presented. In Table 13, ITT population is presented and Table 14 present data for the dMMR population.

Table 13 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety, ITT population (8)

	DUO-E, overall population (ITT)	
	Durvalumab arm (n=238)	Placebo arm (n=241)
Age, years, median (range)	64 (22-84)	64 (31-85)
Geographic region		
Asia	68 (28.6)	68 (28.2)
Non-Asia	170 (71.4)	173 (71.8)
Race, no (%)		
White	136 (57.1)	143 (59.3)
Asian	72 (30.3)	73 (30.3)
Black/African American	11 (4.6)	10 (4.1)
American Indian or Alaska Naïve	6 (2.5)	0
Native Hawaiian or Other Pacific Islander	0	2 (0.8)
Other	8 (3.4)	10 (4.1)
Not reported	5 (2.1)	3 (1.2)
ECOG performance status, no (%)		
0	156 (65.5)	156 (64.7)
1	81 (34.0)	85 (35.3)
Disease status, no (%)		
Recurrent	125 (52.5)	126 (52.3)
Newly diagnosed	113 (47.5)	115 (47.7)
FIGO stage in newly diagnosed patients		

	DUO-E, overall population (ITT)	
	Durvalumab arm (n=238)	Placebo arm (n=241)
I	0	0
II	0	1 (0.4)
III	17 (7.1)	12 (5.0)
IV	96 (40.3)	101 (41.9)
Histology type, no (%)		
Endometrioid	141 (59.2)	139 (57.7)
Serous	58 (24.4)	54 (22.4)
Carcinosarcoma	12 (5.0)	21 (8.7)
Mixed, epithelial	9 (3.8)	11 (4.6)
Clear cell	4 (1.7)	7 (2.9)
Undifferentiated	4 (1.7)	3 (1.2)
Mucinous	1 (0.4)	0
Other	9 (3.8)	6 (2.5)
MMR status, no (%)		
Proficient	192 (80.7)	192 (79.7)
Deficient	46 (19.3)	49 (20.3)
HRRm status, no (%)		
HRRm	26 (10.9)	32 (13.3)
Non-HRRm	138 (58.0)	132 (54.8)
Unknown	74 (31.1)	77 (32.0)
PD-L1 expression, no (%)		
Positive	170 (71.4)	163 (67.6)
Negative	61 (25.6)	75 (31.1)
Unknown	7 (2.9)	3 (1.2)
Previous chemotherapy, no (%)		
Yes	51 (21.4)	51 (21.2)
No	187 (78.6)	190 (78.8)
Previous surgery, no (%)		

	DUO-E, overall population (ITT)	
	Durvalumab arm (n=238)	Placebo arm (n=241)
Yes	205 (86.1)	202 (83.8)
No	33 (13.9)	39 (16.2)
Previous radiotherapy, no (%)		
Yes	73 (30.7)	71 (29.5)

Table 14: Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety, dMMR population (14)

	DUO-E, overall population (ITT)	
	Durvalumab arm (n=46)	Placebo arm (n=49)
Age, years, median (SD)	62.7 (9.04)	62.4 (10.93)
Geographic region		
Asia	14 (30.4)	14 (28.6)
Non-Asia	32 (69.6)	35 (71.4)
Race, no (%)		
White	29 (63.0)	30 (61.2)
Asian	14 (30.4)	15 (30.6)
Black/African American	0	2 (4.1)
American Indian or Alaska Naïve	1 (2.2)	0
Other	1 (2.2)	0
Not reported	1 (2.2)	2 (4.1)
ECOG performance status, no (%)		
0	23 (50.0)	29 (59.2)
1	23 (50.0)	20 (40.8)
Disease status, no (%)		
Recurrent	26 (56.5)	25 (51.0)

	DUO-E, overall population (ITT)	
	Durvalumab arm (n=46)	Placebo arm (n=49)
FIGO stage in newly diagnosed patients		
I		
II		
III	6 (13.0)	3 (6.1)
IV	14 (30.4)	21 (42.9)
Histology type, no (%)		
Endometrioid	33 (71.7)	41 (83.7)
Serous	2 (4.3)	2 (4.1)
Carcinosarcoma	3 (6.5)	2 (4.1)
Mixed, epithelial	3 (6.5)	3 (6.1)
Clear cell	0	0
Undifferentiated	1 (2.2)	0
Mucinous	0	0
Other	4 (8.7)	1 (2.0)
Previous chemotherapy, no (%)		
Yes	6 (13.0)	5 (10.2)
No	40 (87.0)	44 (89.8)

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

AstraZeneca has discussed outcome of DUO-E study in Nordic Advisory Board setting which included clinical experts from Denmark. In that setting it was confirmed that the eligibility criteria in the DUO-E study is comparable to the eligibility criteria relevant for clinical implementation in Denmark.

However clinical experts highlight that in clinical practice when patients MSI status is known, then MSI-H patients would be treated as dMMR patients. Across all three arms of DUO-E, 18 patients were identified to have MSI-H but classified as pMMR by immunohistochemistry test. Correlation between dMMR and MSI status was high, and the impact on DUO-E efficacy analyses were presented at IGCS 2024 (51) and will be further discussed in the application.

Table 15 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (42)	Value used in health economic model (reference if relevant)
Age	63	NA
Gender	Women	NA

6.1.4 Efficacy – results per DUO-E

In the following, efficacy results on PFS (investigator-assessed) and OS for the dMMR population are presented. Results for patients with dMMR and/or MSI-H from DUO-E are presented in section 6.2.3 for the comparison with dostarlimab + CP.

At the data cutoff date (April 12, 2023), there were 312 PFS events (65% maturity) for the durvalumab versus control comparison and 299 PFS events (62% maturity) for the durvalumab + olaparib versus control comparison. The median (range) duration of follow-up in patients censored for PFS was 12.6 months (0.0-31.6) in the control arm and 15.4 months (0.0-29.1) in the durvalumab arm. (14)

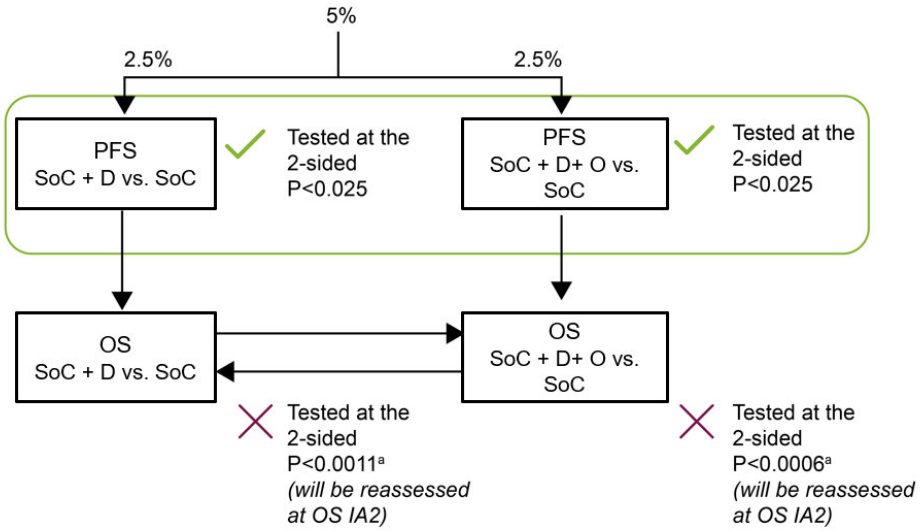
6.1.4.1 Statistical analysis

The primary objectives of the study were to compare PFS (per RECIST 1.1 as assessed by investigator) in the durvalumab + CP arm vs. placebo + CP arm and the durvalumab + Olaparib + CP arm vs. the placebo + CP arm.

The coprimary endpoints were considered to have been met if the null hypotheses were rejected based on the primary analysis of PFS in the full analysis set (ITT population). (50) In order to strongly control the Type I error at 5% (2-sided), a multiple testing procedure (MTP) was used across the key endpoints (PFS and OS) and treatment comparisons of interest (durvalumab + CP vs. SoC and durvalumab + Olaparib + CP vs. placebo + CP). (50) Hypotheses will be tested using a MTP with an alpha-exhaustive recycling strategy (as described in Burman *et al.* 2009). (50, 52) With this approach, hypotheses were tested at the time of primary PFS analysis (OS first interim analysis [1IA]; first data cut off [DCO1]: 12 April 2023) (and will be tested at each subsequent DCO) in a pre-defined order as outlined in Figure 2.

Additional analyses using an unstratified Cox proportional hazard models to determine the consistency of treatment effect between subgroups were also undertaken. (50) This includes analyses by MMR status (stratification factor), however these analyses were not powered for statistical inference.

Figure 2. Multiple testing procedure (50)



Footnote: *[a]For OS the O'Brien-Flemming spending function was used to control type I error across the three OS timepoints. Note two-sided significance level of OS interim analysis 2 & OS full analysis of ~0.0145 and ~0.0206 for the durvalumab + CP vs. placebo + CP; and ~0.0147 and ~0.0207 for the durvalumab + Olaparib + CP vs. placebo + CP, respectively (dependent on the actual number of events observed).*

6.1.4.2 Progression-free survival

In the dMMR population, durvalumab + CP demonstrated a clinically meaningful improvement in median PFS when compared to placebo + CP at the primary analysis (HR 0.42; 95% CI 0.22, 0.80) with an overall maturity of 40.6%. (8) As summarised in Table 16, there were more PFS events in the placebo + CP arm than the durvalumab + CP arm (25 vs. 15, respectively).

The Kaplan-Meier plot for PFS in the dMMR population presented in Figure 3 shows that the placebo + CP and durvalumab + CP arms separate at approximately 4 months from randomization and separation is maintained in favour of the durvalumab + CP arm throughout the follow up period. These data indicate that patients treated with durvalumab + CP had a treatment benefit compared to placebo + CP in this endpoint.(8) Furthermore, the plateau in the KM curve suggests that patients may remain progression-free in the long term, and could ultimately experience the same mortality from other causes as the general population, indicating that these patients could be considered cured.(8) The PFS rate at both 12 and 18 months was also greater in durvalumab + CP arm vs. the placebo + CP arm, further demonstrating the PFS benefit associated with durvalumab + CP in this population. (8)

Table 16: PFS in the dMMR population (8)

	Durvalumab arm (n=46)	Placebo arm (n=49)
Events, n (%)	15 (32.6)	25 (51.0)
Median, months	NR (NR-NR)	7.0 (6.7-14.8)
HR (95% CI) vs Placebo arm	0.42 (0.22, 0.80)	-
PFS rate at 12 months	67.9 (51.1-80.0)	43.3 (27.3-58.3)
PFS rate at 18 months	67.9 (51.1-80.0)	31.7 (16.7-47.9)

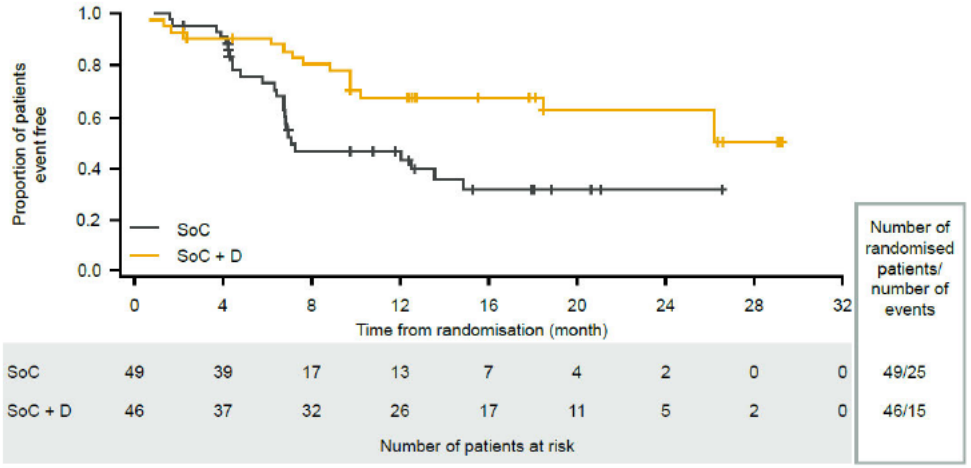


Figure 3: Kaplan-Meier plot for PFS in the dMMR population (8)

6.1.4.3 Overall survival

At DCO1, there were 36.7% of patients in the placebo + CP arm and 15.2% of patients in the durvalumab + CP arm with an OS event, overall, these data had 21.7% maturity.(7) The Kaplan-Meier plot for OS in the dMMR population is presented in Figure 4 along with additional details in Table 17. For the dMMR subpopulation, median duration of follow up for OS was 18.4 (placebo + CP) and 19.1 months (durvalumab + CP). (7)

The OS HR point estimate shows a marked improvement for the durvalumab + CP arm compared with the placebo + CP arm (HR 0.34; 95% CI 0.13, 0.79), representing a 66% reduction in the risk of death in the durvalumab + CP arm compared with the placebo + CP arm. Moreover, the OS rate at both 12 and 18 months was greater in the durvalumab + CP arm vs. the placebo + CP arm, further demonstrating the OS benefit associated with durvalumab maintenance therapy in the durvalumab + CP arm in the dMMR population. (7, 14) Data from Baurain et al 2024 is expected to be published in a peer-reviewed journal in 2025.

Table 17: OS in dMMR population at DCO (12 April 2023) (7, 14)

	Durvalumab arm (n=46)	Placebo arm (n=49)
Events, n (%) (53)	7 (15.2)	18 (36.7)
Median, months	NR (NR-NR)	23.7 (16.9-NR)
HR (95% CI) vs Placebo arm (53)	0.34 (0.13, 0.79)	-
OS rate at 12 months	91.2 (78.2-96.6)	74.4 (59.4-84.6)
OS rate at 18 months	86.1	65.8

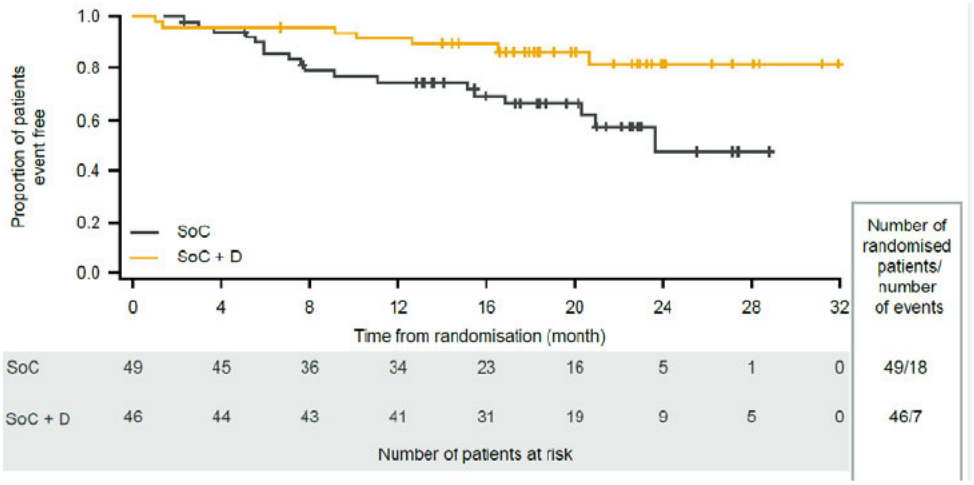


Figure 4: Kaplan-Meier plot of OS in the dMMR population at DCO1 (12 April 2023) (7)

6.2 Efficacy of durvalumab plus carboplatin and paclitaxel compared to dostarlimab plus carboplatin and paclitaxel for primary advanced or recurrent dMMR/MSI-H endometrial cancer

6.2.1 Relevant studies

For the comparison to dostarlimab, the efficacy for durvalumab is derived from the DUO-E study. The systematic literature review only identified one study evaluating the efficacy of dostarlimab in combination with carboplatin and paclitaxel in adult patients with

advanced or recurrent dMMR endometrial cancer: RUBY-1. Table 18 presents an overview of RUBY-1.

RUBY-1 is the first part of a phase 3, randomised, double-blind, multicentre trial evaluating dostarlimab-based therapies in advanced or recurrent endometrial cancer. (13) In this study, dostarlimab in combination with carboplatin and paclitaxel for 6 cycles followed by dostarlimab for up to 3 years was compared to carboplatin and paclitaxel for 6 cycles plus placebo. Patients were stratified at randomization for MMR/MSI status, as well as previous external pelvic radiotherapy, and disease status (recurrent, primary stage III, or primary stage IV). Although the trial recruited patients irrespective of MMR/MSI status, the primary endpoint included testing of investigator-assessed PFS among both patients with dMMR/MSI-H and the overall population. Following initial results, the marketing authorization holder only received regulatory approval (and subsequent reimbursement) for the dMMR/MSI-H population and therefore only efficacy results from this subgroup are presented and discussed here.

Table 18 Overview of study design for additional studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
RUBY (NCT03981796) (13)	Randomized, double blinded, placebo-controlled phase III trial of dostarlimab plus CP versus placebo plus CP	The study is ongoing with a median follow-up of 25.4 months in the first data-cut.	Adults with primary advanced (stage III or IV) or recurrent endometrial cancer. Stratification factors were: MMR/MSI status, prior external pelvic radiotherapy, and disease status (recurrent, primary stage III, or stage IV) N=494	Dostarlimab (500 mg IV) + carboplatin (AUC 5) + paclitaxel (175 mg/m^2) Q3W for 6 cycles followed by dostarlimab (1000 mg Q6W) for up to 3 years N=245	Placebo + carboplatin (AUC 5) + paclitaxel (175 mg/m^2) Q3W for 6 cycles followed by placebo for up to 3 years N=249	**Primary endpoints** • Investigator-assessed PFS according to RECIST v1.1 criteria in patients with dMMR/MSI-H tumours and in the overall trial population • OS in the overall population **Secondary endpoints** • PFS by BICR • ORR based on BICR and investigator assessment • Duration of response based on BICR and investigator assessment • Disease control rate based on BICR and investigator assessment • PFS2 • PROs (EORTC-QLQ-C30, EORTC-QLQ-EN24, EQ-5D-5L) • PK and immunogenicity analyses • Safety and tolerability

6.2.2 Comparability of studies

The DUO-E and RUBY studies have a number of similarities in trial design and inclusion criteria, which can facilitate indirect comparisons. Specifically:

- **Population**: both trials recruited adult patients with newly diagnosed advanced (FIGO stage III/IV) or recurrent endometrial cancer of epithelial histology, that was not amenable to curative surgery.
- **Intervention**: both trials evaluated a PD-(L)1 inhibitor given in combination with carboplatin + paclitaxel for up to 6 cycles, followed by a maintenance phase of PD-(L)1 inhibitor monotherapy.
- **Comparator**: carboplatin (AUC 5-6) in combination with paclitaxel (175 mg/m^2), along with placebo, was given every three weeks for up to six cycles in both studies.
- **Outcomes**: both studies had investigated-assessed PFS (as per RECIST v1.1) as a primary endpoint, with assessments conducted every 12 weeks once the chemotherapy period was complete, and OS and subgroup analyses by MMR or MSI status were protocol-specified analyses.
- **Study Design**: both trials were phase III, randomized, double-blind, placebo-controlled studies.

These core similarities meant it was deemed acceptable to conduct indirect comparisons between the trials. However, despite these similarities, an assessment of potential treatment-effect modifiers and prognostic factors provided further aspects for consideration.

As per the trial protocol for DUO-E, only MMR status was included as a stratification factor, and the European marketing authorization only includes patients with dMMR endometrial cancer. Conversely, either dMMR or MSI-H were included in stratification criteria for RUBY-1, based on local testing practices. A post-hoc analysis of DUO-E has shown that were the stratification to include both dMMR and MSI-H, then 12 pMMR patients would be included in the comparison of durvalumab + CP to placebo + CP, increasing the biomarker positive group by 12.6%. (51)

The DUO-E study included multiple sites in Asia, whereas the RUBY study was conducted in Western Europe and North America. A stratification factor by geographic region was included in the DUO-E study due to an a priori belief that the different treatment paradigms regarding the use of surgery and/or radiation in the treatment of advanced endometrial cancer between some Asian countries and Western Europe and the United States had the potential to significantly impact both short-term and long-term outcomes. The published forest plots of subgroup analysis of PFS from the DUO-E trial show a somewhat attenuated treatment-effect in patients recruited in Asia, (8)and a similar attenuated effect in Asian patients was observed in the AtTEnd trial of atezolizumab + CP compared to placebo + CP in advanced/recurrent endometrial cancer patients. (54)

Patients in DUO-E required at least 12 months since completion of (neo-)adjuvant systemic therapy for patients with recurrent disease, whilst patients in RUBY could be included from

6 months since prior chemotherapy. The proportion of patients from RUBY within 6 to 12 months since prior chemotherapy is not reported. Whilst the concept of platinum-sensitivity is not standard in endometrial cancer, and the exact impact of this on first-line recurrence is unknown, it is assumed to be more prognostic than a treatment-effect modifier for this subset of patients in each study. In other words, the duration of the platinum-free interval for recurrent may reflect impact the effectiveness of carboplatin, it is not expected to impact the relative efficacy of PD-(L)1 inhibitors.

The duration of protocol-specific PD-(L)1 inhibitor use differed between the trials. In DUO-E, durvalumab could be given until disease progression or unacceptable toxicity. In RUBY-1, dostarlimab could be given until disease progression or unacceptable toxicity, up to a maximum of 3 years. Whilst in the DUO-E study, durvalumab could theoretically continue beyond 3 years, as of the data cut-off the maximum duration of treatment received by any patient was 2.7 years. Similarly, the maximum duration of dostarlimab received in RUBY-1 was 2.9 years, and therefore duration of treatment would not have impacted efficacy results.

Table 19. Summary of expected effect modifiers due to differences in trial design

Difference in trial design	Assumed impact on relative efficacy	Rationale for assumption
Inclusion of MSI-H patients in RUBY-1	May slightly improve relative effect of dostarlimab	Post hoc analysis of the DUO-E trial showed that patients with MSI-H had slightly inferior PFS than dMMR patients when treated with carboplatin + paclitaxel, though the outcomes were similar for those treated with durvalumab, resulting in an improved hazard ratio (0.35) in MSI-H patients compared to dMMR patients (0.42).
Inclusion of patients from Asia in DUO-E	Modest decrease in the relative effect of durvalumab	In the ITT population of DUO-E, the hazard ratio for durvalumab vs. placebo was attenuated in patients from Asia (0.98) compared to the rest of the world (0.59). A similar trend was observed in the AtTEnd study where the treatment effect of atezolizumab was better in non-Asian patients (PFS HR 0.65) compared to Asian patients (PFS HR 1.17).
Platinum-free interval of at least 12 months in DUO-E	No impact on relative effect	Both trials included a platinum-free interval. Whilst a platinum-free interval of ≥12 months may result in a greater effect of platinum-based chemotherapy than an interval of ≥6 months, there is no known biological rationale why a longer interval would impact the relative efficacy of supplementing platinum-based chemotherapy with a PD-(L)1 inhibitor, and therefore an anchored indirect comparison should be unbiased by this factor.
Protocol specific discontinuation at 3 years in RUBY	No impact on relative effect	As no patient in either DUO-E or RUBY has been treated for longer than 3 years at the time of data

Difference in trial design	Assumed impact on relative efficacy	Rationale for assumption
		cut-off, neither study's results have been impacted by discontinuation.

6.2.2.1 Comparability of patients across studies

Baseline characteristics of the relevant subgroups (dMMR or dMMR/MSI-H) of the DUO-E and RUBY trials are presented in Table 20. Due to the smaller sample sizes in these subgroups, comparisons within and between studies should be done with caution. To identify which baseline characteristics are of particular interest to compare, variables which could be treatment-effect modifiers were identified based on a review of the pre-specified subgroup analyses of clinical trials evaluating platinum chemotherapy plus immunotherapy treatment for dMMR patients, namely: DUO-E, RUBY-1, NRG-GY018 (pembrolizumab; NCT03914612), and AtTEnd (atezolizumab; NCT03603184). The identified factors were MMR status and geographic region, as discussed in section 6.2.2 above, but also disease status. In the RUBY study, Mirza et al. reported that the efficacy of dostarlimab plus CP in the subgroup of patients with stage III disease was not consistent with those in other subgroups, indicating that disease status may also be an effect modifier for this treatment.

Table 20 suggests that patients in the subgroup populations of RUBY-1 and DUO-E were somewhat similar in terms of age, ECOG performance status, histology, and prior treatments. However, due to the included sites of the study, a greater number of patients of Asian race were recruited into DUO-E. In addition, a higher proportion of patients in RUBY-1 had primary stage III endometrial cancer.

Table 20. Baseline characteristics of patients in studies included for the comparative analysis of efficacy (8, 13)

	DUO-E		RUBY-1	
	Durvalumab + CP (N=46)	Placebo + CP (N=49)	Dostarlimab + CP (N=53)	Placebo + CP (N=65)
Age, median	63.0	63.0	61.0	66.0
≥65 years, n (%)	21 (45.7)	24 (49.0)	23 (43.4)	35 (53.8)
ECOG PS, n (%)				
0	23 (50.0)	29 (59.2)	28 (53.8)	39 (60.0)
1	23 (50.0)	20 (40.8)	24 (46.2)	26 (40.0)
Race, n (%)				
White	29 (63.0)	30 (61.2)	44 (83.0)	56 (86.2)
Black	0	2 (4.1)	4 (7.5)	6 (9.2)

	DUO-E		RUBY-1	
	Durvalumab + CP (N=46)	Placebo + CP (N=49)	Dostarlimab + CP (N=53)	Placebo + CP (N=65)
Asian	14 (30.4)	15 (30.6)	2 (3.8)	0
Other	2 (4.3)	0	1 (1.9)	1 (1.5)
Not Reported	1 (2.2)	2 (4.1)	2 (3.8)	2 (3.1)
Region, n (%)				
Asia	14 (30.4)	14 (28.6)	NA	NA
Rest of World	32 (69.6)	35 (71.4)	53 (100)	65 (100)
Histology, n (%)				
Endometrioid	33 (71.7)	41 (83.7)	45 (84.9)	54 (83.1)
Serous	2 (4.3)	2 (4.1)	0	1 (1.5)
Carcinosarcoma	3 (6.5)	2 (4.1)	4 (7.5)	2 (3.1)
Other	8 (17.4)	4 (8.2)	3 (5.7)	4 (6.2)
Status, n (%)				
Primary stage III	6 (13.0)	3 (6.1)	10 (18.9)	14 (21.5)
Primary stage IV	14 (30.4)	21 (42.9)	16 (30.2)	19 (29.2)
Recurrent	26 (56.5)	25 (51.0)	27 (50.9)	32 (49.2)
Prior chemotherapy, n (%)	6 (13.0)	5 (10.2)	7 (13.2)	9 (13.8)
Prior radiotherapy, n (%)	17 (37.0)	18 (36.7)	19 (35.8)	22 (33.8)

Table 21. Summary of expected effect modifiers due to differences in patient characteristics

Difference in trial population	Assumed impact on relative efficacy	Rationale for assumption
More patients with primary stage III disease in RUBY	May slightly deterioriate the relative effect of dostarlimab	In both the ITT and the dMMR/MSI-H subgroups of RUBY, the relative effect of dostarlimab in stage III patients was inferior (ITT PFS HR 1.03) compared to stage IV (ITT PFS HR 0.57) or recurrent (ITT PFS HR 0.56). There were too few stage III patients to estimate a hazard ratio in DUO-E, though the results for primary stage IV (PFS HR 0.70) and recurrent disease (PFS HR 0.79), are somewhat similar to the overall effect (PFS HR 0.68) for durvalumab vs.

Difference in trial population	Assumed impact on relative efficacy	Rationale for assumption
		placebo, and therefore the impact of disease stage on relative effect is somewhat uncertain.

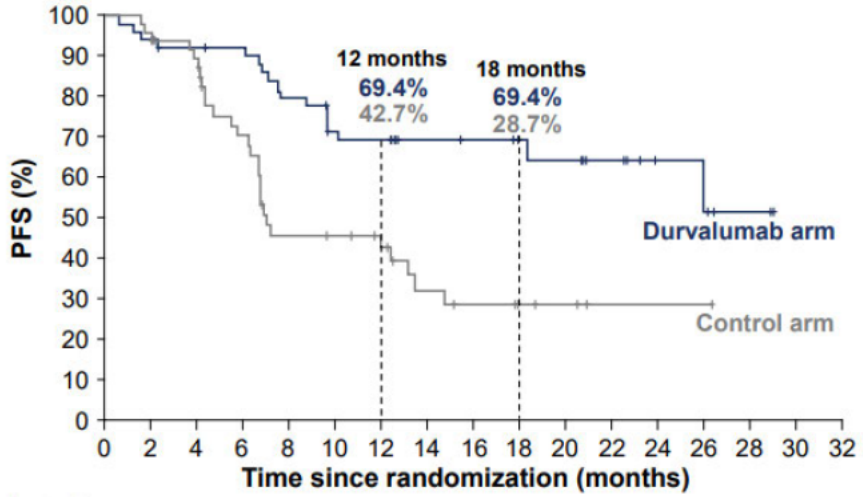
6.2.3 Efficacy – results per DUO-E

Please refer to section 6.1.4 for main efficacy outcomes for DUO-E. In order to mitigate some of the heterogeneity between DUO-E and RUBY, results for the indirect comparison are based on a post hoc analysis of DUO-E including both patients with dMMR and MSI-H endometrial cancer. The results of this subgroup were recently presented at the ICGS Annual Meeting (51). This patient population includes the 95 patients in the dMMR subgroup (durvalumab + CP, n = 46; placebo + CP, n = 49), as well as 12 patients with MSI-H but who are pMMR (durvalumab + CP, n = 9; placebo + CP, n = 3).

6.2.3.1 Investigator-assessed progression-free survival

As of the data cut-off date, 17 (30.9%) patients in the durvalumab arm and 28 (53.8%) patients in the placebo arm of the dMMR/MSI-H subgroup had died or had disease progressed as assessed by the investigator according to RECIST v1.1. Patients in the durvalumab arm had a 63% reduction in the risk of disease progression or death (HR 0.37; 95% CI 0.20, 0.67). Median PFS was not reached in the durvalumab arm but was 7.0 months (95% CI 6.3 to 13.5) in the placebo arm (Figure 5). The PFS analyses of durvalumab + CP vs CP alone for the combined dMMR/MSI-H subpopulations is consistent with analyses for the dMMR subpopulation presented in section 6.1.4.

Figure 5 Investigator-assessed PFS in patients with dMMR/MSI-H advanced or recurrent endometrial cancer from the DUO-E trial (durvalumab vs. placebo)



No. at risk

Durvalumab arm	55	51	49	46	46	45	45	42	39	38	33	32	32	20	20	20	18	18	15	12	12	9	9	7	5	5	5	2	2	1	0	0	0
Control arm	52	48	46	43	41	31	29	20	18	18	17	16	14	11	9	8	7	7	5	4	4	2	2	2	2	2	2	0	0	0	0	0	0

	Control arm (N=52)	Durvalumab arm (N=55)
Events, n (%)	28 (53.8)	17 (30.9)
Median PFS (95% CI),† months	**7.0** (6.3–13.5)	**NR** (NR–NR)
HR (95% CI) vs control‡		**0.37** (0.20–0.67)

6.2.3.2 Overall survival

[redacted]

[redacted]

6.2.4 Efficacy – results per RUBY

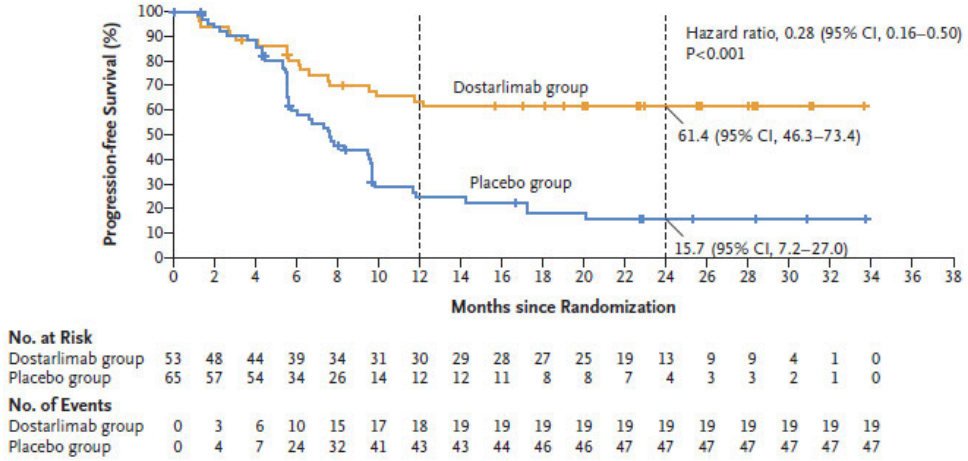
As the primary and key secondary endpoints of DUO-E were investigator-assessed PFS and OS, and these are assumed to be the main endpoints of interest when comparing durvalumab to dostarlimab, only the PFS and OS results from RUBY are presented here.

The published data are from the primary analysis of RUBY (data cut-off 28 September 2022), after a median follow-up of 24.8 months in the dMMR/MSI-H subgroup (range 19.2 to 36.9 months). At this time, 29 of the 52 patients who received dostarlimab (55.8%; one patient randomized to this arm in this subgroup did not receive dostarlimab) had discontinued dostarlimab, and all had discontinued chemotherapy. The primary reasons for dostarlimab discontinuation were progressive disease (n = 13; 25.0%) or adverse events (n = 9; 17.3%). In the placebo arm, 57 of the 65 patients (87.7%) randomized to placebo had discontinued placebo and all had discontinued carboplatin though one patient remained on paclitaxel. The primary reasons for placebo discontinuation were also progressive disease (n = 40; 61.5%) and adverse events (n = 7; 10.8%)

6.2.4.1 Investigator-assessed progression-free survival

As of the data cut-off date, 19 (35.8%) patients in the dostarlimab arm and 47 (72.3%) patients in the placebo arm of the dMMR/MSI-H subgroup had died or had disease progressed as assessed by the investigator according to RECIST v1.1. Patients in the dostarlimab arm had a 72% reduction in the risk of disease progression or death (HR 0.28; 95% CI 0.16, 0.50). Median PFS was not reached in the dostarlimab arm, but the Kaplan–Meier estimate at 24 months was 61.4% (95% CI; 46.3 to 73.4) in the dostarlimab group and 15.7% (95% CI; 7.2 to 27.0) in the placebo group (Figure 7).

Figure 7. Investigator-assessed PFS in patients with dMMR/MSI-H advanced or recurrent endometrial cancer from the RUBY trial (dostarlimab vs. placebo)



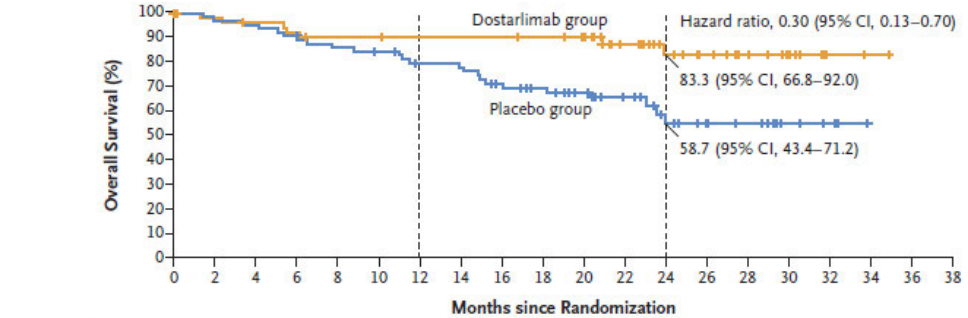
No. at Risk																		
Dostarlimab group	53	48	44	39	34	31	30	29	28	27	25	19	13	9	9	4	1	0
Placebo group	65	57	54	34	26	14	12	12	11	8	8	7	4	3	3	2	1	0
No. of Events																		
Dostarlimab group	0	3	6	10	15	17	18	19	19	19	19	19	19	19	19	19	19	19
Placebo group	0	4	7	24	32	41	43	43	44	46	46	47	47	47	47	47	47	47

Source: Mirza et al. 2023 (Figure 2A)

6.2.4.2 Overall survival

In the dMMR/MSI-H subgroup, 7 (13.2%) patients in the dostarlimab arm and 24 (36.9%) patients in the placebo arm had died. Overall survival at 24 months was 83.3% (95% CI; 66.8 to 92.0) in the dostarlimab group and 58.7% (95% CI; 43.4 to 71.2) in the placebo group (Figure 8). The risk of death was 70% lower in dostarlimab treated patients (HR 0.30; 95% CI, 0.13 to 0.70).

Figure 8. OS in patients with dMMR/MSI-H advanced or recurrent endometrial cancer from the RUBY trial (dostarlimab vs. placebo)



No. at Risk																		
Dostarlimab group	53	50	48	46	44	44	43	43	43	42	41	29	20	16	12	8	2	1	0
Placebo group	65	63	62	59	55	53	48	47	41	37	32	25	16	12	10	5	3	0	
No. of Events																			
Dostarlimab group	0	1	2	4	5	5	5	5	5	5	5	6	7	7	7	7	7	7	7
Placebo group	0	2	3	6	9	10	13	14	18	19	20	21	23	24	24	24	24	24	

Source: Mirza et al. 2023 (Figure 3B)

7. Comparative analyses of efficacy

The comparison between durvalumab plus carboplatin and paclitaxel vs. carboplatin and paclitaxel for primary advanced or recurrent dMMR endometrial cancer was covered by the head-to-head trial, DUO-E. Results of which are presented in section 6.1. Comparative efficacy outcomes are summarized in Table 22.

The following sections will detail the comparative analysis between durvalumab plus carboplatin and paclitaxel vs. dostarlimab plus carboplatin and paclitaxel for primary advanced or recurrent dMMR endometrial cancer. An indirect treatment comparison was conducted to establish the relative efficacy between the two therapies based on the clinical trials, DUO-E and RUBY. An assessment of the comparability of the studies has been presented in section 6.2.2, and concluded that an indirect treatment comparison was feasible to conduct between the studies.

7.1.1 Differences in definitions of outcomes between studies

There are no identified discrepancies in the definition of investigator-assessed PFS or OS between the DUO-E and RUBY, where equivalent definitions of progression (RECIST v1.1), similar censoring rules, and largely comparable timing of assessments were used in both studies.

7.1.2 Method of synthesis

Given the differences in trial designs and patient populations outlined in section 6.2.2, methods for adjusting for the impact of effect modifiers were preferred. As noted in section 6.2.2, the parameters deemed relevant to adjust for are: MMR/MSI status (inclusion of MSI-H in RUBY), region (exclusion of patients from Asia in RUBY), and disease status (more stage III patients included in RUBY). However, due to the smaller sample sizes of the dMMR/MSI-H subgroups (118 patients in RUBY and 107 patients in DUO-E), consideration was given to the role adjustment and weighting would have on the effective sample size and the possibility for inferences. This is particularly relevant for overall survival where, given the considerable efficacy demonstrated by PD-(L)1 inhibitors in this setting, the event numbers are low (i.e., 7 deaths in dostarlimab treated patients and 8 deaths in durvalumab treated patients) and could be impacted by weighting. For example, adjustment for Asian patients in DUO-E would reduce the sample size by nearly one-third. Therefore, an unadjusted analysis is presented. As discussed above, in order to mitigate potential bias due to the include of MSI-H patients in RUBY, data from the recently presented subgroup of dMMR/MSI-H patients from DUO-E is used in the comparative analysis,(51) as shown in section 6.2.3. This was deemed a relevant adjustment as MSI testing is in some cases conducted in Denmark and can be used to assess eligibility for PD-(L)1 inhibitors in this setting.

As both studies share a common comparator (placebo in combination with carboplatin and paclitaxel), an anchored indirect treatment comparison (ITC) was conducted. The

anchored ITC was performed in an unadjusted analysis via a frequentist approach, using the Bucher methodology. The ITC was performed using a fixed effects model as there was insufficient data (n=1 study per comparison) to estimate the between-study heterogeneity of treatment effects in a random effects model. The treatment effects for PFS and OS were modelled as the log-hazard ratio and its standard error. The log-hazard ratio for each study was calculated as the natural logarithm of the reported hazard ratio. The standard error was calculated as the difference between the logarithms of the upper and lower confidence intervals, divided by 2 times the percentile point corresponding to the alpha-level of the interval (e.g., 1.96 for 95% confidence intervals). The results were summarized in terms of the hazard ratio and 95% confidence intervals for durvalumab + CP versus dostarlimab + CP.

The proportional hazards (PH) assumption was assessed using log cumulative hazard plots and Schoenfeld residual plots for both the RUBY and DUO-E trials, see Appendix C.3. Even though the Schoenfeld residual tests mainly do not indicate a violation of the PH assumption (with the exception of PFS in RUBY I), there is some evidence that the PH assumption could be violated based on log cumulative hazards and the residual plots themselves. For any given trial with non-proportional hazards, the hazard ratio can be interpreted as a weighted average of the hazard ratios over smaller intervals of time (on the log scale) (55). As such, the hazard ratio will differ depending on the follow-up of the study. However, both DUO-E and RUBY I had a comparable duration of chemotherapy (up to 6 cycles, with each cycle being 3 weeks) in which the PFS and OS curves showed little separation (see [redacted] in Appendix C.3). This represents a relatively small proportion of the overall follow-up of the two studies, and for this reason, any bias introduced by non-proportional hazards is expected to be low.

Furthermore, there are low numbers of PFS and OS events observed in the dMMR/MSI-H populations of the DUO-E and RUBY I studies, particularly in the intervention arms due to the treatment effects observed. Therefore statistical methods to account for time-varying relative effects were not deemed feasible, as these would be unable to provide a robust or meaningful outcome that can be readily interpreted(56). Restricted mean survival time (RMST) is an outcome that does not rely on proportional hazards, and can provide a meaningful and easily interpreted outcome to compare survival time between treatment arms, and also allow comparisons between studies. This type of analysis has been conducted as a sensitivity analysis, and can be found in Appendix C.4.

7.1.3 Results from the comparative analysis

Comparative efficacy outcomes for both comparators are summarized in Table 22 for primary advanced or recurrent dMMR/MSI-H endometrial cancer.

Table 22 Results from the comparative analysis of durvalumab plus CP vs. placebo plus CP and dostarlimab plus CP for primary advanced or recurrent dMMR(/MSI-H) endometrial cancer

Outcome measure for DUO-E, DCO1 (April 12, 2023) (8)	Durvalumab + CP (N=46)	Placebo + CP (N=49)	Result
PFS, median months (95% CI) dMMR	NR (NR-NR)	7.0 (6.7-14.8)	HR: 0.42 (0.22.0.80)
OS, median months (95% CI) dMMR	NR (NR to NR)	23.7 (16.9-NR)	HR: 0.34 (0.13-0.79)

Outcome measure from ITC	Durvalumab + CP (N=55)	Dostarlimab + CP (N=53)	Result
Investigator-assessed PFS	NA	NA	[redacted]
OS	NA	NA	[redacted]

7.1.4 Efficacy – results per investigator-assessed PFS

The results on investigator-assessed PFS for durvalumab + CP compared to placebo + CP in patients with dMMR advanced/recurrent endometrial cancer are presented in section 6.1.4.2.

The anchored ITC results compared to dostarlimab + CP, without adjustment for differences in the trial populations except for MSI-H status, suggest that there is no significant difference between treatments in terms of PFS (Table 22). Whilst adjustment was not made for disease status or region, disease status was expected to have a modest negative impact on the overall hazard ratio for dostarlimab for the 20% of patients in RUBY with primary stage III disease, and region was expected to have a negative impact on the overall hazard ratio for durvalumab for the 30% of patients recruited from sites in Asia (see section 6.2.2), and therefore biases due to the lack of adjustment are not expected to significant favour either treatment.

7.1.5 Efficacy – results per overall survival

The results for OS for durvalumab + CP compared to placebo + CP in patients with dMMR advanced/recurrent endometrial cancer are presented in section 6.1.4.3.

[redacted]. No adjustments were made for the differences in baseline characteristics or trial design, except for MSI status,

due to the low event count, though results indicate comparable survival benefit between durvalumab and dostarlimab for this patient population.

8. Modelling of efficacy in the health economic analysis

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

8.1.1 Extrapolation of efficacy data

NA

8.1.1.1 Extrapolation of [effect measure 1]

Table 23 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
NA	

8.1.1.2 Extrapolation of [effect measure 2]

NA

8.1.2 Calculation of transition probabilities

Table 24 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
NA			

8.2 Presentation of efficacy data from [additional documentation]

NA

8.3 Modelling effects of subsequent treatments

NA

8.4 Other assumptions regarding efficacy in the model

NA

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

NA

Table 25 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
NA			

Table 26 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
NA			

9. Safety

In this section, safety data is presented from the DUO-E trial on patients treated with durvalumab plus CP and placebo plus CP in the ITT population at DCO1 (April 12th 2023). In DUO-E study, a total of 718 patients were randomized in a 1:1:1 ratio to receive either Placebo plus CP (241 patients), or durvalumab plus CP (238 patients); of these, 709 patients (98.7%) received study treatment; 5 patients in the placebo plus CP arm, and 3 patients in the durvalumab plus CP arm did not receive study treatment.

9.1 Safety data from the clinical documentation

At the time of the primary analysis of PFS, the number of patients exposed, and the totality of exposure and follow-up in the study were considered sufficient to characterize the safety profile of placebo plus CP, and durvalumab plus CP.

Duration of treatment exposure to CP and durvalumab/placebo across treatment arms is presented in Table 27 for the safety analysis set while it for dMMR patient is presented in Table 28. In the FAS, there were 80.1% of patients (575/718) who were pMMR and 19.9% of patients (143/718) who were dMMR. (14)

In the study overall, total exposure to CP was similar in all treatment arms, indicating that treatment with durvalumab did not impact the ability of patients to receive CP. The median duration for actual treatment exposure is defined as the intended exposure [weeks] minus the total duration of dose delays [days].

Table 27 Duration of Exposure in DUO-E overall phase (Safety analysis set, DCO 12 April 2023) (14)

	DUO-E , ITT	
	Durvalumab plus CP (n=235)	**Placebo plus CP (n= 236)**
SoC		
Carboplatin or substitute (intended exposure; weeks)[a]		
Mean SD	17.7 (4.49)	17.4 (4.25)
Paclitaxel or substitute (intended exposure; weeks)[a]		
Mean SD	17.5 (4.60)	17.3 (4.30)
Durvalumab/placebo (Total treatment exposure; weeks)[b]		
Mean SD	49.9 (32.12)	43.9 (27.12)

[a]Intended exposure (weeks) = (minimum of [last dose date where dose > 0 mg + 20 days, date of death, date of DCO] – first dose date + one day)/7.
[b]Total treatment duration = (last dose date + X days or death date or DCO whichever occurred earlier - first dose date +1) / 7. X was defined as the planned frequency in dosing (in days) - 1. For Q2W, X = 13. For Q3W, X = 20. For Q4W, X = 27.

Table 28 Duration of Exposure in DUO-E overall phase, by dMMR status per IVRS (Safety analysis set, DCO 12 April 2023) (14)

	DUO-E, dMMR	
	Durvalumab plus CP (n=44)	**Placebo plus CP (n= 46)**
Durvalumab/placebo (Total treatment exposure; weeks)[b]		
Mean SD	62.5 (37.88)	40.6 (31.89)

In the study overall, most patients experienced at least one AE. AEs of maximum Grade 3 or 4 and SAEs were reported in more than 50% of patients and approximately a third of patients, respectively, across all three treatment arms. The majority of reported deaths due to any cause across all arms were attributed to EC. The number of patients with an AE

leading to death was 8 patients (3.4%) in the placebo + CP arm, and 4 patients (1.7%) in the durvalumab + CP arm. (14)

A summary of AEs reported in the DUO-E trial (safety analysis set, ITT) can be found in Table 29 for the overall phase and Table 30 for the maintenance phase. Table 32 shows the most serious AEs with a frequency ≤2%. Durvalumab + CP were associated with a manageable safety profile, and the safety profiles of each regimen were consistent with the known profiles of each agent.

For the analysis of the dMMR group, Table 31 shows the treatment emergent AEs (safety analysis set, dMMR). Overall, the safety findings for durvalumab + CP and placebo + CP in the dMMR population were broadly aligned with those in the ITT population; the proportion of patients treated with durvalumab + CP experiencing Grade ≥3 AEs was 52.3% and 54.9% in the dMMR population vs. the ITT population, respectively, compared with 60.9% and 56.4% in the placebo + CP arm. There was also a similar proportion of patients who discontinued study treatment in the durvalumab + CP arm due to an AE in the dMMR population vs. the ITT population (20.5% vs. 20.9%, respectively), compared with the placebo + CP arm (15.2% vs. 18.6%, respectively). (14)

Table 29 Overview of safety events in any category in DUO-E (overall phase) (Safety Analysis Set, DCO 12 April 2023).

	Durvalumab plus CP (N=235) (14)	Placebo plus CP (N=236) (14)	Difference, % (95 % CI)
Number of adverse events, n (%)	232 (98.7)	236 (100)	-1.3% (-2.7, 0.2)
Number of serious adverse events*, n	73 (31.1)	73 (30.9)	0.1% (-8.2, 8.5)
Number of CTCAE grade ≥ 3 events, n (%)	129 (54.9)	133 (56.4)	-1.5% (-10.4, 7.5)
Adverse drug reactions, n (%)	224 (95.3)	232 (98.3)	-3.0% (-6.1, 0.2)
Immune mediated AEs	66 (28.1)	16 (6.8)	21.3% (14.7, 27.9)
Number and proportion of patients who had a dose delay or interruption of any study treatment due to adverse events, n (%) (8)	128 (54.5)	118 (50.0)	4.5% (-4.5, 13.5)
Number and proportion of patients who had a dose delay	112 (47.7)	90 (38.1)	9.5% (0.6, 18.4)

	Durvalumab plus CP (N=235) (14)	Placebo plus CP (N=236) (14)	Difference, % (95 % CI)
or interruption of durvalumab/placebo due to adverse events, n (%)			
Number and proportion of patients who discontinue any study treatment due to adverse events, n (%) (8)	49 (20.9)	44 (18.6)	2.2% (-5.0, 9.4)
Number and proportion of patients who CP due to adverse events, n (%) (8)	31 (13.2)	32 (13.6)	-0.4% (-6.5%;5.8%)
Number and proportion of patients who discontinue durvalumab/placebo due to adverse events, n (%)	26 (11.1)	19 (8.1)	3.0% (-2.3, 8.3)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

Table 30 Overview of adverse events in any category in DUO-E maintenance phase (Safety Analysis Set, DCO 12 April 2023). (14)

	Durvalumab plus CP (N=183) (14)	Placebo plus CP (N=169) (14)	Difference, % (95 % CI)
Number of adverse events, n (%)	158 (86.3)	143 (84.3)	1.7% (-5.6, 9.1)
Number of serious adverse events*, n	22 (12.0)	19 (11.2)	0.8% (-5.9, 7.5)
Number of CTCAE grade ≥ 3 events, n (%)	30 (16.4)	28 (16.6)	-0.2% (-7.9, 7.6)
Adverse drug reactions, n (%)	138 (75.4)	120 (71.0)	4.4% (-4.9, 13.7)
Number and proportion of patients who had a dose delay or interruption of	38 (20.8)	18 (10.7)	10.1% (2.6, 17.6)

	Durvalumab plus CP (N=183) (14)	Placebo plus CP (N=169) (14)	Difference, % (95 % CI)
durvalumab/placebo due to adverse events, n (%)			
Number and proportion of patients who discontinue durvalumab/placebo due to adverse events, n (%)	9 (4.9)	4 (2.4)	2.6% (-1.3, 6.4)

Table 31 Treatment emergent AEs by category, patient level, dMMR status in the DUO-E overall phase (safety analysis set, DCO 12 April 2023)

	Durvalumab plus CP (N=44) (14)	Placebo plus CP (N=46) (14)	Difference, % (95 % CI)
Number of adverse events, n (%)	44 (100.0)	46 (100.0)	-
Number of serious adverse events including death, n (%)	13 (29.5)	15 (32.6)	-3.1% (-22.2%;16.0%)
Number of CTCAE grade ≥ 3 events, n (%)	23 (53.3)	29 (63.0)	-10.8% (-31.1%;9.5%)
Any AE with outcome of death, n (%)	0 (0)	1 (2.2)	-2.2% (-6.4%;2.0%)
Any AE leading to discontinuation of durvalumab/placebo, n (%)	5 (11.4)	5 (10.9)	0.5% (-12.5%;13.5%)
Any AE leading to discontinuation of placebo + CP, n (%)	5 (11.4)	4 (8.7)	2.7% (-9.8%;15.1%)
Any AE leading to dose interruption of durvalumab/placebo, n (%)	23 (52.3)	18 (39.1)	13.1% (-7.3%;33.6%)
Any AE leading to dose interruption placebo + CP, n (%)	13 (29.5)	15 (32.6)	-3.1% (-22.2%;16.0%)

Table 32 Most common serious adverse events (frequency ≥2% patients in any treatment groups in DUO-E overall phase) (Safety analysis set, DCO 12 April 2023)

Adverse events	Durvalumab plus CP (N=235) (14)		Placebo plus CP (N=236) (14)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)				
Anemia	1 (0.4)	NA	10 (4.2)	NA
Febrile neutropenia	4 (1.7)	NA	8 (3.4)	NA
Urinary tract infection	2 (0.9)	NA	5 (2.1)	NA
Vomiting	5 (2.1)	NA	2 (0.8)	NA
Hyponatremia	5 (2.1)	NA	4 (1.7)	NA

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Table 33 Adverse events used in the health economic model

Adverse events	Intervention	Comparator
NA		

9.1.1 Safety of durvalumab plus carboplatin and paclitaxel compared to dostarlimab plus carboplatin and paclitaxel in patients with primary advanced or recurrent endometrial cancer

In addition to the indirect comparison of efficacy reported in section 7, selected safety endpoints were also included in the ITC.

For safety outcomes, the ITC used data reported for the full safety analysis sets (i.e., patients who received ≥1 dose of study medication) of both trials. This is aligned with the safety assessments conducted by the EMA and ensures that a sufficient sample size for detecting differences in safety outcomes across treatments. Given that neither MMR nor MSI status is expected to modify the risk of safety outcomes, it is deemed reasonable to use the full safety analysis sets.

The safety endpoints included in the ITC were summary safety outcomes, including the number of patients experiencing any AEs, any serious AEs, any grade ≥3 AEs, any treatment-related AEs (i.e., adverse reactions), and AEs leading to the discontinuation of PD-(L)1 inhibitor/placebo. Dose reductions were not included as dose reductions of durvalumab or dostarlimab were not permitted in the trials and, as stated in the SmPCs, dose escalation or reduction in not recommended for either product in practice.

Odds ratios (OR) were calculated using the AE frequency data and the numbers of patients included in the safety analysis set. The comparison of OR were performed using the Bucher method on the log odds ratio of an event for durvalumab + CP vs. placebo + CP in the DUO-E trial, and the log odds ratio of an event for dostarlimab + CP vs. placebo + CP in the RUBY trial. The 95% confidence interval for the log OR was estimated using the logarithm of the point estimate and standard error, under an assumed normal distribution on the log scale. The log standard error of the point estimate, used in the calculation of confidence intervals, was estimated as the square root of the summed variance of the log odds ratios from the two studies.

The median duration of exposure to PD-(L)1 inhibitor/placebo was comparable between studies (DUO-E: durvalumab 43.0 weeks, placebo 39.2 weeks; RUBY: dostarlimab 43.0 weeks, placebo 36.0 weeks) and the incidence of safety outcomes was similar between placebo arms of both studies (Table 34), supporting the validity of a comparison of safety outcomes between studies. The exception to this is treatment-related adverse events, which were higher in the placebo arm of RUBY (74.4%) than in the placebo arm of DUO-E (60.6%)

Across the endpoints explored in the safety ITC, there was a trend for durvalumab to have a more favourable safety profile than dostarlimab. This is particularly evidence for serious adverse events (OR 0.63; 95% CI 0.37 to 1.09) and adverse events of grade 3 or higher (OR 0.58; 95% CI 0.35 to 0.99). These results are clarified by the fact that the incidence of adverse events in DUO-E was not significantly different between the durvalumab + CP arm and the placebo + CP arm, but in RUBY there was a significantly higher incidence of serious and severe adverse events, adverse reactions, and discontinuations in the dostarlimab + CP arm compared to the placebo + CP arm.

Table 34 Overview of safety outcomes in the indirect comparison

Outcome	DUO-E			RUBY			Durvalumab vs. Dostarlimab
	Durvalumab plus CP (N=235) (53)	Placebo plus CP (N=236) (53)	Difference, % (95 % CI)	Dostarlimab plus CP (N=241)	Placebo plus CP (N=246)	Difference, % (95 % CI)	Difference, % (95 % CI)
Patients with ≥1 adverse events, n (%)	232 (98.7)	236 (100)	-1.3% (-2.7, 0.2) OR: NC (NC, NC)	241 (100)	246 (100)	0.0% (NC, NC) OR: NC (NC, NC)	-1.3% (NC, NC) OR: NC (NC, NC)
Patients with ≥ 1 serious adverse events, n (%)	73 (31.1)	73 (30.9)	0.1% (-8.2, 8.5) OR: 1.01 (0.68, 1.49)	91 (37.8)	68 (27.6)	10.1% (1.8, 18.4) OR 1.59 (1.08, 2.33)	-10.0% (-21.8, 1.8) OR: 0.63 (0.37, 1.09)
Patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	129 (54.9)	133 (56.4)	-1.5% (-10.4, 7.5) OR: 0.94 (0.66, 1.36)	170 (70.5)	147 (59.8)	10.8% (2.4, 19.2) OR 1.61 (1.11, 2.35)	-12.2% (-24.5, 0.1) OR: 0.58 (0.35, 0.99)
Patients with ≥ 1 adverse event related to PD-(L)1 inhibitor/placebo, n (%)	154 (65.5)	143 (60.6)	4.9% (-3.8, 13.6) OR: 1.24 (0.85, 1.80)	203 (84.2)	183 (74.4)	9.8% (2.7, 17.0) OR 1.84 (1.17, 2.88)	-4.9% (-16.2, 6.4) OR: 0.67 (0.37, 1.21)
Patients who discontinue PD-(L)1 inhibitor/placebo due to adverse events, n (%)	26 (11.1)	19 (8.1)	3.0% (-2.3, 8.3) OR: 1.42 (0.76, 2.64)	42 (17.4)	23 (9.3)	8.1% (2.1, 14.1) OR 2.05 (1.19, 3.52)	-5.1% (-13.1, 3.0) OR: 0.69 (0.30, 1.58)

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

NA

Table 35 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
NA								

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

In the DUO-E trial, several patient-reported outcomes measures (PROMs) capturing aspects of HRQoL were collected, including the EORTC QLQ-C30, EORTC QLQ-EN24, and EQ-5D-5L. Specified secondary endpoints in DUO-E related to HRQoL were change from baseline in scores on the EORTC QLQ-30, time to deterioration of scores on the EORTC QLQ-C30, and time to deterioration in symptoms (back/pelvic pain, gastrointestinal, and urological) on the EORTC QLQ-EN24. Specified exploratory endpoints included evaluation of the health status by assessment of the EQ-5D-5L. As the EMA concluded that there were no relevant or clinically meaningful differences between regimens in DUO-E on the evaluated outcomes of the EORTC QLQ-C30 and EORTC QLQ-EN24, (14)and that DMC guidelines recommend using the EQ-5D-5L to assess HRQoL, only the results from the EQ-5D-5L are discussed here. DMC did not assess the EORTC QLQ-C30 or EORTC QLQ-EN24 data for dostarlimab in its assessment, however the EMA concluded that patients on dostarlimab had similar quality of life than patients on placebo in the dMMR/MSI-H population.(57) Given that no meaningful differences in HRQoL were observed between durvalumab and placebo and dostarlimab and placebo in their respective trials, no indirect comparison is presented on the assumption of comparable impact on HRQoL as current standard therapy.

Table 36 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	DUO-E (ITT population)	To assess for relevant differences in HRQoL when adding durvalumab to carboplatin + paclitaxel

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

Patient-reported health state utility was assessed using the EQ-5D-5L. The instrument asks patients to respond to five different dimensions covering mobility, self-care, usual activities, pain/discomfort, anxiety/depression, as well as rate how they feel on the day of assessment via a visual analogue scale. The EQ-5D was designed to evaluate the generic quality of life of individual patients. The instrument is validated and used across countries and patient populations,(58) and was used here in the manner it is validated for.(50)

As the EQ-5D-5L measurements are not being used here to derive valid utilities for use in an economic model, but rather to assess the impact of adding durvalumab to carboplatin + paclitaxel, only factors potentially impacting these inferences are considered in terms of bias.

The protocol-specified timing of EQ-5D-5L collection coincides with protocol-specified days of treatment administration. During chemotherapy cycles, patients are typically burdened by symptoms of treatment toxicity in the days immediately following administration, followed by a period of relative quiescence. During the time patients are on randomized treatment, EQ-5D-5L measurements reflect the HRQoL around the time of treatment administration. Accordingly, the utilities measured may somewhat reflect the toxicity burden of treatments but may not determine if the within-cycle HRQoL is better when adding durvalumab if there is added efficacy.

As HRQoL can change after the disease has progressed, it is relevant to consider the pre- and post-progression states (based on investigator-assessed PFS) when analyzing the utility estimates. As noted below, the EQ-5D-5L was planned to be collected up until PFS2, allowing analysis of a prolonged post-progression period. As introducing durvalumab into the first line setting also changes the treatment pathway, where some patients today receive immune checkpoint inhibitors after first line disease progression but would be unlikely to be retreated with a PD-(L)1 inhibitor in clinical practice, it is relevant to assessment whether the post-progression utility changes as different treatment options exist for patients at this time.

As subgroup analyses on the EQ-5D-5L by MMR status were not protocol specific, they have not been conducted and results presented here are from the ITT population. Whilst MMR status has been identified as a potential treatment effect modifier for durvalumab, once accounting for other factors that may influence HRQoL (e.g., disease progression), it is assumed that MMR status would not have a meaningful impact on inferences on the change in HRQoL due to the addition of durvalumab to carboplatin + paclitaxel.

10.1.2 Data collection

HRQoL measures were collected at baseline (day 1 of cycle 1) and then every 3 weeks (± 3 days) for the first 18 weeks and then every 4 weeks (± 3 days) until PFS2. The EQ-5D-5L and all other PROMs were self-administered and completed at home or at the study site if the assessment time point coincided with a scheduled site visit.

Recorded values on the EQ-5D-5L were mapped to the Danish value set as preferred by DMC. (59) The statistical relationship between EQ-5D-5L health state utility and treatment, and health status was assessed using regression analysis. To account for the repeated measurements in the study, a mixed model for repeated measures (MMRM) method was used to model EQ-5D-5L health state utilities. The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression. Due to censoring, the EQ-5D-5L observations obtained during this period have an unknown/missing health status and therefore, must be omitted from the analysis. The MMRM analysis was performed using the restricted maximum likelihood method with randomized treatment and progression status as fixed effects in the model, either as individual terms, in combination, or with interaction terms.

Compliance rates for the EQ-5D-5L questionnaire were high at baseline and similar between arms (78.7% for durvalumab + CP; 80.0% for placebo + CP) (

Table 37). Compliance rates decreased over time across the treatment arms and after Week 50 started to fall below 50%. MMRM handles missing data implicitly by assuming that a subject's missing data would have followed the trend of their treatment group based on variables included in the model, and is valid when data are missing at random (MAR), conditional on one of the variables included in the MMRM analysis. Therefore, if attrition and missingness can be somewhat explained by treatment or progression status, and the baseline values of patients completing questions (and their expected prognosis) are comparable, then missing data is unlikely to influence our inferences comparing HRQoL between durvalumab and placebo. [redacted]

Table 37 Pattern of missing data and completion

Time point	Durvalumab + CP				Placebo + CP			
	HRQoL population N*	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N*	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Time point	Durvalumab + CP				Placebo + CP			
	HRQoL population N*	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N*	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time point	Durvalumab + CP				Placebo + CP			
	HRQoL population N*	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N*	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Time point	Durvalumab + CP				Placebo + CP			
	HRQoL population N*	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N*	Missing N (%)	Expected to complete N	Completion N (%)
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[redacted]								
[redacted]								
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[redacted]

10.1.3 HRQoL results

Baseline EQ-5D-5L scores were comparable for durvalumab + CP and placebo + CP (Table 37). In both treatment arms, the EQ-5D index value and VAS were similar between arms and remained mostly stable during follow-up ([redacted] Based on the MMRM models, there were no significant differences in EQ-5D-5L utility value between the durvalumab + CP and placebo + CP arms during follow-up, and this is conclusion was sustained when analyzing the data by progression status and treatment arm (Table 38). This is consistent with the conclusions from the EMA based on their assessment of the EORTC QLQ-C30 and the EORTC QLQ-EN24 where there were no meaningful differences in HRQoL.(14)

Table 38 EQ-5D-5L summary utility values from DUO-E using the Danish value set

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]					
[redacted]					
[redacted]					
[redacted]					

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

10.2.1 HSUV calculation

NA

10.2.1.1 Mapping

NA

10.2.2 Disutility calculation

NA

10.2.3 HSUV results

NA

Table 39 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				

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

10.3.1 Study design

NA

10.3.2 Data collection

NA

10.3.3 HRQoL Results

NA

10.3.4 HSUV and disutility results

NA

Table 40 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				

Table 41 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
NA				

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

Table 42 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
NA				

11.2 Medicines– co-administration

NA

11.3 Administration costs

Table 43 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
NA				

11.4 Disease management costs

Table 44 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
NA				

11.5 Costs associated with management of adverse events

Table 45 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
NA		

11.6 Subsequent treatment costs

Table 46 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
NA				

11.7 Patient costs

Table 47 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
NA	

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

NA

12. Results

12.1 Base case overview

Table 48 Base case overview

Feature	Description
NA	

12.1.1 Base case results

Table 49 Base case results, discounted estimates

	[Intervention]	[Comparator]	Difference
NA			

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Table 50 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
NA					

12.2.2 Probabilistic sensitivity analyses

NA

13. Budget impact analysis

Number of patients (including assumptions of market share)

Table 51 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
NA					

Budget impact

Table 52 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
NA					

14. List of experts

NA

15. References

1. Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol. 2022;33(9):860-77.
2. Abu-Rustum N, Yashar C, Arend R, Barber E, Bradley K, Brooks R, et al. Uterine Neoplasms, Version 1.2023, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network: JNCCN. 2023;21(2):181-209.
3. Miller DS, Filiaci VL, Mannel RS, Cohn DE, Matsumoto T, Tewari KS, et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2020;38(33):3841-50.
4. Banning K, Fucinari J, Fielder A, Ruterbusch JJ, Beebe-Dimmer JL, Schwartz AG, et al. Quality of life in endometrial cancer survivors by grade of disease. Cancer Med. 2023;12(12):13675-86.
5. Martins D, O'Sullivan DE, Boyne DJ, Cheung WY, Allonby O, Habash M, et al. Understanding Characteristics, Treatment Patterns, and Clinical Outcomes for Individuals with Advanced or Recurrent Endometrial Cancer in Alberta, Canada: A Retrospective, Population-Based Cohort Study. Current Oncology (Toronto, Ont). 2023;30(2):2277-89.
6. Powell MA, Bjørge L, Willmott L, Novák Z, Black D, Gilbert L, et al. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2024;35(8):728-38.
7. Jean-François Baurain HSC, Jessica Thomes-Pepin, Michael J. Sundborg, Michael A. Gold, Byoung Gie Kim, Stephanie V. Blank, Ji-Houng Liu et al. Durvalumab plus carboplatin/paclitaxel followed by durvalumab with or without olaparib as a first-line treatment for endometrial cancer: Overall survival and additional secondary efficacy endpoints by mismatch repair status in the DUO-E/GOG-3041/ENGOT-EN10 Trial. Presented at SGO 2024; 16-18 March.
8. Westin SN, Moore K, Chon HS, Lee JY, Thomes Pepin J, Sundborg M, et al. Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial. J Clin Oncol. 2024;42(3):283-99.
9. Makker V, MacKay H, Ray-Coquard I, Levine DA, Westin SN, Aoki D, et al. Endometrial cancer. Nature Reviews Disease Primers. 2021;7(1):88.
10. Alexa M, Hasenburg A, Battista MJ. The TCGA Molecular Classification of Endometrial Cancer and Its Possible Impact on Adjuvant Treatment Decisions. Cancers. 2021;13(6):1478.
11. Richman S. Deficient mismatch repair: Read all about it (Review). International Journal of Oncology. 2015;47(4):1189-202.
12. Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, Musa FB, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. The New England Journal of Medicine. 2023;388(23):2159-70.
13. Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novák Z, Black D, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. The New England Journal of Medicine. 2023;388(23):2145-58.
14. Agency EM. Assesment report for Imfinzi - EMEA/H/C/004771. 2024 2024-06-28.
15. Ørtoft G, Høgdall C, Hansen ES, Dueholm M. Survival and recurrence in stage II endometrial cancers in relation to uterine risk stratification after introduction of lymph node resection and omission of postoperative radiotherapy: a Danish Gynecological Cancer Group Study. Journal of Gynecologic Oncology. 2020;31(2):e22.

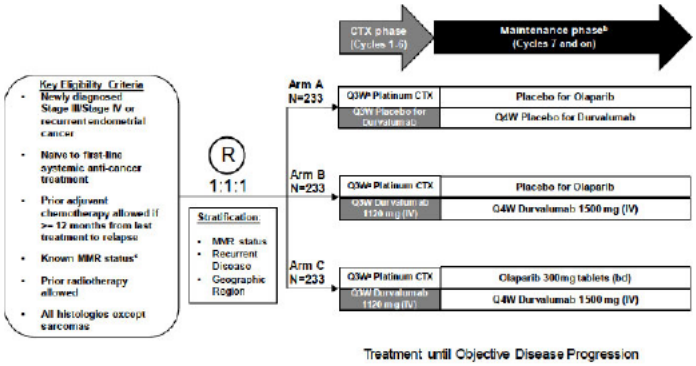
16. Ørtoft G, Lausten-Thomsen L, Høgdall C, Hansen ES, Dueholm M. Lymph-vascular space invasion (LVSI) as a strong and independent predictor for non-locoregional recurrences in endometrial cancer: a Danish Gynecological Cancer Group Study. Journal of Gynecologic Oncology. 2019;30(5):e84.
17. Gruppe DGC. Landsdækkende klinisk database for gynækologisk kræft . National Årsrapport 2021/2022. 2022 30. june 2022.
18. Lorenzi M, Amonkar M, Zhang J, Mehta S, Liaw K-L. Epidemiology of Microsatellite Instability High (MSI-H) and Deficient Mismatch Repair (dMMR) in Solid Tumors: A Structured Literature Review. Journal of Oncology. 2020;2020(1):1807929.
19. De Felice F, Marchetti C, Tombolini V, Panici PB. Immune check-point in endometrial cancer. International Journal of Clinical Oncology. 2019;24(8):910-6.
20. Gruppe DGC. Kap. 1 Indledning. Retningslinjer for visitation, diagnostik, behandling og kontrol af cancer corporis uteri2016. p. 1-7.
21. Jaishuen A, Kunakornporamat K, Viriyapak B, Benjapibal M, Chaopotong P, Petsuksiri J, et al. Incidence and clinical outcomes of non-endometrioid carcinoma of endometrium: Siriraj Hospital experience. Asian Pac J Cancer Prev. 2014;15(6):2905-9.
22. Bristow RE, Purinton SC, Santillan A, Diaz-Montes TP, Gardner GJ, Giuntoli RL. Cost-effectiveness of routine vaginal cytology for endometrial cancer surveillance. Gynecol Oncol. 2006;103(2):709-13.
23. Barbosa Lyliana, Silveira E, Napoleao B, Ribeiro M, Pagani M, Silveira V. EP098/#769 Endometrial cancer: assessment of incidence, staging and survival in a university hospital. Int J Gynecol Cancer. 2022;32(Suppl 3):A87-A.
24. Akhavan S, Mohseni M, Gilani MM, Mousavi AS, Sheikhhasani S, Feizabad E. Prevalence and clinicopathological differences between type I and type II of endometrial cancer. PJMHS. 2021;15(3):992-5.
25. Kristina Lindemann WK, Andreas Kleppe, Kari Anne R. Tobin, Manohar Pradhan, Maria X. Isaksen, Ljiljana Vlatkovic, Hårvard E. Danielsen, Gunnar B. Kristensen, Hanne A Askautrud. Impact of molecular profile on prognosis and relapse pattern in low and intermediate risk endometrial cancer. European Journal of Cancer. 2024;200(113584).
26. Cosgrove CM, Backes FJ, O'Malley D, Bixel KL, Suarez AA, Fowler JM, et al. Endometrial Cancer: Who Lives, Who Dies, Can We Improve Their Story? Oncologist. 2021;26(12):1044-51.
27. Huijgens AN, Mertens HJ. Factors predicting recurrent endometrial cancer. Facts Views Vis Obgyn. 2013;5(3):179-86.
28. Evrard C, Alexandre J. Predictive and Prognostic Value of Microsatellite Instability in Gynecologic Cancer (Endometrial and Ovarian). Cancers (Basel). 2021;13(10).
29. Passarello K, Kurian S, Villanueva V. Endometrial Cancer: An Overview of Pathophysiology, Management, and Care. Seminars in Oncology Nursing. 2019;35(2):157-65.
30. Ferrandina G, Petrillo M, Mantegna G, Fuoco G, Terzano S, Venditti L, et al. Evaluation of quality of life and emotional distress in endometrial cancer patients: A 2-year prospective, longitudinal study. Gynecologic Oncology. 2014;133(3):518-25.
31. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2016;17(8):1114-26.
32. Heo J, Chun M, Oh YT, Noh OK. Psychiatric comorbidities among endometrial cancer survivors in South Korea: a nationwide population-based, longitudinal study. J Gynecol Oncol. 2019;30(2):e15.
33. Gao H, Xiao M, Bai H, Zhang Z. Sexual Function and Quality of Life Among Patients With Endometrial Cancer After Surgery. International Journal of Gynecologic Cancer. 2017;27(3):608-12.

34. Makker V, MacKay H, Ray-Coquard I, Levine DA, Westin SN, Aoki D, et al. Endometrial cancer. Nat Rev Dis Primers. 2021;7(1):88.
35. SEER. Corpus and Uterus, NOS. Recent Trends in SEER Age-Adjusted Incidence Rates, 2000-2020. Avaliable at: https://seer.cancer.gov/statistics-network/explorer/application.html?site=58&data_type=1&graph_type=2&compareBy=age_range&chk_age_range_1=1&chk_age_range_16=16&chk_age_range_62=62&chk_age_range_122=122&chk_age_range_160=160&chk_age_range_166=166&rate_type=2&hdn_sex=3&race=1&stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=0&advopt_show_apc=on&advopt_display=2#resultsRegion0. Last accessed: December 2023 2023 [
36. ESMO. ENDOMETRIAL CANCER: A GUIDE FOR PATIENTS. 2012.
37. Alexa M, Hasenburg A, Battista MJ. The TCGA Molecular Classification of Endometrial Cancer and Its Possible Impact on Adjuvant Treatment Decisions. Cancers (Basel). 2021;13(6).
38. Abu-Rustum N, Yashar C, Arend R, Barber E, Bradley K, Brooks R, et al. Uterine Neoplasms, Version 1.2023, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2023;21(2):181-209.
39. Núria Mulet-Margalef JL, Jordi Badia-Ramentol, Mireya Jimeno, Carolina Sanz Monte, José Luis Manzano Mozo, Alexandre Calon. Challenges and Therapeutic Opportunities in the dMMR/MSI-H Colorectal Cancer Landscape. Cancers (Basel). 2023;15(4):1022.
40. Bradley Corr CC, Daniel Spinosa, Saketh Guntupalli. Endometrial cancer: molecular classification and future treatments. BMJ Med. 2022;1(1):e000152.
41. gruop TN. NORDCAN - Association of the Nordic Cancer Registries. 2024 [updated 2017. Available from: https://nordcan.iarc.fr/en/dataviz/prevalence?mode=cancer&group_populations=1&multiple_cancers=1&cancers=200&sexes=2&group_cancers=0&key=crude_rate&survival=0&populations=208.
42. Medicinrådet. Medicinrådets anbefaling vedr. dostarlimab i kombination med carboplatin og paclitaxel til behandling af avanceret eller tilbagevendende dMMR/MSI-H kræft i livmoderslimhinden. 2024 Aug 28. Contract No.: 190512.
43. DGCG. Onkologisk behandling af endometriecancer. 2023 Oct 18.
44. Gruppe DGC. Kap. 1 Indledning. 2016. Contract No.: 3. revision af guideline -.
45. Robert Shisler JAS, Vivian Wang, Courtney Hebert, Ritu Salani, Ashley S Felix. Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecol Oncol. 2018;148(2):403-13.
46. AstraZeneca. DUO-E Clinical Study Protocol: A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer (DUO-E). January 2023. 2023.
47. AstraZeneca Data on File. Core Data Sheet: IMFINZI. 2023.
48. Schofield DJ, Percival-Alwyn J, Rytelewski M, Hood J, Rothstein R, Wetzel L, et al. Activity of murine surrogate antibodies for durvalumab and tremelimumab lacking effector function and the ability to deplete regulatory T cells in mouse models of cancer. MAbs. 2021;13(1):1857100.
49. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
50. AstraZeneca. DUO-E Clinical Study Report: A Randomised, Multicentre, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination with Durvalumab, Followed by Maintenance Durvalumab with or without

Olaparib in Patients with Newly Diagnosed Advanced or Recurrent Endometrial Cancer. September 2023. 2023.
51. Van Nieuwenhuysen E MK, Tillmanns T et al. . Durvalumab plus carboplatin/paclitaxel followed by durvalumab with/without olaparib for endometrial cancer: mismatch repair deficient and/or microsatellite instability-high subpopulation efficacy analyses from the DUO-E trial. 2024.
52. C-F Burman CS, O Guilbaud. A recycling framework for the construction of Bonferroni-based multiple tests. Stat med. 2009;28(5):739-61.
53. Agency EM. Assessment report Imfinzi. International non-proprietary name: durvalumab Procedure No. EMEA/H/C/004771/0000. Committee for Medicinal Products for Human Use (CHMP); 2018 26 July 2018.
54. Nicoletta Colombo EB, Kenichi Harano, Francesca Galli, Emma Hudson, Yoland Antill, Chel Hun Choi, Manuela Rabaglio, Frederic Marmé, Christian Marth, Gabriella Parma, Lorena Fariñas-Madrid, Shin Nishio, Karen Allan, Yeh Chen Lee, Elisa Piovano, Beatriz Pardo, Satoshi Nakagawa, John McQueen, Claudio Zamagni, Luis Manso, Kazuhiro Takehara, Giulia Tasca, Annamaria Ferrero, Germana Tognon, Andrea Alberto Lissoni, Mariacristina Petrella, Maria Elena Laudani, Eliana Rulli, Sara Uggeri, M Pilar Barretina Ginesta; AtTEnd study group. Atezolizumab and chemotherapy for advanced or recurrent endometrial cancer (AtTEnd): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2024;25(9):1135-46.
55. Wiksten A HN, Piepho HP, et al. . Nonproportional Hazards in Network Meta-Analysis: Efficient Strategies for Model Building and Analysis. . Value in Health. 2020;23:918-27.
56. Freeman SC CN, Sutton AJ, et al. . Challenges of modelling approaches for network meta-analysis of time-to-event outcomes in the presence of non-proportional hazards to aid decision making: Application to a melanoma network. Stat Methods Med Res 2022;31:839-61.
57. Agency EM. Assessment report for Jemperli - Procedure No. EMEA/H/C/005204/II/0023. 2023 2023 - 10 - 12.
58. Medicinrådet. The Danish Medicines Council methods guide for assessing new pharmaceuticals.; 2023.
59. Cathrine Elgaard Jensen SSS, Claire Gudex, Morten Berg Jensen, Kjeld Møller Pedersen, Lars Holger Ehlers The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Appl Health Econ Health Policy. 2021;19(4):579-91.
60. Bucher HC GG, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. . J Clin Epidemiol. 1997;50:683-91.
61. Dissemination CfRa. Systematic reviews: CRD's guidance for undertaking reviews in health care. 2009 Jan.
62. AstraZeneca. Data on File.

Appendix A. Main characteristics of studies included

Table 53 Main characteristic of studies included

Trial name: DUO-E	NCT number: NCT04269200
Objective	This Phase III study will assess the efficacy and safety of durvalumab in combination with platinum-based chemotherapy (paclitaxel + carboplatin) followed by maintenance durvalumab with or without olaparib for patients with newly diagnosed advanced or recurrent endometrial cancer. Target patient population: Adult female patients with histologically confirmed diagnosis of epithelial endometrial carcinoma (excluding sarcomas): newly diagnosed Stage III (measurable disease per Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1), newly diagnosed Stage IV (with or without disease following surgery or diagnostic biopsy), or recurrent (measurable or non-measurable disease per RECIST 1.1) endometrial cancer.
Publications – title, author, journal, year	Shannon Neville Westin et al.,DUO-E/GOG-3041/ENGOT-EN10: a randomized phase III trial of first-line carboplatin (carb) and paclitaxel (pac) in combination with durvalumab (durva), followed by maintenance durva with or without olaparib (ola), in patients (pts) with newly diagnosed (nd) advanced or recurrent endometrial cancer (EC).. JCO 38, TPS6108-TPS6108(2020). DOI:10.1200/JCO.2020.38.15_suppl.TPS6108
Study type and design	Double-blinded randomized placebo-controlled phase 3 study. Enrolled patients were randomly assigned 1:1:1. Patients will be stratified according to MMR status, disease status and geographic region. The investigators, patients, and sponsor were masked during treatment assignment. The study design is presented below. 
Sample size (n)	As part of the global recruitment, approximately 699 eligible patients with endometrial cancer will be recruited from approximately 210 sites and randomised in a 1:1:1 ratio to the study treatments (N=233 patients per arm, total n=699)
Main inclusion criteria	• Age ≥18 years at the time of screening and female. • Histologically confirmed diagnosis of epithelial endometrial carcinoma. All histologies, including carcinosarcomas, will be allowed. Sarcomas will not be allowed.

Trial name: DUO-E	NCT number: NCT04269200
	• Patient must have endometrial cancer in one of the following categories: 1. Newly diagnosed Stage III disease (measurable disease per RECIST 1.1 following surgery or diagnostic biopsy), 2. Newly diagnosed Stage IV disease (with or without disease following surgery or diagnostic biopsy) 3. Recurrence of disease (measurable or non-measurable disease per RECIST 1.1) where the potential for cure by surgery alone or in combination is poor. • Naïve to first line systemic anti-cancer treatment. For patients with recurrent disease only, prior systemic anti-cancer treatment is allowed only if it was administered in the adjuvant setting and there is at least 12 months from date of last dose of systemic anti-cancer treatment administered to date of subsequent relapse • FPPE tumor sample must be available for MMR evaluation. • Has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 7 days of starting study treatment.
Main exclusion criteria	• History of leptomeningeal carcinomatosis. • Brain metastases or spinal cord compression. • Prior treatment with PARP inhibitors. • Any prior exposure to immune-mediated therapy, including (but not limited to) other anti CTLA-4, anti-PD-1, anti-PD-L1, or anti-programmed-cell-death ligand 2 (anti-PD-L2) antibodies, excluding therapeutic anticancer vaccines.
Intervention	Durvalumab: 1120 mg durvalumab IV every 3rd week (+ Carboplatin AUC 5 mg/mL/min Paclitaxel 175 mg/m2 Q3W for 6 cycles) in the chemotherapy phase. 1500 mg durvalumab every 4th week in the maintenance phase. N=233 Durvalumab plus olaparib: 1120 mg durvalumab IV every 3rd week (+ Carboplatin AUC 5 mg/mL/min Paclitaxel 175 mg/m2 Q3W for 6 cycles) in the chemotherapy phase. 1500 mg durvalumab every 4th week and 300 mg Olaparib tablets (bd) in the maintenance phase. (not relevant for this application) N=233
Comparator(s)	Carboplatin and paclitaxel: Carboplatin AUC 5 mg/mL/min Paclitaxel 175 mg/m2 Q3W for 6 cycles N=233
Follow-up time	The median (range) duration of follow-up in patients censored for PFS was 12.6 months (0.0-31.6) in the control arm, and 15.4 months (0.0-29.1) in the durvalumab arm.

Trial name: DUO-E	NCT number: NCT04269200
Is the study used in the health economic model?	NA
Primary, secondary and exploratory endpoints	**Primary endpoint:** Investigator-assessed PFS using RECIST 1.1 **Secondary endpoints:** OS (Investigator assessed) Time to second progression or death (PFS2) Objective response rate (ORR) (Investigator assessed using RECIST 1.1) Duration of response (Investigator assessed using RECIST 1.1) Time to first subsequent therapy or death (TFST) (Investigator assessed) Time to second subsequent therapy or death (TSST) (Investigator assessed) Time to treatment discontinuation or death (TDT) (Investigator assessed) PROs (EORTC QLQ-C30, QLQ-EN24) PK Safety and tolerability
Method of analysis	The primary objectives of the study were to compare PFS (per RECIST 1.1 as assessed by investigator) in the durvalumab + CP arm vs. SoC arm and the durvalumab + olaparib + CP arm vs. the SoC arm. The coprimary endpoints were considered to have been met if the null hypotheses were rejected based on the primary analysis of PFS in the full analysis set (ITT population). In order to strongly control the Type I error at 5% (2-sided), a multiple testing procedure (MTP) was used across the key endpoints (PFS and OS) and treatment comparisons of interest (durvalumab + CP vs. SoC and durvalumab + olaparib + CP vs. SoC). Hypotheses will be tested using a MTP with an alpha-exhaustive recycling strategy (as described in Burman *et al.* 2009). With this approach, hypotheses were tested at the time of primary PFS analysis (OS first interim analysis [1IA]; first data cut off [DCO1]: 12 April 2023) Additional analyses using an unstratified Cox proportional hazard models to determine the consistency of treatment effect between subgroups were also undertaken. This includes analyses by MMR status (stratification factor), however these analyses were not powered for statistical inference.

Trial name: DUO-E	NCT number: NCT04269200
Subgroup analyses	Pre-specified exploratory subgroup analyses of PFS per investigator assessment and OS were performed based on the ITT analysis set and dMMR subset for the ITT analysis set to explore homogeneity of the treatment effect. Additional analyses (to the method of analysis described above) using an unstratified Cox proportional hazard models to determine the consistency of treatment effect between subgroups were also undertaken. This includes analyses by MMR status (stratification factor), however these analyses were not powered for statistical inference.
Other relevant information	

Trial name: RUBY	NCT number: NCT03981796
Objective	The primary objectives of Part 1 of the RUBY study were to compare the progression-free survival (PFS) of participants treated with dostarlimab plus CP followed by dostarlimab to participants administered placebo plus CP followed by placebo, as assessed by the Investigator per Response Evaluation Criteria in Solid Tumours version 1.1. in patients with primary advanced or recurrent endometrial cancer.
Publications – title, author, journal, year	Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer, M.R. Mirza et al. The new England Journal of Medicine, published March 27, 2023.
Study type and design	RUBY is a Phase 3, randomized, double-blind, multicenter study in two parts. Part 1 of the study is to evaluate the efficacy and safety of treatment with dostarlimab plus CP followed by dostarlimab versus treatment with placebo plus CP followed by placebo in participants with primary advanced (Stage III or IV) or recurrent EC. Part 2 is to evaluate the efficacy and safety of dostarlimab plus CP followed by dostarlimab plus niraparib versus placebo plus CP followed by placebo in participants with recurrent or primary advanced (Stage III or IV) endometrial cancer.
Sample size (n)	From July 18, 2019, through February 23, 2021, a total of 607 patients from 113 sites in 19 countries were screened and 494 underwent randomization; 245 were assigned to receive dostarlimab plus CP (dostarlimab group) and 249 were assigned to receive placebo plus CP (placebo group). Seven patients (4 in dostarlimab group and 3 in the placebo group) did not receive treatment and were excluded from the safety analysis. Of the 494 patients who underwent randomization, 118 had dMMR–MSI-H tumours confirmed by source-verified classification (53 in the dostarlimab group and 65 in the placebo group). As of the data-

Trial name: RUBY	NCT number: NCT03981796
	cutoff date of September 28, 2022, a total of 88 patients in the overall population were receiving treatment in one of the two groups
Main inclusion criteria	Diagnosis of severe sickle cell disease as defined by: • Documented SCD genotype (βS/βS, βS/β0, βS/β+, or others) and • History of at least two severe vaso-occlusive events per year requiring medical attention despite hydroxyurea or other supportive care measures in the two year-period prior to provision of informed consent or assent, as applicable Karnofsky (for subjects >16 years of age) or Lansky (for subjects ≤ 16 years of age) Performance Status ≥ 80% Normal transcranial doppler velocity in subjects 16 years of age or younger
Main exclusion criteria	• Available 10/10 HLA-matched related donor • Prior HSCT or contraindications to autologous HSCT • Any contraindications to the use of plerixafor during the mobilization of hematopoietic stem cells (HSCs) and any contraindications to the use of busulfan and any other medicinal products required during the myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients • Unable to receive red blood cell (RBC) transfusion for any reason • Unable or unwilling to comply with standard of care changes in background medical treatment in preparation of, during, or following HSCT, including and not limited to discontinuation of hydroxyurea, voxelotor, crizanlizumab, or L-glutamine • Any history of severe cerebral vasculopathy • Inadequate end organ function • Advanced liver disease • Any prior or current malignancy or immunodeficiency disorder • Immediate family member with a known or suspected Familial Cancer Syndrome • Clinically significant and active bacterial, viral, fungal, or parasitic infection
Intervention	Dostarlimab 500 mg IV + carboplatin AUC 5 mg/mL/min IV + paclitaxel 175 mg/m2 IV Q3W for cycles 1–6 followed by dostarlimab 1,000 mg IV Q6W up to 3 years. N= 245 (53 dMMR/MSI-H)
Comparator(s)	Placebo + carboplatin AUC 5 mg/mL/min IV + paclitaxel 175 mg/m2 IV Q3W for cycles 1–6 followed by placebo Q6W up to 3 years. N= 249 (65 dMMR/MSI-H)
Follow-up time	Median follow-up of 25.4 months (range 19.2 to 37.8) in the overall population Median follow-up of 24.8 months (range 19.2 to36.9) in the dMMR/MSI-H population

Trial name: RUBY	NCT number: NCT03981796
Is the study used in the health economic model?	NA
Primary, secondary and exploratory endpoints	RUBY-1 evaluated dual primary endpoints: • Investigator-assessed PFS according to RECIST v1.1 criteria in patients with dMMR/MSI-H tumours and in the overall trial population. • OS in the overall population Secondary endpoints: • PFS by BICR • ORR • Duration of response • Disease control rate • PFS2 • PROs (EORTC-QLQ-C30; EORTC-QLQ-EN24; EQ-5D-5L) • PK and immunogenicity analyses • Safety and tolerability
Method of analysis	All efficacy analyses were intention-to-treat analyses. The Kaplan–Meier method were used to estimate rates of progression-free survival and overall survival, and a stratified log-rank test for treatment comparisons.
Subgroup analyses	Pre-specified exploratory subgroup analyses of PFS per investigator assessment and OS were performed based on the ITT analysis set and dMMR/MSI-H subset for the ITT analysis set to explore homogeneity of the treatment effect across the following subgroups: • Age (<65 years or ≥65 years) • Race (White or other) • Region (North American, Europe, Western Europe, or Eastern Europe) • Histology (endometrioid carcinoma or other) • Disease status at baseline (recurrent, primary stage III, or primary stage IV) • MMR/MSI status at baseline (dMMR/MSI-H or MMRp/MMS) • Prior external pelvic radiotherapy (yes or no) • Subjects with “no disease” at baseline
Other relevant information	

Appendix B. Efficacy results per study

Results per study

Table 54 Results per study

Results of DUO-E NCT04269200											
				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**		
Median PFS dMMR	Durvalumab + CP	46	NR (NR to NR) months	NA	NA	NA	HR: 0.42	0.22-0.80	NA	PFS was calculated using the KM technique. Confidence interval for median PFS was derived based on Brookmeyer-Crowley method. The HR and CI were estimated from a cox proportional hazards model stratified by: MMR and disease status. The CI was calculated using a profile likelihood approach. The p-value was calculated using a log rank test stratified by variables.	EPAR
	Placebo+ CP	49	7.0 (6.7-14.8) months								
12-month PFS rate	Durvalumab + CP	46	67.6% (51.1-80.0)	24.6 % points	NA	NA	NA	NA	NA		EPAR

Results of DUO-E NCT04269200											
				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		
dMMR	Placebo+ CP	49	43.3% (27.3-58.3)								
18-month PFS rate	Durvalumab + CP	46	67.6% (51.1-80.0)	36.2 % points	NA	NA	NA	NA	NA		EPAR
dMMR	Placebo+ CP	49	31.7% (16.7-47.9)								
Median OS, month	Durvalumab + CP	46	NR (NR to NR) months	NA	NA	NA	HR: 0.34	0.13-0.79	NA	For the OS analysis, the HRs and CIs were estimated from an unstratified Cox proportional hazards model. The HR and CI were estimated from a cox proportional hazards model stratified by: MMR and disease status. The CI was calculated using a profile likelihood approach. The p-value was calculated using a log rank test stratified by variables.	EPAR
dMMR	Placebo+ CP	49	23.7 (16.9-NR) months								

Results of DUO-E NCT04269200											
				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		
12-month survival rate dMMR	Durvalumab + CP	46	91.2% (78.2-96.6)	16.8 % points	NA	NA	NA	NA	NA		EPAR
	Placebo+ CP	49	74.4% (59.4-84.6)								
EQ-5D-5L (Mean (SE)) (all visits)	Durvalumab + CP	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
	Placebo+ CP	[redacted]	[redacted]								

Results of RUBY-1 (NCT03981796)											
				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		
Investigator-assessed PFS at 24 months dMMR/MSI-H	Dostarlimab arm	53	61.4 (46.3-73.4) months	45.7	NA	NA	HR: 0.28	0.16–0.50	P>0.001	The Kaplan–Meier method was used to estimate rates of progression-free survival and overall survival, and a stratified log-rank test for treatment comparisons.	Mirza et al. 2023
	Placebo arm	65	15.7 (7.2-27.0) months								
OS at 24 months dMMR/MSI-H	Dostarlimab arm	53	83.3 (66.8-92.0) months	24.6	NA	NA	HR: 0.30	0.13–0.70	NA	The Kaplan–Meier method was used to estimate rates of progression-free survival and overall survival, and a stratified log-rank test for treatment comparisons.	Mirza et al. 2023
	Placebo arm	65	58.7 (43.4-71.2)								

Appendix C. Comparative analysis of efficacy

C.1 Efficacy of durvalumab plus carboplatin and paclitaxel compared to carboplatin and paclitaxel for primary advanced or recurrent dMMR endometrial cancer

Table 55 Comparative analysis of studies comparing durvalumab + CP to placebo + CP for patients with primary advanced or recurrent dMMR endometrial cancer

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Median PFS, months	DUO-E	NA	NA	NA	HR: 0.42	0.22-0.80	NA	A stratified log-rank test was used for for treatment comparisons.	NA
Median OS, months	DUO-E	NA	NA	NA	HR: 0.34	0.13-0.79	NA	A stratified log-rank test was used for for treatment comparisons.	NA
EQ-5D-5L (Mean (SE)) (all visits)	DUO-E	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	EQ-5D-5L	NA

C.2 Efficacy of durvalumab plus carboplatin and paclitaxel compared to dostarlimab plus carboplatin and paclitaxel for primary advanced or recurrent dMMR/MSI-H endometrial cancer

The authorization for dostarlimab was based on the results of the RUBY study, which reported efficacy outcomes in the dMMR/MSI-H population, according to local testing for either MMR or MSI. The RUBY study main analysis relied on a population composed by patients who were either dMMR or MSI-H, which is not aligned with the main population from DUO-E, therefore precluding any comparison between durvalumab and dostarlimab in dMMR EC.

For this reason, the ITC used data from a post-hoc subgroup of DUO-E with either a positive dMMR test result, or an MSI-H test result. These data were compared with the efficacy results of the dMMR/MSI-H subgroup of RUBY. This comparison was performed to ensure that the populations from both studies were aligned, and to reduce the risk of bias from potential imbalances in the distribution of effect modifiers across studies.

Using RUBY and DUO-E trials, a connected network can be created using the placebo in combination with carboplatin and paclitaxel (CP) as an anchor (common comparator), allowing for anchored ITCs to be performed.

The outcomes of interest for the ITC were:

- **Progression-free survival (PFS)**, defined as time to progression according to RECIST criteria (version 1.1) or death in the absence of progression.
- **Overall survival (OS)**, defined as time to death from any cause

The anchored ITC was performed via a frequentist approach, using the Bucher methodology, due to the simplicity of the comparison being performed. This approach preserves randomization within trials, and yields reliable results subject to the transitivity assumption, which requires that the distribution of effect modifiers is balanced across trials.

The ITC was performed using a fixed effects model as there was insufficient data (n=1 study per comparison) to estimate the between-study heterogeneity of treatment effects in a random effects model. The variance for the indirect evidence was based on the sum of the variances for the direct head-to-head comparisons and therefore the ITC is fundamentally associated with greater uncertainty than a direct comparison.

The treatment effects for PFS and OS were modelled as the log-hazard ratio and its standard error. The log-hazard ratio for each study was calculated as the natural logarithm of the reported hazard ratio. The standard error was calculated as the difference between the logarithms of the upper and lower confidence intervals, divided by 2 times the percentile point corresponding to the alpha-level of the interval (e.g., 1.96 for 95% confidence intervals).

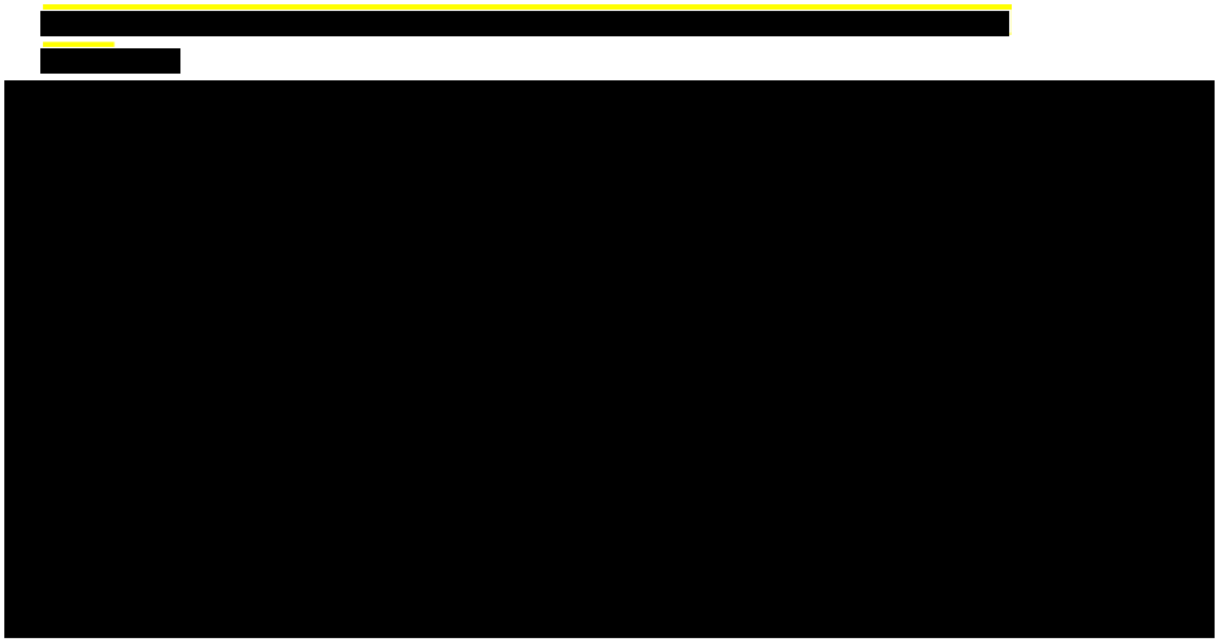
The efficacy ITC results were summarized in terms of the hazard ratio and 95% confidence intervals for durvalumab + CP versus dostarlimab + CP. A hazard ratio of less than 1 indicated that durvalumab + CP was more efficacious than dostarlimab + CP, and vice versa for values above 1.

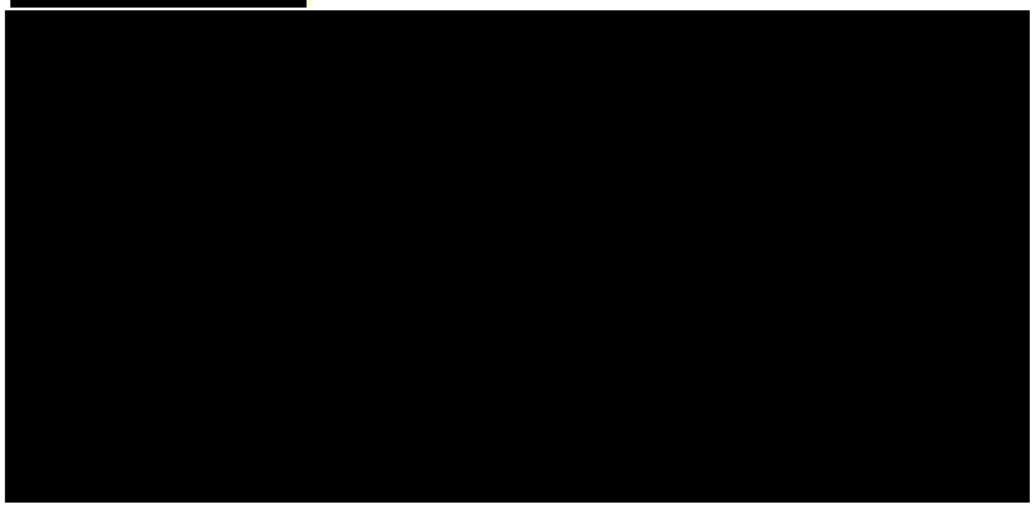
Table 56 Comparative analysis of studies comparing durvalumab in combination with carboplatin and paclitaxel to dostarlimab in combination with carboplatin and paclitaxel for patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer

Outcome	Relative difference in effect				Method used for quantitative synthesis	Result used in the health economic analysis?
	Included studies	Difference	CI	P value		
Investigator-assessed progression-free survival (per RECIST v1.1.)	DUO-E RUBY-1	[redacted]	[redacted]	N/A	The log HRs for the studies included were compared using the Bucher method with fixed effects	N/A
Overall survival	DUO-E RUBY-1	[redacted]	[redacted]	N/A	The log HRs for the studies included were compared using the Bucher method with fixed effects	N/A

(13)

[redacted]





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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Appendix D. Extrapolation

D.1 Extrapolation of [effect measure 1]

NA

D.1.1 Data input

NA

D.1.2 Model

NA

D.1.3 Proportional hazards

NA

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

NA

D.1.5 Evaluation of visual fit

NA

D.1.6 Evaluation of hazard functions

NA

D.1.7 Validation and discussion of extrapolated curves

NA

D.1.8 Adjustment of background mortality

NA

D.1.9 Adjustment for treatment switching/cross-over

NA

D.1.10 Waning effect

NA

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

NA

Appendix E. Serious adverse events

Table 59 Most common SAEs by System Organ Class and Preferred Term (Frequency ≥ 1% patients in any treatment group in SoC, durvalumab + CP, and durvalumab + olaparib CP in DUO-E overall phase) Compared with the durvalumab and olaparib pools (Safety Analysis Set)

System organ class/ Preferred term	Number (%) of patients [a]				
	DUO-E Overall			Durvalumab Pan-tumour Pool (N = 4045)	Olaparib 300 mg bd Tablet Pool (N = 3556)
	SoC (N = 236)	SoC + D (N = 235)	SoC + D + O (N = 238)		
Patients with any SAE	**73 (30.9)**	**73 (31.1)**	**85 (35.7)**	**1448 (35.8)**	**670 (18.8)**
Blood and lymphatic system disorders					
Anaemia	10 (4.2)	1 (0.4)	16 (6.7)	28 (0.7)	146 (4.1)
Febrile neutropenia	8 (3.4)	4 (1.7)	7 (2.9)	0	11 (0.3)
Neutropenia	3 (1.3)	3 (1.3)	5 (2.1)	2 (<0.1)	12 (0.3)
Aplasia pure red cell	0	0	3 (1.3)	0	0
Infections and infestations					
Urinary tract infection	5 (2.1)	2 (0.9)	6 (2.5)	37 (0.9)	22 (0.6)
Sepsis	3 (1.3)	2 (0.9)	4 (1.7)	54 (1.3)	14 (0.4)
COVID-19	3 (1.3)	1 (0.4)	4 (1.7)	0	4 (0.1)
COVID-19 pneumonia	0	1 (0.4)	3 (1.3)	0	3 (0.1)
Urosepsis	3 (1.3)	1 (0.4)	0	11 (0.3)	5 (0.1)
Respiratory, thoracic, and mediastinal disorders					
Pneumonitis	0	1 (0.4)	3 (1.3)	44 (1.1)	10 (0.3)
Pulmonary embolism	4 (1.7)	0	3 (1.3)	31 (0.8)	21 (0.6)
General disorders and administration site conditions					
Pyrexia	1 (0.4)	1 (0.4)	3 (1.3)	52 (1.3)	15 (0.4)
Gastrointestinal disorders					
Diarrhoea	4 (1.7)	0	2 (0.8)	22 (0.5)	5 (0.1)
Vomiting	2 (0.8)	5 (2.1)	1 (0.4)	24 (0.6)	19 (0.5)
Nausea	2 (0.8)	3 (1.3)	1 (0.4)	12 (0.3)	11 (0.3)
Constipation	3 (1.3)	2 (0.9)	0	17 (0.4)	4 (0.1)
Metabolism and nutrition disorders					
Hyponatraemia	4 (1.7)	5 (2.1)	0	18 (0.4)	6 (0.2)
Vascular disorders					
Deep vein thrombosis	1 (0.4)	2 (0.9)	3 (1.3)	2 (<0.1)	7 (0.2)
Injury, poisoning and procedural complications					
Fall	3 (1.3)	1 (0.4)	1 (0.4)	4 (<0.1)	3 (0.1)
Infusion related reaction	3 (1.3)	0	1 (0.4)	7 (0.2)	1 (0.0)
Investigations					
Neutrophil count decreased	4 (1.7)	1 (0.4)	0	0	4 (0.1)

Appendix F. Health-related quality of life

F.1 Statistical methods

A descriptive summary of the EQ-5D health state utilities by arm and study visit, and by arm and progression status was generated, including estimates of mean, standard deviations, median, and interquartile range (IQR) of utility scores in the full analysis set of DUO-E, consisting of all completed EQ-5D-5L measures (excluding EQ-5D-5L with any missing domain responses).

The statistical relationship between EQ-5D-5L health state utility and treatment, and health status was assessed using regression analysis. To account for the repeated measurements in the study, a mixed model for repeated measures (MMRM) method was used to model EQ-5D-5L health state utilities. The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression. Due to censoring, the EQ-5D-5L observations obtained during this period have an unknown/missing health status and therefore, must be omitted from the analysis.

The MMRM analysis was performed using the restricted maximum likelihood method (REML) with the following covariates included as fixed effects:

- (Randomized) treatment
- Progression status (pre-progression, post-progression)
- Treatment + progression status
- Treatment + progression status + treatment * progression status (i.e., both terms and their interaction included)

The correlation of repeated utility measurements within subjects over time was captured via the specification of covariance structures for the MMRM. A hierarchy of covariance structures were tested, in order of most to least flexible, with results from models using the first covariance structure in the sequence that successfully converged for all models presented. As the fit of the unstructured covariance structure, Toeplitz with heterogeneity, autoregressive with heterogeneity, and Toeplitz failed to converge, the autoregression covariance structures were used in order to reach convergence.

For each model, parameter estimates, and marginal ('least square') means are presented including 95% confidence intervals. The marginal ('least square') mean provides a model-based estimate of the mean utility score by status (treatment and/or progression status) that is averaged over observations and with adjustment for repeated measures.

F.2 Missing data assessments

[redacted]

[redacted]

F.3 Results

[redacted]

Table 60. Utility summary statistics

Treatment	Scenario	Subjects (Observations)	Mean (SD)	Median (IQR)
[redacted]				

Table 61. Summary of regression model estimates

	Treatment	Progression Status	Treatment + Progression Status	Treatment * Progression Status
[redacted]				

Values shown in cells are estimate (standard error) and p-value

Table 62. Summary of marginal means

	Treatment	Progression Status	Treatment + Progression Status	Treatment * Progression Status
[redacted]				
[redacted]				
[redacted]				

Values shown in cells are marginal mean (95% CI)

Appendix G. Probabilistic sensitivity analyses

Table 63. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
NA				

Appendix H. Literature searches for the clinical assessment

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

DUO-E is an ongoing phase III, randomised, double-blinded, placebo-controlled, multicentre trial to assess the efficacy and safety of adding durvalumab to induction carboplatin + paclitaxel chemotherapy, followed by durvalumab or durvalumab plus olaparib as maintenance therapy, in patients with advanced or recurrent endometrial cancer. A global systematic literature review of clinical evidence has been conducted to identify relevant literature in the treatment landscape of endometrial cancer.

Original searches for the global SLR were conducted in September – October 2023. A targeted search using similar search terms was conducted in PubMed in early November 2024 to identify if any further studies had been published specifically relevant to the scope of the Danish application for durvalumab.

Table 64 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
MEDLINE, including MEDLINE In-Process, MEDLINE Daily and MEDLINE Epub Ahead of Print	Ovid SP	1946 to 11.09.2023	13.09.2023
Embase	Ovid SP	1974 to 11.09.2023	13.09.2023
CDSR and CENTRAL	Wiley Online	Up until 12.09.2023	13.09.2023
DARE	University of York CRD	Up until 31.03.2015	13.09.2023
MEDLINE, PubMed Central, Bookshelf	PubMed	12.09.2023 to 31.10.2024	05.11.2024

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CRD, Centre for Reviews and Dissemination; DARE, Database of Abstracts of Reviews of Effects

Table 65 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NA			

Table 66 Conference material included in the literature search

Conference	Source	Search strategy	Date of search
ESMO Congress	2023 2022 2021	2023: In the search bar, search 'endometrial OR endometrium OR uterine' and filter to: Abstracts Annals of Oncology 2023 Last month (October 2023 supplement) 2021-2022: Filter by tumour site "endometrial cancer". Filter by format: Select "abstract", "ePoster", "slides"	01.01.2021 – 20.10.2023
ESMO Gynaecological Cancers	2023 2022	Filter by tumour site "endometrial cancer" and "gynaecological malignancies". Filter by format: Select "abstract", "ePoster", "slides". Screen by title and investigate further records which may be relevant	01.01.2021 – 20.10.2023
ASCO Annual Meeting	2023, 2022	Use advanced search function, ensure only the "ASCO Annual Meeting" option is selected under the "Meeting" filter, then select 2023 and 2022 in the "Year" filter section (or search one year at a time if preferred). Session Type: Publication only + Poster Session + Oral Abstract Session Media: Abstracts, Posters Search 1: Search bar: "endometrial" Search 2: Screen by topic: uterine cancer Screen all hits by title first, clicking only those abstracts that may be relevant from the title alone.	01.01.2021 – 20.10.2023

Conference	Source	Search strategy	Date of search
		Screen any potentially relevant abstracts and record only relevant ones in the tracker, ensuring the year of the congress (right hand-side of the abstract) is recorded	
SGO Annual Meeting	2023, 2022:	Using advanced search, search 'endometrial OR endometrium OR uterine' with 2023 in Year and Gynecologic Oncology in Journal, and 176 in Volume. After searching, filter for conference abstracts. Investigate each relevant title further using the abstract preview and download relevant abstract PDFs. Using advanced search, search 'endometrial OR endometrium OR uterine' with 2022 in Year and Gynecologic Oncology in Journal, and 166 in Volume. After searching, filter for conference abstracts. Investigate each relevant title further using the abstract preview and download relevant abstract PDFs.	01.01.2021 – 20.10.2023
IGCS Annual Meeting	2022: Abstract books 2021: Abstract books	Using advanced search function in Adobe, search 'endometrial' and screen the retrieved abstracts with the abstract books. Repeat for 'endometrium' and 'uter' to check for any remaining abstracts not captured by endometrial.	01.01.2021 – 20.10.2023

Abbreviations: ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; IGCS, International Gynecologic Cancer Society; SGO, Society of Gynecologic Oncology

H.1.1 Search strategies

Table 67 Search strategy table for MEDLINE

No.	Query	Results
1	exp endometrial neoplasms/	26110
2	((endometr$ or uterine or uterus) adj3 (cancer$ or tumo?r$ or neoplas$ or carcinom$ or malign$ or adeno$)).ti,ab,kf.	68544
3	1 or 2	72487
4	exp Neoplasm metastasis/ or Neoplasm Recurrence, Local/	344270
5	(advanc$ or stage III or stage 3 or stage IIIa or stage 3a or stage IIIb or stage 3b or stage IIIc or stage 3c$ or stage IV$ or stage 4$ or recur$ or metastat$ or metastas$ or uesectable or non-resectable or noesectable	2547294

No.	Query	Results
	or inoperable or ((new$ or recent$) adj3 (diagnos$ or therap$ or treat$))).ti,ab,kf.	
6	4 or 5	2634609
7	3 and 6	22992
8	Randomized Controlled Trials as Topic/	163884
9	Randomized Controlled Trial/	599679
10	Random Allocation/	106961
11	Double-Blind Method/	176113
12	Single-Blind Method/	32911
13	crossover procedure/	0
14	Placebos.mp. or placebos/ [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word]	38003
15	exp Clinical Trials as Topic/	384387
16	Clinical Trial/	538808
17	Clinical Trial, Phase II/ or Clinical Trial, Phase III/ or Clinical Trial, Phase IV/	62978
18	Controlled Clinical Trial/ or Adaptive Clinical Trial/	95460
19	randomized controlled trial.pt.	599679
20	clinical trial.pt.	538808
21	(clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv).pt.	62978
22	(controlled clinical trial or multicenter study).pt.	429306
23	(clinical adj trial$).ti,ab,kf.	499042
24	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kf.	199388
25	placebo$.ti,ab,kf.	250163
26	(allocat$ adj2 random$).ti,ab,kf.	44404

No.	Query	Results
27	(Randomi?ed adj2 trial$).ti,ab,kf.	436751
28	rct.ti,ab,kf.	34851
29	(single arm adj3 (trial$ or stud$)).ti,ab,kf.	9566
30	(open label adj (trial$ or stud$)).ti,ab,kf.	13595
31	(non blinded adj (trial$ or stud$)).ti,ab,kf.	237
32	(pragmatic trial$ or pragmatic stud$).ti,ab,kf. or Pragmatic Clinical Trial/	4537
33	or/8-32	2052581
34	exp animals/ not exp humans/	5154279
35	(comment or editorial or case reports or historical article).pt.	4165282
36	(case stud$ or case report$).ti.	388026
37	or/34-36	9314137
38	7 and 33	2845
39	38 not 37	2773

Table 68 Search strategy table for Embase

No.	Query	Results
1	exp endometrium tumor/	83251
2	((endometr$ or uterine or uterus) adj3 (cancer$ or tumo?r$ or neoplas$ or carcinom$ or malign$ or adeno$)).ti,ab,kf.	88800
3	1 or 2	119807
4	exp Metastasis/ or exp Advanced cancer/ or exp tumor recurrence/	963210
5	(advanc$ or stage III or stage 3 or stage IIIa or stage 3a or stage IIIb or stage 3b or stage IIIc or stage 3c$ or stage IV$ or stage 4$ or recur$ or metastat$ or metastas$ or uesectable or non-resectable or noesectable or inoperable or ((new$ or recent$) adj3 (diagnos$ or therap* or treat$))).ti,ab,kf.	3612227
6	4 or 5	3773264
7	3 and 6	43347
8	"randomized controlled trial (topic)"/	261200

No.	Query	Results
9	Randomized Controlled Trial/	782363
10	randomization/	98342
11	double blind procedure/	210440
12	single blind procedure/	51698
13	crossover procedure/	75289
14	Placebos.mp. or placebo/ [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	403103
15	exp "clinical trial (topic)"/	443023
16	Clinical Trial/	1069661
17	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	170088
18	Controlled Clinical Trial/ or Adaptive Clinical Trial/ or multicenter study/	779413
19	(clinical adj trial$).ti,ab,kf.	721411
20	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kf.	281645
21	placebo$.ti,ab,kf.	367811
22	(allocat$ adj2 random$).ti,ab,kf.	55072
23	(Randomi?ed adj2 trial$).ti,ab,kf.	587518
24	rct.ti,ab,kf.	57353
25	(single arm adj3 (trial$ or stud$)).ti,ab,kf.	19503
26	(open label adj (trial$ or stud$)).ti,ab,kf.	24445
27	(non blinded adj (trial$ or stud$)).ti,ab,kf.	347
28	(pragmatic trial$ or pragmatic stud$).ti,ab,kf. or pragmatic trial/	4922
29	or/8-28	2949512
30	("conference abstract" or "conference review").pt.	4893000
31	limit 30 to yr="1974-2020"	4158202

No.	Query	Results
32	exp animals/ not exp humans/	5138629
33	editorial.pt.	779227
34	editorial/ or case report/	3655041
35	(case stud$ or case report$).ti.	469977
36	or/31-35	12428501
37	7 and 29	6628
38	37 not 36	5139

Table 69 Search strategy table for the Cochrane Library databases

No.	Query	Results
1	[mh "Endometrial Neoplasms"]	1027
2	((endometr* or uterine or uterus) NEAR/3 (cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno*)):ti,ab,kw	9345
3	#1 OR #2	9346
4	[mh "Neoplasm Metastasis"]	6562
5	(advanc* or "stage III" or "stage 3" or "stage IIIa" or "stage 3a" or "stage IIIb" or "stage 3b" or "stage IIIc" or "stage 3c" or "stage IV" or "stage 4" or recur* or metastat* or metastas* or uesectable or non-resectable or noesectable or inoperable or ((new* or recent*) NEAR/3 (diagnos* or therap* or treat*))):ti,ab,kw	233313
6	#4 OR #5	233420
7	#3 AND #6	3539
8	#7 in Cochrane Reviews	55
9	#7 in Trials	3479

Table 70 Search strategy table for DARE

No.	Query	Results
1	MeSH DESCRIPTOR Endometrial Neoplasms EXPLODE ALL TREES	138

No.	Query	Results
2	((endometr* or uterine or uterus) NEAR3 (cancer* or tumo?r* or neoplas* or carcinom* or malign* or adeno*))	888
3	#1 OR #2	888
4	MeSH DESCRIPTOR Neoplasm Metastasis EXPLODE ALL TREES	705
5	(advanc* or "stage III" or "stage 3" or "stage IIIa" or "stage 3a" or "stage IIIb" or "stage 3b" or "stage IIIc" or "stage 3c" or "stage IV" or "stage 4" or recur* or metastat* or metastas* or uesectable or non-resectable or noesectable or inoperable or ((new* or recent*) NEAR3 (diagnos* or therap* or treat*)))	10039
6	#4 OR #5	10060
7	#3 AND #6 in DARE	105

Table 71 Search strategy table for updated search in PubMed

No.	Query	Results
1	endometrial neoplasms[MeSH Terms]	27692
2	(endomet*[tiab] or uterine[tiab] or uterus[tiab]) and (cancer*[tiab] or tumo*r*[tiab] or neoplas*[tiab] or carcinoma*[tiab] or malign*[tiab] or adeno*[tiab])	104460
3	1 or 2	107429
4	neoplasm metastasis[MeSH Terms] or neoplasm recurrence, local[MeSH Terms]	356466
5	advanc~[tiab] or “stage III*”[tiab] or “stage 3*”[tiab] or “stage IV*”[tiab] or recur*[tiab] or metastat*[tiab] or metastas*[tiab] or unresectable[tiab] or non-resectable[tiab] or nonresectable[tiab] or inoperable	2477961
6	4 or 5	2568653
7	3 and 6	30966
8	randomized controlled trials as topic[MeSH Terms] or randomized controlled trial[MeSH Terms] or random allocation[MeSH Terms] or double blind method[MeSH Terms] or single blind method[MeSH Terms] or crossover design[MeSH Terms]	516176
9	placebo[tiab]	261548

No.	Query	Results
10	clinical trials as topic[MeSH Terms] or clinical trial[MeSH Terms] or controlled clinical trial[MeSH Terms]	400600
11	randomized controlled trial[Publication Type]	629229
12	clinical trial[Publication Type]	1011130
13	or/8-12	1508144
14	animals[MeSH Terms] not humans[MeSH Terms]	5287912
15	comment[Publication Type] or editorial[Publication Type] or case reports[Publication Type] or historical article[Publication Type]	4370963
16	case stud*[ti] or case report*[ti]	431060
17	or/14-16	9658747
18	7 and 13	2072
19	18 not 17	2046
20	durvalumab[tiab] or Imfinzi[tiab] or dostarlimab[tiab] or Jemperli[tiab]	2121
21	19 and 20	32
22	("2023/09/12"[Date - Publication] : "2023/10/31"[Date - Publication])	245417
23	21 and 22	11

H.1.2 Systematic selection of studies

Table 72 Inclusion and exclusion criteria used for assessment of studies

Domain	Inclusion criteria	Exclusion criteria	Changes for local adaption
Population	• Adult women (≥18 years) with histologically confirmed diagnosis of epithelial endometrial carcinoma (newly diagnosed stage III/IV disease or recurrent disease) with any histologic subtypes (i.e. including carcinosarcomas), except sarcomas • Patients treated in the first- or second- line setting; either (1)	• Children or adolescents (<18 years of age) • Patients without endometrial carcinoma • Patients with sarcoma histology • Patients with any other stage of	Focus on studies reporting outcomes for patients with dMMR/MSI-H for efficacy (no restrictions for safety)

	naïve to first-line systemic anti-cancer treatment or (2) with one prior chemotherapy regimen	endometrial cancer (stage I/II)	
Intervention	Systemic anti-cancer treatment from the following classes: • Chemotherapy (e.g. platinum or taxane-based) • Anti-PD(L)-1 (e.g. pembrolizumab, dostarlimab, atezolizumab, avelumab, nivolumab or durvalumab) • PARP inhibitors (e.g. niraparib, rucaparib or olaparib) • Protein kinase inhibitors (e.g. lenvatinib) • Anti-HER2 (e.g. trastuzumab) • Anti-VEGF (e.g. bevacizumab) • Hormonal therapies (medroxyprogesterone, hydroxyprogesterone, tamoxifen, letrozole)[a] • mTOR inhibitors (temsirolimus, vistusertib, everolimus) • Selective Inhibitor of Nuclear Export (e.g., selinexor)	Any other treatment class, such as surgery or radiotherapy	Only durvalumab in combination with carboplatin and paclitaxel or dostarlimab in combination with carboplatin and paclitaxel were in focus
Comparator	Any or none	N/A	Treatments allowing a connected network of studies evaluating durvalumab or dostarlimab
Outcomes	**Efficacy outcomes** • Overall survival (OS) • Progression-free survival (PFS) • PFS2 • Disease response, including objective response rate • Duration of response • Time to subsequent therapy	• Any other outcome • Studies where outcomes are not reported separately for the population of interest	OS and PFS are prioritized as key efficacy outcomes. HRQoL outcomes were not included as the EMA has concluded no difference in HRQoL between

	Safety/tolerability outcomes • Adverse events (any grade or grade 3 and above) • Time to treatment discontinuation • Discontinuation or patient withdrawals due to adverse events • Mortality **HRQoL outcomes, from generic or disease specific measures** • Utility values (e.g. EQ-5D-5L, EQ-5D-3L, SF-6D) • Health-related quality of life values (EORTC QLQ-C30, EORTC QLQ-EN24/Endometrial, SF-36, FACT-G, EQ-5D VAS)		both PD-(L)1 inhibitors and chemotherapy in this setting.
Study design	• RCTs of any design (open label/double/single blind, parallel/cross-over) • Interventional, non-RCTs: • Non-randomised comparative studies • Single-arm trials • Other interventional, prospective studies	Any other study design: • Observational studies (cross-sectional, retrospective, prospective cohort studies) • Registry/database studies • Case-control studies • Secondary research articles (narrative reviews, editorials, commentaries)	N/A
Language	Articles with at least the abstract in the English language	Articles without an abstract or full-text in the English language	N/A
Other	• Studies in humans • Conference abstracts published in or after 2021	• Animal/in vitro studies • Conference abstracts published before 2021	N/A

Table 73 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
DUO-E **(NCT04269200)**	To assess the efficacy and safety of durvalumab in combination with platinum-based chemotherapy (paclitaxel + carboplatin) followed by maintenance durvalumab with or without olaparib for patients with newly diagnosed advanced or recurrent endometrial cancer	Randomised, double-blind, placebo-controlled clinical trial	Adult female patients (≥18 year of age) with a histologically confirmed diagnosis of newly diagnosed Stage III, newly diagnosed Stage IV, or recurrent epithelial EC (excluding sarcomas), and naïve to 1L systemic anti-cancer treatment (prior adjuvant chemotherapy was allowed if ≥12 months from last treatment to relapse for those with recurrent disease)	Durvalumab 1,120 mg (IV) Q3W in combination with platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of six cycles (minimum of four cycles), followed by maintenance durvalumab 1,500 mg (IV) Q4W in combination with olaparib tablets (300 mg) BID in the maintenance phase for patients without objective disease progression (n = 239) Durvalumab 1,120 mg (IV) Q3W in combination with platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of six cycles (minimum of four cycles), followed by maintenance durvalumab 1,500 mg (IV) Q4W in combination with placebo tablets (matched to olaparib) BID in the maintenance phase for patients without objective disease progression (n = 238)	Investigator-assessed progression-free survival (per RECIST v1.1) Median follow-up of 15.4 months for PFS censored patients in the durvalumab + olaparib plus CP arm, 15.4 months in the durvalumab plus CP arm and 12.6 in the placebo plus CP arm	Overall survival [redacted] Other secondary endpoints not included in application are: • Time to second progression or death (PFS2) • Objective response rate (ORR) • Duration of response • Time to first subsequent therapy or death (TFST) • Time to second subsequent

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
				Placebo durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of six cycles (minimum of four cycles), followed by maintenance placebo (matched to durvalumab) Q4W and placebo tablets (matched to olaparib) BID in the maintenance phase for patients without objective disease progression (n = 241)		therapy or death (TSST) • Time to treatment discontinuation or death (TDT)
RUBY **(NCT03981796)**	To evaluate the efficacy and safety of dostarlimab plus carboplatin-paclitaxel followed by dostarlimab versus placebo plus carboplatin-paclitaxel followed by placebo in participants with	Randomised, double-blind, placebo-controlled clinical trial	Adult female patients (≥18 year of age) with a histologically or cytologically confirmed diagnosis of primary Stage III or Stage IV, or first recurrent endometrical cancers (excluding sarcomas), and naïve to systemic anti-cancer treatment (prior [neo-]adjuvant chemotherapy was	Dostarlimab 500 mg (IV) in combination with carboplatin AUC5 (IV) and paclitaxel 175 mg/m^2 (IV) Q3W for the first six cycles, followed by dostarlimab 1000 mg (IV) Q6W for up to 3 years or until disease progression, treatment discontinuation due to toxic effects, patient withdrawal, investigator decision to withdraw the patient, or death (n = 245) Placebo (IV) in combination with carboplatin AUC5 (IV) and paclitaxel 175 mg/m^2 (IV) Q3W for the first six cycles, followed by placebo (IV) Q6W for up to 3	Investigator-assessed progression-free survival (per RECIST v1.1): • In patients with dMMR/MSI-H (median follow-up of 24.8 months) • In all patients (median follow-up of 25.4 months)	Others (not included in this application) are: • Objective response • Disease control • Response duration • Time to second progressive disease

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	recurrent or primary advanced (Stage III or IV) endometrial cancer.		allowed if first recurrence or disease progression ≥6 months from completing treatment)	years or until disease progression, treatment discontinuation due to toxic effects, patient withdrawal, investigator decision to withdraw the patient, or death (n = 249)	Overall survival in all patients	

H.1.3 Excluded fulltext references

NA. See section H.1.4 for literature identification.

H.1.4 Literature identification

The PRISMA diagram for the global SLR is show in Figure 18. An updated PRISMA, including how studies were filtered from the global SLR plus those identified from updated searches in shown in Figure 19. The most common reason for exclusion of studies was that they did not assess durvalumab in combination with carboplatin and paclitaxel or dostarlimab in combination with carboplatin and paclitaxel. As the only studies evaluating these regimens shared a common comparator (placebo + CP), there was no need to include further studies to create a closed network of evidence. Additional reasons for exclusion of records were due to only health-related quality of life or patient-reported outcomes data being included, and therefore no considered necessary for the application. Available data on these outcomes were only from the DUO-E or RUBY studies.

Figure 18. PRISMA flow diagram of studies included in the global SLR

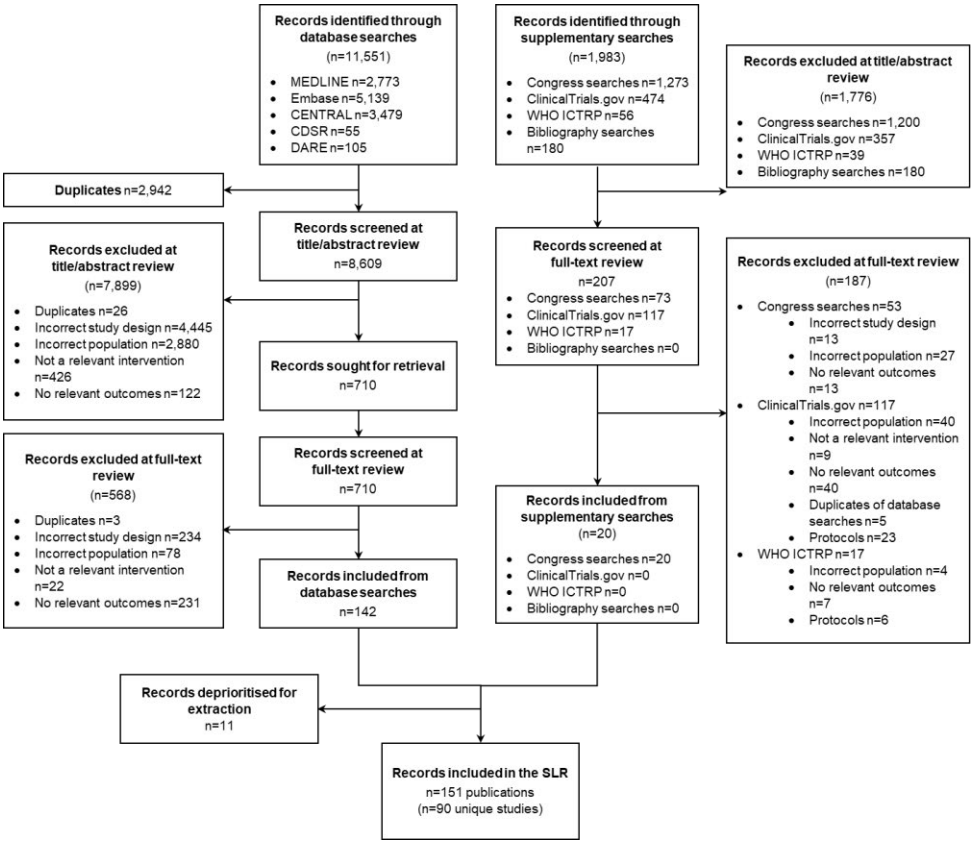
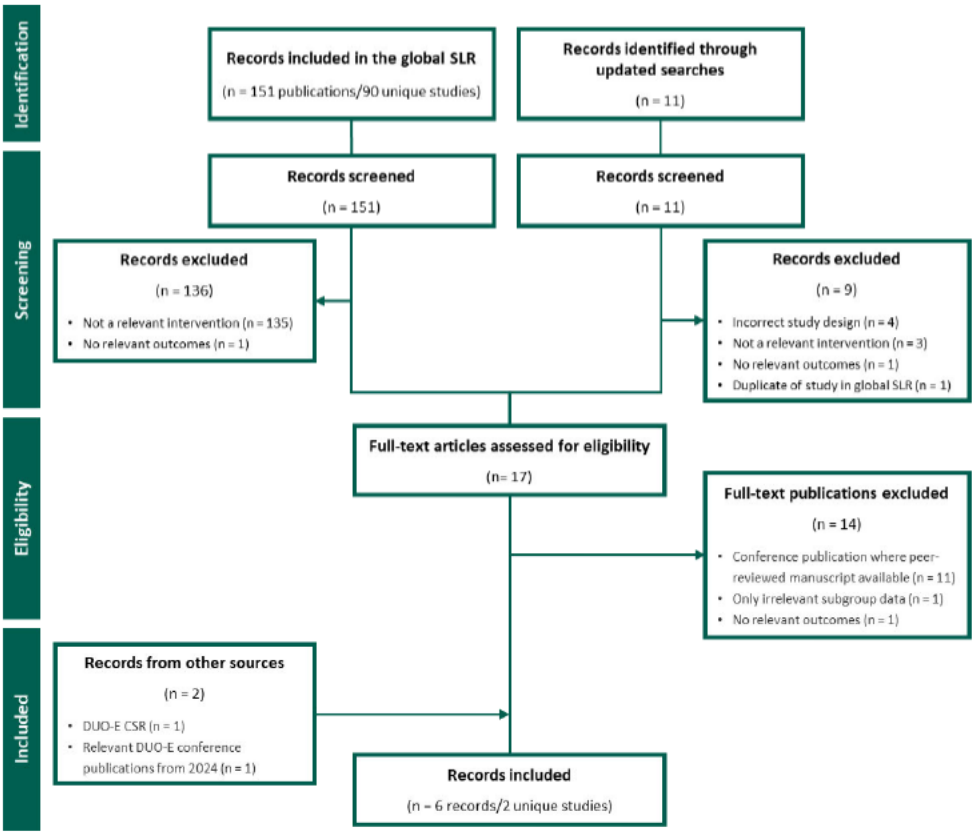


Figure 19. PRISMA flow diagram of studies for the localisation of the SLR



H.1.5 Quality assessment

The quality of the included randomised controlled trials was assessed using the quality assessment tool developed by the University of York CRD. (61)As no non-randomised interventional studies nor observational studies were used in the evidence synthesis, alternative metrics of quality assessment were not required. The quality assessment was completed by one individual and verified by a second independent reviewer.

The main potential sources of bias were unexpected imbalances in discontinuations, which may bias results for or against interventional treatment, and not all measured endpoints being reported in publications. Both RCTs included were appropriately blinded, used an intention-to-treat analysis, and had similar prognostic factors between groups, supporting robustness and generalisability of results.

Table 74 Summary of quality of RCTs, as assessed by the criteria provided by the York Centre for Reviews and Dissemination

Quality domain	DUO-E	RUBY
Randomisation	Unclear	Yes
Allocation concealment	Unclear	Yes

Quality domain	DUO-E	RUBY
Participants/care provider blinding	Yes	Yes
Outcome assessor blinding	Yes	Yes
Balanced groups	Yes	Yes
Unexpected imbalance in discontinuations	No	No
More outcomes measured than reported	No	No
ITT used appropriately	Yes	Yes

H.1.6 Unpublished data

[redacted]

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

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

Table 75 Bibliographic databases included in the literature search

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

Table 76 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NA			

Table 77 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA				

I.1.1 Search strategies

Table 78 Search strategy for [name of database]

No.	Query	Results
NA		

I.1.2 Quality assessment and generalizability of estimates

NA

I.1.3 Unpublished data

NA

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

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

J.1.1 Example: Systematic search for [...]

Table 79 Sources included in the search

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

J.1.2 Example: Targeted literature search for [estimates]

Table 80 Sources included in the targeted literature search

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

Appendix K. Subsequent treatment

[redacted]

Table 81 Subsequent treatment proportions for patients with dMMR status (amongst patients receiving at least one subsequent therapy). Source: Calculations based on the DUO-E Clinical study report. (62)

Treatments	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Treatments	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

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Application for the assessment of dostarlimab in combination with carboplatin and paclitaxel for treatment of adult patients with advanced or recurrent endometrial cancer

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

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Table of contents

Tables and Figures

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AUC	Area under the concentration–time curve
BICR	Blinded Independent Central Review
CI	Confidence interval
CP	Carboplatin-paclitaxel
CR	Complete response
CTCAE v4.03	Common Terminology Criteria for Adverse Events version 4.03
DGCG	Danish Gynaecological Cancer Group
DMC	Danish Medicines Council
dMMR	Mismatch repair deficient
DOR	Duration of response
EC	Endometrial cancer
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
EORTC-QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EOT	End of Treatment
FCR	Fear of cancer recurrence

FIGO	International Federation of Gynaecology and Obstetrics
GOG	Gynaecologic Oncology Group
GVD	Global value dossier
HR	Hazard Ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IA	Interim analysis
ITT	Intention-to-treat
KM	Kaplan Meier
MMR	Mismatch repair
MMRp	Mismatch repair proficient
MSI-H	Microsatellite instability high
MSS	Microsatellite stable
NICE	The National Institute for Health and Care Excellence
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death receptor-1
PD-L1	Programmed cell death ligand-1
PFS	Progression-free survival
PK	Pharmacokinetic
PLD	Patient-level data
PR	Partial response
PRO	Patient-reported outcomes
Q3W	Every three weeks
Q6W	Every six weeks
QOL	Quality of life
RECIST v1.1	Response Evaluation Criteria in Solid Tumours version 1.1
SAE	Serious Adverse Event
TEAE	Treatment-emergent adverse event
US	United States
W	Weeks

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Jemperli
Generic name	Dostarlimab
Therapeutic indication as defined by EMA	JEMPERLI is indicated in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy.
Marketing authorization holder in Denmark	GSK Denmark Delta Park 37, 2665 Vallensbæk Strand, Denmark
ATC code	L01XC40
Combination therapy and/or co-medication	Carboplatin area under the concentration–time curve, 5 mg per millilitre per minute (AUC 5) and paclitaxel 175 mg per square meter of body-surface area
(Expected) Date of EC approval	15th January 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	• Dostarlimab is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy. • Dostarlimab is indicated as monotherapy for the treatment of adult patients with dMMR/MSI-H recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen.
Other indications that have been evaluated by the DMC (yes/no)	• Dostarlimab is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with mismatch repair deficient (dMMR)/ microsatellite instability-high (MSI-H) primary advanced

Overview of the medicine	
	or recurrent endometrial cancer (EC) and who are candidates for systemic therapy. • Dostarlimab is indicated as monotherapy for the treatment of adult patients with dMMR/MSI-H recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen.
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No If no, why not? Dostarlimab is a candidate for the 14-weeks fast-track process and therefore not suitable.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	1 -piece vial concentrate for solution for infusion. One vial of 10 mL concentrate for solution for infusion contains 500 mg of dostarlimab. Each mL of concentrate for solution for infusion contains 50 mg of dostarlimab

2. Summary table

Summary	
Indication relevant for the assessment	Dostarlimab is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) and who are candidates for systemic therapy. Dostarlimab has already been assessed and recommended for the dMMR EC population in first line. The indication is being extended to include all primary advanced or recurrent EC patients in the first line setting.
Dosage regiment and administration	One vial of 10 mL solution for infusion contains 500 mg of dostarlimab. Each mL of solution for infusion contains 50 mg of dostarlimab. 500 mg (1 vial) Q3W for 6 cycles, then 1000mg (2 vials) Q6W until disease progression or up to 3 years treatment duration.
Choice of comparator	Carboplatin area under the concentration–time curve, 5 mg per millilitre per minute (AUC 5) and paclitaxel 175 mg per square meter of body-surface area

Summary	
Prognosis with current treatment (comparator)	If endometrial cancer is detected at an early stage, it is considered surgically curable with a 5-year survival rate of around 80-85%. Local advanced or metastatic endometrial cancer (collectively referred to as advanced endometrial cancer) has a poorer prognosis, with 5-year survival rates of 49% and 28%, respectively, for stages III and IV. Histology and molecular classification are used as prognostic factors. For example, MMRp/MSS tumours have a higher proportion of aggressive histologies (e.g. non-endometrioid tumours such as serous carcinoma) relative to dMMR/MSI-H tumours
Type of evidence for the clinical evaluation	Head-to-head study: A phase 3, global, double-blind, randomized, placebo-controlled trial.
Most important efficacy endpoints (Difference/gain compared to comparator)	**Overall population** OS for the ITT population is a dual primary endpoint in the study. Patients in the dostarlimab plus CP group had a statistically significant 36% reduction in risk of progression or death compared with the placebo plus CP group (HR: 0.64; 95% CI: 0.51, 0.8; p<0.001]. Patients in the dostarlimab plus CP group had a 31% reduction in risk of death compared with the placebo plus CP group (HR: 0.69; 95% CI: 0.54, 0.89; p=0.002]. **MMRp/MSS population** Patients in the dostarlimab plus CP group had a statistically significant 21% reduction in risk of progression or death compared with the placebo plus CP group (HR: 0.76; 95% CI: 0.59, 0.98; p<0.001). Patients in the dostarlimab plus CP group had a 31% reduction in risk of death compared with the placebo plus CP group (HR: 0.79; 95% CI: 0.60, 1.04; p=0.049]
Most important serious adverse events for the intervention and comparator	The incidence of grade 3 or higher adverse events and serious adverse events that occurred or worsened during treatment were approximately 10 percentage points higher in the dostarlimab group than in the placebo group (adverse events, 70.5% vs. 59.8%; serious adverse events, 37.8% vs. 27.6%)
Impact on health-related quality of life	Clinical documentation: EQ-5D-5L
Type of economic analysis that is submitted	Not applicable due to 14-weeks process.

Summary	
Data sources used to model the clinical effects	Not applicable due to 14-weeks process.
Data sources used to model the health-related quality of life	Not applicable due to 14-weeks process.
Life years gained	Not applicable due to 14-weeks process.
QALYs gained	Not applicable due to 14-weeks process.
Incremental costs	Not applicable due to 14-weeks process.
ICER (DKK/QALY)	Not applicable due to 14-weeks process.
Uncertainty associated with the ICER estimate	Not applicable due to 14-weeks process.
Number of eligible patients in Denmark	Incidence: 130 patients with advanced or recurrent endometrial cancer, approx. 80 % of these are MMRp/MSS. All patients (dMMR/MSI-H and pMMR/MSS) who are eligible for chemotherapy will be eligible for dostarlimab. Of the 130 new patients each year 80-85% will be eligible for treatment according to clinical expert.
Budget impact (in year 5)	Not applicable due to 14-weeks process.

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

3.1 The medical condition

3.1.1 Endometrial cancer

Uterine cancer is the 5th most common cancer among women in Denmark, and the most frequent form of gynaecological cancer. The most common form of uterine cancer is cancer of the lining of the uterus (endometrial cancer) (1). Endometrial cancer develops when genomic alterations occur in cells, causing errors in cell proliferation and apoptosis that lead to excessive tissue growth and tumour formation (2).

At a cellular level, endometrial cancer typically progresses as a result of reduced tumour immunosurveillance. Some endometrial cancer cells overexpress programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2), which activates programmed cell death protein-1 (PD-1), an immune checkpoint molecule. PD-L1 and PD-L2 bind PD-1 receptors expressed on T-cells, effectively suppressing the T-cell response and creating a microenvironment that is favourable to tumour survival (3). Due to this, the PD-1 pathway has become a key target for emerging cancer immunotherapies.

The most common symptom associated with endometrial cancer is abnormal vaginal bleeding, which is present in approximately 70% to 90% of patients (4) (5). This includes a change in menstrual cycles, bleeding between menstrual cycles, or bleeding after menopause. Non-bloody abnormal vaginal discharge may also occur (4) (6). In advanced stages of endometrial cancer, other symptoms may be present, including pelvic pain, often during urination or intercourse, back pain, the presence of a mass, or unintentional weight loss (1) (5) (6).

Because most endometrial cancers are symptomatic, the majority are diagnosed early (~80% at stage I), when the cancer is still confined to the uterus (7). Some patients will experience relapse of the disease within a few years of completing primary treatment. This is commonly characterized as incurable endometrial cancer with a median survival of about 12 months (8).

3.1.2 Histology and molecular classification

Molecular classification provides meaningful information that can be utilised in addition to histology and grade, and there is a growing body of evidence to support that these classifications inform a patient's risk and prognosis (7). For example, tumors with p53 abnormal group (p53abn) have a comparatively poor prognosis compared with POLEmut tumors, while tumors that are dMMR or no specific molecular profile (NSMP) have an intermediate prognosis compared with other groups (7). Molecular classification is standard of care in Denmark and is used as a prognostic tool, however it cannot be used as a predictive tool for treatment efficiency (except for dMMR) (9).

3.1.3 Impact in patient health-related quality of life

Primary advanced or recurrent endometrial cancer is associated with a range of debilitating symptoms, resulting in deteriorations in physical functioning and health-related quality of life (HRQoL). Women with endometrial cancer identify pain, fatigue, emotional functioning, and social functioning as key areas to be monitored following

diagnosis (13). Maintaining and improving QoL are important considerations for endometrial cancer and require consideration of potential longer-term impacts of the disease such as pain and social and sexual functioning (13).

Fear of cancer recurrence (FCR) is also a widely reported issue that carries significant burden and affects the QoL of patients (14). Recurrence has a detrimental impact on QoL in patients with endometrial cancer, leading to more anxiety and depression, lower satisfaction with the care received after diagnosis of recurrence, and perceptions of a more threatening illness (15). This highlights the importance of effective treatment that reduce the symptom burden and risk of recurrence of endometrial cancer (14).

3.2 Patient population

3.2.1 Epidemiology of endometrial cancer in DK and patient population relevant for this application

Around 800 women in Denmark are diagnosed with uterine cancer every year, with more than 90% being cancer of the lining of the uterus (endometrial cancer) (16) (17). The disease typically affects older women (median age 63 years) (7), and almost 11,000 patients in Denmark are alive after being diagnosed (17).

Endometrial cancer is diagnosed early in approximately 80% of cases due to obvious symptoms (18). If the disease is detected at an early stage, it is considered surgically curable with a 5-year survival rate of around 80-85%. Locally advanced or metastatic endometrial cancer has a poorer prognosis, with 5-year survival rates of 49% and 28% respectively for stage II and IV (18).

Some patients will experience relapse of the disease within a few years after completing primary treatment. This is characterized as incurable endometrial cancer. In Denmark the incidence of patients with newly diagnosed advanced endometrial cancer is 100 patients per year (16) and furthermore 30 patients with relapsing endometrial cancer (16). Of these 130 patients approximately 80% will be MMRp/MSS. The remaining 20% of the newly diagnosed patients are dMMR/MSI-H, and for this group dostarlimab has already been recommended in 1. Line. In Table 1 the overall incidence and prevalence of endometrial cancer is presented.

Table 1: Incidence and prevalence in the past 5 years

Year	2017	2018	2019	2020	2021
Incidence in Denmark	805	795	834	819	830
Prevalence in Denmark	10 954	11 080	11 240	11 365	11 481

[a] Source: Adapted from Association of Nordic Cancer Registries (NORDCAN data 2023) (17)
[b] Source: Adapted from Global Cancer Observatory (GLOBOCAN data 2020) (19)
[c] Global estimates were based on 185 countries across the world.

There is no official data on the incidence and prevalence of the MMRp/MSS populations, however the estimated numbers in Table 2 are confirmed by a clinical expert: of the 130 patients in total, 80% will be MMRp/MSS. 80-85% of these patients will be eligible for systemic treatment. We are presenting only these numbers, since the dMMR/MSI-H part of the population already receive treatment with dostarlimab.

Table 2: Estimated number of patients eligible for treatment (MMRp/MSS population)

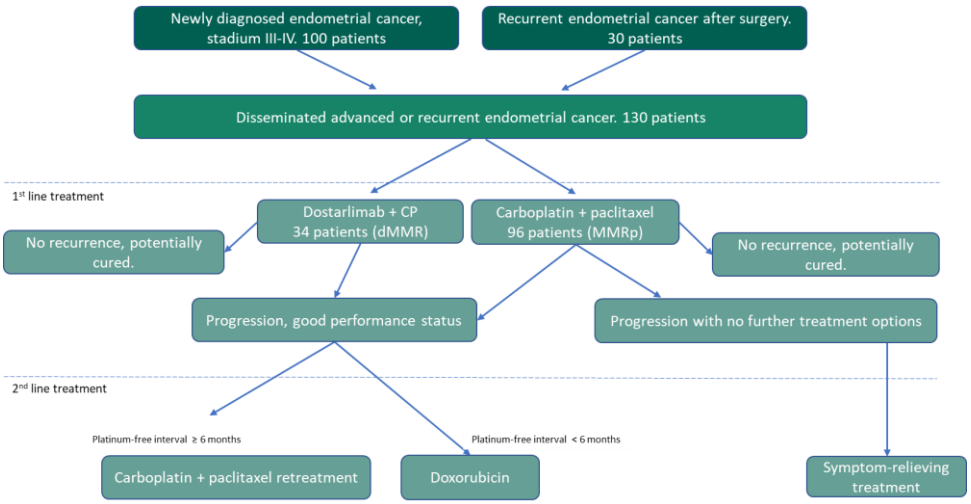
Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	84	84	84	84	84

3.3 Current treatment options

The treatment of endometrial cancer is described in clinical guidelines from the Danish Gynaecological Cancer Group (DGCG) (1). Most patients with early-stage endometrial cancer are treated with curative surgery (16) (13). The treatment algorithm hereafter for primary advanced or recurrent endometrial cancer is illustrated in Figure 1 (12).

According to the guideline from DGCG, advanced and recurrent endometrial cancer can be treated with surgery and/or radiotherapy, supplemented with carboplatin and paclitaxel for up to 6 cycles or Dostarlimab plus CP (1). The aim of the treatment is to prolong survival by limiting further disease progression.

Figure 1: Current treatment guideline primary advanced or recurrent endometrial cancer



Source: Created by GSK based on DMC recommendation of dostarlimab 2L (12) and DMC recommendation of dostarlimab 1L dMMR (18) and DGCG updated guidelines (1)

3.4 The intervention

Dostarlimab is a monoclonal antibody that binds to the receptor, programmed cell death-1 (PD-1), thereby inhibiting its binding to the ligands programmed cell death-ligand-1 and -2 (PD-L1 and -2). The PD-1 receptor is present on the surface of immune cells, and when the receptor is activated via PD-L1 binding it causes a negative feedback response that inhibits T cell-mediated cell death (20). PD-L1 is overexpressed on many tumour cells, which protects the tumour cells from the immune system response. By breaking the PD-L1/PD-1 interaction in tumour cells, dostarlimab may counteract this protection, increasing T cell-mediated cell death in tumours with many mutation-associated neoantigens (21).

Overview of intervention	
Indication relevant for the assessment	Treatment of adult patients with advanced or recurrent endometrial cancer in combination with paclitaxel and carboplatin
ATMP	N/A
Method of administration	IV infusion over 30 minutes
Dosing	500 mg (1 vial) Q3W for 6 cycles, then 1000mg (2 vials) Q6W

Overview of intervention	
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Up to 3 years or until disease progression
Necessary monitoring, both during administration and during the treatment period	No
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	1-piece concentrated liquid solution for infusion. One vial of 10 mL solution for infusion contains 500 mg of dostarlimab. Each mL of solution for infusion contains 50 mg of dostarlimab.

3.4.1 Description of ATMP

N/A

3.4.2 The intervention in relation to Danish clinical practice

As investigated in the RUBY trial, dostarlimab is an add on to existing standard treatment (carboplatin and paclitaxel for 6 cycles) for patients with endometrial cancer in the 1st line setting. Dostarlimab plus CP has already been recommended in first line patients with dMMR/MSI-H EC.

3.5 Choice of comparator(s)

The Danish standard treatment option for patients with primary advanced or first recurrent disease who have low potential for cure by surgery alone was, until recently, platinum-containing combination chemotherapy (1). Prior combinations evaluated in the advanced/recurrent endometrial cancer population include docetaxel + carboplatin, doxorubicin + cisplatin, and doxorubicin + cisplatin + paclitaxel (8) (10) (11) (22). For the dMMR/MSI-H population both the DGCG clinical guidelines and the Medicines Council

has adopted dostarlimab plus carboplatin + paclitaxel as standard of care in recent years (1) (23).

A landmark phase 3 open-label trial published results in 2012 (with an updated publication in 2020) showing that the carboplatin + paclitaxel regimen was associated with an ORR of ~50 % among patients with primary advanced/first recurrent endometrial cancer (24) (25). This trial also reported that carboplatin + paclitaxel demonstrated comparable efficacy to the triplet paclitaxel + doxorubicin + cisplatin regimen based on OS and progression-free survival (PFS) outcomes and was associated with a more favourable toxicity profile (24). Response rates to carboplatin + paclitaxel range from 50% to 60% in clinical studies of patients with primary advanced/first recurrent endometrial cancer (24) (25) (26).

As carboplatin + paclitaxel is also a common adjuvant therapy for newly diagnosed, high-risk patients, the concept of re-treatment with the same combination in recurrent disease has been explored, albeit minimally. While those who are considered platinum-resistant (disease recurs ≤6 months from the last platinum-containing chemotherapy) may not benefit from re-treatment, data have indicated that those who are platinum-sensitive (disease recurs >6 months from the last platinum containing chemotherapy) demonstrate favourable response rates (50%) to the platinum containing regimen after recurrence (27).

The RUBY trial compares dostarlimab plus CP with placebo plus CP, as CP has been considered SOC for many years in the treatment of EC patients (28).

Overview of comparator	
Generic name	Carboplatin
ATC code	L01XA02
Mechanism of action	After intracellular activation, the molecule acquires alkylating properties, causing linkage to, and possibly cross-linking of the guanine bases in the DNA double strand, inhibiting cell division.
Method of administration	Solution for IV infusion.
Dosing	5 mg per millilitre per minute (AUC 5).

Overview of comparator	
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	The product must be diluted prior to infusion with a dextrose solution or a sodium chloride solution to concentrations as low as 0.5 mg/ml.
Treatment duration/ criteria for end of treatment	Carboplatin was administered in the first 6 cycles of study treatment in RUBY.
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Available as vials of 15 ml or 45 ml concentrate for solution, 10 mg/ml.

Overview of comparator	
Generic name	Paclitaxel
ATC code	L01CD01
Mechanism of action	Antimitotic, which affects the functioning of microtubules, which is essential for the cell's necessary functions in interphase and mitosis.
Method of administration	Available as sterile powder or solution for IV infusion
Dosing	175 mg per square meter of body-surface area
Dosing in the health economic model (including relative dose intensity)	N/A
Should the pharmaceutical be administered with other medicines?	Paclitaxel as sterile powder must be reconstituted using a sodium chloride solution, a lactated Ringer's solution, or an acetated Ringer's solution suitable for infusion. Paclitaxel as a solution for IV infusion must be diluted prior to infusion with a dextrose solution or a sodium chloride solution, or a mix of the two, to a concentration of 0.3-1.2 mg/ml.
Treatment duration/ criteria for end of treatment	Paclitaxel was administered in the first 6 cycles of study treatment in RUBY.

Overview of comparator	
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Available as vials of 16.7 ml, 25 ml, 50 ml concentrate for solution, 6 mg/ml. Also available as 20 ml or 100 mg sterile powder, 5 mg/ml.

3.6 Cost-effectiveness of the comparator(s)

The comparator (CP) consists of two well-known generic compounds. They have been used to treat endometrial and ovarian cancer for the past 20+ years. CP has therefore not been evaluated by the DMC. However, CP has been used as a comparator in the assessment of dostarlimab in second line and first line dMMR/MSI-H assessment and is also the current standard of care in 1st line endometrial cancer in the MMRp/MSS part of the population (17) (18).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 3 presents the outcome measures included in the present application and the definitions and method of measurement for each outcome. The rationale for including each outcome and the validity of the outcomes is presented later in this section.

Table 3: Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression-free survival (PFS) (28)	Median duration of follow-up: 25.4 months	The time from the date of randomization to the earliest date of radiographic assessment of PD or death by any cause in the absence of PD, whichever occurred first per RECIST v.1.1	Initial tumour imaging at screening was performed within 28 days of the first dose of study intervention. Radiographic evaluations to assess the extent of disease was conducted Q6W (±7 days) until Week 25, followed by Q9W (±7 days) until Week 52. Subsequent tumour imaging was performed every 12 weeks (±7 days) until radiographic PD is

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			documented by Investigator assessment per RECIST v1.1 followed by one additional imaging assessment 4-6 weeks later, or subsequent anticancer therapy was started, whichever occurs first. Thereafter, scans may be performed per standard of care.
Overall survival (OS) (29)	Median duration of follow-up: 37.2 months	OS is defined as the time from randomization to death from any cause.	Time measured from randomization until death from any cause.

* Time point for data collection used in analysis (follow up time for time-to-event measures)

3.7.2 Validity of outcomes

PFS and OS are generally considered the gold standard measures of efficacy in oncology clinical trials and are required by regulatory authorities for the approval of new cancer treatments. PFS and OS as endpoints in trials are easily and precisely measured and based on objective and quantitative assessment. Thus, we included them as efficacy outcomes in the present application.

The primary evaluation of PFS, as determined by the Investigator, was performed per RECIST v.1.1, which represents standardized World Health Organization response criteria, and are well-established criteria for patients with solid tumours (29).

In the DMC assessment of dostarlimab in both the 2nd line treatment of endometrial cancer and 1st line dMMR/MSI-H endometrial cancer, OS and PFS were used as efficacy endpoints. It is described in the protocol, that the overall survival and progression-free disease measures are critical for assessing the value of the medicine to patients, because improved OS with the least toxicity is the optimal measure for cancer treatment and PFS reflects the burden and duration of the disease (12) (23).

In Section 6, PFS and OS will be presented for both the ITT population and the MMRp population. For safety, only data for the ITT will be presented due to a larger sample size in Section 9.

4. Health economic analysis

Not applicable.

4.1 Model structure

N/A

4.2 Model features

N/A

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	N/A	
Perspective	N/A	
Time horizon	N/A	
Cycle length	N/A	
Half-cycle correction	N/A	
Discount rate	N/A	
Intervention	N/A	
Comparator(s)	N/A	
Outcomes	N/A	

5. Overview of literature

In this section, the literature used in the application is presented. Since the RUBY trial is a head-to-head study comparing dostarlimab plus CP with placebo plus CP both in terms of efficacy, safety and health-related quality of life, no systematic literature search was needed. The RUBY trial is described in more details in Appendix A.

5.1 Literature used for the clinical assessment

The application is based on a head-to-head study (RUBY) with a comparator relevant to Danish clinical practice.

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Full paper Powell MA, Bjørge L, Willmott L, et al. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin–paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. Ann Oncol. 2024 Aug; 35 (8): 728-738. (30)	RUBY	NCT03981796	Start: 18/07/19 Estimated Completion: 26/11/26 Data cut-off: 22/09/23	Dostarlimab plus CP vs. placebo plus CP For ITT and MMRp/MSS population
Full paper Mirza MR, Chase DM, Slomovitz BMet al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. Mar 2023; 388:2145-2158 (28)	RUBY	NCT03981796	Start: 18/07/19 Estimated Completion: 26/11/26 Data cut-off: 28/09/22	Dostarlimab plus CP vs. placebo plus CP For ITT and MMRp/MSS population

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

The health-related quality of life data included in the application is based on a head-to-head study (RUBY) with a comparator relevant to Danish clinical practice.

Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Powell MA, Bjørge L, Willmott L, et al. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin–paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. Ann Oncol. 2024 Aug; 35 (8): 728-738. (30)	Health state/Advanced or Recurrent endometrial cancer	Section 10.1
Mirza MR, Chase DM, Slomovitz BMet al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. Mar 2023; 388:2145-2158 (28)	Health state/Advanced or Recurrent endometrial cancer	Section 10.1

5.3 Literature used for inputs for the health economic model

Not applicable.

Table 7 Relevant literature used for input to the health economic model

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

6. Efficacy

6.1 Efficacy of dostarlimab plus carboplatin-paclitaxel compared to placebo plus carboplatin-paclitaxel for the treatment of adult patients with advanced or recurrent endometrial cancer

6.1.1 Relevant studies

In adult patients with recurrent or advanced endometrial cancer, the efficacy of dostarlimab has been assessed in the RUBY-1 trial where dostarlimab plus CP was compared head-to-head with placebo plus CP. As the study is a head-to-head study, no additional studies were used in the comparison of dostarlimab and CP. Table 8 presents an overview of RUBY-1, and additional information can be found in Appendix A.

The RUBY trial is a phase 3, randomized, double-blinded, multicenter trial conducted in 2 parts. RUBY-1 evaluates dostarlimab plus CP for 6 cycles followed by dostarlimab for up to 3 years; RUBY-2 evaluates dostarlimab plus CP for 6 cycles followed by dostarlimab plus niraparib for up to 3 years. RUBY-2 opened for enrolment when enrolment for RUBY-1 was complete; patients included in RUBY-1 were not eligible to take part in RUBY-2. RUBY-2 is ongoing since April 2023 and will not be presented in this application. Thus, this application is based solely on ITT and MMRp/MSS results from RUBY-1.

Efficacy results in the following are presented for the ITT population that included all 494 randomized subjects: 245 subjects in the dostarlimab plus CP group and 249 subjects in the placebo plus CP group. Patient demographics and baseline disease characteristics were reported at the IA1 data cut (28 September 2022); baseline characteristics remained unchanged due to no new enrolments and thus were not updated for the IA2 data cut (22 September 2023). [redacted] (Table 9) and were generally representative of patients with primary advanced/recurrent endometrial cancer in Denmark.

Table 8: Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
RUBY (NCT03981796) (30) (28)	Randomized, double blinded, placebo controlled, phase III trial of dostarlimab plus CP versus placebo plus CP.	The study is ongoing with a median follow-up of 25.4 months in the first data-cut and 37.2 months in the second data-cut. The primary completion is expected by November 2026	Adults with primary advanced (stage III or IV) or first recurrent endometrial cancer. Stratification factors used in RUBY-1 were MMR/MSI status, prior external pelvic radiotherapy, and disease status (i.e. primary stage III, primary stage IV or recurrent) RUBY part 1: n=494	A total of 245 subjects were randomly assigned to dostarlimab 500 mg IV + carboplatin AUC 5 IV + paclitaxel 175 mg/m2 IV Q3W for cycles 1–6 followed by dostarlimab 1,000 mg IV Q6W up to 3 years	A total of 249 subjects were randomly assigned to placebo + carboplatin AUC 5 IV + paclitaxel 175 mg/m2 IV Q3W for cycles 1–6 followed by placebo Q6W up to 3 years	**Primary endpoints** • Investigator-assessed PFS according to RECIST v1.1 criteria in patients with dMMR/MSI-H tumours and in the overall trial population. • OS in the overall population **Secondary endpoints** • PFS by BICR • ORR based on BICR and investigator assessment • Duration of response based on BICR and investigator assessment • Disease control rate based on BICR and investigator assessment • PFS2 • PROs (EORTC-QLQ-C30; EORTC-QLQ-EN24; EQ-5D-5L) • PK and immunogenicity analyses **Exploratory endpoints** • Genetic research • Biomarkers in tumour tissue and/or blood **Safety endpoints** • TEAEs • Clinical laboratory values • Vital signs • Physical examination • ECOG PS • ECG parameters

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						Concomitant medication

6.1.2 Comparability of studies

Not applicable due to head-to-head study.

6.1.2.1 Comparability of patients across studies

As the comparison of dostarlimab plus CP vs placebo plus CP was based on a direct comparative analysis with data from the head-to-head study RUBY, only baseline characteristics from the RUBY trial are presented in Table 9. According to clinical expert the population in the RUBY trial is comparable to the Danish patient population.

In the RUBY trial patients with carcinosarcomas were included even though they are known to have a poorer prognosis than other patients with advanced EC. This was done to secure a wide representation of the different histologic types and separates the RUBY trial from other trials conducted at the moment.

Table 9: Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	RUBY			
	MMRp/MSS population		Overall population (ITT)	
	Dostarlimab (N=192)	Placebo (N=184)	Dostarlimab (N=245)	Placebo (N=249)
Age, years				
Median (range)	XXXX	XXXX	64 (41–81)	65 (28–85)
≥65, n (%)	XXXX	XXXX	118 (48.2)	135 (54.2)
Race or ethnic group, n (%)				
White	XXXX	XXXX	189 (77.1)	191 (76.7)
Black	XXXX	XXXX	28 (11.4)	31 (12.4)
Others	XXXX	XXXX	9 (3.7)	9 (3.6)
Unknown or not reported	[redacted]	[redacted]	19 (7.8)	18 (7.2)
ECOG performance category, n/total, n (%)				
0	[redacted]	[redacted]	145/241 (60.2)	159/246 (64.6)

	RUBY			
	MMRp/MSS population		Overall population (ITT)	
	Dostarlimab (N=192)	Placebo (N=184)	Dostarlimab (N=245)	Placebo (N=249)
1	[redacted]	[redacted]	96/241 (39.8)	86/246 (35.0)
2	[redacted]	[redacted]	0	1/246 (0.4)
FIGO stage at diagnosis, n (%)				
I	[redacted]	[redacted]	64 (26.1)	71 (28.5)
II	[redacted]	[redacted]	13 (5.3)	13 (5.2)
III	[redacted]	[redacted]	74 (30.2)	64 (25.7)
IV	[redacted]	[redacted]	74 (30.2)	86 (34.5)
Unknown	[redacted]	[redacted]	20 (8.2)	15 (6.0)
Disease status, n (%)				
Primary stage III	[redacted]	[redacted]	44 (18.0)	47 (18.9)
Primary stage IV	[redacted]	[redacted]	84 (34.3)	83 (33.3)
Recurrent	[redacted]	[redacted]	117 (47.8)	119 (47.8)
BMI				
Median (range)	[redacted]	[redacted]	30.8 (17.6–60.6)	32.8 (17.7–68.0)
Histologic type, n (%)				
Carcinosarcoma	[redacted]	[redacted]	25 (10.2)	19 (7.6)
Endometrioid	[redacted]	[redacted]	134 (54.7)	136 (54.6)
Mixed carcinoma ≥10% of carcinosarcoma, clear-cell, or serous histologic type	[redacted]	[redacted]	10 (4.1)	9 (3.6)
Serous adenocarcinoma	[redacted]	[redacted]	50 (20.4)	52 (20.9)
Clear-cell adenocarcinoma	[redacted]	[redacted]	8 (3.3)	9 (3.6)

	RUBY			
	MMRp/MSS population		Overall population (ITT)	
	Dostarlimab (N=192)	Placebo (N=184)	Dostarlimab (N=245)	Placebo (N=249)
Mucinous adenocarcinoma	[redacted]	[redacted]	0	1 (0.4)
Undifferentiated carcinoma	[redacted]	[redacted]	1 (0.4)	2 (0.8)
Other	[redacted]	[redacted]	17 (6.9)	21 (8.4)
MMR-MSI status, n (%)				
dMMR/MSI-H	[redacted]	[redacted]	53 (21.6)	65 (26.1)
pMMR/MSS	[redacted]	[redacted]	192 (78.4)	184 (73.9)
Previous external pelvic radiotherapy, n (%)				
Yes	[redacted]	[redacted]	41 (16.7)	45 (18.1)
No	[redacted]	[redacted]	204 (83.3)	204 (81.9)

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

GSK has consulted a clinical expert, who confirms that the study population is fully comparable to the Danish patient population eligible for treatment. However, since the application is following a 14-week process a health economic model and analysis have not been made. Table 10 is therefore not relevant.

Table 10: Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
N/A	N/A	N/A

6.1.4 Efficacy – results per RUBY

In the following, efficacy data on PFS and OS for the ITT population and the MMRp/MSS population are presented.

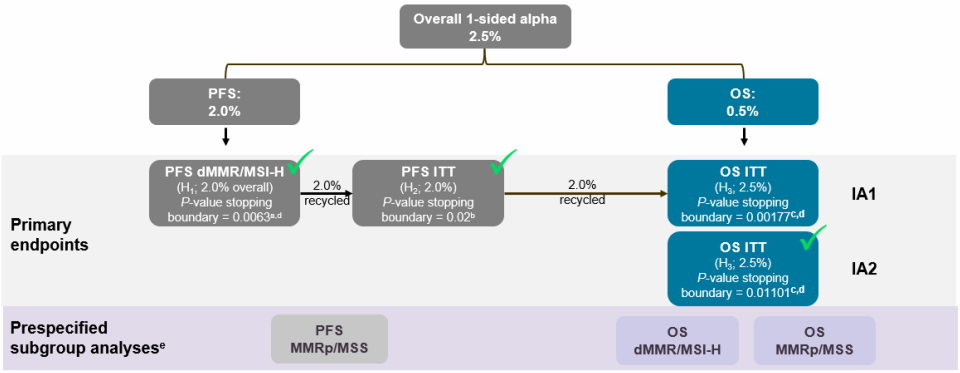
Efficacy endpoints in this section are presented in order of the statistical analyses:

- PFS [investigator-assessed; IA1]:
    - Overall population
    - Prespecified exploratory analyses in the source-verified MMRp/MSS population
- OS [IA2]:
    - Overall population
    - Prespecified exploratory analyses in the source-verified MMRp/MSS population

6.1.4.1 Statistical analysis

The graphical method was used for multiplicity control of multiple hypotheses of primary end points and family-wise one-sided type I error (alpha) was controlled at 0.025 (see Figure 2). On the basis of the graphical method, an alpha level of 0.02 was initially allocated to hypotheses regarding progression-free survival by investigator assessment and an alpha level of 0.005 was initially allocated to hypotheses regarding overall survival. For progression-free survival, hypotheses were hierarchically tested in the dMMR/MSI-H population and then in the overall population; overall survival was tested in the overall population. If the null hypotheses for progression-free survival were all rejected, the 0.02 alpha level would be recycled to the hypothesis of overall survival, which would be tested at a one-sided alpha level of 0.025; otherwise, overall survival would be tested only at the initially allocated one-sided alpha level of 0.005.

Figure 2: RUBY-1 statistical testing and multiplicity control strategy



[a] Hypothesis for PFS dMMR/MSI (H1) was tested at IA1 with 0.63% alpha spent from the overall alpha level (2.0%) initially allocated.
[b] Since null hypothesis (H01) for H1 was rejected at IA1, the 2.0% alpha for (H1) was recycled to hypothesis testing of PFS ITT (H2). H2 was tested at alpha level (2.0%)= 2.0% recycled + 0% initially allocated.
[c] Since both null hypotheses (H01 and H02) were rejected, 2.0% alpha for the family of hypothesis testing of PFS was recycled to testing of OS (H3). H3 was tested at alpha level (2.5%)= 2.0% recycled + 0.5% initially allocated.
[d] Stopping boundaries and alpha spent at each IA were adjusted based on the actual number of events/information fraction observed based on the prespecified alpha spending function at the time of

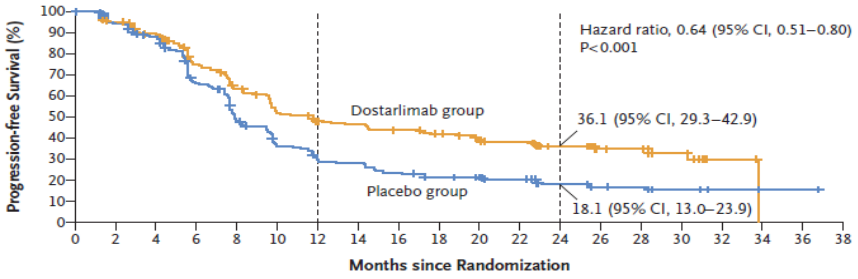
analysis; P-value stopping boundary (IA1)= 0.0063 for PFS dMMR/MSI-H; P-value stopping boundary (IA1)=0.00177 for OS ITT; P-value stopping boundary (IA2)=0.01101 for OS ITT.
[e] Not formally tested.

6.1.4.2 Primary endpoint: Progression-free survival (investigator-assessed)

6.1.4.2.1 PFS in the overall population

Patients in the dostarlimab plus CP group had a statistically significant 36% reduction in risk of progression or death compared with the placebo plus CP group (HR: 0.64; 95% CI: 0.51, 0.80; p<0.001) (Figure 3) (28). The estimated probability of PFS at 12 months was 48.2% (95% CI: 41.3, 54.8) with dostarlimab plus CP and 29.0% (95% CI: 23.0, 35.2) with placebo plus CP (31). At 24 months, the estimated probability of PFS was twice as high in the dostarlimab plus CP group compared with the placebo plus CP group (36.1% [95% CI: 29.3, 42.9] and 18.1% [95% CI: 13.0, 23.9], respectively) (28).

Figure 3: Kaplan-Meier estimates of PFS in the overall population (investigator-assessed; IA1)



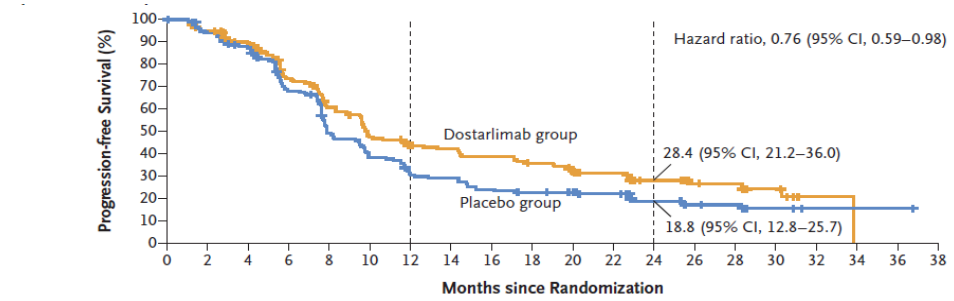
No. at Risk																				
Dostarlimab group	245	220	197	157	130	105	94	90	84	78	66	52	34	23	22	12	2	0		
Placebo group	249	219	200	144	103	74	59	57	48	42	39	32	20	14	13	5	2	1	1	0
No. of Events																				
Dostarlimab group	0	12	25	55	80	103	110	113	118	122	127	128	131	132	132	133	134	135		
Placebo group	0	14	29	77	115	141	155	157	166	170	170	172	175	176	176	177	177	177	177	177

Source: Mirza et al. 2023

6.1.4.2.2 PFS in the MMRp/MSS population

Patients in the dostarlimab plus CP group had a 24% reduction in risk of progression or death (HR: 0.76; 95% CI: 0.59, 0.98) compared with the placebo plus CP group (Figure 4) (28). The median duration of follow-up for the PFS analysis was 25.7 months (range: 19.4, 37.8) in the MMRp/MSS population. There was sustained separation of the KM curves from approximately 8 months; the estimated probability of PFS at 12 and 24 months was 43.5% (95% CI: 35.7, 51.0) and 28.4% (95% CI: 21.2, 36.0) in the dostarlimab plus CP group and 30.6% (95% CI: 23.6, 37.8) and 18.8% (95% CI: 12.8, 25.7), respectively, in the placebo plus CP group (28) (31).

Figure 4: Kaplan-Meier estimates of PFS in the MMRp/MSS population (investigator-assessed; IA1)



No. at Risk																			
Dostarlimab group	192	172	153	118	96	74	64	61	56	51	41	33	21	14	13	8	1	0	
Placebo group	184	162	146	110	77	60	47	45	37	34	31	25	16	11	10	3	1	1	1	0
No. of Events																			
Dostarlimab group	0	9	19	45	65	86	92	94	99	103	108	109	112	113	113	114	115	116	
Placebo group	0	10	22	53	83	100	112	114	122	124	124	125	128	129	129	130	130	130	130	130

Source: Mirza et al. 2023

6.1.4.2.3 Diagnostic tests for PFS in the MMRp/MSS population

[redacted]

Figure 5: PFS INV cumulative log-log plot for the MMRp/MSS data set – IA1 data cut

Source: GSK data on file 2024

Figure 6: PFS INV Schoenfeld residuals plot for the MMRp/MSS data set – IA1 data cut

Source: GSK data on file 2024.

Figure 7: PFS INV quantile-quantile plot for the MMRp/MSS data set – IA1 data cut

Source: GSK data on file 2024.

[redacted]

Figure 8: PFS INV hazard rate plots for the MMRp/MSS data set – IA1 data cut

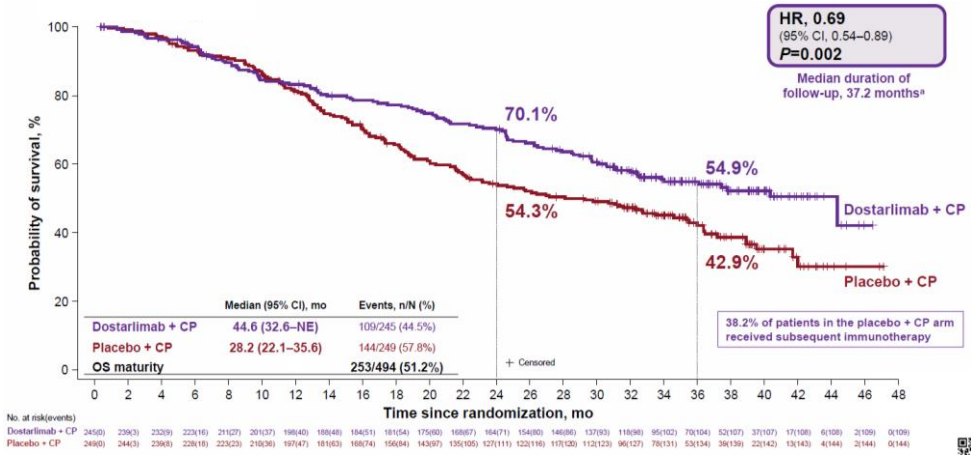
Source: GSK data on file 2024.

6.1.4.3 Primary endpoint: Overall survival

6.1.4.3.1 OS in the overall population

At 51.2% OS maturity, patients in the dostarlimab plus CP group had a statistically significant 31% reduction in risk of death compared with the placebo plus CP group (HR: 0.69; 95% CI: 0.54, 0.89; p=0.002) (Figure 9). The median duration of follow-up for OS analysis was 37.2 months (range: 31.0, 49.5) in the overall population. A clinically meaningful 16.4-month improvement in OS was achieved for patients in the dostarlimab plus CP group compared with the placebo plus CP group (median OS of 44.6 months vs 28.2 months, respectively). The Kaplan-Meier curves diverged from around the 10- to 12-month mark and continued with a clear and sustained separation over the time analyzed. At 24 months, the estimated probability of OS was 70.1% for the dostarlimab plus CP group and 54.3% for the placebo plus CP group (30). At 36 months, the estimated probability of OS was 54.9% for the dostarlimab plus CP group and 42.9% for the placebo plus CP group. Approximately 17.1% of all patients in the dostarlimab plus CP group and 38.2% of all patients in the placebo plus CP group received subsequent immunotherapy (30). OS data at IA2 were consistent with OS data observed at IA1 (30).

Figure 9: Kaplan-Meier estimates of OS in the overall population (IA2)

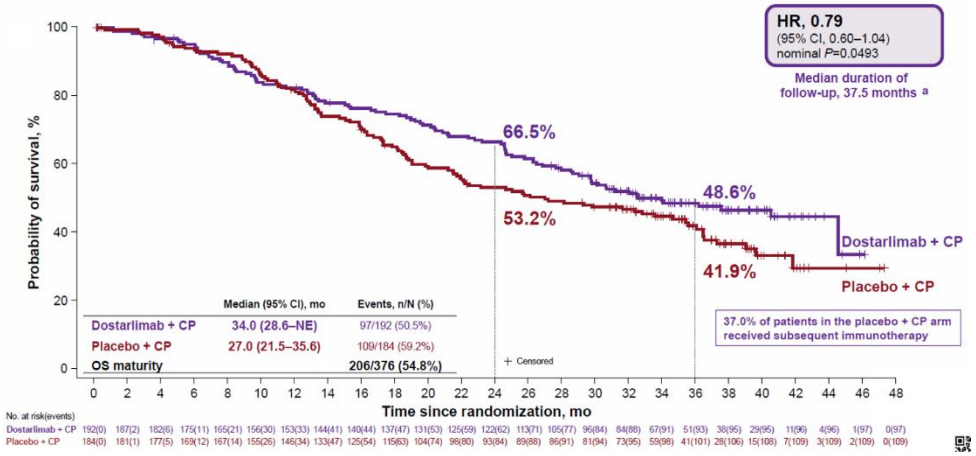


Source: Powell et al. 2024

6.1.4.3.2 OS in the MMRp/MSS population

At 54.8% OS maturity, MMRp/MSS patients in the dostarlimab plus CP group had a 21% reduction in risk of death compared with the placebo plus CP group (HR: 0.79; 95% CI: 0.60, 1.04; nominal p=0.0493). A clinically meaningful improvement of 7 months in OS was observed for patients in the dostarlimab plus CP group vs the placebo plus group (median OS 34.0 months vs 27.0 months, respectively) (Figure 10). The median duration of follow-up for the OS analysis was 37.5 months (range: 31.2, 49.5) in the MMRp/MSS population. After 12 months, there was a clear and sustained separation in the Kaplan-Meier curves. At 24 months, the estimated probability was 66.5% for the dostarlimab plus CP group and 53.2% for the placebo plus CP group. At 36 months, the estimated probability was 48.6% for the dostarlimab plus CP group and 41.9% for the placebo plus CP group (30). Approximately 17.7% of all patients in the dostarlimab plus CP group and 37.0% of all patients in the placebo plus CP group received subsequent immunotherapy (30).

Figure 10: Kaplan-Meier estimates of OS in the MMRp/MSS population (IA2)



Source: Powell et al. 2024

6.1.4.3.3 Diagnostic tests for OS in the MMRp/MSS population

[redacted]

Figure 11: OS cumulative log-log plot for the MMRp/MSS data set – IA2 data cut

Source: GSK data on file 2024

Figure 12: OS Schoenfeld residuals plot for the MMRp/MSS data set – IA2 data cut

Source: GSK data on file 2024

Figure 13: OS quantile-quantile plot for the MMRp/MSS data set – IA2 data cut

Source: GSK data on file 2024

[redacted]

Figure 14: OS hazard rate plots for the MMRp/MSS data set – IA2 data cut

Source: GSK data on file 2024

6.1.5 Discontinuations

The median treatment duration in the ITT and MMRp/MSS population is 43 weeks (range: 3.0 to 192.6 weeks) and 39 weeks (range: 3.0 to 190.7 weeks) in the dostarlimab

plus CP arm. The median treatment duration in the ITT and MMRp/MSS population is 36 weeks (range: 2.1 to 193.1 weeks) and 36 weeks (range: 2.1 to 187.0 weeks) in the placebo plus CP arm (31).

At the IA2 data cut (22 September 2023), 46.9% of patients in the dostarlimab plus CP group remained in the study (11.0% still on study treatment; 35.9% in follow-up), along with 35.7% of the placebo plus CP group (8.8% still on study treatment; 26.9% in follow-up). In the overall population, 61.2% of patients had 3 years of expected follow-up (defined as the time from randomization to the date of the data-cut) in the dostarlimab plus CP group, while 59.0% of patients had 3 years of expected follow-up in the placebo plus CP group (31) (30).

In both arms, the most common reason for dostarlimab or placebo discontinuation was PD according to RECIST v.1.1 criteria per investigator assessment (46.1% dostarlimab plus CP, 67.1% placebo plus CP). The most common reason for discontinuation for carboplatin or paclitaxel was AE (31).

Discontinuation of dostarlimab or placebo because of adverse events occurred in 19.1% of patients in the dostarlimab group and in 8.1% of patients in the placebo group. The most common adverse events leading to discontinuation of dostarlimab or placebo were maculopapular rash and infusion-related reaction (1.2% each) in the dostarlimab group and thrombocytopenia (1.2%) in the placebo group (28) (30) (31).

Table - I: Summary of reasons for discontinuation of study treatment (dostarlimab or placebo) in the overall population

Reasons for discontinuation of treatment n (%)	Dostarlimab plus CP n=241	Placebo plus CP n=246	Total n=487
AE	53 (22.0)	25 (10.2)	78 (16.0)
Clinical Progression	7 (2.9)	8 (3.3)	15 (3.1)
PD according to RECIST V1.1 CRITERIA per investigator assessment	111 (46.1)	165 (67.1)	276 (56.7)
Risk to subject, as judged by the investigator, sponsor, or both	3 (1.2)	2 (0.8)	5 (1.0)
Severe non-compliance with the protocol, as judged by	1 (0.4)	1 (0.4)	2 (0.4)

the investigator, sponsor, or both			
Subject becomes pregnant	0	0	0
Withdrawal by subject	21 (8.7)	8 (3.3)	29 (6.0)
Lost to follow-up	1 (0.4)	1 (0.4)	2 (0.4)
Death from any cause	0 (0)	1 (0.4)	1 (0.2)
Sponsor decision to terminate study	0	0	0
Confirmed complete response, treated for at least 3 years with study treatment	7 (2.9)	3 (1.2)	10 (2.1)
Other	10 (4.1)	10 (4.1)	20 (4.1)

Source: supplement to Powell et al. 2024

6.1.6 Subsequent treatments

In the overall population, a higher proportion of patients (173/249 patients, 69.5%) in the placebo arm received subsequent anticancer therapy than patients in the dostarlimab arm (120/245 patients, 49.0%). Of the 173 patients in the placebo arm and 120 patients in the dostarlimab arm who received subsequent anticancer therapy, 54.9% of patients (95/173) in the placebo arm received subsequent immunotherapy compared to 35.0% of patients (42/120) in the dostarlimab arm (29). The most common subsequent immunotherapy in both arms was the combination of pembrolizumab plus levantinib that was received in 10.2% of patients in the dostarlimab arm.

In the MMRp/MSS population, 72.8% of patients (134/184) in the placebo arm and 54.7% of patients (105/192) in the dostarlimab arm received follow-up anticancer therapy. Of the 134 patients in the placebo arm who received follow up anticancer therapy, 50.7% (68/134) received subsequent immunotherapy; of the 105 patients in the dostarlimab arm who received follow-up anticancer therapy, 32.4% (34/105) received subsequent immunotherapy. Of the 68 patients in the placebo arm who received subsequent immunotherapy in the MMRp/MSS population, 20 (29.4%) received pembrolizumab and 43 (63.2%) received pembrolizumab plus lenvatinib.

Table - II describes the distribution of subsequent therapies. These numbers have been confirmed to reflect Danish clinical practice by a Danish expert, except for the

MMRp/MSI-H group where no patients in DK (outside clinical studies) have been treated with immunotherapy due to missing reimbursement.

Table - II: Subsequent immunotherapy use

	ITT population		MMRp/MSS	
	Dostarlimab plus CP (n=192)	Placebo plus CP (n=184)	Dostarlimab plus CP (n=245)	Placebo plus CP (n=249)
Any follow-up anticancer therapy, n (%)	120 (49.0)	173 (69.5)	105 (54.7)	134 (72.8)
Immunotherapy	42 (17.1)	95 (38.2)	34 (17.7)	68 (37.0)
Pembrolizumab	13 (5.3)	41 (16.5)	9 (4.7)	20 (10.9)
Pembrolizumab - Lenvatinib	25 (10.2)	45 (18.1)	22 (11.5)	43 (23.4)
Dostarlimab	0	3 (1.2)	0	0
MK7694A	0	1 (0.4)	0	0
Pembrolizumab – tamoxifen	1 (0.4)	0	0	0
Retifanlimab – epacadostat	1 (0.4)	2 (0.8)	0	2 (1.1)
Investigational product	1 (0.4)	1 (0.4)	1 (0.5)	1 (0.5)
Atezolizumab – ipatasertib	1 (0.4)	1 (0.4)	0	1 (0.5)
Avelumab – axitinib	0	1 (0.4)	0	1 (0.5)

Bevacizumab – atezolizumab	0	1 (0.4)	0	1 (0.5)
Durvalumab - cediranib	0	2 (0.8)	0	2 (1.1)
Durvalumab – Olaparib	2 (0.8)	0	2 (1.0)	0
Nivolumab - BMS986207 – COM701	0	1 (0.4)	0	1 (0.5)
Nivolumab – lucitanib	0	1 (0.4)	0	1 (0.5)
SGN-ALPV	0	1 (0.4)	0	1 (0.5)

Source: Powell et al. 2024

7. Comparative analyses of efficacy

7.1 Differences in definitions of outcomes between studies

Not applicable due to head-to-head study.

7.2 Method of synthesis

Not applicable due to head-to-head study.

7.3 Results from the comparative analysis

Please see Table 11 below.

Table 11: Results from the comparative analysis of dostarlimab plus carboplatin-paclitaxel vs. placebo plus carboplatin-paclitaxel for the ITT-population and the MMRp/MSS population

	Overall population			MMRp/MSS poulation		
Outcome measure	**Dostarlimab plus CP (N=)**	**Placebo plus CP (N=x)**	**Result**	**Dostarlimab plus CP (N=x)**	**Placebo plus CP (N=x)**	**Result**
Probability of progression-free survival at 24 months	36.1% [95% CI: 29.3, 42.9]	18.1% [95% CI: 13.0, 23.9]	36% [HR: 0.64 95% CI: 0.51, 0.80 p<0.001]	28.4% [95% CI: 21.2, 36.0]	18.8% [95% CI: 12.8, 25.7]	24% [HR: 0.76 95% CI: 0.59, 0.98 p<0.001]
Probability of survival at 36 months	54.9% [95% CI: 48.2, 61.2]	42.9% [95% CI: 36.3, 49.3]	31% [HR: 0.69 95% CI: 0.54, 0.89 P=0.002]	48.6% [95% CI: 41.0, 55.7]	41.9% [95% CI: 34.3, 49.4]	21% [HR: 0.79 95% CI: 0.60, 1.04 Nominal p=0.049]

7.4 Efficacy – results per [outcome measure]

Not applicable due to head-to-head study; see section 6.

8. Modelling of efficacy in the health economic analysis

Not applicable.

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

Not applicable.

8.1.1 Extrapolation of efficacy data

Not applicable.

8.1.1.1 Extrapolation of [effect measure 1]

Not applicable.

Table 12: Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A

Method/approach	Description/assumption
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.2 Extrapolation of [effect measure 2]

Not applicable.

8.1.2 Calculation of transition probabilities

Not applicable.

Table 13: Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
N/A	N/A	N/A	N/A

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

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

Not applicable.

Table 14: Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
N/A	N/A	N/A	N/A

Table 15: Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
N/A	N/A	N/A	N/A

9. Safety

In this section we present safety data from the RUBY trial on patients treated with dostarlimab plus CP and placebo plus CP for the ITT population.

9.1 Safety data from the clinical documentation

The safety analysis set for the double-blind phase of the RUBY trial consisted of all randomized subjects in the ITT analysis set, who received at least one or more cycle of treatment. For a summary of the safety data specific for the MMRp/MSS population go to Appendix E.

Safety in the RUBY trial was assessed through monitoring of treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, and physical examination. All AEs were assessed by the investigator for intensity according to Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) (28).

The most common adverse events that occurred or worsened during treatment were nausea (54.4% of patients in the dostarlimab group and 46.3% of patients in the placebo group), alopecia (53.9% and 50.0%), fatigue (52.3% and 54.9%), peripheral neuropathy (44.0% and 41.9%) and anaemia (37.8% and 42.7%). Maculo-papular rash were the

adverse event with the largest differences between the treatment groups and were reported more frequently in the dostarlimab group than in the placebo group (14.1% vs. 3.7%) (28).

The safety profile for dostarlimab plus CP was consistent with that seen in the first interim analysis. The most frequently reported treatment-emergent adverse events (TEAEs; 40%) in both treatment arms were primarily related to chemotherapy. Anemia was also seen at 40% in the placebo plus CP arm. These common TEAEs were grade 1 or 2 in most patients except for anemia, which was grade 2 or 3 in most patients. Serious treatment-related AEs were experienced by 19.5% of patients in the dostarlimab arm and 12.2% of patients in the placebo arm (30) (31).

The most common immune-related adverse events were hypothyroidism (12.0% in the dostarlimab group and 2.8% of those in the placebo group), rash (7.1% and 2.0%), arthralgia (6.6% and 6.5%), and an increase in alanine aminotransferase levels (6.2% and 1.2%) (28) (31).

An overview of the safety events in the treatment phase is presented in Table 16. A summary of timing of the TEAEs in more than 20% of patients in both arms can be found in Appendix E.

Table 16: Overview of safety events. Adverse events that occurred or worsened during treatment in the ITT population. The median duration of follow-up was 37.2 months (range 31.0 to 49.5)

	Dostarlimab plus CP (N=241)	Placebo plus CP (N=246)	Difference, % (95 % CI)
Number of adverse events, n	XXXX	XXXX	XXXX
Number and proportion of patients with ≥1 adverse events, n (%)	XXXX	XXXX	XXXX
Number of serious adverse events, n	XXXX	XXXX	XXXX
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	XXXX	XXXX	XXXX

	Dostarlimab plus CP (N=241)	Placebo plus CP (N=246)	Difference, % (95 % CI)
Number of CTCAE grade ≥ 3 events, n	XXXX	XXXX	XXXX
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	XXXX	XXXX	XXXX
Number of adverse reactions, n	XXXX	XXXX	XXXX
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	XXXX	XXXX	XXXX
Number and proportion of patients who had a dose reduction, n (%)	XXXX	XXXX	XXXX
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	XXXX	XXXX	XXXX
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	XXXX	XXXX	XXXX
Any treatment-related irAE	XXXX	XXXX	XXXX

Source: GSK RUBY-1 CSR

The incidences of grade 3 or higher adverse events and serious adverse events that occurred or worsened during treatment were each approximately 10 percentage points higher in the dostarlimab group than in the placebo group (adverse events, 72.2% vs. 60.2%; serious adverse events, 39.8% vs. 28.0%) (28).

Discontinuation of dostarlimab or placebo in the ITT population due to adverse events occurred in 24.9% in the dostarlimab group and in 16.3% in the placebo group. The most common adverse events leading to discontinuation were maculopapular rash and infusion-related reaction (1.2% each) in the dostarlimab group and thrombocytopenia (1.2%) in the placebo group (28). Discontinuation of dostarlimab or placebo due to AEs occurred in 19.1% of patients in the dostarlimab arm and 8.1% of patients in the placebo arm. The most common AEs leading to discontinuation of dostarlimab or placebo were infusion-related reaction (1.2%) and maculopapular rash (1.2%) in patients in the dostarlimab group and thrombocytopenia (1.2%) and rash (0.8%) in patients in the placebo group (30).

Five deaths due to adverse events occurred in the dostarlimab group, none in the placebo group. One death that was reported by the investigator as related to the dostarlimab regimen occurred during the first six cycles (myelosuppression), one death was related to dostarlimab and occurred during the 90-day safety follow-up (hypovolemic shock), and three were judged not to be related to the dostarlimab regimen (28).Table 17 shows serious events occurring in >2 % in each group due to the limited frequency of serious adverse events. According to the DMC application template, a list of all SAEs with frequency of ≥5% recorded in the study should be presented. However, no SAEs had a frequency of ≥5%; thus, this list could not be provided. A full list of SAEs reported in the study is presented in Appendix E.

Table 17: Serious adverse events occurring in >2% of patients in either group. The median duration of follow-up was 37.2 months (range 31.0 to 49.5) in the ITT population

Adverse events	Dostarlimab plus CP (N= 241)		Placebo plus CP (N= 246)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)				
Sepsis	8 (3.3)	N/A	1 (0.4)	N/A
Pulmonary embolism	8 (3.3)	N/A	5 (2.0)	N/A
Pyrexia	7 (2.9)	N/A	2 (0.8)	N/A

Adverse events	Dostarlimab plus CP (N= 241)		Placebo plus CP (N= 246)	
Dyspnoea	5 (2.1)	N/A	1 (0.4)	N/A
Muscular weakness	5 (2.1)	N/A	1 (0.4)	N/A
Vomiting	5 (2.1)	N/A	3 (1.2)	N/A
Anaemia	3 (1.2)	N/A	6 (2.4)	N/A
Asthenia	2 (0.8)	N/A	6 (2.4)	N/A
Urinary tract infection	3 (1.2)	N/A	5 (2.0)	N/A

Source: Powell et al. 2024

Since the application is following a 14-week process a health economic model and analysis have not been made.

Table 18: Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
N/A				

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

Not applicable.

Table 19: Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
N/A								

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

In this section, the HRQoL data relevant for the assessment of dostarlimab plus CP versus placebo plus CP is described. Health related quality of life data was collected in the RUBY trial—including EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-EN24. To support this submission, we are going to present the EQ-5D-5L data because they are preferred by the Medicines Council (32).

Table 20: Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	Data is obtained through the RUBY trial	Describe purpose of HRQoL instrument (clinical effectiveness, utilities, disutilities etc.)

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instruments

In the RUBY trial HRQoL data was collected using EQ-5D-5L. The instrument was used at baseline and at check-ups in the manner it is validated for (31). The data collection of EQ-5D-5L is described in the section below. EQ-5D was designed to evaluate the generic quality of life of individual patients. The descriptive system is a preference based HRQoL measurement with one question for each of the 5 dimensions that include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The instrument is validated and used across countries and patient population (32).

One important aspect of HRQoL, particular in cancer trials, is that the HRQoL can change rapidly after the disease has progressed. Therefore, it is essential to consider the pre- and post-progression states when analysing the utility estimates. To determine whether patients in the study were in a pre- or post-progression health state, PFS was used. Progression was defined as the time from the date of randomization to the earliest date of radiographic assessment of PD or death by any cause in the absence of PD, whichever occurred first. Tumour response was evaluated using RECIST v.1.1. If at a patient's tumour assessment visit, confirmed progression had not been established, then the

patient was in a pre-progression state for that visit. At the next scheduled visit if the patient had a confirmed progression, the health state of the patient was updated to post-progression for that visit and subsequent visits.

Overall, the demographics in RUBY are well-balanced between treatment arms and the population is representative of the expected population of Danish patients with primary advanced or recurrent EC, as presented in Table 9 and Table 10.

10.1.2 Data collection

QoL measurements in RUBY were collected at baseline (Cycle 1 Day 1), on day 1 of each treatment cycle, at the end of the treatment cycle, and at safety and survival follow-up visits. The primary endpoint in RUBY was met at the first data-cut (IA1), therefore no updates to the PFS and thereby utilities by progression were made at second data-cut (IA2). A summary of completion and missing data points is presented in Table 21.

Table 21: Pattern of missing data and completion ITT population

	Dostarlimab plus CP				CP			
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL Population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Dostarlimab plus CP				CP			
	HRQoL population	Missing	Expected to complete	Completion	HRQoL Population	Missing	Expected to complete	Completion
Time point	N	N (%)	N	N (%)	N	N (%)	N	N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Dostarlimab plus CP				CP			
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL Population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Dostarlimab plus CP				CP			
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL Population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The completion rate was high (95%-100%) over treatment visits (i.e., through cycle 35) in both arms, and remained strong and durable (close to 80% - 100%) at 'end of treatment' and after. Most visits had a total number of patients (two arm combined) with missingness ≤ 10 at a visit, which was too small to compare characteristics of patients with vs. without missing EQ-5D to draw any meaningful conclusion.

A mixed-effects model for repeated measures (MMRM) was performed to compare between-treatment differences adjusting for correlations across multiple time points within a patient and controlling for the baseline value. Adjusted mean difference and 95% confidence intervals (CIs) are presented to illustrate the effect of treatment. Adjusted means and standard error bars were plotted over time. The MMRM model includes patient, treatment, analysis visit, and treatment-by-visit interaction as explanatory variables and the baseline value as a covariate together with the baseline-by-visit interaction. Treatment, visit, and treatment-by-visit interactions were fixed effects in the model; patient was treated as a random effect. An unstructured covariance matrix was used to model the subject variance, and the Kenward-Roger approximation was used to estimate the degrees of freedom. Restricted maximum likelihood estimation was used. Overall adjusted mean estimates and estimates of the treatment difference were derived, representing the average treatment effect over visits giving each visit equal weight. As the fit of the unstructured covariance structure failed to converge, the covariance structures Toeplitz with heterogeneity and autoregressive with heterogeneity were used to reach convergence.

10.1.3 HRQoL results

[redacted]

Figure 15: Change from Baseline and Confidence Interval in EQ-5D-5L utility score (ITT

population)

Abbreviations: Cx=cycle, EOT=End of treatment, SFU=Safety follow-up visit, SVFU= Survival follow-up visit

Source: GSK RUBY-1 CSR

Figure 16: Change from Baseline and Confidence Interval in EQ-5D-5L Visual Analogue Scores (ITT population)

Abbreviations: BSLN=Baseline, Cx=cycle, EOT=End of treatment, SFU=Safety follow-up visit, SVFU= Survival follow-up visit, WPB=Worst post baseline

Source: GSK RUBY-1 CSR

[redacted]

Table 22: Analysis of Change from Baseline in EQ-5D-5L Utility Score, Mixed Effects Model for Repeated Measures, ITT population, Danish population weights

	Dostarlimab plus CP		CP		Dostarlimab plus CP vs. CP
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Dostarlimab plus CP		CP		Dostarlimab plus CP vs. CP
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Not applicable.

10.2.1 HSUV calculation

Not applicable.

10.2.1.1 Mapping

Not applicable.

10.2.2 Disutility calculation

Not applicable.

10.2.3 HSUV results

Not applicable.

Table 23 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

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

Not applicable.

10.3.1 Study design

Not applicable.

10.3.2 Data collection

Not applicable.

10.3.3 HRQoL Results

Not applicable.

10.3.4 HSUV and disutility results

Not applicable.

Table 24: Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

Table 25: Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

11. Resource use and associated costs

Not applicable.

11.1 Medicines - intervention and comparator

Not applicable.

Table 26: Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A				

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

Not applicable.

Table 27: Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
N/A				

11.4 Disease management costs

Not applicable.

Table 28: Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
N/A				

11.5 Costs associated with management of adverse events

Not applicable.

Table 29: Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
N/A		

11.6 Subsequent treatment costs

Not applicable.

Table 30: Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A				

11.7 Patient costs

Not applicable.

Table 31: Patient costs used in the model

Activity	Time spent [minutes, hours, days]
N/A	

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

Not applicable.

12. Results

Not applicable.

12.1 Base case overview

Not applicable.

Table 32: Base case overview

Feature	Description
N/A	

12.1.1 Base case results

Not applicable.

Table 33: Base case results, discounted estimates

	[Intervention]	[Comparator]	Difference
N/A			

12.2 Sensitivity analyses

Not applicable.

12.2.1 Deterministic sensitivity analyses

Not applicable.

Table 34: One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
N/A					

12.2.2 Probabilistic sensitivity analyses

Not applicable.

13. Budget impact analysis

Not applicable.

Table 35: Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
N/A					

14. List of experts

GSK has received input for this application from a Danish clinical expert within endometrial cancer:

[redacted]

15. References

1. DGCG. Onkologisk behandling af endometriecancer. dgcg.dk. [Online] 03 10, 2023. http://dgcg.dk/images/retningslinier/Corpuscancer/DGCG_Onko_bh_endometriecancer_V.2.0_AdmGodk_100320236326.pdf.

2. Endometrial cancer. Morice, P, et al. 10023, 2016, Lancet, Vol. 387, pp. 1094-1108.

3. A review of immune checkpoint blockade therapy in endometrial cancer. Green, AK, Feinberg, J and Makker , V. s.l. : Am Soc Clin Oncol Educ Book, 2020, Vol. 40, pp. 238-244.

4. The presence of postmenopausal bleeding as prognostic parameter in patients with endometrial cancer: a retrospective multi-center study. Seebacher, V, et al. 2009, BMC Cancer, Vol. 9, p. 460.

5. Cancer of the corpus uteri: 2021 update. Koskas, M, et al. suppl 1, 2021, Int J Gynaecol Obstet., Vol. 155, pp. 45-60.

6. (ACS), American Cancer Society. cancer.org. Signs and symptoms of endometrial cancer. [Online] 2019. https://www.cancer.org/cancer/endometrial-cancer/detection-diagnosis-staging/signs-and-symptoms.html.

7. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Concin, N, et al. 2021, International Journal of Gynecological Cancer, Vol. Bd. 31.

8. Randomized phase II study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma: a Japanese Gynecologic Oncology Group study (JGOG2041). Nomura H, Aoki D, Takahashi F, et al. 2011, Ann Oncol., pp. 22(3):636-642.

9. Dansk Gynækologisk Cancer Gruppe. Risikostratificering af endometriecancer. s.l. : DGCG, 2023.

10. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynecologic oncology group study. Thigpen JT, Brady MF, Homesley HD, et al. 2004, J Clin Oncol., pp. 22(19):3902-3908.

11. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. Fleming GF, Brunetto VL, Cella D, et al. 2004, J Clin Oncol, pp. 22(11):2159-2166.

12. Medicinrådet. Medicinrådets anbefaling vedrørende dostarlimab til behandling af dMMR/MSI-high kræft i livmoderslimhinden - version 2.0. Bilag til Medicinrådets

anbefaling vedr. dostarlimab til kræft i livmoderslimhinden. [Online] 2023. https://medicinraadet-classic.azureedge.net/media/dfxcvqox/bilag-til-medicinr%C3%A5dets-anbefaling-vedr-dostarlimab-til-kr%C3%A6ft-i-livmoderslimhinden-vers-2-0.pdf.

13. Life after endometrial cancer: A systematic review of patient-reported outcomes. Shisler, R, et al. 2, 2018, Gynecol Oncol., Vol. 148, pp. 403-413.

14. Fear of recurrence among older breat, ovarian, endometrial, and colorectal cancer survivors: Findings from the WHI LILAC study. Krok-Schoen, JL, et al. 7, 2018, Psychooncology, Vol. 27, pp. 1810-1815.

15. Recurrent cancer is associated with dissatisfaction with care: a logitudinal analysis among ovarian and endometrial cancer patients. de Rooij, BH, Ikiz, H and Boll, D. 3, 2018, Int J Gynecol Cancer, Vol. 28, pp. 614-622.

16. (DGCG), Dansk Gynækologisk Cancer Gruppe. Retningslinjer for visitation, diagnostik, behandling og kontrol af cancer corporis uteri. Kap 1. Indledning. Retningslinjer for visitation, diagnostik, behandling og kontrol af cancer corporis uteri. s.l. : DGCG, 2016, Vol. 3. udgave, pp. 1-7.

17. NORDCAN, Association of the Nordic Cancer Registries. Kræftstatistik: Nøgletal og figurer: Danmark Livmoder. [Online] 2017. https://gco.iarc.fr/media/nordcan/factsheets/93/dk/countries/208/livmoder-200-danmark-208.pdf.

18. Dansk Gynækologisk Cancer Database. Landsdækkende klinisk database for gynækologisk kræft. National Årsrapport 2019/2020. 2021.

19. Observatory, Global Cancer. gco.iarc.fr. Cancer factsheet (GLOBOCAN 2020) 1-year, 3-year, and 5-year prevalence rates: Analysis tables for endometrial cancer. [Online] 2020. https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=population&mode_population=countries&population=900&populations=900&key=asr&sex=2&cancer=24&type=2&statistic=1&prevalence=1&population_group=5&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=.

20. Targeted therapies in gynecological cancers: a comprehensive review of clinical evidence. Wang, q, et al. 1, 2020, Signal Transduct Target Ter., Vol. 5, p. 137.

21. Immune check-point in endometrial cancer. De Felice, F, et al. 8, 2019, int J Clin Oncol., Vol. 24, pp. 910-916.

22. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer

Group. Aapro MS, van Wijk FH, Bolis G, et al. 2003, Ann Oncol., pp. 14(3):441-448.

23. Medicinrådet. Medicinrådets anbefaling vedr. dostarlimab i kombination med carboplatin og paclitaxel til behandling af avanceret eller tilbagevendende dMMR/MSI-H kræft i livmoderslimhinden. s.l. : Medicinrådet, 2024.

24. Carboplatin and paclitaxel for advanced endometrial cancer: final overall survival and adverse event analysis of a phase III trial (NRG Oncology/GOG0209). Miller DS, Filiaci VL, Mannel RS, et al. 2020, J Clin Oncol, pp. 38(33):3841-3850.

25. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. . Miller D, Filiaci V, Fleming G, et al. 2012.

26. A randomized phase II/III study of paclitaxel/carboplatin/metformin versus paclitaxel/carboplatin/placebo as initial therapy for measurable stage III or IVA, stage IVB, or recurrent endometrial cancer: An NRG Oncology/GOG. Bae-Jump VL, Sill M, Gehurig PA. 2020.

27. Retreatment with carboplatin and paclitaxel for recurrent endometrial cancer: A retrospective study of the Memorial Sloan Kettering Cancer Center experience. Rubinstein M, Halpenny D, Makker V, Grisham RN, Aghajanian C, Cadoo K. 2019, Gynecol Oncol Rep. , p. 28.

28. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. Mirza, MR, et al. 23, 2023, M England J Med, Vol. 388, pp. 2145-2158.

29. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). Eisenhauer, EA, et al. 2, 2009, Eur J Cancer, Vol. 45, pp. 228-247.

30. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. Powell, MA, Bjørge , L and Willmott, L. 8, s.l. : Ann Oncol, Aug 2024, Vol. 35, pp. 728-738.

31. GSK. A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel ersus Placebo plus Carboplatin.paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY). s.l. : GSK, 2023. Clinical Study Report.

32. Medicinrådet. The Danish Medicines Council methods guide for assessing new pharmaceuticals. medicinraadet.dk. [Online] 2023. https://medicinraadet.dk/media/5eibukbr/the-danish-medicines-council-methods-guide-for-assessing-new-pharmaceuticals-version-1-3.pdf.

33. Dansk Gynækologisk Cancer Gruppe. Retningslinjer for visitation, diagnostik, behandling og kontrol af cancer corporis uteri. Kap. 5. Onkologisk behandling. 2019. pp. 1-20. 4. udgave.

34. Epidemiology of Microsatellite Instability High (MSI-H) and Deficient Mismatch Repair (dMMR) in Solid Tumors: A Structured Literature Review. Lorenzi, M, et al. 22, 2020, J Oncol., Vol. 2020, pp. 1-17.

35. Predictive and Prognostic Value of Microsatellite Instability in Gynecologic Cancer (Endometrial and Ovarian). Evrard, c and Alexandre, J. 10, Basel : Cancers, May 18, 2021, Vol. 13, pp. 24-34.

36. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; A TransPORTEC initiative. Stelloo, E, et al. 6, 2015, Mod Pathol., Vol. 28, pp. 836-844.

37. Time to first recurrence, pattern of recurrence and survival after recurrence in endometrial cancer according to the molecular classification. Sigenhaler, F, Lindemann, K and Epstein E. 2, s.l. : Gynecol Oncol, 2022, Vol. 165, pp. 230-238.

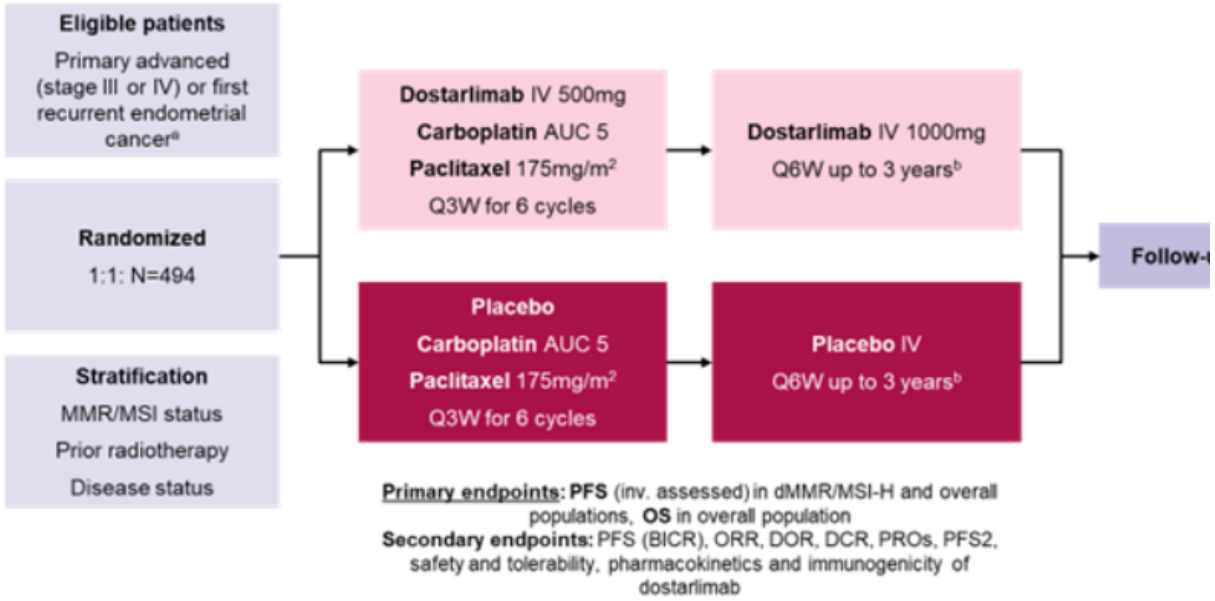
38. Dostarlimab for primary advanced or recurrent (A/R) endometrial cancer (EC): Outcomes by blinded independent central review (BICR) of the RUBY trial (ENGOT-EN6-NSGO/GOG-3031/RUBY). Hietanen, S, Coleman, RL and Monk, BJ. 16_suppl, 2023, Journal of Clinical Oncology, Vol. 41, pp. 5503-5503.

Appendix A. Main characteristics of studies included

Table 36: Main characteristics of studies included

Trial name: RUBY	NCT number: 03981796
Objective	The primary objectives of Part 1 of the RUBY study were to compare the progression-free survival (PFS) of participants treated with dostarlimab plus CP followed by dostarlimab to participants administered placebo plus CP followed by placebo, as assessed by the Investigator per Response Evaluation Criteria in Solid Tumours version 1.1. in patients with primary advanced or recurrent endometrial cancer.
Publications – title, author, journal, year	Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer, M.R. Mirza et al. The new England Journal of Medicine, published March 27, 2023. (28) Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin–paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. Powell MA, Bjørge L, Willmott L, et al. Ann Oncol. 2024 Aug; 35 (8): 728-738. (30)
Study type and design	RUBY is a Phase 3, randomized, double-blind, multicenter study in two parts. Part 1 of the study is to evaluate the efficacy and safety of treatment with dostarlimab plus CP followed by dostarlimab versus treatment with placebo plus CP followed by placebo in participants with primary advanced (Stage III or IV) or recurrent EC. Part 2 is to evaluate the efficacy and safety of dostarlimab plus CP followed by dostarlimab plus niraparib versus placebo plus CP followed by placebo in participants with recurrent or primary advanced (Stage III or IV) endometrial cancer. An overview of the treatment design for part 1 is presented below.

Trial name: RUBY	NCT number: 03981796



The RUBY study consists of a Screening Period (Day -28 to Day -1), a Treatment Period, an End of Treatment Visit, a Safety Follow-up Visit, and a Survival Assessment Period. Following informed consent, participants who met the eligibility criteria for Part 1 were randomized 1:1 to the following study arms:

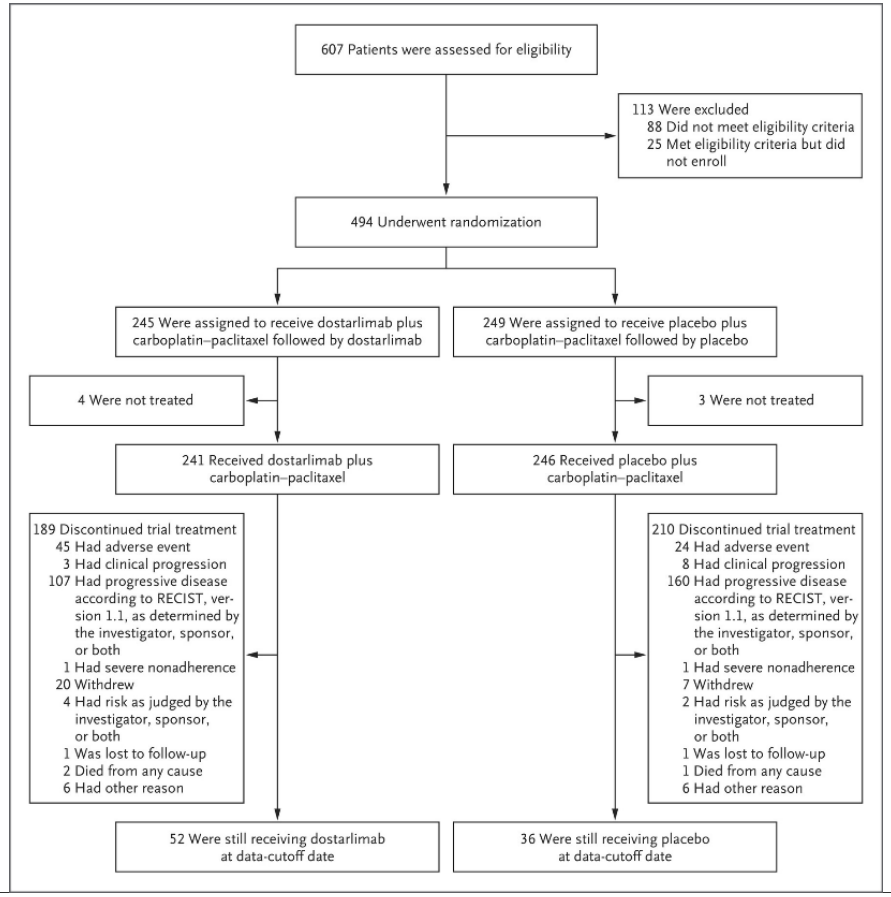
- Arm 1: Participants received dostarlimab IV plus CP followed by dostarlimab IV.
- Arm 2: Participants received placebo IV plus CP followed by placebo IV.

Randomization was stratified by 3 stratification factors:

- MMR/MSI status: Determined by local IHC, PCR, or next-generation sequencing test, or by central IHC testing when local testing was not available. The MMR/MSI status for randomization was derived from the data entered at the time of randomization.

Trial name: RUBY	NCT number: 03981796
	• Prior external pelvic radiotherapy (yes or no): Determined from radiation therapy history provided by investigators at the time of randomization. • Disease status (recurrent, primary Stage III, or primary Stage IV): Derived from the cancer history and disease stage provided by investigators at the time of randomization. Data provided for the most recent FIGO stage and recurrence status were used to assign the participant to the appropriate stratum. If recurrence was selected, participants were assigned to recurrent strata. If no recurrence was selected, then participants were assigned to primary Stage III or primary Stage IV based on most recent FIGO stage. Approximately 470 participants were planned for enrolment in Part 1. The participant, Investigator, study staff, the sponsor study team, and its representatives were blinded to the assigned treatment from the time of randomization until database lock as described in the protocol. Treatment assignment could be unblinded by the Investigator for urgent or non-urgent clinical reasons. Study intervention assignment was available to the Investigator upon request for poststudy intervention planning.
Sample size (n)	From July 18, 2019, through February 23, 2021, a total of 607 patients from 113 sites in 19 countries were screened and 494 underwent randomization; 245 were assigned to receive dostarlimab plus CP (dostarlimab group) and 249 were assigned to receive placebo plus CP (placebo group). Seven patients (4 in dostarlimab group and 3 in the placebo group) did not receive treatment and were excluded from the safety analysis. Of the 494 patients who underwent randomization, 118 had dMMR–MSI-H tumours confirmed by source-verified classification (53 in the dostarlimab group and 65 in the

placebo group). As of the data-cutoff date of September 28, 2022, a total of 88 patients in the overall population were receiving treatment in one of the two groups The disposition of patients is presented below:



Trial name: RUBY	NCT number: 03981796
Main inclusion criteria RUBY part 1	• Female participant is at least 18 years of age. • Participant has histologically or cytologically proven endometrial cancer with recurrent or advanced disease. • Participant must have primary Stage III or Stage IV disease or first recurrent endometrial cancer with a low potential for cure by radiation therapy or surgery alone or in combination and meet at least one of the following criteria; 1. Participant has primary Stage IIIA to IIIC1 disease with presence of evaluable or measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) version (v).1.1 based on Investigator's assessment. Lesions that are equivocal or can be representative of post-operative change should be biopsied and confirmed for the presence of tumour. 2. Participant has primary Stage IIIC1 disease with carcinosarcoma, clear cell, serous, or mixed histology (containing greater than or equal to [>=] 10 percent carcinosarcoma, clear cell, or serous histology) regardless of presence of evaluable or measurable disease on imaging; 3. Participant has primary Stage IIIC2 or Stage IV disease regardless of the presence of evaluable or measurable disease; 4. Participant has first recurrent disease and is naïve to systemic anticancer therapy; 5. Participant has received prior neo-adjuvant/adjuvant systemic anticancer therapy and had a recurrence or progression of disease (PD) >=6 months after completing treatment (first recurrence only). • Participant has an ECOG performance status of 0 or 1. Participant has adequate organ function.
Main exclusion criteria RUBY part 1	• Participant has received neo-adjuvant/adjuvant systemic anticancer therapy for primary Stage III or IV disease and: 1. has not had a recurrence or PD prior to first dose on the study OR 2. has had a recurrence or PD within 6 months of completing systemic anticancer therapy treatment prior to first dose on the study. • Participant has had >1 recurrence of endometrial cancer. • Participant has received prior therapy with an anti-programmed cell death protein 1 (anti-PD-1), anti-PD-ligand 1 (anti-PD-L1), or anti-PD-ligand 2 (anti-PD-L2) agent. • Participant has received prior anticancer therapy (chemotherapy, targeted therapies, hormonal therapy, radiotherapy, or immunotherapy) within 21 days or <5 times the half-life of the most recent therapy prior to Study Day 1, whichever is shorter.

Trial name: RUBY	NCT number: 03981796
	• Participant has a concomitant malignancy, or participant has a prior non-endometrial invasive malignancy who has been disease-free for <3 years or who received any active treatment in the last 3 years for that malignancy. Non-melanoma skin cancer is allowed. • Participant has known uncontrolled central nervous system metastases, carcinomatosis meningitis, or both. • Participant has not recovered (that is [i.e.], to Grade <=1 or to Baseline) from cytotoxic therapy induced AEs or has received transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF], or recombinant erythropoietin) within 21 days prior to the first dose of study drug. • Participant has not recovered adequately from AEs or complications from any major surgery prior to starting therapy. • Participant is currently participating and receiving study treatment or has participated in a study of an investigational agent and received study treatment or used an investigational device within 4 weeks of the first dose of treatment. • Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active infection requiring systemic therapy. Participant has received, or is scheduled to receive, a live vaccine within 30 days before first dose of study treatment, during study treatment, and for up to 180 days after receiving the last dose of study treatment.
Intervention	Dostarlimab 500 mg IV + carboplatin AUC 5 IV + paclitaxel 175 mg/m2 IV Q3W for cycles 1–6 followed by dostarlimab 1,000 mg IV Q6W up to 3 years. N= 245
Comparator(s)	Placebo + carboplatin AUC 5 IV + paclitaxel 175 mg/m2 IV Q3W for cycles 1–6 followed by placebo Q6W up to 3 years. N= 249
Follow-up time	Median follow-up of 25.4 months (range 19.2 to 37.8) in the overall population Median follow-up of XX months (range XX to XX) in the MMRp/MSS population

Trial name: RUBY	NCT number: 03981796
Is the study used in the health economic model?	Not applicable.
Primary, secondary and exploratory endpoints	RUBY-1 evaluated dual primary endpoints: • Investigator-assessed PFS according to RECIST v1.1 criteria in patients with dMMR/MSI-H tumours and in the overall trial population. PFS for the pMMR/MSS was a prespecified subgroup analysis. • OS: Analysis of OS in the dMMR/MSI-H and MMRp/ MSS subsets of the ITT analysis set was also pre-specified and evaluated at IA2. The OS analyses for dMMR/MSI-H and MMRp/MSS populations were performed on MMR/MSI status based on source verified data. Secondary endpoints: • PFS by BICR • ORR based on BICR and investigator assessment • Duration of response based on BICR and investigator assessment • Disease control rate based on BICR and investigator assessment • PFS2 (prespecified in the dMMR/MSI-H and MMRp/MSS populations) • PROs (EORTC-QLQ-C30; EORTC-QLQ-EN24; EQ-5D-5L) • PK and immunogenicity analyses Exploratory endpoints: • Genetic research • Biomarkers in tumour tissue and/or blood Safety endpoints: • TEAEs • Clinical laboratory values • Vital signs • Physical examination • ECOG PS • ECG parameters • Concomitant medication

Trial name: RUBY	NCT number: 03981796
Method of analysis	All efficacy analyses were intention-to-treat analyses. The Kaplan–Meier method was used to estimate rates of progression-free survival and overall survival, and a stratified log-rank test for treatment comparisons.
Subgroup analyses	Pre-specified exploratory subgroup analyses of PFS per investigator assessment and OS were performed based on the ITT analysis set and dMMR/MSI-H subset for the ITT analysis set to explore homogeneity of the treatment effect across the following subgroups: • Age (<65 years or ≥65 years) • Race (White or other) • Region (North American, Europe, Western Europe, or Eastern Europe) • Histology (endometrioid carcinoma or other) • Disease status at baseline (recurrent, primary stage III, or primary stage IV) • MMR/MSI status at baseline (dMMR/MSI-H or MMRp/MMS) • Prior external pelvic radiotherapy (yes or no) • Subjects with “no disease” at baseline
Other relevant information	

Appendix B. Efficacy results per study

Table 37: Results per RUBY

Results of RUBY-1 (NCT03981796)											
				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, investigator assessed (probability at 24 months)	Dostarlimab	245	36.1% (29.3-42.9)	n/a	n/a	n/a	36%	0.51-0.80	<0.001	PFS is based on the Kaplan-Meier estimator. The 95% confidence intervals of the hazard ratios reported were based on the Cox regression model and were not used for hypothesis testing. All P values reported were based on the stratified log-rank test.	Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. Mirza, MR, et al. 23, 2023, M England J Med, Vol. 388, pp. 2145-2158.
	Carboplatin plus paclitaxel	249	18.1% (13.0-23.9)								
OS	Dostarlimab	245	44.6 months (32.6-NE)	16.4 months	n/a	n/a	31%	0.54-0.89	0.0020	The survival rates are based on the Kaplan–	Overall survival in

Results of RUBY-1 (NCT03981796)												
				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		
	Carboplatin plus paclitaxel	249	28.2 months (22.1-25.6)							Meier estimator. The 95% confidence intervals of the hazard ratios reported were based on the Cox regression model and were not used for hypothesis testing. All P values reported were based on the stratified log-rank test.	patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. Powell, MA, Bjørge, L and Willmott, L. 8, s.l. : Ann Oncol, Aug 2024, Vol. 35, pp. 728-738.

Results of RUBY-1 (NCT03981796)												
				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 BICR (probability at 24 months)	Dostarlimab	245	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	PFS is based on the Kaplan-Meier estimator. The 95% confidence intervals of the hazard ratios reported were based on the Cox regression model and were not used for hypothesis testing. All P values reported were based on the stratified log-rank test.	GSK RUBY-1 CSR
	Carboplatin plus paclitaxel	249	XXXX								
Objective response rate (Denominator is the number of participants with target or non-target	Dostarlimab	212	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX		GSK RUBY-1 CSR
	Carboplatin plus paclitaxel	219	XXXX								

Results of RUBY-1 (NCT03981796)											
				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		
lesions at baseline)											

Appendix C. Comparative analysis of efficacy

Not Applicable.

Table 38: Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A									

Appendix D. Extrapolation

Not applicable.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

D.1.2 Model

D.1.3 Proportional hazards

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

D.1.5 Evaluation of visual fit

D.1.6 Evaluation of hazard functions

D.1.7 Validation and discussion of extrapolated curves

D.1.8 Adjustment of background mortality

D.1.9 Adjustment for treatment switching/cross-over

D.1.10 Waning effect

D.1.11 Cure-point

D.2 Extrapolation of [effect measure 2]

Appendix E. Serious adverse events

Table - III: Overview of safety events. Adverse events that occurred or worsened during treatment in the MMRp/MSS population. The median duration of follow-up was 37.2 months (range 31.0 to 49.5)

	Dostarlimab plus CP (N=189)	Placebo plus CP (N=181)	Difference, % (95 % CI)
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX
XXXX	XXXX	XXXX	XXXX

Source: GSK RUBY-1 CSR

Table - IV: Summary of Timing of TEAEs in More Than 20% of Patients in Either Arm

	Dostarlimab plus CP (n=241)			Placebo plus CP (n=246)		
	Overall	<cycle 7	≥cycle 7	Overall	<cycle 7	≥cycle 7
Number of patients eligible for TEAE evaluation	**241**	**241**	**185**	**246**	**246**	**184**
Any grade TEAEs in more than 20% of patients in either arm, no. (%)						
Fatigue	125 (51.9)	116 (48.1)	34 (18.4)	134 (54.5)	124 (50.4)	34 (18.5)
Alopecia	129 (53.5)	129 (53.5)	11 (5.9)	123 (50.0)	122 (49.6)	10 (5.4)
Nausea	130 (53.9)	116 (48.1)	34 (18.4)	113 (45.9)	105 (42.7)	19 (10.3)
Neuropathy peripheral	106 (44.0)	101 (41.9)	15 (8.1)	101 (41.1)	99 (40.2)	8 (4.3)
Anemia	91 (37.8)	85 (35.3)	30 (16.2)	104 (42.3)	98 (39.8)	23 (12.5)
Arthralgia	86 (35.7)	64 (26.6)	39 (21.1)	86 (35.0)	69 (28.0)	26 (14.1)
Constipation	83 (34.4)	77 (32.0)	19 (10.3)	88 (35.8)	76 (30.9)	17 (9.2)
Diarrhea	75 (31.1)	64 (26.6)	27 (14.6)	71 (28.9)	60 (24.4)	18 (9.8)
Myalgia	63 (26.1)	58 (24.1)	11 (5.9)	68 (27.6)	65 (26.4)	11 (6.0)
Hypomagnesemia	52 (21.6)	46 (19.1)	13 (7.0)	70 (28.5)	67 (27.2)	12 (6.5)
Peripheral sensory neuropathy	51 (21.2)	45 (18.7)	17 (9.2)	47 (19.1)	46 (18.7)	5 (2.7)
Decreased appetite	52 (21.6)	43 (17.8)	11 (5.9)	43 (17.5)	41 (16.7)	4 (2.2)
Dyspnea	44 (18.3)	39 (16.2)	15 (8.1)	50 (20.3)	43 (17.5)	12 (6.5)

	Rash	55 (22.8)	46 (19.1)	15 (8.1)	34 (13.8)	31 (12.6)	5 (2.7)

Source: Supplement to Mirza et al. 2023

Appendix F. Health-related quality of life

Table - V: Pattern of missing data and completion MMRp/MSS population

	Dostarlimab plus CP				CP			
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL Population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Dostarlimab plus CP				CP			
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL Population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Dostarlimab plus CP				CP			
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL Population N	Missing N (%)	Expected to complete N	Completion N (%)
XXX	[redacted]							
XXX	[redacted]							
XXX	[redacted]							
XXX	[redacted]							
XXX	[redacted]							
XXX	[redacted]							
XXX	[redacted]							

Source: GSK RUBY-1 CSR

Figure 17: Change from Baseline and Confidence Interval in the EQ-5D-5L utility score (MMRp/MSS population)

Abbreviations: Cx=cycle, EOT=End of treatment, SFU=Safety follow-up visit, SVFU= Survival follow-up visit
Source: GSK RUBY-1 CSR

Figure 18: Change in Baseline and Confidence Interval in EQ-5D-5L Visual Analogue Score (MMRp/MSS population)

[redacted]

Abbreviations: BSLN=Baseline, Cx=cycle, EOT=End of treatment, SFU=Safety follow-up visit, SVFU= Survival follow-up visit, WPB=Worst post baseline
Source: GSK RUBY-1 CSR

Table - VI: Analysis of Change from Baseline in EQ-5D-5L Utility Score, Mixed Effects Model for Repeated Measures, MMRp/MSS population, Danish population weights

	Dostarlimab plus CP (N=181)		CP (N=174)		Dostarlimab plus CP vs. CP
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Dostarlimab plus CP (N=181)		CP (N=174)		Dostarlimab plus CP vs. CP
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: GSK RUBY-1 CSR

Table - VII: Summary of Analysis of EQ-5D-5L Visual Analogue Scores Change from Baseline over Time, ITT population

	Dostarlimab plus CP (N=245)		CP (N=249)		Dostarlimab plus CP vs. CP
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Dostarlimab plus CP (N=245)		CP (N=249)		Dostarlimab plus CP vs. CP
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Dostarlimab plus CP (N=245)		CP (N=249)		Dostarlimab plus CP vs. CP
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: GSK RUBY-1 CSR

Table - VIII: Summary of Analysis of EQ-5D-5L Visual Analogue Scores Change from Baseline over Time, MMRp/MSS population

	Dostarlimab plus CP (N=192)		CP (N=184)		Dostarlimab plus CP vs. CP
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	Dostarlimab plus CP (N=192)		CP (N=184)		Dostarlimab plus CP vs. CP
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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	Dostarlimab plus CP (N=192)		CP (N=184)		Dostarlimab plus CP vs. CP
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Source: GSK RUBY-1 CSR

Appendix G. Probabilistic sensitivity analyses

Not applicable.

Table 39: Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
N/A				

Appendix H. Literature searches for the clinical assessment

Not applicable.

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

Table 40: Bibliographic databases included in the literature search

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

Table 41: Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A			

Table 42: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A				

H.1.1 Search strategies

Table 43: of search strategy table for [name of database]

No.	Query	Results
N/A		

H.1.2 Systematic selection of studies

Table 44: Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
N/A			

Table 45: Overview of study design for studies included in the analyses

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

H.1.3 Excluded fulltext references

H.1.4 Quality assessment

H.1.5 Unpublished data

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

Not applicable.

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

Table 46: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
N/A			

Table 47: Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A			

Table 48: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A				

I.1.1 Search strategies

Table 49: Search strategy for [name of database]

No.	Query	Results
N/A		

I.1.2 Quality assessment and generalizability of estimates

I.1.3 Unpublished data

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

Not applicable.

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

J.1.1 Example: Systematic search for […]

Table 51: Sources included in the search

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

J.1.2 Example: Targeted literature search for [estimates]

Table 52: Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
N/A			

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk

Ansøgning om vurdering af pembrolizumab i kombination med kemoterapi til førstelinje-behandling af avanceret eller tilbagevendende dMMR eller pMMR kræft i livmoderen

Farveskema til tekstfremhævning	
Farve på fremhævet tekst	**Definition af fremhævet tekst**
	Fortrolige oplysninger

Kontaktoplysninger

Kontaktoplysninger	
Virksomhed	**MSD Danmark ApS**
Navn	Tenna Bekker
Titel	Market Access Manager
Telefonnummer	+45 2892 1882
E-mail	tenna.bekker@msd.com

Indholdsfortegnelse

Tabeller og figurer

Medicinrådets tabeller

Supplerende figurer og tabeller

Forkortelser

AE	*Adverse Event*
AEOSI	*Adverse Event of Special Interest*
ApaT	*All Participants as Treated*
BICR	*Blinded Independent Central Review*
CHMP	*Committee for Medicinal Products for Human Use*
CI	*Confidence Interval*
CT	Computer tomografi
dMMR	*Mismatch Repair Deficient*
ECOG	*Eastern Cooperative Oncology Group*
EMA	*European Medicines Agency* (Det Europæiske Lægemiddelagentur)
EORTC QLQ-C30	*European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30*
EQ-5D	*EuroQoL-5 Dimension Questionnaire*
ESMO	*European Society for Medical Oncology*
FA	*Final analysis*
FAS	*Full analysis set*
FACT-G	*Functional Assessment of Cancer Therapy – General*
FACT-En TOI	*Functional Assessment of Cancer Therapy-Endometrial Trial Outcome Index*
HR	*Hazard Ratio*
HRQoL	*Health-Related Quality of Life*
IA	Interimanalyse
IA1	Interimanalyse 1
ICH	*International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use*
IHC	Immunhistokemi
ITT	*Intention-to-treat*
iTEAE	*Immune mediated Treatment Emergent Adverse Events*
IPCW	*Inverse Probability of Censoring Weights*
IQR	*Inter Quartile Range*
IV	Intravenøs
KM	Kaplan-Meier
LS	*Least Squares*
LVSI	*Lymphovascular space invasion*
MedDRA	*Medical Dictionary for Regulatory Activities*
MR	Magnetisk resonans
MDT	Multi Disciplinære Teams
MMR	*Mismatch Repair*
MSD	Merck Sharp & Dohme
MSI	Mikrosatelit instabilitet
NA	*Not Applicable*
OS	*Overall Survival*
PFS	*Progression-free Survival*
pMMR	*Mismatch Repair Proficient*
POLE	*Polymerase epsilon*
PRO	*Patient Reported Outcome*
PS	*Performance status*
Q1W	Hver uge
Q3W	Hver 3. uge
Q4W	Hver 4. uge
Q6W	Hver 6. uge
QOL	*Quality of Life*
RECIST1.1	*Response Evaluation Criteria in Solid Tumors version 1.1*
SAE	*Serious Adverse Event*
SE	*Standard Error*

SOC	*Standard of Care*

Læsevejledning

Medicinrådets ansøgningsskema version 1.4 er anvendt. For at følge de prædefinerede tabeller og deres nummerering, har vi nummereret ekstra tabeller med romertal, fx tabel XI. Ansøgningen er skrevet på dansk. Nogle begreber er bibeholdt på engelsk; disse er angivet med *kursiv.* Fortrolige oplysninger er markeret med gult.

1. Oplysninger om lægemidlet

Lægemiddelinformationer	
Handelsnavn	KEYTRUDA ®
Generisk navn	Pembrolizumab
Indikation som formuleret af Det Europæiske Lægemiddelagentur (EMA)	KEYTRUDA, i kombination med carboplatin og paclitaxel, er indiceret til førstelinjebehandling af primær avanceret eller recidiverende endometriecancer hos voksne, som er egnet til systemisk behandling.
Indehaver af markedsføringstilladelse i Danmark	MSD Danmark ApS
ATC-kode	L01FF02
Kombinationsbehandling og/eller samtidig behandling	Nej
(Forventet) Dato for EU-godkendelse	EC-godkendelse 24. oktober 2024
Har lægemidlet fået en betinget markedsføringstilladelse?	Nej
Har lægemidlet været i 'accelerated assessment' hos EMA?	Nej
Har lægemidlet 'orphan drug designation'? (medtag dato)	Nej
Andre indikationer godkendt af EMA	Se Appendix K
Andre indikationer, der er blevet evalueret af Medicinrådet (ja/nej)	Se Appendix K
Fælles nordisk vurdering (JNHB)	Er den nuværende behandlingspraksis ens på tværs af de nordiske lande (DK, FI, IS, NO, SE)? Ja Er produktet egnet til en fælles nordisk vurdering? Nej Hvis ikke, hvorfor? MSD Danmark ønsker, at vurderingen er fokuseret på den kliniske relevans i det danske sundhedsvæsen og at danske klinikere er involveret i denne vurdering. Vi ønsker også, at den nye behandling bliver hurtigt tilgængelig for danske læger og patienter. Begge dele mener vi, at Medicinrådet er rigtig gode til. Samtidig har de hidtidige erfaringer med det nordiske

Lægemiddelinformationer	
	samarbejde ikke været positive ift. sagsbehandlingstiden. Vi ønsker derfor ikke en vurdering i JNHB.
Udlevering	BEGR/NBS
Emballage – typer, størrelser/antal enheder og koncentrationer	4 ml konc.t.inf.væsk.opl a 25 mg/ml

2. Oversigtstabel

Oversigt	
Indikation, der er relevant for vurderingen	KEYTRUDA, i kombination med carboplatin og paclitaxel, er indiceret til førstelinjebehandling af primær avanceret eller recidiverende endometriecancer hos voksne, som er egnet til systemisk behandling.
Doseringsregime og administrationsform	200 mg pembrolizumab iv Q3W i kombination med 175 mg/m^2 paclitaxel iv på dag 1 samt carboplatin AUC 5 mg/ml/min iv på dag 1 i 6 serier, efterfulgt af vedligeholdelsesbehandling med 400 pembrolizumab iv Q6W i op til 14 serier. Pembrolizumab blev administreret som intravenøs infusion over 30 minutter. Paclitaxel blev administreret som intravenøs infusion over 3 timer. Carboplatin blev administreret som intravenøs infusion over 30 til 60 minutter.
Valg af komparator	pMMR: Carboplatin + paclitaxel dMMR: Dostarlimab i komb. med carboplatin + paclitaxel
Prognose med aktuel behandling (komparator)	I Danmark er 47,6% af patienter i lav-risikogruppen med en 5-års OS-rate på 91%. Patienter i mellem (17,5%), mellem-høj (16%) og høj risiko (15%) har 5-års OS-rater på henholdsvis 84%, 75%, og 59%. Patienter med avanceret/metastatisk sygdom (3,9%) har den laveste 5-års OS-rate på 12% (1).
Type af dokumentation til den kliniske evaluering	Ansøgningen er baseret på en direkte sammenligning fra NRG-GY018 for så vidt angår pMMR-subgruppen og på en indirekte sammenligning af dMMR-resultaterne fra NRG-GY018 og RUBY-1
Vigtigste effektmål (forskel/forbedring	**HR progressionsfri overlevelse (PFS)** Pembro + kemo vs kemo (pMMR): 0,57 (0,44; 0,74) Pembro + kemo vs dostar + kemo (dMMR) (24 mdr):

Oversigt	
sammenlignet med komparator)	[redacted] **HR samlet overlevelse (OS)** Pembro + kemo vs kemo (pMMR): 0,79 (0,53; 1,17) Pembro + kemo vs dostar + kemo (dMMR): [redacted] **Sikkerhed** Pembro + kemo vs kemo (andel med ≥1 alvorlig uønsket hændelse): [redacted] Pembro + kemo vs dostar + kemo: Sammenholdt er der ikke noget der taler for, at der er forskel på sikkerhedsprofilen af de to kombinationsbehandlinger.
Vigtigste alvorlige uønskede hændelser for interventionen og komparatoren	Pembro + kemo vs kemo: Forekomst af alvorlige uønskede hændelser med en frekvens >2% var som følger i pembrolizumab+SOC- vs. placebo+SOC-gruppen: anæmi (4,2% vs. 3,4%), febril neutropeni (2,9% vs. 1,3%), urinvejsinfektion (2,1% vs. 1,6%), og fald i antal af hvide blodceller (2,1% vs. 1,1 %). Pembro + kemo vs dostar + kemo: Forekomst af alvorlige uønskede hændelser med en frekvens >2% var som følger i dostarlimab+SOC- vs. placebo+SOC-gruppen: sepsis (3,3% vs. 0,4%), pulmonær embolisme (2,5% vs. 2,0%), pyrexia (2,5% vs. 0,8%), dyspnø (2,1% vs. 0,4%), asthenia (0,8% vs. 2,4%), anæmi (1,2% vs. 2,4%), urinvejsinfektion (1,2% vs. 2,0%), og muskulær svaghed (2,1% vs. 0,4 %).
Konsekvens for helbredsrelateret livskvalitet	NA
Type af sundhedsøkonomisk analyse, der indsendes	NA
Datakilder, der bruges til at modellere klinisk effekt	NA
Datakilder, der bruges til at modellere den helbredsrelaterede livskvalitet	NA
Vundne leveår	NA
Vundne QALY	NA
Inkrementelle omkostninger	NA
ICER (DKK/QALY)	NA

Oversigt	
Usikkerhed forbundet med ICER-estimatet	NA
Antal egnede patienter i Danmark	Incidens: ca. 100 patienter per år Prævalens: NA
Budgetkonsekvens (i år 5)	NA

3. Patientpopulation, intervention, valg af komparator(er) og relevante effektmål

3.1 Sygdommen

Endometriecancer (EC) eller livmoderkræft er den 5. hyppigste cancertype blandt kvinder i Danmark og den hyppigste gynækologiske cancer (2). Livmoderkræft opstår som regel efter overgangsalderen og ses sjældent før 40-årsalderen. Aldersmaksimum er omkring 70 år (2). Sygdommen opdages oftest i de tidligste stadier, fordi det mest almindelige symptom er uventede blødninger fra skeden. Risikoen for at udvikle livmoderkræft afhænger bl.a. af østrogen. Langvarig og konstant påvirkning af østrogen og manglende tilførsel af progesteron øger risikoen for at udvikle livmoderkræft. Derudover har kvinder, som aldrig har været gravide, større risiko for at udvikle livmoderkræft, sammenlignet med kvinder, som har fået børn (3).

Som andre kræftformer inddeles kræft i livmoderen i stadier, afhængig af tumors udbredelse (begrænset til endometriet; involvering af myometriet; udbredelse til cervical stroma, vagina eller parametriet; metastaser i nærtliggende organer; fjernmetastaser) og lymfeknudeinvolvering (N0; N1) (4). Ved diagnosen har 70-75% lokaliseret sygdom (stadie I-II), mens 12% har regional sygdom (stadie III-IVA), og cirka 5% har fjernmetastaser (stadie IVB) (5, 6).

Risikoinddeling af livmoderkræft foretages præ- og postoperativt. Den præoperative inddeling anvendes til at planlægge operativt indgreb baseret på grad, omfang af myometrieinvasion, og histologi (4). Den postoperative risikoinddeling suppleres i Danmark med molekylær undersøgelse af p53, *mismatch repair* (MMR) og POLE, samt histopatologi, LVSI (*lymphovascular space invasion*), og grad (4, 7). I henhold til ESMO-retningslinjerne testes *mismatch-repair (MMR) deficiency* ved brug af immunhistokemi (IHC) for 4 proteiner, der er involveret i *mismatch-repair pathway*. Fuldt tab af ekspression af ét eller flere af disse MMR-proteiner er tilstrækkeligt til diagnosticering af *MMR-deficiency* (dMMR) (8). Ændringer i *MMR-pathways* fører til manglende reparation af DNA,

hvilket efterfølgende ændrer ellers stabilt antal af DNA mikrosatellit områder. Høj mikrosatellit instabilitet (MSI-H) kan testes ved DNA-sekventering. I dansk klinisk praksis anvendes primært IHC (MMR test), som kan suppleres med sekventering (MSI test) (2). Der er høj overensstemmelse mellem MSI-H og dMMR i livmoderkræft (9).

Patienterne inddeles i 5 risikogrupper, dvs. lav, mellem, mellem-høj, høj, og avanceret/metastatisk (2). I Danmark er 47,6% af patienter i lav-risikogruppen med en 5-års OS-rate på 91%. Patienter i mellem (17,5%), mellem-høj (16%) og høj risiko (15%) har 5-års OS-rater på henholdsvis 84%, 75%, og 59%. Patienter med avanceret/metastatisk sygdom (3,9%) har den laveste 5-års OS-rate på 12% (1).

Det kliniske studie, som ligger til grund for denne indikationsudvidelse er NRG-GY018. Heri indgår patienter med målbar sygdom i stadie III-IVA, og patienter med målbar eller ikke-målbar sygdom i stadie IVB eller med recidiv.

3.2 Patientpopulation

Årligt diagnosticeres ca. 600 danske kvinder med livmoderkræft på tværs af stadier (2).

I 2021 var der 11.481 danske kvinder, der levede med livmoderkræft (3).

Tabel 1. Incidens og prævalens i de seneste 5 år

År	2018/2019	2019/2020	2020/2021	2021/2022	2022/2023
Incidens i Danmark	591	601	642	537	NA
Prævalens i Danmark	NA	NA	NA	11 481	NA

Som nævnt ovenfor er ansøgningen her baseret på studiet NRG-GY018, der inkluderede patienter med målbar sygdom i stadie III-IVA, og patienter med målbar eller ikke-målbar sygdom i stadie IVB eller med recidiv. I Medicinrådets anbefaling af dostarlimab + kemoterapi til dMMR-populationen er det estimeret, at omkring 30 patienter årligt vil kandidere til behandlingen (10), hvilket må antages også at gælde for denne kombination. Den forventede fordeling mellem dMMR- og pMMR-populationen er ca. 30% og 70% (11), hvorfor vi antager, at yderligere ca. 70 patienter i pMMR-grupppen vil kandidere til behandling.

Tabel 2. Estimater for antallet af patienter, der er egnede til behandling (10, 11)

År	2025	2026	2027	2028	2029
Antal patienter i Danmark, som er egnede til behandling i de kommende år (dMMR/pMMR)	100 (30/70)	100 (30/70)	100 (30/70)	100 (30/70)	100 (30/70)

3.3 Nuværende behandlingstilbud

Den primære behandling af endometriecancer er kirurgisk, hvor målet er makroskopisk radikal operation og korrekt stadieinddeling (2). For patienter i stadie III-IVA med restsygdom efter operation, for alle stadie IVB-patienter, og kemo-naïve patienter med ikke-lokaliseret recidiv er førstelinje standardbehandlingen carboplatin og paclitaxel (2).

For dMMR patienter har standardbehandlingen siden august 2024 været kemoterapi kombineret med dostarlimab, som i RUBY-1 studiet viste signifikant forbedring af PFS og OS (2, 12).

Patienter kan i anden linje få genbehandling med carboplatin og paclitaxel. Behandling med doxorubicin, pegyleret liposomalt doxorubicin, ugentlig paclitaxel eller deltagelse i klinisk forsøg er også muligheder (2). dMMR/MSI-H, immunterapi-naïve patienter kan tilbydes dostarlimab monoterapi (13, 14). Andenlinje behandling med pembrolizumab + lenvatinib (15) til patienter uanset MMR-status, revurderes p.t. af Medicinrådet (16).

3.4 Intervention

Interventionen er pembrolizumab i kombination med kemoterapi i form af carboplatin og paclitaxel. De enkelte lægemiddelstoffer er beskrevet i tabellerne herunder.

Pembrolizumab er et antistof, der binder til *Programmed cell Death-1* (PD-1) receptoren og blokerer interaktionen med liganderne PD-L1 and PD-L2. PD-1 receptoren er en negativ regulator af T-celle aktivitet og er vist at være involveret i kontrollen af T-celle medieret immunrespons. Pembrolizumab øger T-celleresponset, inklusiv anti-tumorresponset, ved at blokere PD-1's binding til PD-L1 and PD-L2. PD-L1 og PD-L2 er udtrykt på *antigen presenting cells* og kan udtrykkes af tumorceller eller andre celler i tumorens mikromiljø.

Oplysningerne i tabellerne stammer fra studieprotokollen og fra de respektive lægemidlers produktresuméer (17-19).

Oversigt over interventionen	Pembrolizumab
Indikation, der er relevant for vurderingen	KEYTRUDA, i kombination med carboplatin og paclitaxel, er indiceret til førstelinjebehandling af primær avanceret eller recidiverende endometriecancer hos voksne, som er egnet til systemisk behandling.

Oversigt over interventionen	Pembrolizumab
ATMP	Nej
Administrationsform	Pembrolizumab blev administreret som intravenøs infusion over 30 minutter. Paclitaxel blev administreret som intravenøs infusion over 3 timer. Carboplatin blev administreret som intravenøs infusion over 30 til 60 minutter.
Dosering	200 mg pembrolizumab iv Q3W i kombination med 175 mg/m^2 paclitaxel iv på dag 1 samt carboplatin AUC 5 mg/ml/min iv på dag 1 i 6 serier, efterfulgt af vedligeholdelsesbehandling med 400 pembrolizumab iv Q6W i op til 14 serier.
Dosering i den sundhedsøkonomiske model (herunder relativ dosisintensitet)	NA
Skal lægemidlet administreres sammen med anden medicin?	Nej
Behandlingsvarighed/-kriterier for behandlingsophør	Patienterne blev behandlet med pembrolizumab indtil progression eller uacceptable bivirkninger, dog maksimalt i 20 serier.
Nødvendig monitorering, både under administration og i behandlingsperioden	
Behov for diagnostik eller andre test (f.eks. *companion diagnostic*). Hvordan er disse inkluderet i modellen?	Nej
Pakningsstørrelse(r)	4 ml konc.t.inf.væsk.opl a 25 mg/ml

Oversigt over interventionen	Carboplatin
Indikation, der er relevant for vurderingen	Carboplatin er ikke formelt indiceret til livmoderkræft men til fremskreden ovariecancer og småcellet lungecancer. Er som nævnt i afsnit 3.3 anbefalet af det videnskabelige selskab og er i praksis del af dansk standardbehandling.
ATMP	Nej
Administrationsform	Pembrolizumab blev administreret som intravenøs infusion over 30 minutter. Paclitaxel blev administreret som

Oversigt over interventionen	Carboplatin
	intravenøs infusion over 3 timer. Carboplatin blev administreret som intravenøs infusion over 30 til 60 minutter.
Dosering	200 mg pembrolizumab iv Q3W i kombination med 175 mg/m^2 paclitaxel iv på dag 1 samt carboplatin AUC 5 mg/ml/min iv på dag 1 i 6 serier, efterfulgt af vedligeholdelsesbehandling med 400 pembrolizumab iv Q6W i op til 14 serier.
Dosering i den sundhedsøkonomiske model (herunder relativ dosisintensitet)	NA
Skal lægemidlet administreres sammen med anden medicin?	Nej
Behandlingsvarighed/-kriterier for behandlingsophør	Patienterne blev behandlet med kemoterapi indtil progression eller uacceptable bivirkninger. Patienter med målbar sygdom jf. RECIST-kriterier eller med partielt respons efter 6. serie kunne fortsætte med kemoterapi (i kombination med pembrolizumab eller placebo) i op til 10 serier.
Nødvendig monitorering, både under administration og i behandlingsperioden	
Behov for diagnostik eller andre test (f.eks. *companion diagnostic*). Hvordan er disse inkluderet i modellen?	Nej
Pakningsstørrelse(r)	5 ml htgl, indeholdende 50 mg carboplatin, 10mg/ml. 15 ml htgl, indeholdende 150 mg carboplatin, 10mg/ml. 50 ml htgl , indeholdende 450 mg carboplatin, 10mg/ml. 100 ml htgl, indeholdende 600 mg carboplatin, 10mg/ml.

Oversigt over interventionen	Paclitaxel
Indikation, der er relevant for vurderingen	Carboplatin er ikke formelt indiceret til livmoderkræft men til ovariekarcinom, mammakarcinom, avanceret ikke-småcellet lungekarcinom og AIDS-relateret Karposis sarkom. Er som nævnt i afsnit 3.3 anbefalet af det videnskabelige selskab og er i praksis del af dansk standardbehandling.

Oversigt over interventionen	Paclitaxel
ATMP	Nej
Administrationsform	Pembrolizumab blev administreret som intravenøs infusion over 30 minutter. Paclitaxel blev administreret som intravenøs infusion over 3 timer. Carboplatin blev administreret som intravenøs infusion over 30 til 60 minutter.
Dosering	200 mg pembrolizumab iv Q3W i kombination med 175 mg/m^2 paclitaxel iv på dag 1 samt carboplatin AUC 5 mg/ml/min iv på dag 1 i 6 serier, efterfulgt af vedligeholdelsesbehandling med 400 pembrolizumab iv Q6W i op til 14 serier.
Dosering i den sundhedsøkonomiske model (herunder relativ dosisintensitet)	NA
Skal lægemidlet administreres sammen med anden medicin?	Nej
Behandlingsvarighed/-kriterier for behandlingsophør	Patienterne blev behandlet med kemoterapi indtil progression eller uacceptable bivirkninger. Patienter med målbar sygdom jf. RECIST-kriterier eller med partielt respons efter 6. serie kunne fortsætte med kemoterapi (i kombination med pembrolizumab eller placebo) i op til 10 serier.
Nødvendig monitorering, både under administration og i behandlingsperioden	
Behov for diagnostik eller andre test (f.eks. *companion diagnostic*). Hvordan er disse inkluderet i modellen?	Nej
Pakningsstørrelse(r)	5 ml htgl. indeholdende 30 mg paclitaxel, 6 mg/ml. 16,7 ml htgl. indeholdende 100 mg paclitaxel, 6 mg/ml. 25 ml htgl. indeholdende 150 mg paclitaxel, 6 mg/ml. 50 ml htgl. indeholdende 300 mg paclitaxel, 6 mg/ml. 100 ml htgl. indeholdende 600 mg paclitaxel, 6 mg/ml.

3.4.1 Beskrivelse af ATMP

NA

3.4.2 Interventionen i forhold til dansk klinisk praksis

Såfremt pembrolizumab i kombination med kemoterapi anbefales til denne indikation, vil kombinationen erstatte den nuværende standardbehandling til pMMR-patienterne (kemoterapi) og indgå som et supplement til den nuværende standardbehandling til dMMR-patienterne (dostarlimab i kombination med kemoterapi). Det forventes ikke, at 2. linjebehandlingen ændres, hvis pembrolizumab anbefales.

3.5 Valg af komparator(er)

Som beskrevet i afsnit 3.3 er nuværende standardbehandling afhængig af patientens MMR-status: pMMR-patienter behandles med kombinationskemoterapi i form af carboplatin+paclitaxel og dMMR-patienter behandles med dostarlimab i kombination med carboplatin+paclitaxel. Disse kombinationer er således komparatorer i ansøgningen.

Beskrivelserne herunder er baseret på studierne NRG-GY018 (19-21), RUBY-1 (12, 22) og lægemidlernes respektive produktresuméer.

Oversigt over komparator	
Generisk navn	Dostarlimab
ATC-kode	L01FF07
Virkningsmekanisme	Dostarlimab er et antistof, der binder til Programmed cell Death-1 (PD-1) receptoren og blokerer interaktionen med liganderne PD-L1 and PD-L2.
Administrationsform	konc.t.inf.væsk.opl
Dosering	500 mg dostarlimab iv Q3W i kombination med carboplatin AUC5 (*area under the curve*) mg/ml/min iv Q3W i 6 serier og paclitaxel 175 mg/m^2 iv Q3W i 6 serier efterfulgt af vedligeholdelsesbehandling med 1.000 mg dostarlimab iv Q6W i op til 3 år.
Dosering i den sundhedsøkonomiske model (herunder relativ dosisintensitet)	NA
Bør lægemidlet administreres sammen med anden medicin?	Nej
Behandlingsvarighed/-kriterier for behandlingsophør	Patienterne blev behandlet indtil progression eller død, uacceptable bivirkninger, patientens tilbagekaldelse af samtykke eller lægens beslutning - dog maksimum i 3 år.

Oversigt over komparator	
Behov for diagnostik eller andre test (f.eks. *companion diagnostic*)	Nej
Pakningsstørrelse(r)	10 ml konc.t.inf.væsk.opl a 50 mg/ml

Oversigt over komparator	
Generisk navn	Carboplatin
ATC-kode	L01XA02
Virkningsmekanisme	Cytostatikum med alkylerende virkning. Alkylerende stoffer danner kovalente bindinger med biologisk vigtige makromolekyler og skader deres funktion. Specielt sker der en binding til og evt. krydsbindning af DNA. Efterfølgende processering eller reparation af læsionerne kan forårsage enkelt- eller dobbeltbrud på DNA-strengen og celledød.
Administrationsform	konc.t.inf.væsk.opl
Dosering	dMMR: 500 mg dostarlimab iv Q3W i kombination med carboplatin AUC5 (*area under the curve*) mg/ml/min iv Q3W i 6 serier og paclitaxel 175 mg/m^2 iv Q3W i 6 serier efterfulgt af vedligeholdelsesbehandling med 1.000 mg dostarlimab iv Q6W i op til 3 år. pMMR: 200 mg pembrolizumab iv Q3W i kombination med carboplatin AUC 5 mg/ml/min iv og paclitaxel 175 mg/m^2 iv på dag 1 i 6 serier efterfulgt af vedligeholdelsesbehandling med 400 pembrolizumab iv Q6W i op til 14 serier.
Dosering i den sundhedsøkonomiske model (herunder relativ dosisintensitet)	NA
Bør lægemidlet administreres sammen med anden medicin?	Nej

Oversigt over komparator	
Behandlingsvarighed/-kriterier for behandlingsophør	Patienterne blev behandlet indtil progression eller død, uacceptable bivirkninger, patientens tilbagekaldelse af samtykke eller lægens beslutning - dog maksimum i 6 serier.
Behov for diagnostik eller andre test (f.eks. *companion diagnostic*)	Nej
Pakningsstørrelse(r)	5 ml htgl. indeholdende 50 mg carboplatin, 10mg/ml. 15 ml htgl. indeholdende 150 mg carboplatin, 10mg/ml. 50 ml htgl. indeholdende 450 mg carboplatin, 10mg/ml. 100 ml htgl. indeholdende 600 mg carboplatin, 10mg/ml.

Oversigt over komparator	
Generisk navn	Paclitaxel
ATC-kode	L01CD01
Virkningsmekanisme	Antimitotikum, som påvirker funktionen af mikrotubuli. Cellens mikrotubulinsystemer (tentrådsapparat) er målet for en række cytostatika, der bindes til mikrotubuli. Virkningen er dels en fastlåsning i celledelingens metafase, dels hæmning af andre cellulære processer som motilitet, signaltransduktion, intracellulære transportmekanismer, association af receptorer med cellemembranen og hormonsekretion.
Administrationsform	konc.t.inf.væsk.opl
Dosering	dMMR: 500 mg dostarlimab iv Q3W i kombination med carboplatin AUC5 (*area under the curve*) mg/ml/min iv Q3W i 6 serier og paclitaxel 175 mg/m^2 iv Q3W i 6 serier efterfulgt af vedligeholdelsesbehandling med 1.000 mg dostarlimab iv Q6W i op til 3 år. pMMR: 200 mg pembrolizumab iv Q3W i kombination med carboplatin AUC 5 mg/ml/min iv og paclitaxel 175 mg/m^2 iv på dag 1 i 6 serier efterfulgt af vedligeholdelsesbehandling med 400 pembrolizumab iv Q6W i op til 14 serier.

Oversigt over komparator	
Dosering i den sundhedsøkonomiske model (herunder relativ dosisintensitet)	NA
Bør lægemidlet administreres sammen med anden medicin?	Nej
Behandlingsvarighed/-kriterier for behandlingsophør	Patienterne blev behandlet indtil progression eller død, uacceptable bivirkninger, patientens tilbagekaldelse af samtykke eller lægens beslutning - dog maksimum i 6 serier.
Behov for diagnostik eller andre test (f.eks. *companion diagnostic*)	Nej
Pakningsstørrelse(r)	5 ml htgl. indeholdende 30 mg paclitaxel, 6 mg/ml. 16,7 ml htgl. indeholdende 100 mg paclitaxel, 6 mg/ml. 25 ml htgl. indeholdende 150 mg paclitaxel, 6 mg/ml. 50 ml htgl. indeholdende 300 mg paclitaxel, 6 mg/ml. 100 ml htgl. indeholdende 600 mg paclitaxel, 6 mg/ml.

3.6 Omkostningseffektivitet af komparator(er)

Dostarlimab i kombination med kemoterapi er anbefalet af Medicinrådet i august 2024 og er således vurderet at være omkostningseffektiv til indikationen (10).

3.7 Relevante effektmål

3.7.1 Definition af effektmål inkluderet i ansøgningen

I ansøgningen anvender vi samlet overlevelse (*overall survival, OS),* progressionsfri overlevelse (*progression-free survival, PFS)* og helbredsrelateret livskvalitet (HRQoL) som endepunkter for effekten af pembrolizumab + kemoterapi. Vi anvender OS og PFS i de statistiske sammenligninger og beskriver resultaterne vedr. livskvalitet deskriptivt. Alle er veletablerede endepunkter i vurderinger af lægemidler til gynækologisk kræft, og er anvendt Medicinrådets vurdering af dostarlimab + kemoterapi til denne indikation (10).

OS er i NRG-GY018 defineret som tiden fra randomisering til død af enhver årsag. Patienter, der oplevede sygdoms-progression eller påbegyndte ny onkologisk behandling blev fulgt op telefonisk hver 12. uge indtil død, tilbagekaldelse af samtykke eller afslutning af studiet, hvad end der kom først. Deltagere, som fortsat var i live på tidspunktet for analysen, blev censoreret på datoen for seneste kontakt (19).

PFS er et kombineret endepunkt, i NRG-GY018 defineret som tiden fra randomisering til første dokumenterede sygdomsprogression eller død af enhver årsag, hvad end der opstod først. Vi vil i afsnit 6.1.4 redegøre for antal events, både samlet og for hhv. død og progression. Progression blev defineret per RECIST1.1 og vurderet af investigator. Der blev scannet ≤ 28 dage før første serie (baseline) og derefter hver 9. uge (+/- 7 dage) og 12 måneder frem; derefter hver 12. uge (+/- 7 dage). Der blev censoreret efter reglerne, som fremgår af Tabel I (19).

Tabel I - Regler for censorering for den primære analyse af PFS i NRG-GY018

Situation	Primære analyse
Sygdomsprogression eller død dokumenteret efter ≤1 manglende sygdomsvurdering, og før evt. ny kræftbehandling er påbegyndt	Progredieret på dato for dokumenteret sygdomsprogression eller død.
Sygdomsprogression eller død dokumenteret umiddelbart efter ≥2 på hinanden følgende manglende sygdomsvurderinger eller efter evt. ny kræftbehandling er påbegyndt.	Censoreret ved sidste sygdomsvurdering foretaget inden dato for ≥2 på hinanden følgende manglende sygdomsvurdering og ny kræftbehandling, hvis tilfældet.
Ingen sygdomsprogression og ingen død; Ingen ny kræftbehandling påbegyndt	Censoreret ved sidste kontakt
Ingen sygdomsprogression og ingen død; Ny kræftbehandling påbegyndt	Censoreret ved sidste kontakt

HRQoL blev i NRG-GY018 vurderet ved FACT-En, som består af det generelle *Functional Assessment of Cancer Therapy – General* (FACT-G) spørgeskema, som inkluderer fire underskalaer (fysisk, socialt/familierelateret, emotionelt og funktionelt velbefindende) samt en række endometrie-cancer specifikke spørgsmål.

I RUBY-1 anvendte man EQ-5D-5L, som er et generisk spørgeskema vedr. helbredsrelateret livskvalitet, som evaluerer patientens selvrapporterede tilstand inden for domænerne bevægelighed, personlig pleje, sædvanlige aktiviteter samt smerte/ubehag og angst/depression.

I tabellen herunder er de relevante effektmål fra studiet og deres definitioner listet.

Tabel 3. Effektmål, der er relevante for ansøgningen

Effektmål	Tidspunkt*	Definition	Hvordan blev effektmålet undersøgt (dataindsamlingsmetode)
Samlet overlevelse (OS)	Den mediane opfølgningstid i NRG-GY018 fra interimanalysen var i dMMR-populationen 13,6 måneder (range: 0,5 – 39,4 måneder). I pMMR-populationn var den 8,7 måneder (range: 0,1 – 37,2	Tid fra randomisering til død af enhver årsag eller til dato for sidste kontakt.	Patienter der oplevede sygdomsprogression eller påbegyndte ny onkologisk behandling blev fulgt op med henblik på OS status hver 3.mdr i 2 år og efter hver 6.mdr i 3 år x. indtil død, tilbagekaldelse af samtykke eller afslutning af

Effektmål	Tidspunkt*	Definition	Hvordan blev effektmålet undersøgt (dataindsamlingsmetode)
	måneder) (21). I den supplerende analyse var den hhv. 19,2 måneder (0,6; 47,4) (dMMR) og 15,3 måneder (0,5; 45,6) (pMMR). I RUBY-1 var den mediane opfølgningstid i dMMR-populationen 24,8 måneder (range: 19,2 – 36,9) (22).		studiet, hvad end der kom først.
Progressions-fri overlevelse (PFS)	Som for OS	Tid fra randomisering til første dokumenterede sygdomsprogression eller død af enhver årsag, hvad end der kom først (i NRG-GY018 desuden tid til sidste kontakt, hvis hverken progression eller død var indtruffet.)	Progression vurderet per RECIST1.1 af investigator hver 9./12. uge.
Helbredsrelateret livskvalitet (HRQoL)	NRG-GY018 Data blev indsamlet elektronisk før administration af studiemedicin ved baseline og ved uge 6, 18, 30 og 54. RUBY-1 Data blev indsamlet ved baseline, ved dag 1 i hver cyklus, ved endt behandling og derefter ved hver overlevelses-opfølgning.	NRG-GY018 HRQoL blev vurderet ved FACT-En, som består af det generelle *Functional Assessment of Cancer Therapy – General* (FACT-G) spørgeskema, som inkluderer fire underskalaer (fysisk, socialt/familierelateret, emotionelt og funktionelt velbefindende) samt en række endometrie-cancer specifikke spørgsmål. RUBY-1	NRG-GY018 Trial Outcome Index (TOI) er summen af scores for de fysiske og funktionelle subskalaer og de endometrie-cancer specifikke spørgsmål. Resultaterne kan ligge i intervallet 0-120, hvor en højere score repræsenterer højere livskvalitet. RUBY-1 Vurderet ved EQ-VAS, en visuel analog skala, der giver et aggregeret estimat for patientens selvrappor-terede helbredstilstand på en skala fra 0 til 100 (0 og

Effektmål	Tidspunkt*	Definition	Hvordan blev effektmålet undersøgt (dataindsamlingsmetode)
		HRQoL blev vurderet ved EQ-5D-5L, som er et generisk spørgeskema vedr. helbredsrelateret livskvalitet, som evaluerer patientens selvrapporterede tilstand inden for domænerne bevægelighed, personlig pleje, sædvanlige aktiviteter samt smerte/ubehag og angst/depression.	100 er hhv. det værst og det bedst tænkelige helbred).

* Tidspunkt for dataindsamling anvendt i analyse (opfølgningstid for *time-to-event* effektmål)

4. Sundhedsøkonomisk analyse

Idet ansøgningen vurderes i Medicinrådets 14-ugers proces, er afsnittet ikke udfyldt.

4.1 Modelstruktur

NA

4.2 Modelkarakteristika

Tabel 4. Funktioner i den sundhedsøkonomiske model

Modelfunktioner	Beskrivelse	Begrundelse
NA		

5. Oversigt over litteratur

5.1 Litteratur anvendt til den kliniske vurdering

Den kliniske vurdering af interventionen baserer sig på NRG-GY018, og Medicinrådets anbefaling af komparator i dMMR-populationen baserer sig på RUBY-1. Vi har ikke foretaget søgninger for at identificere yderligere evidens til sammenligningen.

Tabel 5. Relevant litteratur inkluderet i vurderingen af effekt og sikkerhed

Reference	Studienavn	NCT-identifikator	Studiedatoer	Anvendt ved sammenligning af
Eskander RN et al: Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. NEJM 2023; 388:2159-2170 (19)	NRG-GY018	NCT03914612	Start: Juli 2019 Slut: Januar 2023 Data *cut-off:* 6. dec. 2022 (pMMR)/ 16. dec. 2022 (dMMR)	Pembrolizumab i kombination med kemoterapi vs dostarlimab i kombination med kemoterapi i dMMR Pembrolizumab i kombination med kemoterapi vs kemoterapi i pMMR
Supplementary Appendix. NEJM 2023; 388 (19)	Som ovenfor	Som ovenfor	Som ovenfor	Som ovenfor
Protocol. NEJM 2023; 388 (19)	Som ovenfor	Som ovenfor	Som ovenfor	Som ovenfor
CHMP Assessment Report. KEYTRUDA. Procedure No. EMEA/H/C/003820/II/0153. EMA 19 September 2024 (21)	Som ovenfor	Som ovenfor	Som ovenfor Supplerende analyser baseret på data *cut-off:* 18. aug. 2023	Som ovenfor
NRG-GY018 Clinical Study Report. Merck. December 2023 (*data-on-file*) (20)	Som ovenfor	Som ovenfor	Som ovenfor	Som ovenfor
Mirza MT et al: Dostarlimab for Primary	ENGOT-EN6/GOG-3031/RUBY	NCT03981796	Start: 18. juli 2019	Pembrolizumab i kombination med kemoterapi

Reference	Studienavn	NCT-identifikator	Studiedatoer	Anvendt ved sammenligning af
Advanced or Recurrent Endometrial Cancer. NEJM 2023; 388: 2145-2158 (22)			Data *cut-off:* 28. sept 2022 Foventet afslutning: November 2026	vs dostarlimab i kombination med kemoterapi i dMMR
Powell MA et al. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomised ENGOT-EN6/GOG-3031/RUBY trial. Ann Oncol 2024; 35(8): 728-738 (23)	Som ovenfor	Som ovenfor	Data *cut-off:* 22. sept 2023	Som ovenfor
CHMP Assessment Report. JEMPERLI. Procedure No. EMEA/H/C/005204/II/0023. EMA 12 October 2023 (12)	Som ovenfor	Som ovenfor	Som ovenfor	Som ovenfor

5.2 Litteratur anvendt til vurdering af helbredsrelateret livskvalitet

NA

Tabel 6. Relevant litteratur inkluderet for (dokumentation af) helbredsrelateret livskvalitet (se afsnit 10)

Reference (Fuld citation inkl. referencenummer)	Helbredsstadie/fald i nytteværdi (disutility)	Henvisning til sted i ansøgning, hvor dataene er beskrevet/anvendt
NA		

5.3 Litteratur anvendt til input i den sundhedsøkonomiske model

NA

Tabel 7. Relevant litteratur anvendt til input i den sundhedsøkonomiske model

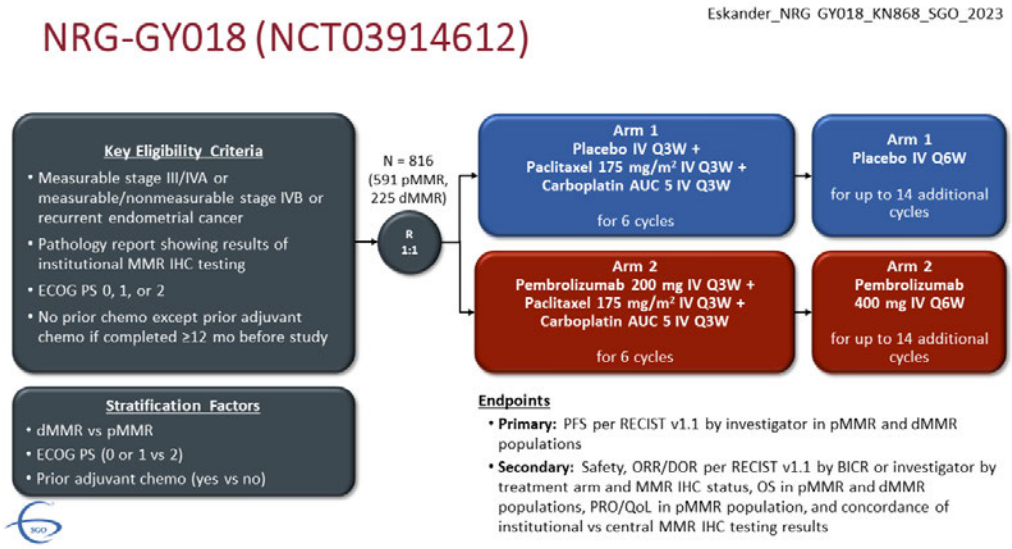
Reference (Fuld citering inkl. referencenummer)	Input/estimat	Identifikationsmetode	Reference til sted i ansøgning, hvor dataene er beskrevet/anvendt
NA			

6. Effekt

6.1 Effekt af pembrolizumab i kombination med kemoterapi til førstelinjebehandling af avanceret eller tilbagevendende dMMR eller pMMR kræft i livmoderen

6.1.1 Relevante studier

NRG-GY018 er et internationalt, multicenter, randomiseret, dobbeltblindet, placebo-kontrolleret, fase 3-studie af pembrolizumab i kombination med kemoterapi sammenlignet med kemoterapi alene til 1. linjebehandling af avanceret eller tilbagevendende kræft i livmoderen. Se Figur I for en oversigt over studiedesignet. Forsøget blev finansieret af *National Cancer Institute* (NCI), som leverede pembrolizumab og placebo uden beregning. Der blev ydet finansiering fra MSD gennem et forskningssamarbejde og en udviklingsaftale med NCI. Studiet er også benævnt KEYNOTE-868.



Figur I Studiedesign NRG-GY018

Deltagerne var kvinder ≥ 18 år med bekræftet avanceret, metastatisk (FIGO 2009 stadie III/IVA/IVB) eller recidiverende livmoderkræft, uanset histologisk subtype (bortset fra carcinosarcom). Deltagerne var i en *Eastern Cooperative Oncology Group Performance Status* (ECOG PS) score på 0-2. Tidligere kemoterapi var ikke tilladt, undtagen adjuverende behandling, hvis afsluttet min. 12 måneder før inklusion i studiet.

Deltagerne blev randomiseret 1:1 til at modtage pembrolizumab + carboplatin + paclitaxel efterfulgt af pembrolizumab alene, eller placebo + carboplatin + paclitaxel efterfulgt af placebo alene. Randomisering skete centralt ved brug af et interaktivt *voice/web response system*. Tildeling af henholdsvis pembrolizumab eller placebo skete dobbelt-maskeret.

Patienterne blev stratificeret efter MMR status (dMMR vs. pMMR), ECOG *performance status* (0 eller 1 vs. 2), og tidligere adjuverende behandling (ja vs. nej). Studiebehandlingen ophørte ved bekræftet sygdomsprogression, ved sygdomstilbagefald eller uacceptabel toxicitet, ved investigators eller patientens beslutning om at stoppe deltagelse i studiet, hvis patienten blev gravid eller efter færdiggørelse af 20 serier af aktiv behandling, svarende til ca. 2 års behandling. Det primære effektmål i studiet var progressionsfri overlevsle (PFS) vurderet af investigator per RECIST1.1. Studiet var designet og *powered* til at kunne vurdere effekten på PFS i både dMMR og pMMR-populationen.

MMR-status blev vurderet ved ICH, men som beskrevet i afsnit 3.1 er der i livmoderkræft høj overensstemmelse mellem dMMR og MSI-H.

Studiet blev påbegyndt i juli 2019 og rekruttering var afsluttet i august 2022. En planlagt interimanalyse (IA) blev udført med data *cut-off* 6. dec. 2022 (pMMR-populationen) og 16. dec. 2022 (dMMR-populationen). Her var resultaterne vedr. det primære effektmål statistisk signifikante, og analysen blev således den endelige fsva. PFS. I forbindelse med EMAs godkendelse blev der udført en ikke-præspecificeret, supplerende analyse med data *cut-off* 18. august 2023, dvs. med ca. 9 måneders yderligere opfølgning siden interimanalysen. I ansøgningen præsenterer vi data fra begge analyser.

Tabel II Udførte analyser i NRG-GY018

Analyse	Endepunkter	Kriterier for at foretage analysen	Faktiske data *cut-off*	Median opfølgningstid [IQR]
FA (PFS) IA (OS)	PFS OS (deskriptiv)	Når *accrual* til begge populationer er afsluttet og mindst 50 % *information fraction* er opnået i begge MMR-populationer.	6. dec 2022 (pMMR) 16. dec 2022 (dMMR)	8,7 mdr. (0,1-37,2) (pMMR) 13,6 mdr (0,6-39,4) (dMMR)
Supplerende analyse	PFS (deskriptiv) OS (deskriptiv)	Ikke præspecifieret	18. aug 2023	15,3 mdr (0,5- 45,6) (pMMR) 19,2 mdr (0,6- 47,4) (dMMR)

Ved data *cut-off* 6. dec. 2022 havde 58% af de patienter i pMMR-populationen, som ophørte med studiemedicin, modtaget efterfølgende kræftbehandling. I pembrolizumab+SOC-gruppen modtog 19,3% efterfølgende immunterapi og 13,1% efterfølgende behandling med lenvatinib. I placebo+SOC gruppen var andelene noget højere: 45,0% for immunterapi og 36,1% for lenvatinib (21). Se Tabel III herunder.

Tabel III Efterfølgende behandling i NRG-GY018 ved IA (pMMR)

	Paclitaxel + Carboplatin + Pembrolizumab (N=145)	Paclitaxel + Carboplatin + Placebo (N=169)	Total (N=314)
Started Study Treatment	145 (100.0)	169 (100.0)	314 (100.0)
Discontinued Study Treatment	145 (100.0)	169 (100.0)	314 (100.0)
Received Any Subsequent Systemic Anti-cancer Therapy	67 (46.2)	115 (68.0)	182 (58.0)
Subsequent systemic therapy by type			
Any Anti-PD-1/PD-L1	28 (19.3)	76 (45.0)	104 (33.1)
atezolizumab	0 (0.0)	1 (0.6)	1 (0.3)
durvalumab	1 (0.7)	2 (1.2)	3 (1.0)
nivolumab	0 (0.0)	2 (1.2)	2 (0.6)
pembrolizumab	27 (18.6)	72 (42.6)	99 (31.5)
Any Anti-angiogenic	32 (22.1)	70 (41.4)	102 (32.5)
bevacizumab	12 (8.3)	7 (4.1)	19 (6.1)
bevacizumab awwb	2 (1.4)	1 (0.6)	3 (1.0)
bevacizumab bvzr	0 (0.0)	1 (0.6)	1 (0.3)
cediranib	1 (0.7)	2 (1.2)	3 (1.0)
lenvatinib	19 (13.1)	61 (36.1)	80 (25.5)

I dMMR-populationen var de tilsvarende tal for efterfølgende immunonkologisk behandling 19,1% i pembro+SOC-gruppen og 54,5% i placebo+SOC-gruppen, og for lenvatinib 6,4% og 7,8 % (21). Se Tabel IV herunder.

Tabel IV Efterfølgende behandling i NRG-GY018 ved IA (dMMR)

	Paclitaxel + Carboplatin + Pembrolizumab (N=47)	Paclitaxel + Carboplatin + Placebo (N=77)	Total (N=124)
Started Study Treatment	47 (100.0)	77 (100.0)	124 (100.0)
Discontinued Study Treatment	47 (100.0)	77 (100.0)	124 (100.0)
Received Any Subsequent Systemic Anti-cancer Therapy	20 (42.6)	51 (66.2)	71 (57.3)
Subsequent systemic therapy by type			
Any Anti-PD-1/PD-L1	9 (19.1)	42 (54.5)	51 (41.1)
durvalumab	1 (2.1)	1 (1.3)	2 (1.6)
pembrolizumab	8 (17.0)	40 (51.9)	48 (38.7)
retifanlimab	0 (0.0)	1 (1.3)	1 (0.8)
Any Anti-angiogenic	4 (8.5)	9 (11.7)	13 (10.5)
bevacizumab	0 (0.0)	3 (3.9)	3 (2.4)
cediranib	1 (2.1)	0 (0.0)	1 (0.8)
lenvatinib	3 (6.4)	6 (7.8)	9 (7.3)

Det er vigtigt at notere sig, at studiedeltagere blev *unblinded* i februar 2023 efter det primære endepunkt (PFS) opnåede statistisk signifikans i begge populationer. På tidspunktet for den supplerende analyse havde næsten alle deltagere (99,2%) i placebo+SOC gruppen afbrudt studie-behandlingen, og størstedelen havde skiftet til behandling med et immunterapi-holdigt regime (21).

I pMMR-populationen var der 21,9% I pembrolizumab+SOC-gruppen, der efterfølgende modtog behandling med immunterapi og [redacted]% med lenvatinib. I placebo+SOC gruppen var andelene noget højere: 42,9% for immunterapi og [redacted]% for lenvatinib (20, 21). Se Tabel V herunder.

Tabel V Efterfølgende behandling i NRG-GY018 ved supplerende analyse (pMMR)

	Paclitaxel + Carboplatin + Pembrolizumab (N=215)	Paclitaxel + Carboplatin + Placebo (N=275)	Total (N=490)
Started Study Treatment	215 (100.0)	275 (100.0)	490 (100.0)
Discontinued Study Treatment	215 (100.0)	275 (100.0)	490 (100.0)
Received Any Subsequent Systemic Anti-cancer Therapy	115 (53.5)	175 (63.6)	290 (59.2)
Subsequent systemic therapy by type			
Any Anti-PD-1/PD-L1	47 (21.9)	118 (42.9)	165 (33.7)
atezolizumab	0 (0.0)	3 (1.1)	3 (0.6)
durvalumab	2 (0.9)	4 (1.5)	6 (1.2)
nivolumab	0 (0.0)	2 (0.7)	2 (0.4)
pembrolizumab	45 (20.9)	110 (40.0)	155 (31.6)
Any Anti-angiogenic	52 (24.2)	102 (37.1)	154 (31.4)
bevacizumab	17 (7.9)	17 (6.2)	34 (6.9)
bevacizumab awwb	2 (0.9)	1 (0.4)	3 (0.6)
bevacizumab bvzr	0 (0.0)	1 (0.4)	1 (0.2)
cediranib	2 (0.9)	3 (1.1)	5 (1.0)
lenvatinib	32 (14.9)	78 (28.4)	110 (22.4)
lenvatinib mesilate	2 (0.9)	7 (2.5)	9 (1.8)

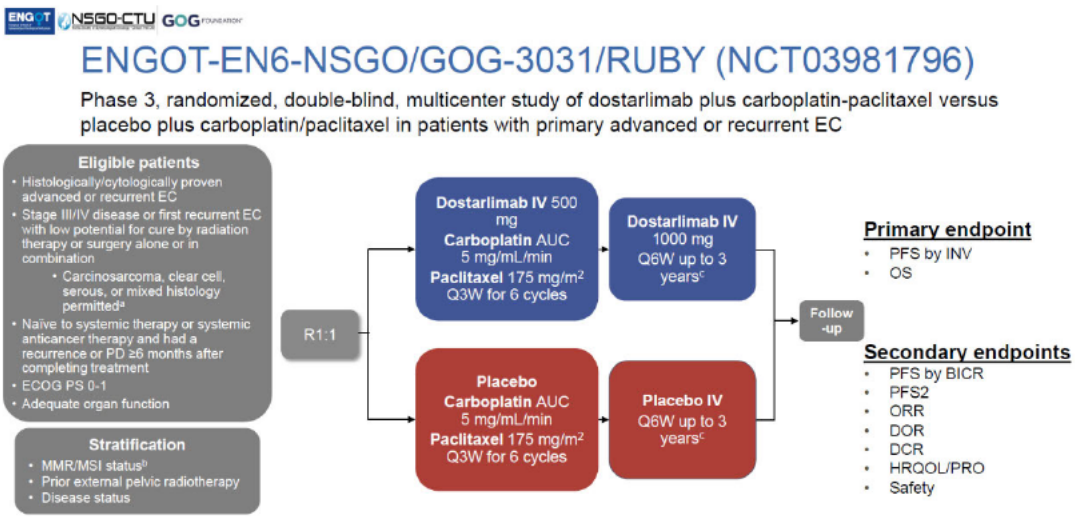
I dMMR-populationen var der 17,9% I pembrolizumab+SOC-gruppen, der efterfølgende modtog behandling med immunterapi og [redacted] med lenvatinib. I placebo+SOC gruppen var andelene noget højere: 51,0% for immunterapi og [redacted] for lenvatinib (20, 21). Se Tabel VI herunder.

Tabel VI Efterfølgende behandling i NRG-GY018 ved supplerende analyse (dMMR)

[redacted]

RUBY-1

RUBY-1 er et internationalt, multicenter, randomiseret, dobbeltblindet, placebo-kontrolleret, fase 3-studie af dostarlimab i kombination med kemoterapi sammenlignet med kemoterapi alene til 1. linjebehandling af avanceret eller tilbagevendende kræft i livmoderen. Se Figur II for en oversigt over studiedesignet.



Figur II Studiedesign RUBY-1

Deltagerne var kvinder ≥ 18 år med bekræftet avanceret, metastatisk (FIGO 2009 stadie III/IV) eller recidiverende livmoderkræft. Deltagerne var i en *Eastern Cooperative Oncology Group Performance Status* (ECOG PS) score på 0-1. Tidligere kemoterapi var ikke tilladt,

undtagen (neo)adjuverende behandling, hvor patienter havde recidiv mindst 6 måneder efter afsluttet behandling.

Deltagerne blev randomiseret 1:1 til at modtage dostarlimab + carboplatin + paclitaxel efterfulgt af dostarlimab alene, eller placebo + carboplatin + paclitaxel efterfulgt af placebo alene. Patienterne blev stratificeret efter MMR/MSI-status, tidligere strålebehandling af bækkenet og sygdomsstadie. Studiebehandlingen ophørte ved bekræftet sygdomsprogression, ved sygdomstilbagefald eller uacceptabel toxicitet, ved investigators eller patientens beslutning om at stoppe deltagelse i studiet, hvis patienten blev gravid eller efter færdiggørelse af 3 års aktiv behandling. De primære effektmål i studiet var progressionsfri overlevelse (PFS) vurderet af investigator per RECIST1.1, og samlet overlevelse (OS). Studiet var designet og *powered* til at kunne vurdere effekten på PFS i dMMR-populationen og på PFS og OS i den samlede population (*all-comers*).

MMR/MSI-status blev vurderet ved både ICH og sekventering. Som beskrevet i afsnit 3.1 er der i livmoderkræft høj overensstemmelse mellem dMMR og MSI-H.

Studiet blev påbegyndt i juli 2019. Resultater inkluderet i ansøgninger stammer fra interimanalysen med data *cut-off* 28. sept. 2022. Forventet slutdato for studiet er november 2026.

Tabel VII Udførte analyser i RUBY-1

Interim analyse	Endepunkter	Kriterier for at foretage analysen	Faktiske data cut-off	Median opfølgningstid [IQR]
IA Part 1	PFS (dMMR) PFS (all-comers) OS (all-comers)	Efter ca. 77 PFS-hændelser Efter ca. 170 OS-hændelser, svarende til 53% af *information fraction*	28. sept. 2022	24,79 mdr. (dMMR) 25,38 mdr. (*all-comers*)

Efterfølgende behandling med immunterapi i dMMR-populationen var fordelt på 15,1% i dostarlimab+SOC-gruppen og 38,5% i placebo+SOC-gruppen (12).

Inkluderet i ansøgningen

For effektdata rapporterer vi resultater fra ITT dMMR- og pMMR-kohorterne i NRG-GY018 og fra dMMR-gruppen i RUBY-1. For sikkerhedsdata inkluderer vi data fra *all patients as treated* (APaT) populationen og for livskvalitetsdata fra *patient reported outcomes final analysis set* (PRO FAS) populationen for begge studier.

Tabel 8. Oversigt over studiedesign for studier inkluderet i sammenligningen

Studienavn, NCT-nummer (reference)	Studiedesign	Studiets varighed	Patientpopulation	Intervention	Komparator	Effektmål og opfølgningstid
A Phase III Randomized, Placebo-controlled Study of Pembrolizumab (MK-3475, NSC #776864) in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer (NRG-GY018, KEYNOTE-868). NCT03914612	Internationalt, multicenter, randomiseret, dobbeltblindet, placebokontrolleret, fase 3-studie	Startdato: 16. jul 2019 Slutdato: Januar 2023	Kvinder ≥ 18 år med bekræftet avanceret, metastatisk (FIGO 2009 stadie III/IVA/IVB) eller recidiverende livmoderkræft, uanset histologisk subtype bortset fra carcinosarcoma; Eastern Cooperative Oncology Group Performance Status (ECOG PS) score på 0-2. Tidligere kemoterapi var ikke tilladt, undtagen adjuverende behandling hvis afsluttet min. 12 mnd før inklusion til studie.	Pembrolizumab 200 mg iv Q3W i 6 serier plus carboplatin AUC 5 mg/mL/min + paclitaxel 175 mg/m2 iv Q3W i 6 serier efterfulgt af pembrolizumab 400 mg Q6W i 15 serier	Carboplatin AUC 5 mg/mL/min + paclitaxel 175 mg/m2 iv Q3W i 6 serier	**Primære effektmål** **Progressionsfri overlevelse (PFS)** – per RECIST 1.1 og vurderet af investigator. PFS-data er fra IA, samt den supplerende analyse, hvor den mediane opfølgningstid var 15.3 mdr (0,5; 45,6) i pMMR population og 19.2 mdr (0,6; 47,4) i dMMR population. **Sekundære effektmål** **Uønskede hændelser (AE)** **Objektiv responsrate (ORR)** – per RECIST1.1 ved BICR vurderet per behandlingsarm og per MMR-status. Resultaterne er ikke medtaget i ansøgningen. **Objektiv responsvarighed (DOR)** –

Studienavn, NCT-nummer (reference)	Studiedesign	Studiets varighed	Patientpopulation	Intervention	Komparator	Effektmål og opfølgningstid
						per RECIST1.1 ved BICR vurderet per behandlingsarm og per MMR-status for patienter med målbar sygdom ved inklusion. Resultaterne er ikke medtaget i ansøgningen. **Samlet overlevelse (OS).** OS-data for pMMR og dMMR kohorter er fra IA og den supplerende analyse. **Quality of life (QoL) and patient-reported outcome (PRO)** – målt ved FACT/En-TOI, FACT/GOG-Ntx, PROMIS-*fatigue* og -*physical function*. ***Incidence of pembrolizumab treatment and self-reported neurotixicity***. Resultaterne afventes. **Overensstemmelse mellem**

Studienavn, NCT-nummer (reference)	Studiedesign	Studiets varighed	Patientpopulation	Intervention	Komparator	Effektmål og opfølgningstid
						Institutional Mismatch Repair (MMR) immunhistokemi (IHC) testning og centraliseret MMR IHC. Resultaterne afventes. **Effekt af pembrolizumab på PFS og OS ved Program Death Ligand 1 (PD-L1) IHC.** Resultaterne afventes. **Sammenhæng mellem PD-L1 IHC og MMR-status.** Resultaterne afventes. **Progressionsfri overlevelse 2 (PFS2)** – defineret som tid fra randomisering til vurdering af progression eller død ved den første kræftbehandling, som fulgte efter studie intervention.
A Phase 3, Randomized, Double-blind, Multicente	Internationalt, multicenter, randomiseret, dobbeltblindet,	Startdato: 15. jul 2019	Kvinder ≥ 18 år med bekræftet avanceret, metastatisk (FIGO 2009	Dostarlimab 500 mg iv Q3W i 6 serier	Carboplatin AUC 5 mg/mL/min +	**<u>Primære effektmål</u>** **Progressionsfri overlevelse (PFS)** – per

Studienavn, NCT-nummer (reference)	Studiedesign	Studiets varighed	Patientpopulation	Intervention	Komparator	Effektmål og opfølgningstid
r Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel Versus Placebo Plus Carboplatin-paclitaxel in Patients With Recurrent or Primary Advanced Endometrial Cancer (RUBY/ENGOT-EN6/GOG-3031) NCT03981796	placebokontrolleret, fase 3-studie	Forventet slutdato: 26. nov 2026	stadie III/IVA/IVB) eller recidiverende livmoderkræft; Eastern Cooperative Oncology Group Performance Status (ECOG PS) score på 0-1; tidligere neo-adjuvant/adjuverende systemisk behandling med et tilbagefald eller progression af sygdom (PD) >=6 måneder efter afslutningen af behandlingen (kun første tilbagefald).	plus carboplatin AUC 5 mg/mL/min + paclitaxel 175 mg/m2 iv Q3W i 6 serier efterfulgt af dostarlimab 1000 mg Q6W op til 3 år	paclitaxel 175 mg/m2 iv Q3W i 6 serier	RECIST 1.1 og vurderet af investigator. PFS-data er fra IA i part 1, hvor den mediane opfølgningstid var 24,79 mdr. (dMMR/MSI-H) 25,38 mdr. (all-comers). **Samlet overlevelse (OS).** OS-data for all-comers population med den mediane opfølgningstid på 25,38mdr. **<u>Sekundære effektmål</u>** **Progressionsfri overlevelse (PFS)** – baseret på BICR vurdering i dMMR/MSI-H og all-comers population. Resultaterne er ikke medtaget i ansøgningen. **Uønskede hændelser (AE)** – vurdering af *treatment-emergent adverse events*

Studienavn, NCT-nummer (reference)	Studiedesign	Studiets varighed	Patientpopulation	Intervention	Komparator	Effektmål og opfølgningstid
						(TEAEs), bivirkninger og antal af patienter med *study drug discontinuation* pga. AE i all comers population. **Objektiv responsrate (ORR)** – vurderet ved BICR og ved investigator i dMMR/MSI-H og all-comers population. Resultaterne er ikke medtaget i ansøgningen. **Objektiv responsvarighed (DOR)** – vurderet ved BICR og ved investigator i dMMR/MSI-H og all-comers population. Resultaterne er ikke medtaget i ansøgningen. ***Disease control rate* (DCR)** – vurderet ved BICR og ved investigator i dMMR/MSI-H og all-comers population. Resultaterne

Studienavn, NCT-nummer (reference)	Studiedesign	Studiets varighed	Patientpopulation	Intervention	Komparator	Effektmål og opfølgningstid
						er ikke medtaget i ansøgningen. **Patient-reported outcome (PRO)** – målt ved EQ-5D-5L og EORTC-QlQ-C30 og -QLQ-EN24 i dMMR/MSI-H og all-comers population. **Progressionsfri overlevelse 2 (PFS2)** – defineret som tid fra randomisering til vurdering af progression eller død ved den første kræftbehandling, som fulgte efter studie intervention. Målt i dMMR/MSI-H og all-comers population

6.1.2 Sammenlignelighed af studier

Som det ses af studiebeskrivelserne i 6.1.1 varierer behandlingsvarigheden på tværs af studierne, med en behandlingsvarighed på 3 år i RUBY-1 og ca. 2 år i NRG-GY018. Dette forhindrer ikke en sammenligning af de kliniske resultater fra studierne, men bør indregnes i en evt. efterfølgende sammenligning af omkostningerne forbundet med de to regimer.

6.1.2.1 Sammenlignelighed af patienter på tværs af studier

I tabellen herunder ses baselinekarakteristika for de relevante subgrupper fra hhv. NRG-GY018 og RUBY-1.

Som det ses, er der små forskelle mellem studierne for så vidt angår histologiske undertyper. Det er dog vurderingen, at dette ikke har afgørende betydning for sammenligneligheden af studierne, idet endometrioide tumorer udgør hovedparten af patienterne i alle subgrupper.

Færre patienter i RUBY-1 har modtaget tidligere strålebehandling end i NRG-GY018, men på baggrund af PFS-resultaterne i patienter hhv. med og uden strålebehandling vurderer vi, at forskellen ikke spiller en væsentlig rolle.

Overordnet er der således ingen markante baselineforskelle mellem studiernes patientpopulationer. Det relativt lave antal patienter i RUBY-1 introducerer dog en vis usikkerhed i forbindelse med tolkning af resultaterne fra dette studie.

Table 9 Patienternes baselinekarakteristika

	NRG-GY018 - pMMR		NRG-GY018 - dMMR		RUBY-1 – dMMR	
	Pembro+ SoC N=293	SoC N=295	Pembro+ SoC N=112	SoC N=113	Dostar+ SoC N=53	SoC N=65
Medianalder (range)	66 (31-93)	65 (29-90)	67 (38-81)	66 (37-85)	61 (45-81)	66 (39-85)
Etnicitet, n (%)						
Hvid	212 (72,4)	212 (71,9)	92 (82,1)	86 (76,1)	44 (83)	56 (86)
Sort	45 (15,4)	51 (17,3)	11 (9,8)	9 (8,0)	4 (8)	6 (9)
Asiatisk	17 (5,8)	14 (4,7)	3 (2,7)	4 (3,5)	2 (4)	0
American Indian/Alaska Native	2 (0,7)	2 (0,7)	0	2 (1,8)	0	1(2)
Native Hawaiian/ Other Pacific Islander	1 (0,3)	3 (1,0)	0	0	1 (2)	0
Ukendt/ikke rapporteret	15 (5,1)	12 (4,1)	6 (5,4)	12 (10,7)	2 (4)	2 (3)
Multiracial	1 (0,3)	3 (1,0)	0	0	-	-
ECOG *performance status*, n (%)						
0	196 (66,)	198 (67,1)	72 (64,3)	72 (64,6)	22/52 (54)	39/65 (60)
1	88(30,0)	88 (29,8)	39 (34,8)	35 (31,0)	24/52 (46)	26/65 (40)

	NRG-GY018 - pMMR		NRG-GY018 - dMMR		RUBY-1 – dMMR	
	Pembro+ SoC N=293	SoC N=295	Pembro+ SoC N=112	SoC N=113	Dostar+ SoC N=53	SoC N=65
2	9 (3,1)	9 (3,1)	1 (0,9)	5 (4,4)	-	-
Histologi, n (%)						
Carcinosarkom	-	-	-	-	4 (8)	1 (2)
Endometrioid	158 (53,9)	146 (49,5)	88 (78,6)	92 (81,5)	44 (83)	56 (86)
G1	54 (18,4)	46(15,6)	21 (18,8)	35 (31,0)	-	-
G2	51 (17,4)	58 (19,7)	52 (46,4)	41 (36,3)	-	-
G3	53 (18,1)	42 (14,2)	15 (13,4)	16 (14,2)	-	-
Mixed epithelial/ carcinoma	6 (2,0)	11 (3,7)	3 (2,7)	2 (1,8)	2 (4)	4 (6)
Serøs adeno-karcinom	78 (26,6)	72 (26,6)	4 (3,6)	1 (0,9)	1 (2)	1 (2)
Clear-cell adeno-karcinom	17 (5,8)	20 (6,8)	1 (0,9)	0	0	0
Mucøs adeno-karcinom	-	-	-	-	0	0
Adenosarcoma NOS	24 (8,2)	33 (11,2)	12 (10,7)	14 (12,4)	-	-
(U)differen-tieret	7 (2,4)	6 (2,0)	4 (3,6)	4 (3,5)	0	0
Andre/*pending*	3 (1,0)	7 (2,4)	-	-	2 (4)	3 (5)
Tidligere behandling, n (%)						
Kemoterapi						
Ja	72 (24,6)	77 (26,1)	5 (4,5)	8 (7,1)	-	-
Nej	221 (75,4)	218 (73,9)	107 (95,5)	105 (92,9)	-	-
Radioterapi						
Ja	114 (38,9)	119 (40,3)	41 (36,6)	55 (48,7)	8 (15)	13 (20)
Nej	179 (61,1)	176 (59,7)	71 (63,4)	58 (51,3)	45 (85)	52 (80)
Operation						
Ja	261 (89,1)	254 (83,1)	98 (87,5)	105 (92,9)	-	-

	NRG-GY018 - pMMR		NRG-GY018 - dMMR		RUBY-1 – dMMR	
	Pembro+ SoC N=293	SoC N=295	Pembro+ SoC N=112	SoC N=113	Dostar+ SoC N=53	SoC N=65
Nej	29 (9,9)	46 (15,4)	14 (12,5)	8 (7,1)	-	-
Manglende data	3 (1,0)	4 (1,4)	0	0	-	-

6.1.3 Sammenlignelighed af studiepopulation(er) med danske patienter, der er egnede til behandling

I tabellen herunder ses tilgængelige data for danske patienter med kræft i livmoderen (1) (5, 7, 9). Medianalderen er alene opgjort for patienter med fremskreden/metastatisk kræft, og tidligere behandling er opgjort for patienter, der ikke er i stadie IV.

Danske patienter er lidt ældre end studiepopulationerne, men har nogenlunde sammenlignelig fordeling på histologiske undertyper. Det er vanskeligt at sammenligne tallene for tidligere behandling direkte, men baseret på input fra danske klinikere er fordelingen i NRG-GY018 i overensstemmelse med, hvad man forventer i klinisk praksis. Samlet set vurderer vi, at baselinekarakteristika i studierne stemmer fint overnes med de danske målpopulationer.

Tabel 10. Karakteristika i den relevante danske population

	Værdi i dansk population 2019/2020	Værdi anvendt i sundhedsøkonomisk model (reference)
Alder (år)		
<70	52,6%	NA
>=70	47,4%	
Median (advanced/metastatic)	71 (29-94)	
Histologi		
Endometrioid carcinom	77,2%	
Mixed epithelial/ carcinoma	<1%	
Serøs adenokarcinom	10,0%	
Clear cell adenokarcinom	4,2%	
Mucøs adenokarcinom	<1%	
(U)differentieret	1,3%	
Tidligere behandling (%)		
Kemoterapi	17,2%	
Radioterapi	9,3%	

6.1.4 Effekt – resultater i pMMR-populationen i NRG-GY018

En gennemgang af årsagerne til ikke-færdiggjort behandling og de væsentligste effektresultater for pMMR ITT-populationen kan findes herunder. Se Appendix B for flere resultater.

Årsager til ikke-færdiggjort behandling

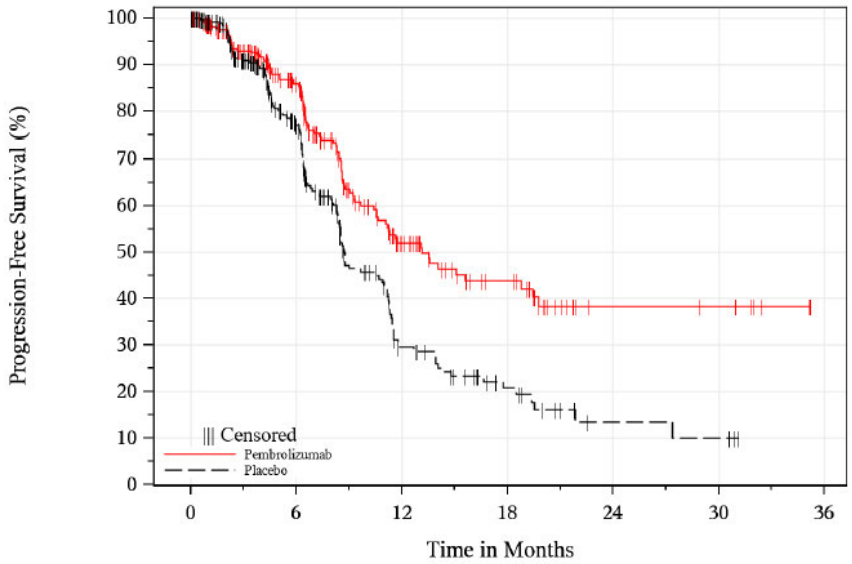
Ved tidspunktet for interimanalysen var der 19 patienter i pembrolizumab+SOC-gruppen og 22 patienter i placebo+SOC-gruppen som ikke var påbegyndt behandling efter randomisering. Der var henholdsvis 52,7% af patienterne i pembrolizumab+SOC-gruppen og 62,1% i placebo+SOC-gruppen, der var stoppet med behandlingen før tid. I begge grupper var den hyppigste årsag radiografisk sygdomsprogression, og det ses samtidig, at det var en hyppigere årsag i placebo+SOC-gruppen end i pembrolizumab+SOC-gruppen (36,4% vs. 29,1%) (20, 21). Ved data *cut-off* for IA, var 46,2% af patienter fortsat i behandling i pembrolizumab+SOC-gruppen og 37,5% i placebo+SOC-gruppen (20, 21). Se Tabel VIII.

Tabel VIII Årsager til ikke-færdiggjort behandling i pMMR-populationen

	Pembrolizumab+SOC pMMR n (%)	Placebo+SOC pMMR n (%)
Patienter i populationen	294	294
Status for behandling ved IA		
Påbegyndt behandling	275	272
Færdiggjort behandling	3 (1,1)	1 (0,4)
Afbrudt behandling	145 (52,7)	169 (62,1)
Bivirkninger/AEs	36 (13,1)	17 (6,3)
Sygdomsprogression	80 (29,1)	99 (36,4)
Alternativ kræftbehandling uden sygdomsprogression	2 (0,7)	3 (1,1)
Symptomatisk forværring	2 (0,7)	2 (0,7)
Død	6 (2,2)	2 (0,7)
Patient *off-treatment* pga. anden sygdom	4 (1,5)	1 (0,4)
Tilbagekaldelse af patientens samtykke	11 (4,0)	11 (4,0)
Andet	4 (1,5)	36 (13,3)
I fortsat behandling	127 (46,2)	102 (37,5)

Progressionsfri overlevelse (PFS)

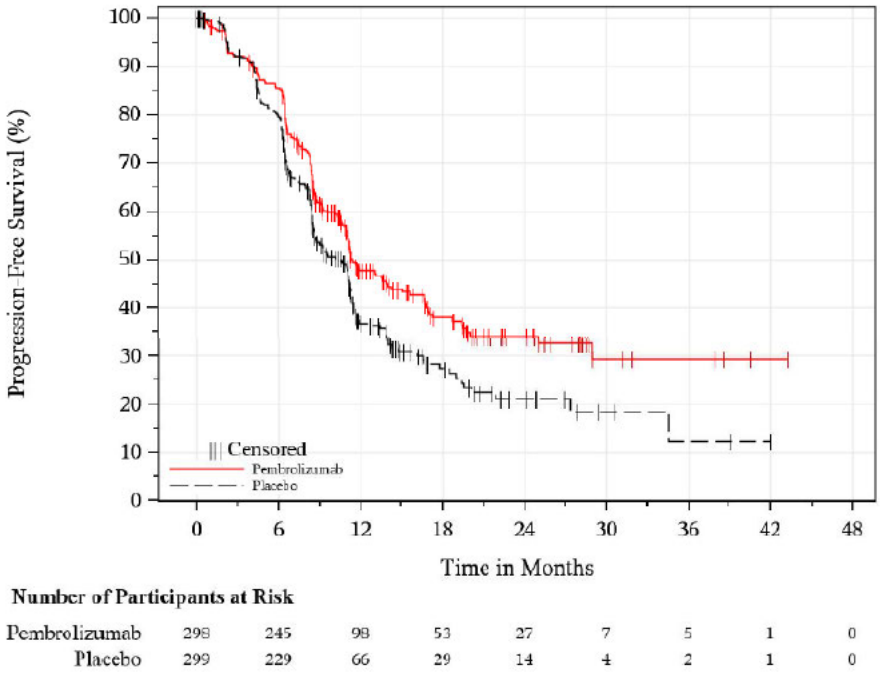
Ved interimanalysen resulterede behandling med pembrolizumab+SOC i en statistisk signifikant og klinisk relevant forbedring af PFS per RECIST1.1 vurderet ved investigator sammenlignet med SOC med en HR på 0,57 (95% CI: 0,44; 0,74), p<0,0001. Dette betyder en 43% reduktion i risikoen for sygdomsprogression eller død ved at tillægge pembrolizumab til nuværende standardbehandling. Ved den supplerende analyse var HR 0,74 (95%CI: 0,60; 0,91), p=0,0022. Ved interimanalysen var medianen for PFS større i pembrolizumab+SOC-gruppen vs. placebo+SOC-gruppen (13,1 vs. 8,7 mdr.). På Kaplan-Meier kurven for PFS med data *cut-off* 6. december 2022 (Figur III) ses, at efter ca. 5 måneder adskilles kurverne med færre hændelser i pembrolizumab+SOC-gruppen end i SOC-gruppen. Ved 12 måneder var de estimerede PFS-rater fra KM-kurven henholdsvis 52,0% i pembrolizumab+SOC-gruppen og 29,5% i SOC-gruppen, og ved 24 måneder var de 38,3% i pembrolizumab+SOC-gruppen og 13,5% i SOC-gruppen, resulterende i forskel på henholdsvis 22,5%-point ved 12 måneder og 24,8%-point ved 24 måneder (20, 21).



Number of Participants at Risk

Pembrolizumab	294	162	57	29	7	6	0
Placebo	294	144	36	15	4	3	0

Database Cutoff Date: 06 December 2022.



Database Cutoff Date: 18AUG2023.

Figur III Progressionsfri overlevelse for pMMR-patienter i NRG-GY018

Ved interimanalysen var der i pMMR-gruppen af patienter i pembrolizumab+SOC-gruppen forekommet 95 hændelser (32,3% af patienterne), hvoraf 12 var dødsfald og 83 var progression. For placebo+SOC-gruppen var antallet af hændelser 138 (46,9% af patienterne) fordelt på 15 dødsfald og 123 tilfælde af sygdomsprogression (20, 21).

Tabel IX Progressionsfri overlevelse for pMMR-patienter i NRG-GY018

	Pembrolizumab+SOC		Placebo+SOC	
	IA (n = 294)	Supp.analyse (n = 298)	IA (n = 294)	Supp.analyse (n = 299)
Antal events (%)	95 (32,3)	163 (54,7)	138 (46,9)	187 (62,5)
Antal dødsfald (%)	12 (4,1)	23 (7,7)	15 (5,1)	23 (7,7)
Antal med progression (%)	83 (28,2)	140 (47,0)	123 (41,8)	164 (54,8)
Median PFS **(95% CI)** (Q1; Q3)	13,1 (10,6; 19,5) (7,3; NR)	11,4 (10,9; 15,1) (7,1; NR)	8,7 (8,4; 11,0) (6,2; 14,3)	10,6 (8,7; 11,3) (6,3; 19,4)
HR for PFS (95% CI) & p-værdi				
Interimanalyse	0,57 (95% CI: 0,44; 0,74); p<0,0001			
Supplerende analyse	0,74 (95% CI: 0,60; 0,91); p=0,0022			

Som det ses af ovenstående, ændrer HR sig markant fra interimanalysen til den supplerende analyse. Det skyldes formentlig, at hovedparten af patienterne i kontrolarmen afbrød studiebehandlingen kort efter afblindingen i februar 2023 og i mange tilfælde begyndte på ny behandling, før investigator vurderede, om sygdommen var progredieret eller ej (som nævnt i 6.1.1). I overensstemmelse med censoreringsreglerne beskrevet i Tabel I, blev patienter ikke censoreret ved sidste vurdering før ny behandling eller ved sidste vurdering før progression eller død forekom efter to på hinanden følgende manglende besøg. Det betyder, at PFS-hændelser på ny behandling og/eller efter to på hinanden følgende manglende besøg tæller med i analysen. Dette introducerede en vis bias, da ca. 40% i placebo+SOC-gruppen efterfølgende modtog IO-behandling, mod ca. 20% i pembrolizumab+SOC-gruppen. Af den grund bør resultaterne fra interimanalysen tillægges størst værdi i vurdering af PFS.

Proportional hazards

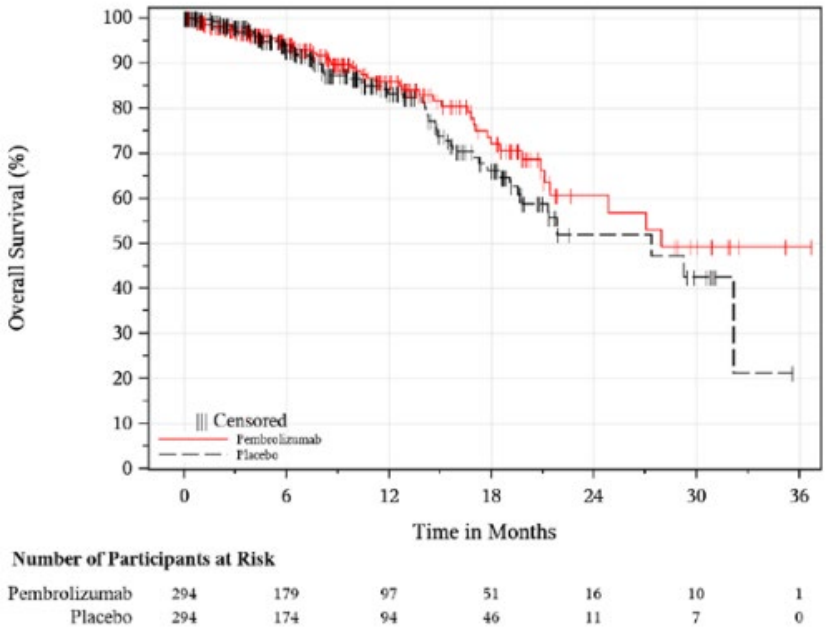
Antagelsen om *proportional hazards* vedr. PFS vurderet af investigator er testet ved brug af Schoenfelds residual test. Se Figur IV herunder. Plottet her afviger ikke signifikant fra 0, idet p-værdien er [redacted] og antagelsen om *proportional hazards* kan på den baggrund ikke afvises (20).

Figur IV Proportional Hazards Testing (pMMR PFS)

Samlet overlevelse (OS)

Ved tidspunktet for interimanalysen var der forekommet 27,2% (99 ud af 364) af hændelser (21). OS data vurderes derfor som umodent og beskrivelsen af resultater er deskriptiv. P-værdier er nominale.

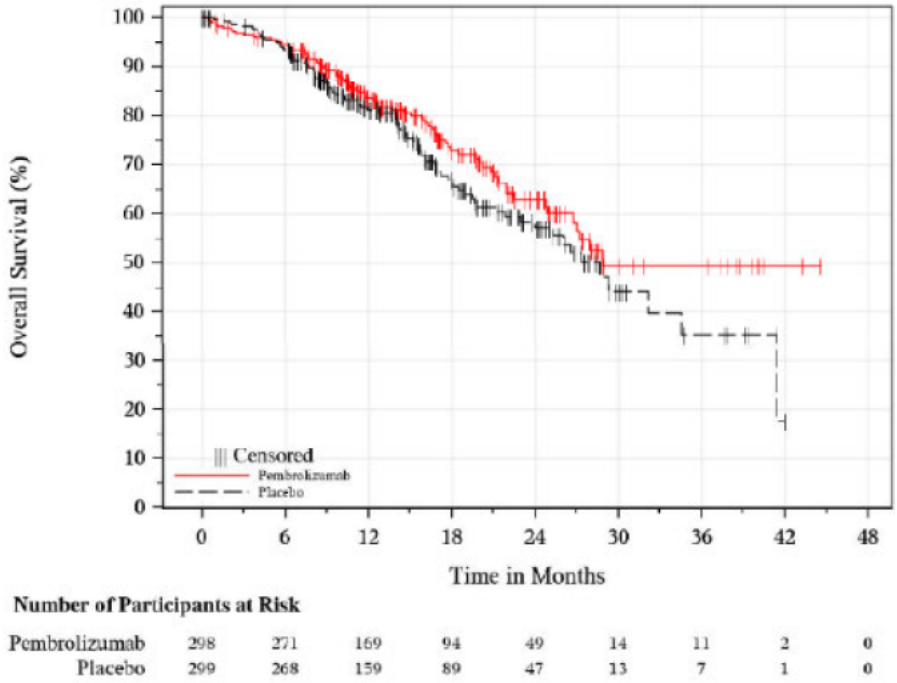
Ved interimanalysen ses en Hazard Ratio (HR) på 0,79 (95% CI: 0,53; 1,17), p=0,1157 og ved den supplerende analyse var HR 0,80 (95% CI: 0,59; 1,08); p=0,0683. Den KM-estimerede OS-rate ved 24 måneder var i pembrolizumab+SOC-gruppen 60,7% (95% CI: 47,52; 71,46) og i placebo+SOC-gruppen: 52,0% (95% CI: 38,42; 63,97). Se Tabel X og Figur V (21). Om end analyserne alene er deskriptive, peger de dog i retning af en potentiel overlevelsesgevinst ved tillæg af pembrolizumab til nuværende standardbehandling.



Number of Participants at Risk

Pembrolizumab	294	179	97	51	16	10	1
Placebo	294	174	94	46	11	7	0

Database Cutoff Date: 06 December 2022.



atabase Cutoff Date: 18AUG2023.

Figur V Samlet overlevelse for pMMR-patienter i NRG-GY018

Som nævnt i 6.1.1 gik mange patienter i kontrolarmen over på behandling med immunterapi og/eller lenvatinib efter afblindingen i februar 2023. Dette kan have haft indflydelse på OS-resultaterne. Til brug for CHMPs vurdering af resultaterne blev der derfor udarbejdet følsomhedsanalyser, der tog højde for efterfølgende behandlinger i begge arme (21). Der er udført én følsomhedsanalyse ved brug af *Inverse Probability of Censoring Weights* (IPCW)-metoden og én ved brug af en *2-stage* model; begge tilgange er beskrevet i NICE's DSU *Technical Support Document* 16 (24). Resultaterne af følsomhedsanalyserne er præsenteret i Tabel X nedenfor, sammen med resultater af ikke-justerede analyser fra interimanalysen og fra den supplerende analyse. Som det ses, er resultaterne af følsomhedsanalyserne konsistente og bør derfor inddrages i vurderingen af effekten på samlet overlevelse i pMMR-populationen.

Tabel X Samlet overlevelse for pMMR-patienter i NRG-GY018

	Pembrolizumab+SOC		**Placebo+SOC**	
	IA (n = 294)	**Supp.analyse (n = 298)**	**IA (n = 294)**	**Supp.analyse (n = 299)**
Antal dødsfald (%)	45 (15,3)	77 (25,8)	54 (18,4)	92 (30,8)
Median OS	27,96	28,9	27,37	28,7
(95% CI)	(21,42; NR)	(26,8; NR)	(19,52; NR)	(24,0; 34,6)
(Q1; Q3)	(17,05; NR)	(17,5; NR)	(14,82;32,17)	(15,3; 41,4)

HR for OS (95% CI) & p-værdi	
Interimanalyse	0,79 (95% CI: 0,53; 1,17); p=0,1157
Supplerende analyse	0,80 (95% CI: 0,59; 1,08); p=0,0683
Følsomhedsanalyse (IPCW)	0,68 (95% CI: 0,39; 1,26); p=0,1231
Følsomhedsanalyse (*2-stage*)	0,70 (95% CI: 0,50; 0,98); p= NA

Proportional hazards

Antagelsen om *proportional hazards* vedr. OS er testet ved brug af Schoenfelds residual test. Se Figur VI herunder. Plottet afviger ikke signifikant fra 0, idet p-værdien er [redacted] og antagelsen om *proportional hazards* kan på den baggrund ikke afvises (20).

Figur VI Proportional Hazard Testing (pMMR OS)

6.1.5 Effekt – resultater i dMMR-populationen i NRG-GY018

En gennemgang af årsagerne til ikke-færdiggjort behandling og de væsentligste effektresultater for dMMR ITT-populationen kan findes herunder. Se Appendix B for flere resultater.

Årsager til ikke-færdiggjort behandling

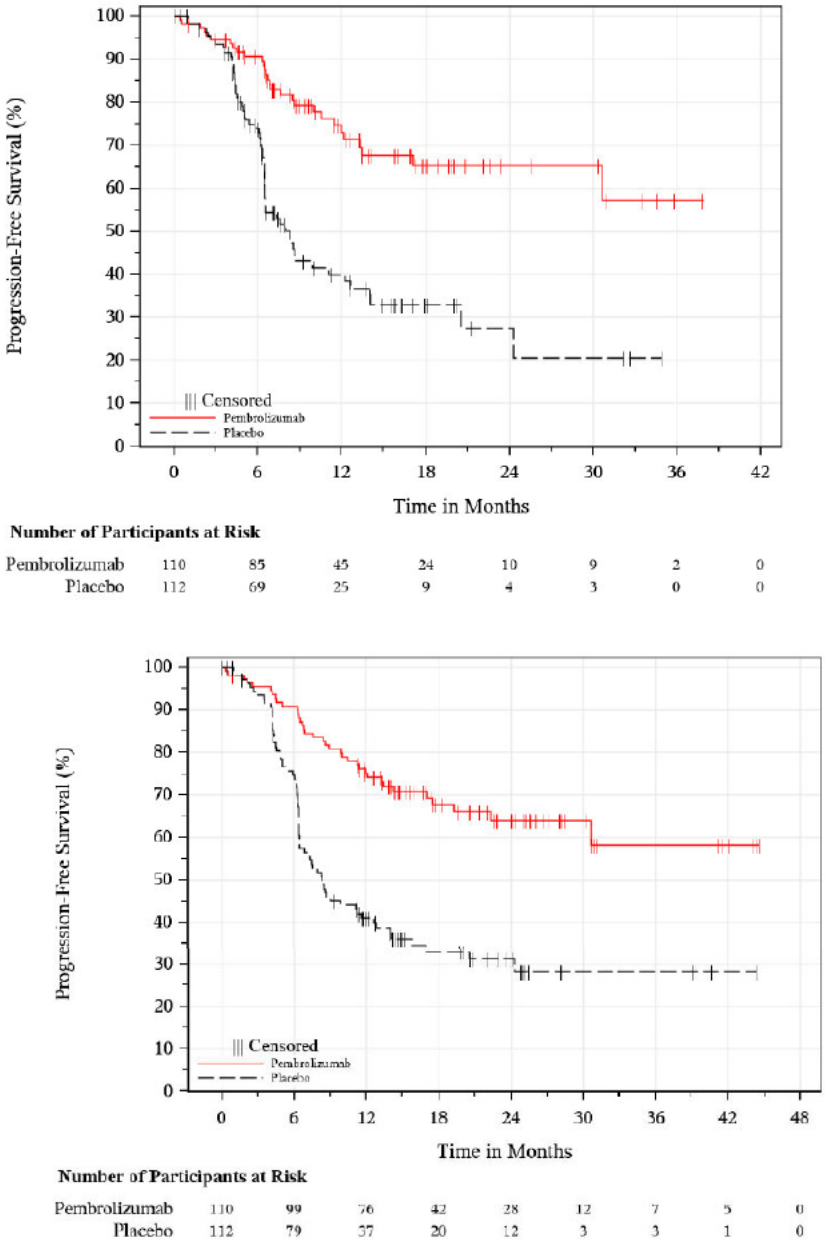
Der var 3 patienter i pembrolizumab+SOC-gruppe og 7 patienter i placebo+SOC-gruppen som ikke startede behandling efter randomisering. Der var henholdsvis 52,3% af patienterne i pembrolizumab+SOC-gruppen og 99,0% i placebo+SOC-gruppen, der stoppede behandlingen før tid. I begge grupper var den hyppigste årsag sygdomsprogression, og det ses samtidig, at det var en hyppigere årsag i placebo+SOC-gruppen end i pembrolizumab+SOC-gruppen (50,5% vs. 21,5%) (20, 21). Ved data *cut-off* for den supplerende analyse var 28,0% af patienter fortsat i behandling i pembrolizumab+SOC-gruppen og 0,0% i placebo+SOC-gruppen (21). Se Tabel XI.

Tabel XI Årsager til ikke-færdiggjort behandling i dMMR-populationen

	Pembrolizumab+SOC dMMR n (%)	Placebo+SOC dMMR n (%)
Patienter i populationen	110	112
Status for studiemedicin ved supplerende analyse		
Påbegyndt behandling	107	105
Færdiggjort behandling	21 (19,6)	1 (1,0)
Afbrudt behandling	56 (52,3)	104 (99,0)
Bivirkninger/AEs	21 (19,6)	6 (5,7)
Sygdomsprogression	23 (21,5)	53 (50,5)
Symptomatisk forværring	0 (0,0)	3 (2,9)
Død	1 (0,9)	2 (1,9)
Patient *off-treatment* pga.anden sygdom	1 (0,9)	1 (1,0)
Tilbagekaldelse af patientens samtykke	6 (5,6)	4 (3,8)
Andet	4 (3,7)	35 (33,3)
I fortsat behandling	30 (28,0)	0 (0,0)

Progressionsfri overlevelse (PFS)

I dMMR-gruppen af patienter resulterede behandling med pembrolizumab+SOC ved interimanalysen i en statistisk signifikant og klinisk relevant forbedring af PFS per RECIST1.1 vurderet ved investigator sammenlignet med SOC med en HR på 0,34 (95% CI: 0,22; 0,53), p<0,0001. Dette betyder en 66% reduktion i risikoen for sygdomsprogression eller død ved at tillægge pembrolizumab til nuværende standardbehandling. Ved den supplerende analyse var HR 0,35 (95% CI: 0,23; 0,52); p<0,001. Ved interimanalysen var medianen ikke nået i pembrolizumab+SOC-gruppen, mens den var 8,3 måneder (6,5; 12,3) i placebo+SOC-gruppen. På Kaplan-Meier kurverne for PFS (Figur VII) ses, at efter ca. 5 mdr. adskilles kurverne med færre events i pembrolizumab+SOC-gruppen end i SOC-gruppen. Ved 12 måneder var de estimerede PFS-rater fra KM-kurven henholdsvis 73,0% i pembrolizumab+SOC-gruppen og 40,0% i SOC-gruppen, og ved 24 måneder var de 65,2% i pembrolizumab+SOC-gruppen og 27,4% i SOC-gruppen, resulterende i forskel på henholdsvis 33%-point ved 12 måneder og 37,8%-point ved 24 måneder (21).



Figur VII Progressionsfri overlevelse for dMMR-patienter i NRG-GY018

Ved IA var der i dMMR-gruppen af patienter i pembrolizumab+SOC-gruppen forekommet 29 hændelser (26,4% af patienterne), hvoraf 6 var dødsfald og 23 var progression. For placebo+SOC-gruppen var antallet af hændelser 60 (53,6% af patienterne) fordelt på 5 dødsfald og 55 tilfælde af sygdomsprogression (21).

Tabel XII Progressionsfri overlevelse for dMMR-patienter i NRG-GY018

	Pembrolizumab+SOC		Placebo+SOC	
	IA (n = 110)	Supp.analyse (n = 110)	IA (n = 112)	Supp.analyse (n = 112)

Antal dødsfald (%)	29 (26,4) 6 (5,5) 23 (20,9)	36 (32,7) 8 (7,3) 28 (25,5)	60 (53,6) 5 (4,5) 55 (49,1)	70 (62,5) 7 (6,3) 63 (56,3)
Median PFS **(95% CI)** (Q1; Q3)	NR (30,7; NR) (11,5; NR)	NR (30,7; NR) (12,1; NR)	8,3 (6,5; 12,3) (5,4; 24,3)	8,3 (6,5; 12,7) (5,9; NR)
HR for PFS (95% CI) & p-værdi IA Supplerende analyse			0,34 (95% CI: 0,22; 0,53); <0,0001 0,35 (95% CI: 0,23; 0,52); p<0,001	

Proportional hazards

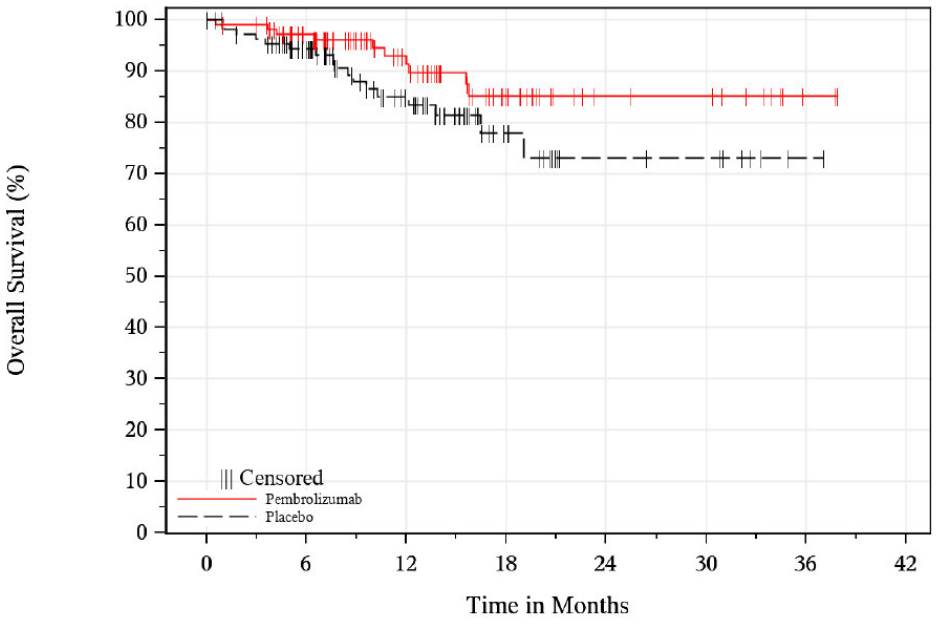
Antagelsen om *proportional hazards* vedr. PFS vurderet af investigator er testet ved brug af Schoenfelds residual test. Se herunder. Plottet her afviger ikke signifikant fra 0, idet p-værdien er [redacted] og antagelsen om *proportional hazards* kan på den baggrund ikke afvises (20).

Figur VIII Proportional hazards test (dMMR PFS)

Samlet overlevelse (OS)

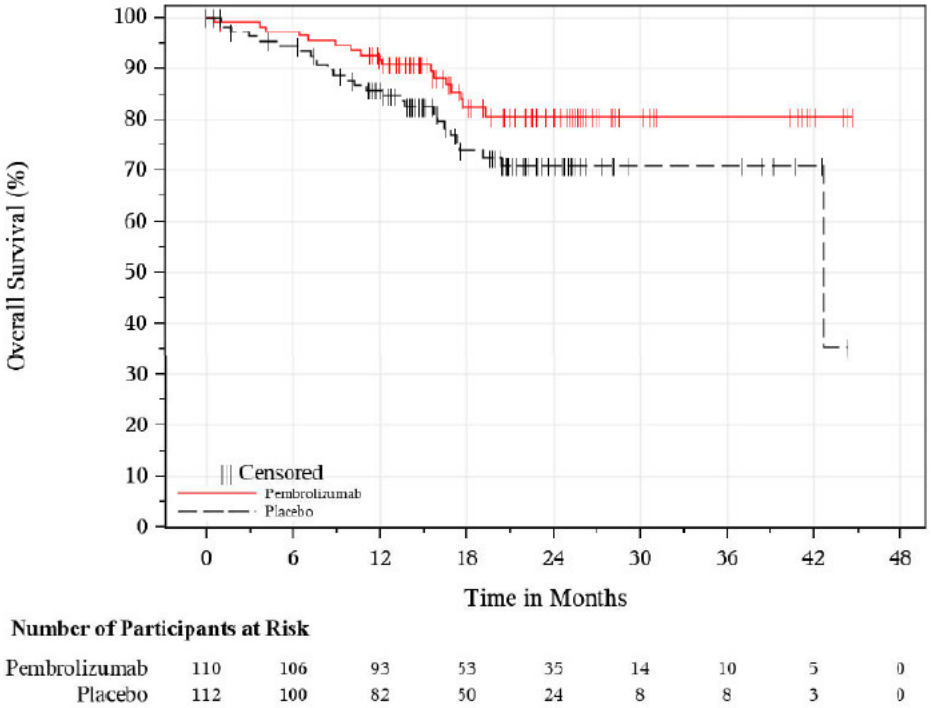
Ved interimanalysen var der forekommet 18% (27 ud af 150) af hændelser (21). OS data vurderes derfor som umodent og beskrivelsen af resultater er deskriptiv. P-værdier er nominale.

Ved interimanalysen ses en Hazard Ratio (HR) på 0,55 (95% CI: 0,25; 1,19), p=0,0617 og ved den supplerende analyse var HR 0,57 (95% CI: 0,31; 1,04); p=0,0323. De KM-estimerede OS-rater ved 24 måneder var 85,1% (95% CI: 73,22; 92,03) hhv. 73,0% (95% CI: 56,44; 84,12). Se Tabel XIII (21). Om end analyserne alene er deskriptive, peger de dog i retning af en klinisk relevant overlevelsesgevinst ved tillæg af pembrolizumab til nuværende standardbehandling.



Number of Participants at Risk

Pembrolizumab	110	88	55	29	12	11	2	0
Placebo	112	87	52	18	8	7	1	0



Figur IX Samlet overlevelse for dMMR-patienter i NRG-GY018

Som nævnt i 6.1.1 gik mange patienter i kontrolarmen over på behandling med immunterapi og/eller lenvatinib efter afblindingen i februar 2023. Dette kan have haft indflydelse på OS-resultaterne. Til brug for CHMPs vurdering af resultaterne blev der derfor udarbejdet følsomhedsanalyser, der tog højde for efterfølgende behandlinger i begge arme (21). Der er for dMMR-populationen udført en følsomhedsanalyse ved brug af *Inverse Probability of Censoring Weights* (IPCW)-metoden. Resultaterne af følsomhedsanalyserne er præsenteret i Tabel XIII nedenfor, sammen med resultater af ikke-justerede analyser fra interimanalysen og fra den supplerende analyse.

Tabel XIII Samlet overlevelse for dMMR-patienter i NRG-GY018

	Pembrolizumab+SOC		**Placebo+SOC**	
	IA (n = 110)	**Supp.analyse (n = 110)**	**IA (n = 112)**	**Supp.analyse (n = 112)**
Antal dødsfald (%)	10 (9,1)	17 (15,5)	17 (15,2)	27 (24,1)
Median OS (95% CI) (Q1; Q3)	NR (NR; NR)	NR (NR; NR) (NR; NR)	NR (NR; NR)	42,7 (42,7; NR) (17,4; NR)
HR for PFS (95% CI) & p-værdi				
Interimanalyse	0,55 (95% CI: 0,25; 1,19); p=0,0617			
Supplerende analyse	0,57 (95% CI: 0,31; 1,04); p=0,0323			
Følsomhedsanalyse (IPCW)	0,54 (95% CI: 0,22, 1,69); p=0,1602			

Proportional hazards

Antagelsen om *proportional hazards* vedr. OS er testet ved brug af Schoenfelds residual test. Se Figur X herunder. Plottet afviger ikke signifikant fra 0, idet p-værdien er [redacted] og antagelsen om *proportional hazards* kan på den baggrund ikke afvises (20).

Figur X Proportional Hazard Testing (dMMR OS)

6.1.6 Effekt – resultater i dMMR-populationen i RUBY-1

En gennemgang af årsagerne til ikke-færdiggjort behandling og de væsentligste effektresultater for dMMR ITT-populationen kan findes herunder. Se Appendix B for flere resultater.

Årsager til ikke-færdiggjort behandling

Ved data-cut for interimanalysen var 23 (44,3%) hhv. 8 (12,3%) af patienterne fortsat i behandling med mindst én af komponenterne i studiebehandlingen. Samtlige patienter var ophørt behandling med mindst én af komponenterne. Uønskede hændelser var den hyppigste årsag til behandlingsophør med dostarlimab og sygdomsprogression var den hyppigste årsag til behandlingsophør med placebo (12). Se Tabel XIV.

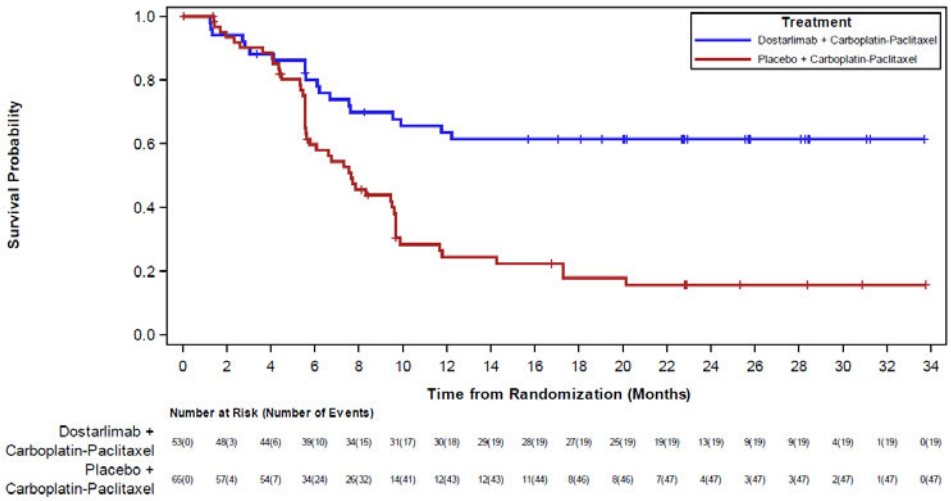
Tabel XIV Årsager til ikke-færdiggjort behandling i RUBY-1

	Dostarlimab+SOC dMMR n (%)	Placebo+SOC dMMR n (%)
Patienter i populationen	52	65

Status for studiemedicin		
I fortsat behandling	23 (44,3)	8 (12,3)
Ophørt behandling med mindst én komponent	52 (100,0)	65 (100,0)
Dostarlimab/placebo	*29 (55,8)*	*57 (87,7)*
Paclitaxel	*52 (100,0)*	*64 (98,5)*
Carboplatin	*52 (100,0)*	*65 (100,0)*
Ophørt med alle komponenter	59 (55,8)	56 (86,2)
Hyppigste årsager til behandlingsophør		
Uønskede hændelser	18 (34,6)	22 (33,9)
Dostarlimab/placebo	*9 (17,3)*	*7 (10,8)*
Paclitaxel	*4 (7,7)*	*10 (15,4)*
Carboplatin	*5 (9,6)*	*5 (7,7)*
Sygdomsprogression per RECIST1.1	15 (28,8)	44 (67,7)
Dostarlimab/placebo	*13 (25,0)*	*40 (61,5)*
Paclitaxel	*1 (1,9)*	*2 (3,1)*
Carboplatin	*1 (1,9)*	*2 (3,1)*

Progressionsfri overlevelse (PFS)

I dMMR-gruppen af patienter ses ved interimanalysen en HR på 0,28 (95% CI: 0,132; 0,495), p<0,0001. Ved 24 måneder var de estimerede PFS-rater fra KM-kurven henholdsvis 61,4% i dostarlimab+SOC-gruppen og 15,7% i SOC-gruppen (12).



Figur XI Progressionsfri overlevelse for dMMR-patienter i RUBY-1

Ved interimanalysen var der i dostarlimab+SOC-gruppen forekommet 19 hændelser (35,8% af patienterne), hvoraf 3 var dødsfald og 16 var progression. For placebo+SOC-

gruppen var antallet af hændelser 47 (72,3% af patienterne) fordelt på 3 dødsfald og 44 tilfælde af sygdomsprogression (12).

Tabel XV Progressionsfri overlevelse for dMMR-patienter i RUBY-1

	Dostarlimab + SoC N (%)	Placebo + SoC N (%)
	N = 53	N = 65
Antal hændelser (%) **Død** **Sygdomsprogression**	19 (35,8) 3 (5,7) 16 (30,2)	47 (72,3) 3 (4,6) 44 (67,7)
PFS kvartiler (måneder) (95% CI) **25%** **50%** **75%**	 6,7 (4,1; 12,2) NR (11,8; NR) NR (NR; NR)	 5,6 (4,1; 5,6) 7,7 (5,6; 9,7) 11,8 (9,7; NR)
HR for PFS (95% CI), p-værdi	0,28 (95% CI: 0,162; 0,495); <0,0001	

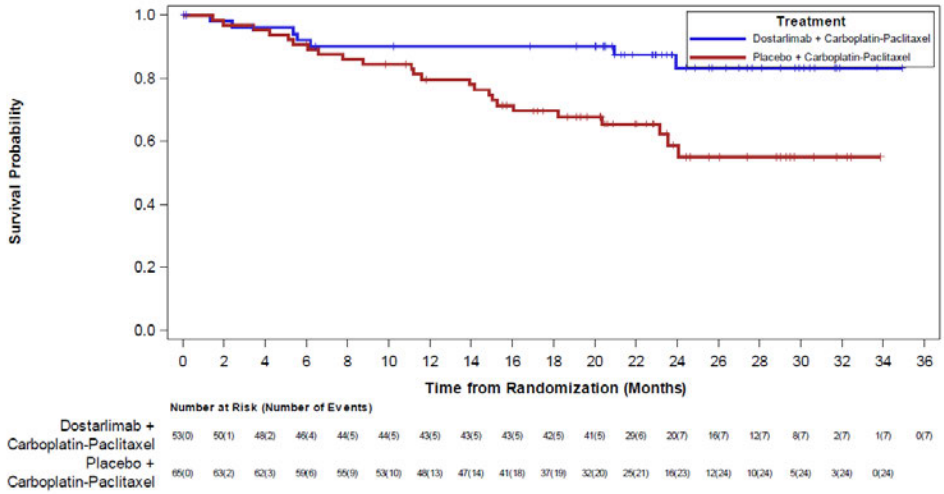
Proportional hazards

Antagelsen om *proportional hazards* vedr. PFS vurderet af investigator er testet ved brug af Schoenfelds residual test. Se Figur XII herunder. Plottet her afviger signifikant fra 0, idet p-værdien er [redacted] og antagelsen om *proportional hazards* må på den baggrund afvises (25).

Figur XII Proportional Hazard Testing (dMMR PFS)

Samlet overlevelse (OS)

Ved interimanalysen ses en Hazard Ratio (HR) på 0,30 (95% CI: 0,127; 0,699), p=0,0016. De KM-estimerede OS-rater ved 24 måneder var hhv. 83,3% (95% CI: 66,8; 92,8) og 58,7% (95% CI: 43,4; 71,2). Se Tabel XVI (12).



Figur XIII Samlet overlevelse for dMMR-patienter i RUBY-1

Tabel XVI Samlet overlevelse for dMMR-patienter i RUBY-1

	Dostarlimab + SoC N (%)	Placebo + SoC N (%)
	N = 53	N = 65
Antal hændelser (%)	7 (13,2)	24 (36,9)
OS kvartiler (måneder) (95% CI) **25%** **50%** **75%**	 NR (21,0; NR) NR (NR; NR) NR (NR; NR)	 14,9 (7,8; 23,2) NR (23,2; NR) NR (NR; NR)
HR for OS (95% CI) & p-værdi	0,30 (0,127; 0,699) p= 0,0016	

Proportional hazards

Antagelsen om *proportional hazards* vedr. OS er testet ved brug af Schoenfelds residual test. Se Figur XIV herunder. Kurven viser nogenlunde samme billede som for PFS. P-værdien er [redacted] (25). Ifølge Medicinrådet er der ikke styrke nok til at afvise, at der skulle være proportionelle hazards.

Figur XIV Proportional Hazard Testing (dMMR OS)

7. Komparative analyser af effekt

I afsnittet her beskriver vi den indirekte sammenligning af pembrolizumab + kemoterapi vs. dostarlimab + kemoterapi fsva. dMMR-patienterne. Tabel 11 er dog også udfyldt for den direkte sammenligning af pembrolizumab + kemoterapi vs. kemoterapi fsva. pMMR-populationen.

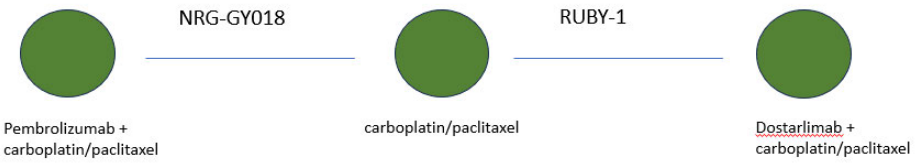
7.1.1 Forskelle i definitioner af effektmål mellem studierne

Som beskrevet i afsnit 3.7 indgår effektmålene OS og PFS i den komparative analyse. I både NRG-GY018 og RUBY-1 er OS defineret som tiden fra randomisering til død uanset årsag, mens PFS er defineret som tiden fra randomisering til dokumenteret progression eller død uanset årsag. Der er således overensstemmelse mellem definitionerne på tværs af studierne.

7.1.2 Syntesemetode

Som beskrevet i afsnit 5 er de to studiers respektive designs og PICO'er samt baselinekarakteristika for de inkluderede patienter tilpas ens til, at det giver mening at foretage en netværksmetaanalyse af resultaterne for dMMR-subpopulationerne.
Egnethedsvurderingen er foretaget med udgangspunkt i guidelines fra hhv. *International Society for Pharmacoeconomics and Outcomes Research* (ISPOR), *National Institute for Health and Clinical Excellence* (NICE) og *Preferred Reporting System for Systematic Reviews and Meta-Analyses* (PRISMA).

De to studier er kombineret i dette netværk



Figur XV Netværk

NRG-GY018 sammenligner pembrolizumab + carboplatin/paclitaxel med carboplatin/paclitaxel. RUBY-1 sammenligner dostarlimab + carboplatin/paclitazel med carboplatin/paclitaxel. Carboplatin/paclitaxel er således den fælles komparator, der knytter netværket sammen.

Formålet med netværksmetaanalyserne er at frembringe effektestimater på effektmålene OS og PFS for pembrolizumab + kemoterapi vs dostarlimab + kemoterapi til førstelinjebehandling af primær avanceret eller recidiverende kræft i livmoderen hos dMMR-populationen af voksne, som er egnet til systemisk behandling.

Analyserne blev udført ved brug af *fixed-effects* modeller baseret på hazard ratios vedr. pembrolizumab + kemoterapi fra data-cut i december 2023, som beskrevet i EPAR (21) og på hazard ratios vedr. dostarlimab + kemoterapi fra data-cut i september 2023, som beskrevet i artiklen af Mirza et al (22). Som beskrevet i afsnit 6.1.5 blev der for dMMR-populationen i NRG-GY018 udført en IPCW-følsomhedsanalyse for at justere for påvirkningen på den samlede overlevelse af efterfølgende behandlinger med immunterapi og/eller lenvatinib. Netværksmetaanalysen er dog udført med den ikke-justerede OS HR.

Som nævnt i 6.1.4- 6.1.6 blev antagelsen om *proportional hazards* testet og blev afvist for PFS for så vidt angår dMMR-subpopulationen i RUBY-1. Kurven for OS vurderes at være nogenlunde som kurven for PFS. Derfor blev der udregnet både tidskonstante og tidsvarierende hazard ratioer for PFS og OS, baseret på tidsvarierende HR fremkommet ved digitalisering af Kaplan-Meier kurverne fra hhv. NRG-GY018 og RUBY-1. En beskrivelse af metoden bag analyserne kan ses i Appendix C.

7.1.3 Resultater fra den komparative analyse

I tabellen herunder præsenteres resultaterne af de komparative statistiske analyser af hhv. OS og PFS for dMMR-subpopulationen, baseret på netværksmetaanalysen.

Tabel 11. Resultater fra den komparative analyse

dMMR Effektmål	NRG-GY018 (N=225)	RUBY-1 (N=118)	Resultat (pembro + kemo vs dostar + kemo)
Samlet overlevelse (OS)	HR: 0,57 (95% CI: 0,31; 1,04) (21, 25)	HR: 0,32 (95% CI: 0,17; 0,63) (12, 25)	HR: [redacted] Tidsvarierende HR (95% CI) 3 mdr: [redacted] 6 mdr: [redacted] 9 mdr: [redacted] 12 mdr: [redacted] 18 mdr: [redacted] 24 mdr: [redacted]

dMMR Effektmål	NRG-GY018 (N=225)	RUBY-1 (N=118)	Resultat (pembro + kemo vs dostar + kemo)
			30 mdr: [redacted] 36 mdr: [redacted] 42 mdr: [redacted] 48 mdr~: [redacted]
Progressionsfri overlevelse (PFS)	HR: 0,35 (95% CI: 0,23; 0,52) (21, 25)	HR: 0,28 (95% CI: 0,16; 0,50) (22, 25)	HR: [redacted] Tidsvarierende HR (95% CI) 3 mdr: [redacted] 6 mdr: [redacted] 9 mdr: [redacted] 12 mdr: [redacted] 18 mdr: [redacted] 24 mdr: [redacted] 30 mdr: [redacted] 36 mdr*: [redacted] 42 mdr*: [redacted] 48 mdr*: [redacted]

~baseret på model extrapolationer. Modellen er en *fixed effects fractional polynomial model* (P1=1, P2=0,5; *scale and 2nd shape-Gompertz*)

*baseret på model extrapolationer. Modellen er en *fixed effects fractional polynomial model* (P1=1, P2=-1; *scale and 2nd shape-Gompertz*)

7.1.4 Effekt – resultater fra den indirekte sammenligning vedr. samlet overlevelse (OS)

De indirekte sammenligninger af pembrolizumab + kemoterapi vs. dostarlimab + kemoterapi fra netværksmetaanalysen peger ikke i retning af betydende forskelle i samlet overlevelse mellem de to kombinationsbehandlinger for så vidt angår dMMR-subpopulationen.

7.1.5 Effekt – resultater fra den indirekte sammenligning vedr. progressionsfri overlevelse (PFS)

De indirekte sammenligninger af pembrolizumab + kemoterapi vs. dostarlimab + kemoterapi fra netværksmetaanalysen peger ikke i retning af betydende forskelle i progressionsfri overlevelse mellem de to kombinationsbehandlinger for så vidt angår dMMR-subpopulationen.

8. Modellering af effekt i den sundhedsøkonomiske analyse

Idet vurderingen foretages i Medicinrådets 14-ugers proces, er afsnittet ikke relevant.

8.1 Præsentation af effektdata fra den kliniske dokumentation, der anvendes i modellen

NA

8.1.1 Ekstrapolering af effektdata

NA

8.1.1.1 Ekstrapolering af [effektmål 1]

NA

Tabel 12, Oversigt over antagelser vedr. ekstrapolering af [effektmål]

Metode/tilgang	Beskrivelse/antagelse

8.1.1.2 Ekstrapolering af [effektmål 2]

NA

8.1.2 Beregning af transitionssandsynligheder

NA

Tabel 13. Transitioner i den sundhedsøkonomiske model

Helbredsstadie(fra)	Helbredsstadie (til)	Beskrivelse af metode	Reference

8.2 Præsentation af effektdata fra [yderligere dokumentation]

NA

8.3 Modelleringseffekter af efterfølgende behandlinger

NA

8.4 Andre antagelser vedrørende effekt i modellen

NA

8.5 Oversigt over den modellerede gennemsnitlige behandlingslængde og -tid i modellens helbredsstadier

NA

Tabel 14. Estimater i modellen

	Modelleret gennemsnit [effektmål] (reference i Excel)	Modelleret median [effektmål] (reference i Excel)	Observeret median fra relevant studie

Tabel 15. Oversigt over modelleret gennemsnitlig behandlingslængde og -tid i modellens helbredsstadier, ikke-diskonteret og ikke justeret for halvcykluskorrektion (juster tabellen i henhold til modellen)

Behandling	Behandlingslængde [måneder]	Helbredsstadie 1 [måneder]	Helbredstadie 2 [måneder]

9. Sikkerhed

9.1 Sikkerhedsdata fra den kliniske dokumentation

NRG-GY018

Sikkerhedsdata i afsnittet her er baseret på All-Participants-as-Treated (APaT) populationen. APaT populationen består af alle randomiserede patienter, som modtog mindst 1 dosis studiemedicin. Patienterne indgår i den gruppe, der svarer til den studiemedicin, de faktisk modtog.

Data er fra interimanalysen (IA) efter en median opfølgningstid på henholdsvis 8,7 mnd (0,1; 37,2) i pMMR population og 13,6 mnd (0,6; 39,4) i dMMR population (20). Den mediane behandlingsvarighed (*estimated Time-on-Treatment*) i pMMR population ved IA var længere i pembrolizumab+SOC-gruppen sammenlignet med placebo+SOC-gruppen [redacted]. I dMMR-populationen var den mediane behandlingsvarighed ved IA også længere i pembrolizumab+SOC gruppen sammenlignet med placebo+SOC gruppen [redacted] (20). Den mediane behandlingsvarighed med paclitaxel/docetaxel og carboplatin var mellem 106-108 i begge arme i både dMMR- og pMMR-populationen, hvilket svarer til de protokol-specificerede 6 serier kemoterapi Q3W (20).

Uønskede hændelser (adverse events) er i studieprotokollen defineret som *'any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention´* (19). Progression af sygdommen er ikke en uønsket hændelse. Bivirkninger (*drug-related adverse events*) er uønskede hændelser, som blev vurderet at være relateret til studiebehandlingen.

Der blev monitoreret for uønskede hændelser gennem hele studiet og i 30 dage efter endt behandling, og 90 dage for alvorlige uønskede hændelser og uønskede hændelser af særlig interesse. Analysen inkluderede frekvens, årsag og udfald af den uønskede hændelse samt ændringer i vitalparametre og laboratorieværdier.

I Appendix E listes alle alvorlige uønskede hændelser registreret i APaT populationen i NRG-GY018 samt antal patienter med ≥1 af disse (21). Desuden findes en liste over immunmedierede uønskede hændelser samt infusionsrelaterede reaktioner, som kaldes '*adverse events of special interest*' (AEOSI) i APaT population for dMMR og pMMR patienter. Det er prædefineret i studieprotokollen, hvilke immunmedierede uønskede hændelser samt infusionsrelaterede reaktioner, der indgår under AEOSI definitionen. Listen over AEOSI observeret mindst én gang i studiet findes også i Appendix E. Listen over AEOSI er konsistent med den kendte risiko i forbindelse med behandling med pembrolizumab. Det blev ikke identificeret nye indikationsspecifikke AEOSI i forbindelse med kombinationsbehandling. Som forventet er der generelt en højere incidens af AEOSI i pembrolizumab+SOC-gruppen sammenlignet med placebo+SOC-gruppen, men generelt er incidensen sammenlignelig med den kendte bivirkningsprofil for pembrolizumab i kombination med kemoterapi. Der var [redacted] af pMMR-patienterne i

pembrolizumab+SOC-gruppen, der oplevede en AEOSI sammenlignet med [redacted] i placebo+SOC-gruppen (20). For dMMR population blev AEOSI observeret i henholdsvis [redacted] af patienterne i pembrolizumab+SOC-gruppen og i [redacted] af patienterne i placebo+SOC-gruppen. De hyppigst rapporterede AEOSI var infusionsreaktioner, som blev observeret i samme omfang i behandlingsarmene (20). Disse er især relateret til taxol-platin-kemoterapi. ~~Eksponeringsjusteret~~ AEOSI justeret for eksponering til pembrolizumab var primært drevet af lav-gradshændelser som hypo- og hyperthyroidisme samt colitis.

I Appendix L vises *poolede* sikkerhedsdata fra patienter inkluderet i NRG-GY018 og andre studier med pembrolizumab i kombination med kemoterapi (n=6093). Disse kan bruges som et referencedatasæt (21). Det skal nævnes, at studierne inkluderet i dette referencesæt er udført i en lang række forskellige tumortyper (ikke-småcellet lungekræft, hoved-hals kræft, triple-negativ brystkræft, småcellet lungekræft, spiserørskræft og livmoderhalskræft) inkluderende patienter med forskellige baggrundskarakteristika, og at kemoterapiregimerne udgøres af både mono- og kombinationsregimer, der yderligere varierer i behandlingsvarighed.

I Tabel 16 ses sikkerhedshændelser opgjort ved IA og angivet for den samlede population, uanset MMR-status (20, 21). Vedr. dosisreduktion skal det bemærkes, at protokollen alene muliggjorde dosisreduktion af carboplatin/paclitaxel. Pembrolizumab kunne pauseres ved behov. De angivne antal og andele er for patienter, der måtte dosisreduceres eller pauseres pga. uønskede hændelser, og ikke pga. bivirkninger.

Den mediane varighed af eksponering for studieintervention var som nævnt ovenfor længere i pembrolizumab+SOC sammenlignet med placebo+SOC-gruppen i både pMMR- og dMMR-populationen. Den længere eksponering i pembrolizumab+SOC-gruppen bør tages i betragtning ved fortolkningen af resultaterne.

Tabel 16. Oversigt over sikkerhedshændelser opgjort ved IA i NRG-GY018

	Pembrolizumab+SOC (n=382)	Placebo+SOC (n=377)	Forskel, % (95 % CI)
Antal uønskede hændelser, n	7685	5951	NA
Antal og andel af patienter med ≥ 1 uønskede hændelser, n (%)	376 (98,4%)	375 (99,5%)	[redacted]
Antal alvorlige uønskede hændelser*, n	314	167	NA
Antal og andel af patienter med ≥ 1 alvorlige uønskede hændelser*, n (%)	132 (34,6%)	73 (19,4%)	[redacted]

	Pembrolizumab+SOC (n=382)	Placebo+SOC (n=377)	Forskel, % (95 % CI)
Antal CTCAE-grad ≥ 3 hændelser, n	744	452	NA
Antal og andel af patienter med ≥ 1 CTCAE-grad ≥ 3 hændelser§, n (%)	225 (58,9%)	174 (46,2%)	[redacted]
Antal bivirkninger, n	4452	3440	NA
Antal og andel af patienter med ≥ 1 bivirkninger, n (%)	365 (95,5%)	358 (95,0%)	[redacted]
Antal og andel af patienter med dosisreduktion, n (%)	NA	NA	NA
Antal og andel af patienter, der ophører med behandlingen uanset årsag, n (%)	192 (50,3%)	246 (65,3%)	[redacted]
Antal og andel af patienter, som ophører med behandlingen på grund af uønskede hændelser, n (%)	[redacted]	[redacted]	NA

* En alvorlig uønsket hændelse er en hændelse eller en bivirkning, som uanset dosis resulterer i død, er livstruende, medfører hospitalsindlæggelse eller forlængelse af hospitalsophold, resulterer i betydelig eller vedvarende invaliditet eller uarbejdsdygtighed eller fører til en medfødt anomali eller misdannelse (der henvises til ICH's komplette definition).

**ITT population

§ CTCAE v. 5.0 skal anvendes, hvis den er tilgængelig.

Som det fremgår af Tabel 16, var raterne af patienter med én eller flere uønskede hændelser eller bivirkninger i pembrolizumab+SOC-gruppen generelt sammenlignelig med raterne i placebo+SOC-gruppen (89,4% vs 99,5% og 95,5% vs 95,0%). Som forventet blev der observeret lidt flere CTCAE-grad ≥ 3 bivirkninger i pembrolizumab+SOC-gruppen sammenlignet med placebo+SOC-gruppen (58,9% vs. 46,2%) (21). Incidencen var dog lavere end i det *poolede* dataset fra studier med kombinationsbehandling med pembrolizumab og kemoterapi (78,5%) i Appendix L.

Ifølge CSR er sikkerhedsbilledet i pMMR- og-dMMR populationerne for begge arme sammenligneligt, når der justeres for *drug exposure*. Der ses kun lidt højere antal af grad

3-5 AEs i pembrolizumab+SOC-gruppen i pMMR populationen [redacted] hændelse/100 person-mnd). Der var lidt flere patienter i pembrolizumab+SOC-gruppen, der ophørte behandling på grund af en uønsket hændelse end i placebo+SOC-gruppen ([redacted] i pMMR-populationen og [redacted] i dMMR-populationen) (20). Dette var formentligt drevet af højere antal af deltager som ophørte pembrolizumab i pembrolizumab+SOC-gruppen ([redacted] i pMMR og [redacted] i dMMR) sammenlignet med antal af deltager som ophørte placebo i placebo+SOC-gruppen ([redacted] i pMMR og [redacted] i dMMR), samt den længere behandlingsvarighed i pembrolizumab+SOC-gruppen.

Det er ikke registreret alvorlige uønskede hændelser med en frekvens på ≥ 5 % (21). Forekomst af alvorlige uønskede hændelser med en frekvens >2% var som følger i pembrolizumab+SOC vs. placebo+SOC-gruppen: anæmi (4,2% vs. 3,4%), febril neutropeni (2,9% vs. 1,3%), urinvejsinfektion (2,1% vs. 1,6%), og fald i antal af hvide blodceller (2,1% vs. 1,1 %).

Tabel 17. Alvorlige uønskede hændelser i APaT population med frekvens på ≥ 5 % ved IA

Uønskede hændelser	Intervention (N=x)		Komparator (N=x)	
	Antal patienter med uønskede hændelser	Antal uønskede hændelser	Antal patienter med uønskede hændelser	Antal uønskede hændelser
Uønsket hændelse, n (%)	N/A	N/A	N/A	N/A

* En alvorlig uønsket hændelse er en hændelse eller en bivirkning, som uanset dosis resulterer i død, er livstruende, medfører hospitalsindlæggelse eller forlængelse af hospitalsophold, resulterer i betydelig eller vedvarende invaliditet eller uarbejdsdygtighed eller fører til en medfødt anomali eller misdannelse (der henvises til ICH's komplette definition).

Idet der ikke er indsendt en sundhedsøkonomisk model, er Tabellerne 18 og 19 ikke relevante i sagen her.

Tabel 18. Uønskede hændelser anvendt i den sundhedsøkonomiske model

Uønskede hændelser	Intervention	Komparator

RUBY-I

Sikkerhedsdata i afsnittet her er baseret på *All-Participants-as-Treated (APaT) all-comers* populationen fra RUBY/ENGOT EN-6/GOG-3031 studiet. APaT-populationen består af alle randomiserede patienter, som modtog mindst 1 dosis studiemedicin. Patienterne indgår i den gruppe, der svarer til den studiemedicin, de faktisk modtog. Data er fra interimanalysen fra part 1 med data *cut-off* d. 28. september 2022. Median opfølgningstid var 25,38 måneder i begge behandlingsgrupper. I *all-comers* populationen var den mediane behandlingsvarighed 43,00 uger (3,0-150,9 uger) for dostarlimab+SOC-gruppen og 36,00 uger (2,1-165,1 uger) for placebo+SOC-gruppen (12). I dMMR-population var den

mediane behandlingsvarighed også længere i pembrolizumab+SOC-gruppen sammenlignet med placebo+SOC-gruppen (76,5 vs. 31,86 uger) (12). Den mediane behandlingsvarighed med paclitaxel og carboplatin var 18 uger i begge behandlingsgrupper, som svarer til 6 serier carboplatin/paclitaxel-behandling.

Som det ses af Tabel XVII blev der rapporteret mindst én uønsket hændelse hos alle patienter i begge behandlingsarme. Hos 170 patienter (70,5%) i dostarlimab+SOC-gruppen samt 147 (59,8%) i placebo+SOC-gruppen var disse grad ≥3. Alvorlige uønskede hændelser af enhver grad blev rapporteret i 91 patienter (37,8%) i dostarlimab+SOC-gruppen og i 68 (27,6%) i placebo+SOC-gruppen (12).

Tabel XVII Oversigt over sikkerhedshændelser i RUBY-I

	Dostarlimab+SOC (N=241)	Placebo + SOC (N=246)	Forskel, % (95 % CI)
Antal uønskede hændelser, n	NA	NA	NA
Antal og andel af patienter med ≥ 1 uønskede hændelser, n (%)	241 (100%)	246 (100%)	NA
Antal alvorlige uønskede hændelser*, n	NA	NA	NA
Antal og andel af patienter med ≥ 1 alvorlige uønskede hændelser*, n (%)	91 (37,8%)	68 (27,6%)	NA
Antal CTCAE-grad ≥ 3 hændelser, n	NA	NA	NA
Antal og andel af patienter med ≥ 1 CTCAE-grad ≥ 3 hændelser§, n (%)	170 (70,5%)	147 (59,8%)	NA
Antal bivirkninger, n	NA	NA	NA
Antal og andel af patienter med ≥ 1 bivirkninger, n (%)	236 (97,9%)	243 (98,8%)	NA
Antal og andel af patienter med dosismodifikation+, n	NA	NA	NA

	Dostarlimab+SOC (N=241)	Placebo + SOC (N=246)	Forskel, % (95 % CI)
(%) – som følge af en bivirkning			
Antal og andel af patienter, der ophører med behandlingen uanset årsag, n (%)	57 (23,7%)	41 (16,7%)	NA
Antal og andel af patienter, som ophører med behandlingen på grund af bivirkninger, n (%)	NA	NA	NA

Det er ikke registreret alvorlige uønskede hændelser med en frekvens på ≥ 5 % (12). Forekomst af alvorlige uønskede hændelser med en frekvens >2% var som følger i dostarlimab+SOC-gruppen vs. placebo+SOC-gruppen: Sepsis (3,3% vs. 0,4%), pulmonær embolisme (2,5% vs. 2,0%), pyrexia (2,5% vs. 0,8%), dyspnø (2,1% vs. 0,4%), asthenia (0,8% vs. 2,4%), anæmi (1,2% vs. 2,4%), urinvejsinfektion (1,2% vs. 2,0%) og muskulær svaghed (2,1% vs. 0,4 %) (12).

Der var 56,8% af patienterne i dostarlimab+SOC-gruppen, der oplevede en immunmedieret bivirkning (iTEAEs) sammenlignet med 35,8% i placebo+SOC-gruppen. Som det ses i Tabel XIX var de mest rapporterede immunmedierede bivirkninger relateret til dostarlimab: Hypothyroidisme (11,2%), udslæt (6,6%), arthralgi (5,8%) og forhøjet ALAT (5,8%). De fleste immunmedierede bivirkninger var af grad 1-2. Grad ≥3 iTEAEs relateret til dostarlimab/placebo blev observeret i 12,4% af patienterne i dostarlimab+SOC- og i 3,3% i placebo+SOC-gruppen (12).

Tabel XVIII Oversigt over bivirkninger med potential immunmedieret årsag i RUBY-I

Table 87. Most frequently occurring immune-related TEAEs (reported in ≥3% of participants in either arm) (overall population, Safety Analysis Set)

Category, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=241)		Placebo + carbo/pac (N=246)	
	All events	Dostarlimab-related	All events	Placebo-related
Any immune-related AE	**137 (56.8%)**	**92 (38.2%)**	**88 (35.8%)**	**38 (15.4%)**
Arthralgia	32 (13.3%)	14 (5.8%)	31 (12.6%)	16 (6.5%)
Infusion-related reaction	31 (12.9%)	4 (1.7%)	30 (12.2%)	0
Hypothyroidism	27 (11.2%)	27 (11.2%)	8 (3.3%)	7 (2.8%)
Hypersensitivity/ Drug hypersensitivity	6 (2.5%)/ 7 (2.9%)	0/ 0	4 (1.6%)/ 11 (4.5%)	1 (0.4%)/ 1 (0.4%)
Rash	21 (8.7%)	16 (6.6%)	6 (2.4%)	5 (2.0%)
Rash maculo-papular	16 (6.6%)	11 (4.6%)	0	0
Pruritus	15 (6.2%)	8 (3.3%)	4 (1.6%)	3 (1.2%)
ALT increased	15 (6.2%)	14 (5.8%)	2 (0.8%)	2 (0.8%)
AST increased	12 (5.0%)	10 (4.1%)	1 (0.4%)	1 (0.4%)
Hyperthyroidism	8 (3.3%)	8 (3.3%)	1 (0.4%)	1 (0.4%)

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel; TEAE=treatment-emergent adverse event.

I dMMR population var der 17,3% af patienterne i dostarlimab+SOC-gruppen, der ophørte dostarlimab på grund af en uønsket hændelse. Der var 10,8% som ophørte behandling med placebo pga. AEs i placebo+SOC-gruppen (12).

Deskriptiv sammenligning af sikkerhed

Overordnet er sikkerhedsprofilen for pembrolizumab+SOC sammenlignelig med sikkerhedsprofilen på dostarlimab+SOC. Andelen af patienter med ≥ 1 uønskede hændelser (pembrolizumab+SOC: 98,4% vs. dostarlimab+SOC: 100%) samt andelen af patienter med ≥ 1 bivirkninger (pembrolizumab+SOC: 95,5% vs. dostarlimab+SOC: 97,9%) var næsten identisk i de to grupper. Dette var også tilfældet for andelen af patienter med ≥ 1 alvorlige uønskede hændelser (pembrolizumab+SOC: 34,6% vs. dostarlimab+SOC: 37,8%). I begge studier ses der en større andel af alvorlige og ≥ grad 3 uønskede hændelser i interventionsarmene sammenlignet med komparatorarmene med absolutte forskelle på hhv. [redacted] og [redacted] i NRG-GY018, og 10,2%-point og 10,7 %-point i RUBY-1. Som forventet ses der flere immunrelaterede uønskede hændelse (AEOSI i NRG-GY018, iTEAEs i RUBY) i interventionsarmene. Andelen af patienter der pga. uønskede hændelser ophører pembrolizumab i NRG-GY018 er sammenlignelig med andelen af patienter, der ophører dostarlimab i RUBY-1 ([redacted]% vs. 17,4%) (12, 20). Sammenholdt er der således ikke noget der taler for, at der er forskel på sikkerhedsprofilen af de to kombinationsbehandlinger.

9.2 Sikkerhedsdata fra ekstern litteratur anvendt i den sundhedsøkonomiske model

Idet ansøgningen vurderes i Medicinrådets 14-ugers proces, er afsnittet ikke udfyldt.

Tabel 19. Uønskede hændelser, der forekommer hos mere end X % af patienter

Uønskede hændelser	Intervention (N=x)			Komparator (N=x)			Forskel, % (95 % CI)	
	Antal patienter med uønskede hændelser	Antal uønskede hændelser	Frekvens anvendt i den sundhedsøkonomiske model for intervention	Antal patienter med uønskede hændelser	Antal uønskede hændelser	Frekvens anvendt i den sundhedsøkonomiske model for komparator	Antal patienter med uønskede hændelser	Antal uønskede hændelser
Uønsket hændelse, n								

10. Dokumentation af helbredsrelateret livskvalitet

Da ansøgningen vurderes i Medicinrådets 14-ugers proces uden sundhedsøkonomisk analyse, er dele af afsnittet her ikke relevant og derfor ikke udfyldt.

I KEYNOYE-868 blev livskvalitet - vurderet ved den sygdomsspecifikke skala *Functional Assessment of Cancer Therapy-Endometrial Trial Outcome Index* (FACT-En TOI) – undersøgt som et sekundært effektmål (19).

I RUBY-1 blev livskvalitet vurderet ved *global health status* på *European Organization For Research And Treatment of Cancer* (EORTC) QLQ-C30 spørgeskemaet som et eksplorativt effektmål (12, 22).

Tabel 20. Oversigt over inkluderede instrumenter til helbredsrelateret livskvalitet

Måleinstrument	Kilde	Udnyttelse
FACT-En TOI	NRG-GY018	Klinisk effekt
EORTC-QLQ-C30	RUBY-1	Klinisk effekt

10.1 Helbredsrelateret livskvalitet

10.1.1 Studiedesign og måleinstrument – NRG-GY018

FACT-En er et selvadministreret spørgeskema med 43 spørgsmål. Spørgeskemaet består af det generelle *Functional Assessment of Cancer Therapy – General* (FACT-G) spørgeskema, som inkluderer fire underskalaer (fysisk, socialt/familierelateret, emotionelt og funktionelt velbefindende) samt en række endometrie-cancer specifikke spørgsmål. *Trial Outcome Index* (TOI) er summen af scores for de fysiske og funktionelle subskalaer og de endometrie-cancer specifikke spørgsmål. Resultaterne kan ligge i intervallet 0-120, hvor en højere score repræsenterer højere livskvalitet (26).

10.1.2 Dataindsamling – NRG-GY018

Data blev indsamlet elektronisk før administration af studiemedicin ved baseline og ved uge 6, 18, 30 og 54.

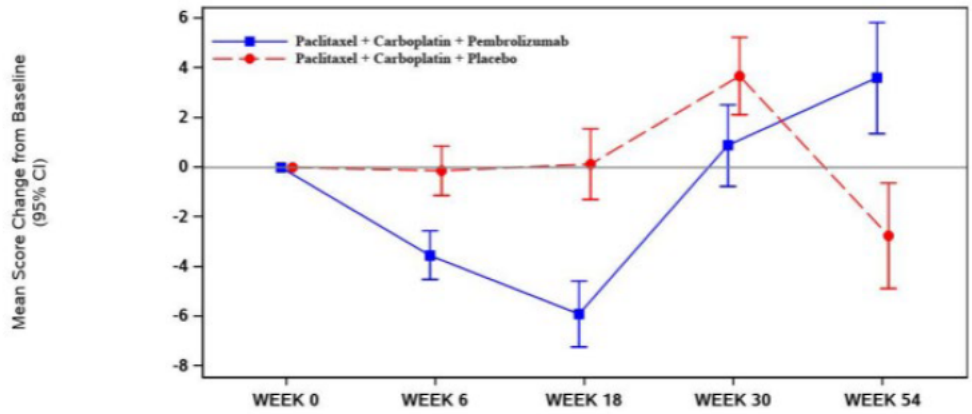
I Tabel 21 ses antal patienter, for hvem der mangler data fordi de er udgået af studiet (*'missing by design'*) eller af andre årsager (*'non-completers'*) (20).

Tidspunkt	Population for helbredsrelateret livskvalitet N	Manglende værdier N (%)	Forventet at fuldføre N	Fuldførelse N (%)
	Antal patienter ved randomisering	Antal patienter, for hvem der mangler data (% af patienter ved randomisering)	Antal patienter "i risiko" på tidspunkt X	Antal patienter, der fuldførte (% af patienter der forventes at fuldføre)
Baseline				
Uge 6				
Uge 18				
Uge 30				
Uge 54				

Tabel 21 Mønster med manglende data og fuldførelse - NRG-GY018

10.1.3 Resultater for helbredsrelateret livskvalitet – NRG-GY018

Data er, jf. protokollen, opgjort for pMMR FAS-populationen, som er de patienter, der havde en valid baseline PRO-måling og mindst én opfølgende PRO-måling (19, 21). I figuren herunder ses de gennemsnitlige ændringer i FACT-En TOI fra baseline og ved de forskellige opfølgningstidspunkter for både interventionen og komparatoren. Analyserne er baseret på en *missing at random*-model med behandlingsarm, alder ved randomisering, før-behandlings QoL/PRO-score, vurderingstidspunkt og *treatment-by-time* interaktion som kovariater. Resultaterne er fra IA med data *cut-off* 6. december 2022 (20).



Figur XVI Gennemsnitlige ændringer i FACT-En TOI i NRG-GY018

I Figur XV ses de gennemsnitlige ændringer i FACT-En TOI (21) og i Tabel 22 ses ændringen fra baseline til uge 18 (20).

Baseret på figuren og tabellen er der ikke noget der tyder på, at tillæg af pembrolizumab påvirker den patientoplevede livskvalitet.

Tabel 22 Sammenfattet statistik om helbredsrelateret livskvalitet i NRG-GY018

	Intervention		Komparator		Intervention vs. Komparator
	N	Gennemsnit (SD)	N	Gennemsnit (SD)	Ændring i *least squares mean* (95% CI) fra baseline til uge 18
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uge 18	[redacted]	[redacted]	[redacted]	[redacted]	

10.1.4 Studiedesign og måleinstrument – RUBY-1

EORTC-QLQ-C30 er et selvadministreret spørgeskema med 30 spørgsmål. Spørgeskemaet inkluderer fem funktionelle skalaer (fysik, rolle, kognition, emotionel og social), tre symptomskalaer (fatigue, smerte og kvalme/opkast) og en generel helbredsstatusskala (*global health status*). Resultater for hvert udfald bliver målt med en score fra 0-100. En høj score på den globale skala repræsenterer et højt funktionsniveau.

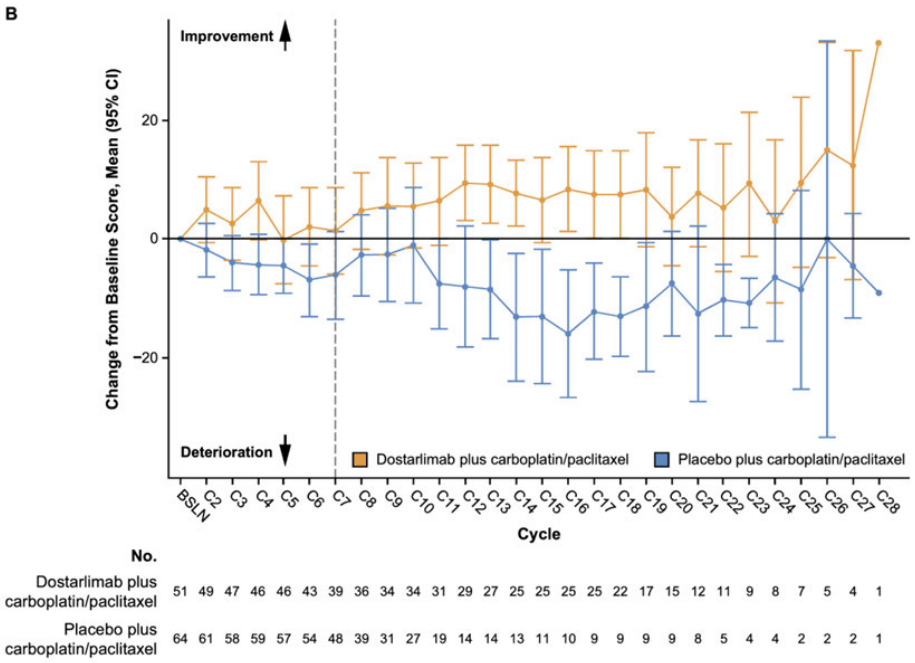
10.1.5 Dataindsamling - RUBY-1

Data blev indsamlet ved baseline, ved dag 1 i hver cyklus, ved endt behandling og derefter ved hver overlevelsesopfølgning (22).

Der er endnu ikke publiceret detaljerede PRO-data fra RUBY-1, hvorfor vi ikke kan redegøre for antal patienter, for hvem der mangler data fordi de er udgået af studiet (*'missing by design'*) eller af andre årsager (*'non-completers'*).

10.1.6 Resultater for helbredsrelateret livskvalitet - RUBY-1

Resultaterne i Figur XVI herunder er baseret på data *cut-off* 28. september 2022 (22).



Figur XVII Gennemsnitlige ændringer i EORTC-QLQ-C30 i RUBY-1

Baseret på Figur XVI er der ikke noget der tyder på, at tillæg af dostarlimab påvirker den patientoplevede livskvalitet.

10.2 Nytteværdier anvendt i den sundhedsøkonomiske model

NA

10.2.1 Beregning af nytteværdier

10.2.1.1 Mapping

10.2.2 Beregning af disutility-værdier

10.2.3 Resultater af nytteværdier

Tabel 23. Oversigt over nytteværdier (HSUV'er) [og disutility-værdier]

	Resultater [95 % CI]	Instrument	Anvendt takst (værdi angivet)	Kommentarer
NA				

10.3 Nytteværdier målt i andre studier end dem, der danner grundlag for relativ effekt

NA

10.3.1 Studiedesign

10.3.2 Dataindsamling

10.3.3 Resultater for helbredsrelateret livskvalitet

10.3.4 Resultater for nytteværdier

Tabel 24. Oversigt over nytteværdier (HSUV'er) [og disutility-værdier]

	Resultater [95 % CI]	Instrument	Anvendt takst (værdi angivet)	Kommentarer
NA				

Tabel 25. Oversigt over litteraturbaserede nytteværdier (HSUV'er)

	Resultater [95 % CI]	Instrument	Anvendt takst (værdi angivet)	Kommentarer
NA				

11. Ressourceforbrug og tilknyttede omkostninger

- NA

11.1 Lægemidler - intervention og komparator

Tabel 26. Lægemidler anvendt i modellen

Lægemiddel	Dosis	Relativ dosisintensitet	Frekvens	Hætteglasdeling
NA				

11.2 Lægemidler - co-administration

11.3 Administrationsomkostninger

Tabel 27. Administrationsomkostninger anvendt i modellen

Administrationstype	Frekvens	Enhedsomkostning [DKK]	DRG-kode	Reference
NA				

11.4 Omkostninger til sygdomshåndtering

Tabel 28. Omkostninger til sygdomshåndtering anvendt i modellen

Aktivitet	Frekvens	Enhedsomkostning [DKK]	DRG-kode	Reference
NA				

11.5 Omkostninger forbundet med håndtering af uønskede hændelser

Tabel 29. Omkostning forbundet med håndtering af uønskede hændelser

	DRG-kode	Enhedsomkostning/DRG-takst
NA		

11.6 Efterfølgende behandlingsomkostninger

NA

Tabel 30. Lægemidler ved efterfølgende behandlinger

Lægemiddel	Dosis	Relativ dosisintensitet	Frekvens	Hætteglasdeling
NA				

11.7 Patientomkostninger

NA

Tabel 31. Patientomkostninger anvendt i modellen

Aktivitet	Tidsforbrug [minutter, timer, dage]
NA	

11.8 Andre omkostninger (f.eks. omkostninger til hjemmesygeplejersker, omkostninger til ambulant rehabilitering og palliativ pleje)

NA

12. Resultater

NA

12.1 Oversigt over base case

Tabel 32. Oversigt over base case

Funktion	Beskrivelse
NA	

12.1.1 Base case-resultater

Tabel 33. Base case-resultater, diskonterede estimater

	[Intervention]	[Komparator]	Forskel
NA			

12.2 Følsomhedsanalyser

NA

12.2.1 Deterministiske følsomhedsanalyser

Tabel 34 Resultater af one-way følsomhedsanalyser

	Ændring	Årsag/ baggrund/ kilde	Inkremen-telle omkostnin-ger (DKK)	Inkrementel effekt (QALY)	ICER (DKK/QALY)
NA					

12.2.2 Probabilistiske følsomhedsanalyser

13. Budgetkonsekvensanalyse

NA

Antal patienter (herunder antagelser om markedsandel)

Tabel 35. Antal nye patienter, der forventes behandlet i løbet af den næste femårsperiode, hvis lægemidlet indføres (justeret for markedsandel)

	År 1	År 2	År 3	År 4	År 5
NA					

Budgetkonsekvens

Tabel 36. Forventet budgetkonsekvens ved at anbefale lægemidlet til indikationen

	År 1	År 2	År 3	År 4	År 5
NA					

14. Liste over eksperter

NA

15. Referencer

1. Ortoft G, Hogdall C, Hansen ES, Dueholm M. Predictive value of the new ESGO-ESTRO-ESP endometrial cancer risk classification on survival and recurrence in the Danish population. Int J Gynecol Cancer. 2021;31(8):1116-24.
2. DGCG. Retningslinjer: Corpuscancer. 2024.
3. Bekæmpelse K. Livmoderkræft [Available from: https://www.cancer.dk/livmoderkraeft-uteruscancer/.
4. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021;31(1):12-39.
5. DGCG. Landsdækkende klinisk database for gynækologisk kræft: National Årsrapport 2017/2018 og 2018/2019: DGCG; 2019 [Available from: http://dgcg.dk/images/rsrapport_DGCD_2017-19.pdf.
6. DGCG. Landsdækkende klinisk database for gynækologisk kræft: National Årsrapport 2021/2022 2022 [Available from: http://dgcg.dk/images/DGCD%20rsrapport%202021-20225724.pdf.
7. Suhaimi SS, Ab Mutalib NS, Jamal R. Understanding Molecular Landscape of Endometrial Cancer through Next Generation Sequencing: What We Have Learned so Far? Front Pharmacol. 2016;7:409.
8. Oaknin A, Bosse TJ, Creutzberg CL, Giornelli G, Harter P, Joly F, et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[☆]. Annals of Oncology. 2022;33(9):860-77.
9. Stelloo E, Jansen AML, Osse EM, Nout RA, Creutzberg CL, Ruano D, et al. Practical guidance for mismatch repair-deficiency testing in endometrial cancer. Annals of Oncology. 2017;28(1):96-102.
10. Medicinraadet. Dostarlimab (Jemperli) i kombination med carboplatin og paclitaxel. 2024 28-Aug-2024.
11. Leon-Castillo A, Horeweg N, Peters EEM, Rutten T, Ter Haar N, Smit V, et al. Prognostic relevance of the molecular classification in high-grade endometrial cancer for patients staged by lymphadenectomy and without adjuvant treatment. Gynecol Oncol. 2022;164(3):577-86.
12. CHMP extension of indication variation assessment report EMA/483641/2023. Assessment report. European Medicines Agency; 2023 12-10-2023.
13. Oaknin A, Tinker AV, Gilbert L, Samouelian V, Mathews C, Brown J, et al. Clinical Activity and Safety of the Anti-Programmed Death 1 Monoclonal Antibody Dostarlimab for Patients With Recurrent or Advanced Mismatch Repair-Deficient Endometrial Cancer: A Nonrandomized Phase 1 Clinical Trial. JAMA Oncol. 2020;6(11):1766-72.
14. Medicinraadet. Medicinrådets anbefaling vedrørende dostarlimab til behandling af dMMR/MSI-high kræft i livmoderslimhinden - version 2.0. Recommendation. 2022 16-11-2022.
15. Makker V, Colombo N, Casado Herraez A, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N Engl J Med. 2022;386(5):437-48.
16. Medicinraadet. Lenvatinib (Lenvima) i kombination med pembrolizumab (Keytruda). 2024.
17. Lægemiddelstyrelsen. PRODUKTRESUMÉ for Carboplatin "Accord", koncentrat til infusionsvæske, opløsning. 2024 02-12-2024.
18. Lægemiddelstyrelsen. PRODUKTRESUMÉ for Paclitaxel "Accord", koncentrat til infusionsvæske, opløsning. 2023.
19. Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, Musa FB, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. N Engl J Med. 2023;388(23):2159-70.

20. Clinical study report IA: A Phase III Randomized, Placebo-controlled Study og Pembrolizumab (MK-3475, NSC #776864) in Addition to Paclitaxel and Carboplatin for Measurable Stage III or IVA, Stage IVB or Recurrent Endometrial Cancer. MSD; 2023 15-Dec-2023. Report No.: P868V01MK3475.
21. CHMP extension of indication variation assessment report EMA/89258/2024. Assessment report. European Medicines Agency; 2024 19-09-2024.
22. Mirza MR, Chase DM, Slomovitz BM, dePont Christensen R, Novak Z, Black D, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023;388(23):2145-58.
23. Powell MA, Bjorge L, Willmott L, Novak Z, Black D, Gilbert L, et al. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. Ann Oncol. 2024;35(8):728-38.
24. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting Survival Time Estimates in the Presence of Treatment Switching. NICE Decision Support Unit Technical Support Documents. London2014.
25. AQ P. Systematic literature review and network meta-analysis of first-line treatments for advanced or recurrent endometrial carcinoma. Technical report. 2024.
26. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11(3):570-9.

Appendix A. Studiekarakteristika

Tabel 37. Vigtigste karakteristika for inkluderede studier

Studienavn: NRG-GY018	NCT-nummer: NCT03914612
Formål	Formålet med studiet var at sammenligne effekt og sikkerhed af pembrolizumab i kombination med kemoterapi med kemoterapi til førstelinjebehandling af patienter med avanceret eller tilbagevendende dMMR eller pMMR kræft i livmoderslimhinden.
Publikationer – titel, forfatter, tidsskrift, år	**Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer.** R. N. Eskander, M. W. Sill, L. Beffa, R. G. Moore, J. M. Hope, F. B. Musa, et al. N Engl J Med 2023 Vol. 388 Issue 23 Pages 2159-2170 Derudover er følgende publiceret på baggrund af studiet: **Overall survival and progression-free survival by PD-L1 status among endometrial cancer patients treated with pembrolizumab plus carboplatin/paclitaxel as compared to carboplatin/paclitaxel plus placebo in the NRG GY018 trial**. R. Eskander, M. Sill, L. Beffa, R. Moore, J. Hope, F. Musa, et al. Gynecologic Oncology, Volume 190, S5, 2024 **Pembrolizumab versus placebo in addition to carboplatin and paclitaxel for measurable stage 3 or 4a, stage 4b or recurrent endometrial cancer: The phase 3, NRG GY018 study (LBA 10).** R. Eskander, M. Sill, L. Beffa, R. Moore, J. Hope, F. Musa, et al. Gynecologic Oncology 2023 Vol. 176 Pages S42-S43 **Overall survival, progression-free survival by PD-L1 status, and blinded independent central review results with pembrolizumab plus carboplatin/paclitaxel (CP) versus placebo plus CP in patients with endometrial cancer: results from the NRG GY018 trial**. Eskander RN, Sill M, Miller A, et al. Presented at: 2024 Society of Gynecologic Oncology Annual Meeting on Women's Cancer; March 15-18, 2024; San Diego, CA. **LBA43 Updated response data and analysis of progression free survival by mechanism of mismatch repair loss in endometrial cancer (EC) patients (pts) treated with pembrolizumab plus carboplatin/paclitaxel (CP) as compared to CP plus placebo (PBO) in the NRG GY018 trial**. R. N. Eskander, M. Sill, A. Miller, L. Beffa, R. Moore, J. Hope, et al. Annals of Oncology 2023 Vol. 34 Pages S1284
Studietype og -design	NRG-GY018/KEYNOTE-868 er et internationalt, multicenter, randomiseret, dobbeltblindet, placebokontrolleret, fase 3-studie. Inkluderede patienter blev randomiseret 1:1 vha. et centralt, interaktivt *voice/web response* system. Tildeling af behandling skete dobbelt-maskeret. Patienterne blev stratificeret efter MMR status (dMMR eller pMMR), ECOG-*performance status* (0 eller 1 vs. 2) og forudgående adjuverende behandling (yes/no). På baggrund af studieresultater har EMA godkendt pembrolizumab i kombination med carboplatin og paclitaxel til førstelinjebehandling af nydiagnosticeret patienter i stadie III/IVA/IVB og af patienter med tilbagevendende kræft i livmoderslimhinden.

Studienavn: NRG-GY018	NCT-nummer: NCT03914612
	Studiet er fortsat igangværende.
Antal forsøgsdeltagere (N)	n=1064 (screenet) n= 810 (randomiseret)
Primære inklusionskriterier	*Female ≥18 years of age.* *Adequate organ function as defined in the study protocol.* *ECOG PS of 0, 1, or 2.* *Measurable Stage III, measurable Stage IVA, Stage IVB (with or without measurable disease), or recurrent (with or without measurable disease) endometrial cancer. In participants with measurable disease, lesions were defined and monitored by RECIST 1.1.* *Pathology report showing results of institutional MMR IHC testing (submission of tumour specimens for centralized MMR IHC testing was required before Step 2 registration/stratification/randomisation).* *One of the following confirmed histologic subtypes of EC: endometrioid adenocarcinoma, serous adenocarcinoma, dedifferentiated/ undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified.* *As prior therapy, participants may have received:* *No prior chemotherapy for treatment of EC.* *Prior adjuvant chemotherapy (e.g., paclitaxel/carboplatin alone or as a component of concurrent chemotherapy and radiation therapy [with or without cisplatin]) provided adjuvant chemotherapy was completed ≥12 months before.* *Prior radiation therapy completed at least 4 weeks before.* *Prior hormonal therapy discontinued at least 3 weeks before.* *Interval or cytoreductive surgery, after start of treatment on this study, and before documentation of disease progression, was NOT permitted.* *For participants of childbearing potential: negative urine or serum pregnancy test.* *Informed consent before study entry.* *Participants with prior or concurrent malignancy whose natural history or treatment did not have the potential to interfere with safety or efficacy assessment of the investigational regimen were eligible.* *Participants with treated brain metastases were eligible if follow-up brain imaging after CNS-directed therapy showed no evidence of progression, and they had been off steroids for at least 4 weeks and remained clinically stable.*

Studienavn: NRG-GY018	NCT-nummer: NCT03914612
Primære eksklusionskriterier	*History of a severe hypersensitivity reaction to monoclonal antibody or pembrolizumab and/or its excipients; and/or a severe hypersensitivity reaction to paclitaxel and/or carboplatin.* *Active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids. Participants with vitiligo, endocrine deficiencies including type I diabetes mellitus, thyroiditis managed with replacement hormones including physiologic corticosteroids were eligible.* *Patients with endometrial sarcoma, including carcinosarcoma* *History of (non-infectious) pneumonitis that required steroids, or current pneumonitis.* *Uncontrolled intercurrent illness that would limit compliance with study requirements.* *Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; and cirrhosis.* *For participants with chronic HBV infection, HBV viral load must have been undetectable on suppressive therapy, if indicated. Participants with a history of HCV infection must have been treated and cured, or with undetectable HCV viral load if under treatment.* *Prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 therapeutic antibody or similar agents.* *Diagnosis of immunodeficiency or were receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days randomisation.* *Participation and received investigational cancer-directed study therapy within 4 weeks.* *Pregnant or lactating*
Intervention	Pembrolizumab 200 mg administreret i.v. på dag 1 af hver 3-ugers cyklus i løbet af seks serier efterfulgt af 14 serier af pembrolizumab 400 mg administreret i 6-uges cyklus i kombination med Carboplatin AUC 5 mg/mL/min og paclitaxel 175 mg/m^2 administreret i.v. på dag 1 af hver 3-ugers cyklus i løbet af seks serier n = 110 (dMMR) n= 294 (pMMR)
Komparator(er)	Placebo 200 mg administreret i.v. på dag 1 af hver 3-ugers cyklus i løbet af seks serier efterfulgt af 14 serier af placebo 400 mg administreret i 6-uges cyklus i kombination med

Studienavn: NRG-GY018	NCT-nummer: NCT03914612
	Carboplatin AUC 5 mg/mL/min og paclitaxel 175 mg/m^2 administreret i.v. på dag 1 af hver 3-ugers cyklus i løbet af seks serier n = 112 (dMMR) n= 294 (pMMR)
Opfølgningstid	Denne ansøgning baserer sig på resultater fra interimanalysen (IA), med en median opfølgningstid på henholdsvis 8,7 mnd (0,1; 37,2) i pMMR population og 13,6 mnd (0,6; 39,4) i dMMR population (20, 21) og på en supplerende analyse, med ca. 9 måneders længere opfølgningstid.
Bruges studiet i den sundhedsøkonomiske model?	NA
Primære, sekundære og eksploratoriske endepunkter	**Endepunkter inkluderet i denne ansøgning:** Progressionsfri overlevelse (PFS) per RECIST 1.1, vurderet af investigator i to studiepopulationer, dvs. dMMR og pMMR, udgjorde det primære effektmål i studiet og er inkluderet i ansøgningen. Samlet overlevelse (OS) var et sekundært endepunkt og er inkluderet i ansøgningen. Sikkerhed i form af uønskede hændelser (AEs) vurderet per CTCAE var et sekundært effektmål og er inkluderet i ansøgningen. Helbredsrelateret livskvalitet målt ved EORTC-QLQ-C30 *Global Score* var et sekundært effektmål og er inkluderet i ansøgningen. **Andre endepunkter:** Sekundære effektmål var objektiv responsrate (ORR) per RECIST 1.1 og vurderet ved BICR eller investigator, *duration of response (DOR)*, *physical function* per *Patient-Reported Outcomes Measurement Information System (PROMIS)-physical function scale*, livskvalitet per *Functional Assessment of Cancer Therapy (FACT) - Endometrial Trial Outcome Index (En TOI)* og forværret fatigue, målt på PROMIS-Fatigue scale (short form) i pMMR patienterne.
Analysemetode	Den primære hypotese er evalueret ved at sammenligne resultater vedr. PFS mellem grupperne i de to separate populationer af dMMR og pMMR patienter ved brug af en stratificeret log-rank test. Hazard ratioer er estimeret ved brug af en stratificeret Cox regressions model. Hændelsesrater er estimeret ved brug af Kaplan-Meier metoden. Antagelsen om proportional hazards er testet ved Schoenfelds residuals. *The overall Type I error rate was strongly controlled at a 0.025 (one-sided) alpha level. The trial used the graphical method of Maurer and Bretz to control multiplicity for multiple hypotheses, as well as interim analyses. A Lan-DeMets spending function approximate O'Brien-Fleming type of stopping boundary was used for the efficacy interim analysis in each MMR population.*

Studienavn: NRG-GY018	NCT-nummer: NCT03914612
	Den planlagte *sample size* er ca. 590 deltagere i pMMR gruppen og 220 deltagere i dMMR gruppen. Studiet er event-drevet. *Each population (dMMR and pMMR) had one futility interim, one efficacy interim and one final analysis for PFS. An interim efficacy analysis occurred after the population (both pMMR and dMMR) completed accrual and a sufficient number of PFS events (50% information fraction) were observed, whichever was later. In each group, at the time of the final PFS analysis (significant interim or final analysis), an interim OS futility analysis was performed and the OS interim analysis results released along with the PFS results, at that time.* OS blev ikke formelt testet ved interimanalysen. Forskel mellem behandlingsarme i dMMR og pMMR population var vurderet ved stratificeret long-rank test.
Undergruppeanalyser	Der blev udført præspecificerede subgruppeanalyser i dMMR og pMMR populationerne baseret på ECOG performance status (0 eller 1 vs. 2), alder, etnicitet og histologi.
Andre relevante oplysninger	

Studienavn: ENGOT-EN6 / RUBY part 1	NCT-nummer: NCT03981796

Formål	Formålet med studiet var at sammenligne effekt og sikkerhed af dostarlimab i kombination med kemoterapi med kemoterapi til førstelinjebehandling af patienter med avanceret eller tilbagevendende livmoderkræft.
Publikationer – titel, forfatter, tidsskrift, år	**Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer**. M. R. Mirza, D. M. Chase, B. M. Slomovitz, R. dePont Christensen, Z. Novak, D. Black, et al. N Engl J Med 2023 Vol. 388 Issue 23 Pages 2145-2158 **Efficacy and safety of dostarlimab in combination with chemotherapy in patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer in a phase 3, randomized, placebo-controlled trial (ENGOT-EN6-NSGO/GOG-3031/RUBY)**. M. A. Powell, D. Cibula, D. M. O'Malley, I. Boere, M. S. Shahin, A. Savarese, et al. Gynecol Oncol 2024 **Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial.** M. A. Powell, L. Bjorge, L. Willmott, Z. Novak, D. Black, L. Gilbert, et al. Ann Oncol 2024 **Population pharmacokinetics and exposure-response relationships of dostarlimab in primary advanced or recurrent endometrial cancer in part 1 of RUBY.** Kuchimanchi M, Jørgensen TL, Hanze E, André T, Jain A, Berton D, Alskär O, Zub O, Oaknin A, Shahin MS, Koliadi A, Pothuri B, Krivak T, Pishchyk M, Segev Y, Backes FJ, Gennigens C, Bouberhan S, Zajic S, Melhem M, Buscema J. Br J Clin Pharmacol. 2024 **Safety of dostarlimab in combination with chemotherapy in patients with primary advanced or recurrent endometrial cancer in a phase III, randomized, placebo-controlled trial (ENGOT-EN6-NSGO/GOG-3031/RUBY).** Auranen A, Powell MA, Sukhin V, Landrum LM, Ronzino G, Buscema J, Bauerschlag D, Lalisang R, Bender D, Gilbert L, Armstrong A, Safra T, Nevadunsky N, Sebastianelli A, Slomovitz B, Ring K, Coleman R, Podzielinski I, Stuckey A, Teneriello M, Gill S, Pothuri B, Willmott L, Sharma S, Dabrowski C, Antony G, Stevens S, Mirza MR, Fleming E. Ther Adv Med Oncol. 2024. **Patient-reported outcomes in the subpopulation of patients with mismatch repair-deficient/microsatellite instability-high primary advanced or recurrent endometrial cancer treated with dostarlimab plus chemotherapy compared with chemotherapy alone in the ENGOT-EN6-NSGO/GOG3031/RUBY trial.** Valabrega G, Powell MA, Hietanen S, Miller EM, Novak Z, Holloway R, Denschlag D, Myers T, Thijs AM, Pennington KP, Gilbert L, Fleming E, Zub O, Landrum LM, Ataseven B, Gogoi R, Podzielinski I, Cloven N, Monk BJ, Sharma S, Herzog TJ, Stuckey A, Pothuri B, Secord AA, Chase D, Vincent V, Meyers O, Garside J, Mirza MR, Black D. Int J Gynecol Cancer. 2025
Studietype og -design	RUBY part 1 er et internationalt, multicenter, randomiseret, dobbeltblindet, placebokontrolleret, fase 3-studie. Inkluderede patienter blev randomiseret 1:1. Patienterne blev stratificeret efter MMR/MSI status, *prior pelvic radioterapi* (yes/no) og sygdom stadie (*recurrent, primary Stage III, eller primary Stage IV*). På baggrund af studieresultater har EMA godkendt dostarlimab i kombination med carboplatin og paclitaxel til førstelinjebehandling af

Studienavn: ENGOT-EN6 / RUBY part 1	NCT-nummer: NCT03981796
	nydiagnosticerede patienter i stadie III/IVA/IVB og af patienter med tilbagevendende kræft i livmoder.
Antal forsøgsdeltagere (N)	n=607 (screenet) n= 494 (randomiseret)
Primære inklusionskriterier	*Female participant is at least 18 years of age.* *Participant has histologically or cytologically proven endometrial cancer with recurrent or advanced disease.* *Participant must have primary Stage III or Stage IV disease or first recurrent endometrial cancer with a low potential for cure by radiation therapy or surgery alone or in combination and meet at least one of the following criteria;* • *Participant has primary Stage IIIA to IIIC1 disease with presence of evaluable or measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version (v).1.1 based on Investigator's assessment. Lesions that are equivocal or can be representative of post-operative change should be biopsied and confirmed for the presence of tumor;* • *Participant has primary Stage IIIC1 disease with carcinosarcoma, clear cell, serous, or mixed histology (containing greater than or equal to [>=] 10 percent carcinosarcoma, clear cell, or serous histology) regardless of presence of evaluable or measurable disease on imaging;* • *Participant has primary Stage IIIC2 or Stage IV disease regardless of the presence of evaluable or measurable disease;* • *Participant has first recurrent disease and is naïve to systemic anticancer therapy;* • *Participant has received prior neo-adjuvant/adjuvant systemic anticancer therapy and had a recurrence or progression of disease (PD) >=6 months after completing treatment (first recurrence only).* *Participant has an ECOG performance status of 0 or 1.* *Participant has adequate organ function.*
Primære eksklusionskriterier	*Participant has received neo-adjuvant/adjuvant systemic anticancer therapy for primary Stage III or IV disease and:* • *has not had a recurrence or PD prior to first dose on the study OR* • *has had a recurrence or PD within 6 months of completing systemic anticancer therapy treatment prior to first dose on the study.* *Participant has had >1 recurrence of endometrial cancer.*

Studienavn: ENGOT-EN6 / RUBY part 1	NCT-nummer: NCT03981796
	Participant has received prior therapy with an anti-programmed cell death protein 1 (anti-PD-1), anti-PD-ligand 1 (anti-PD-L1), or anti-PD-ligand 2 (anti-PD-L2) agent. *Participant has received prior anticancer therapy (chemotherapy, targeted therapies, hormonal therapy, radiotherapy, or immunotherapy) within 21 days or <5 times the half-life of the most recent therapy prior to Study Day 1, whichever is shorter.* *Participant has a concomitant malignancy, or participant has a prior non-endometrial invasive malignancy who has been disease-free for <3 years or who received any active treatment in the last 3 years for that malignancy. Non-melanoma skin cancer is allowed.* *Participant has known uncontrolled central nervous system metastases, carcinomatosis meningitis, or both.* *Participant has not recovered (that is [i.e.], to Grade <=1 or to Baseline) from cytotoxic therapy induced AEs or has received transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF], or recombinant erythropoietin) within 21 days prior to the first dose of study drug.* *Participant has not recovered adequately from AEs or complications from any major surgery prior to starting therapy.* *Participant is currently participating and receiving study treatment or has participated in a study of an investigational agent and received study treatment or used an investigational device within 4 weeks of the first dose of treatment.* *Participant is considered a poor medical risk due to a serious, uncontrolled medical disorder, nonmalignant systemic disease, or active infection requiring systemic therapy.* *Participant has received, or is scheduled to receive, a live vaccine within 30 days before first dose of study treatment, during study treatment, and for up to 180 days after receiving the last dose of study treatment.*
Intervention	Dostarlimab 500 mg administreret i.v. på dag 1 af hver 3-ugers cyklus i løbet af seks serier efterfulgt af dostarlimab 1000 mg administreret i 6-uges cyklus op til 3 år i kombination med Carboplatin AUC 5 mg/mL/min og paclitaxel 175 mg/m^2 administreret i.v. på dag 1 af hver 3-ugers cyklus i løbet af seks serier n = 245 (*all-comers*) n= 53 dMMR/MSI-H
Komparator(er)	Placebo administreret i.v. på dag 1 af hver 3-ugers cyklus i løbet af seks serier efterfulgt af placebo administreret i 6-uges cyklus op til 3 år

Studienavn: ENGOT-EN6 / RUBY part 1	NCT-nummer: NCT03981796
	i kombination med Carboplatin AUC 5 mg/mL/min og paclitaxel 175 mg/m^2 administreret i.v. på dag 1 af hver 3-ugers cyklus i løbet af seks serier n = 249 (*all-comers*) n= 65 dMMR/MSI-H
Opfølgningstid	I denne ansøgning præsenteres resultater fra part 1 af RUBY studiet. Ved data cut-off var en median opfølgningstid på henholdsvis 24,79 mnd i dMMR/MSI-H population og 25,38 mnd i *all-comers* population.
Bruges studiet i den sundhedsøkonomiske model?	NA
Primære, sekundære og eksploratoriske endepunkter	**Primære endepunkter inkluderet i denne ansøgning:** Primært effektmål i studiet var progressionsfri overlevelse (PFS) per RECIST 1.1, vurderet af investigator i henholdsvis alle deltagere og deltagere med dMMR/MSI-H kræft og samlet overlevelse (OS) i alle deltagere. Sikkerhed i form af uønskede hændelser (AEs) var et sekundært effektmål og er inkluderet i ansøgningen. Helbredsrelateret livskvalitet målt ved EQ-5D-5L, QLQ-C30 og Endometrial Cancer Module (QLQ-EN24) var et sekundært effektmål. **Andre endepunkter:** Sekundære effektmål var PFS ved BICR, objektivt responsrate (ORR) baseret på BICR og vurderet af investigator, *duration of response* (DOR) baseret på BICR og vurderet af investigator, og PFS2.
Analysemetode	*The graphical method was used for multiplicity control of multiple hypotheses of primary end points and family-wise one-sided type I error (alpha) was controlled at 0.025. On the basis of the graphical method, an alpha level of 0.02 was initially allocated to hypotheses regarding progression-free survival by investigator assessment and an alpha level of 0.005 was initially allocated to hypotheses regarding overall survival. For progression-free survival, hypotheses were hierarchically tested in the dMMR–MSI-H population and then in the overall population; overall survival was tested in the overall population. If the null hypotheses for progression-free survival were all rejected, the 0.02 alpha level would be recycled to the hypothesis of overall survival, which would be tested at a one-sided alpha level of 0.025; otherwise, overall survival would be tested only at the initially allocated one-sided alpha level of 0.005.* *The sample size was driven by the analysis of the primary end point of progression-free survival as determined by investigator assessment. A planned enrollment of approximately 470 patients in the overall population would include approximately 118 patients with dMMR–MSI-H tumors and would provide a power of approximately 89% to detect a*

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	significant difference in progression-free survival between the treatment groups at a one-sided alpha level of 0.02 among patients with dMMR–MSI-H tumors. The sample size and power calculation corresponded to an assumed hazard ratio for disease progression or death of 0.50, with one interim analysis planned for when approximately 77 events had occurred and the final analysis planned for when 91 events had occurred in the dMMR–MSI-H population. *The 95% confidence intervals of the hazard ratios reported were based on the Cox regression model and were not used for hypothesis testing. All P values reported were based on the stratified log-rank test. Additional details regarding the multiplicity-control strategy, sample-size determination, and statistical analysis are provided in the Supplementary Appendix, protocol, and statistical analysis plan (22).*
Undergruppeanalyser	Der blev udført præspecificerede, eksplorative subgruppeanalyser i dMMR/MSI-H og *all-comers* populationer baseret på alder, etnicitet, region, histologi, sygdomsstadie ved baseline, MMR/MSI-status, *prior pelvic radiotherapy*, og for patienter med ingen sygdom ved baseline.
Andre relevante oplysninger	NA

Appendix B. Resultater vedr. effekt pr. studie

Resultater pr. studie

Tabel 38. Resultater af PFS og OS i NRG-GY018

Resultater af PFS og OS i NRG-GY018 ITT studiepopulation af pMMR patienter ved interimanalysen

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	Studiearm	N	Resultat (CI)	Forskel	95 % CI	*P*-værdi	Forskel	95 % CI	*P*-værdi		
Median progression-free survival	Pembro+SOC	294	13,1 (10,6; 19,5)	NA	NA	NA	HR: 0,57	0,44;0,74	<0,0001	Hazard ratios blev estimeret ved brug af en stratificeret Cox regression model.	(21)
	Placebo+SOC	294	8,7 (8,4; 11,0)								
PFS rate 6 mdr	Pembro+SOC	294	85,8% (80,6; 89,8)	8,7 %-point	NA	NA	NA	NA	NA	Event rater over tid blev estimeret indenfor hver gruppe ved brug af Kaplan-Meier metoden.	(21)
	Placebo+SOC	294	77,1% (70,9; 82,1)								
PFS rate	Pembro+SOC	294	52,0% (43,8; 59,5)	22,5 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	**Studiearm**	**N**	**Resultat (CI)**	**Forskel**	**95 % CI**	***P*-værdi**	**Forskel**	**95 % CI**	***P*-værdi**		
12 mdr	Placebo+SOC	294	**29,5% (22,4; 37,0)**								
PFS rate 24 mdr	Pembro+SOC	294	38,3% (28,8; 47,7)	24,8 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	294	**13,5% (6,9; 22,2)**								
PFS rate 36 mdr	**Pembro+SOC**	294	**NR (NR; NR)**	NA	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	294	**NR (NR; NR)**								
Median overall survival	Pembro+SOC	294	27,96 (21,41; NR)	NA	NA	NA	HR: 0,79	0,53;1,17	0,1157	Hazard ratios blev estimeret ved brug af en stratificeret Cox regression model.	(21)
	Placebo+SOC	294	27,37 (19,52; NR)								
OS rate	Pembro+SOC	294	**94,0% (90,03; 96,43)**	1,2 %-point	NA	NA	NA	NA	NA	Event rater over tid blev estimeret indenfor hver	(21)

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	Studiearm	N	Resultat (CI)	Forskel	95 % CI	*P*-værdi	Forskel	95 % CI	*P*-værdi		
6 mdr	Placebo+SOC	294	92,8% (88,43; 95,53)							gruppe ved brug af Kaplan-Meier metoden.	
OS rate 12 mdr	Pembro+SOC	294	85,9% (79,71; 90,34)	2,6 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	294	83,3% (76,67; 88,17)								
OS rate 24 mdr	Pembro+SOC	294	60,7% (47,52; 71,46)	8,7 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	294	52,0% (38,42; 63,97)								
OS rate 36 mdr	Pembro+SOC	294	49,3% (33,50; 63,26)	NA	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	294	NR (NR; NR)								

Resultater af PFS og OS i NRG-GY018 ITT studiepopulation af pMMR patienter ved den supplerende analyse

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	Studiearm	N	Resultat (CI)	Forskel	95 % CI	*P*-værdi	Forskel	95 % CI	*P*-værdi		
Median progression-free survival	Pembro+SOC	298	11,4 (10,9; 15,1)	NA	NA	NA	HR: 0,74	0,60; 0,91	0,0022	Hazard ratios blev estimeret ved brug af en stratificeret Cox regression model.	(21)
	Placebo+SOC	299	10,6 (8,7; 11,3)								
PFS rate 6 mdr	Pembro+SOC	298	85,5% (80,9; 89,1)	5,6 %-point	NA	NA	NA	NA	NA	Event rater over tid blev estimeret indenfor hver gruppe ved brug af Kaplan-Meier metoden.	(21)
	Placebo+SOC	299	79,9% (74,8; 84,1)								
PFS rate 12 mdr	Pembro+SOC	298	47,7% (41,4; 53,7)	10,9 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	299	36,8% (30,8; 42,9)								
PFS rate 24 mdr	Pembro+SOC	298	34,1% (27,5; 40,8)	12,9 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	299	21,2% (15,0; 28,1)								

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	Studiearm	N	Resultat (CI)	Forskel	95 % CI	*P*-værdi	Forskel	95 % CI	*P*-værdi		
PFS rate 36 mdr	Pembro+SOC	298	29,4% (21,0; 38,3)	NA	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	299	18,5% (4,0; 25,7)								
Median overall survival	Pembro+SOC	298	28,9 (26,8; NR)	NA	NA	NA	HR: 0,80	0,59; 1,08	0,0683	Hazard ratios blev estimeret ved brug af en stratificeret Cox regression model.	(21)
	Placebo+SOC	299	28,7 (24,0; 34,6)								
OS rate 6 mdr	Pembro+SOC	298	94,5% (91,2; 96,6)	1,1 %-point	NA	NA	NA	NA	NA	Event rater over tid blev estimeret indenfor hver gruppe ved brug af Kaplan-Meier metoden.	(21)
	Placebo+SOC	299	93,4% (89,9; 95,7)								
OS rate 12 mdr	Pembro+SOC	298	83,8% (78,7; 87,7)	2,6 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	299	81,2% (75,9; 85,4)								

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	**Studiearm**	**N**	**Resultat (CI)**	**Forskel**	**95 % CI**	***P*-værdi**	**Forskel**	**95 % CI**	***P*-værdi**		
OS rate 24 mdr	Pembro+SOC	298	63,0% (54,5; 70,3)	4,7 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	299	58,3% (50,1; 65,6)								
OS rate 36 mdr	Pembro+SOC	298	49,5% (37,9; 60,1)	14,2 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	299	35,3% (21,6; 49,4)								

Resultater af PFS og OS i NRG-GY018 ITT studiepopulation af dMMR patienter ved interimanalysen

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	**Studiearm**	**N**	**Resultat (CI)**	**Forskel**	**95 % CI**	***P*-værdi**	**Forskel**	**95 % CI**	***P*-værdi**		
Median progression-free survival	Pembro+SOC	110	NR (30,7; NR)	NA	NA	NA	HR: 0,34	0,22;0,53	<0,0001	Hazard ratios blev estimeret ved brug af en stratificeret Cox regression model.	(21)
	Placebo+SOC	112	8,3 (6,5; 12,3)								
PFS rate 6 mdr	Pembro+SOC	110	90,6% (83,3; 94,8)	16,8 %-point	NA	NA	NA	NA	NA	Event rater over tid blev estimeret indenfor hver gruppe ved brug af Kaplan-Meier metoden.	(21)
	Placebo+SOC	112	73,8% (64,1; 81,3)								
PFS rate 12 mdr	Pembro+SOC	110	73,0% (62,0; 81,3)	33,0 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	112	40,0% (29,3; 50,4)								
PFS rate 24 mdr	Pembro+SOC	110	65,2% (52,7; 75,2)	37,8 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	112	27,4% (15,2; 41,1)								

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	**Studiearm**	**N**	**Resultat (CI)**	**Forskel**	**95 % CI**	***P*-værdi**	**Forskel**	**95 % CI**	***P*-værdi**		
PFS rate 36 mdr	Pembro+SOC	110	57,1 (37,5; 72,6)	NA	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	112	NR (NR; NR)								
Median overall survival	Pembro+SOC	110	NR (NR; NR)	NA	NA	NA	HR: 0,55	0,25; 1,19	0,0617	Hazard ratios blev estimeret ved brug af en stratificeret Cox regression model.	(21)
	Placebo+SOC	112	NR (NR; NR)								
OS rate 6 mdr	Pembro+SOC	110	97,2% (91,52; 99,08)	2,9 %-point	NA	NA	NA	NA	NA	Event rater over tid blev estimeret indenfor hver gruppe ved brug af Kaplan-Meier metoden.	(21)
	Placebo+SOC	112	94,3% (87,80; 97,41)								
OS rate 12 mdr	Pembro+SOC	110	91,3% (82,27; 95,88)	6,3 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	112	85,0% (75,38; 91,13)								

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	**Studiearm**	**N**	**Resultat (CI)**	**Forskel**	**95 % CI**	***P*-værdi**	**Forskel**	**95 % CI**	***P*-værdi**		
OS rate 24 mdr	Pembro+SOC	110	85,1% (73,22; 92,03)	12,1 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	112	73,0% (56,44; 84,12)								
OS rate 36 mdr	Pembro+SOC	110	85,1% (73,22; 92,03)	12,1%-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	112	73,0% (56,44; 84,12)								

Resultater af PFS og OS i NRG-GY018 ITT studiepopulation af dMMR patienter ved den supplerende analyse

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	**Studiearm**	**N**	**Resultat (CI)**	**Forskel**	**95 % CI**	***P*-værdi**	**Forskel**	**95 % CI**	***P*-værdi**		
Median progress	Pembro+SOC	110	NR (30,7; NR)	NA	NA	NA	HR: 0,35	0,23; 0,52	<0,0001		(21)

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	Studiearm	N	Resultat (CI)	Forskel	95 % CI	*P*-værdi	Forskel	95 % CI	*P*-værdi		
ion-free survival	Placebo+SOC	112	8,3 (6,5; 12,7)							Hazard ratios blev estimeret ved brug af en stratificeret Cox regression model.	
PFS rate 6 mdr	Pembro+SOC	110	90,8% (83,6; 95,0)	16,1 %-point	NA	NA	NA	NA	NA	Event rater over tid blev estimeret indenfor hver gruppe ved brug af Kaplan-Meier metoden.	(21)
	Placebo+SOC	112	74,7% (65,3; 81,9)								
PFS rate 12 mdr	Pembro+SOC	110	75,2% (65,9; 82,2)	34,2 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	112	41,0% (31,6; 50,3)								
PFS rate 24 mdr	Pembro+SOC	110	64,0% (53,0; 73,2)	32,9 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	112	31,1% (21,7; 40,9)								
PFS rate	Pembro+SOC	110	58,2 (42,7; 70,9)	29,9 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	**Studiearm**	**N**	**Resultat (CI)**	**Forskel**	**95 % CI**	***P*-værdi**	**Forskel**	**95 % CI**	***P*-værdi**		
36 mdr	Placebo+SOC	112	28,3 (18,5; 38,8)								
Median overall survival	Pembro+SOC	110	NR (NR; NR)	NA	NA	NA	HR: 0,57	0,31; 1,04	0,0323	Hazard ratios blev estimeret ved brug af en stratificeret Cox regression model.	(21)
	Placebo+SOC	112	42,7 (42,7; NR)								
OS rate 6 mdr	Pembro+SOC	110	97,3% (91,7; 99,1)	2,9 %-point	NA	NA	NA	NA	NA	Event rater over tid blev estimeret indenfor hver gruppe ved brug af Kaplan-Meier metoden.	(21)
	Placebo+SOC	112	94,4% (88,0; 97,4)								
OS rate 12 mdr	Pembro+SOC	110	91,7% (84,6; 95,6)	6,0 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	112	85,7% (77,4; 91,1)								
OS rate	Pembro+SOC	110	80,7% (70,3; 87,7)	9,8 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	Studiearm	N	Resultat (CI)	Forskel	95 % CI	*P*-værdi	Forskel	95 % CI	*P*-værdi		
24 mdr	Placebo+SOC	112	70,9% (59,8; 79,4)								
OS rate 36 mdr	Pembro+SOC	110	80,7% (70,3; 87,7)	9,8 %-point	NA	NA	NA	NA	NA	Som ovenfor	(21)
	Placebo+SOC	112	70,9% (59,8; 79,4)								

Resultater af PFS og OS i RUBY-I ITT studiepopulation af dMMR/MSI-H patienter ved primary analysis

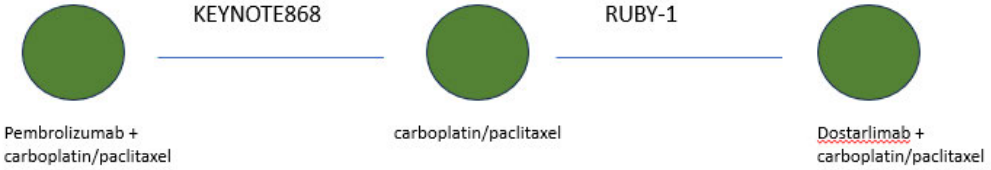
Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	**Studiearm**	**N**	**Resultat (CI)**	**Forskel**	**95 % CI**	***P*-værdi**	**Forskel**	**95 % CI**	***P*-værdi**		
Median progression-free survival	Dostar+SOC	53	NR (11,8; NR)	NA	NA	NA	HR: 0,28	0,162; 0,495	<0,0001	Hazard ratios blev estimeret ved brug af en stratificeret Cox regression model.	(12)
	Placebo+SOC	65	7,7 (5,6; 9,7)								
PFS rate 6 mdr	Dostar+SOC	53	80,2% (66,3; 88,8)	20,5 %-point	NA	NA	NA	NA	NA	Event rater over tid blev estimeret indenfor hver gruppe ved brug af Kaplan-Meier metoden.	(12)
	Placebo+SOC	65	59,7% (46,2; 70,9)								
PFS rate 12 mdr	Dostar+SOC	53	63,5% (48,5; 75,3)	39,1 %-point	NA	NA	NA	NA	NA	Som ovenfor	(12)
	Placebo+SOC	65	24,4% (13,9; 36,4)								
PFS rate 24 mdr	Dostar+SOC	53	63,5% (48,5; 75,3)	47,8 %-point	NA	NA	NA	NA	NA	Som ovenfor	(12)
	Placebo+SOC	65	15,7% (7,2; 27,0)								

Resultater af NRG-GY018			NCT-nummer: NCT03914612								
				Estimeret absolut forskel i effekt			Estimeret relativ forskel i effekt			Beskrivelse af metoder anvendt til estimering	Referencer
Effektmål	**Studiearm**	**N**	**Resultat (CI)**	**Forskel**	**95 % CI**	***P*-værdi**	**Forskel**	**95 % CI**	***P*-værdi**		
Median overall survival	Dostar+SOC	53	**NR (NR; NR)**	NA	NA	NA	HR: 0,30	0,127; 0,699	0,0016	Hazard ratios blev estimeret ved brug af en stratificeret Cox regression model.	(12)
	Placebo+SOC	65	**NR (23,2; NR)**								
OS rate 12 mdr	Dostar+SOC	53	**90,1% (84,6; 95,6)**	10,5 %-point	NA	NA	NA	NA	NA	Event rater over tid blev estimeret indenfor hver gruppe ved brug af Kaplan-Meier metoden.	(12)
	Placebo+SOC	65	**79,6% (67,5; 87,6)**								
OS rate 24 mdr	Dostar+SOC	53	**83,3% (66,8; 92,0)**	24,6 %-point	NA	NA	NA	NA	NA	Som ovenfor	(12)
	Placebo+SOC	65	**58,7% (43,4; 71,2)**								

Appendix C. Komparativ analyse af effekt

For den komparative analyse af pembrolizumab + SoC vs SoC i pMMR-populationen henviser vi til 6.1.4, til Appendix B og til Tabel 11.

Herunder følger en nærmere beskrivelse af netværksmetaanalysen og i Tabel 40 er resultaterne præsenteret. Som beskrevet i Afsnit 7 er netværksmetaanalysen foretaget ud fra følgende netværk, med carboplatin/paclitaxel som fælles komparator.



[redacted]

[redacted]

Tabel 39. Komparativ analyse af studier, der sammenligner pembrolizumab + kemoterapi med dostarlimab + kemoterapi

Effektmål		Absolut forskel i effekt			Relativ forskel i effekt			Metode anvendt til kvantitativ syntese	Er resultat anvendt i den sundheds-økonomiske analyse?
	Studier inkluderet i analysen	Forskel	CI	P-værdi	Forskel	CI	P-værdi		
Samlet overlevelse (OS)	NRG-GY018 RUBY-1	NA	NA	NA	HR: [redacted]	(95% CI: [redacted]	NA	Se beskrivelse ovenfor	Nej
Progressionsfri overlevelse (PFS)	NRG-GY018 RUBY-1	NA	NA	NA	3 mdr: [redacted] 6 mdr: [redacted]	[redacted]	NA	Se beskrivelse ovenfor	Nej

Effektmål		Absolut forskel i effekt			Relativ forskel i effekt			Metode anvendt til kvantitativ syntese	Er resultat anvendt i den sundheds-økonomiske analyse?
	Studier inkluderet i analysen	Forskel	CI	P-værdi	Forskel	CI	P-værdi		
					9 mdr: [redacted]				
					12 mdr: [redacted]				
					18 mdr: [redacted]				
					24 mdr: [redacted]				
					30 mdr: [redacted]				
					36 mdr: [redacted]				
					42 mdr: [redacted]				
					48 mdr: [redacted]				

Appendix D. Ekstrapolering

NA

D.1 Ekstrapolering af [effektmål 1]

D.1.1 Datainput

D.1.2 Model

D.1.3 Proportionale hazarder

D.1.4 Vurdering af statistisk fit (AIC og BIC)

D.1.5 Vurdering af visuel fit

D.1.6 Vurdering af hazard-funktioner

D.1.7 Validering og diskussion af ekstrapolerede kurver

D.1.8 Justering af baggrundsdødelighed

D.1.9 Justering for behandlingsskift/overkrydsning

D.1.10 Aftagende effekt

D.1.11 Kureringspunkt

D.2 Ekstrapolering af [effektmål 2]

Appendix E. Alvorlige uønskede hændelser

Tabel A Participants With Serious Adverse Events Up to 90 Days After Last Dose by Decreasing Frequency of Preferred Term (Incidence ≥1% in One or More Treatment Groups) (APaT Population) (21)

	Pembrolizumab + Chemotherapy		Placebo + Chemotherapy		Pooled Safety Dataset for Pembrolizumab + Chemotherapy		Pembrolizumab Monotherapy Reference Safety Dataset	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants in population	382		377		3,473		7,631	
with one or more adverse events	132	(34.6)	73	(19.4)	1,613	(46.4)	2,742	(35.9)
with no adverse events	250	(65.4)	304	(80.6)	1,860	(53.6)	4,889	(64.1)
Anaemia	16	(4.2)	13	(3.4)	90	(2.6)	65	(0.9)
Febrile neutropenia	11	(2.9)	5	(1.3)	218	(6.3)	8	(0.1)
Urinary tract infection	8	(2.1)	6	(1.6)	33	(1.0)	67	(0.9)
White blood cell count decreased	8	(2.1)	4	(1.1)	2	(0.1)	0	(0.0)
Dyspnoea	7	(1.8)	0	(0.0)	18	(0.5)	91	(1.2)
Hyperglycaemia	7	(1.8)	0	(0.0)	4	(0.1)	12	(0.2)
Neutrophil count decreased	7	(1.8)	7	(1.9)	12	(0.3)	1	(0.0)
Pulmonary embolism	7	(1.8)	8	(2.1)	53	(1.5)	78	(1.0)
Sepsis	7	(1.8)	5	(1.3)	46	(1.3)	56	(0.7)
COVID-19	6	(1.6)	0	(0.0)	7	(0.2)	0	(0.0)
Diarrhoea	6	(1.6)	3	(0.8)	64	(1.8)	70	(0.9)
Embolism	6	(1.6)	1	(0.3)	8	(0.2)	13	(0.2)
Hypokalaemia	6	(1.6)	2	(0.5)	21	(0.6)	9	(0.1)
Acute kidney injury	5	(1.3)	3	(0.8)	61	(1.8)	65	(0.9)
Nausea	5	(1.3)	2	(0.5)	32	(0.9)	30	(0.4)
Platelet count decreased	5	(1.3)	0	(0.0)	21	(0.6)	0	(0.0)
Pleural effusion	5	(1.3)	0	(0.0)	31	(0.9)	88	(1.2)
Pneumonia	5	(1.3)	2	(0.5)	163	(4.7)	272	(3.6)
Pyrexia	5	(1.3)	0	(0.0)	77	(2.2)	79	(1.0)
Seizure	5	(1.3)	1	(0.3)	10	(0.3)	15	(0.2)
Atrial fibrillation	4	(1.0)	3	(0.8)	15	(0.4)	28	(0.4)
Hyponatraemia	4	(1.0)	3	(0.8)	21	(0.6)	43	(0.6)
Hypotension	4	(1.0)	2	(0.5)	12	(0.3)	13	(0.2)
Neutropenia	4	(1.0)	3	(0.8)	50	(1.4)	3	(0.0)
Syncope	4	(1.0)	3	(0.8)	13	(0.4)	22	(0.3)
Dehydration	3	(0.8)	5	(1.3)	23	(0.7)	44	(0.6)
Vomiting	3	(0.8)	4	(1.1)	48	(1.4)	32	(0.4)
Abdominal pain	2	(0.5)	6	(1.6)	9	(0.3)	43	(0.6)
Infusion related reaction	1	(0.3)	4	(1.1)	18	(0.5)	5	(0.1)
Pneumonitis	1	(0.3)	0	(0.0)	61	(1.8)	136	(1.8)
Thrombocytopenia	0	(0.0)	0	(0.0)	44	(1.3)	10	(0.1)

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Serious adverse events up to 90 days of last treatment are included.

For KEYNOTE-868, reporting of unrelated serious adverse events between 30 and 90 days of last dose are not required.

MedDRA preferred terms "Neoplasm Progression", "Malignant Neoplasm Progression" and "Disease Progression" not related to the drug are excluded.

Database cutoff date for KEYNOTE-868: 16 December 2022 for dMMR participants and 06 December 2022 for pMMR participants.

Tabel B [redacted]

Tabel C [redacted]

Table D Definition of AEOSI (19)

AEOSI	Preferred Terms
Adrenal Insufficiency	Addison´s disease Adrenal insufficiency Adrenocortical insufficiency acute Secondary adrenocortical insufficiency
Arthritis	Autoimmune arthritis Immune-mediated arthritis
Cholangitis Sclerosing	Cholangitis sclerosing Immune-mediated cholangitis
Colitis	Autoimmune colitis Colitis Colitis microscopic Enterocolitis Immune-mediated enterocolitis
Encephalitis	Encephalitis Encephalitis autoimmune
Gastritis	Gastritis Gastritis erosive Immune-mediated gastritis
Guillai-Barre Syndrome	Exonal neuropathy Demyelinating polyneuropathy Guillai-Barre Syndrome
Haemolytic Anaemia	Haemolytic Anaemia
Hepatitis	Autoimmune hepatitis Drug-induced liver injury Hepatitis Hepatitis acute Immune-mediated hepatitis
Hyperthyroidism	Hyperthyroidism Grave´s disease
Hypoparathyroidism	Hypoparathyroidism
Hypophysitis	Hypophysitis Hypopituitarism Lymphocytic hypophysitis
Hypothyroidism	Autoimmune hypothyroidism Hypothyroidism Immune-mediated hypothyroidism Myxoedema Primary hypothyroidism
Infusion Reactions	Anaphylactic reaction Anaphylactoid reaction Cytokine release syndrome Drug hypersensitivity Hypersensitivity Infusion related reaction Serum sickness
Myastenic Syndrome	Myasthenia gravis Myasthenic syndrome
Myelitis	Myelitis Myelitis transverse
Myocarditis	Autoimmune myocarditis Myocarditis
Myositis	Autoimmune myositis Dermatomyositis Myopathy Myositis Necrosis myositis Rhabdomyolysis

Nephritis	Acute kidney injury Autoimmune nephritis Glomerulonephritis Glomerulonephritis acute Glomerulonephritis membranous Nephritis Nephrotic syndrome Renal failure Tubulointerstitial nephritis
Optic neuritis	Optic neuritis
Pancreatitis	Autoimmune pancreatitis Pancreatitis Pancreatitis acute
Pneumonitis	Autoimmune lung disease Immune-mediated lung disease Interstitial lung disease Organising pneumonia Pneumonitis
Sarcoidosis	Cutaneous sarcoidosis Pulmonary sarcoidosis Sarcoidosis
Severe Skin Reactions	Dermatitis bullous Dermatitis exfoliative Dermatitis exfoliative generalised Erythema multiforme Exfoliative rash Lichen planus Oral lichen planus Pemphigoid Pemphigus Pruritus Pruritus genital Rash Rash erythematous Rash maculo-papular Rash pruritic Ras pustular Skin necrosis Stevens-Johnson syndrome Toxic skin eruption
Thyroiditis	Autoimmune thyroiditis Immune-mediated thyroiditis Silent thyroiditis Thyroid disorder Thyroiditis Thyroiditis acute
Type 1 Diabetes Mellitus	Diabetic ketoacidosis Type 1 diabetes mellitus
Uveitis	Chorioretinitis Iridocyclitis Iritis Uveitis
Vasculitis	Central nervous system vasculitis Giant cell arteritis Vasculitis

Appendix F. Helbredsrelateret livskvalitet

NA

Appendix G. Probabilistiske følsomhedsanalyser

NA

Tabel 40. Oversigt over parametre i PSA

Inputparameter	Punktestimat	Nedre grænse	Øvre grænse	Sandsynlighedsfordeling
NA				

Appendix H. Litteratursøgninger for den kliniske vurdering

H.1 Effekt og sikkerhed af intervention og komparator(er)

NA

Tabel 41. Bibliografiske databaser inkluderet i litteratursøgningen

Database	Platform/kilde	Relevant periode for søgningen	Dato for gennemført søgning
NA			

Tabel 42. Andre kilder inkluderet i litteratursøgningen

Kilde	Placering/kilde	Søgestrategi	Dato for søgning
NA			

Tabel 43. Konferencemateriale inkluderet i litteratursøgningen

Konference	Kilde til abstracts	Søgestrategi	Søgte ord/udtryk	Dato for søgning
NA				

H.1.1 Søgestrategier

NA

Tabel 44. Søgestrategi for [navn på database]

Nr.	Forespørgsel	Resultater
NA		

H.1.2 Systematisk valg af studier

NA

Tabel 45. Inklusions- og eksklusionskriterier anvendt til vurdering af studier

Klinisk effekt	Inklusionskriterier	Eksklusionskriterier	Ændring, lokal tilpasning
NA			

Tabel 46. Oversigt over studiedesign for studier inkluderet i analyserne

Studie/tid	Formål	Studiedesign	Patient-population	Interven-tion og kompara-tor (prøvestør-relse (n))	Primært effektmål og opfølg-nings-periode	Sekundært effektmål og opfølg-nings-periode
NA						

H.1.3 Ekskluderede fuldtekstreferencer

NA

H.1.4 Kvalitetsvurdering

NA

H.1.5 Ikke-offentliggjorte data

NA

Appendix I. Litteratursøgninger for helbredsrelateret livskvalitet

I.1 Helbredsrelateret livskvalitet

NA

Tabel 47. Bibliografiske databaser inkluderet i litteratursøgningen

Database	Platform	Relevant periode for søgningen	Dato for gennemført søgning
NA			

Tabel 48. Andre kilder inkluderet i litteratursøgningen

Kildenavn	Placering/kilde	Søgestrategi	Dato for søgning
NA			

Tabel 49. Konferencemateriale inkluderet i litteratursøgningen

Konference	Kilde til abstracts	Søgestrategi	Søgte ord/udtryk	Dato for søgning
NA				

I.1.1 Søgestrategier

Tabel 50. Søgestrategi for [navn på database]

Nr.	Forespørgsel	Resultater
NA		

I.1.2 Kvalitetsvurdering og generaliserbarhed af estimater

I.1.3 Ikke-offentliggjorte data

Appendix J. Litteratursøgninger for input til den sundhedsøkonomiske model

J.1 Ekstern litteratur til input i den sundhedsøkonomiske model

NA

J.1.1 Eks. systematisk søgning efter [...]

Tabel 51. Kilder inkluderet i søgningen

Database	Platform/kilde	Relevant periode for søgningen	Dato for gennemført søgning
NA			

J.1.2 Eks. målrettet litteratursøgning efter [estimater]

Tabel 52. Kilder inkluderet i den målrettede litteratursøgning

Kildenavn/ database	Placering/kilde	Søgestrategi	Dato for søgning

Appendix K. Øvrige indikationer godkendt af EMA og vurderet af Medicinrådet

Melanom
KEYTRUDA som monoterapi er indiceret til behandling af voksne og unge i alderen 12 år og derover med avanceret (ikke-resektabelt eller metastatisk) melanom.

KEYTRUDA som monoterapi er indiceret til adjuverende behandling af voksne og unge i alderen 12 år og derover med stadie IIB-, IIC- eller III-melanom, som har fået foretaget komplet resektion. **Vurderet af MR**

Ikke-småcellet lungecancer (NSCLC)
KEYTRUDA, i kombination med platinbaseret kemoterapi som neoadjuverende behandling, og efterfulgt af monoterapi som adjuverende behandling, er indiceret til behandling af voksne med resektabel ikke-småcellet lungecancer med høj risiko for recidiv. **Vurderet af MR**

KEYTRUDA som monoterapi er indiceret til adjuverende behandling af voksne med ikke-småcellet lungecancer med høj risiko for recidiv efter komplet resektion og platinbaseret kemoterapi.

KEYTRUDA som monoterapi er indiceret til førstelinjebehandling af metastatisk ikke-småcellet lungecancer hos voksne, hvis tumorer udtrykker PD-L1 med tumour proportion score (TPS) ≥ 50% uden EGFR- eller ALK-positive mutationer i tumor. **Vurderet af MR**

KEYTRUDA, i kombination med pemetrexed og platinbaseret kemoterapi, er indiceret til førstelinjebehandling af metastatisk ikke-planocellulær ikke-småcellet lungecancer hos voksne uden EGFR- eller ALK-positive mutationer i tumorer. **Vurderet af MR**

KEYTRUDA, i kombination med carboplatin og enten paclitaxel eller nab-paclitaxel, er indiceret til førstelinjebehandling af metastatisk planocellulær ikke-småcellet lungecancer hos voksne. **Vurderet af MR**

KEYTRUDA som monoterapi er indiceret til behandling af lokalt avanceret eller metastatisk ikke-småcellet lungecancer hos voksne efter tidligere behandling med minimum én kemoterapi, og hvis tumorer udtrykker PD-L1 med TPS ≥ 1%. Patienter med EGFR- eller ALK-positive mutationer i tumor bør også have været i targeteret behandling inden behandling med KEYTRUDA.

Klassisk Hodgkins lymfom (cHL)

KEYTRUDA som monoterapi er indiceret til behandling af recidiverende eller refraktært klassisk Hodgkins lymfom hos voksne og pædiatriske patienter i alderen 3 år og derover, som har oplevet svigt af autolog stamcelletransplantation (ASCT), eller har oplevet svigt efter at have fået mindst 2 forudgående behandlinger, når ASCT ikke er en behandlingsmulighed.

Urotelialt karcinom
KEYTRUDA, i kombination med enfortumab vedotin, er indiceret til førstelinjebehandling af ikke-resektabelt eller metastatisk urotelialt karcinom hos voksne. **Vurderet af MR**

KEYTRUDA som monoterapi er indiceret til behandling af lokalt avanceret eller metastatisk urotelialt karcinom hos voksne, som tidligere har fået platinbaseret kemoterapi. **Vurderet af MR**

KEYTRUDA som monoterapi er indiceret til behandling af lokalt avanceret eller metastatisk urotelialt karcinom hos voksne, som er uegnede til cisplatinbaseret kemoterapi, og hvis tumorer udtrykker PD-L1 med en kombineret positiv score (CPS) ≥ 10. **Vurderet af MR**

Planocellulært hoved-hals karcinom (HNSCC)
KEYTRUDA som monoterapi eller i kombination med platinbaseret kemoterapi og 5-fluorouracil (5-FU) er indiceret til førstelinjebehandling af metastatisk eller ikke-resektabelt recidiverende planocellulært hoved-hals karcinom hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 1. **Vurderet af MR**

KEYTRUDA som monoterapi er indiceret til behandling af recidiverende eller metastatisk planocellulært hoved-hals karcinom hos voksne, hvis tumorer udtrykker PD-L1 med TPS ≥ 50% og med sygdomsprogression under eller efter platinbaseret kemoterapi. **Vurderet af MR**

Renalcellekarcinom (RCC)
KEYTRUDA, i kombination med axitinib, er indiceret til førstelinjebehandling af avanceret renalcellekarcinom hos voksne. **Vurderet af MR**

KEYTRUDA, i kombination med lenvatinib, er indiceret til førstelinjebehandling af avanceret renalcellekarcinom hos voksne. **Vurderet af MR**

KEYTRUDA som monoterapi er indiceret til adjuverende behandling af voksne med renalcellekarcinom med øget risiko for recidiv efter nefrektomi, eller efter nefrektomi og resektion af metastatiske læsioner. **Vurderet af MR**

Cancertyper med høj mikrosatellitinstabilitet (MSI-H) eller mismatch repair-defekt (dMMR)
Kolorektal cancer (CRC)
KEYTRUDA som monoterapi er indiceret til voksne med kolorektal cancer med MSI-H eller dMMR i følgende settings:
- førstelinjebehandling af metastatisk kolorektal cancer **Vurderet af MR**

- behandling af ikke-resektabel eller metastatisk kolorektal cancer efter tidligere fluoropyrimidinbaseret kombinationsbehandling.

Ikke-kolorektal cancer
KEYTRUDA som monoterapi er indiceret til behandling af følgende tumorer med MSI-H eller dMMR hos voksne med:
- avanceret eller recidiverende endometriecancer med sygdomsprogression under eller efter tidligere behandling med platinbaseret terapi i enhver setting, og som ikke er egnet til kurativ operation eller strålebehandling
- ikke-resektabel eller metastatisk ventrikelkræft, tyndtarmskræft eller galdevejskræft med sygdomsprogression under eller efter mindst en forudgående behandling.

Esophagus karcinom
KEYTRUDA, i kombination med platin- og fluoropyrimidinbaseret kemoterapi, er indiceret til førstelinjebehandling af lokalt avanceret ikke-resektabelt eller metastatisk karcinom i esophagus eller HER-2 negativ adenokarcinom i den gastroesophageale overgang, hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 10. **Vurderet af MR**

Triple-negativ brystkræft (TNBC)
KEYTRUDA, i kombination med kemoterapi som neoadjuverende behandling, og efterfulgt af monoterapi som post-operativ adjuverende behandling, er indiceret til behandling af voksne med lokalt avanceret eller tidlig triple-negativ brystkræft med høj risiko for recidiv. **Vurderet af MR**

KEYTRUDA, i kombination med kemoterapi, er indiceret til behandling af lokalt recidiverende ikkeresektabel eller metastatisk triple-negativ brystkræft hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 10 og som ikke har fået forudgående kemoterapi for metastatisk sygdom. **Vurderet af MR**

Endometriecancer (EC)
KEYTRUDA, i kombination med lenvatinib, er indiceret til behandling af avanceret eller recidiverende endometriecancer hos voksne med sygdomsprogression under eller efter tidligere behandling med platinbaseret terapi i enhver setting, og som ikke er egnet til kurativ operation eller strålebehandling. **Vurderet af MR**

Cervixcancer
KEYTRUDA, i kombination med kemostrålebehandling (udvendig strålebehandling efterfulgt af brachyterapi), er indiceret til behandling af FIGO 2014 stadie III - IVA lokal avanceret cervixcancer hos voksne, som ikke har modtaget forudgående definitiv behandling. **Vurderet af MR**

KEYTRUDA, i kombination med kemoterapi med eller uden bevacizumab, er indiceret til behandling af persisterende, recidiverende eller metastatisk cervixcancer hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 1. **Vurderet af MR**

Adenokarcinom i ventrikel eller den gastroesophageale overgang (GEJ)

KEYTRUDA, i kombination med trastuzumab, fluoropyrimidin- og platinbaseret kemoterapi, er indiceret til førstelinjebehandling af lokalt avanceret ikke-resektabelt eller metastatisk HER2-positiv adenokarcinom i ventrikel eller den gastroesophageale overgang hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 1. **Vurderet af MR**

KEYTRUDA, i kombination med fluoropyrimidin- og platinbaseret kemoterapi, er indiceret til førstelinjebehandling af lokalt avanceret ikke-resektabelt eller metastatisk HER2-negativ adenokarcinom i ventrikel eller den gastroesophageale overgang hos voksne, hvis tumorer udtrykker PD-L1 med CPS ≥ 1. **Vurderet af MR**

Galdevejskræft (Biliary Tract Carcinoma (BTC))
KEYTRUDA, i kombination med gemcitabin og cisplatin, er indiceret til førstelinje-behandling af lokalt avanceret ikke-resektabel eller metastatisk galdevejskræft hos voksne. **Under vurdering af MR**

Appendix L. Uønskede hændelser hos patienter behandlet med pembrolizumab + kemoterapi på tværs af studier

		Combination Therapy (N=6093)	
		All AEs % (n)	Gr 3-5 AEs n
Infections and infestations			
Common	Pneumonia	6.6% (405)	223
Blood and lymphatic system disorders			
Very common	Anaemia	53.3% (3248)	1129
Very common	Neutropenia	24.0% (1462)	885
Very common	Thrombocytopenia	13.2% (804)	241
Common	Febrile Neutropenia	5.1% (310)	299
Common	Leukopenia	9.6% (584)	234
Common	Lymphopenia	3.3% (200)	91
Uncommon	Haemolytic Anaemia[a]	0.1% (8)	7
Uncommon	Eosinophilia	0.7% (45)	4
Rare	Immune Thrombocytopenia	0.05% (3)	2
Immune system disorders			
Common	Infusion Reactions[b]	7.1% (435)	77
Rare	Sarcoidosis	0.03% (2)	0
Endocrine disorders			
Very common	Hypothyroidism[c]	13.7% (834)	18
Common	Adrenal Insufficiency[d]	1.1% (66)	26
Common	Hyperthyroidism[e]	5.8% (355)	8
Common	Thyroiditis[f]	1.2% (72)	7
Uncommon	Hypophysitis[g]	0.7% (42)	23
Rare	Hypoparathyroidism	0.03% (2)	0
Metabolism and nutrition disorders			
Very common	Hypokalaemia	12.3% (747)	222
Very common	Decreased Appetite	26.7% (1629)	119
Common	Hyponatraemia	8.5% (520)	188
Common	Hypocalcaemia	4.7% (289)	43
Uncommon	Type 1 Diabetes Mellitus[h]	0.3% (20)	19
Psychiatric disorders			
Very common	Insomnia	10.7% (654)	9

Nervous system disorders			
Very common	Neuropathy Peripheral	14.1% (861)	57
Very common	Headache	14.0% (852)	19
Very common	Dizziness	10.0% (612)	15
Common	Dysgeusia	8.5% (516)	3
Common	Lethargy	1.0% (61)	2
Uncommon	Encephalitis[i]	0.1% (9)	9
Uncommon	Epilepsy	0.1% (7)	3
Rare	Myasthenic Syndrome[j]	0.08% (5)	5
Rare	Guillain-Barre Syndrome[k]	0.07% (4)	4
Rare	Optic Neuritis	0.02% (1)	1
Rare	Meningitis (Aseptic)	0.02% (1)	1
Eye disorders			
Common	Dry Eye	3.0% (180)	1
Uncommon	Uveitis[l]	0.2% (10)	0
Cardiac disorders			
Common	Cardiac Arrhythmia (Including Atrial Fibrillation)[m]	3.9% (236)	56
Uncommon	Myocarditis[n]	0.2% (11)	9
Uncommon	Pericardial Effusion	0.4% (24)	8
Uncommon	Pericarditis	0.1% (7)	2
Vascular disorders			
Common	Hypertension	6.9% (419)	175
Uncommon	Vasculitis[o]	0.5% (33)	5
Respiratory, thoracic and mediastinal disorders			
Very common	Dyspnoea	11.7% (710)	77
Very common	Cough	15.0% (916)	5
Common	Pneumonitis[p]	3.8% (232)	86
Gastrointestinal disorders			
Very common	Diarrhoea	35.6% (2168)	240
Very common	Nausea	52.4% (3190)	184
Very common	Vomiting	27.9% (1699)	184
Very common	Abdominal Pain[q]	19.1% (1161)	76
Very common	Constipation	32.2% (1964)	22
Common	Colitis[r]	2.7% (162)	76
Common	Gastritis[s]	2.1% (126)	9
Common	Dry Mouth	4.4% (267)	1
Uncommon	Pancreatitis[t]	0.4% (25)	19
Uncommon	Gastrointestinal Ulceration[u]	0.4% (24)	4
Rare	Pancreatic Exocrine Insufficiency	(0)	0
Rare	Small Intestinal Perforation	0.03% (2)	2
Rare	Coeliac Disease	(0)	0
Hepatobiliary disorders			
Common	Hepatitis[v]	1.1% (65)	47
Rare	Cholangitis Sclerosing[w]	0.03% (2)	2
Skin and subcutaneous tissue disorders			
Very common	Alopecia	23.6% (1438)	6
Very common	Pruritus[x]	14.0% (851)	6
Very common	Rash[y]	20.4% (1245)	4
Common	Severe Skin Reactions[z]	2.5% (153)	129
Common	Dermatitis	1.5% (93)	4
Common	Erythema	3.3% (199)	3
Common	Dry Skin	5.2% (314)	2
Common	Dermatitis Acneiform	2.0% (119)	2
Common	Eczema	1.2% (74)	1
Uncommon	Psoriasis	0.6% (37)	5
Uncommon	Lichenoid Keratosis[aa]	0.1% (8)	1
Uncommon	Vitiligo[bb]	0.5% (33)	0
Uncommon	Papule	0.2% (10)	0
Rare	Stevens-Johnson Syndrome	0.03% (2)	2
Rare	Erythema Nodosum	0.07% (4)	0

Rare	Hair Colour Changes	0.02% (1)	0
Musculoskeletal and connective tissue disorders			
Very common	Musculoskeletal Pain[cc]	13.2% (807)	41
Very common	Arthralgia	16.0% (973)	38
Common	Myositis[dd]	9.1% (556)	23
Common	Pain In Extremity	7.2% (441)	12
Common	Arthritis[ee]	1.6% (95)	9
Uncommon	Tenosynovitis[ff]	0.3% (20)	1
Rare	Sjogren's Syndrome	0.02% (1)	0
Renal and urinary disorders			
Common	Acute Kidney Injury	3.2% (194)	100
Uncommon	Nephritis[gg]	0.7% (40)	22
Uncommon	Cystitis Noninfective	0.2% (14)	0
General disorders and administration site conditions			
Very common	Fatigue	35.1% (2141)	256
Very common	Asthenia	17.7% (1077)	164
Very common	Pyrexia	17.6% (1074)	48
Very common	Oedema[hh]	13.2% (804)	24
Common	Influenza Like Illness	2.5% (155)	2
Common	Chills	3.0% (181)	0
Investigations			
Very common	Alanine Aminotransferase Increased	17.4% (1063)	177
Very common	Aspartate Aminotransferase Increased	17.0% (1038)	149
Very common	Blood Creatinine Increased	10.2% (623)	32
Common	Blood Bilirubin Increased	4.9% (296)	50
Common	Blood Alkaline Phosphatase Increased	6.8% (417)	44
Common	Hypercalcaemia	1.7% (106)	21
Uncommon	Amylase Increased	0.7% (40)	10

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