Medicinrådet

Bilag til Medicinrådets anbefaling vedr. dostarlimab i kombination med carboplatin og paclitaxel til behandling af avanceret eller tilbagevendende dMMR/MSI-H kræft i livmoderslimhinden

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. dostarlimab i kombination med carboplatin og paclitaxel
2. Ansøgers endelige ansøgning vedr. dostarlimab i kombination med carboplatin og paclitaxel

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03.07.2024
CAF/MGK

Forhandlingsnotat

Dato for behandling i Medicinrådet	28.08.2024
Leverandør	GlaxoSmithKline (GSK)
Lægemiddel	Jemperli (dostarlimab)
Ansøgt indikation	Til behandling af patienter med dMMR/MSI-H avanceret eller tilbagevendende endometriekræft, som er kandidater til systemisk behandling.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Jemperli (dostarlimab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Jemperli	500 mg	1 stk.	42.427,75	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.
[redacted]

Aftaleforhold

Amgros har en aftale med leverandøren som gælder til den 30.09.2026.

Konkurrencesituationen

Der er på nuværende tidspunkt ingen direkte konkurrence på området. I

[redacted]

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Paknings-størrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Jemperli	500 mg	1 stk.	500 mg IC hver 3. uge i 6 serier og 1000 mg IV hver 6. uge herefter	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

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

Konklusion

[redacted]

Application for the assessment of dostarlimab in combination with carboplatin and paclitaxel for treatment of adult patients with advanced or recurrent mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer

Contact information

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

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Tables and Figures

Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AUC	Area under the concentration–time curve
BICR	Blinded Independent Central Review
BMI	Body mass index
BSA	Body surface area
CEA	Cost effectiveness analysis
CI	Confidence interval
CP	Carboplatin-paclitaxel
CR	Complete response
CTCAE v4.03	Common Terminology Criteria for Adverse Events version 4.03
CUA	Cost-Utility Analysis
D	Death from any course
DGCG	Danish Gynaecological Cancer Group
DMC	Danish Medicines Council
dMMR	Mismatch repair deficient
DOR	Duration of response
DSU	Decision Support Unit
EC	Endometrial cancer
ECG	Electrocardiogram
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
HSUV	Health state utility value
HTA	Health technology assessment
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
KM	Kaplan Meier
MAIC	Matching adjusted indirect comparison
MMR	Mismatch repair
MMRp	Mismatch repair proficient
MSI-H	Microsatellite instability high
NICE	The National Institute for Health and Care Excellence
ORR	Objective response rate
OS	Overall survival

OWSA	One-way sensitivity analysis
PD	Progressed Disease
PD-1	Programmed cell death receptor-1
PD-L1	Programmed cell death ligand-1
PFD	Progression-free disease
PFS	Progression-free survival
PK	Pharmacokinetic
PLD	Patient-level data
PR	Partial response
PRO	Patient-reported outcomes
PSM	Partitioned survival model
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
SD	Stable disease
TEAE	Treatment-emergent adverse event
TTD	Time to discontinuation
US	United States
W	Weeks

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Jemperli
Generic name	Dostarlimab
Therapeutic indication as defined by EMA	JEMPERLI is indicated in combination with carboplatin and paclitaxel (CP) 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 (1).
Marketing authorization holder in Denmark	GSK Denmark Delta Park 37, 2665 Vallensbæk Strand
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
Date of EC approval	7th December 2023
Has the pharmaceutical 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 as monotherapy for the treatment of adult patients with recurrent or advanced dMMR/MSI-H endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen (1).
Other indications that have been evaluated by the DMC (yes/no)	Yes
Dispensing group	BEGR/NBS

Overview of the pharmaceutical	
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	
Therapeutic indication relevant for the assessment	Dostarlimab is indicated in combination with carboplatin and paclitaxel for the treatment of adult patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer and who are candidates for systemic therapy (1).
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 4 cycles, then 1000mg (2 vials) Q6W until disease progression
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
Prognosis with current treatment (comparator)	If the disease 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.
Type of evidence for the clinical evaluation	Head-to-head study
Most important efficacy endpoints (Difference/gain compared to comparator)	Patients in the dostarlimab plus CP group had a statistically significant 72% reduction in risk of progression or death compared with the placebo plus CP group (HR: 0.28; 95% CI: 0.16, 0.50; p<0.001) Patients in the dostarlimab plus CP group had a 70% reduction in risk of death compared with the placebo plus CP group (HR 0.30; 95% CI: 0.13, 0.70; nominal p=0.0016
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 each approximately 10 percentage points higher in the

Summary	
	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 [redacted] [redacted] Health economic model: Better than comparator
Type of economic analysis that is submitted	Cost-utility analysis Partitioned survival model
Data sources used to model the clinical effects	Ruby trial, a phase III RSC (NCT03981796)
Data sources used to model the health-related quality of life	Ruby trial, a phase III RSC (NCT03981796)
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	810,304 DKK
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	Top five parameters with the largest overall impact: • Cost per unit (DKK) dostarlimab plus CP • Time horizon • Dostarlimab+CP completion rate per cycle (cycle 16) • OS HR • Total cost for average total treatment duration: Dostarlimab
Number of eligible patients in Denmark	Incidence: 30 new patients per year Prevalence: N/A
Budget impact (in year 5)	22.06 million

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) (2). 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 (3).

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 (2) (5) (6). 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 (7). In Denmark, approx. 100 patients are newly diagnosed with advanced endometrial cancer (8) and approx. 30 patients with relapsing endometrial cancer every year (8).

3.1.2 MMR/MSI Status

The Mismatch repair (MMR) system is a cellular system that, among other things, repairs errors in DNA strands (9). An inherited or somatic mutation in one of the genes MLH1, MSH2, MSH6 or PMS2 can cause dMMR. In tissues with dMMR, mutations accumulate. This occurs particularly in the so-called microsatellite regions of DNA, whereby dMMR can often be identified by a high degree of instability in these DNA regions (MSI-H/Microsatelite Instability-High) (9). Functional defects in the MMR system in tumour tissue

cause an accumulation of so-called mutation-associated neoantigens that can be recognized by the immune system (10). Neoantigens are tumour-specific and thus also patient-specific. Thereby, an active immune response plays an important role in fighting dMMR/MSI-H tumours, providing a rationale for immunotherapy for patients with these tumours. dMMR/MSI-H is most often caused by somatic changes but can also be hereditary (Lynch syndrome) (11).

According to the literature, approximately 22-30% of endometrial cancer cases are dMMR/MSI-H, regardless of disease stage (12) (13). However, the scientific committee estimates that the proportion is somewhat lower in patients with advanced or recurrent endometrial cancer (14). No studies elucidate this.

3.1.3 Impact on 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 (15). 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 (15).

Fear of cancer recurrence (FCR) is also a widely reported issue that carries significant burden and affects the QoL of patients (16). 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 (17). This highlights the importance of effective treatment that reduce the symptom burden and risk of recurrence of endometrial cancer (16).

3.2 Patient population

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

Around 800 women are diagnosed with uterine cancer every year, with more than 90% being cancer of the lining of the uterus (endometrial cancer) (8) (18). The disease typically affects older women (median age 63 years) (19), and almost 11,000 patients in Denmark are alive after being diagnosed (18).

Endometrial cancer is diagnosed early in approximately 80% of cases due to obvious symptoms (20). 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 (20).

Some patients will experience relapse of the disease within a few years after completing primary treatment. This is characterized as incurable endometrial cancer with a median survival of around 12 months (21). In Denmark the incidence of patients with newly diagnosed advanced endometrial cancer is 100 patients per year (8) and furthermore 30 patients with relapsing endometrial cancer (8), of these 22-30% are dMMR/MSI-H (12) (13). Based on these numbers approximately 30 new patients per year are expected to be candidates for treatment with dostarlimab in combination with paclitaxel and carboplatin (5).

It is unknown to what extent MMR/MSI status affects the patient's prognosis (22). However, there are a number of factors of important prognostic significance. These include histology (endometrioid/serous or clear-cell adenocarcinoma or carcinosarcoma), molecular biological factors (especially POLE and p53) and hormone receptor positivity (11) (23).

In Table 1 the incidence and prevalence of endometrial cancer is presented. The subgroup of the population relevant to this application is the dMMR/MSI-H population. There is no official data on the incidence and prevalence of the dMMR/MSI-H populations, however the estimated numbers in Table 2 are confirmed by a clinical expert.

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[a]		10 954	11 080	11 240	11 365	11 481
				1-year prevalence	**3-year prevalence**	**5-year prevalence**
Global prevalence[b,c]	N			343.524	929.672	1.415.213
	Rate per 100,000			8.9	24,1	36,6

[a] Source: Adapted from Association of Nordic Cancer Registries (NORDCAN data 2023) (18)
[b] Source: Adapted from Global Cancer Observatory (GLOBOCAN data 2020) (24)
[c] Global estimates were based on 185 countries across the world.

Table 2: Estimated number of patients eligible for treatment, based on 2 years treatment

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

Source: Clinical expert

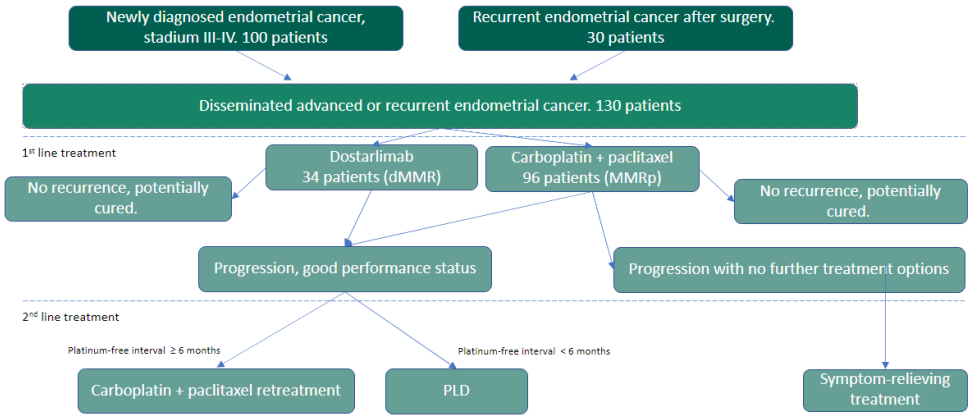
3.3 Current treatment options

The treatment of endometrial cancer is described in clinical guidelines from the Danish Gynaecological Cancer Group (DGCG) (2). Most patients with early-stage endometrial cancer are treated with curative surgery (8) (15). The treatment algorithm hereafter for primary advanced or recurrent endometrial cancer is illustrated in

Figure 1 (11).

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, depending on the MMR/MSI status (2). 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/MSI status, in combination with carboplatin and paclitaxel. Until then the standard treatment choice for patients with primary disseminated endometrial cancer was carboplatin plus paclitaxel (2). According to clinical expert patients with dMMR/MSI-H EC in first line are already being treated with dostarlimab plus CP for up to two years based on individual application to the regional drug committees.

Figure 1: Overview of treatment algorithm for patients with primary advanced or recurrent endometrial cancer



Source: Created by GSK based on DMC recommendation of dostarlimab 2L (11) and DGCG updated guidelines (2)

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 (25). 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 (12).

Overview of intervention	
Therapeutic indication relevant for the assessment	Treatment of adult patients with advanced or recurrent dMMR/ MSI-H endometrial cancer in combination with paclitaxel and carboplatin (1)
Method of administration	IV infusion over 30 minutes
Dosing	500 mg (1 vial) Q3W for 6 cycles, then 1000mg (2 vials) Q6W
Dosing in the health economic model (including relative dose intensity)	500 mg (1 vial) Q3W for 6 cycles, then 1000mg (2 vials) Q6W

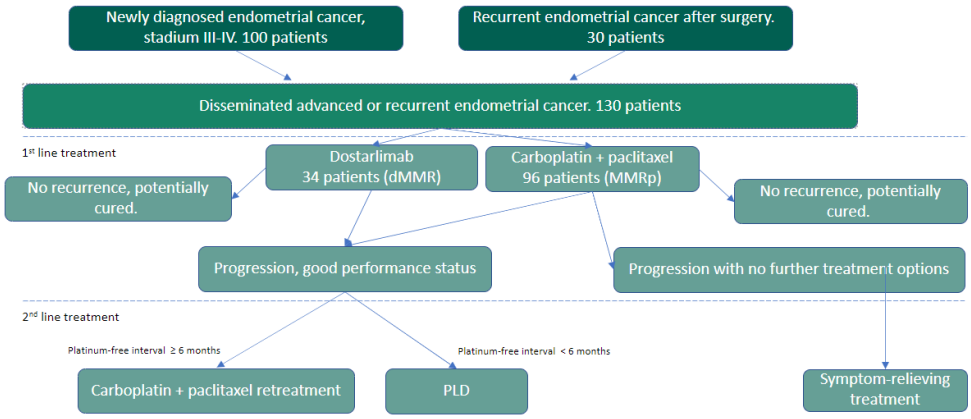
Overview of intervention	
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Up to 3 years or until disease progression
Necessary monitoring, both during administration and during the treatment period	No
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	dMMR or MSI-H test is needed. These tests are already standard of care in Danish clinical practice
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 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 dMMR/MSI-H EC in the 1st line setting. This is already reflected in the newly updated clinical guideline from DGCG. Dostarlimab is already approved by the DMC in the 2nd line setting (

Figure 1). Introducing dostarlimab in 1st line treatment will over time replace the current use in 2nd line.

Figure 2: Overview of suggested treatment algorithm for patients with primary advanced or recurrent endometrial cancer



Source: Created by GSK based on DMC recommendation of dostarlimab 2L (11) and DGCG updated guidelines (2)

The biomarker testing of dMMR/MSI-H is being performed at the time of diagnosis in Danish clinical practice (2).

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 (2). Prior combinations evaluated in the advanced/recurrent endometrial cancer population include docetaxel + carboplatin, doxorubicin + cisplatin, and doxorubicin + cisplatin + paclitaxel (7) (9) (10) (26).

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 (27) (28). 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 (27). Response rates to carboplatin + paclitaxel range from 50% to 60% in clinical studies of patients with primary advanced/first recurrent endometrial cancer (27) (28) (29).

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 (14).

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. Therefore, since the change in DGCG clinical guidelines were made based on the data presented in this application, the comparator presented will be carboplatin + paclitaxel in combination (2) (30).

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).
Dosing in the health economic model (including relative dose intensity)	N/A
Should the pharmaceutical 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

Overview of comparator	
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.
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 is also the current standard of care in 1st line endometrial cancer.

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), dMMR/MSI-H population PFS rate at 24 months	Median duration of follow-up: 24.8 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 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), dMMR/MSI-H population OS rate at 24 months	Median duration of follow-up: 24.8 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)

3.7.1.1 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 (31).

In the DMC assessment of dostarlimab in the 2nd line treatment of 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 (11).

4. Health economic analysis

Treatment with Dostarlimab plus CP is considered to have added benefit compared to the current standard of care treatment with carboplatin and paclitaxel. Therefore, a cost-utility analysis (CUA) was performed in excel. This is in line with the methods guide from the Danish Medicines Council (32).

4.1 Model structure

A partitioned survival model (PSM) was developed to model costs and health outcomes for patients receiving dostarlimab plus CP relative to placebo plus CP. The model was evaluated for a lifetime time horizon by means of a cost-utility analysis. The primary outcome of the model is the incremental cost-effectiveness ratio (ICER).

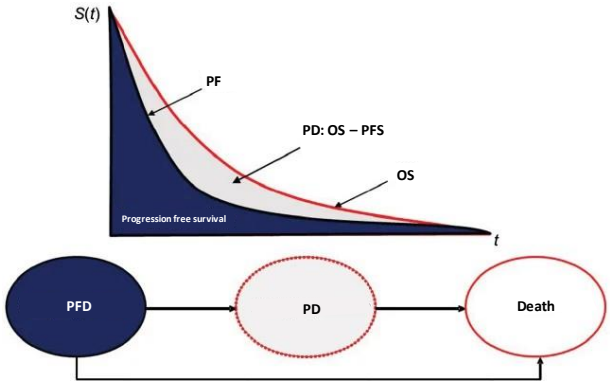
A clear separation of progression free survival (PFS) Kaplan Meier (KM) curves was seen when dostarlimab plus CP was compared to CP. Thus, the cost-effectiveness was evaluated using a PSM. Such a structure is widely used within oncology by various authorities worldwide and is well understood by clinicians. In a review performed by NICE in 2017, it was found that 73% of the files reviewed by NICE used a PSM (33).

The model included three *mutually exclusive* health conditions, namely:

1. Progression-free disease (PFD)
2. Progressed disease (PD)
3. Death, from any cause (D)

The selected health conditions are consistent with the clinical endpoints evaluated in the RUBY study, including the primary endpoints of PFS and OS. To estimate the proportion of patients who received or had already stopped treatment during the PFD period, the curve for PFS also included the curve for the time to discontinuation (TTD) of treatment. Figure 3 shows a schematic representation of the PSM.

Figure 3: Schematic representation of the PSM



To estimate the number of patients occupying the three health states, parametric survival curves and flexible curves were fitted to the PFS and OS data from the RUBY trial. The best fitting and clinically appropriate curves were extrapolated beyond the duration of the trial over a lifetime time horizon. PFD state membership was estimated from the extrapolated PFS KM curve, the state membership of the dead state was estimated using the extrapolated OS KM curve (Death=1-OS), and finally the PD state membership was estimated to be the difference between the OS and PFS curves (PD=OS-PFS).

4.2 Model features

Table 4 presents a summary of the model features.

Table 4: Features of the economic model

Model features	Description	Justification
Patient population	Adult patients were included in the model from the time they were diagnosed with dMMR/MSI-H primary advanced or relapsed EC and eligible for systemic therapy	No deviation from section 3.2 and in line with the patients enrolled in RUBY.

Model features	Description	Justification
Perspective	Limited societal perspective	According to DMC methods guide
Time horizon	Lifetime (36 years)	Patients were included at an age of 64, informed by median age in RUBY, up to a maximum of 99 years.
Cycle length	Weekly cycle length, defined as 7 days.	In line with the RUBY time-to-event survival analysis.
Half-cycle correction	No	Considering the short cycle length, no half cycle correction was applied
Discount rate	3.5 %	According to DMC methods guide
Intervention	Dostarlimab plus CP	
Comparator(s)	CP	According to national treatment guideline. Validated by Danish clinical expert
Outcomes	OS, PFS	The PFS and OS extrapolations are based on the RUBY trial for both dostarlimab plus CP and CP

5. Overview of literature

In this section, the literature used in the present application is presented. Since the RUBY trial is a head-to-head study comparing dostarlimab with carboplatin and paclitaxel 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. Main characteristics of studies included

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	Used in comparison of
Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. Mansoor R. Mirza et al. N Engl J Med 2023; 388:2145-2158 DOI: 10.1056/NEJMoa2216334 (30)	RUBY	NCT03981796	Start: 18/07/19 Completion: 26/11/26 (ESTIMATED) Data cut-off 28/09/22	Dostarlimab plus CP vs. placebo plus CP For ITT and dMMR/MSI-H population
Dostarlimab for primary advanced or recurrent (A/R) endometrial cancer (EC): Outcomes by blinded independent central review (BICR) of the RUBY trial. Powell et al. suppl 16, 2023, Journal of Clinical Oncology, Årg. 41, s. 5503-55-03. https://doi.org/10.1200/JCO.2023.41.16_suppl.5503 (34)	RUBY	NCT03981796	Start: 18/07/19 Completion: 26/11/26 (ESTIMATED) Data cut-off 28/09/22	Dostarlimab plus CP vs. placebo plus CP For ITT and dMMR/MSI-H population

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

The Global SLR for dostarlimab plus chemotherapy in endometrial cancer is designed to identify disutilities as part of the HRQoL search, based on search terms found in Table 41 in Appendix I. Literature searches for health-related quality of life

The HRQoL SLR only identified one study (Hildebrandt et al. 2014), which did not include AE disutilities. In the absence of relevant disutility data, a pragmatic approach was used to parameterise the adverse event disutilities, by performing a targeted literature searches to source the disutility values. The search first focused on values accepted in previous NICE submissions specific to EC, then where values could not be identified, other gynaecological cancers were used to inform the inputs. As such the model uses sources that have previously been accepted by NICE. Two NICE submissions included

disutilities which were relevant to the list of adverse events: TA779 (dostarlimab for previously treated advanced or recurrent EC) and TA673 (niraparib for ovarian, fallopian tube and peritoneal cancer). Where no disutility value was found in either of these submissions, the publications referenced in these documents were used (e.g., studies for renal cell carcinoma and non-small cell lung cancer were referenced in TA779, so were used in the model). Given the absence of relevant disutility evidence identified in the HRQoL SLR, a pragmatic approach to source disutility values was followed, using values accepted in previous HTA. Nevertheless, it is important to note that AEs disutilities are not a key driver in the model, therefore, the choice of disutility value has little to no bearing on the overall cost-effectiveness.

The literature included in the model to inform the HRQoL are listed in Table 6.

Table 6: Relevant literature included for (documentation of) health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. Mansoor R. Mirza et al. N Engl J Med 2023; 388:2145-2158 DOI: 10.1056/NEJMoa2216334 (30)	Health state/Advanced or Recurrent endometrial cancer	Table 17: Overview of health state utility values [and disutilities]
NICE. Dostarlimab for previously treated advanced or recurrent endometrial cancer with high microsatellite instability or mismatch repair deficiency. Published 16 March 2022. TA779 Committee papers (nice.org.uk), page 161. Accessed February 2024 (35)	Disutility/adverse event	Table 17: Overview of health state utility values [and disutilities]

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
NICE. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. Guidance. [Online] May 2020. https://www.nice.org.uk/guidance/ta673/documents/committee-papers, page 156, Accessed February 2024 (36)	Disutility/adverse event	Table 17: Overview of health state utility values [and disutilities]
Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer. Guidance. [Online] September 2016. https://www.nice.org.uk/guidance/ta411/documents/committee-papers, page 173 and 177, Accessed February 2024 (37)	Disutility/adverse event	Table 17: Overview of health state utility values [and disutilities]
Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer. 2008 Dec;62(3):374-80. doi: 10.1016/j.lungcan.2008.03.019. Epub 2008 May 8. PMID: 18467000. (38)	Disutility/adverse event	Table 17: Overview of health state utility values [and disutilities]

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Swinburn P, Lloyd A, Nathan P, et al. Elicitation of health state utilities in metastatic renal cell carcinoma. Curr Med Res Opin 2010;26:1091-6. DOI: 10.1185/03007991003712258 (39)	Disutility/adverse event	Table 17: Overview of health state utility values [and disutilities]
Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes 2008;6:84. doi: 10.1186/1477-7525-6-84 (40)	Disutility/adverse event	Table 17: Overview of health state utility values [and disutilities]

5.3 Literature used for inputs for the health economic model

The data used for the health economic model was primarily obtained from the head-to-head study RUBY, with the exception of AE incidence rates for subsequent treatments. These were found in an ad-hoc literature search and confirmed by clinical expert.

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
Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. Mansoor R. Mirza et al. N Engl J Med 2023; 388:2145-2158 DOI: 10.1056/NEJMoa2216334	Overall survival Progression Free Survival	N/A	Data is described in Section 6 and 9.

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
(30)			
Oaknin A, Tinker A V., Gilbert L, Samouëlian 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. (41)	Incidence rate of adverse event in second line subsequent treatment: dostarlimab	Ad-hoc literature search	Data is described in Section 9 and 11.
Gladieff L, Ferrero A, De Rauglaudre G, Brown C, Vasey P, Reinthaller A, Pujade-Lauraine E, Reed N, Lorusso D, Siena S, Helland H, Elit L, Mahner S. Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in partially platinum-sensitive ovarian cancer patients: results from a subset analysis of the CALYPSO phase III trial. Ann Oncol. 2012 May;23(5):1185-1189. doi: 10.1093/annonc/mdr441. Epub 2011 Oct 5. PMID: 21976386. (42)	Incidence rate of adverse event in second line subsequent treatment: carboplatin/paclitaxel	Ad-hoc literature search	Data is described in Section 9 and 11.

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Mathews C, Lorusso D, Coleman RL, Boklage S, Garside J. An Indirect Comparison of the Efficacy and Safety of Dostarlimab and Doxorubicin for the Treatment of Advanced and Recurrent Endometrial Cancer. Oncologist. 2022 Dec 9;27(12):1058-1066. doi: 10.1093/oncolo/oyac188. Erratum in: Oncologist. 2022 Nov 18;: PMID: 36124638; PMCID: PMC9732237. (43)	Incidence rate of adverse event in second line subsequent treatment: doxorubicin	Ad-hoc literature search	Data is described in Section 9 and 11.
Mileshkin L, Edmondson R, O'Connell RL, Sjoquist KM, Andrews J, Jyothirmayi R, Beale P, Bonaventura T, Goh J, Hall M, Clamp A, Green J, Lord R, Amant F, Alexander L, Carty K, Paul J, Scurry J, Millan D, Nottley S, Friedlander M; PARAGON study group. Phase 2 study of anastrozole in recurrent estrogen (ER)/progesterone (PR) positive endometrial cancer: The PARAGON trial - ANZGOG 0903. Gynecol Oncol. 2019 Jul;154(1):29-37. doi: 10.1016/j.ygyno.2019.05.007. Epub 2019 May 23. PMID: 31130288. (44)	Incidence rate of adverse event in second line subsequent treatment: letrozole	Ad-hoc literature search	Data is described in Section 9 and 11.

6. Efficacy of dostarlimab in adult patients with recurrent or advanced dMMR/MSI-H endometrial cancer

6.1 Efficacy of dostarlimab compared to carboplatin and paclitaxel for the treatment of adult patients with recurrent or advanced mismatch repair deficient/microsatellite instability-high endometrial cancer

6.1.1 Relevant studies

In adult patients with recurrent or advanced dMMR/MSI-H 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 and overview of RUBY-1, and additional information can be found in Appendix A. Main characteristics of studies included

The RUBY trial is a phase 3, randomised, double-blind, multicentre trial conducted in 2 parts (30). RUBY-1 evaluate dostarlimab plus CP for 6 cycles followed by dostarlimab for up to 3 years; RUBY-2 evaluate dostarlimab plus CP for 6 cycles followed by dostarlimab plus niraparib for up to 3 years (45). 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 (30). RUBY-2 is ongoing as of April 2023 and will not be presented in this application. Thus, this application is based solely on results from RUBY-1.

Efficacy results in the following are presented for the dMMR/MSI-H population that included all 118 randomised subjects with dMMR/MSI-H status: 53 subjects in the dostarlimab plus CP group and 65 subjects in the placebo plus CP group. As the EMA-approved indication for dostarlimab is currently only for the dMMR/MSI-H population, and this population was predefined as a subgroup in the RUBY-1 trial, we will be presenting the efficacy results for this population only.

Table 8: Overview of study design for the RUBY-1 trial

Trial name, NCT-number	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
RUBY (NCT03981796)	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. 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 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	A total of 249 subjects were randomly assigned to 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	**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 • Concomitant medication

Source: Mirza et al. 2023

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.

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

	RUBY			
	dMMR/MSI-H population		Overall population (ITT)	
	Dostarlimab (N=53)	Placebo (N=65)	Dostarlimab (N=245)	Placebo (N=249)
Age, years				
Median (range)	61 (45–81)	66 (39–85)	64 (41–81)	65 (28–85)
≥65, n (%)	23 (43)	35 (54)	118 (48.2)	135 (54.2)
Race or ethnic group, n (%)				
White	44 (83)	56 (86)	189 (77.1)	191 (76.7)
Black	4 (8)	6 (9)	28 (11.4)	31 (12.4)
Asian	2 (4)	0 7 (2.9)	8 (3.2)	8 (3)
American Indian or Alaska Native	0	1 (2)	1 (0.4)	1 (0.4)
Native Hawaiian or other Pacific Islander	1 (2)	0	1 (0.4)	0
Unknown or not reported	2 (4)	2 (3)	19 (7.8)	18 (7.2)
ECOG performance category, n/total, n (%)				
0	28/52 (54)	39/65 (60)	145/241 (60.2)	160/246 (65.0)
1	24/52 (46)	26/65 (40)	96/241 (39.8)	86/246 (35.0)

	RUBY			
	dMMR/MSI-H population		Overall population (ITT)	
	Dostarlimab (N=53)	Placebo (N=65)	Dostarlimab (N=245)	Placebo (N=249)
FIGO stage at diagnosis, n (%)				
I	18 (34)	22 (34)	65 (26.5)	71 (28.5)
II	3 (6)	5 (8)	13 (5.3)	13 (5.2)
III	14 (26)	20 (31)	75 (30.6)	65 (26.1)
IV	14 (26)	15 (23)	72 (29.4)	84 (33.7)
Unknown	4 (8)	3 (5)	20 (8.2)	16 (6.4)
Disease status, n (%)				
Primary stage III	10 (19)	14 (22)	45 (18.4)	47 (18.9)
Primary stage IV	16 (30)	19 (29)	83 (33.9)	83 (33.3)
Recurrent	27 (51)	32 (49)	117 (47.8)	119 (47.8)
BMI				
Median (range)	30.6 (20.1–54.4)	35.5 (17.9–58.1)	30.8 (17.6–60.6)	32.8 (17.7–68.0)
Histologic type, n (%)				
Carcinosarcoma	4 (8)	1 (2)	25 (10.2)	19 (7.6)
Endometrioid	44 (83)	56 (86)	134 (54.7)	136 (54.6)
Mixed carcinoma ≥10% of carcinosarcoma, clear-cell, or serous histologic type	2 (4)	4 (6)	10 (4.1)	9 (3.6)
Serous adenocarcinoma	1 (2)	1 (2)	50 (20.4)	52 (20.9)
Clear-cell adenocarcinoma	0	0	8 (3.3)	9 (3.6)
Mucinous adenocarcinoma	0	0	0	1 (0.4)
Undifferentiated carcinoma	0	0	1 (0.4)	2 (0.8)
Other	2 (4)	3 (5)	17 (6.9)	21 (8.4)

	RUBY			
	dMMR/MSI-H population		Overall population (ITT)	
	Dostarlimab (N=53)	Placebo (N=65)	Dostarlimab (N=245)	Placebo (N=249)
MMR-MSI status, n (%)				
dMMR–MSI-H	53 (100)	65 (100)	53 (21.6)	65 (26.1)
pMMR–MSS	0	0	192 (78.4)	184 (73.9)
Previous external pelvic radiotherapy, n (%)				
Yes	8 (15)	13 (20)	41 (16.7)	45 (18.1)
No	45 (85)	52 (80)	204 (83.3)	204 (81.9)

Source: Mirza et al. 2023

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. Relevant characteristics used in the health economic model are presented in Table 10.

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)
Age	63 years (11)	63.3 years (age at baseline in RUBY dMMR/MSI-H population)
Gender	Women	Women
Patient weight	N/A	89.17 kg (weight at baseline in RUBY dMMR/MSI-H population)
BSA	N/A	1.962 m^2 (BSA at baseline in RUBY dMMR/MSI-H population)

6.1.4 Efficacy – results per RUBY

In the following, efficacy results on PFS (investigator-assessed and BICR) and OS for the dMMR/MSI-H population are presented. The dMMR/MSI-H was a predefined sub-

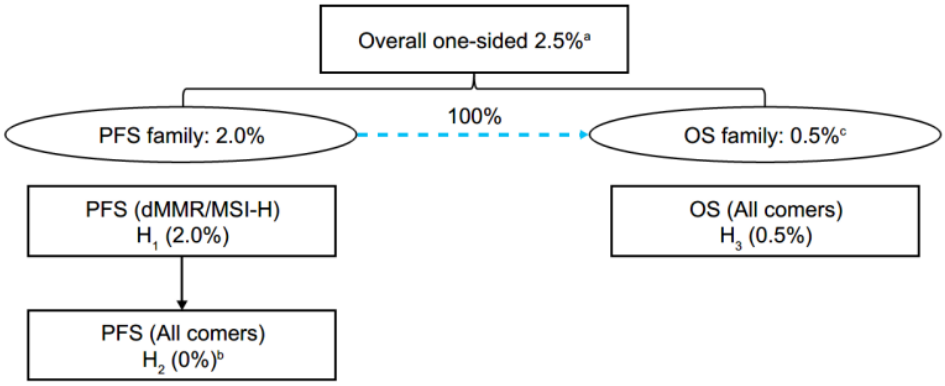
population in the RUBY study. Furthermore, the dMMR/MSI-H population is the EMA approved population in first line (1). For progression free survival, hypotheses were hierarchically tested in the dMMR/MSI-H population and then in the overall population.

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 4). 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 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.

Figure 4: Multiplicity Control Strategy

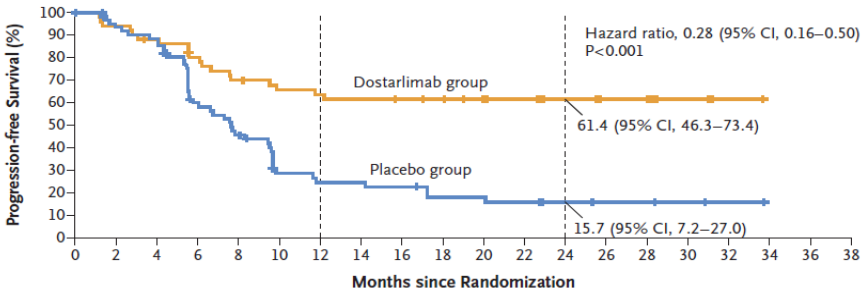


Source: Supplement to Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for primary advanced or recurrent endometrial cancer. N Engl J Med.

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

The median duration of follow-up was 24.8 months (range: 19.2, 36.9). Patients in the dostarlimab plus CP group had a statistically significant 72% reduction in risk of progression or death compared with the placebo plus CP group (HR: 0.28; 95% CI: 0.16, 0.50; p<0.001) (Figure 5) (30). For the dostarlimab plus CP and placebo plus CP groups, the estimated probability of PFS at 12 months was 63.5% (95% CI: 48.5, 75.3) and 24.4% (95% CI: 13.9, 36.4), respectively (46). At 24 months, the estimated probability of PFS was 4 times higher in the dostarlimab plus CP group compared with the placebo plus CP group (61.4% [95% CI: 46.3, 73.4] and 15.7% [95% CI: 7.2, 27.0], respectively). After approximately 12 months, a sustained separation of the KM curves was observed, with no further progression events reported in the dostarlimab plus CP group (30).

Figure 5: Kaplan-Meier estimates of PFS in the dMMR/MSI-H population (investigator-assessed)



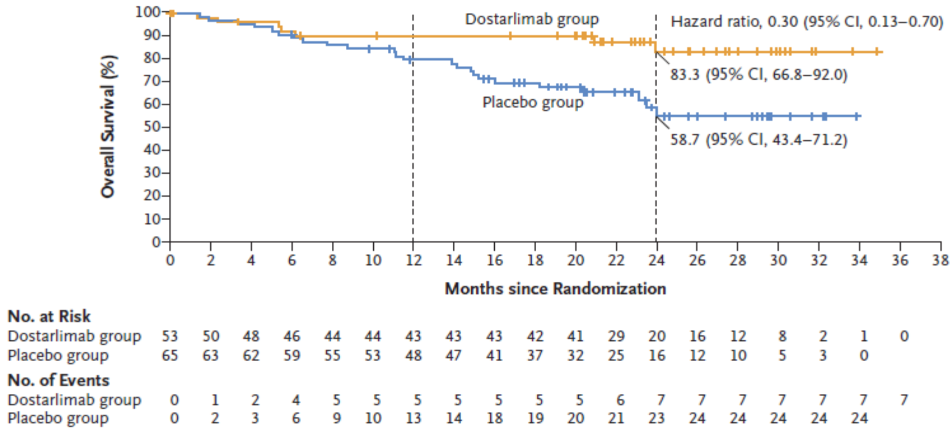
No. at Risk																		
Dostarlimab group	53	48	44	39	34	31	30	29	28	27	25	19	13	9	9	4	1	0
Placebo group	65	57	54	34	26	14	12	12	11	8	8	7	4	3	3	2	1	0
No. of Events																		
Dostarlimab group	0	3	6	10	15	17	18	19	19	19	19	19	19	19	19	19	19	19
Placebo group	0	4	7	24	32	41	43	43	44	46	46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

Source: Mirza et al. 2023

6.1.4.3 Prespecified subgroup analysis: Overall survival dMMR/MSI-H

Patients in the dostarlimab plus CP group had a 70% reduction in risk of death compared with the placebo plus CP group (HR 0.30; 95% CI: 0.13, 0.70; nominal p=0.0016) (Figure 6), indicating an unprecedented clinically meaningful survival benefit with the dostarlimab plus CP regimen (30) (46). The estimated probability of survival at 12 and 24 months was 90.1% (95% CI: 77.8, 95.7) and 83.3% (95% CI: 66.8, 92.0), respectively, in the dostarlimab plus CP group and 79.6% (95% CI: 67.5, 87.5) and 58.7% (95% CI: 43.4, 71.2), respectively, in the placebo plus CP group (30). With a median follow-up time of approximately 2 years, 24 events had been observed in the placebo plus CP group compared with 7 events in the dostarlimab plus CP group.

Figure 6: Kaplan-Meier estimates of OS in the dMMR/MSI-H population



Source: Mirza et al. 2023

[redacted]

[redacted]

[redacted]

[redacted]

6.1.4.4 Secondary endpoint: Progressions-free survival (BICR)

[redacted]

[redacted]

[redacted]

[redacted]

6.1.4.5 Discontinuation in the dMMR/MSI-H population

As of the data cutoff date, 75.5% of participants (n=39) in the dostarlimab plus CP arm and 50.8% of participants (n=33) in the placebo plus CP arm remained ongoing in the study. Death due to disease progression was the most frequently reported reason for discontinuation from the study. The median duration of follow-up was 24.79 months and was consistent between treatment arms (30).

In both treatment arms, the most common reason for dostarlimab or placebo discontinuation was PD according to RECIST v.1.1 criteria per Investigator assessment (25.0% dostarlimab plus CP, 61.5% placebo plus CP). The most common reason for discontinuation for carboplatin or paclitaxel was AE (30) (46).

Discontinuation of dostarlimab or placebo because of adverse events occurred in 17.3% of patients in the dostarlimab group and in 10.8% 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 (30) (46).

[redacted]

Reasons for discontinuation of treatment	Dostar-limab plus CP (N=52)	Placebo plus CP (N=65)	Total (N=117)
[redacted]			

[redacted]

6.1.4.6 Subsequent treatment for the dMMR/MSI-H population

[redacted] Input

from clinical expert states, that immunotherapy would not be prescribed in second line, if used in first line as no study has shown a beneficial result of re-introducing immunotherapy.

[redacted] The distribution of patients receiving either immunotherapy or chemotherapy corresponds to a high degree to Danish clinical practice and guidelines for patients not treated with immunotherapy in the first line setting.

Further details can be found in **Error! Reference source not found.** in Appendix B. Efficacy results per study

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 dMMR/MSI-H patient population

Outcome measure	Dostarlimab plus CP (N=53)	Placebo plus CP (N=65)	Result
Probability of progression-free survival at 24 months	61.4% [95% CI: 46.3, 73.4]	15.7% [95% CI: 7.2, 27.0]	45,7% [HR: 0.28; 95% CI: 0.16, 0.50; P<0.001]

Outcome measure	Dostarlimab plus CP (N=53)	Placebo plus CP (N=65)	Result
Probability of survival at 24 months	83.3% [95% CI: 66.8, 92.0]	58.7% [95% CI: 43.4, 71.2]	24,6% [HR: 0.30; 95% CI: 0.13, 0.70; nominal p=0.0016]

Source: Mirza et al. 2023

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

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

The efficacy for dostarlimab plus CP and for CP was determined based on the data obtained from the RUBY study. In the PSM, the PFS and OS Kaplan-Meier (KM) curves are used directly to model the PFD-state, the PD-state, and the D-state. A detailed description on how the different KM curves are used in the model is described in Table - I.

Table - I: PSM model input

Model input	Description
PFD	The proportion of patients in the pre-progression state is estimated by extrapolating PFS KM curves.
PD	The proportion of patients in the post-progression state is estimated as the difference between OS and PFS curves over time (i.e., post-progression = OS – PFS).
Death	Survival is estimated by extrapolating OS KM curves (i.e., death = 1 - OS).

8.1.1 Extrapolation of efficacy data

Efficacy data were used directly from RUBY to extrapolate survival curves for the dMMR/MSI-H population for PFS, time to treatment discontinuation (TTD) and OS for

both dostarlimab plus CP and CP. The RUBY study provided data up to a median follow-up of 24.8 months (primary data cut off 28th of September 2022) (46). To apply a lifetime time horizon in the CEA, extrapolation beyond the follow-up period was required. Data from the RUBY trial underwent comprehensive survival analysis that covered standard parametric analyses (including independent, dependent, and flexible where necessary), non-parametric and semi-parametric analyses.

For treatments included in the RUBY study, survival curves were fitted to the time-to-event patient-level data (PLD), based on Decision Support Unit (DSU) guidance from the NICE (47). Survival curves for all endpoints of interest in the model were fitted using individually modelled standard parametric curves: exponential, Weibull, Gompertz, log-logistic, log-normal, generalised Gamma and Gamma.

Additionally, dependent parametric curves were fitted to the PLD for all endpoints. These parametric curves were fitted to the dostarlimab plus CP and CP arms simultaneously with a covariate for treatment (reference = CP arm). As per the NICE DSU guidelines, parametric curves were jointly fitted to the data: exponential, Weibull, Gompertz, log-normal, log-logistic, generalised Gamma and Gamma (47).

As the results of the survival analysis for PFS indicated that standard parametric models may not capture the shape of the hazard for dostarlimab plus CP or CP, flexible spline analyses were also fitted to the PLD for PFS. The flexible spline analyses were used as this was the preferred method of flexible survival modelling by a panel of experts with in-depth knowledge of survival analyses, (48) and it is used in HTAs. The hazards, normal and odds distributions were modelled with up to three knots explored.

All analyses were carried out in R using the 'survival' package, in RStudio version 1.3.959. A detailed description of the chosen methodology and results for the PFS and OS extrapolations is presented in Appendix D. Extrapolation

8.1.1.1 Extrapolation of PFS

[redacted]

[redacted] Supplementary survival analyses of seven parametric dependent (by treatment covariate) models for PFS are presented in Appendix D. Extrapolation

Table 12: Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	RUBY-1 primary data cut off (September 2022)
Model	[redacted]
Assumption of proportional hazards between intervention and comparator	No

Method/approach	Description/assumption
Function with best AIC fit	[redacted]
Function with best BIC fit	AIC goodness of fit statistics are more reliable for the assessment of statistical fit, as BIC goodness of fit statistics penalize models which are complex (i.e., have more coefficients, such as the flexible models). Therefore, for more complex models, such as flexible spline models, our analysis only outputs AIC statistics.
Function with best visual fit	[redacted]
Function with best fit according to evaluation of smoothed hazard assumptions	[redacted]
Validation of selected extrapolated curves (external evidence)	UK clinical experts at an advisory board held by GSK in March 2023 (50). The conclusions were confirmed by one Danish clinical expert afterwards.
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	Yes

Method/approach	Description/assumption
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

[redacted]

[redacted]

[redacted]

Table - II: Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	RUBY primary data cut off (September 2022)
Model	Independent models were considered for use in the base-case analyses. A pseudo-piecewise approach was used in the base case for dostarlimab plus CP and CP, utilising the KM for the full follow-up period, to increase the accuracy of the estimates by making use of all the data available. The pseudo-piecewise functionality uses the observed data up until the median follow-up or the end of the observed period (as selected by the user) followed by the tail of the standard parametric curve (based on the full dataset).
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	[redacted]
Function with best BIC fit	[redacted]
Function with best visual fit	[redacted]
Function with best fit according to evaluation of smoothed hazard assumptions	[redacted]
Validation of selected extrapolated curves (external evidence)	UK clinical experts at an advisory board held by GSK in March 2023. The conclusions were confirmed by one Danish clinical expert afterwards.
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	Yes

Method/approach	Description/assumption
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.1.1.3 Extrapolation of TTD

[redacted]

[redacted]

Table - III: Summary of assumptions associated with extrapolation of TTD

Method/approach	Description/assumption
Data input	RUBY-1 primary data cut off (September 2022)
Model	Only independent parametric models were considered for TTD, given that a treatment effect is not applicable to discontinuation in the same manner as PFS and OS. Accordingly, dependent parametric models were not a suitable to extrapolate the TTD data. A pseudo-piecewise analysis was conducted utilizing the KM for the full follow-up to improve the accuracy of the TTD estimations by using all observed data.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	[redacted]
Function with best BIC fit	[redacted]
Function with best visual fit	[redacted]
Function with best fit according to evaluation of smoothed hazard assumptions	[redacted]

Method/approach	Description/assumption
Validation of selected extrapolated curves (external evidence)	UK clinical experts at an advisory board held by GSK in March 2023. The conclusions were confirmed by one Danish clinical expert afterwards.
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

[redacted]

[redacted]

[redacted]

8.1.2 Calculation of transition probabilities

N/A

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]

N/A

8.3 Modelling effects of subsequent treatments

Patients are assumed to receive second-line subsequent treatment following disease progression from first-line therapy. Subsequent treatment regimen data used in the model base case were informed by a Danish clinical expert, presented in Table - IV. Subsequent treatment regimens are population-specific; hence the base case includes regimens received by patients in the dMMR/MSI-H subgroup.

Table - IV: Base-case second line subsequent treatment regimens

Primary treatment	Subsequent treatment	Second-line regimen (%)
Dostarlimab plus CP	Dostarlimab	0%
	Carboplatin and paclitaxel	32%

Primary treatment	Subsequent treatment	Second-line regimen (%)
	Doxorubicin	32%
	Letrozole	16%
	No treatment*	20%
CP	Dostarlimab	45%
	Carboplatin and paclitaxel	36%
	Doxorubicin	9%
	Letrozole	0%
	No treatment*	10%

Source: informed by clinical expert. *GSK assumption

8.4 Other assumptions regarding efficacy in the model

N/A

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

[redacted]

	Modelled average [PFS] (reference in Excel)	Modelled median [PFS] (reference in Excel)	Observed median from RUBY study
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

	Modelled average [OS] (reference in Excel)	Modelled median [OS] (reference in Excel)	Observed median from RUBY study
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Treatment	Treatment length [years]	Health state PF [years]	Health state PD [years]
[redacted]	[redacted]	[redacted]	[redacted]

9. Safety

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

9.1 Safety data from RUBY

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 dMMR/MSI-H population go to Appendix E. Serious adverse events

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) (30).

TEAEs were defined as any AE or SAE that occurred on or after the start of study intervention, or worsened from baseline in intensity or frequency, through 90 days after last dose of study intervention or until the start of alternate anticancer therapy (whichever occurred first) (30) (46).

The most common adverse events that occurred or worsened during treatment were nausea (53.9% of patients in the dostarlimab group and 45.9% of patients in the placebo group), alopecia (53.5% and 50.0%), and fatigue (51.9% and 54.5%). Rash and maculopapular rash were the adverse events with the largest differences between the treatment groups and were reported more frequently in the dostarlimab group than in the placebo group (22.8% vs. 13.8% for rash and 14.1% vs. 3.7% for maculopapular rash) (30).

The most common immune-related adverse events were hypothyroidism (11.2% in the dostarlimab group and 2.8% of those in the placebo group), rash (6.6% and 2.0%), arthralgia (5.8% and 6.5%), and an increase in alanine aminotransferase levels (5.8% and 0.8%) (30) (46).

An overview of the safety events in the treatment phase is presented in **Error! Reference source not found.**.

[redacted]

	Dostarlimab plus CP (N= 241)	Placebo plus CP (N= 246)	Difference, % (95 % CI)
[redacted]	[redacted]	[redacted]	N/A
[redacted]	[redacted]	[redacted]	N/A
[redacted]	[redacted]	[redacted]	N/A
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	N/A
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	N/A
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

	Dostarlimab plus CP (N= 241)	Placebo plus CP (N= 246)	Difference, % (95 % CI)
[redacted]			
[redacted]	[redacted]	[redacted]	N/A
[redacted]			

Go to Appendix E. Serious adverse events for additional information of dose modifications.

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, 70.5% vs. 59.8%; serious adverse events, 37.8% vs. 27.6%) (30).

Discontinuation of dostarlimab or placebo in the ITT population due to adverse events occurred in 17.4% in the dostarlimab group and in 9.3% 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 (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 (30).

Table 14 shows serious events occurring in >2 % in each group due 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. Serious adverse events

Table 14: Serious events occurring in >2% of patients in either group. The median duration of follow-up was 25.4 months (range, 19.2 to 37.8) in the overall population

	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	6 (2.5)	N/A	5 (2.0)	N/A
Pyrexia	6 (2.5)	N/A	2 (0.8)	N/A
Dyspnoea	5 (2.1)	N/A	1 (0.4)	N/A
Muscular weakness	5 (2.1)	N/A	1 (0.4)	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: Mirza et al. 2023

The model considers the impact of AEs to the costs and quality of life of patients receiving dostarlimab plus CP and CP. Only treatment-related grade ≥3 AEs in ≥5% of patients in either treatment group in the ITT population of the RUBY trial were included in the model.

AEs were incorporated as one-off events and the impact was attributed to the first cycle of the model, under the assumption that AEs are likely to occur very soon after treatment initiation and only require acute care. The cost and QALY impact of AEs were calculated as the sum product of the AE rates for each treatment and the cost per treatment/disutility for each event. The primary treatment AE rates applied in the model are presented in **Error! Reference source not found.**.

[redacted]

Adverse events	Dostarlimab plus CP (n= 241)	Placebo plus CP (n= 246)		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)				
[redacted]				

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

External literature was used to inform the model with AE incidence rates for the included second-line subsequent treatments. The subsequent treatment AE rates applied in the model are presented in Table 15. Only grade ≥3 AEs in ≥5% of patients in the presented studies were included in the model, and only those AEs that are included for first line treatment are considered for subsequent treatment options

Table 15: Adverse events in second-line subsequent treatment used in the health economic model

	Dostarlimab (n= 129)		CP (n= 180)		Doxorubicin (n= 249)		Letrozole (n= 82)	
Adverse events	**Frequency used in economic model, n (%)**	**Source**	**Frequency used in economic model, n (%)**	**Source**	**Frequency used in economic model, n (%)**	**Source**	**Frequency used in economic model, n (%)**	**Source**
Anaemia	19 (14.7)	(41)	8 (4.4)	(42)	38 (15.3)	(43)	7 (8.5)	(44)
Neutropenia	0 (0.0)	(41)	91 (50.6)	(42)	112 (45.0)	(43)	0 (0.0)	(44)
Neutrophil count decrease	0 (0.0)	(41)	0 (0.0)	(42)	25 (10.0)	(43)	0 (0.0)	(44)
Hypertension	0 (0.0)	(41)	0 (0.0)	(42)	0 (0.0)	(43)	0 (0.0)	(44)
White blood cell count decreased	0 (0.0)	(41)	0 (0.0)	(42)	20 (8.0)	(43)	0 (0.0)	(44)
Hypokalaemia	0 (0.0)	(41)	0 (0.0)	(42)	0 (0.0)	(43)	0 (0.0)	(44)
Pulmonary em-bolism	0 (0.0)	(41)	0 (0.0)	(42)	0 (0.0)	(43)	0 (0.0)	(44)

	Dostarlimab (n= 129)		CP (n= 180)		Doxorubicin (n= 249)		Letrozole (n= 82)	
Lymphocyte count decreased	0 (0.0)	(41)	0 (0.0)	(42)	0 (0.0)	(43)	0 (0.0)	(44)
Abdominal pain	7 (5.4)	(41)	0 (0.0)	(42)	0 (0.0)	(43)	0 (0.0)	(44)

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 16: Overview of included HRQoL instrument

Measuring instrument	Source	Utilization
EQ-5D-5L	Data is obtained from the RUBY trial	Used to derive health state utility values for the PFD and the PD state to inform the health economic model.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

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 (46). 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. A summary of completion and missing data points is presented in **Error! Reference source not found.**.

[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]								

	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]

	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]

	Number of records	Number of subjects
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

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 within 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 in order to reach convergence.

10.1.3 HRQoL results

Error! Reference source not found.

[redacted]

[redacted]

[redacted]

[redacted]

An analysis of the change in baseline of Danish utility values at the different time points including a comparison between treatment arms are shown in **Error! Reference source not found.**.

[redacted] A similar table with EQ-5D VAS is found in Appendix F. Health-related quality of life.

[redacted]

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

	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]					

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

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

10.2.1 HSUV calculation

As valid HRQoL data were collected in clinical trials, these data have been used to inform the health states in the model. The EQ-5D-5L data from RUBY have been indexed with Danish preference weights from Jensen et al. 2021 in line with recommendations from the Danish Medicines Council (32) (51). The model applies age-adjustment to the HRQoL data in alignment with the method guidance from the DMC (52).

10.2.1.1 Mapping

Not applicable.

10.2.2 Disutility calculation

The disutilities associated with second line subsequent treatment is not included in the analysis due to the paucity of evidence in the published literature on the proportion of patients experiencing AEs during second-line therapy.

10.2.3 HSUV results

The sum product of the disutility and the occurrence of adverse reactions per treatment arm used in the model is listed in Table 17.

The sum product of the disutility was assigned once in the first cycle of the model because it is unknown when in time the specific side effects occur during treatment and how long they last. The sum product is calculated by multiplying the percentage by which a specific adverse reaction occurs by the disutility of the adverse reaction in question. Since the disutilities used to inform AEs are not based on Danish value tariffs, there are some uncertainties when comparing them to the observed results from RUBY that have been converted to the Danish value tariffs. However, due to the paucity of available data these values were included in the base case analysis.

Table 17: Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV PFD	[redacted]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
HSUV PD	[redacted]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
AE disutility				
Anaemia	-0.119	EQ-5D	UK	(39)
Neutropenia	-0.090	EQ-5D	UK	(40)
Neutrophile count decreased	0.000	N/A	N/A	Assumed to have no utility impact – NICE dostarlimab 2 line (35)
Hypertension	-0.020	EQ-5D	UK	NICE: TA381 (36)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
White blood cell count decreased	0.000	N/A	N/A	Assumed to have no utility impact – NICE dostarlimab 2 line (35)
Hypokalaemia	-0.074	EQ-5D	UK	(40)
Pulmonary embolism	-0.320	N/A	N/A	NICE: TA411 (37)
Lymphocyte count decreased	0.000	N/A	N/A	Assumed to equal neutrophil count decreased
Abdominal pain	-0.069	EQ-5D	N/A	(38)

10.3 Presentation of the 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

10.3.2 Data collection

10.3.3 HRQoL Results

10.3.4 HSUV and disutility results

Table 18: Overview of health state utility values [and disutilities]

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

Table 19: 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

To estimate the resource use and associated costs of treating dMMR/MSI-H EC patients with dostarlimab plus CP and SoC, data from RUBY, the available summary of product characteristics (SmPC) of all included medicines, input from a Danish clinical expert, assumptions and Danish clinical guidelines were applied. A description of each cost element and how it was valued in the health economic analysis is presented in the following sections.

11.1 Medicine costs – intervention and comparator

All drug costs included in the model were based on the pharmacy purchasing price (PPP) obtained in February 2024. The PPP of the available packages of each treatment is presented in Table 20. Medicine costs for subsequent treatments is presented in Table 24.

Patients in RUBY received 500 mg of dostarlimab intravenously for the first six treatment cycles followed by 1000 mg per treatment cycle thereafter or placebo for all treatment cycles, in addition to carboplatin AUC 5 mg/ml/min plus paclitaxel 175 mg/m^2 administered intravenously every 3 weeks for six treatment cycles. (45) Dostarlimab is available in 500 mg strength and comes in a single vial. Carboplatin is available in 10 mg/ml strength as a single vial as either 15 ml or 45 ml package sizes, with both options included in the model. Paclitaxel is available both as concentrate for solution for infusion, 6 mg/ml, or as powder for infusion, 5 mg/ml. Only the concentrate for solution for infusion, 6 mg/ml in the package size 16,7 ml was included in the model. Acquisition costs were applied to the PFD health state based on the TTD curve in line with how treatment was received in the RUBY trial. The dosing and unit costs for CP were assumed to be the same for patients receiving CP with or without dostarlimab.

Table 20: Medicine costs used in the model

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Dostarlimab	500 mg	1 stk. concentrate for solution for infusion vials	42,427.75

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Carboplatin	10 mg/ml	15 ml concentrate for solution for infusion vials	95.00
Carboplatin	10 mg/ml	45 ml concentrate for solution for infusion vials	226.00
Paclitaxel	6 mg/ml	16.7ml concentrate for solution for infusion vials	110.50

Source: Medicinpriser.dk

To explore the impact of pharmaceutical wastage on costs, wastage is accounted for in the base case of the model. Costs associated with the model are based on the combination of vial/packages that minimises wastage in monetary terms (rather than by volume) based on baseline RUBY cohort characteristics. In Excel, selection of dose combination with wastage is done via linear optimization. The problem is defined as a minimization problem with the objective junction to minimize the cost pr. cycle. The constraints are that the dose must be at least the dose pr. cycle, and the number of each pack size must be whole numbers.

11.2 Medicine costs – co-administration

Not applicable.

11.3 Administration costs

The dosage regimen for dostarlimab, carboplatin and paclitaxel are included according to the RUBY protocol and Danish clinical guidelines (2) (46):

Dostarlimab plus CP: 6 cycles of carboplatin, paclitaxel and dostarlimab once every 3rd week, followed by dostarlimab once every 6th week as monotherapy.

CP: Once every 3rd week for 6 cycles.

To incorporate intravenous administration costs into the model, a unit cost of 1,314 DKK based on the DRG 2024 tariff “13MA98” was assumed for the first six treatment cycles in both treatment arms, followed by the same unit cost of 1,314 DKK for the following cycles in the dostarlimab plus CP arm.

Table 21: Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
I.V. infusion	Every 3rd week	1,314	13MA98, Diagnosis: DC549 Procedure: BWAA62	DRG 2024
I.V. infusion	Every 6th week	1,314	13MA98, Diagnosis: DC549 Procedure: BWAA62	DRG 2024

11.4 Disease management costs

The disease management costs and associated DRG 2024 tariffs included in the model are presented in Table 22.

Table 22: Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Outpatient Visit (Consultant Oncologist)	every 3rd week, for 6 cycles, then every 6th week	1,314	13MA98	DRG 2024
CT scan	Every 12th week	2,440	30PRO6	DRG 2024
Blood test	Every 3rd week for 6 cycles, then every 6th week	22.02	-	Lægeforeningen, takstkort 29A

Resource use estimates for patients on dostarlimab and comparator therapies are derived from clinical expert opinion, gathered through a resource use interview, conducted to support the application, summarised in Table - V.

Table - V: Health state resource use

		Health state	Cycle 0-18	Cycle 19+
Dostarlimab plus CP	Outpatient Visit (Consultant Oncologist)	PFS	0.33	0.17
		PD	0.33	0.33

		Health state	Cycle 0-18	Cycle 19+
	CT scan	PFS/PD	0.08	0.08
	Blood test	PFS/PD	0.33	0.17
CP	Outpatient Visit (Consultant Oncologist)	PFS	0.33	0.17
		PD	0.33	0.33
	CT scan	PFS/PD	0.08	0.08
	Blood test	PFS/PD	0.33	0.17

Source: clinical expert

11.5 Costs associated with management of adverse events

Costs for managing AEs were included in the model. The AEs included in the model were based on the number of grade ≥3 AEs that occurred in the RUBY trial. 4 adverse events (neutropenia, neutrophil count decreased, white blood cell count decreased, and lymphocyte count decreased) were included in the model but with no unit cost associated in the base-case, based on input from a Danish clinical expert stating that these adverse events will not require treatment. One-off costs associated with adverse events were obtained using DRG 2024 tariffs. It was assumed that each AE is only experienced once per patient, therefore, the total cost of each AE is applied within the first cycle of the model in both treatment arms as a one-off cost. To derive the total costs associated with AEs by treatment, unit costs obtained from DRG 2024 tariffs were multiplied by the AE incidence rates outlined in **Error! Reference source not found.**.

Table 23: Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff [DKK]
Anaemia	13MA98	1,314
Neutropenia	-	0
Neutrophil count decreased	-	0
Hypertension	13MA98	1,314
White blood cell count decreased	-	0

	DRG code	Unit cost/DRG tariff [DKK]
Hypokalemia	13MA98	1,314
Pulmonary embolism	13MA01	21,976
Lymphocyte count decreased	-	0
Abdominal Pain	06MA11	7,818

11.6 Subsequent treatment costs

Patients are assumed to receive second-line subsequent treatment following disease progression from first-line therapy.

Table 24: Medicine costs of subsequent treatments

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
Dostarlimab	500 mg	1 pcs. concentrate for solution for infusion vials	42,427.75	500 mg every 3 weeks for 4 cycles followed by 1000 mg every 6 weeks for all cycles up to 2 years	1.02 years
Paclitaxel	6 mg/ml	16.7ml concentrate for solution for infusion vials	100.50	175 mg/m2	0.27 year
	6 mg/ml	50 ml concentrate for solution for infusion vials	201.50	175 mg/m2	0.27 year
Carboplatin	10 mg/ml	15 ml concentrate for solution for infusion vials	95	444.57 mg/m2	0.27 year
	10 mg/ml	45 ml concentrate for	226	444.57 mg/m2	0.27 year

Medicine	Strength	Package size	Pharmacy purchase price [DKK]	Relative dose intensity	Average duration of treatment
		solution for infusion vials			
Caelyx pegylated liposomal (Doxorubicin)	2 mg/ml	10 ml concentrate for solution for infusion vials	3,700	70 mg/m2	0.18 year
Letrozole	2.5 mg	100 pcs. tablets	145	2.5 mg	0.27 year

Subsequent treatment regimens are population-specific, and the distribution of patients has been estimated by a clinical expert. It is assumed, that 50% of patients will be platinum sensitive based on the DMC assessment of dostarlimab second line treatment of dMMR/MSI-H EC (11).

Subsequent treatment drug costs were calculated based on available formulations, recommended dose and duration, pack sizes and unit costs from medicinpriser.dk. The recommended dose of subsequent treatment was based on the relevant SmPCs (1) (53) (54) (55) (56). Wastage was modelled for subsequent chemotherapies, in line with first-line treatment. A unit cost of 1,314 DKK based on the DRG 2024 tariff "13MA98" was applied to incorporate administration costs, in line with first-line treatment.

The total cost of subsequent treatments was calculated as the weighted average of the proportion of patients (see Table - IV) receiving each subsequent treatment in each treatment arm multiplied by the sum of the relevant drug acquisition and administration costs. This was multiplied by the number of regimen cycles received over the duration of treatment as sourced from published literature and applied as a one-off cost upon transition into the PD state.

The costs associated with AEs related to subsequent treatment were applied as a one-off cost at the start of subsequent treatment upon progression into the PD state. The AEs cost for each subsequent treatment were calculated by multiplying the incidence rate of each AE outlined in Table 15 with the respective unit costs outlined in

Table 23. The total AE costs for each subsequent treatment regimen applied to the dostarlimab plus CP and CP arms were calculated as the AE costs by subsequent treatment weighted by the proportion of patients receiving each second-line treatment in the treatment arms.

11.7 Patient costs

Patient and transportation costs are included in the model. Patient time was estimated using the average hourly salary in Denmark after tax. The numbers are calculated based on LONS20 in Statistics Denmark in line with the guidance document on valuation of unit costs. The current estimate is DKK 203/hour. In addition to patient time is also time and costs associated with transportation to and from the hospital. This was estimated based on the guidance document from the DMC, which estimates a total cost of DKK 140 (57).

All treatment regimens included in the model are IV, and therefore a hospital visit is required for each treatment administration. The relevant SmPCs (1) or pro.medicin.dk (54) (56) have been consulted to estimate the duration of each administration, please see Table 25 for the duration of the administration of each treatment regimen.

Table 25: Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Outpatient visit	1 hour
Blood test	0.5 hours
CT scan	1 hour

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

DGCG clinical guidelines recommends that all patients with EC should be tested using immunohistochemistry (IHC) to identify tumours with dMMR (8). Since testing has become standard of care for all patients with EC, testing costs are not included within the base-case analysis. To explore the impact of including IHC testing costs, the functionality of doing so has been incorporated in the model.

12. Results

12.1 Base case overview

An overview of the base case is presented in Table 26.

Table 26: Base case overview

Feature	Description	
Comparator	Carboplatin Paclitaxel (CP)	
Type of model	Partitioned survival model	
Time horizon	35.70 years (lifetime)	
Treatment line	1st line. Subsequent treatment lines are included in the model.	
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in the RUBY study (46). Danish population weights were used to estimate health-state utility values	
Costs included	Pharmaceutical costs Hospital costs Costs of adverse events Patient costs Transportation costs Second line subsequent treatment costs	
Dosage of pharmaceutical	Based on weight in the RUBY trial	
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	
Inclusion of waste	Yes	
Average time in model health state Health state – PFD Health state - PD Death	Dostarlimab plus CP [redacted] [redacted] [redacted]	CP [redacted] [redacted] [redacted]

12.1.1 Base case results

The base case results are summarised in Table 27.

Table 27: Base case results, discounted estimates

	Dostarlimab plus CP	CP	Difference
Pharmaceutical costs	[redacted]	[redacted]	[redacted]
Pharmaceutical costs – co-administration	N/A	N/A	N/A
Administration	17,740	8,090	9,650
Disease management costs/Health state costs	255,361	137,395	117,966
Costs associated with management of adverse events	1,449	1,376	72
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Patient costs	1,491	754	737
Palliative care costs	N/A	N/A	N/A
Total costs	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]		

12.2 Sensitivity analyses

Deterministic one-way sensitivity analysis (OWSA) and probabilistic sensitivity analyses (PSA) were conducted to explore the level of uncertainty in the model results.

12.2.1 Deterministic sensitivity analyses

The OWSA involved varying one parameter at a time and assessing the subsequent impact on the incremental QALYs and incremental costs. By varying each parameter individually, the sensitivity of the model results to that parameter was assessed. The OWSA was conducted by allocating a 'low' value and a 'high' value to each parameter; the low value is the lower bound of the 95% CI, the high value is the upper bound of the 95% CI. In the absence of CI data, the standard error (SE) was assumed to be 20% of the mean for all variables. The estimated SE was used to predict the upper and lower bound of the parameters' CI. The model parameters that were included in the OWSA can be found in the "Model parameters" sheet of the model: Inside the sheet, removing the "0" in column "L" excludes the chosen parameter from the OWSA, while adding a "0" includes the chosen parameter.

A tornado diagram (**Error! Reference source not found.**) graphically presents the parameters which have the greatest effect on the ICER. **Error! Reference source not found.** presents the ten most sensitive parameters.

[redacted]

[redacted]

[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]					
[redacted]					

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

12.2.2 Probabilistic sensitivity analyses

To assess the uncertainty surrounding the included variables in the model, a PSA was performed with 5,000 iterations. Multiple parameters included in the model are not necessarily fixed values, but rather a continuum that includes a certain variability. The performed PSA evaluated the impact on the model results when multiple parameters included in the model were varied simultaneously. The model parameters that were included in the PSA can be found in the "Model parameters" sheet of the model: Parameters can be excluded from the PSA in the "Model Parameters" sheet in the "Probabilistic" column by setting the cell to the corresponding cell in the "Mean" column. An overview of the PSA data and a description of how correlation between the model parameters is handled in the model is presented in Appendix G. Probabilistic sensitivity analyses

Total costs, QALYs, and incremental cost per QALY gained for dostarlimab plus CP versus CP for the dMMR/MSI-H population generated through the PSA are presented in Table - VI.

Table - VI: PSA results for dostarlimab + CP versus CP for the dMMR/MSI-H population

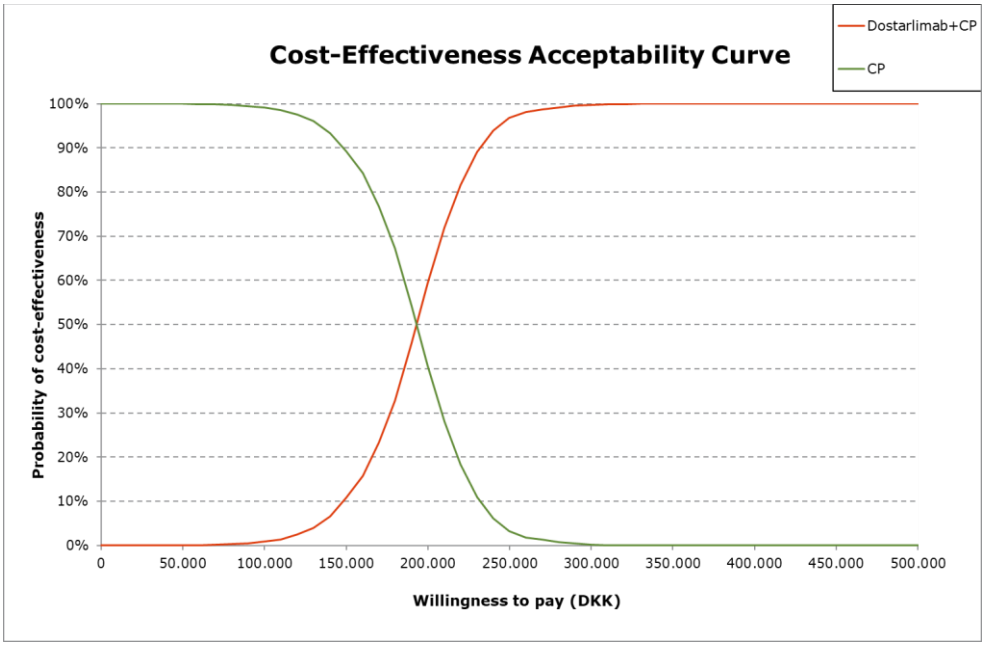
Intervention	Total costs (DKK)	Total LYs	Total QALYs	Inc. costs (DKK)	Inc. LYs	Inc. QALYs	ICER (DKK/QALY)
Dostarlimab plus CP	[redacted]	[redacted]	[redacted]	-	-	-	-
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ICEP presented in **Error! Reference source not found.** shows that all iterations of the PSA resulted in an ICER in the north-east quadrant of the QALY plane indicating dostarlimab plus CP is more costly and more effective than CP.

[redacted]

The Cost-effectiveness Acceptability Curve (CEAC) is presented in Figure 7, indicating that dostarlimab plus CP is cost-effective at WTP of DKK 300,000.

Figure 7: The Cost-effectiveness Acceptability Curve



13. Budget impact analysis

13.1 Number of patients (including assumptions of market share)

An estimated 100 patient are diagnosed with advanced endometrial cancer each year and 30 patients with relapsed endometrial cancer (8) (18). 22-30% of these being dMMR/MSI-H (12) (13), approximate 30 new patients. A market share of 100% is expected if dostarlimab plus CP is recommended. This means that all 30 patients are expected to be candidates for treatment with dostarlimab plus CP each year.

Table 28: Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Dostarlimab plus CP	30	30	30	30	30
CP	0	0	0	0	0
			Non-recommendation		

	Year 1	Year 2	Year 3	Year 4	Year 5
Dostarlimab plus CP	0	0	0	0	0
CP	30	30	30	30	30

13.2 Budget impact

Table 29: Expected budget impact (in DKK) of recommending dostarlimab plus CP for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
Dostarlimab plus CP is recommended	18.604.695	30.698.243	31.341.454	31.946.687	32.505.732
Dostarlimab plus CP is NOT recommended	7.359.250	8.913.551	9.744.806	10.138.132	10.445.727
Budget impact of the recommendation	11.245.446	21.784.692	21.596.648	21.808.555	22.060.005

14. List of experts

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

[redacted]

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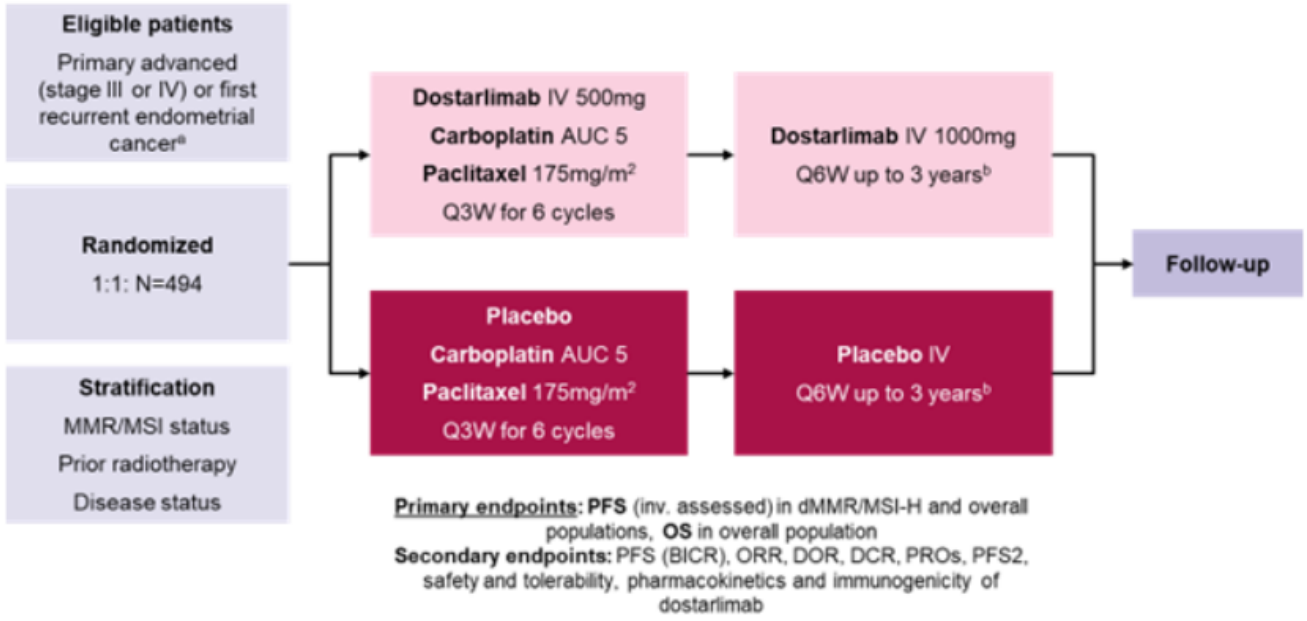
Appendix A. Main characteristics of studies included

Table 30: Main characteristics of RUBY

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.
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



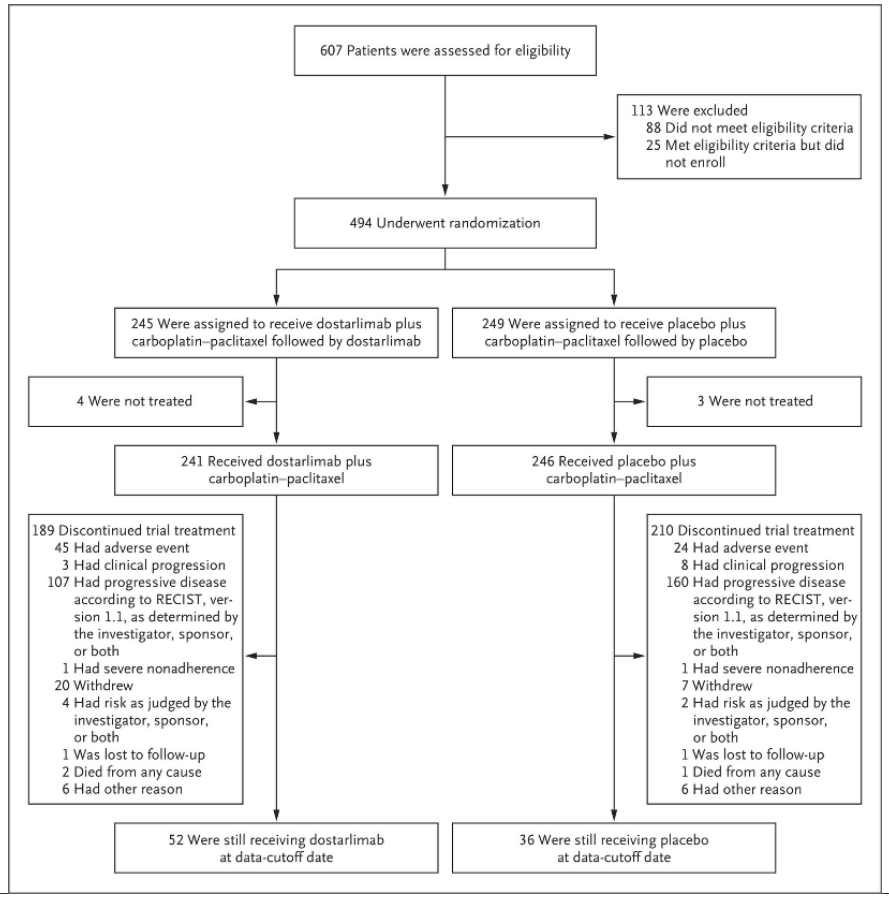
The RUBY study consists of a Screening Period (Day -28 to Day -1), a Treatment Period, an End of Treatment Visit, a Safety Follow-up Visit, and a Survival Assessment Period. Following informed consent, participants who met the eligibility criteria for Part 1 were randomized 1:1 to the following study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

Trial name: RUBY	NCT number: 03981796
	• 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. • 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 post-study 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.
- 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.

Trial name: RUBY	NCT number: 03981796
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
Is the study used in the health economic model?	Yes
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 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

Trial name: RUBY	NCT number: 03981796
	• Biomarkers in tumour tissue and/or blood Safety endpoints: • TEAEs • Clinical laboratory values • Vital signs • Physical examination • ECOG PS • ECG parameters • Concomitant medication
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, further description regarding extrapolation can be found in Appendix D.
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

[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		
[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		
[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		
[redacted]											

Table - VII: Response rates for dMMR/MSI-H and overall population in RUBY

	dMMR/MSI-H		Overall	
	Dostarlimab plus CP (N=53)	Placebo plus CP (N=65)	Dostarlimab plus CP (N=245)	Placebo plus CP (N=249)
Patients with evaluable disease at baseline, no. of patients	49	58	212	219

ORR,no., (% ; 95% CI)	38 (77.6; 3.4–88.2)	40 (69.0; 55.5–80.5)	149 (70.3; 63.6–76.3)	142 (64.8; 58.1–71.2)
CR	15 (30.6)	12 (20.7)	53 (25.0)	43 (19.6)
PR	23 (46.9)	28 (48.3)	96 (45.3)	99 (45.2)
SD	6 (12.2)	10 (17.2)	42 (19.8)	49 (22.4)
No disease	0	1 (1.7)	0	1 (0.5)
PD	2 (4.1)	4 (6.9)	9 (4.2)	16 (7.3)
NE	3 (6.1)	3 (5.2)	12 (5.7)	11 (5.0)
DCR, no., (%; 95% CI)	44 (89.8; 77.8–96.6)	51 (87.9; 76.7–95.0)	191 (90.1; 85.3–93.8)	192 (87.7; 82.6–91.7)
Responders, no. of patients	38	40	149	142
DOR, median, months (95% CI)	NE (10.1–NE)	5.4 (3.9–8.1)	10.6 (8.2–17.6)	6.2 (4.4–6.7)
DOR ≥12 months, no. (%)	22 (57.9)	7 (17.5)	60 (40.3)	29 (20.4)
Probability of DOR, % (95% CI)				
6 months	76.1 (59.0–86.8)	46.2 (30.2–60.7)	69.4 (60.9–76.4)	50.8 (42.2–58.8)
12 months	62.1 (44.4–75.5)	19.2 (8.6–33.1)	47.3 (38.6–55.5)	22.6 (15.9–30.0)
24 months	62.1 (44.4–75.5)	13.2 (4.6–26.3)	38.0 (29.4–46.5)	13.0 (7.5–20.2)

Source: Supplement to Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for primary advanced or recurrent endometrial cancer. N Engl J Med. DOI: 10.1056/NEJMoa2216334

[redacted]

	Dostarlimab plus CP (N=53)	Placebo plus CP (N=65)	Total (N=118)
[redacted]	[redacted]	[redacted]	[redacted]
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	Dostarlimab plus CP (N=53)	Placebo plus CP (N=65)	Total (N=118)
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	Dostarlimab plus CP (N=53)	Placebo plus CP (N=65)	Total (N=118)
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	Dostarlimab plus CP (N=53)	Placebo plus CP (N=65)	Total (N=118)
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Appendix C. Comparative analysis of efficacy

Not applicable.

Table 31: 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

1.1. Extrapolation of PFS

1.1.1. Data input

RUBY-1 primary data cut off (September 2022) for the dMMR/MSI-H population.

[redacted]

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Distribution	Knots	Dostarlimab + CP	CP
	[redacted]	[redacted]	[redacted]
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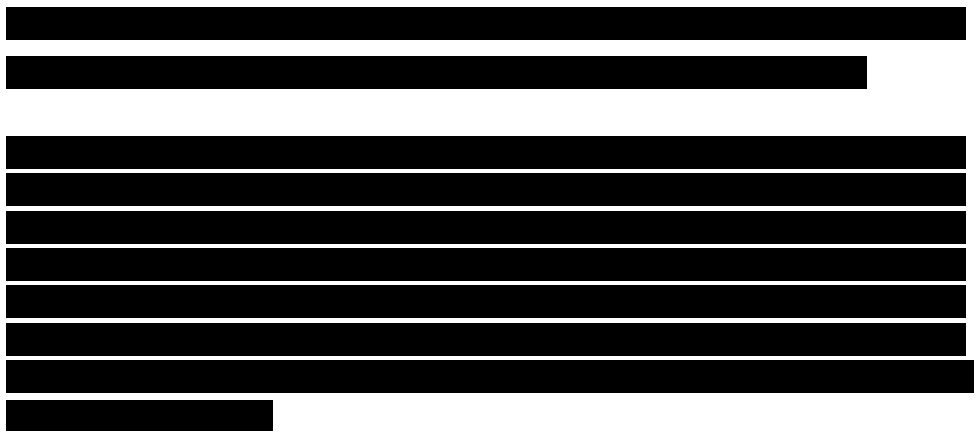
Seven parametric dependent (by treatment covariate) models were fitted to each arm of the study data; exponential, Weibull, Gompertz, log-logistic, log-normal, generalised Gamma and Gamma distribution (**Error! Reference source not found.** and xx

). A summary of the goodness-of-fit statistics for the PFS extrapolations is available in Table - VIII.

Table - VIII: AIC and BIC statistical goodness-of-fit data for PFS by INV – dMMR/MSI-H data set (dependent models) IA1 datacut

Distribution	Combined	
	AIC	BIC

[redacted]



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Distribution	Dostarlimab plus CP		CP	
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1.2.10. Cure-point

N/A

Appendix E. Serious adverse events

[redacted]

System organ class, n (%) Preferred term, n (%)	Dostarlimab plus CP (N=241)	Placebo plus CP (N=246)	Total (N=487)
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System organ class, n (%) Preferred term, n (%)	Dostarlimab plus CP (N=241)	Placebo plus CP (N=246)	Total (N=487)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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System organ class, n (%) Preferred term, n (%)	Dostarlimab plus CP (N=241)	Placebo plus CP (N=246)	Total (N=487)
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]In addition to the picture of serious adverse events, specific immune related adverse events in this trial are relevant. Find the summary of immune-related adverse events for the overall population in **Error! Reference source not found.**.

Table - IX: Immune-related Adverse Events: Summary of treatment-emergent immune-related adverse events by immune-related adverse event category and preferred term (Overall population, Safety analysis set)

Category, n (%) Preferred term, n (%)	Dostarlimab plus CP (N=241)		Placebo plus CP (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%)

Source: Supplement to Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for primary advanced or recurrent endometrial cancer. N Engl J Med. DOI: 10.1056/NEJMoa2216334

Dose reduction of dostarlimab is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability (1). Dose modifications for chemotherapy in the overall population are listed below.

Table - X: Dose Modifications of Carboplatin and Paclitaxel

	Dostarlimab plus CP (N=241)	Placebo plus CP (N=246)
Carboplatin, no. (%)		
Patients with any infusion interruptions	20 (8.3)	18 (7.3)
Patients with any infusion delays >3 days as determined by investigator	88 (36.5)	88 (35.8)
Patients with any missed infusions	1 (0.4)	3 (1.2)

Patients with any intended dose reduction	17 (7.1)	22 (8.9)
Any TEAE leading to discontinuation of carboplatin	24 (10.0)	19 (7.7)
Paclitaxel, no. (%)		
Patients with any infusion interruptions	38 (15.8)	45 (18.3)
Patients with any infusion delays >3 days as determined by investigator	85 (35.3)	82 (33.3)
Patients with any missed infusions	4 (1.7)	4 (1.6)
Patients with any intended dose reduction	56 (23.2)	54 (22.0)
Any TEAE leading to discontinuation of paclitaxel	24 (10.0)	23 (9.3)

Source: Supplement to Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for primary advanced or recurrent endometrial cancer. N Engl J Med. DOI: 10.1056/NEJMoa2216334

Safety data in this application is data based on the full study population, as no specific safety differences is expected between the dMMR/MSI-H population and the overall population. Nevertheless, an overall summary of treatment-emergent adverse events only for the dMMR/MSI-H population is included below to cover the specific population for this application.

[redacted]

Adverse event category	Dostarlimab plus CP (N=52)	Placebo plus CP (N=65)	Total (N=117)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Adverse event category	Dostarlimab plus CP (N=52)	Placebo plus CP (N=65)	Total (N=117)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Appendix F. Health-related quality of life

[redacted]

	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]					
[redacted]					

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

Appendix G. Probabilistic sensitivity analyses

[redacted]

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[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]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[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]

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
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Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
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Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
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Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
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Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix H. Literature searches for the clinical assessment

Not Applicable.

1.1. Efficacy and safety of the intervention and comparator(s)

Table 32 Bibliographic databases included in the literature search

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

Table 33 Other sources included in the literature search

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

Table 34 Conference material included in the literature search

Conference	Source of ab-stracts	Search strategy	Words/terms searched	Date of search
N/A				

1.1.1. Search strategies

Table 35 of search strategy table for [name of database]

No.	Query	Results
N/A		

1.1.2. Systematic selection of studies

Table 36 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
N/A		

Table 37 Overview of study design for studies included in the technology assessment

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						

1.1.3. Quality assessment

N/A

1.1.4. Unpublished data

N/A

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

1.1. Health-related quality-of-life search

Table 38: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
MEDLINE			22.02.2023

Table 39: Other sources included in the literature search

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

Table 40: Conference material included in the literature search

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

1.1.1. Search strategies

Table 41: Search strategy for MEDLINE

Search Num-ber	Search Terms	Original SLR (10 Nov 2021)	SLR Update #1 (22 Feb 2023)
1	exp endometrial neoplasms/ or ((endometrial or endo-metrium or uterine or uterus) adj3 (cancer$ or neo-plasm$ or hyperplas$ or malignan$ or carcinoma$ or sarcoma$ or adenocarcinoma$ or tumor$ or tu-mour$)).ti,ab.	59,567	63417
2	exp Neoplasm Metastasis/ or (advanced or recurrent or recurrence or metastas$ or metastat$ or end-stage or late-stage or terminal or stage 3$ or stage iii$ or stage three or stage iii$ or stage 4$ or stage iv or stage four).ti,ab.	2,019,500	2189517
3	1 and 2	17,539	18943
4*	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6 or disutilit$ or standard gamble$ or time trade off or time tradeoff or tto or hui or hui1 or hui2 or hui3 or	24,907	28633

	health utility idex or health utilities index or eq or euroqol or euro qol or eq5d$ or eq 5d$ or euroqual or euro qual).ti,ab,kw.		
5*	((health$ adj2 year$ adj2 equivalent$) or (health adj3 (utilit$ or status)) or (utilit$ adj3 (valu$ or measur$ or health or life or estimat$ or elicit$ or disease or score$ or weight)) or (preference$ adj3 (valu$ or measur$ or health or life or estimat$ or elicit$ or disease or score$ or instrument or instruments))).ti,ab,kw.	99,212	110517
6	3 and (4 or 5)	22	32
7	Review.pt.	2,876,482	3109679
8	Systematic Review.pt. or Systematic Reviews as Topic/ or Meta-Analysis.pt. or exp Network Meta-Analysis/ or exp Meta-Analysis as Topic/ or Cochrane Database of Systematic Reviews.jn.	265,459	328516
9	(systematic$ or systematic or pubmed or medline or Embase or Cochrane or meta-analysis or meta analysis or metaanalysis or meta-analyses or meta analyses or metaanalyses or meta-analyzed or meta analyzed or metaanalyzed or meta-analysed or meta analysed or metaanalysed or ((indirect or mixed or multiple) and treatment comparison)).ti,ab.	743,736	865809
10	7 not (8 or 9)	2,611,129	2797002
11	case reports/ or case study/ or case report$.jw. or Editorial.pt. or Letter.pt. or Note.pt.	3,764,163	3969420
12	(Ephemera or "Introductory Journal Article" or News or "Newspaper Article" or Editorial or Comment or Overall).pt. or in vitro Techniques/ or in vitro study/ or (commentary or editorial or comment or letter or mice or rat or mouse or animal or murine).ti.	3,148,598	3301741
13	or/10-12	8,237,413	8695000
14	6 not 13	20	30
15	14 not ((exp animal/ or nonhuman/) not exp human/)	20	30
16	(202108$ or 202109$ or 202110$ or 202111$ or 202112$ or 2022$ or 2023$).ed,dt.	--	3072865
17	15 and 16	--	13

1.1.2. Quality assessment and generalizability of estimates

N/A

1.1.3. Unpublished data

N/A

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

Not available.

1.2. External literature for input to the health economic model

1.2.1. Ex. Systematic search for […]

Table 42: Sources included in the search

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

1.2.2. Ex. Targeted literature search for [estimates]

Table 43: 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