

Single Technology Appraisal

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Contents:

The following documents are made available to stakeholders:

Access the [final scope](#) and [final stakeholder list](#) on the NICE website.

- 1. Company submission from AbbVie:**
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
- 3. Patient group, professional group, and NHS organisation submissions from:**
 - a. British Gynaecological Cancer Society
 - b. Ovacome Ovarian Cancer Charity
 - c. Ovarian Cancer Action
 - d. Target Ovarian Cancer
- 4. Expert personal perspectives from:**
 - a. Prof Jonathan A Ledermann – Clinical expert, nominated by AbbVie
 - b. Agnieszka Michael – Clinical expert, nominated by British Gynaecological Cancer Society
 - c. Rachel Downing – Patient expert, nominated by Target Ovarian Cancer
 - d. Angela Ankrett – Patient expert, nominated by Ovarian Cancer Action
- 5. External Assessment Report** prepared by Peninsula Technology Assessment Group (PenTAG)
- 6. External Assessment Report – factual accuracy check**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Company evidence submission

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Abbreviations

Abbreviation	Definition
ADC	Antibody-drug conjugate
AE	Adverse event
AESI	Adverse event of special interest
AIBW	Adjusted ideal body weight
AIC	Akaike information criterion
BGCS	British Gynaecological Cancer Society
BIA	Budget impact analysis
BIC	Bayesian information criterion
BICR	Blinded independent central review
BNF	British National Formulary
BRCA	Breast cancer susceptibility gene
BSA	Body surface area
CA-125	Cancer-antigen 125
CC	Complication and comorbidity
CDF	Cancer Drugs Fund
CDx	Companion diagnostic
CE	Conformité Européenne
CEM	Cost-effectiveness model
CI	Confidence interval
CSR	Clinical study report
CT	Computed tomography
DOR	Duration of response
DoT	Duration of treatment
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for the Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FOLR1	Folate receptor 1
FR α	Folate receptor alpha
G20	Group of 20

Abbreviation	Definition
GCIG	Gynecologic Cancer Intergroup
GDP	Gross domestic product
GP	General practitioner
GPI	Glycosylphosphatidylinositol
GTG	Gynae Trials Group
HER2	Human epidermal growth factor receptor
HGS	High grade serous
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
IC Chemo	Investigator's choice of chemotherapy
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
IRP	International Recognition Procedure
ITT	Intention-to-treat
IV	Intravenous
IVD	In vitro diagnostic
KM	Kaplan-Meier
LSM	Least squares mean
LY	Life year
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MIB	Medtech Innovation Briefing
MMRM	Mixed model for repeated measures
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reached
OC	Ovarian cancer
OCAFP	Ovarian Cancer Audit Feasibility Pilot
ONS	Office for National Statistics
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAG	Patient advocacy group
PARP	Poly (adenosine diphosphate-ribose) polymerase

Abbreviation	Definition
PAS	Patient access scheme
PD	Progressed disease
PFS	Progression-free survival
PFS2	Time to second disease progression or death
PH	Proportional hazards
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRO	Patient reported outcome
PROC	Platinum-resistant ovarian cancer
PS2+	Positive staining intensity ≥ 2
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSSRU	Personal Social Services Research Unit
PT	Preferred term
Q3W	Every 3 weeks
QALY	Quality-adjusted life year
QLQ-OV208	Quality of Life Questionnaire ovarian cancer module
QoL	Quality of life
RCT	Randomised control trial
RDI	Relative dose intensity
RoB2	Cochrane Risk of Bias 2
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of product characteristics
SOC	System organ class
TA	Technology Appraisal
TEAE	Treatment-emergent adverse event
TSD	Technical Support Document
TTR	Time to response
UK	United Kingdom
VAS	Visual analogue scale

Executive summary

Ovarian cancer (OC) ranks as the deadliest gynaecological cancer, making it extremely severe (1, 2). It occurs due to the uncontrolled growth of abnormal cells in the ovaries, fallopian tube and primary peritoneum (3). Patients with advanced OC are typically treated with surgery and platinum-based chemotherapies, along with poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors in the first-line and the addition of bevacizumab for certain presentations. However, 80% will ultimately relapse, and almost all will develop platinum resistant ovarian cancer (PROC), which is the incurable, and eventual palliative stage of a patient's OC journey, and the focus of this submission (4, 5).

Patients with PROC endure a very poor prognosis and experience the worst survival outcomes among patients with OC of generally no more than 12 months (5-9). The standard of care for PROC has not evolved in the last two decades, and patients cycle through sequential single agent chemotherapies (10). These chemotherapies show limited efficacy in terms of survival benefit as well as inadequate tumour response rates (5-9). Moreover, patients face severe side effects — such as pain, fatigue, nausea, hair loss and haematological issues — that greatly diminish quality of life (QoL), leading some to discontinue treatment and trade meaningful progression-free survival (PFS) to avoid these debilitating adverse events (AEs) (1, 11, 12). PROC is thus a severe disease, with an undeniably high unmet need.

Mirvetuximab

Mirvetuximab soravtansine (referred to as mirvetuximab throughout) is anticipated to be indicated for the treatment of adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens (13), and referred to as FR α positive PROC throughout. Mirvetuximab is a first-in-class FR α -targeted antibody-drug conjugate (ADC), addressing a critical unmet need in PROC by providing the first treatment to demonstrate a statistically significant and clinically meaningful overall survival (OS) benefit compared with single agent chemotherapy in a Phase 3 RCT (Section 2) (1, 14).

Clinical evidence for mirvetuximab

The efficacy and safety of mirvetuximab for the treatment of patients with FR α positive PROC have been conclusively demonstrated in MIRASOL, a global, multicentre, open-label, Phase 3 randomised controlled trial (RCT) directly comparing mirvetuximab with

Investigator's choice of chemotherapy (IC Chemo) (1, 14, 15). This global study included 30 patients from the United Kingdom (UK), and as communicated by multiple UK clinicians, these results are highly relevant in a population reflective of current UK clinical practice, as they demonstrate meaningful outcomes for women with urgent unmet need but limited therapeutic options.

In MIRASOL, after a median follow-up of 28.35 months at the final data cut (26th September 2024), the benefit observed in the primary efficacy endpoint (progression-free survival [PFS]) was consistent with the primary data cut (6th March 2023; Appendix K), with a median PFS of 5.59 months vs 3.98 months, mirvetuximab vs IC Chemo respectively, and a hazard ratio (HR) of 0.63 (95% confidence interval [CI]: 0.513, 0.785; $p < 0.0001$), representing a 37% reduction in the risk of tumour progression or death. Notably, this benefit was consistent across subgroups and concordant with the sensitivity analysis by blinded independent central review (BICR).

Mirvetuximab demonstrated a statistically significant and clinically meaningful OS benefit compared with IC Chemo with a 32% reduction in the risk of death (HR: 0.68; 95% CI: 0.54, 0.84) and a median OS of 16.85 months vs 13.34 months, respectively. UK clinicians have highlighted these results as being highly significant and particularly meaningful given that they were observed in a contemporary PROC population, in whom historically it has been extremely difficult to demonstrate an OS benefit.

The objective response rate (ORR) observed with mirvetuximab (41.9%) was more than double that in the IC Chemo arm (15.9%; odds ratio [OR]: 3.75; 95% CI: 2.40, 5.85; $p < 0.0001$). In the mirvetuximab group, 5.7% of patients achieved a complete response, compared with 0% of the IC Chemo patients. Tumour shrinkage (encompassing complete and partial response, and stable disease) was observed for 80.1% of patients treated with mirvetuximab, compared with 56.2% of patients treated with IC Chemo.

Economic evidence for mirvetuximab

A de novo cost-effectiveness analysis using data obtained from MIRASOL, demonstrated that mirvetuximab represents a cost-effective treatment option for patients with PROC (Section 3). Considering the poor prognosis and substantial symptom burden for patients with PROC and their carers, at the patient access scheme (PAS) price for mirvetuximab and with a disease severity modifier of 1.7 applied, mirvetuximab is associated with incremental quality-adjusted life years (QALY) of [REDACTED] and incremental costs of [REDACTED], resulting in an incremental cost-effectiveness ratio (ICER) of [REDACTED] per QALY.

Conclusion

Alongside being a first-in-class ADC and the first targeted therapy in PROC via FR α expression, mirvetuximab is the first treatment to demonstrate a statistically significant overall survival benefit in PROC compared with IC chemo. Mirvetuximab delivers both a highly targeted and pronounced tumour response, rapidly reducing the disease volume while positively impacting the symptomatic burden and preserving QoL effectively addressing the key therapeutic needs in PROC management.

As such and considering its superior efficacy and manageable safety profile vs IC Chemo, mirvetuximab presents a cost-effective, innovative targeted therapy and a new standard of care for eligible PROC patients with urgent high unmet needs. Importantly, this breakthrough therapy for FR α positive PROC also contributes to three of the UK's health priorities: cancer, women's health and precision medicines (16-18).

1. Decision problem, description of the technology and clinical care pathway

1.1. Decision problem

The submission covers the technology's anticipated full marketing authorisation for this indication.

The objective of this appraisal is to determine the clinical and cost-effectiveness of mirvetuximab soravtansine (referred to as mirvetuximab throughout the document) in line with its anticipated marketing authorisation, "for the treatment of adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens" (13), and referred to as FR α positive platinum-resistant ovarian cancer (PROC) throughout. FR α positivity is defined using Roche's VENTANA® FOLR1 (FOLR-2.1) companion diagnostic (CDx) assay based on high expression, i.e. $\geq 75\%$ of tumour cells with moderate and/or strong membrane staining (PS2+) (1, 19).

Details of the decision problem addressed in this submission are provided in Table 1, with rationale provided for any differences from the National Institute for Health and Care Excellence (NICE) final scope (20).

Table 1. The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with FR α -positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer	Adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens	As mentioned in the response to the draft scope and decision problem form, the target population addressed in this submission is in line with the anticipated licensed indication (13)
Intervention	Mirvetuximab soravtansine	Mirvetuximab soravtansine	N/A
Comparator(s)	- Paclitaxel monotherapy - Pegylated liposomal doxorubicin hydrochloride monotherapy	Pooled chemotherapy, including - Paclitaxel monotherapy - Pegylated liposomal doxorubicin hydrochloride monotherapy	The comparators are in line with the NICE scope and best represented by the pooled chemotherapy arm of the MIRASOL trial which included clinician's choice between paclitaxel, pegylated liposomal doxorubicin, and topotecan, modelled as a single 'pooled chemotherapy' arm in line with the MIRASOL trial. These chemotherapies are the recommended therapies in PROC as per the BGCS guidelines (21), and are reflected in UK market research data (22).
Outcomes	- Overall survival - Progression-free survival - Response rate - Adverse effects of treatment - Health-related quality of life	- Overall survival - Progression-free survival - Response rate - Adverse effects of treatment - Health-related quality of life	N/A

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	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	• Number of previous lines of therapy • Previous poly (ADP-ribose) polymerase inhibitor treatment • Previous bevacizumab • BRCA status	N/A	Subgroup analysis was conducted for the clinical data (presented for the suggested subgroups in Section 2.8 and Appendix C). These analyses were exploratory only and therefore are not included in the economic model.
Special considerations including issues related to equity or equality	–	As a result of gender inequalities, magnified challenges for rare cancers and geographic and socioeconomic variation in treatment access, patients with OC (including PROC) are subject to health inequality concerns (2, 16, 17, 23-26). The benefits of mirvetuximab may contribute to reducing inequalities through earlier diagnosis of eligible patients, increasing treatment options and choice in an underserved, rare, disease area which affects women.	OC is a cancer affecting the female reproductive system. In the UK, there is a clear gender health gap in which women experience an additional 3 years of ill health and disability compared with men (17), underscoring the urgent need to improve women's health outcomes (17). OC is the most lethal gynaecological cancer in the UK (27) and patients with PROC experience the poorest outcomes (5). OC is rare and severe, posing unique challenges such as delayed screening, late/incorrect diagnosis, lack of treatment options, feelings of isolation, and reduced QoL. Therefore, health inequalities remain a major barrier to care for patients living with rare cancers. Not all patients in England have equal access to ovarian cancer treatments. Research has shown that there are geographic and socioeconomic variations in terms of treatment

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	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			access, hence leading to variations in health outcomes. Gender inequalities, challenges of rare cancer and disparities in treatment access create inequalities for patients with PROC. Mirvetuximab aims to contribute to addressing these challenges in patients with FRα positive PROC through its innovative, targeted medicine approach, offering significant survival benefits, a manageable safety profile, and preservation of QoL compared with chemotherapy.

Abbreviations: ADP, adenosine diphosphate; BGCS, British Gynaecological Cancer Society; BRCA, Breast Cancer susceptibility gene; FR α , folate receptor alpha; N/A, not applicable; NICE, National Institute for Health and Care Excellence; OC, ovarian cancer; PROC, platinum-resistant ovarian cancer; QoL; quality of life; UK, United Kingdom.

1.2. Description of the technology being evaluated

The summary of product characteristics (SmPC) or information for use, and the United Kingdom (UK) public assessment report are provided in Appendix A.

A description of mirvetuximab is provided in Table 2.

Table 2. Technology being evaluated

UK approved name and brand name	Mirvetuximab soravtansine (ELAHERE™; referred to as mirvetuximab herein)
Mechanism of action	Mirvetuximab is a first-in-class FRα-targeted ADC comprising a FRα-binding antibody, cleavable linker, and the cytotoxic maytansinoid DM4 payload, a highly potent tubulin inhibitor designed to kill the targeted cancer cells (1, 13). Upon binding to FRα, mirvetuximab is internalised followed by intracellular release of DM4 via proteolytic cleavage (Figure 1). DM4 disrupts the microtubule network within the cell, resulting in cell cycle arrest and apoptotic cell death of the targeted cancer cells (13). This effect extends through diffusion of DM4 catabolites across the cell membrane to neighbouring tumour cells (bystander killing), enabling the conjugate to be active against tumours with heterogeneous expression of FRα. Notably, mirvetuximab does not require sensitivity to platinum compounds. Figure 1. Mirvetuximab mechanism of action Abbreviations: FRα, folate receptor-α; MIRV, mirvetuximab.
Marketing authorisation/CE mark status	MHRA marketing authorisation is anticipated in [REDACTED].
Indications and any restriction(s) as described in the summary of product characteristics	Mirvetuximab as monotherapy is anticipated to be indicated for the treatment of adult patients with folate receptor-α (FRα) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens.

Method of administration and dosage	The recommended dose of mirvetuximab is 6 mg/kg adjusted ideal body weight (AIBW) [†] administered Q3W (21-day cycle) as an IV infusion [‡] until disease progression or unacceptable toxicity. Dosing based on AIBW reduces exposure variability for patients who are either under or overweight (Appendix A).
Additional tests or investigations	Higher expression of FRα (FOLR1) is observed in OCs with higher histologic grades, more advanced stages, and higher resistance to chemotherapy, with elevated levels of FOLR1 associated with increased cancer progression (28). PROC patients who express high levels[¶] of FRα are eligible for targeted treatment with mirvetuximab. The VENTANA[®] FOLR1 immunohistochemical assay (Roche) is a class C, CE-marked diagnostic test to detect membrane and cytoplasmic FRα expression by formalin-fixed, paraffin-embedded normal tissue sections in tissue microarrays and tumour sample sections from OC patients. Scoring of tissue sections is performed by pathologists (29). In MIRASOL (the Phase 3 pivotal trial for mirvetuximab), a scoring method based on a positive membrane stain intensity level of 2 or greater (PS2+), was used to assess patient FRα expression, using the VENTANA[®] FOLR1 test (1). The PS2+ scoring method requires the pathologist to assess the percentage of tumour cells with moderate (2) and/or strong (3) membrane staining compared with the total number of viable tumour cells. To be considered FRα-positive (high expression) and eligible for treatment with mirvetuximab, $\geq 75\%$ of viable tumour cells must exhibit 2 and/or 3 membrane staining intensity. In MIRASOL, the proportion of screened patients with positive FRα expression was 32% (1). The cost of the test (including pathologist time and cost of consumables) has been included in the economic model.
List price and average cost of a course of treatment	• Mirvetuximab is available at a list price of £4,950 per 100 mg vial • The average cost of a course of treatment with mirvetuximab (LIST price) is: £152,865[§]
Patient access scheme (if applicable)	A simple PAS is being submitted for mirvetuximab. The proposed mirvetuximab price with the PAS applied is [REDACTED] per 100 mg vial

Source: Draft SmPC (Appendix A).

[†]The total dose of mirvetuximab is calculated based on each patient's AIBW using the following formula: AIBW = Ideal Body Weight (IBW [kg]) + 0.4*(Actual weight [kg] – IBW); Female IBW [kg] = 0.9*height [cm] – 92; [‡]Mirvetuximab requires dilution with 5% glucose for IV infusion. Mirvetuximab is incompatible with normal saline; [¶] $\geq 75\%$ of viable tumour cells with 2+ membrane staining intensity.

[§]Discontinuation from mirvetuximab corresponds with that used within the CEM.

Abbreviations: ADC, antibody-drug conjugate; AIBW, adjusted ideal body weight; BGCS, British Gynaecological Cancer Society; CE, Conformité Européenne; ESMO, European Society for Medical Oncology; FOLR1, folate receptor 1; FR α , folate receptor alpha; HGS, high grade serous; IBW, ideal body weight; IV, intravenous; MHRA, Medicines and Healthcare products Regulatory Agency; OC, ovarian cancer; PAS, patient access scheme; PROC, platinum-resistant ovarian cancer; PS2+, positive staining intensity ≥ 2 ; Q3W, every 3 weeks; SmPC, summary of product characteristics; UK, United Kingdom.

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1.3. Health condition and position of the technology in the treatment pathway

Ovarian cancer (OC) is rare, severe and diagnosed late (1); around 80% of patients relapse after first-line treatment and almost all relapsed patients eventually develop platinum-resistant ovarian cancer (PROC) (4, 5).

- OC is the deadliest gynaecological cancer (27) and the 6th leading cause of cancer deaths in females in the United Kingdom (UK; 2017–2019) (2). The overall 5-year relative survival for OC in the UK is below the European average.
- The rarity of OC, the non-specific symptoms and the lack of validated screening programmes delay patients' diagnosis resulting in ~70% of women diagnosed with OC at an advanced stage and one-third of patients waiting >3 months for a correct diagnosis (30, 31). Additionally, younger patients face additional inequalities as they find it harder to get a diagnosis due to age-related diagnostic bias.
- Around 90% of all OC is epithelial in origin (32), of which ~70% are classed as high grade serous (HGS) (33). HGS is the most aggressive form of OC (34–36), accounting for 70–90% of OC-related deaths (34, 37, 38).
- While most patients respond well to first-line multi-modality treatment of surgery and platinum-based chemotherapies, ~80% relapse after first-line and nearly all patients with recurrent disease eventually develop PROC (4, 5), which is the incurable phase of OC and the focus of this submission. An estimated 2,144 women in England develop epithelial HGS PROC each year.

Patients with PROC have the poorest prognosis among patients with OC, with a median overall survival (OS) of ≤12 months and a substantial negative impact on quality of life (QoL)

- Platinum-resistance is a key prognostic factor and a major contributor to OC mortality in HGS OC (27). Patients with PROC face the worst survival prognosis amongst patients with OC with a median OS of ≤12 months (5).
- Patients become increasingly symptomatic as PROC progresses due to malignant ascites, bowel obstruction, and an inability to tolerate medication or take food (10). They also experience substantial psychological distress such as anxiety, depression, loss of behavioural and emotional control (39, 40), mental insecurity, guilt and loss of feminine identity (41).
- Patients report their disease negatively impacts their ability to do normal daily activities as well as affecting their hobbies (42). The burden also extends to caregivers, with almost half reporting elevated anxiety (40).

For patients with PROC, the reliance on decades-old chemotherapies and the absence of targeted therapies highlight an urgent need for more effective and tolerable treatments to address this critical gap in care

- To date, there have been no new treatments for patients with PROC in England/Wales for two decades, reflected in several suspended or terminated NICE appraisals (43–47). Importantly, no Phase III RCT has ever shown a statistically significant overall survival benefit versus chemotherapy in this population.
- Standard of care primarily consists of single agent non-platinum chemotherapies (e.g. weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan). These chemotherapies offer limited survival benefits and short-lived tumour responses, with objective response rates (ORR) as low as 10–15%, progression-free survival (PFS) typically 3–4 months, and OS of less than 12 months (5–9).

- Additionally, chemotherapy adverse events (AEs) can have such a negative impact on quality of life (QoL) that patients are willing to trade meaningful PFS time in order to avoid severe AEs (48). Side effects such as nausea and hair loss have a negative impact on patients' wellbeing, while chemotherapy-related haematologic side effects from multiple treatment cycles are associated with high treatment and economic burden and may lead to patients discontinuing therapy (1, 11, 12).
- Given the poor outcomes with existing therapies and the high treatment burden, there is a substantial unmet need for therapies that provide significant survival benefits and improve or maintain QoL for patients with PROC.

Mirvetuximab soravtansine is a first-in-class antibody-drug conjugate (ADC) targeting folate receptor alpha (FR α), addressing a critical unmet need in PROC by providing statistically significant and clinically meaningful survival benefits through a targeted therapy approach (1, 14)

- Mirvetuximab marks a substantial innovation in the PROC setting, being the first targeted therapy utilising a FR α expression biomarker-directed strategy, to deliver a highly potent cytotoxic agent directly to tumour cells enabling a precision-led approach for patients with high FR α expression, who are most likely to respond to treatment.
- Mirvetuximab is the first treatment to demonstrate a statistically significant OS benefit in a Phase 3 randomised controlled trial (RCT; MIRASOL) in PROC compared with chemotherapy. It addresses the high unmet need in PROC where there is an urgent need for clinically effective, less toxic, targeted therapies.
- As well as improving OS, mirvetuximab also demonstrated a statistically significant and clinically meaningful improvement in PFS compared with IC Chemo, with a differentiated and manageable safety profile and improved QoL versus chemotherapy (Section 2).
- The proposed positioning of mirvetuximab is for adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens.
- In recognition of mirvetuximab's benefits, it has been approved by the European Medicines Agency (EMA) for the treatment of adult patients with FR α positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens, and the Food and Drug Administration (FDA) for the treatment of adult patients with FR α positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens (49, 50), and is anticipated to receive UK marketing authorisation in [REDACTED]. Additionally, the current National Comprehensive Cancer Network (NCCN) guidelines recommend mirvetuximab as a preferred single-agent targeted therapy for recurrent PROC in patients with high FR α expression (51).

Mirvetuximab soravtansine may contribute to reducing inequalities by offering an innovative treatment in a highly underserved and rare disease area affecting women, whilst aligning with ongoing government health priorities

- This is especially relevant given the UK has the largest gender health gap in the G20, with women living an average of 3 more years in ill health and disability than men (17).
- Compared with patients with common cancers, patients with rare cancers like PROC face health inequalities related to delayed diagnosis, limited treatment options (52), and geographic and socioeconomic disparities in treatment access (53, 54), all of which contribute to poorer outcomes.

- The introduction of mirvetuximab aligns with the Government's priorities to improve outcomes for rare and less common cancers as emphasised in the National Cancer Plan consultation and the Government's push for equitable access to precision medicine (55).

1.3.1. Disease overview

The target population in this submission is adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens. Platinum-resistant high grade serous (HGS) ovarian, fallopian tube, or primary peritoneal cancer is referred to as PROC throughout the submission.

Ovarian cancer (OC) is a term used to describe the uncontrolled growth of abnormal cells in the ovaries, fallopian tube, and primary peritoneum (1). Approximately 90% of all OC is epithelial in origin, with the remainder originating in stromal or germ cells (32). Of the OCs originating from epithelial cells, approximately 70% are classed as HGS (OCs that are high grade and originate in the secretory cells of the fallopian tube) (33, 56). Sections 1.3.2–1.3.3 present insights into OC, highlighting PROC (which has the highest unmet need) where PROC-specific data are available.

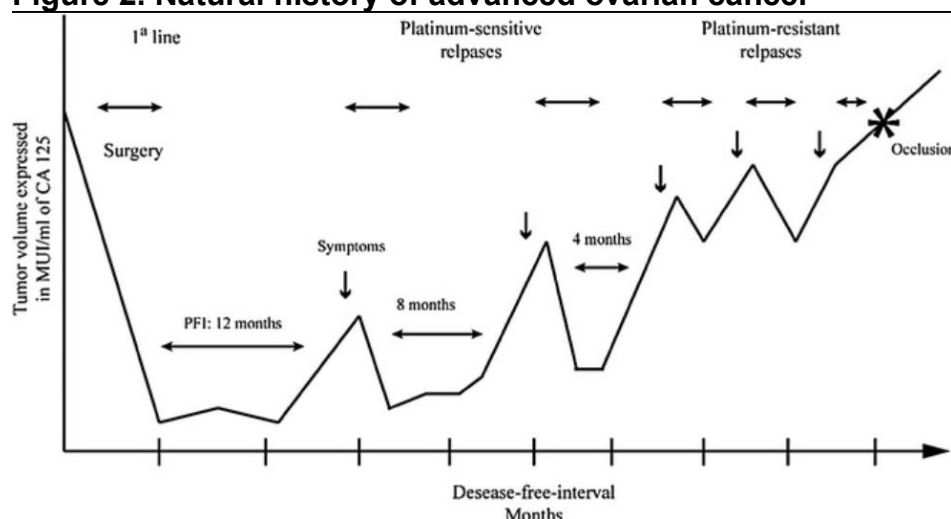
The signs and symptoms of OC at diagnosis are typically non-specific, and can include abdominal pain or bloating, frequent or urgent urination, gastrointestinal issues including nausea, vomiting, anorexia, early satiety, dyspepsia, abdominal cramping, and changes in bowel habits (57). Patients also often experience ascites, pleural effusion, and venous thromboembolism (58-61). Clinical symptoms worsen as OC progresses. Due to the lack of specific symptoms and the absence of validated screening programmes, early-stage OC is underdiagnosed, and symptoms can go undetected until advanced stages. As a result, a substantial proportion of women (~70%) have advanced disease (International Federation of Gynecology and Obstetrics [FIGO] Stage 3 and 4)^a at the time of OC diagnosis (62), and around 40%

^a At FIGO Stage 3, the tumour involves one or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes, whereas at Stage 4, there are metastasis beyond the peritoneal cavity or parenchymal intra-abdominal metastases

of cases are only diagnosed after an emergency admission, leading to poorer outcomes (31). Notably, one-third of UK patients wait >3 months from their first general practitioner (GP) visit for an accurate OC diagnosis (30, 62), and younger patients are further disadvantaged due to age-related diagnostic bias; they find it harder to get a diagnosis and have to self-advocate for specific tests.

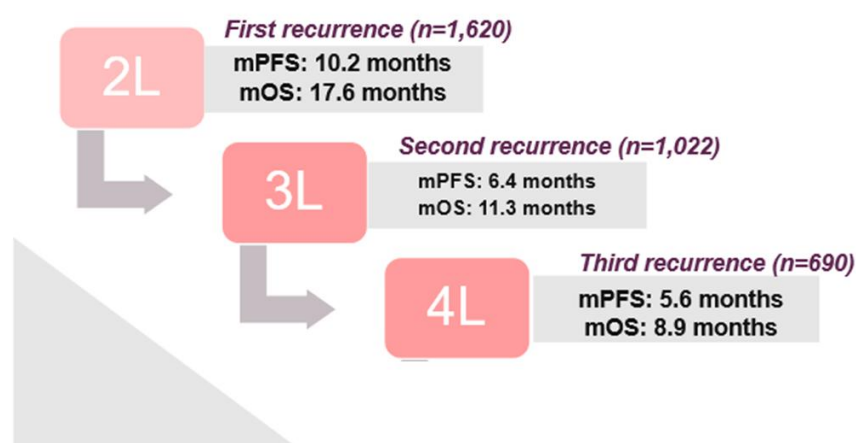
Standard of care treatment for OC is typically surgery with platinum-based chemotherapies in the first-line (discussed further in Section 1.3.3). While many patients initially respond positively to treatment, around 80% with advanced disease will relapse within 3 years and recurrent disease is generally incurable (4, 5). With each relapse, the duration of response to treatment decreases (Figure 2), and eventually almost all patients with recurrent disease will become resistant to platinum-based chemotherapy (1, 63). This is referred to as platinum-resistant ovarian cancer (PROC), and is the focus of this submission. The British Gynaecological Cancer Society (BGCS) (21) defines PROC as “progression with an interval of less than 6 months after completion of platinum-based chemotherapy”. Notably, patient outcomes worsen with each recurrence and subsequent line of treatment (Figure 3) (64). As such, there is a significant unmet need for patients with PROC as their disease is incurable and treatment options are limited.

Figure 2. Natural history of advanced ovarian cancer



Source: adapted from Gianneli (2016) (63).
Abbreviations: PFI, platinum free interval.

Figure 3. Patient outcomes at subsequent recurrences and lines of treatment



Source: adapted from Hanker (2012) (64).

Abbreviations: 2L, second line, 3L, third line, 4L, fourth line; mOS, median overall survival; mPFS, median progression-free survival.

Epidemiology

OC, which includes fallopian tube and primary peritoneal cancer, is a type of rare cancer (23-25). Approximately 7,110 women are diagnosed with OC each year in England (65) and 310 women per year in Wales (66). Overall, the age-standardised incidence rate of OC is estimated to be 24.6 cases per 100,000 person-years in England (65) and 17.8 per 100,000 person-years in Wales (66). The risk of OC has been shown to increase with age, family history of OC, and germline mutations in the breast cancer susceptibility (BRCA) 1/2 genes (67). In the UK, a retrospective medical record study including 296 patients demonstrated that the mean age of diagnosis of PROC was 59.2 years (standard deviation [SD]: 10.7 years) (68).

Although no published studies were identified for the national incidence or prevalence of PROC specifically, estimates based on clinician input and the annual incidence of OC suggest around 2,144 women in England develop epithelial HGS PROC each year (see Company budget impact analysis [BIA] submission, Section 3). Of patients tested for FR α expression, an estimated 32% of patients with PROC are expected to have high FR α expression ($\geq 75\%$ of viable tumour cells exhibit 2 and/or 3 membrane staining intensity), a requirement for mirvetuximab eligibility, resulting in approximately [REDACTED] eligible patients in this population (1, 11, 29) (see Company BIA submission, Section 3).

1.3.2. Disease burden

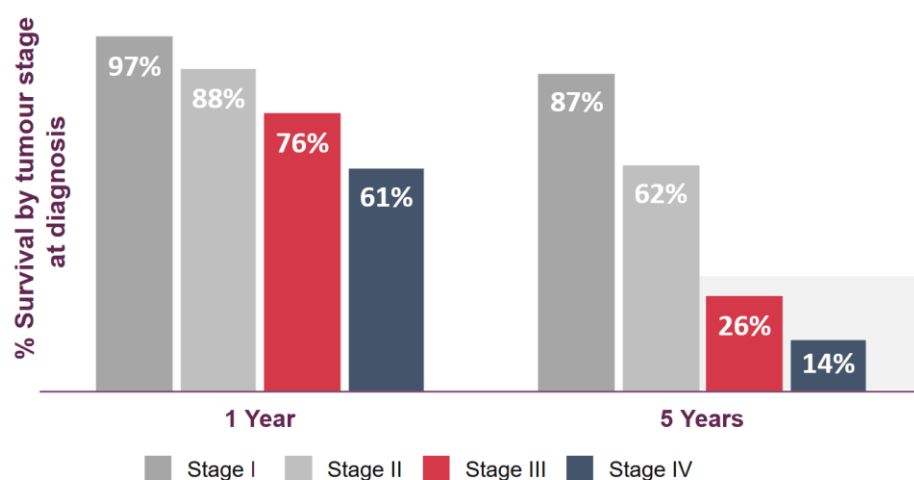
Clinical burden

OC is the most lethal gynaecological cancer in the UK (27) and the 6th most common cause of cancer death in females, accounting for 5% of all cancer deaths in females (2017–2019), representing 11 deaths per day (2).

OC mortality is strongly related to age, with the highest mortality rates being in older women (2). In the UK in 2017–2019, 45% of OC deaths were in females aged 75 years and over (2). Due to the high rate of OC recurrence, there have only been modest improvements in 5-year survival rates for OC over recent decades.

Alarming, overall 5-year relative survival for OC in the UK is below the European average (69). Survival rates diminish with each successive tumour stage at diagnosis, with a 5-year survival rate of 14–26% in patients with advanced staged (Stage III–IV) OC vs 62% in Stage II and 87% in Stage I (Figure 4) (1, 33, 35, 70-72).

Figure 4. Survival by tumour stage at diagnosis



Source: Gaitskell, 2022 (35); Eurohealth, 2022 (70).

The most common and aggressive form of epithelial OC is HGS (34-36), which accounts for 70–90% of OC-related deaths (34, 37, 38) and has the poorest prognosis, with a 5-year survival rate of approximately 31% (35).

Development of platinum-resistance is one of the strongest prognostic factors in OC and one of the main drivers of mortality in OC with HGS histology (27). Patients with PROC have a very poor prognosis and worse survival outcomes than patients with

platinum-sensitive OC (5). PROC is especially difficult to treat with current standard of care therapies, characterised by a median overall survival (OS) of ≤ 12 months, limited and short-lived tumour responses, with objective response rates (ORR) as low as 10–15%, including the likely inability of achieving complete tumour responses, and a short period of progression-free survival (PFS: 3–4 months) (5-9).

Quality of life (QoL)

PROC has a detrimental impact on quality of life (QoL). Factors contributing to a reduced QoL include the impact of a PROC diagnosis and associated symptoms, limitations in current treatment options and the impact on QoL for care-givers, which combined contribute to a feeling of hopelessness. There is thus a clear unmet need for treatments that minimise the QoL impact on patients with this incurable cancer, and their carers.

Impact of PROC diagnosis and symptoms on quality of life

Cancer-related symptoms greatly affect patient QoL, both in the number and severity of symptoms (42).

Physical symptoms

Almost all patients with PROC become increasingly symptomatic with abdominal pain due to malignant ascites, increasing tumour mass leading to bowel obstruction, an inability to tolerate medication or food, and declining performance status precluding further anticancer therapy (10). Bowel obstruction represents one of the most severe complications in the late phase of PROC, affecting up to 50% of patients (73, 74). Further to this, clinicians have also noted that gastrointestinal and bowel-related symptoms carry a negative impact for patients with PROC, with bowel obstruction being the most profound contributor to death. Symptoms of bowel obstruction in PROC are difficult to manage and often require hospitalisation, posing a significant burden on patients, their caregivers, and the healthcare system (73). As such, treatment selection to reduce the tumour burden is aimed at delaying and avoiding this significant complication as much as is possible.

AbbVie conducted a focus group discussion with a patient advocacy group (PAG), where PAG representatives shared that the most challenging symptoms for patients were:

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- **Bowel obstructions** – “[patients] are absolutely terrified about this. If they are following low fibre diet, they feel incredibly socially isolated because suddenly they can’t go out for meals anymore or if they do, it takes extraordinary amounts of planning and looking at menus in advance”.
- **Recurrent ascites** – “having to be drained time and time again, or having a permanent drain, feeling like you’re living in a distorted body, actual draining is a very traumatic experience”.
- **Pleural effusions** – “feeling breathless, really scary for people”

In a prospective observational study assessing the symptoms of patients with PROC, the most common disease-related symptoms were fatigue (92%), worry (89%), and trouble sleeping (76%) (75), with abdominal-related symptoms including abdominal swelling, bloating, and/or fullness, and abdominal pain, discomfort and/or cramps, fatigue, anorexia, and anxiety reported in another study (76). Thus, there is a clear unmet need for treatments that not only prolong survival but also improve symptom control for patients with an incurable cancer.

Emotional symptoms

The World Ovarian Cancer Coalition’s Every Woman Study™ (2018), involving 1,531 women from 44 countries, reported that women’s mental and emotional wellbeing are as important as physical wellbeing in terms of QoL (77). Indeed, multiple studies have found that women with OC (including PROC) report higher levels of psychological distress compared with women in the general population, as well as in comparison with women with other types of cancer (39). Notably, patients with OC in the UK are almost twice as likely to experience clinically-significant depression and over four times more likely to experience clinically-significant anxiety than women without OC (78). Patients have also underscored the impact that OC has on “family and other personal relationships as well as work, volunteering and hobbies”, as seen in Target Ovarian Cancer UK’s response to the NICE draft scope for mirvetuximab (79). These findings are reflected in the patient perspectives shared by PAG representatives with AbbVie, particularly for patients with PROC: “*Being told that you’re platinum-resistant is an extremely scary place to be. They start*

thinking...Am I looking at end-of-life care? My options are running out. I'm not responding to platinum anymore. There is huge amount of anxiety and worry".

Recurrent OC (including PROC), which is incurable, is also associated with a negative impact on emotional wellbeing compared with women who are newly diagnosed (42). The psychological distress experienced typically manifests as anxiety, depression, and loss of behavioural and emotional control (39, 40). Many patients with PROC or recurrent OC reported limitations in activities such as moving a table, using a vacuum cleaner, going for a walk or a bicycle ride, and climbing several flights of stairs compared with those without recurrence (42). This is further supported by an Adelphi real-world evidence (RWE) study commissioned by AbbVie across five countries including the UK. The study reported that over 50% of patients with PROC required additional support/care, with 50% requiring help with transportation (e.g. to attend events), 53% requiring help with house cleaning or home maintenance, 38% requiring help with shopping and meal preparation, and 38% requiring help with finances (80). Most women with recurrent disease also reported they were able to do less than they desired (64.7%) and that they were limited in work and other routine daily activities (71.6%) compared with women without recurrence (14% and 21%, respectively) (80).

Furthermore, OC treatment can cause early or surgical menopause and impact fertility in younger women (81). It is well established that loss of fertility during treatment with cancer can be more distressing than cancer itself (41). In addition, many patients with OC experience mental insecurity and become distressed through a perceived lack of support and avoidance from friends and family (41). This can often be driven by a reduction in the level of intimacy with a partner or spouse causing feelings of guilt and loss of feminine identity (41), as captured in patient testimonies such as: *"It's completely affected me. Body image, anxiety, my personality has changed."* (82).

Impact of treatment on QoL

Patients with advanced OC (including PROC) experience treatment-related side effects that negatively affect QoL. Grade 3+ adverse events (AE) are reported in 54% to 65% of patients with PROC treated with chemotherapy (83-85), and often

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without any improvement in disease-related symptoms. A Gynaecologic Cancer Intergroup (GCIg) study reported that 44% of chemotherapy-treated patients with PROC experienced pain, 37% experienced fatigue, and 32% experienced abdominal bloating/discomfort (86). In another study involving 102 patients with PROC, 73% reported being negatively affected by treatment side effects, which included nausea (41%) and hair loss (51%), neither of which improved over time (75). Of note, 47–58% of women report that alopecia is the most disturbing anticipated aspect of receiving chemotherapy (87, 88). Patients with PROC also experience haematological AEs associated with chemotherapy, including neutropenia, anaemia, and thrombocytopenia (1, 11, 12), contributing to the high treatment burden and impeding the continuation of treatment (1, 11, 12).

The treatment burden and impact on patients QoL is further demonstrated by the patient perspectives obtained by AbbVie (89):

- *“I didn’t feel like eating, tired, laying on the couch all the time. First year I didn’t want to go anywhere. So, I missed weddings and different life events.”*
- *“Every time you get another round, all of the side effects get worse. I lost my hair, the nausea, I was having diarrhoea again, the fatigue. It was a lot...especially with chemo that they bring you so close to death without actually letting you get there because you feel like you’re going to die. It’s traumatic.”*
- *“I lost probably 40 pounds. I couldn’t eat. I had to go to the hospital once a week to get fluid infusions, because I couldn’t drink, because everything came up. It was absolutely horrible. If this was going to be my life, that was the end of it. I didn’t really want to continue like that.”*

Notably, these treatment-related AEs have such a negative impact on QoL that patients with advanced OC are willing to trade meaningful PFS time in order to avoid severe AEs, highlighting the substantial treatment burden of this disease (48).

Impact on caregiver QoL

The negative impact on mental wellbeing also extends to caregivers, with a study of 798 women with OC and 373 caregivers reporting that over 42% of caregivers reported elevated anxiety (40). In another study, 55% of caregivers reported feeling

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moderately or extremely anxious or depressed (90). Men, who are often partner-caregivers, are often underrepresented in caregiver literature and hence their distress is often underreported and underestimated (91).

The Adelphi RWE study commissioned by AbbVie in five countries, including the UK, found that caregivers for patients with PROC spend an average of 35.4 hours per week providing care, with partners/spouses spending 26.0 hours per week and children over 18 years spending 24.1 hours per week (80).

Economic burden

Direct costs

Disease management and treatment-related side effects in patients with OC are associated with considerable resource use and direct costs to health systems (68, 92-97). A systematic literature review (SLR) of 17 studies in PROC^b reported that the overall average annual per patient cost was €24,111, with an annual cost per patient of €42,547 in Stage 4 OC. This equates to an overall average cost per patient of £20,696.70, and £36,522.10 in Stage 4 OC.^c Of these costs, advanced chemotherapy, hospitalisations, and surgery accounted for 87.2% of direct healthcare costs (92).

Additionally, toxicity associated with current PROC treatments pose a significant additional economic burden due to the management of side effects such as neutropenia, anaemia, and thrombocytopenia (Section 3.5.5) (98). In a retrospective study, patients with PROC in the UK required an average hospital stay of 6.5 days per month (68).

Indirect costs

Although there is limited UK specific indirect cost data, evidence from wider populations demonstrates that OC is also associated with indirect costs borne by reduced productivity from working-age patients and caregivers (68, 92-97).

^bStudies were conducted in the US, Iran, Canada, Belgium, Spain, Thailand, Portugal, and Australia.

^cConverted to Great British pounds (GBP) using a currency exchange rate of 1 Euro to 0.8584 GBP

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In a global study across 11 countries, the UK was found to have an OC-related socioeconomic burden of \$7.6 billion (£5.7 billion) equating to 0.24% of gross domestic product (GDP), with \$653 million (£489 million) of this coming from healthcare expenditure.^d Other indirect cost categories of patient time, labour productivity, informal caregiving, and mortality losses accounted for \$32.5 million (£24.3 million), \$52.5 million (£39.3 million), \$95.7 million (£71.6 million) and \$6.7 billion (£5 billion), respectively.^e Notably, the UK was second only to the US in the magnitude of the cost burden (99). Taken together, there is a clear and substantial economic burden associated with OC in the UK.

1.3.3. Clinical pathway of care

Current treatments for OC

Treatment for OC generally comprises of surgery and platinum/taxane based chemotherapy with the approach dependent on disease stage (11). For patients with advanced disease, treatment options are influenced by factors such as patient age, comorbidities, extent of disease, or patient condition with many patients treated with chemotherapy at first line with interval cytoreductive surgery considered during the chemotherapy phase (100).

Standard first-line treatment of advanced OC comprises of surgery with platinum-taxane based doublet chemotherapy, with the addition of bevacizumab for certain clinical presentations (21) (Figure 5). If patients demonstrate clinical response to their platinum doublet chemotherapy, poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors (olaparib, niraparib, and rucaparib) and/or bevacizumab are given as maintenance treatment (dependent on biomarker status of the patient) (21, 101).

The majority of patients initially respond well to this multi-modality treatment (4, 5). However, within 3 years approximately 80% will relapse, at which point the disease generally becomes incurable (4, 5). As per the BGCS guidelines (21), patients who

^dConverted to GBP using a currency exchange rate of 1 US dollar to 0.7484 GBP

^eConverted to Great British pounds (GBP) using a currency exchange rate of 1 Euro to 0.8584 GBP
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continue to experience disease progression more than 6 months after their last platinum treatment, are considered to be platinum-sensitive, and typically receive repeated lines of platinum-based therapy (21).

Figure 5. Current pharmacological treatment pathway in England/Wales (NICE)

1L	Induction	Platinum-based Chemotherapy (TA55)			Platinum-based Chemotherapy plus Bevacizumab**	
	Maintenance	Olaparib (TA962, BRCA+)	Niraparib (TA673, CDF, HRD+/-)	Rucaparib (TA1055, BRCA-, HRD+/-)	Olaparib + Bevacizumab (TA946, HRD+)	Bevacizumab* (HRD+/-)

2L+	Platinum sensitive (progression >6 months)			Platinum resistant (progression <=6 months)	
	Induction	Platinum-based Chemotherapy (TA389)			
2L+	Maintenance	Olaparib^ (TA908, BRCA+)	Niraparib^ (TA784, BRCA+/-)	Rucaparib^ (TA1007, BRCA+/-)	PLD or Paclitaxel (TA389)

^Not current practice to retreat with PARPi; **NHSE clinical policy for bevacizumab 15 mg/kg and 7.5 mg/kg, *NHSE clinical policy for Bevacizumab 7.5 mg/kg.
 Sources: TA962 (102); TA673 (103); TA946 (104); TA908 (105); TA784 (106); TA1007 (107); TA389 (108); TA1055 (101).
 Abbreviations: 1L, first line; 2L+, second line plus; BRCA, BReast CAncer gene mutation; CDF, Cancer Drugs Fund; HRD, homologous recombination deficient; NHSE, National Health Service England; NICE, National Institute for Health and Care Excellence; PARPi, poly (adenosine diphosphate-ribose) polymerase inhibitor; PLD, pegylated liposomal doxorubicin; TA, technology appraisal.

Patients who experience disease progression within 6 months from their last platinum treatment are considered to have PROC. As previously mentioned, each disease relapse is associated with a shorter response to treatment, and eventually almost all patients will become resistant to platinum-based therapy and be diagnosed with PROC (1, 63).

Current treatments for PROC

PROC is a severe and incurable phase of OC. The goals of therapy for clinicians treating patients with PROC are to improve or maintain health-related quality of life (HRQoL) and where possible, extend time to further progression and prolong survival (73, 109-111). Similarly, for patients, “it is really about the quality of life at this stage. Patients don’t want to prolong life at any cost. It’s not even a big bucket list. It’s about being able to spend good time with family, see friends, enjoy their garden.” At this stage of the disease, patients are “having to take a decision to do something that’s going to make them feel rotten without actually knowing what the outcome is going to be” (112).

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NICE guidance (Technology Appraisal [TA]389) for patients with PROC recommends paclitaxel and pegylated liposomal doxorubicin (108), in line with the comparators in the NICE final scope for mirvetuximab. As per BGCS guidelines, the recommended therapies in PROC consist of non-platinum chemotherapy (e.g. weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan^f) administered as a single agent (21). The BGCS guideline recommendations are reflected in the chemotherapy usage in UK clinical practice, and also supported by market research data collected by AbbVie between August–October 2024 on patients with PROC, which shows that at second-line, 14% of patients with PROC receive paclitaxel, 45% receive pegylated liposomal doxorubicin, and 9% receive topotecan; and at third-line, 25% of patients with PROC receive paclitaxel, 36% receive pegylated liposomal doxorubicin, and 4% receive topotecan (22).^g The BGCS guidelines are also broadly in line with other key clinical guidelines, including European Society for Medical Oncology (ESMO) (33), Scottish Intercollegiate Guidelines Network (SIGN) (113), and National Comprehensive Cancer Network (NCCN) (51).

1.3.4. Unmet need in PROC

Patients with PROC have a very poor prognosis and the worst survival outcomes among patients with OC, with a median OS of ≤ 12 months and a PFS typically 3–4 months (5). As disease progresses, physical complications like bowel obstructions and pain worsen while emotional distress (e.g. anxiety, depression, loss of feminine identity) becomes more pronounced (73-76) (see Section 1.3.2 on physical and emotional symptoms related to PROC).

Available therapies for PROC offer response rates as low as 10–15%) and low survival benefit, often at the cost of significant toxicity (5-9). Common side effects – fatigue, nausea, diarrhoea, alopecia and asthenia – can be intolerable, and can lead to patients stopping treatment altogether (48) (see Section 1.3.3 on current treatments for PROC and Section 1.3.2 on impact of treatment on QoL).

^fTopotecan is recommended by the BGCS guidelines (21), however it is not recommended by NICE (108).

^gThe market research does not sum to 100% as regimens/interventions not included in the NICE scope were also reported (such as interventions approved in Scotland, e.g. bevacizumab).

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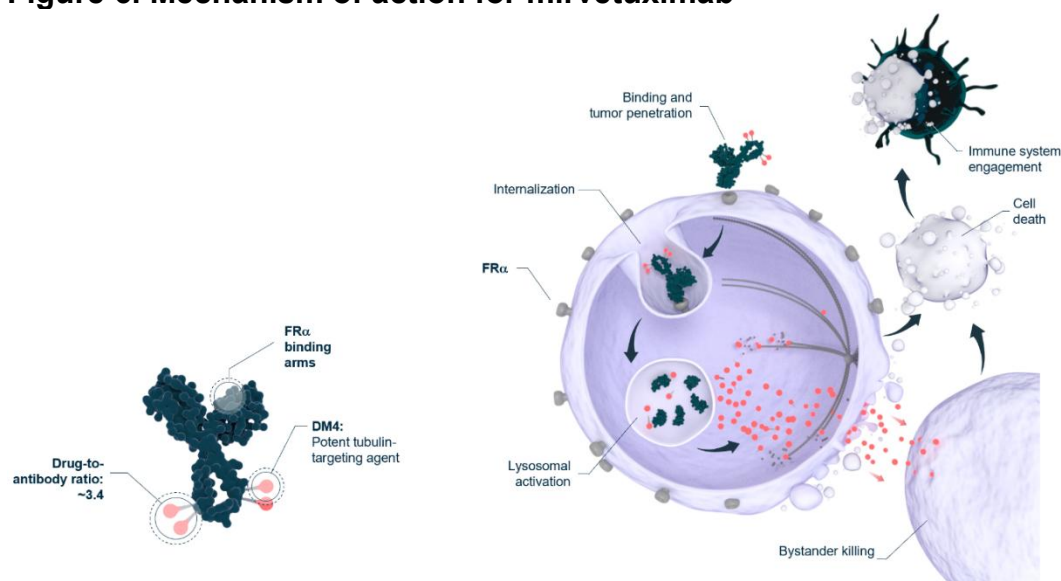
To date, there have been no new treatments for patients with PROC in England/Wales for two decades, reflected in several suspended or terminated NICE appraisals (10, 43-47). The persistent lack of innovation is a key concern for patients with PROC, as highlighted by Ovacome, a UK OC charity: “They [our members] have shared their concerns that treatment options are limited and lines of treatment to control the disease will be exhausted leaving symptom control only.” In the past decade, clinical studies of many novel anti-cancer therapies, including immune checkpoint inhibitors, targeted therapies, and small molecule inhibitors, have failed in the PROC space (10). Importantly, no large, randomised Phase 3 study in PROC has shown a statistically significant OS benefit versus chemotherapy, except mirvetuximab in MIRASOL (114). The critical unmet need in PROC is also recognised within the clinical community, as evidenced by the BGCS guidelines and the UK Gynae Trials Group (GTG) key strategic priorities that emphasise the need for more effective, less toxic and biomarker-led treatment options (21, 115).

1.3.5. Mirvetuximab soravtansine

Mirvetuximab is a first-in-class FR α -targeted antibody-drug conjugate (ADC). ADCs consist of a monoclonal antibody targeting a tumour-specific cell-surface protein (in this case FR α), and a highly potent cytotoxic maytansinoid (DM4) payload, connected by a chemical linker designed to stay intact until delivered to the tumour cell (116-118). This approach allows targeted delivery of the cytotoxic DM4 and selective killing of tumour cells (29). Additionally, this delivery mechanism avoids the systemic toxicity consequences the highly potent DM4 would otherwise exert if not conjugated to an antibody for targeted tumour delivery (116-118).

Upon binding to the FR α receptor, mirvetuximab is internalised into the cell followed by intracellular release of DM4 via proteolytic cleavage. DM4 and its active metabolites disrupt the microtubule network within the cell, resulting in cell cycle arrest and apoptotic cell death. Also, DM4 and its metabolites can enter neighbouring cells after release from target cells to induce bystander cytotoxicity; effective for heterogeneous and metastatic tumour cells (Figure 6) (119, 120).

Figure 6. Mechanism of action for mirvetuximab



Source: Based on Ab et al, 2015 (121) and mirvetuximab soravtansine EMA SmPC (13).
Abbreviations: EMA, European Medicines Agency; FRα, folate receptor alpha; SmPC, summary of product characteristics.

Increased levels of FRα are associated with chemotherapy resistance (122). FRα is a glycosylphosphatidylinositol (GPI)-anchored cell-surface glycoprotein encoded by the folate receptor 1 (*FOLR1*) gene (29). Folates and folate receptors have long been a focus of oncology research as a means of targeting cytotoxic treatments to tumour cells (123, 124). FRα is highly expressed in approximately 90% of ovarian carcinomas with minimal expression in healthy tissue, making it an attractive and clinically relevant target for OC therapy (29, 125, 126). In PROC, an estimated 32% of patients have high FRα expression (≥75% of viable tumour cells exhibit 2 and/or 3 membrane staining intensity) (1, 11, 29). Patients eligible for treatment with mirvetuximab are identifiable with a standard immunohistochemistry companion diagnostic test that measures FRα protein expression levels, enabling the identification of patients most likely to benefit from treatment (Section 1.3.6 and Appendix J).

As OC is a highly heterogeneous disease with distinct sub-clonal populations and diverse phenotypes, a predictive biomarker (e.g. FRα) to accompany a targeted therapy would allow for a precision medicine management strategy. Currently, there are no targeted treatments reimbursed in England/Wales for PROC, with mirvetuximab anticipated to be the first. The lack of available targeted therapy

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options is a major limitation in PROC treatment, as targeted drug delivery can minimise drug-mediated toxicities on adjacent tissues/organs and may help reduce damage leading to organ failures associated with traditional approaches (127). Health economic models show that precision medicine reduces unnecessary treatments and hospitalisations by ensuring that only the patients most likely to benefit from specific therapies receive them, thus lowering overall healthcare costs (128). This also aligns with the ongoing government focus on precision medicine, women's health, and rare and less common cancers (16-18, 55, 129, 130).

Mirvetuximab addresses an area of significant unmet need in PROC where patients face limited efficacy and high AE burden with standard of care chemotherapies. Mirvetuximab was approved by the European Medicines Agency (EMA) for the treatment of adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens, in November 2024, and the Food and Drug Administration (FDA) for the treatment of adult patients with FR α positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens in March 2024 (49, 50), with Medicines and Healthcare Products Regulatory Agency (MHRA) approval anticipated in [REDACTED]. Additionally, in recognition of the benefits that mirvetuximab brings, the current NCCN guidelines (v1.2025) recommend mirvetuximab as the preferred single-agent targeted therapy for recurrent PROC in patients with high FR α expression (category 2A) (51).

1.3.6. Companion diagnostic

Mirvetuximab is the first-in-class FR α -targeted ADC and as such, a diagnostic test is required to assess eligibility for mirvetuximab. Patients expressing positive FR α ($\geq 75\%$ viable tumour cells with membrane staining at moderate 2+ and/or strong 3+ intensity levels) by immunohistochemistry (IHC), assessed by a Conformité Européenne (CE)-marked, in vitro diagnostic (IVD) are eligible for treatment with mirvetuximab. If a CE-marked IVD is not available, an alternative validated test should be used (131).

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In MIRASOL (discussed in detail in Section 2.3), FR α expression was determined using the Roche VENTANA® FOLR1 (FOLR1-2.1) RxDx Assay (14). The Roche VENTANA® FOLR1 (FOLR1-2.1) RxDx Assay is a CE marked (class C), qualitative IHC assay for the assessment of the expression of FR α protein (131). The assay is for use with OptiView DAB IHC Detection Kit for staining on a BenchMark ULTRA instrument, a platform already available across NHS laboratories. As with other IHC assays, the test is conducted using a tissue sample from biopsy and results interpreted by qualified pathologists in conjunction with histological examination, relevant clinical information, and proper controls (131). It is standard practice for a biopsy to be taken on diagnosis of OC therefore it is anticipated that patients will not need to provide an additional biopsy sample for FR α testing, as stored tissue samples can be analysed on diagnosis of PROC (126).

In MIRASOL, the proportion of screened patients with positive FR α expression was 32% (1) and UK clinicians indicated this was in line with what they would expect in UK practice. Further details of the companion diagnostic test used to assess FR α status in MIRASOL are provided in Appendix K.

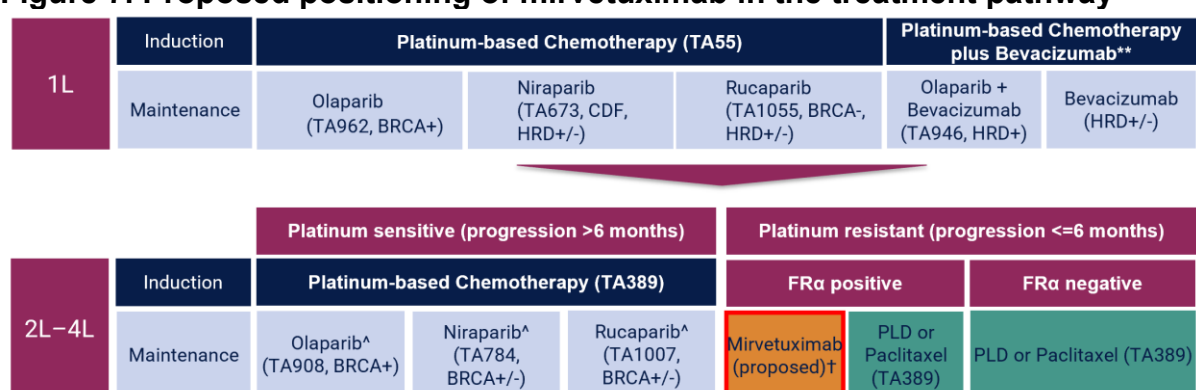
1.3.7. Positioning of mirvetuximab soravtansine

As discussed in Section 1.3.1, OC is a rare disease often diagnosed late, with ~70% of women being diagnosed at an advanced stage (62). Although patients with OC initially respond well to first-line chemotherapy, ~80% of patients experience disease recurrence (1, 132). Nearly all patients with recurrent disease eventually develop platinum-resistance in addition to facing cumulative toxicity from repeated chemotherapy cycles (1, 10, 63). The focus of this submission is on the PROC patient population who are FR α positive (defined as $\geq 75\%$ of viable tumour cells exhibiting 2 and/or 3 membrane staining intensity) and face a significant unmet need stemming from a lethal diagnosis, with the lowest survival rates among patients with OC (5). Patients with PROC have for years lacked treatment options that provide a meaningful tumour response, significant survival benefit or maintain a tolerable safety profile (83-85). The proposed positioning of mirvetuximab as a monotherapy is “for adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens (Figure 7). This patient

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population was the focus of the pivotal Phase 3 clinical trial MIRASOL and is in line with the anticipated MHRA marketing authorisation. The MIRASOL trial compared mirvetuximab with investigator's choice chemotherapy (IC Chemo; paclitaxel, pegylated liposomal doxorubicin, topotecan), and forms the main evidence base for clinical and cost effectiveness in this submission (Sections 2.2 to 2.6, and 3.1 to 3.4).

Figure 7. Proposed positioning of mirvetuximab in the treatment pathway



^Not current practice to retreat with PARPi; **NHSE clinical policy for bevacizumab 15 mg/kg and 7.5 mg/kg; *NHSE clinical policy for Bevacizumab 7.5 mg/kg; †for patients with high FRα expression, defined as ≥75% of viable tumour cells exhibiting 2 and/or 3 membrane staining intensity. Sources: TA962 (102); TA673 (103); TA946 (104); TA908 (105); TA784 (106); TA1007(107); TA389 (108); TA1055 (101).

Abbreviations: 1L, first line; 2L, second line; 4L, fourth line; BRCA, BRCA gene mutation; CDF, Cancer Drugs Fund; HRD, homologous recombination deficient; NHSE, National Health Service England; NICE, National Institute for Health and Care Excellence; PARPi, poly (adenosine diphosphate-ribose) polymerase inhibitor; PLD, pegylated liposomal doxorubicin; TA, technology appraisal.

1.4. Equality considerations

1.4.1. Background

PROC, the most underserved population of OC, is unique amongst cancers affecting women; it is rare, severe and incurable with low survival outcomes and there have been no new treatments in 20 years. The equality issues stemming from this are three-fold:

1. inequalities related to the gender health gap in the UK
2. inequalities related to the rarity of PROC
3. inequalities related to geographical and socioeconomic variation in access in the UK.

Mirvetuximab has the potential to reduce some of these health inequalities by offering a targeted therapy that improves survival and reduces AE burden with

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traditional chemotherapies for women with FRα positive PROC. Furthermore, the companion diagnostic potentially enables eligible patients to be identified earlier.

1.4.2. Inequalities related to the gender health gap in the UK

‘Sex’ is a protected characteristic under the Equality Act 2010 and PROC is a severe disease affecting the female sex. A recognised gender health gap exists in UK care: the UK has the largest gender health gap within the Group of 20 (G20) international forum and also ranks 12th globally (17), with women experiencing an additional 3 years of ill health and disability compared with men (17). Gynaecology was one of the worst affected therapy areas during the COVID-19 pandemic, with gynaecology waiting lists increasing greatly across the UK between the start of the pandemic and winter 2021/22 and showing no signs of abating. In July 2024, 46% of gynaecology patients on waiting lists were waiting longer than the National Health Service (NHS) target of 18 weeks and nearly 30,000 women were waiting for over a year (17). Extensive wait times lead to more advanced conditions for patients, including cancers left undiagnosed, resulting in more complex, labour-intensive, and costly interventions (17). This is especially pertinent for conditions such as OC, where delayed diagnoses result in poorer outcomes, contributing to the gender health gap highlighted above. As per the Government’s commitments to enhance women’s health outcomes and ensure all patients have access to the most appropriate treatment (17, 129, 130), targeted therapy with mirvetuximab could contribute to improving health outcomes in this area of high unmet need by identifying eligible patients earlier and by delaying disease progression and improving QoL.

1.4.3. Inequalities related to the rarity of PROC

Improving outcomes for rare and less common cancers was identified as a key area of focus in the recent Government National Cancer Plan consultation document (55). PROC, which includes fallopian tube and primary peritoneal cancer, is a type of rare cancer (23-25). Notably, the FDA and EMA have both granted mirvetuximab orphan designation, which reflects not only the rarity but also the life threatening nature of PROC (23, 133). This is supported by patient experiences with one patient noting that “So few people know about ovarian cancer. It’s not like breast cancer. It’s not like brain cancer. Nobody knows about it.” (89).

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Patients with rare cancers face additional health inequalities compared with patients with common cancers. They face unique challenges, including lack of screening, late/incorrect diagnosis, lack of therapy options, difficulty in accessing innovative therapies, feelings of isolation, and greatly reduced QoL (52). One-third of UK patients wait >3 months from their first GP visit for an accurate OC diagnosis, and most patients are at advanced stages when OC is diagnosed (Section 1.3.1) (30, 62). Younger patients are particularly disadvantaged due to age-related diagnostic bias; they find it harder to get a diagnosis and have to self-advocate for specific tests. This insight is reflected in patients consulted by AbbVie recalling that specialists diagnosed diverticulitis or infection, and deemed OC unlikely due to their age (89):

- *“a specialist suggested that I had diverticulitis. Ovarian cancer didn’t enter the radar really for me or for them. I think because of my history [no family history of cancer] and my age.”*
- *“two gynaecologists brushed off as an infection and gave me antibiotics saying ‘Oh no, cancer at your age’ I mean I was 45...so they said it is not likely...until I eventually ended up in the ER. I repeatedly told them how I’ve now developed a fever; that I was really worried and had a bad feeling it could be some sort of abdominal cancer.”*

Furthermore, a fifth of patients with OC do not receive any treatment until 9 months after their diagnosis (134) and close to a third of advanced OC patients do not receive any form of treatment (31). The delays in diagnosis and access to treatment are associated with poorer outcomes; women with Stage IV disease are 10 times more likely to die within two months than women with Stage I disease (31, 62, 134). Mirvetuximab offers a novel treatment option in the PROC setting which has not seen a new treatment in over two decades, underscoring the importance of innovative treatments especially for patients with rare cancers facing limited treatment options.

1.4.4. Inequalities related to geographical and socioeconomic variation in UK cancer care access

Not all patients in England have equal access to treatment options, with Pickwell-Smith et al (2025) and the Ovarian Cancer Audit Feasibility Pilot (OCAFP) noting geographic variations in OC treatment access (53, 54). Delays and treatment inequalities might contribute to the worse outcomes experienced by patients from more deprived areas. Patients from more deprived areas are less likely to receive surgery or chemotherapy, and women living in the most deprived quintile are 50% more likely to die within two months of diagnosis than those in the least deprived (53, 54). Pickwell-Smith et al (2025) suggested patients from more deprived backgrounds may face financial constraints, work commitments and caregiving duties that lead to reduced treatment uptake, particularly where the benefits of potentially toxic treatments are marginal (53). For patients with PROC, standard of care chemotherapies offer limited survival benefits and low tumour response rates, along with distinct side effects that adversely affect QoL and treatment continuation (53, 54). Mirvetuximab may help to address these barriers to care, thereby addressing health inequalities across regions, by providing an effective, well tolerated, and innovative treatment option for patients with PROC.

2. Clinical effectiveness

The efficacy and safety evidence base to support the use of mirvetuximab in patients with folate receptor alpha (FR α)-positive platinum-resistant ovarian cancer (PROC) comes from MIRASOL, a global, open-label, Phase 3 multicentre randomised controlled trial (RCT) of mirvetuximab compared with Investigators choice of chemotherapy (IC Chemo)

- The trial included 453 patients from 136 global sites, including 30 patients from the United Kingdom (UK).
- The primary endpoint in MIRASOL was investigator-assessed progression-free survival (PFS).
- Key secondary endpoints included overall survival (OS), investigator-assessed objective response rate (ORR) and health-related quality of life (HRQoL) assessed by the European Organisation for Research and Treatment of Cancer (EORTC)-Quality of Life Questionnaire (QLQ)-OV28. Other secondary endpoints included duration of response (DOR), safety, and progression-free survival 2 (PFS2).
- The population, comparators, and outcomes in the MIRASOL study are aligned with the decision problem specified in the National Institute for Health and Care Excellence (NICE) scope.

Results of MIRASOL demonstrate that mirvetuximab drove a statistically significant and clinically meaningful OS benefit (the first in a PROC Phase 3 trial to do so), along with rapid and durable tumour responses compared with patients receiving IC Chemo

- The final data cut (26th September 2024) demonstrated a clinically meaningful PFS benefit with a hazard ratio (HR) of 0.63 (95% confidence interval [CI]: CI: 0.513, 0.785; $p < 0.0001$), representing a 37% reduction in the risk of tumour progression or death. This benefit remained consistent with the statistically significant result in the primary data analysis (6th March 2023; Appendix K).
- MIRASOL also met the key secondary efficacy endpoints of OS ($p = 0.0004$) and ORR ($p < 0.0001$).
 - Mirvetuximab was associated with a statistically significant OS benefit compared with IC Chemo in patients with PROC, with a 32% reduction in the risk of death in patients randomised to mirvetuximab (HR: 0.68; 95% CI: 0.54, 0.84; $p = 0.0004$) and a median OS of 16.85 months vs 13.34 months for mirvetuximab and IC chemo, respectively.
 - Mirvetuximab investigator-assessed, confirmed ORR was 41.9%, more than double the IC Chemo ORR of 15.9% (odds ratio [OR]: 3.75; 95% CI: 2.40, 5.85; $p < 0.0001$), with 5.7% of mirvetuximab-treated patients achieving a complete response. No patients who received IC Chemo achieved complete response. Additionally, 36.1% of patients receiving mirvetuximab achieved partial response vs 15.9% of IC Chemo patients. MIRASOL demonstrated tumour shrinkage in >80% of mirvetuximab-treated patients.
- Analyses of additional secondary efficacy endpoints demonstrated an increase in DOR for mirvetuximab vs IC Chemo, and the PFS benefit for mirvetuximab over IC Chemo was maintained beyond first progression while preserving crucial aspects of quality of life.
 - The median DOR was 6.93 months (95% CI: 5.78, 8.84) among the 86 patients in the mirvetuximab group who had a partial or complete response, compared with 4.44 months (95% CI: 4.17, 5.75) among the 32 patients in the IC Chemo

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group (HR: 0.62; 95% CI: 0.41, 0.93; p=0.020). The rapidity of tumour response was observed with the median time to response (TTR) per investigator assessment in patients randomised to mirvetuximab of 1.54 months (range: 1.1 to 7.2 months) compared with 2.71 months (range: 1.2 to 8.2 months) in patients receiving IC Chemo.

- Mirvetuximab demonstrated a continued benefit beyond first progression, with a statistically significant 41% reduction in the risk of second progression or death compared with IC Chemo (HR: 0.59; 11.01 vs 7.59 months, respectively; p<0.0001).
- Patients treated with mirvetuximab were more likely to maintain or improve HRQoL assessed by the EORTC QLQ-OV28, with significant improvements observed vs IC Chemo in the change from baseline least-square mean scores (LSM) analysis for the subscales measuring abdominal/gastrointestinal symptoms and attitude toward disease and treatment.

Mirvetuximab demonstrated a manageable safety profile, associated with lower rates of Grade 3+ treatment emergent adverse events (TEAE), serious TEAEs, and fewer TEAE drug discontinuations than IC Chemo

- Mirvetuximab was associated with lower rates of Grade 3+ TEAEs compared with IC Chemo (44% vs 55%), serious TEAEs (25% vs 33%), and fewer study drug discontinuations due to TEAEs (11% vs 15%). Major chemotherapy toxicities such as haematological adverse events (AE) and alopecia were lower with mirvetuximab than IC Chemo.
- Mirvetuximab demonstrated a manageable safety profile, with predominantly low-grade, ocular, gastrointestinal and neurosensory events that were resolved with appropriate treatment/management. The majority (84%) of ocular events were low grade (Grade ≤2) with only 2% of patients permanently discontinuing mirvetuximab due to these events. Most ocular events were resolved to Grade 1 or 0 with best supportive care and dose modification.

Mirvetuximab is anticipated to be the first targeted treatment available in England/Wales for the PROC setting, representing a key innovation in this incurable stage of OC

- Mirvetuximab is the first treatment to demonstrate a statistically significant OS benefit in a Phase 3 RCT in PROC compared with chemotherapy. It addresses the high unmet need in PROC where there is an urgent need for clinically effective, less toxic, targeted therapies.
- Mirvetuximab is a first-in-class FRα antibody drug conjugate (ADC) selectively targeting tumour cell surface FRα. This enables targeted delivery of a highly cytotoxic DM4 payload via biomarker-directed tumour cell kill and in addition, has the ability to induce a wider killing range of tumour cell death (bystander effect) (28, 135).

2.1. Identification and selection of relevant studies

An SLR was conducted on 4th March 2024 and updated on 20th November 2024, to identify all relevant clinical evidence on the efficacy and safety of mirvetuximab and/or comparators for the treatment of patients with PROC. The SLR and update were conducted from a global perspective, and therefore studies assessing any pharmacological intervention were included. However, only studies including

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mirvetuximab or comparators used in clinical practice in England or Wales (paclitaxel, pegylated liposomal doxorubicin, and topotecan) are included in this submission. The SLR identified 65 publications reporting on 40 unique trials that were considered relevant to the submission. See Appendix B for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

Of the included studies, two publications reporting two Phase 3 studies were identified that evaluated mirvetuximab for the treatment of PROC (1, 136). One study, MIRASOL, was a head-to-head study evaluating mirvetuximab vs the comparators within the NICE scope for this appraisal, and within the anticipated licence population (FR α positive PROC, with FR α positivity defined as $\geq 75\%$ viable tumour cells with membrane staining at moderate 2+ and/or strong 3+ intensity levels) and thus forms the main evidence base for this submission. It should be noted that an additional Phase 2 study evaluating mirvetuximab (SORAYA) was identified in the SLR but was excluded at title/abstract screening on study design as it was a single-arm clinical trial.

2.2. List of relevant clinical effectiveness evidence

Mirvetuximab has a robust evidence package spanning 682 patients across four clinical trials (Phase 1 first-in-human, Phase 2 SORAYA, and Phase 3 FORWARD-1 and MIRASOL) (1, 11, 136, 137). Earlier trials have informed the design of subsequent trials and shaped the overall clinical development programme. The clinical evidence SLR included two of these trials, MIRASOL and FORWARD-1, based on the relevant selection criteria (Appendix B). However, MIRASOL is the only trial that evaluated the population in the anticipated marketing authorisation (adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens).

The Phase 1 study identified the optimal dosing regimen via dose escalation (mirvetuximab 6 mg/kg adjusted ideal body weight [AIBW] every 3 weeks [Q3W]). This was taken forward into a dose expansion phase, confirming clinical activity and characterising the safety profile (137). The results of the Phase 1 study informed the

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design of the Phase 3 FORWARD-1 study in regard to number of prior lines of therapy received and FR α expression levels (136). FORWARD-1 enrolled PROC patients with medium/high FR α expression and 1–3 prior lines of systemic therapy, using an alternative and simplified FR α scoring approach from that employed during the Phase 1 study ($\geq 50\%$ of tumour cells with observable staining at 10 $\times$ magnification). As the primary endpoint was not statistically significant, exploratory FR α rescoring was conducted using the PS2+ scoring methodology from the Phase 1 study. Findings indicated a dilution of mirvetuximab efficacy due to enrolling approximately 34% of patients with lower-than-expected FR α expression levels (FR α $< 50\%$ which would have precluded enrolment into the study) (138). Further analysis confirmed positive efficacy findings in patients with high FR α expression ($\geq 75\%$ PS2+), who observed the highest response rates in this population (1). As FORWARD-1 was not conducted solely in the population addressed in this submission in terms of high FR α expression, it does not form part of the evidence base.

Learnings from the Phase 1 and FORWARD-1 studies regarding 1–3 prior lines of therapy and high FR α expression level using the PS2+ scoring methods, were applied in the almost-parallel initiation of Phase 2 single-arm SORAYA and Phase 3 MIRASOL (vs IC Chemo) studies (1). SORAYA included patients with high FR α expression, mandated prior bevacizumab therapy, and demonstrated clinically meaningful antitumour activity with a safety profile consistent with prior study programme findings (11). This Phase 2 single-arm study was used to inform the accelerated FDA approval and does not align with the target population in this submission, since the study restricted the population to patients who had all previously received bevacizumab. In addition, the SORAYA trial did not include a comparator arm, and therefore this study does not form part of the evidence base for the submission.

MIRASOL was a Phase 3, randomised, open-label study in adult patients with platinum-resistant, advanced HGS epithelial ovarian, primary peritoneal, or fallopian tube cancers with high FR α expression who had received 1–3 prior lines of systemic regimens (Table 3) (1, 14). It is the pivotal/registrational study used to inform the EMA approval and the MHRA International Recognition Procedure (IRP) Marketing

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Authorisation application. MIRASOL demonstrated statistically significant improvements in clinically meaningful endpoints, including PFS (meeting its primary endpoint), OS, and ORR, as well as a manageable safety profile, consistent with the findings of SORAYA. MIRASOL forms the main evidence base for this submission, in line with the target population in the decision problem.

For completeness, the SORAYA (11) and FORWARD-1 (136) publications are included in the reference pack, with brief overviews included in Appendix L.

Table 3. Clinical effectiveness evidence

Study and publications	MIRASOL (NCT04209855) (1, 15)
Study design	Phase 3, randomised, open-label
Population	Adult patients with platinum-resistant, HGS ovarian, primary peritoneal, or fallopian tube cancers with high FR α expression ($\geq 75\%$ expression at $\geq 2+$ intensity) who received 1–3 prior lines of systemic treatment regimens
Intervention(s)	Mirvetuximab 6 mg/kg AIBW Q3W
Comparator(s)	IC Chemo, as one of the following regimens as determined by the investigator prior to randomisation: • Paclitaxel (80 mg/m²) administered on Days 1, 8, 15, and 22 of a 4-week cycle • Pegylated liposomal doxorubicin (40 mg/m²) administered on Day 1 of a 4-week cycle • Topotecan ○ 4 mg/m² administered on Days 1, 8, and 15 of a 4-week cycle, or ○ 1.25 mg/m² administered on Days 1 to 5 of a 3-week cycle
Indicate if study supports application for marketing authorisation	Yes (UK, EU)
Indicate if study used in the economic model	Yes
Rationale if study not used in model	—
Reported outcomes specified in the decision problem	• PFS • OS • ORR • HRQoL • Safety

All other reported outcomes

- DOR
- PFS2
- Subsequent therapies
- **Duration of treatment**

Bold text indicates outcomes included in the economic model (Section 3.3)

Source: Data on file, MIRASOL CSR (15); Moore et al, 2023 (1).

Abbreviations: AIBW, adjusted ideal body weight; CSR, clinical study report; DOR, duration of response; FR α , folate receptor alpha; HGS, high grade serous; HRQoL, health-related quality of life; IC Chemo; Investigator’s choice of chemotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, time to second disease progression; Q3W, every 3 weeks; UK, United Kingdom.

2.3. Summary of methodology of the relevant clinical effectiveness evidence

2.3.1. Summary of methodology

A summary of the methodology of the pivotal MIRASOL trial is provided in Table 4, with the trial design presented in Figure 8.

Table 4. Summary of pivotal trial methodology

Trial name	MIRASOL (NCT04209855)
Trial design	Phase 3, randomised, open-label study of mirvetuximab vs IC Chemo
Blinding	Not applicable as this was an open-label study. An open-label design was used because each trial drug has a unique dose, examination schedule, and safety profile
Treatment allocation	Patient numbers were assigned in sequential order as patients signed the pre-screening informed consent to participate. The investigator certified that the patient satisfied all eligibility criteria at screening and continued to satisfy all inclusion and exclusion criteria prior to dosing. Eligible patients were randomly assigned 1:1 to mirvetuximab 6 mg/kg AIBW Q3W or IC Chemo (paclitaxel, pegylated liposomal doxorubicin, or topotecan). Cycle 1 Day 1 occurred within 7 calendar days from randomisation. Patients were stratified as follows: • Number of prior therapies (1 vs 2 vs 3) • IC Chemo (paclitaxel, pegylated liposomal doxorubicin, or topotecan) chosen prior to randomisation
Eligibility criteria for participants	Key inclusion criteria • Female patients ≥ 18 years of age • Confirmed diagnosis of HGS EOC, primary peritoneal cancer, or fallopian tube cancer • Patients must have had platinum-resistant disease: ○ Patients who only had 1 line of platinum-based therapy must have received at least 4 cycles of platinum therapy,

Company evidence submission for mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Trial name	MIRASOL (NCT04209855)

- must have had a response (complete response or partial response) and then progressed between >3 months and ≤6 months after the date of the last dose of platinum therapy
 - Patients who had received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum therapy
- A patient's tumour must have high FRα expression as defined by the VENTANA® FOLR1 assay (≥75% of viable tumour cells must have exhibited level 2 and/or 3 membrane staining intensity (Section 1.3.6)
- Patients must have had ≥1 lesion that meets the definition of measurable disease by RECIST v1.1
- Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, and for whom single-agent therapy was appropriate as the next line of treatment
- ECOG PS of 0 or 1
- Time from prior therapy:
 - Systemic antineoplastic therapy (5 half-lives or 4 weeks, whichever is shorter)
 - Focal radiation completed at least 2 weeks prior to first dose of study drug
- Patients must have had stabilised or recovered (Grade 1 or baseline) from all prior therapy-related toxicities

Key exclusion criteria

- Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumours containing any of the above histologies, or low-grade or borderline ovarian tumour
- Patients with primary platinum-refractory disease, defined as disease that did not respond to (complete response or partial response) or has progressed within 3 months of the last dose of first-line platinum-containing chemotherapy
- Patients with prior wide-field radiotherapy affecting at least 20% of the bone marrow
- Patients with >Grade 1 peripheral neuropathy per CTCAE
- Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular oedema, macular degeneration, presence of papilledema, and/or monocular vision
- Patients with serious concurrent illness or clinically relevant active infection, including, but not limited to the following: active hepatitis B or C infection (whether on active antiviral therapy), HIV infection, active cytomegalovirus infection, any other

Trial name	MIRASOL (NCT04209855) concurrent infectious disease requiring IV antibiotics within 2 weeks before starting study drug • Patients with history of multiple sclerosis or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome) • Patients with clinically significant cardiac disease • Patients assigned to pegylated liposomal doxorubicin stratum only: LVEF below the institutional limit of normal as measured by ECHO or MUGA scan • Patients with a history of haemorrhagic or ischemic stroke within 6 months prior to randomisation • Patients with a history of cirrhotic liver disease • Patients with a previous clinical diagnosis of non-infectious ILD Full eligibility criteria are available in the MIRASOL CSR (14)
Settings and locations where data were collected	136 sites enrolled all 453 patients (30 patients were from the UK)
Concomitant medications	All concomitant medications and supportive therapy taken within 4 weeks of C1D1 and through 30 days after the last dose of study drug were recorded in the clinical database. Antiemetic and antidiarrhoeal medications An antiemetic medication was recommended before each mirvetuximab dose; additional antiemetics and/or antidiarrhoeal medications could be used any time at the discretion of the treating physician. Folate-containing supplements Folate-containing supplements should not have been taken during the study. Antineoplastic therapy All non-study related antineoplastic therapy, including but not limited to cytotoxic, immunotherapy, and VEGF-targeted therapy, was prohibited while on study drug. Hematopoietic growth factors Patients receiving recombinant erythropoietin or darbepoetin-α before study start could continue to receive pretreatment doses. The use of erythropoietic and granulocyte growth factors in accordance with ASCO guidelines (139) could be implemented at the discretion of the treating physician. Anticoagulants The use of anticoagulant agents was allowed. Directions were provided for patients who were using apixaban and rivaroxaban due to CYP3A interaction potential. Contraception WCBP must have agreed to use highly effective contraceptive method(s) while on study drug and for at least 3 months after the

Trial name	MIRASOL (NCT04209855) last dose of mirvetuximab or at least 6 months after the last dose of paclitaxel, pegylated liposomal doxorubicin, or topotecan. Other concomitant medications Medications for the treatment of AEs or cancer symptoms (e.g. packed red blood cells and pain medications) were allowed. Prophylactic use of steroids and/or antihistamines was considered if needed. Additionally, medications (not addressed above) used to treat underlying medical conditions at study entry, including antiemetics and antidiarrheals, were allowed to continue.
Trial treatments	Mirvetuximab arm All patients received single-agent mirvetuximab at 6 mg/kg AIBW IV administered Q3W. IC Chemo arm Patients who were randomised to paclitaxel, pegylated liposomal doxorubicin, or topotecan may have received premedication at the discretion of the investigator or according to institutional guidelines. • Paclitaxel was administered at 80 mg/m² as a 1-hour IV infusion on Days 1, 8, 15, and 22 of a 4-week cycle • Pegylated liposomal doxorubicin was administered at 40 mg/m² as a 1 mg/min IV infusion on Day 1 of a 4-week cycle. After Cycle 1, if tolerated, pegylated liposomal doxorubicin could be delivered as a 1-hour IV infusion • Topotecan was administered at 4 mg/m² as a 30-min IV infusion on Days 1, 8, and 15 of a 4-week cycle. Alternatively, topotecan could be administered at 1.25 mg/m² as a 30-min IV infusion on Days 1 to 5 of a 3-week cycle
Primary endpoint(s)	PFS, defined as the time from date of randomisation until investigator-assessed PD or death, whichever occurred first • PFS was defined based on radiological assessments and determined by the investigator, with an additional sensitivity analysis by BICR
Secondary endpoints	Key secondary endpoints • Objective response, including best response of complete response or partial response as assessed by the investigator • OS defined as the time from date of randomisation until the date of death • Primary PRO assessment, defined as the number of patients achieving at least a 15-point absolute improvement at Week 8 or Week 9 in the abdominal/GI subscale of EORTC QLQ-OV28 Other secondary endpoints • DOR, defined as the time from initial response until investigator-assessed PD for all patients who achieve a confirmed objective response (complete response or partial response) • CA-125 response determined using the GCIG criteria (140) • PFS2, defined as the time from date of randomisation until second disease progression or death, whichever occurred first

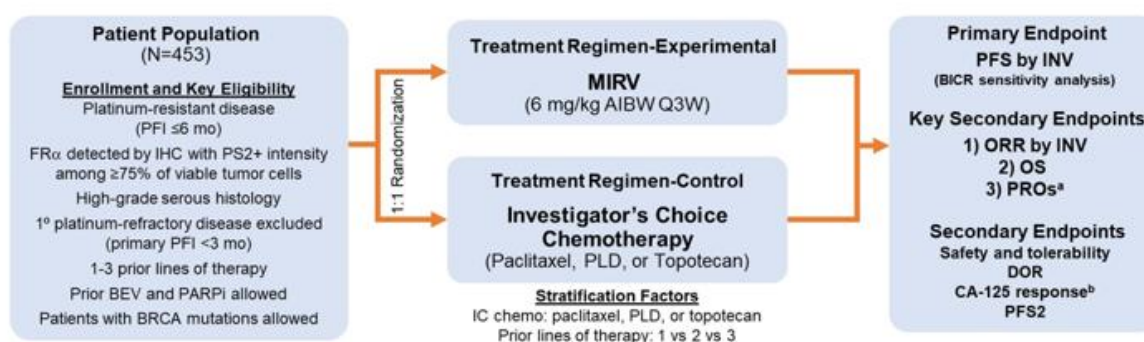
Company evidence submission for mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Trial name	MIRASOL (NCT04209855)
Exploratory endpoints	- To compare safety and tolerability of mirvetuximab vs IC Chemo - EORTC QLQ-C30/OV-28, EQ-5D-5L, and PGIS - Mirvetuximab, TAb, DM4, and S-methyl DM4 concentrations - Immunogenicity (defined as the presence of ADA) - Soluble FRα levels and other biomarkers
Subgroup analyses	Efficacy endpoints (PFS_{INV}, OS, and ORR_{INV}) were analysed with the following subgroups of patients (all analyses were unstratified): - BRCA status (mutant vs wild-type/unknown) - Age (<65 years vs $\geq$65 years) - Baseline ECOG PS (0 vs 1) - Number of prior lines of therapy (1 vs 2 vs 3 vs 1 or 2) - Prior exposure to BEV (yes vs no) - Prior exposure to PARP inhibitor (yes vs no vs uncertain) - Primary platinum-free interval ($\leq$12 months vs >12 months) - Most recent platinum-free interval ($\leq$3 months vs >3 months) - Country (USA vs rest of world) - Stage at diagnosis (I–III vs IV) - Weight at baseline ($\leq$60 kg, 60–80kg, >80kg)

Source: Data on file, MIRASOL CSR (15); Moore et al, 2023 (1).

Abbreviations: ADA, anti-drug antibodies; AE, adverse event; AIBW, adjusted ideal body weight; ASCO, American Society of Clinical Oncology; BEV, bevacizumab; BICR, blinded independent central review; CA125, cancer antigen 125; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; ECHO, echocardiography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOC, epithelial ovarian cancer; EORTC, European Organisation for Research and Treatment of Cancer; FOLR1, folate receptor 1; FR α , folate receptor alpha; GCIg, Gynaecologic Cancer Intergroup; GI, gastrointestinal; HGS, high grade serous; HIV, human immunodeficiency virus; IC Chemo, investigator's choice of chemotherapy; ILD, interstitial lung disease; INV, by investigator; IV, intravenous; LVEF, left ventricular ejection fraction; MUGA, multigated acquisition scan; ORR, objective response rate; OS, overall survival; PARP, poly (adenosine diphosphate-ribose) polymerase; PD, progressive disease; PFS, progression-free survival; PFS2, time to second disease progression; PGIS, patient global impression of severity; PRO, patient reported outcome; QLQ, quality of life Questionnaire; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TAb, total antibody; UK, United Kingdom; USA, United States of America; VEGF, vascular endothelial growth factor; WCBP, women of childbearing potential.

Figure 8. MIRASOL trial design



Source: Moore et al, 2023 (1).

aPROs were measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument;

bGynecological Cancer InterGroup (GCIG) criteria

Abbreviations: AIBW, adjusted ideal body weight; BEV, bevacizumab; BRCA, BRCA1/2 gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC Chemo, investigator's choice of chemotherapy; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (adenosine diphosphate-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomisation until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient reported outcomes; PS2+, positive staining intensity ≥2, Q3W, every 3 weeks.

2.3.2. Patient disposition

In total, 453 patients were randomised into the MIRASOL trial; 227 patients were assigned to the mirvetuximab arm and 226 to the IC Chemo arm (Figure 9). While Figure 9 presents the primary reasons for treatment discontinuation, Table 5 outlines the primary reasons for patients discontinuing the study as a whole.

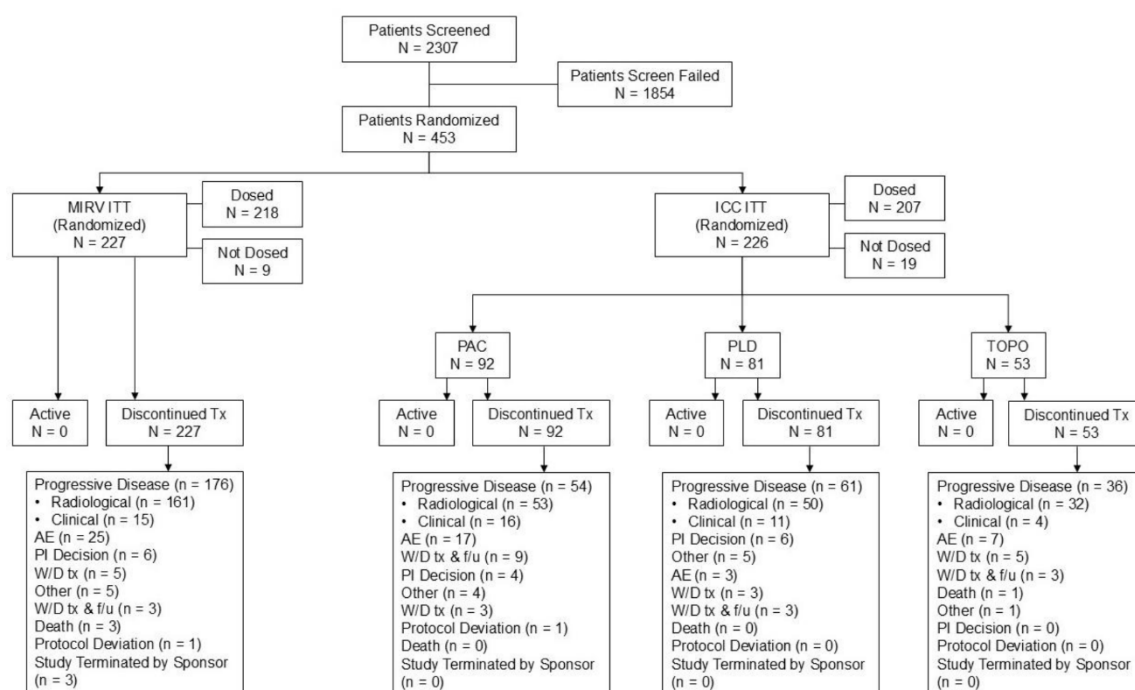
Of the 227 patients randomised to mirvetuximab, 218 received treatment. Of the patients treated with mirvetuximab, progressed disease (PD; 176 patients, 78%) and AEs (25 patients, 11%) were the most common reasons for treatment discontinuation. All 227 patients were permanently discontinued from the study with death being the primary reason (161 patients, 71%). At the time of study closure, 44 patients remained alive in the mirvetuximab arm, all of whom had a follow-up of at least 24 months. Four of these patients remained progression-free.

Of the 226 patients randomised to IC Chemo, 207 received treatment. Of the patients treated with IC Chemo, PD and AEs were the most common reasons for discontinuation (PD 151 patients, 67%; AEs 27 patients, 12%). All 226 patients were permanently discontinued from the study with death being the primary reason

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(177 patients, 78%). At the time of study closure, 18 patients remained alive in the IC Chemo arm after a follow-up of at least 24 months, all of whom had progressed.

Figure 9. MIRASOL participant flow diagram



Source: Data on file, MIRASOL final CSR (14).

Abbreviations: AE, adverse event; f/u, follow-up; CSR, clinical study report; ICC, investigator's choice chemotherapy; ITT, intent-to-treat; MIRV, mirvetuximab; PAC, paclitaxel; PI, principal investigator; PLD, pegylated liposomal doxorubicin; TOPO, topotecan; tx, treatment; W/D, withdrawal.

Table 5. Primary reason for study discontinuation

Primary Reason for Study Discontinuation	Mirvetuximab (N=227)	IC Chemo (N=226)
Death	161 (71)	177 (78)
PI Discretion	1 (<1)	1 (<1)
Lost to follow-up	5 (2)	2 (<1)
Withdrew consent	10 (4)	24 (11)
Study terminated by sponsor	44 (19)	18 (8)
Other	6 (3)	4 (2)

Source: Data on file, MIRASOL final CSR (14).

Abbreviations: IC Chemo, investigator's choice chemotherapy; investigator's choice chemotherapy.

2.3.3. Baseline characteristics

Key patient characteristics at baseline for MIRASOL are presented in Table 6. All patients were HGS, mostly epithelial in origin (80.4%), and had previous exposure to taxanes (99.6%), bevacizumab (62.0%), and PARP inhibitors (55.6%).

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Demographics, disease characteristics, and prior lines of therapy were broadly similar between mirvetuximab and IC Chemo groups for key factors such as:

- Age
- Ethnicity
- Primary cancer diagnosis
- Stage at initial diagnosis
- BRCA mutation status
- Prior exposure to bevacizumab and PARP inhibitors
- Platinum-free interval.

Table 6. Baseline demographic and clinical characteristics – ITT population[†]

Characteristic	Mirvetuximab (N=227)	IC Chemo (N=226)
Age, years		
Median (range)	64 (32–88)	62 (29–87)
≥65 years, n (%)	107 (47.1)	92 (40.7)
Race, n (%) [‡]		
White	156 (68.7)	145 (64.2)
Black or African American	8 (3.5)	5 (2.2)
Asian	28 (12.3)	25 (11.1)
Not reported	32 (14.1)	49 (21.7)
Other	3 (1.3)	2 (0.9)
Ethnic group, n (%) [‡]		
Hispanic or Latino	12 (5.3)	15 (6.6)
Not Hispanic or Latino	177 (78.0)	163 (72.1)
Unknown	2 (0.9)	2 (0.9)
Not reported	35 (15.4)	45 (19.9)
Missing data	1 (0.4)	1 (0.4)
Primary cancer diagnosis, n (%)		
Epithelial ovarian cancer	182 (80.2)	182 (80.5)
Fallopian tube cancer	27 (11.9)	23 (10.2)
Primary peritoneal cancer	16 (7.0)	20 (8.8)
Other	2 (0.9)	1 (0.4)

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Characteristic	Mirvetuximab (N=227)	IC Chemo (N=226)
Stage at initial diagnosis, n (%) [†]		
IA or IIA	7 (3.1)	1 (0.4)
IIB or IIC	2 (0.9)	8 (3.5)
IIIA	14 (6.2)	16 (7.1)
IIIB	16 (7.0)	11 (4.9)
IIIC	107 (47.1)	120 (53.1)
IV	76 (33.5)	65 (28.8)
Missing data	5 (2.2)	5 (2.2)
ECOG performance-status score, n (%) [§]		
ECOG PS 0	130 (57.3)	120 (53.1)
ECOG PS 1	97 (42.7)	101 (44.7)
ECOG PS 2	0	3 (1.3)
Missing data	0	2 (0.9)
BRCA mutation, n (%)		
BRCA1 positive	24 (10.6)	29 (12.8)
BRCA2 positive	9 (4.0)	7 (3.1)
Negative or unknown	198 (87.2)	190 (84.1)
Previous lines of systemic therapy		
1	29 (12.8)	34 (15.0)
2	90 (39.6)	88 (38.9)
3	108 (47.6)	104 (46.0)
Previous exposure, n (%)		
Bevacizumab	138 (60.8)	143 (63.3)
PARP inhibitor	124 (54.6)	128 (57)
Taxane	227 (100)	224 (99.1)
Doxorubicin or pegylated liposomal doxorubicin	130 (57.3)	134 (59)
Topotecan	1 (0.4)	2 (0.9)
Primary platinum-free interval, n (%) ^{††}		
≤12 months	144 (64)	142 (62.8)
>12 months	81 (36)	84 (37.2)
Missing data	1 (0.4)	0

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Characteristic	Mirvetuximab (N=227)	IC Chemo (N=226)
Platinum-free interval, n (%) ^{†‡}		
≤3 months	88 (38.8)	99 (43.8)
>3 to ≤6 months	138 (60.8)	124 (54.9)
>6 months	1 (0.4)	3 (1.3)

Source: Data on file, MIRASOL final CSR (14); Moore et al, 2023 (1).

[†]Percentages may not total 100 because of rounding; [‡]Race and ethnic group were reported by the participants; [¶]Stage at diagnosis was assessed according to the ovarian cancer staging system used by the local institution; [§]ECOG PS scores are assessed on a scale of 0 to 5, with higher scores indicating greater disability; ^{††}Primary platinum-free interval was defined as the time from last dose of first-line platinum therapy to the date of disease progression or relapse after first-line therapy; ^{‡‡}Platinum-free interval was defined as the time from last dose of the latest line of platinum therapy to the date of disease progression or relapse after that line of therapy.

Abbreviations: BRCA1, BRCA1 gene 1; ECOG, Eastern Cooperative Oncology Group; IC Chemo, investigator's choice of chemotherapy; ITT, intention-to-treat; PARP, poly (adenosine diphosphate-ribose) polymerase; PS, performance score.

2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1. Analysis populations

The intention-to-treat (ITT) population was the primary dataset for all efficacy analyses. All results focus on the ITT and Safety populations; data from the per-protocol, cancer-antigen 125 (CA-125)-evaluable, response evaluation, pharmacokinetic, and longitudinal period population are not presented. A comprehensive statistical analysis plan (SAP) is available in the MIRASOL clinical study report (CSR) (14).

2.4.2. Summary of statistical analyses

A summary of the statistical analyses undertaken in the pivotal trial (MIRASOL) is provided in Table 7.

Table 7. Summary of statistical analyses

Trial	MIRASOL
Hypothesis objective	Primary objective: To compare the PFS of patients randomised to mirvetuximab vs IC Chemo
Statistical analysis of primary endpoint	- The primary endpoint of PFS was calculated based on the ITT population - The primary endpoint of PFS was tested using stratified log-rank test (stratified by the stratification factors used in randomisation) If the primary endpoint of PFS is statistically significant at 2-sided alpha level of 0.05, the hierarchical testing procedure was used to

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Trial	MIRASOL
	test the key secondary endpoints in the following order at 2-sided alpha level of 0.05 to control the study-wise type I error • ORR per RECIST 1.1 criteria as assessed by the Investigator • OS (time from randomisation to death from any cause) • Primary PRO endpoint of abdominal/GI Symptom Scale of EORTC QLQ-OV28
Statistical analysis of secondary endpoints	Key secondary endpoints • ORR was analysed using a CMH test stratified by the randomisation stratification factors to test for differences between the mirvetuximab arm and the IC Chemo arm • OS was summarised using the ITT population. Distribution was estimated using the Kaplan-Meier method • For EORTC QLQ-OV28 Abdominal/GI subscale scores: ○ If a patient's score increased by 15 points or greater from baseline to Week 8/9 assessment, the patient was categorised as "Improved" ○ If a patient's score increased by less than 15 points from baseline to Week 8/9 assessment, the patient was categorised as "Unimproved" ○ If a patient died or progressed prior to Week 8/9 assessment, the patient was categorised as "Unimproved" ○ A CMH test stratified by the randomisation stratification factors to test for differences between the mirvetuximab arm and the IC Chemo arm was performed Secondary endpoints • The distribution of DOR was summarised using the Kaplan-Meier method. Because DOR was analysed for the subset of patients who achieved a best overall response of complete response or partial response, the primary comparison between treatments utilised the unstratified log-rank test. The chi-square p-values from the log-rank tests were reported • TTR was summarised in patients with a confirmed best overall response of complete response or partial response only with the simple summary statistics • Analysis of PFS2 was conducted using the same method as in the PFS analysis Exploratory PRO endpoints • Statistical comparisons were made using two-sided tests at the $\alpha=0.05$ significance level unless stated otherwise. Due to the exploratory nature of the analyses, adjustments for multiple comparisons were not made
Statistical analysis of safety endpoints	• The main safety summary tables used data from the Safety population. Patients were analysed according to the actual study drug received • TEAEs[†] and laboratory values were summarised descriptively

Trial	MIRASOL
Sample size and power calculation	The primary endpoint of this study was PFS_{INV}. The study was designed to test the null hypothesis that the survival function for PFS was the same between the mirvetuximab arm and the IC Chemo arm vs the alternative hypothesis that the survival function for PFS was different between the mirvetuximab and IC Chemo groups. The study had 90% power to detect a HR of 0.7. Sample size and power were determined with the following assumptions: • Median PFS for the IC Chemo arm was 3.5 months • Median PFS for the mirvetuximab arm was 5.0 months • Overall attrition rate for PFS event was approximately 13% in both groups • Median OS for the IC Chemo arm was 12 months • Median OS for the mirvetuximab arm was 17.5 months
Data management and patient withdrawal	Partial dates were allowed in the clinical database for anticancer therapy start dates, AE onset and resolution dates, concomitant medication start and stop dates, and concomitant procedure dates. Missing dates were allowed in the clinical database for anticancer therapy stop date, prior cancer systemic therapy start date, stop date, and date of progression. No imputation methods were used to replace missing data unless otherwise stated in the SAP (141)

Source: Data on file, MIRASOL final CSR (14); Data on file, MIRASOL SAP (141); Data on file, MIRASOL Patient Reported Outcomes Report (142).

†TEAEs were defined as AEs with an onset date on or after the first dose of study drug, and within 30 days of the last dose of study drug or prior to the start of a new anticancer treatment, whichever occurred first.

Abbreviations: AE, adverse event; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CSR, clinical study report; DOR, duration of response; EORTC, European Organisation for Research and Treatment of Cancer; GCIG, Gynecological Cancer InterGroup, HR, hazard ratio; IC Chemo, Investigator's choice of chemotherapy; INV, by investigator; ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient reported outcome; QLQ, quality of life questionnaire; RECIST, Response Evaluation Criteria for Solid Tumours; SAP, statistical analysis plan; TEAE, treatment-emergent adverse event; TTR, time to response.

2.5. Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of MIRASOL was conducted using the Cochrane Risk of Bias 2 (RoB2) tool (143). The algorithm's risk of bias judgement indicated low concern of bias in the randomisation process, in deviations from intended intervention, in missing outcome data and in selection of the reported result. No aspects of the RoB2 tool score high. Overall, algorithm-based assessment indicated some concerns around the risk of bias in MIRASOL (Appendix B). This was due to 'some concerns' being identified in the outcome measurement domain because of the trials open-label design and the primary outcome (PFS) being investigator-assessed.

However, the assessor-based evaluation indicated a low risk of bias, as investigator-Company evidence submission for mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

assessed PFS is considered the most robust analysis for PFS, as supported by the GCIG (144). Additionally, the investigator-assessed results, including PFS, were consistent with results based on a blinded independent central review (BICR) (14). MIRASOL is therefore considered to have a low risk of bias. Other outcomes, such as OS, are not prone to open-label biases (145, 146).

The quality assessment of each randomised controlled trial (RCT) identified in the SLR is provided in Appendix B.

2.6. Clinical effectiveness results of the relevant studies

2.6.1. MIRASOL

Clinical efficacy results are presented for the final data cut (26th September 2024). Data from the previous (6th March 2023) data cut for all endpoints were consistent with the final data cut and are presented in Appendix K for completeness.

Primary endpoint: PFS by investigator assessment

Mirvetuximab was associated with a clinically meaningful 37% reduction in the risk of tumour progression or death compared with IC Chemo. The consistency of PFS results across data cut-offs and sensitivity analyses highlight the benefit associated with mirvetuximab compared with IC Chemo for patients with FR α positive PROC.

PFS results for the MIRASOL trial are mature and reported for a median duration of follow up of 28.35 months (95% confidence interval [CI]: 24.97, not reached [NR]) for patients in the ITT population.

The final data cut (26th September 2024) continued to demonstrate a clinically meaningful PFS with a hazard ratio (HR) of 0.63 (95% CI: 0.513, 0.785; $p < 0.0001$), representing a 37% reduction in the risk of tumour progression or death in the mirvetuximab group compared with the IC Chemo group (Figure 10). It remained consistent with the statistically significant result in the primary data analysis (6th March 2023; Appendix K), The median PFS was significantly longer in the mirvetuximab group, with 5.59 months (95% CI: 4.34, 5.88) vs 3.98 months (95% CI: 2.86, 4.47) for mirvetuximab vs IC Chemo patients, respectively (Table 8).

Parametric models developed from these results for modelling purposes are presented in Section 3.3.4.

Sensitivity analysis results by BICR were concordant with the investigator assessment primary analysis (median PFS: 5.82 months vs 4.34 months, HR 0.70; 95% CI: 0.547, 0.890; p=0.0035).

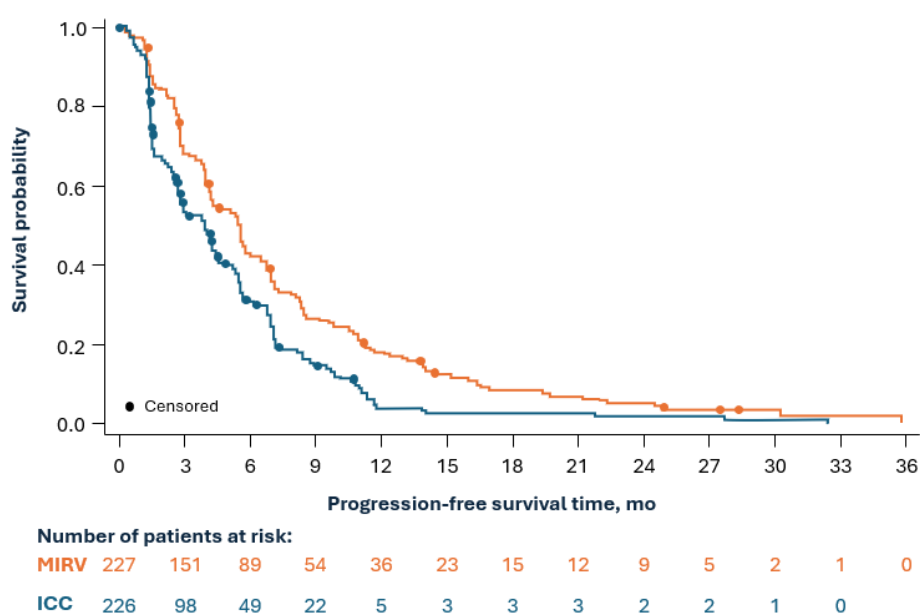
Table 8. Summary of PFS_{INV} results – ITT population (September 2024 DCO)

	Mirvetuximab (N=227)	IC Chemo (N=226)
September 2024 DCO		
Number of patients with events, n (%)	204 (89.9)	174 (77.0)
Disease progression	190 (83.7)	158 (69.9)
Death	14 (6.2)	16 (7.1)
Number of patients censored, n (%)	23 (10.1)	52 (23.0)
Estimated PFS time (months)		
Median (95% CI)	5.59 (4.34, 5.88)	3.98 (2.86, 4.47)
25th percentile (95% CI)	2.86 (2.66, 3.02)	1.58 (1.48, 1.64)
75th percentile (95% CI)	9.86 (8.34, 11.37)	7.03 (5.75, 7.52)
Stratified analysis with IRT randomisation values		
Cox PH model, HR (95% CI)	0.63 (0.513, 0.785)	
Two-sided P-value from Log-rank test	<0.0001	

Source: Data on file, MIRASOL final CSR (14).

Abbreviations: CI, confidence interval; CSR, clinical study report; DCO, data cut-off; HR, hazard ratio; IC Chemo, Investigator's choice of chemotherapy; IRT, Interactive Response Technology; ITT, intention-to-treat; PFS, progression-free survival; PFS_{INV}, progression-free survival assessed by investigator; PH, proportional hazards.

Figure 10. KM plot for PFS_{INV} – ITT population (September 2024 DCO)



Source: Data on file, MIRASOL final CSR (14).

Abbreviations: CSR, clinical study report; DCO, data cut-off; KM, Kaplan-Meier; ICC, Investigator's choice of chemotherapy; ITT, intention-to-treat; MIRV, mirvetuximab; PFS_{INV}, progression-free survival per investigator.

Key secondary endpoint: Overall survival

Mirvetuximab was associated with a statistically significant and clinically meaningful OS benefit compared with IC Chemo in patients with PROC, with a 32% reduction in the risk of death in patients randomised to mirvetuximab. As such, mirvetuximab is the first treatment to have demonstrated a statistically significant OS benefit in a Phase 3 trial in FRα positive PROC.

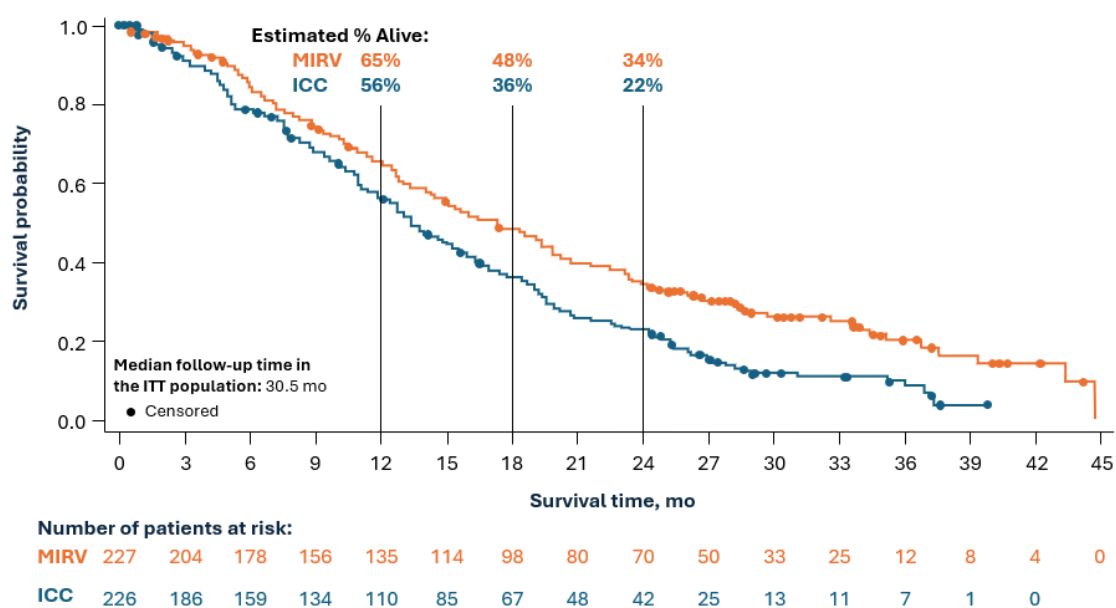
At the final data cut-off (26th September 2024), median OS after 30.49 months of follow up was significantly longer in the mirvetuximab group, 16.85 months (95% CI: 14.36, 19.78) vs 13.34 months (95% CI: 11.37, 15.15) in the IC Chemo group (HR: 0.68; 95% CI: 0.54, 0.84; p=0.0004) (Figure 11). This represents a 32% reduction in the risk of death in patients randomised to mirvetuximab. Landmark estimates extrapolated from these results for modelling purposes are presented in Section 3.3.4. At the time of study closure, there were still 44 patients alive in the mirvetuximab arm, vs 18 patients alive in the IC Chemo arm.

Table 9. Summary of OS results – ITT population (September 2024 DCO)

	Mirvetuximab (N=227)	IC Chemo (N=226)
September 2024 DCO		
Patients with death events, n (%)	162 (71.4)	177 (78.3)
Patients censored, n (%)	65 (28.6)	49 (21.7)
OS time (months)		
Median (95% CI)	16.85 (14.36, 19.78)	13.34 (11.37, 15.15)
25th percentile (95% CI)	8.64 (6.70, 10.48)	7.39 (4.99, 8.77)
75th percentile (95% CI)	32.66 (26.02, 37.62)	21.62 (19.32, 25.23)
Stratified analysis with IRT randomisation values		
Cox PH model, HR (95% CI)	0.68 (0.543, 0.840)	
Two-sided p-value from Log-rank test	0.0004	

Source: Data on file, MIRASOL final CSR (14).

Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; IC Chemo, Investigator's choice of chemotherapy; IRT, Interactive Response Technology; ITT, intention-to-treat; NR, not reached; OS, overall survival; PH, proportional hazards.

Figure 11. KM plot for OS – ITT population (September 2024 DCO)

Source: Data on file, MIRASOL final CSR (14).

Abbreviations: DCO, data cut-off; KM, Kaplan-Meier; ICC, Investigator's choice of chemotherapy; ITT, intention-to-treat; MIRV, mirvetuximab; OS, overall survival.

Key secondary endpoint: Objective response rate

Mirvetuximab demonstrated a more pronounced effect on tumour shrinkage, more than doubling the IC Chemo ORR of 15.9%, as evidenced by the investigator-assessed confirmed ORR of 41.9%. In addition, 5.7% of mirvetuximab treated patients achieved a complete response compared with no patients who received IC Chemo.

The percentage of patients with an investigator-assessed objective response was significantly higher in the mirvetuximab group (41.9%; 95% CI: 35.4, 48.6) than in the IC Chemo group (15.9%; [95% CI: 11.4, 21.4]; odds ratio [OR]: 3.75; [95% CI: 2.40, 5.85]; $p < 0.0001$; Table 10). Among the patients in the mirvetuximab group, 13 (5.7%) had a complete response and 82 (36.1%) had a partial response, compared with 0 and 36 patients (15.9%), respectively, in the IC Chemo group (Figure 12). There was also a lower proportion of patients with PD in the mirvetuximab group (13.7%) vs the IC Chemo group (27.9%). Notably, tumour shrinkage (encompassing complete and partial response, and stable disease) was observed for 80.1% of patients treated with mirvetuximab (regardless of the line of treatment, including primary platinum resistance), vs 56.2% of patients treated with IC Chemo.

ORR BICR results were generally concordant with investigator assessed ORR (ORR of 35.7% [95% CI: 29.5, 42.3] vs 14.6% [95% CI: 10.3, 19.9]; OR: 3.18 [95% CI: 2.011, 5.022]; $p < 0.0001$).

Meaningful active tumour response benefits and symptomatic improvement are therefore realised sooner for mirvetuximab patients given the observed higher response rates.

Table 10. Summary of ORR results – ITT population (September 2024 DCO)

	Mirvetuximab (N=227)	IC Chemo (N=226)
Best overall response, n (%)		
Complete response	13 (5.7)	0
Partial response	82 (36.1)	36 (15.9)
Stable disease	87 (38.3)	91 (40.3)
Progressive disease	31 (13.7)	63 (27.9)
Not evaluable	14 (6.2)	36 (15.9)
ORR, n (%) [†]	95 (41.9)	36 (15.9)
95% CI	(35.4, 48.6)	(11.4, 21.4)
Difference in ORR (95% CI)	25.9 (17.9, 33.9)	

Company evidence submission for mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

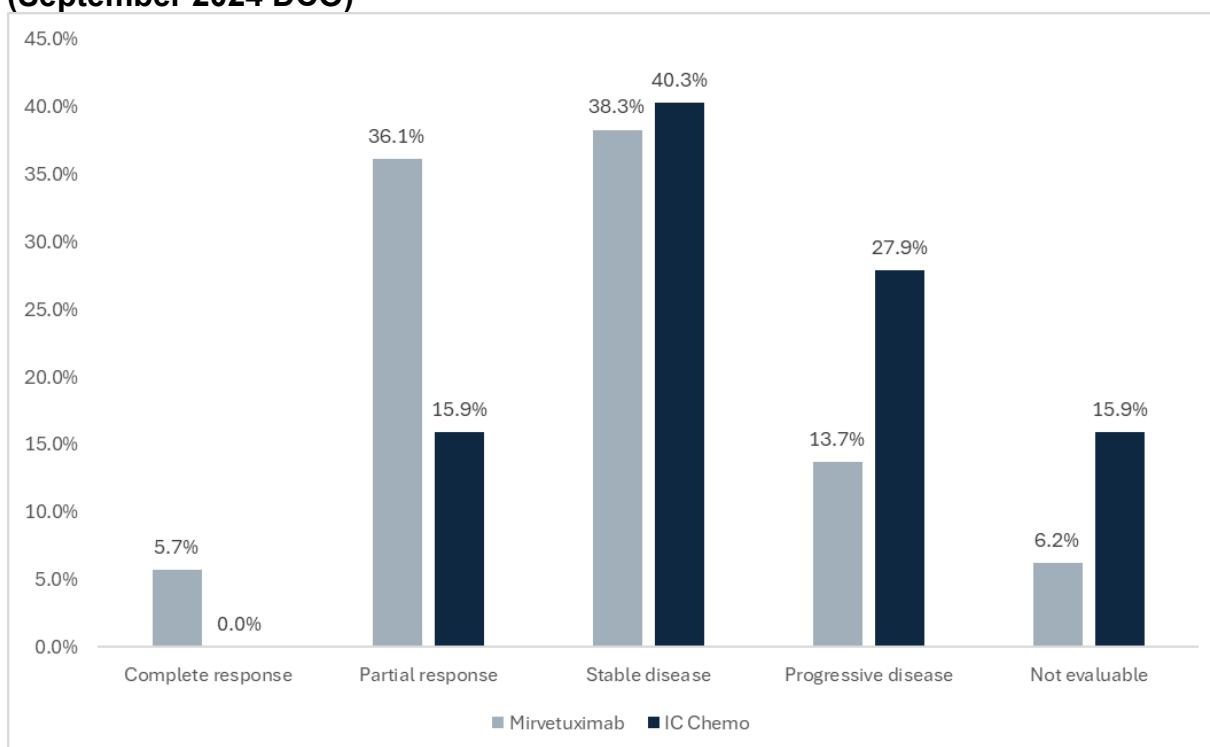
	Mirvetuximab (N=227)	IC Chemo (N=226)
Stratified on randomisation factors		
Odds ratio (95% CI)	3.75 (2.400, 5.852)	
2-sided p-value	<0.0001	

Source: Data on file, MIRASOL final CSR (14).

†ORR is the sum of patients whose Best overall response was 'partial response' or 'complete response'.

Abbreviations: CI, confidence interval; CSR, clinical study report; DCO, data cut-off; IC Chemo, Investigator's choice of chemotherapy; ITT, intention-to-treat; ORR, objective response rate.

Figure 12. Summary of best overall response results – ITT population (September 2024 DCO)



Source: Data on file, MIRASOL final CSR (14).

Abbreviations: CI, confidence interval; CSR, clinical study report; DCO, data cut-off; IC Chemo, Investigator's choice of chemotherapy; ITT, intention-to-treat.

Key secondary endpoint: EORTC QLQ-OV28

The Quality of Life Questionnaire ovarian cancer module (QLQ-OV28) is a validated OC-specific instrument containing key subscales such as abdominal and gastrointestinal symptoms, peripheral neuropathy, attitudes toward the disease and treatment and sexual functioning (147).

The proportion of patients achieving a pre-specified 15-point or greater improvement in the abdominal/gastrointestinal subscale at Week 8 or 9 was a key secondary endpoint in MIRASOL. This 15-point threshold corresponds to a 15% improvement and was based on the literature.

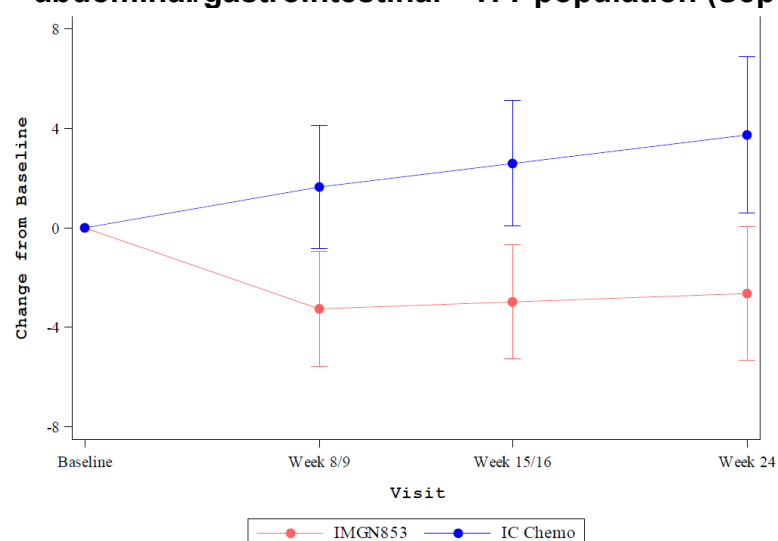
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At Week 8/9, 34/162 (21%) patients in the mirvetuximab group achieved the 15-point improvement compared with 23/150 (15%) patients in the IC Chemo group ($p=0.2659$). However, since the 15-point threshold was considered to be stringent, a pre-specified sensitivity analysis using an 11.1-point threshold was conducted, which resulted in a nominally significant p -value. It found that 47/162 (29.0%) mirvetuximab-treated patients and 27/150 (18.0%) IC Chemo-treated patients demonstrated an improvement in abdominal and gastrointestinal scores at Week 8/9 ($p=0.0325$) (148).

Significant improvements were observed for mirvetuximab in the mixed model for repeated measures (MMRM) change-from-baseline analysis for the abdominal/gastrointestinal symptom and 'attitude toward disease and treatment' subscales. In the abdominal/gastrointestinal symptom subscale, differences in least squares mean (LSM) scores varied between -5.0 to -6.0 at Weeks 8/9, 15/16, and 24 favouring mirvetuximab (nominal $p<0.005$ at all 3-time points) (Figure 13). The difference in LSM score in the 'attitude toward disease and treatment' subscale was 8.0 at Week 8/9 and widened to 10.2 at Week 24 (nominal $p\leq 0.0001$ or less at all 3 timepoints) (Figure 14). No significant differences between groups were demonstrated in the other two subscales (peripheral neuropathy and sexual function) between mirvetuximab and IC Chemo, showing that HRQoL was preserved vs IC Chemo (Figure 15, Figure 16).

Taken collectively, the results demonstrate that mirvetuximab either improves or maintains crucial aspects of HRQoL in this population while for chemotherapy, a worsening trend was observed for the subscales mentioned.

Figure 13. LS Means ($\pm$ 95% CI) of change from baseline in EORTC QLQ-OV28 – abdominal/gastrointestinal – ITT population (September 2024 DCO)[†]

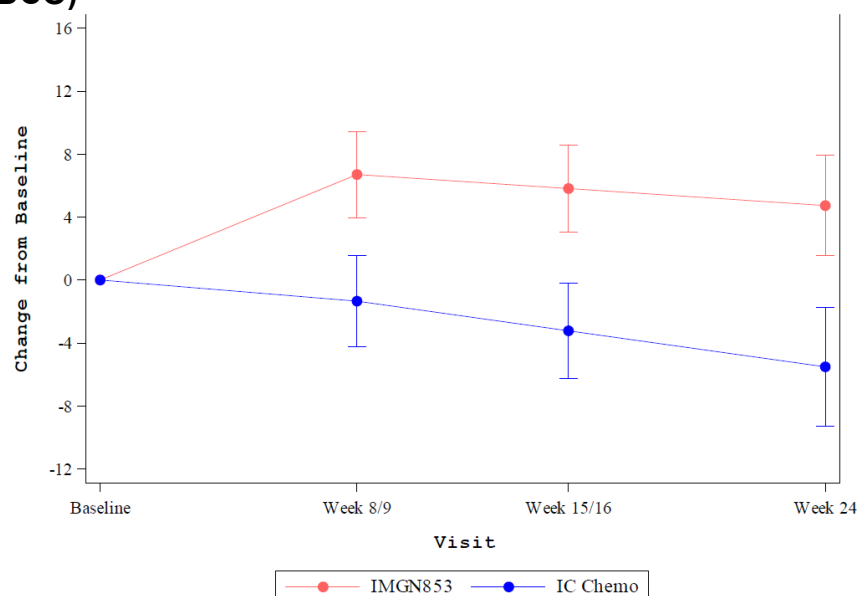


Source: Data on file, MIRASOL final CSR (14).

[†]A positive change from baseline indicates a deterioration while a negative change indicates improvement.

Abbreviations: CI, confidence interval; DCO, data cut-off; EORTC QLQ-OV28, European Organisation for Research and Treatment of Cancer Quality of life Questionnaire ovarian cancer module; IMGN853, mirvetuximab; ITT, intention-to-treat; IC Chemo, Investigator's choice of chemotherapy; LS, least squares.

Figure 14. LS Means ($\pm$ 95% CI) of change from baseline in EORTC QLQ-OV28 – attitude toward disease and treatment – ITT population (September 2024 DCO)[†]



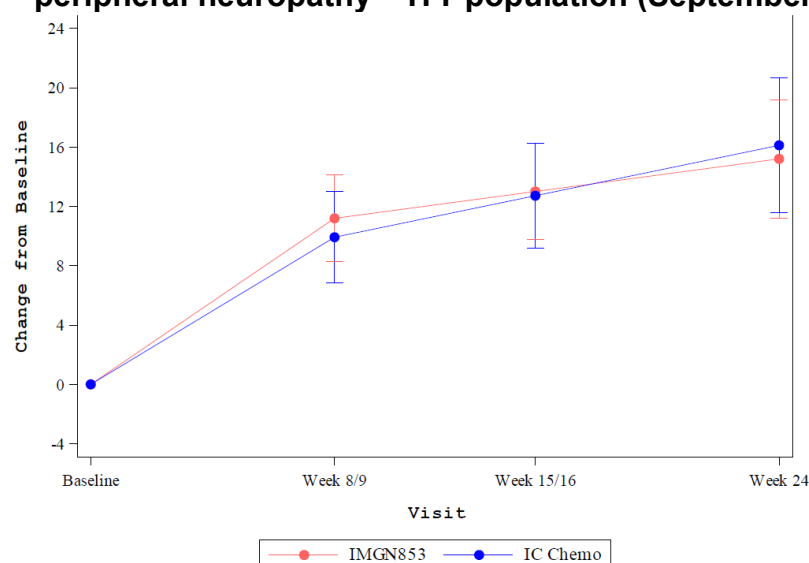
Source: Data on file, MIRASOL final CSR (14).

[†]A positive change from baseline indicates an improvement while a negative change indicates deterioration.

Abbreviations: CI, confidence interval; DCO, data cut-off; EORTC QLQ-OV28, European Organisation for Research and Treatment of Cancer Quality of life Questionnaire ovarian cancer module; IMGN853, mirvetuximab; ITT, intention-to-treat; IC Chemo, Investigator's choice of chemotherapy; LS, least squares.

Company evidence submission for mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Figure 15. LS Means ($\pm$ 95% CI) of change from baseline in EORTC QLQ-OV28 – peripheral neuropathy – ITT population (September 2024 DCO)[†]

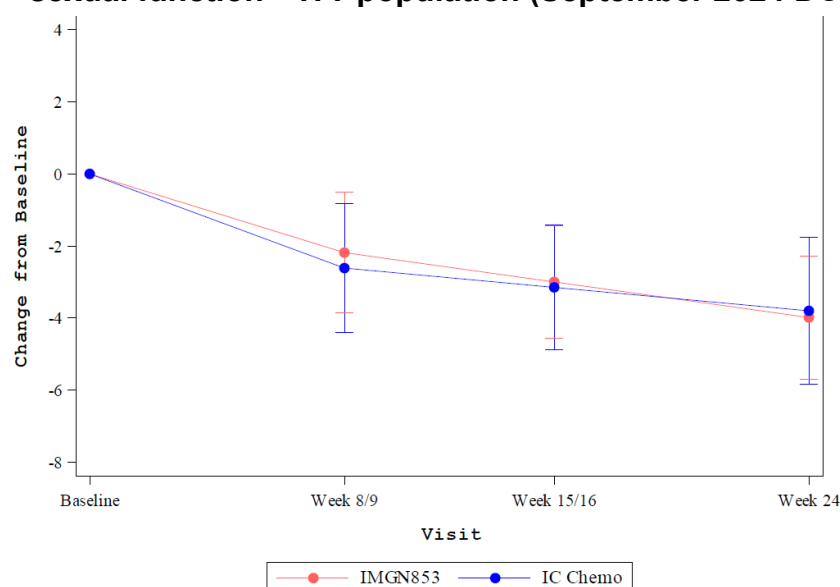


Source: Data on file, MIRASOL final CSR (14).

[†]A positive change from baseline indicates a deterioration while a negative change indicates improvement.

Abbreviations: CI, confidence interval; DCO, data cut-off; EORTC QLQ-OV28, European Organisation for Research and Treatment of Cancer Quality of life Questionnaire ovarian cancer module; IMGN853, mirvetuximab; ITT, intention-to-treat; IC Chemo, Investigator's choice of chemotherapy; LS, least squares.

Figure 16. LS Means ($\pm$ 95% CI) of Change from Baseline in EORTC QLQ-OV28 – sexual function – ITT population (September 2024 DCO)[†]



Source: Data on file, MIRASOL final CSR (14).

[†]A positive change from baseline indicates an improvement while a negative change indicates deterioration.

Abbreviations: CI, confidence interval; DCO, data cut-off; EORTC QLQ-OV28, European Organisation for Research and Treatment of Cancer Quality of life Questionnaire ovarian cancer module; IMGN853, mirvetuximab; ITT, intention-to-treat; IC Chemo, Investigator's choice of chemotherapy; LS, least squares.

Company evidence submission for mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Secondary endpoint: Duration of response

A substantially higher number of patients randomised to mirvetuximab had either complete or partial response per investigator compared with IC chemo (95 and 36 respectively). Among the 86 mirvetuximab-treated patients with recorded duration of response (DOR), the median was significantly greater: 6.93 months (95% CI: 5.78, 8.84 months) compared with 4.44 months (95% CI: 4.17, 5.72 months) in the 32 IC Chemo patients with response (HR: 0.62; p=0.0203; Table 11 and Figure 17). The median time to response (TTR) per investigator was faster in patients randomised to mirvetuximab at 1.54 months (range: 1.1 to 7.2 months) compared with 2.71 months (range: 1.2 to 8.2 months) in IC Chemo-treated patients.

Table 11. Summary of DOR results per investigator – ITT population† (September 2024 DCO)

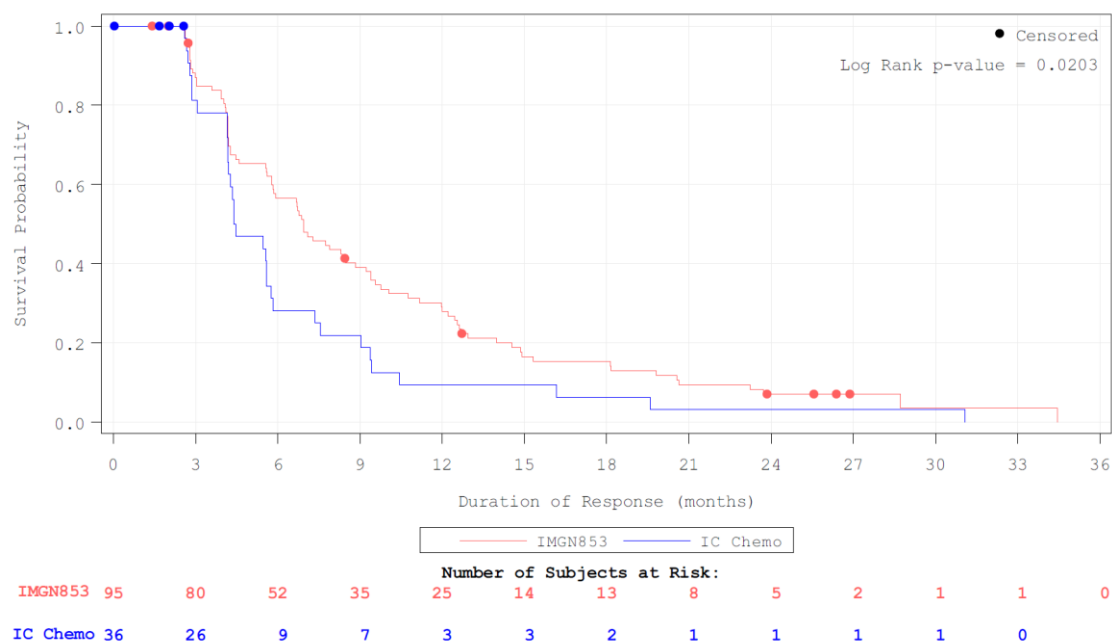
	Mirvetuximab (N=95)	IC Chemo (N=36)
Number of patients with events, n (%)	86 (90.5)	32 (88.9)
Number of patients censored, n (%)	9 (9.5)	4 (11.1)
Estimated duration of response time (months)		
Median (95% CI)	6.93 (5.78, 8.84)	4.44 (4.17, 5.75)
25 th percentile (95% CI)	4.17 (3.58, 4.47)	4.14 (2.73, 4.27)
75 th percentile (95% CI)	12.55 (9.76, 14.92)	7.46 (5.55, 10.45)
Time to response (months)		
Median (range)	1.54 (1.1, 7.2)	2.71 (1.2, 8.2)
Unstratified analysis		
Cox PH model, HR (95% CI)	0.62 (0.409, 0.934)	
Two-sided P-value from Log-rank test	0.0203	

Source: Data on file, MIRASOL final CSR (14).

†Patients who had CR or PR

Abbreviations: CI, confidence interval; CR, complete response; DCO, data cut-off; DOR, duration of response; HR, hazard ratio; IC Chemo, Investigator's choice of chemotherapy; ITT, intention-to-treat; PH, proportional hazards; PR, partial response.

Figure 17. KM for DOR – ITT population (September 2024 DCO)



Source: Data on file, MIRASOL final CSR (14).

Abbreviations: CSR, clinical study report; DCO, data cut-off; DOR, duration of response; KM, Kaplan-Meier; IC Chemo, Investigator's choice of chemotherapy; IMGN853, mirvetuximab; ITT, intention-to-treat.

Secondary endpoint: Time to second disease progression or death

PFS2 was defined as the time from date of randomisation until second disease progression, end of next line of therapy, or death (whichever comes first), regardless of whether the patient received new anti-cancer treatment. There was demonstration of a continued benefit beyond first progression with mirvetuximab, extending into the subsequent treatment line, associated with a significant and clinically meaningful 41% reduction in the risk of second progression or death compared with IC Chemo (HR: 0.59; median 11.01 vs 7.59 months, respectively; $p < 0.0001$; Table 12 and Figure 18).

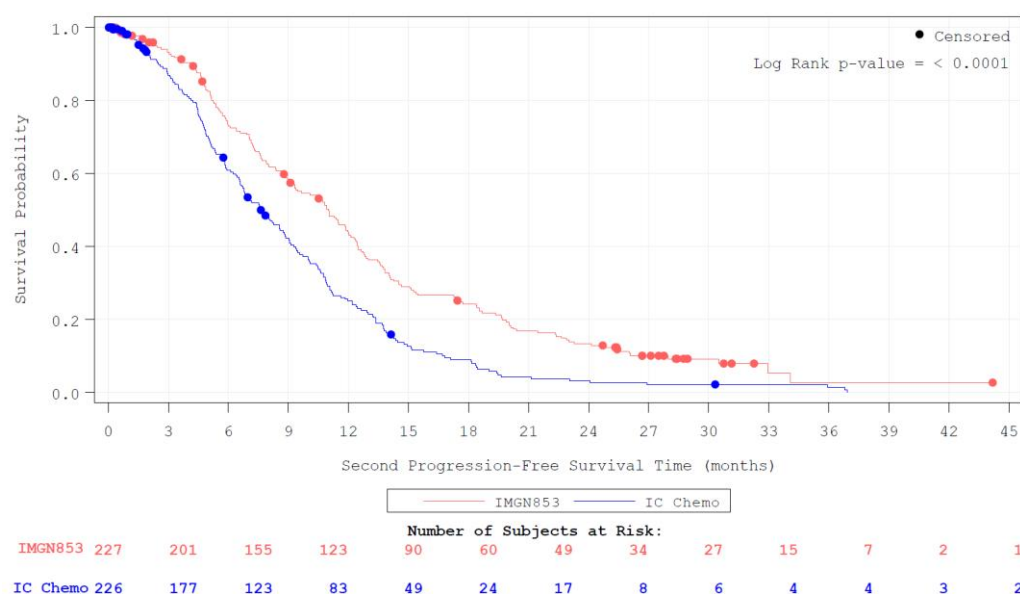
Table 12. Summary of PFS2 results per investigator – ITT population (September 2024 DCO)

Number of Patients, n (%)	Mirvetuximab (N=227)	IC Chemo (N=226)
Number of patients with events, n (%)	192 (84.6)	198 (87.6)
Disease progression	39 (17.2)	53 (23.5)
Death	58 (25.6)	60 (26.5)
End of next-line treatment	95 (41.9)	85 (37.6)
Number of patients censored, n (%)	35 (15.4)	28 (12.4)
Estimated progression free survival time (months)		
Median (95% CI)	11.01 (9.30, 12.02)	7.59 (6.60, 8.84)
25th percentile (95% CI)	5.85 (5.16, 7.06)	4.60 (3.94, 5.06)
75th percentile (95% CI)	17.71 (14.26, 19.88)	11.96 (10.84, 13.37)
Stratified analysis with IRT randomisation values		
Cox PH model, HR (95% CI)	0.59 (0.480, 0.728)	
Two-sided P-value from Log-rank test	<0.0001	

Source: Data on file, MIRASOL final CSR (14).

Abbreviations: CI, confidence interval; CSR, clinical study report; DCO, data cut-off; HR, hazard ratio; IC Chemo, Investigator's choice of chemotherapy; IRT, Interactive Response Technology; ITT, intention-to-treat; PD, progressed disease; PFS2, time to second disease progression; PH, proportional hazards.

Figure 18. KM for PFS2 – ITT population (September 2024 DCO)



Source: Data on file, MIRASOL final CSR (14).

Abbreviations: CSR, clinical study report; DCO, data cut-off; KM, Kaplan-Meier; IC Chemo, Investigator's choice of chemotherapy; IMGN853, mirvetuximab; ITT, intention-to-treat; PFS2, time to second progression-free survival.

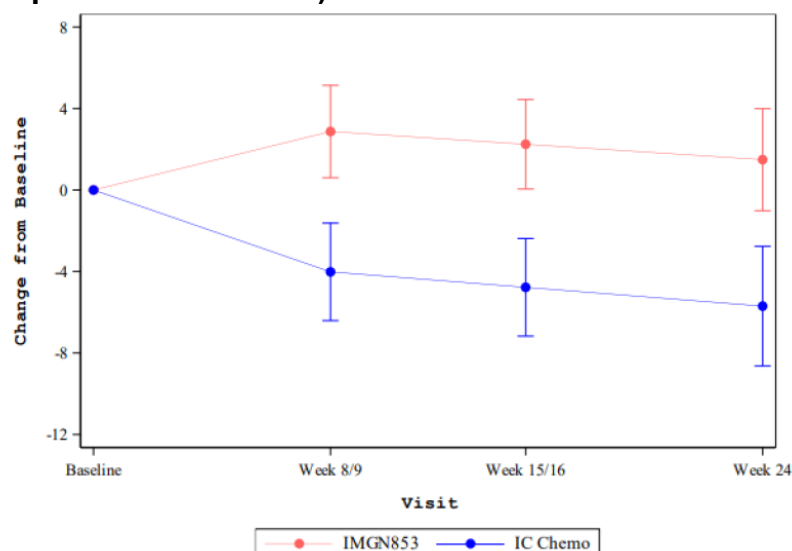
Exploratory endpoint: EQ-5D-5L

A total of 166 patients from the mirvetuximab arm, and 155 patients from the IC Chemo arm were assessed using a MMRM model for EQ-5D visual analogy scale

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(VAS) score (Figure 19). At all three timepoints (Weeks 8/9, Weeks 15/16, and Week 24), results significantly favoured mirvetuximab (nominal $p \leq 0.0003$ at all three timepoints), demonstrating patients' perception of overall health was maintained with mirvetuximab while decreasing across time for patients receiving IC Chemo.

Figure 19. Change from baseline in EQ-5D-5L VAS scores – ITT population (September 2024 DCO)[†]



Source: Data on file, MIRASOL PRO report (142)

[†]A positive change from baseline indicates a improvement while a negative change indicates deterioration.

Abbreviations: DCO, data cut-off; IC Chemo, Investigator's choice of chemotherapy; IMGN853, mirvetuximab; ITT, intention-to-treat; VAS, visual analogue scale.

The impact of treatment and disease state on health state utility was assessed using the EQ-5D-5L index (149). The EQ-5D-5L analysis used in the cost-effectiveness model is described in further detail in Section 3.4.6.

Exploratory endpoint: EORTC QLQ-C30

Change from baseline in the EORTC QLQ-C30 scores for key subscales, such as Global Health Status/Quality of life, physical functioning, role functioning and fatigue symptoms, was analysed using an MMRM methodology.

Deterioration was observed for Global Health Status/Quality of life, physical functioning and fatigue symptoms for patients receiving IC Chemo, while scores for mirvetuximab-treated patients remained stable. Regarding role functioning, a trend to deterioration was observed in both arms with more deterioration observed for IC Chemo patients.

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At all timepoints (Week 8/9, Week 15/16, Week 24), statistically significant differences between treatment groups were observed in mean changes from baseline for the key subscales highlighted above, consistently favouring mirvetuximab. The differences in LSM scores from Week 8/9 to Week 24 increased across various subscales: Global Health Status/Quality of Life from 7.0 to 7.4 (nominal $p < 0.0005$), physical functioning from 6.3 to 9.9 (nominal $p < 0.0001$), role functioning from 7.4 to 9.6 (nominal $p < 0.001$), and fatigue symptoms from -8.3 to -11.1 (nominal $p < 0.0001$), all showing statistical significance at these timepoints.

Overall, mirvetuximab maintained stable EORTC QLQ-C30 scores over time whereas IC Chemo was associated with progressive deterioration across the key subscales. Increasing differences in mean change from baseline between treatment groups were observed across timepoints, favouring mirvetuximab vs IC Chemo.

Duration of treatment

Duration of treatment (DoT) was defined as the time patients continued to receive study drug until disease progression, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminated the study in the safety population.

Patients received a median of:

- Mirvetuximab: 7.0 cycles (mean: 9.2; range: 1 to 51 cycles); median duration: 4.98 months
- IC Chemo: 3.0 cycles (mean: 4.5; range: 1 to 30 cycles); median duration: 2.96 months
 - Paclitaxel: 4.0 cycles (mean: 4.5; range: 1 to 9 cycles); median duration: 3.80 months
 - Pegylated liposomal doxorubicin: 3.0 cycles (mean: 4.6; range: 1 to 30 cycles); median duration: 2.76 months
 - Topotecan:
 - 1.25 mg/m²: 6.0 cycles (mean: 9.1; range 1 to 19 cycles); median duration: 5.01 months
 - 4.0 mg/m²: 2.0 cycles (mean: 3.2; range: 1 to 12 cycles); median duration: 2.10 months.

The superior efficacy and tolerability profile of mirvetuximab were reflected in the median DoT (4.98 months in the mirvetuximab arm and 2.96 months in the IC Chemo arm).

2.7. Subsequent treatments

In total, 67% of mirvetuximab-treated patients and 65% of IC Chemo-treated patients received subsequent treatments (Table 13). The proportion of patients receiving different subsequent treatments were broadly similar between mirvetuximab and IC Chemo groups, except for taxanes (35.2% vs 26.1%, respectively) and anthracyclines (25.1% vs 9.3%, respectively). Notably, UK clinicians confirmed the most common subsequent treatments are likely to be taxanes, anthracyclines, and gemcitabine, alongside enrolling in clinical trials. This is broadly aligned with the subsequent therapies received in MIRASOL (Table 13), demonstrating generalisability to UK clinical practice. Modelling of commonly used subsequent treatments is detailed in Section 3.5.3.

Table 13. Subsequent treatments – ITT population (September 2024 DCO)

	Mirvetuximab (N=227)	IC Chemo (N=226)
Number (%) of patients receiving new anti-cancer therapy	152 (67.0)	147 (65.0)
New anti-cancer therapy		
Taxanes (e.g. paclitaxel)	80 (35.2)	59 (26.1)
Topotecan	20 (8.8)	24 (10.6)
Platinum compounds	42 (18.5)	42 (18.6)
Anthracyclines (e.g. doxorubicin)	57 (25.1)	21 (9.3)
Chemotherapy (other)	50 (22.0)	56 (24.8)
Bevacizumab	42 (18.5)	35 (15.5)
Hormonal therapy	7 (3.1)	5 (2.2)
Kinase inhibitors	12 (5.3)	10 (4.4)
Mirvetuximab	2 (<1)	16 (7.1)
PARP inhibitors	10 (4.4)	7 (3.1)
PD-1/PD-L1 inhibitors	14 (6.2)	16 (7.1)
Gemcitabine	54 (23.8)	58 (25.7)
Other	22 (9.7)	24 (10.6)

Source: Data on file, MIRASOL final CSR (14).

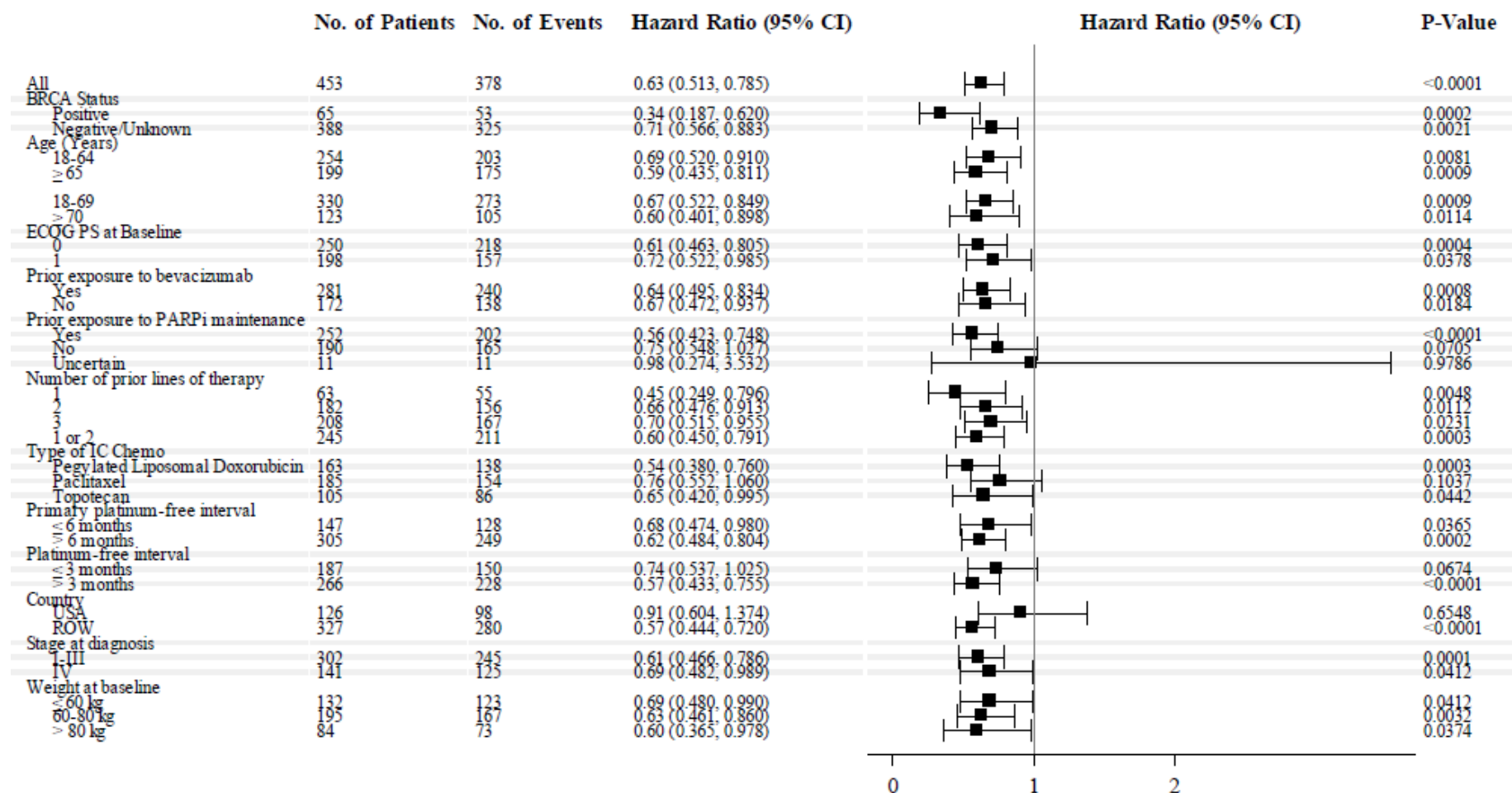
Abbreviations: DCO, data cut-off; IC Chemo, Investigator's choice of chemotherapy; ITT, intention-to-treat; PARP, poly (adenosine diphosphate-ribose) polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

2.8. Subgroup analysis

In MIRASOL, subgroup analyses were performed for PFS, ORR, OS, and PFS2. All subgroup analyses were exploratory and unstratified, however results for PFS, ORR, OS, and PFS2 across subgroups were broadly consistent with those of the primary analysis using the ITT population, and favoured mirvetuximab over IC Chemo.

Subgroup analysis results for the primary endpoint, PFS, are presented in Figure 20. This consistent PFS trend favouring mirvetuximab over IC Chemo was observed (supported by overlapping CIs) across subgroups such as age, *BRCA* mutation status, Eastern Cooperative Oncology Group (ECOG) status, number of prior lines of therapy, prior exposure to PARP inhibitor maintenance, stage of diagnosis, and weight at baseline. A summary of the results for ORR, OS, and PFS2 subgroup analyses is presented in Appendix C.

Figure 20. Forest plot for PFS (primary endpoint) by subgroup analysis per ITT population (September 2024 DCO)



Source: Data on file, MIRASOL final CSR (15).

Abbreviations: BRCA, breast cancer gene; CI, confidence interval DCO, data cut-off; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; IC Chemo, Investigators choice of chemotherapy; ITT, intention-to-treat; PARPi, poly (adenosine diphosphate-ribose) polymerase inhibitor; PFS, progression-free survival; PS, performance status; ROW, rest of world; USA, United States of America.

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2.9. Meta-analysis

No meta-analysis is available for the specific population of interest (adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens).

2.10. Indirect and mixed treatment comparisons

MIRASOL directly compared mirvetuximab with IC Chemo in adults with FR α positive PROC. Therefore, indirect and mixed treatment comparisons were not deemed necessary or appropriate to support the clinical effectiveness of mirvetuximab in the proposed treatment setting.

2.11. Adverse reactions

2.11.1. MIRASOL

Overview of adverse events

The differentiated safety profile of mirvetuximab in MIRASOL after a median follow-up time of 28.35 months at the 26th September 2024 data cut was consistent with the findings from the previously reported mirvetuximab studies (Phase 1 first-in-human, Phase 2 SORAYA, and Phase 3 FORWARD-1 and MIRASOL 6th March 2023 data cut) (1, 11, 136, 137), and consists predominantly of low-grade ocular, gastrointestinal, and neurosensory events. A summary of overall safety is presented in Table 14.

Table 14. Overview of TEAEs until the data cut-off date – Safety population (September 2024 DCO)

Adverse event, n (%)	Mirvetuximab (N=218)	IC Chemo (N=207)
TEAE		
All grades	211 (97)	194 (94)
Grades 3+	97 (44)	113 (55)
Study drug-related TEAE		
All grades	191 (88)	167 (81)
Grades 3+	59 (27)	77 (37)
Serious TEAE		
All grades	55 (25)	69 (33)
Grades 3+	47 (22)	60 (29)
Serious drug-related TEAE		
All grades	21 (10)	16 (8)
Grades 3+	17 (8)	16 (8)
TEAE leading to study drug discontinuation		
All grades	25 (11)	31 (15)
Grades 3+	12 (6)	22 (11)
Study drug-related TEAE leading to study drug discontinuation		
All grades	19 (9)	17 (8)
Grades 3+	7 (3)	11 (5)
TEAE leading to death	4 (2)	5 (2)
Study drug-related TEAE leading to death	0	1 (<1)

Source: Data on file, MIRASOL final CSR (15).

Abbreviations: CSR, clinical study report; DCO, data cut-off; IC Chemo, Investigator's choice of chemotherapy; TEAE, treatment emergent adverse event.

Overview of treatment-emergent adverse events

Adverse events were coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version and summarised per system organ class (SOC) and preferred term (PT). As in other trials, treatment-emergent AEs (TEAEs) were graded 1–5 (150):

- Grade 1–2: mild or moderate TEAEs that generally do not impact patients significantly and may at most require minimal intervention.
- Grade 3–4: serious TEAEs that interfere with a patient's ability to do basic things. Patients likely to need to be seen by their doctor for medical intervention or hospitalisation.

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- Grade 5: fatal TEAEs.

Grade 3+ TEAEs occurred less frequently in patients treated with mirvetuximab compared with those treated with IC Chemo irrespective of causality (44% vs 55% respectively, Table 14). The most commonly reported Grade 3+ TEAEs in the mirvetuximab arm were keratopathy (10%), blurred vision events (8%), and cataracts (5%; Table 15 and Figure 21). In the IC Chemo arm, the most commonly reported Grade 3+ TEAEs were neutropenia (17%), anaemia (10%), and thrombocytopenia (6%). Grade 3+ TEAEs that were suspected to be related to a study drug were lower in the mirvetuximab arm compared with the IC arm (27% vs 37%, respectively).

Patients treated with mirvetuximab reported fewer serious adverse events (SAE) than IC Chemo. SAEs of any grade were reported in 25% of patients in the mirvetuximab arm and 33% of patients in the IC Chemo arm. The most common SAEs in both arms were gastrointestinal disorders; respiratory, thoracic and mediastinal disorders; infections; and blood and lymphatic system disorders. Despite patients receiving mirvetuximab for a longer duration than IC Chemo patients (Sections 2.11.1 and 3.3.5), fewer patients treated with mirvetuximab reported TEAEs leading to discontinuation of study drug compared with those treated with IC Chemo (11% vs 15%, respectively). This pattern was also observed for Grade 3+ TEAEs leading to study discontinuation (6% vs 11%, respectively).

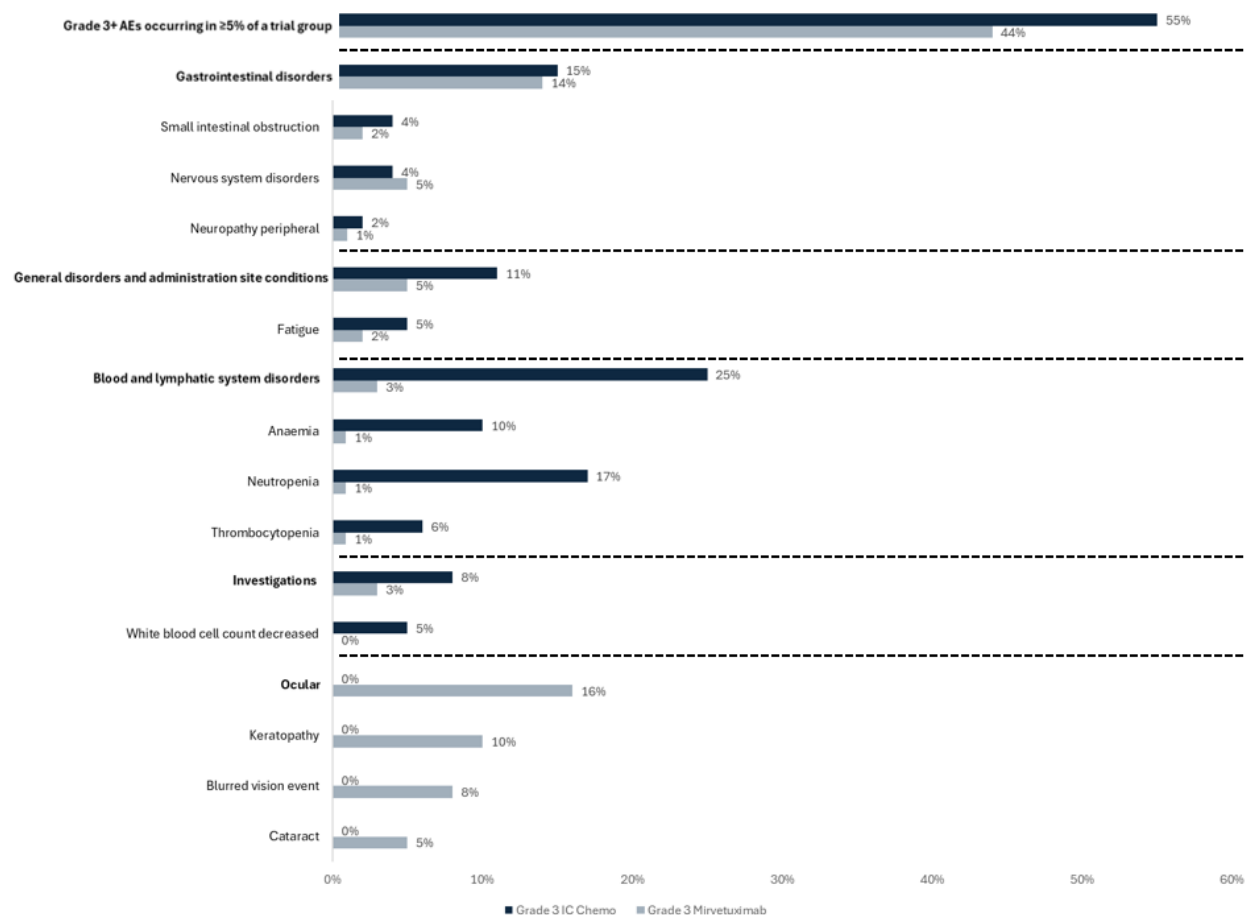
Table 15. Most common Grade 3+ TEAEs by organ class – Safety population (September 2024 DCO)

Adverse event, n (%)	Mirvetuximab (N=218)	IC Chemo (N=207)
Grade 3+ AEs occurring in ≥5% of a trial group	97 (44)	113 (55)
Gastrointestinal disorders	30 (14)	31 (15)
Small intestinal obstruction	4 (2)	8 (4)
Nervous system disorders	11 (5)	9 (4)
Neuropathy peripheral	3 (1)	4 (2)
General disorders and administration site conditions	10 (5)	22 (11)
Fatigue	5 (2)	11 (5)
Blood and lymphatic system disorders	6 (3)	51 (25)
Anaemia	2 (<1)	21 (10)
Neutropenia	2 (<1)	36 (17)
Thrombocytopenia	2 (<1)	13 (6)
Investigations	6 (3)	17 (8)
White blood cell count decreased	0	10 (5)
Ocular	34 (16)	0
Keratopathy	21 (10)	0
Blurred vision event	18 (8)	0
Cataract	11 (5)	0

Source: Data on file, MIRASOL final CSR (15).

Abbreviations: AE, adverse event; CSR, clinical study report; DCO, data cut-off; IC Chemo, Investigator's choice of chemotherapy; TEAE, treatment-emergent adverse event.

Figure 21. Most common Grade 3+ TEAEs by preferred term – Safety population (September 2024 DCO)



Source: Data on file, MIRASOL final CSR (15).

Abbreviations: AE, adverse event; CSR, clinical study report; DCO, data cut-off; IC Chemo, Investigator's choice of chemotherapy; TEAE, treatment-emergent adverse event.

Common treatment-emergent adverse events

A total of 211 (97%) patients treated with mirvetuximab reported a TEAE of any grade (Table 16). The most common TEAEs among these patients were blurred vision (43%), keratopathy (33%), and abdominal pain (31%). Among patients treated with IC Chemo, 194 (94%) patients reported TEAEs of any grade. The most common among these patients were anaemia (34%), nausea (29%), and neutropenia (29%).

Fewer patients treated with mirvetuximab reported neutropenia (11% vs 29%), anaemia (10% vs 34%), or alopecia (1% vs 14%) compared with those treated with IC Chemo.

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A greater proportion of mirvetuximab-treated patients than IC Chemo treated patients reported ocular TEAEs, including blurred vision (43% vs 2%), keratopathy (33% vs 0%) and dry eye (29% vs 2%) (further information on ocular TEAEs is provided below and Section 2.13).

Table 16. Adverse events reported by preferred term by ≥10% of patients – Safety population (September 2024 DCO)

	Mirvetuximab (N=218)	IC Chemo (N=207)
Any TEAE reported by ≥10% of patients	211 (97)	194 (94)
Blood and lymphatic system disorders		
Neutropenia	25 (11)	60 (29)
Anaemia	21 (10)	71 (34)
Thrombocytopenia	18 (8)	34 (16)
Eye disorders		
Vision blurred	94 (43)	5 (2)
Keratopathy	72 (33)	0 (0)
Dry eye	64 (29)	5 (2)
Photophobia	42 (19)	1 (<1)
Cataract	37 (17)	1 (<1)
Visual acuity reduced	29 (13)	0
Gastrointestinal disorders		
Abdominal pain	68 (31)	32 (15)
Diarrhoea	63 (29)	37 (18)
Constipation	59 (27)	40 (19)
Nausea	58 (27)	60 (29)
Vomiting	39 (18)	37 (18)
Stomatitis	8 (4)	23 (11)
General disorders and administration site conditions		
Fatigue	66 (30)	52 (25)
Asthenia	42 (19)	36 (17)
Nervous system disorders		
Neuropathy peripheral	48 (22)	30 (14)
Peripheral sensory neuropathy	21 (10)	12 (6)
Headache	31 (14)	20 (10)
Metabolism and nutrition disorders		
Decreased appetite	39 (18)	28 (14)
Investigations		
Aspartate aminotransferase increased	25 (11)	9 (4)
Skin and subcutaneous tissue disorders		
Alopecia	3 (1)	29 (14)
Musculoskeletal and connective tissue disorders		
Arthralgia	34 (16)	11 (5)
Respiratory, thoracic and mediastinal disorders		
Cough	23 (11)	14 (7)
Dyspnoea	17 (8)	27 (13)

Source: Data on file, MIRASOL final CSR (15).

Abbreviations: AE, adverse event; DCO, data cut-off; IC Chemo, Investigator's choice of chemotherapy.

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Adverse events of interest

The MIRASOL trial did not specify any all-grade grouped-term AEs of special interest (AESI). However, certain TEAEs are highly relevant to patients and clinicians, namely haematological TEAEs, ocular TEAEs, peripheral neuropathy, and pneumonitis; - a few of which are discussed in more detail in the draft UK SmPC. A summary of AEs of interest is presented in Table 17, and discussed below.

Table 17. Summary of adverse events of interest – Safety population (September 2024 DCO)

Adverse event, n (%)	Mirvetuximab (N=218)	IC Chemo (N=207)
Haematological TEAES	40 (18)	91 (44)
No action taken	N/A	N/A
Dose delayed	17 (8)	63 (30)
Dose reduced	3 (1)	116 (8)
Permanent discontinuation	2 (<1)	6 (3)
Ocular TEAES	125 (57)	18 (9)
No action taken	50 (23)	18 (9)
Dose delayed/not given	31 (14)	0
Dose reduced	39 (18)	0
Permanent discontinuation	5 (2)	0
Peripheral neuropathy TEAES	82 (38)	47 (23)
No action taken	65 (30)	23 (11)
Dose delayed/not given	1 (<1)	5 (2)
Dose reduced	13 (6)	14 (7)
Permanent discontinuation	5 (2)	3 (1)
Pneumonitis TEAES	26 (12)	1 (<1)
No action taken	5 (2)	0
Dose delayed/not given	11 (5)	1 (<1)
Dose reduced	1 (<1)	0
Permanent discontinuation	9 (4)	0

Source: Data on file, MIRASOL final CSR (15).

Abbreviations: CSR, clinical study report; DCO, data cut-off; IC Chemo, Investigator's choice of chemotherapy; N/A, not available; TEAE, treatment-emergent adverse event.

Haematological treatment-emergent adverse events

Haematological TEAEs of any grade with mirvetuximab were less common than those seen with IC Chemo (11% neutropenia; 10% anaemia; 8% thrombocytopenia with mirvetuximab vs 29%; 34%; 16% with IC Chemo, respectively). Study-drug related haematological TEAEs were reported in 42 (19%) mirvetuximab treated patients, compared with 91 (44%) patients treated with IC Chemo. The proportion of Grade 3+ haematological TEAEs, was lower with mirvetuximab treated patients (6 patients, 3%) compared with the 51 (25%) patients treated with IC Chemo (Table 15). Grade 3+ anaemia, neutropenia, or thrombocytopenia was experienced by two patients (<1%) each in the mirvetuximab treated group, compared with 21 (10%) patients experiencing Grade 3+ anaemia, 36 (17%) experiencing neutropenia, and 13 (6%) experiencing thrombocytopenia in the IC Chemo treated group. Notably, these haematological TEAEs are among the most expensive to manage (Section 3.5.5).

Ocular treatment-emergent adverse events

Ocular toxicities were reported more frequently in the mirvetuximab treatment group than with IC Chemo but were observed to be generally low grade and manageable. Almost all patients had complete resolution or partial improvement (defined as a decrease in severity by one or more grades from the worst grade at last follow-up).

A total of 125 (57%) patients treated with mirvetuximab reported ocular TEAEs, compared with the 18 (9%) patients treated with IC Chemo. However, of the 125 patients treated with mirvetuximab who reported ocular TEAEs, the majority were Grade ≤ 2 in severity (84%), with 34 (16%) patients treated with mirvetuximab reported Grade 3+ ocular TEAEs (IC Chemo, 0 patients; Table 16). The most common TEAEs for patients treated with mirvetuximab (all grades; Grade 3+) were blurred vision (43%, 8%), keratopathy (33%, 10%), dry eye (29%, 4%) compared with IC Chemo (blurred vision (2%, 0%), keratopathy (0%, 0%) and dry eye (2%, 0%).

Resolution outcomes of ocular TEAEs for patients treated with mirvetuximab demonstrated that 58% reported complete resolution, and an additional 34% of patients had partial improvement, with most events resolving to Grade 1. The most common

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actions taken due to ocular TEAEs in patients treated with mirvetuximab were no action (23%), dose reductions (18%), and dose delayed (14%), with just five (2%) patients permanently discontinuing from mirvetuximab due to these ocular TEAEs (Table 17).

Peripheral neuropathy treatment-emergent adverse events

A total of 48 (22%) patients treated with mirvetuximab reported peripheral neuropathy, compared with the 30 (14%) of patients treated with IC Chemo. Most peripheral neuropathy TEAEs reported in patients treated with mirvetuximab were Grade ≤ 2 , with only 3 patients (1%) reporting Grade 3 and no patients reporting Grade 4. This was similar in IC Chemo, with 4 patients (2%) reporting Grade 3 peripheral neuropathy and no one reporting Grade 4. Resolution rates of peripheral neuropathy were comparable between mirvetuximab and IC Chemo for both complete (18% vs 21% respectively) and partial resolution (11% vs 15%, respectively). Peripheral neuropathy resulted in the mirvetuximab dose being reduced in 6% and delayed or not given in 4% of patients. The proportions were comparable in IC Chemo, with 8% dose reductions and 6% delayed or not given. Permanent discontinuations due to peripheral neuropathy were low and observed in 1% of mirvetuximab-treated patients and 2% of IC Chemo-treated patients.

Additional analysis of baseline characteristics showed that 56% of mirvetuximab treated patients who developed Grade 2/3 peripheral neuropathy had pre-existing Grade 1 peripheral neuropathy, suggesting this to be an important predisposing factor for the development of Grade 2+ peripheral neuropathy, an opinion which, along with the cumulative effects from prior systemic chemotherapies was echoed by clinicians at a recent advisory board.

Pneumonitis treatment-emergent adverse events

A total of 26 (12%) patients treated with mirvetuximab reported any pneumonitis (grouped term) TEAEs, compared with one (<1%) patient treated with IC Chemo. Most pneumonitis TEAEs reported in patients treated with mirvetuximab were predominantly Grade ≤ 2 in severity, with Grade 3+ events occurring in four (2%) patients. The patient who was treated with IC Chemo reported a pneumonitis event that was Grade 2 in

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severity. Nine (4%) patients discontinued mirvetuximab due to TEAEs of pneumonitis, while 8% had a dose delayed or not given and 1% had a dose reduction. The dose was not given in the one patient treated with IC Chemo who reported pneumonitis.

2.12. Ongoing studies

The ongoing clinical trial programme for mirvetuximab does not contain any studies in patients with FR α positive PROC which are expected to read out in the next 12 months.

2.13. Interpretation of clinical effectiveness and safety evidence

The efficacy and safety of mirvetuximab for the treatment of patients with FR α positive PROC have been conclusively demonstrated in MIRASOL, a global, multicentre, open-label, Phase 3 RCT directly comparing mirvetuximab with IC Chemo; the first trial to demonstrate a statistically significant and clinically meaningful OS benefit in this patient population compared with chemotherapy (1, 14). This global study included 30 UK patients, and as communicated by multiple UK clinicians, these results are highly relevant in a population reflective of current UK clinical practice and demonstrate meaningful outcomes for women with limited treatment options and an urgent unmet need. In the context of a rare and difficult to treat disease area for which there has been no new treatment in 20 years, mirvetuximab represents an innovative new therapy.

Due to the high rate of OC recurrence, there have only been modest improvements in 5-year survival rates for OC over recent decades. Alarming, overall 5-year relative survival for OC in the UK is below the European average (69). HGS cancer is the most common and aggressive type of epithelial OC, exhibiting high levels of tumour heterogeneity which can impact variability in clinical outcomes, including response to treatment and clinical outcomes (151, 152). Patients with PROC face the poorest prognosis among those with OC, typically resulting in an overall survival of less than 12 months (5, 27).

The standard of care for patients with PROC has not evolved in the last two decades, and patients cycle through sequential single agent chemotherapies (10). These chemotherapies show limited efficacy in terms of survival benefit and limited tumour

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response rates (5-8). Moreover, chemotherapy-associated AEs not only negatively impact QoL but can also impede the continuation of treatment (1, 11, 12).

As mirvetuximab is the first treatment to demonstrate a statistically significant and clinically meaningful OS benefit in a Phase 3 trial in FR α positive PROC compared with chemotherapy, it addresses an area of high unmet need in a patient population with very few effective and tolerable therapeutic alternatives. This is in contrast to various other novel anti-cancer therapies, including immune checkpoint inhibitors, targeted therapies, and small molecule inhibitors, which have failed to make a substantial impact in the treatment of PROC over the past decade (10).

Mirvetuximab represents a significant innovation as a first-in-class FR α -targeted ADC and the first biomarker therapy in PROC. Mirvetuximab targets a patient population with the highest probability of treatment success, characterised by delayed progression, strong tumour response, and extended survival time.

2.13.1. Principal findings from the clinical evidence base

In MIRASOL, after a median follow-up of 28.35 months at the final data cut (26th September 2024), the benefit observed in the primary efficacy endpoint (PFS) was consistent with the primary data cut (6th March 2023; Appendix K), (median PFS of 5.59 months vs 3.98 months, respectively; HR: 0.63; 95% CI: 0.513, 0.785; $p < 0.0001$), representing a 37% reduction in the risk of tumour progression or death. Notably, this benefit was consistent across subgroups and the sensitivity analysis by BICR.

The key secondary endpoint results observed in MIRASOL further demonstrate the therapeutic value of mirvetuximab. Mirvetuximab demonstrated a statistically significant and clinically meaningful OS benefit compared with IC Chemo with a 32% reduction in the risk of death (median OS of 16.85 months vs 13.34 months, respectively; HR: 0.68; 95% CI: 0.54, 0.84). UK clinicians have highlighted these results as being highly significant and particularly meaningful given that they were observed in a contemporary PROC population, reflective of UK clinical practice.

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The pronounced effect of disease burden reduction was demonstrated by the tumour shrinkage observed in >80% of patients treated with mirvetuximab (regardless of the line of treatment, including primary platinum resistance) compared with 55% of those treated with IC Chemo (153). Consequently, an ORR of 41.9% was achieved with mirvetuximab, more than double the rate achieved with IC Chemo (15.9%). Obtaining a complete tumour response in PROC is difficult to achieve and uncommon (5-9), however 13 (5.7%) mirvetuximab patients experienced a complete tumour response (vs 0% with IC Chemo) (1).

Results of MIRASOL also demonstrate that mirvetuximab drives rapid and durable responses compared with IC Chemo. Patients randomised to mirvetuximab had a faster TTR compared with IC Chemo (1.54 vs 2.71 months) among those who achieved complete or partial response, while treatment with mirvetuximab demonstrated an increase in DOR compared with IC Chemo (median DOR of 6.93 months in the mirvetuximab group who had a response compared with median DOR of 4.44 months in the IC Chemo group who had a response). Clinicians consider these results highly important and clinically significant, given that tumour responses to chemotherapy can often be inconsistent and typically show minimal improvement. Clinicians also felt that the pronounced depth of response (>80% tumour shrinkage responses) coupled with a rapid onset of action (as observed with TTR), demonstrates that mirvetuximab has the potential to provide fast and noticeable symptomatic improvement for patients due to the speed and volume of tumour regression.

The secondary endpoint analyses also support the favourable PFS results, with the PFS2 results demonstrating that the benefit of mirvetuximab vs IC Chemo is maintained beyond first progression. Mirvetuximab was associated with a statistically significant and clinically meaningful 41% reduction in the risk of second progression or death compared with IC Chemo (HR: 0.59; 11.01 vs 7.59 months, respectively; $p < 0.0001$). The benefit observed for PFS and PFS2 with mirvetuximab treatment is important given that the interval between relapses shortens with each subsequent relapse whilst the cumulative toxicity from further chemotherapy increases, and therefore improved intervention at first relapse is critical (63, 154). Notably, the benefit in PFS2 was observed for

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mirvetuximab despite similar levels and selections of subsequent treatments (67% vs 65% respectively), indicating that the treatment effect of mirvetuximab persists through to the next line of therapy, and contributes to the observed OS benefit.

As the use of chemotherapy is associated with a high treatment burden, particularly haematological side effects and alopecia, it is worth noting that mirvetuximab demonstrated a more favourable safety profile compared with chemotherapy for these side effects (Grade 3+ anaemia: <1% vs 10%; Grade 3+ neutropenia: <1% vs 17%; Grade 3+ thrombocytopenia: <1% vs 6%; all Grade alopecia: 1% vs 14%). Compared with IC Chemo, mirvetuximab was also associated with lower rates of Grade 3+ TEAEs (44% vs 55%), SAEs (25% vs 33%), and fewer discontinuations due to TEAEs (11% vs 15%) despite the longer duration of mirvetuximab treatment (4.98 months in the mirvetuximab arm vs 2.96 months in the IC Chemo arm). Mirvetuximab treatment was associated with higher occurrence of ocular TEAEs, however, the ocular TEAEs were generally manageable and resolvable, with predominately Grade ≤ 2 ocular TEAEs and the majority of ocular AEs resolving to Grade 1 or 0 with best supportive care and dose modification, with just five (2%) patients permanently discontinuing from mirvetuximab due to these ocular TEAEs.

The clinical and safety results may have also contributed to the improvement and maintenance of HRQoL assessed by the EORTC QLQ-OV28 observed in MIRASOL, with significant benefits observed in the LSM analysis of the abdominal/gastrointestinal symptom and attitude toward the disease and treatment subscales. The QLQ-OV28 modules focus on abdominal/gastrointestinal symptoms, as these symptoms, often stemming from ascites, bowel obstructions, and peritoneal carcinomatosis, substantially impact QoL. The benefit of mirvetuximab on QoL is further supported by the EQ-5D VAS results, with significant differences favouring mirvetuximab observed at all three time points vs IC Chemo (Weeks 8/9, Weeks 15/16, and Week 24), as well as EORTC QLQ-C30 results showing statistically significant benefits in the LSM analysis of the key subscales. Notably, an improved patient QoL based on the patient report outcome (PRO) instruments evaluated, aligns strongly with the higher ORR and the potential for greater tumour shrinkage and therefore symptomatic improvement for patients treated with mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

with mirvetuximab vs IC Chemo. These PRO results favouring mirvetuximab provided support for the differentiated safety profile of mirvetuximab compared with IC Chemo.

2.13.2. Strengths and limitations of the clinical evidence base

MIRASOL is a robust, high-quality, Phase 3 RCT comparing mirvetuximab against IC Chemo, involving 453 patients recruited globally across 136 sites (including 30 patients from the UK). The MIRASOL trial and its results are relevant to the decision problem outlined in the NICE scope as well as the anticipated marketing authorisation, specifically the population of interest, which is adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens. The trial directly compared the intervention and comparator of interest for this appraisal in a PROC population that is representative of patients who would receive mirvetuximab in routine clinical practice in the UK. As such, it is expected that the benefits reported from this trial are likely to be reflected in clinical practice in England and Wales.

The primary endpoint in MIRASOL was investigator-assessed PFS. Investigator-assessed PFS is considered the most robust analysis for PFS, as supported by a recent consensus paper from the GCIG (144). PFS data were mature with long term follow up (28.35 months), providing confidence in the statistically significant and clinically meaningful benefits of mirvetuximab in this setting. Furthermore, the HR for PFS was 0.63 (95% CI: 0.513, 0.785), representing a 37% reduction in the risk of tumour progression or death in the mirvetuximab group compared with the IC chemo group. The consistency of PFS was further demonstrated by the results across data cut-offs (Appendix K) and sensitivity analyses (i.e. BICR) highlighting the benefit associated with mirvetuximab compared with IC Chemo for patients with FR α positive PROC.

A key secondary endpoint in MIRASOL was OS. Mirvetuximab is the first treatment to demonstrate a statistically significant OS benefit in a Phase 3 trial in PROC compared with chemotherapy. This serves an area of high unmet need in PROC where clinical studies of many novel therapies have failed to make a substantial impact in the past two

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decades (10). With a median follow-up of 30 months, OS showed a high level of data maturity not often seen in oncology trials and a HR of 0.68, indicating that patients randomised to mirvetuximab had a 32% reduction in the risk of death vs IC Chemo. The secondary endpoints of ORR and PFS2 were consistent with the PFS and OS analyses, demonstrating statistically significant and clinically meaningful benefits for mirvetuximab vs IC Chemo. Notably, the safety profile observed in the MIRASOL trial at the September 2024 data cut was consistent with previous mirvetuximab studies as observed in a total of 682 patients across four clinical trials (Phase 1 first-in-human, Phase 2 SORAYA, and Phase 3 FORWARD-1 and the MIRASOL March 2023 data cut) (1, 11, 136, 137), demonstrating mirvetuximab is well-tolerated by patients with FR α positive PROC.

Based on clinical expert opinion received during an advisory board conducted by AbbVie on 21st November 2024, clinicians felt the comparator and subsequent treatments used in MIRASOL were broadly aligned with UK clinical practice, and the trial endpoints were reflective of how they would measure clinical effectiveness in UK clinical practice. They also highlighted that, based on the significant and clinically meaningful results for ITT population, they would not expect to use mirvetuximab differently for different subgroups.

A possible limitation of the evidence package was the requirement to censor patients at the end of the MIRASOL study, once the protocol defined number of events had been reached. This resulted in 44 patients in the mirvetuximab arm who were censored because they reached the final study visit; these patients were known to be alive prior to the data lock. The corresponding number of patients in the IC Chemo arm was 18 patients, with 6 of these 18 patients having crossed over to receive mirvetuximab as a subsequent therapy. Further discussion on the context of these censored patients, particularly regarding long-term survival and survival extrapolations, can be found in Section 3.3.3.

Another possible limitation of the evidence is that MIRASOL was an open-label trial. Blinding was not feasible because each drug had a unique dose, examination schedule,

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and safety profile. Consequently, the RoB2 tool identified 'some concerns' in the outcome measurement domain. However, consistent results are seen in investigator-assessed and BICR analyses. The robustness of the efficacy results observed in MIRASOL is also supported by outcomes such as OS, which is not prone to open-label biases, with studies showing similar effects for PROs (145, 146).

2.13.3. Patient perspective

The value of mirvetuximab is further demonstrated by the patient perspectives obtained by AbbVie (89), where patients shared their experiences of mirvetuximab treatment, noting that it was life changing:

- *“It was like a life changer. All of a sudden, I can go grocery shopping, cook dinners for the family. I can live a fairly normal life. It’s 100% better with Elahere (mirvetuximab). I want to be able to see my grandchildren grow up, and I can’t be healthy and do the things I want to do if I didn’t have a medication like Elahere to help me.”*
- *“I celebrated it. I can do anything, travel, see friends. I didn’t do any socialising when I was on frontline chemo. I’m getting ready next week to go [on holiday]. I’m going for 13 days. I couldn’t have done that with chemo.”*
- *“It was Elahere, which has changed my life. I got two years of living a normal life...I had no side effects coming out of the chair, which meant usually I’m very tired and I have a hard time walking because my neuropathy is quite bad, but with Elahere, nothing. I was able to live a life. I could yell at my kids and take care of my grandchildren, and I could cook. I could go to the opera. I could go to Sweden and see my family without having to think about how am I going to handle the flight? Am I going to be able to walk through the airport? Am I actually be able to do anything when I’m there, visiting my sisters, my cousins, my uncle? It was life changing. It gave me my life back. I could be a person instead of a sick person.”*

- *“To have [MIRV] as an option and to see myself doing so well on it and feeling, you know, next to normal on it, it just gives you peace, it gives you hope...I’m able to be like out in the world and do all the things and live my life. So that’s why I feel the way I do about this treatment instead of frontline because I don’t have that isolation, you know, I don’t feel sick constantly.”*

2.13.4. Conclusions

PROC is the most severe and incurable phase of OC (27). Patients with PROC have a very poor prognosis, with life expectancy typically less than 12 months (5-9). To date, there have been no new treatments for patients with PROC in England/Wales for 20 years, reflected in several suspended or terminated NICE appraisals (43-47). The data from MIRASOL should be viewed within the context of a difficult to treat end-of-life disease.

Overall, these data demonstrate that the clinical benefit of mirvetuximab is superior to that of standard of care chemotherapy and addresses key areas of unmet clinical need for patients with FR α positive PROC. Mirvetuximab delivers a statistically significant and clinically meaningful survival benefit, as well as rapid and durable responses compared with chemotherapy, while demonstrating a manageable safety profile and preserving HRQoL.

As such and, considering its superior efficacy and manageable safety profile vs IC Chemo, mirvetuximab represents an innovative targeted therapy and a new standard of care for eligible patients with FR α positive PROC with high unmet needs. Importantly, this breakthrough therapy for eligible patients with PROC may also contribute to three of the UK’s ongoing health priorities: cancer, women’s health, and precision medicine (16-18).

3. Cost effectiveness

The cost-effectiveness analysis demonstrates that mirvetuximab is a cost-effective treatment option for the treatment of folate receptor alpha (FR α) positive platinum-resistant ovarian cancer (PROC) compared with pooled chemotherapy

A de novo cost-effectiveness model was developed to evaluate the cost effectiveness of mirvetuximab compared with pooled chemotherapy (paclitaxel, pegylated liposomal doxorubicin, and topotecan) in adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens.

- As per the National Institute for Health and Care Excellence (NICE) reference case, the cost perspective is the National Health Service (NHS) and Personal Social Services (PSS) in England and Wales, and the outcome perspective is direct health effects for patients.
- A lifetime time horizon is considered and annual discount rates of 3.5% are applied.
- The analysis is structured as a partitioned survival model with three health states: progression-free, progressed, and death.
- Overall survival (OS), progression-free survival (PFS) and duration of treatment (DoT) data were extrapolated from the MIRASOL trial using parametric survival models, and adverse event (AE) data were analysed from the MIRASOL trial.
- Health state utility values (HSUV) were taken from published literature for the pooled chemotherapy arm, and generated using a mixed model of EQ-5D-5L data from MIRASOL for the mirvetuximab arm.
- Modelled cost types include drug acquisition, administration, adverse events, disease management, palliative care and testing costs.
- FR α positive PROC has an estimated proportional quality-adjusted life year (QALY) shortfall of 96% under current standard of care, reflecting the poor prognosis and substantial symptom burden for patients; a severity modifier of 1.7 therefore applies.
- In the base-case deterministic analysis, mirvetuximab is associated with discounted incremental costs and (severity-weighted) QALYs of [REDACTED] and [REDACTED], respectively, vs pooled chemotherapy; the resulting incremental cost-effectiveness ratio (ICER) is [REDACTED] per QALY gained. The probabilistic ICER is [REDACTED] per QALY gained.
- Sensitivity analysis demonstrated the results are most sensitive to the OS distribution chosen for mirvetuximab and utility values. All other scenarios tested had an impact of less than 15% on the ICER.

3.1. Published cost-effectiveness studies

An SLR was conducted on 4th March 2024 and updated on 20th November 2024 to identify economic evaluations in PROC. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (155), and a detailed description of the SLR methods, full results, and quality assessment of the identified economic evaluations are presented in Appendix E. Fifteen economic evaluations were identified (Table 18).

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Table 18. Summary list of published cost-effectiveness studies

Study, intervention/ comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Ball, 2018 (156) Bevacizumab + CT (PLD, paclitaxel or topotecan) vs CT only	• CUA. • PSM with 3 health states (Alive with no progression [pre-progression health state], alive with disease progression [post-progression health state] and death.). • 7-year time horizon. • Payer perspective: Canada • 1 month cycle length.	PROC	Total QALYs: Bevacizumab + CT: 1.1055; CT only: 0.9926	Total costs (CAD 2016): Bevacizumab + CT: \$79,086; CT only: \$54,982	\$213,424
Chappell, 2016 (157) Bevacizumab + CT (PLD, paclitaxel or topotecan). vs CT only	• Cost-effectiveness analysis. • Decision-tree model. • Perspective: US	Platinum-resistant recurrent advanced epithelial ovarian cancer	NR	Total costs (USD 2014): Bevacizumab 10mg/kg biweekly dose: CT: \$21,611; CT + bevacizumab: \$66,511 Bevacizumab 15 mg/kg once-every-3-weeks dose: CT: \$18,857; CT + bevacizumab: \$48,861 Weekly paclitaxel: CT: \$18,056; CT + bevacizumab: \$59,263 PLD: CT: \$27,776;	NR

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Study, intervention/comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				CT + bevacizumab: \$79,117 Weekly topotecan: CT: \$18,998; CT + bevacizumab: \$61,147	
Lai, 2024 (158) BevBiol vs BevBiol + CT	- Cost-effectiveness analysis. - PSM with 3 health states (PF, PD, and death). 2-year time horizon. - Payer perspective: Taiwan - Weekly cycle length with half-cycle corrections.	Participants aged ≥20 years with epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. They had received three cycles of bevacizumab + platinum CT and experienced PD <6 months after completing platinum treatment	Total QALYs: CT: 10.31; Bevbiol + chemotherapy: 12.33	Total cost (NTD 2022): CT: NT\$9,183,149.117; Bevbiol + CT: NT\$18,391,728.31	NT\$4,555,877.995
			Incremental QALYs: 2.021	Incremental costs (NTD 2022): NT\$9,208,579.191	-
Luealon, 2016 (159) 1) Gemcitabine followed by BSC, 2) PLD followed by BSC, 3) gemcitabine followed by topotecan, or 4) PLD followed by topotecan vs BSC	- Cost-effectiveness analysis. - Markov model with 5 health states (Cancer 1, PD 1, cancer 2, PD 2, and death). 2-year time horizon. - Health care provider perspective: Thailand 1 month cycle length.	Platinum-resistant or refractory epithelial ovarian cancer	Total QALYs: 2nd line CT followed by BSC: BSC: 0.14; Gemcitabine: 0.39; PLD: 0.393	Total costs (THB 2011): 2nd line CT followed by BSC: BSC: ฿26,862.17; Gemcitabine: ฿113,000.15; PLD: ฿124,302.57	Gemcitabine followed by BSC: ฿344,643.61 PLD followed by BSC: ฿385,322.17
			Total QALYs: 2nd line CT followed by 3rd line CT: Gemcitabine followed by topotecan: 0.432; PLD followed by topotecan: 0.435	Total costs (THB 2011): 2nd line CT followed by 3rd line CT: Gemcitabine followed by topotecan: ฿139,788.38; PLD followed by topotecan: 151,135.34	Gemcitabine followed by topotecan: ฿385,856.34 PLD followed by topotecan: ฿420,299.08
Neyt, 2018 (160) Bevacizumab vs Standard CT	- CUA. - Markov model with 2 health states (PF, PD).	PROC	Total QALYs (mean (97.5% CI): Bevacizumab: 0.18 (-0.07, 0.47)	Total costs (EUR 2014), mean (97.5% CI): Bevacizumab: €30,259 (€29,611, €30,880)	€172,370

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Study, intervention/comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
	- Lifetime time horizon. - Health care payer (government and patient) perspective: Belgium 3 weeks cycle length with half-cycle correction applied.				
Peters, 2022 (161) No intervention (hospice) vs TPN, CT, TPN + CT	- CUA. - Monte Carlo simulation. - Time horizon: the time of the post-gastrostomy tube management decision until death. - Societal perspective: US	Platinum-resistant, recurrent ovarian cancer with inoperable MBO	Total QALYs, mean (95% CI): Hospice: 0.051 (0.051, 0.052); TPN + CT: 0.089 (0.89, 0.090); TPN: 0.071 (0.071, 0.071); CT: 0.053 (0.053, 0.054)	Total costs (USD 2021), mean (95% CI): Hospice: \$14,591 (\$14,527, \$14,654); TPN + CT: \$49,741 (\$49,329, \$50,162); TPN: \$36,045 (\$35,742, \$36,348); CT: \$22,672 (\$14,527, \$14,654)	Hospice: reference; TPN + CT: \$918,538; TPN: \$1.1 million; CT: \$3.7 million
Rocconi, 2006 (162) BSC vs 2L CT monotherapy; 2L combination therapy; 3L therapy after progression on 2L monotherapy; 3L CT after progression on 2L combination therapy	- Cost-effectiveness analysis. - Decision analysis model. - Third party payer perspective: US	Platinum-resistant recurrent ovarian cancer	NR	Total costs (USD 2004): BSC: \$49 million; 2L monotherapy \$113 million; 2L combination: \$314 million; 3L previous monotherapy: \$316 million; 3L previous combination: \$517 million	NR
Stinson, 1999 (163) Paclitaxel vs Topotecan, altretamine, etoposide	- Cost-minimisation analysis. - Third party payer perspective: US	Platinum-resistant/refractory ovarian cancer	NR	Costs per cycle (USD 1996): Paclitaxel: \$2,628; Topotecan: \$4,659; Altretamine: \$746;	NR

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Study, intervention/comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				Etoposide: \$1,930 Total cost (USD 1996): Paclitaxel: \$15,767; Topotecan: \$18,635; Altretamine: \$4,477; Etoposide: \$7,721	
Wysham, 2017 (164) Bevacizumab + CT vs CT only	- Cost-effectiveness analysis. - Decision-tree model with 4 health states (GI perforation, PFS, disease progression, hospice). 15-month time horizon. - Payer perspective: US 1 month cycle length.	Platinum-resistant recurrent ovarian cancer	Total QALYs: CT: 462.65; Bevacizumab + CT: 608.09	Total costs (USD 2015): CT: \$57,87; Bevacizumab + CT: \$117,568	\$410,455
Wallbillich, 2016 (165) SoC CT (priority sequence of (1) PLD, (2) paclitaxel, then (3) topotecan) vs Genomic-based therapy	- CUA. - Decision-tree model. 1 year time horizon. - Payer perspective: US	Platinum-resistant recurrent ovarian cancer	Total QALYs: Genomic strategy: 0.71; SoC: 0.68	Mean cost per patient (USD 2014): Genomic strategy: \$90,271; SoC: \$74,926	\$479,303
Wolford, 2020 (166) Niraparib vs Rucaparib, olaparib, non-platinum based therapies (PLD with or without trabectedin; topotecan, pemetrexed,	- Cost-effectiveness analysis. - Markov model with 5 health states (Response, haematologic complications [Grade 3+], non-hematologic complications [Grade	Platinum-resistant recurrent ovarian cancer	Total QALmonths: Niraparib: 7.0; Rucaparib: 8.0; Olaparib: 7.0; Non-platinum based therapies: 5.8; Bevacizumab + non-platinum based therapies (AURELIA): 6.8	Total costs (USD NR): Niraparib: \$26,708.75; Rucaparib: \$23,523.99; Olaparib: \$22,402.34; PLD: \$11,746.54; Topotecan: \$9,003.95; Pemetrexed: \$16,415.07;	NR

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Study, intervention/comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
paclitaxel, and nab-paclitaxel), bevacizumab + non-platinum based therapies (bevacizumab combined with either PLD, topotecan, or paclitaxel)	3+], progression [next-line and onward], and death). - Lifetime time horizon. - Patient and third-party payer perspective: NR 1 month cycle length.			Abraxane: \$11,457.44; Trabectedin/PLD: \$18,414.57; Bevacizumab/Paclitaxel: \$19,727.88; Bevacizumab/PLD: \$23,209.57; Bevacizumab/Topotecan: \$20,078.51	
Zhu, 2024 (167) Mirvetuximab soravtansine vs IC Chemo	- CUA. - Markov model with 3 health states (progression free, progressed disease, and death). - Lifetime time horizon (20 years). - US healthcare payers' perspective. 1 year cycle length.	Platinum-resistant recurrent ovarian cancer with high folate receptor-alpha	Incremental QALYs (MIRV vs IC): 0.90	Incremental costs (USD 2023): Full cost (baseline results): 538,251 70% cost: 339,703 50% cost: 207,338 30% cost: 74,973 10% cost: -57,392	Full cost: 596,189 70% cost: 376,264 50% cost: 229,653 30% cost: 83,042 10% cost: Dominant
		Platinum-resistant recurrent ovarian cancer with high folate receptor-alpha – bevacizumab naïve patients	Incremental QALYs (MIRV vs IC): 1.09	Incremental costs (USD 2023): Full cost (baseline results): 575,674 70% cost: 367,216 50% cost: 228,244 30% cost: 89,272 10% cost: -49,700	Full cost: 530,061 70% cost: 338,120 50% cost: 210,159 30% cost: 82,198 10% cost: Dominant
		Platinum-resistant recurrent ovarian cancer with high FR α – bevacizumab pretreated patients	Incremental QALYs (MIRV vs IC): 0.53	Incremental costs (USD 2023): Full cost (baseline results): 188,248 70% cost: 337,286 50% cost: 202,310 30% cost: 67,334 10% cost: -67,643	Full cost: 1,011,310 70% cost: 631,960 50% cost: 379,060 30% cost: 126,160 10% cost: Dominant
	CUA.	Recurrent, platinum-resistant epithelial	Change in expected QALYs: 0.212	Total costs (CAD 2014), per cycle:	\$240,100

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Study, intervention/ comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
CDA-AMC (CADTH), 2016 (168) Bevacizumab + CT (PLD, paclitaxel or topotecan) vs CT only	- PSM (area under the curve) with 3 health states (PFS, PD and death). 6–8 year time horizon. - Payer perspective: Canada	ovarian, fallopian tube or primary peritoneal cancer with no more than two prior CT regimens (defined as number of lines of therapy/ treatment since diagnosis with ovarian cancer)		Bevacizumab: not disclosed; Paclitaxel: \$156.75; Topotecan: \$2,397.00; PLD: \$2,390.50; Gemcitabine: \$210.55	
			Best case estimate of change in expected QALYs using parametric gamma curve for OS, loss of treatment effect at the end of trial follow-up: 0.173	Total costs (CAD 2014), per cycle: Bevacizumab: not disclosed; Paclitaxel: \$156.75; Topotecan: \$2,397.00; PLD: \$2,390.50; Gemcitabine: \$210.55	Change from baseline submitted ICER using parametric gamma curve for OS, loss of treatment effect at the end of trial follow-up: \$49,367 ICER estimate: \$289,467
			Change in expected QALYs using KM lower 95% with gamma tail for OS, loss of treatment effect at the end of trial follow-up: 0.116	Total costs (CAD 2014), per cycle: Bevacizumab: not disclosed; Paclitaxel: \$156.75; Topotecan: \$2,397.00; PLD: \$2,390.50; Gemcitabine: \$210.55	Change from baseline submitted ICER using KM lower 95% with gamma tail for OS, loss of treatment effect at the end of trial follow-up: \$185,551 ICER estimate: \$425,651
NICE, 2016 (TA389) (108), Topotecan or paclitaxel vs PLD	- CUA. - PSM with 3 health states (PFS, PD and death). - Life-time (15 years) time horizon. - NHS and personal social services perspective.	Platinum resistant/ refractory ovarian cancer	Base case probabilistic results Total QALYs (discounted) PLD: 1.004 Paclitaxel: 0.981 Topotecan: 1.025 Incremental QALYs (discounted): Topotecan vs PLD: 0.044 Paclitaxel vs PLD: -0.022 Base case deterministic results	Base case probabilistic results Total costs (discounted) PLD: £14,232 Paclitaxel: £15,132 Topotecan: £21,232 Incremental cost (discounted) Topotecan vs PLD: £6,100 Paclitaxel vs PLD: £901 Base case deterministic results Total costs (discounted) PLD: £14,320 Paclitaxel: £15,095	Base case probabilistic results Topotecan vs PLD: £139,697 Paclitaxel vs, PLD: strictly dominated Excluding dominated options Topotecan vs PLD: £324,188 Base case deterministic results

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Study, intervention/ comparator	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			Total QALYS (discounted) PLD: 1.004 Paclitaxel: 0.971 Topotecan: 1.020 Incremental QALYs (discounted): Topotecan vs PLD: 0.049 Paclitaxel vs PLD: -0.033	Topotecan: £21,271 Incremental costs (discounted) Topotecan vs PLD: £6,176 Paclitaxel vs PLD: £775	Topotecan vs PLD: £127,117 Paclitaxel vs, PLD: strictly dominated Excluding dominated options Topotecan vs PLD: £449,553
SMC (1063/15), 2015 (169) Bevacizumab + paclitaxel vs Paclitaxel	- CUA. - Area under the curve economic model with 3 health states (PFS, PD and death). 10-year time horizon. - Payer perspective: Scotland - Weekly cycle length.	Platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in a sub-group eligible for treatment with paclitaxel.	Incremental QALY gain: 0.591	Costs per course (GBP NR): Bevacizumab + paclitaxel: £27,041	£55,090

Abbreviations: BSC, best supporting care; CAD, Canadian dollars; CDA-AMC, Canadian Agency for Drugs and Technologies in Health; CI, confidence interval; CT, chemotherapy; CUA, cost-utility analysis; EUR, Euro; FR α , folate receptor alpha; GBP, Great British pounds; IC Chemo, Investigators choice of chemotherapy; ICER, incremental cost-effectiveness ratio; MIRV, mirvetuximab; N/A, not available; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; NR, not reported; NT, New Taiwan; PD, progressed disease; PF, progression-free; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PROC, platinum-resistant recurrent ovarian cancer; PSM, partitioned survival model; QALY, quality-adjusted life year; SLR, systematic literature review; SMC, Scottish Medicines Consortium; SoC, standard of care; TPN, total parenteral nutrition; US, United States; USD, United States dollar.

3.2. Economic analysis

Although economic evaluations of mirvetuximab in the relevant population were identified (Section 3.1), these were in settings outside of the UK. A de novo economic model was therefore developed in Microsoft® Excel 365.

3.2.1. Patient population

The population included in the model is adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens. The patient population is aligned with the ITT population of the MIRASOL trial and the expected licensed indication, and referred to as FR α positive PROC throughout. FR α positivity is defined using the VENTANA® FOLR1 (FOLR-2.1) CDx assay based on high expression, i.e. $\geq 75\%$ of tumour cells with moderate and/or strong membrane staining (PS2+) (19).

3.2.2. Model structure

The cost-effectiveness model (CEM) is structured as a three-state partitioned survival model (PSM). The model structure is presented in Figure 22, and an illustrative example of the PSM approach is presented in Figure 23. The model is comprised of three mutually exclusive health states:

- **Pre-progression:** Patients are progression-free; health state membership is defined by the PFS curve.
- **Post-progression:** Patients have experienced disease progression, and health state membership is defined as the proportion of patients who are alive minus the proportion of patients who have not progressed (%OS – %PFS).
- **Death:** The absorbing state, the proportion of patients in the death state is defined as 1 minus the proportion of patients alive ($1 - \%OS$).

Modelled clinical outcomes were validated with clinical experts based in England and Wales and health economic experts at the advisory board held by AbbVie in November

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- Key trial endpoints (OS and PFS) can be used directly in a PSM to inform model health states
- Long-term extrapolations of OS and PFS can be validated by clinical experts, and the most appropriate survival distribution chosen; use of a Markov model would not allow for alternative approaches within the same structure.
- PSMs have been widely used in oncology modelling, including previous NICE appraisals in OC (103, 104, 108) and economic evaluations identified in the SLR (Section 3.1).

Patients enter the model in the pre-progression health state and are at risk of transitioning^h to the post-progression or death state in any model cycle.

The proportion of patients alive was defined using the OS curve and the proportion alive and progression-free was determined using the PFS curve. The proportion of patients on treatment was defined by the DoT curve. Given the different administration frequency of the components of the chemotherapy comparator arm in MIRASOL, DoT was considered independently for each of paclitaxel, pegylated liposomal doxorubicin, and topotecan within the pooled chemotherapy arm.

Patients receive pre-progression treatments as directed by their respective dosing schedules. Patients may experience Grade 3+ TEAEs associated with pre-progression treatments. Once patients have progressed, they remain in the post-progression state until death (absorbing health state). During the post-progression state, a proportion of patients may receive post-progression treatments. The survival benefit of post-progression treatments was not explicitly modelled and was assumed to be reflected in the OS of pre-progression treatments.

Patients accrue costs, life years (LY) and quality-adjusted life years (QALY) over the modelled time horizon (lifetime; 40.8 years). The model includes costs associated with pre-progression treatment, post-progression treatment, TEAEs, disease management,

^h Note that the PSM structure captures transitions between states implicitly rather than explicitly.

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testing, and terminal care. Pre-progression and post-progression health state utilities for the mirvetuximab and pooled chemotherapy arms were adjusted for aging to capture HRQoL of patients over a lifetime.

A cycle length of 1 week is assumed in order to capture different dosing schedules for modelled treatments; 1 week was also considered sufficiently short to capture differences between mirvetuximab and pooled chemotherapy. A half-cycle correction is appliedⁱ using the life table method.

Table 19 presents the key features of the current economic analysis, and a previous appraisal in recurrent OC (TA389; including PROC).

Table 19. Features of the economic analysis

Factor	Previous evaluations	Current evaluation	
	TA389	Chosen values	Justification
Model type	CUA (PSM)	CUA (PSM)	The NICE reference case specifies CUA as the preferred form of economic evaluation (170)
Health effects measure	QALYs	QALYs	The NICE reference case specifies that health effects should be expressed in QALYs (170)
Time horizon	Lifetime (15 years)	Lifetime (40.8 years)	Assumes a maximum age of 100 years (starting age of 59.2 years; Section 3.3.1). The NICE reference case recommends to model a lifetime horizon to capture all differences in costs and benefits between treatments (170)
Cycle length	Not reported	One week	To accurately capture the different dosing schedules for comparators and is sufficiently short to capture all relevant differences between mirvetuximab and pooled chemotherapy
Half cycle correction	Not applied	Applied	To account for events and transitions occurring at any point in the modelled cycle

ⁱ Note that half-cycle correction is not applied for adverse event costs or testing costs, which are assumed to be applied at time zero

Factor	Previous evaluations	Current evaluation	
	TA389	Chosen values	Justification
Discount rate	Costs: 3.5% annually Outcomes: 3.5% annually	Costs: 3.5% annually Outcomes: 3.5% annually	In line with the NICE reference case (170)
Perspective	Costs: NHS and PSS Outcomes: All health effects for patients	Costs: NHS and PSS Outcomes: All health effects for patients	In line with the NICE reference case (170)
Source of utilities	• Tengs 2000 (171) • Brown 1998 (172)	• EQ-5D-5L from MIRASOL mapped to EQ-5D-3L • Wysham, 2017 (164)	Utility values for mirvetuximab have been derived from MIRASOL, in line with NICE guidance (170); utility values for pooled chemotherapy were taken from the published literature, as the reported values better reflect the quality of life experienced by chemotherapy patients (112).
Source of costs	• NHS reference costs (2011/12) • PSSRU (2012) • BNF (2013)	• NHS reference costs (2023/24) • PSSRU (2024) (173) • BNF/eMIT (2025)	In line with the NICE reference case (170)

Abbreviations: BNF, British National Formulary; CUA, cost-utility analysis; eMIT, Drugs and pharmaceutical electronic market information tool; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSM, partitioned survival model; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year.

3.2.3. Intervention technology and comparators

Intervention

The intervention considered in the analysis is mirvetuximab 6 mg/kg (AIBW) intravenous (IV) infusion on Day 1 of each treatment cycle Q3W until disease progression or unacceptable toxicity, in line with MIRASOL and the anticipated MHRA marketing authorisation (19).

Mirvetuximab is dosed based on AIBW, which was calculated in the MIRASOL trial based on the following formula (174):

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$$AIBW = IBW [kg] + 0.4 * (Actual\ weight [kg] - IBW)$$

$$Female\ IBW [kg] = 0.9 * height [cm] - 92$$

Comparators

The comparators considered in the economic analysis are clinician's choice between paclitaxel, pegylated liposomal doxorubicin, and topotecan, modelled as a single 'pooled chemotherapy' arm in line with the MIRASOL trial. These chemotherapies are the recommended therapies in PROC as per the BGCS guidelines (21), and are reflected in UK market research data (22).^j

Modelled doses are aligned with the MIRASOL trial protocol (19). For paclitaxel, pegylated liposomal doxorubicin, and topotecan, the MIRASOL dose differed from the dosing in the relevant SmPC (Table 20). Modelled doses were validated with two clinical experts who considered dosing in MIRASOL for the included chemotherapies to reflect current clinical practice in England and Wales.

^j Market share data collected in August to October 2024 showed that paclitaxel, pegylated liposomal doxorubicin and topotecan were used in 14%, 45% and 9% of second-line PROC patients, respectively, and in 25%, 36% and 4% of third-line PROC patients, respectively.

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Table 20. Pooled chemotherapy dosing schedule of treatments

Component	Dosing schedule		Rationale for modelled dose
	Modelled (MIRASOL)	SmPC	
Paclitaxel	80 mg/m ² IV infusion on Days 1, 8, 15, and 22 of a 4-week cycle	175 mg/m ² IV infusion once every 3-week treatment cycle	Clinical experts noted that weekly administration of paclitaxel is associated with better efficacy. In TA389, the company modelled the 80 mg/m ² regimen for paclitaxel, as it was reflective of clinical practice. The Committee noted that the best estimates were those based on current clinical practice (108)
Pegylated liposomal doxorubicin	40 mg/m ² IV infusion on Day 1 of each 4-week cycle	50 mg/m ² IV infusion of Day 1 of each 4-week treatment cycle	Clinical expert opinion suggested that 50 mg/m ² doses are associated with higher toxicity than 40 mg/m ² . In addition, Phase 2 trials demonstrated therapeutic equivalence between 40 and 50 mg/m ² doses of pegylated liposomal doxorubicin (175, 176). In TA389, the Committee noted that a 40 mg/m ² dose of pegylated liposomal doxorubicin has become standard practice and the licensed dose is often adjusted to balance against toxicity (108).
Topotecan	Patients receive either: • 4 mg/m² IV infusion on Days 1, 8, and 15 of a 4-week cycle • 1.25 mg/m² IV infusion on Days 1 to 5 of a 3-week cycle	1.5 mg/m ² IV infusion on Days 1 to 5 of each 3-week treatment cycle	1.25 mg/m ² dose is associated with decreased toxicity and a similar clinical outcome as the 1.5 mg/m ² dose; a dose of 4 mg/m ² demonstrated comparable OS rates to a 1.5 mg/m ² dose (177)

Abbreviations: IV, intravenous; OS, overall survival; SmPC, summary of product characteristics; TA, technology appraisal.

3.3. Clinical parameters and variables

Clinical data used in the cost-effectiveness model include:

- Patient characteristics
- Survival curves
 - OS
 - PFS
 - DoT
- Background mortality
- AEs.

3.3.1. Patient characteristics

In order to best reflect the patient population who would receive mirvetuximab in clinical practice, baseline characteristics were aligned with RWE wherever available; in the absence of other evidence, baseline characteristics for body surface area (BSA) and AIBW were taken from the ITT population of MIRASOL (N=453; September 2024 data cut). Modelled baseline characteristics are presented in Table 21.

Table 21. Patient demographics and characteristics

	Value	Reference
Age (years)	59.2	Parikh et al, 2018 (68)
Percent female (%)	100%	
BSA (m ²)	1.73	MIRASOL (174)
AIBW (kg)	59.05	

Abbreviations: AIBW, adjusted ideal bodyweight; BSA, body surface area; SD, standard deviation.

3.3.2. Overview of survival extrapolations

Estimates of OS, PFS, and DoT were extrapolated based on patient-level data from MIRASOL in line with guidance from NICE Technical Support Document (TSD) 14 and TSD 21 (178, 179).

Parametric functions considered for extrapolation included exponential, Weibull, lognormal, log-logistic, Gompertz, gamma and generalised gamma distributions. As the standard parametric curves provided a good visual fit to the Kaplan-Meier (KM) curves, flexible models were not considered. As per NICE Decision Support Unit (DSU) guidance, the suitability of parametric survival models was evaluated based on the following criteria (178):

- **Testing the proportional hazards (PH) assumption:** The PH assumption was examined to check whether the treatment effect is proportional over time between reference and comparator arms. The following were used to evaluate the PH assumption:
 - Examination of the log-cumulative hazard plots
 - Inspection of the Schoenfeld residuals
 - Validation with clinical experts based in England/Wales at an advisory board held by AbbVie in November 2024.
- **Akaike Information Criterion (AIC)/Bayesian Information Criterion (BIC) tests:** AIC and BIC provide statistical tests of the relative fit of parametric survival models. These tests weight the improved fit of models with the potentially inefficient use of additional parameters. Lower AIC and BIC values indicate better fit of the parametric survival model to the observed data.
- **Visual inspection:** Assessing how closely the parametric survival models visually fit the KM curve.
- **Examination of smoothed hazard plots:** Assessing the trend in the hazard over time for both the observed data and the predicted extrapolations.
- **Clinical plausibility of modelled survival functions:** Clinician input was used to validate the long-term extrapolation of OS data beyond the trial follow-up, and the most appropriate survival functions for the modelling of PFS and DoT.

To prevent implausible estimates, PFS was capped such that it did not exceed OS and DoT was capped such that it did not exceed PFS. OS was bound by age- and gender-matched general population mortality rates (Section 3.3.6).

A summary of base-case survival extrapolation approaches is presented in Table 22.

Table 22. Summary of base-case survival extrapolation approach

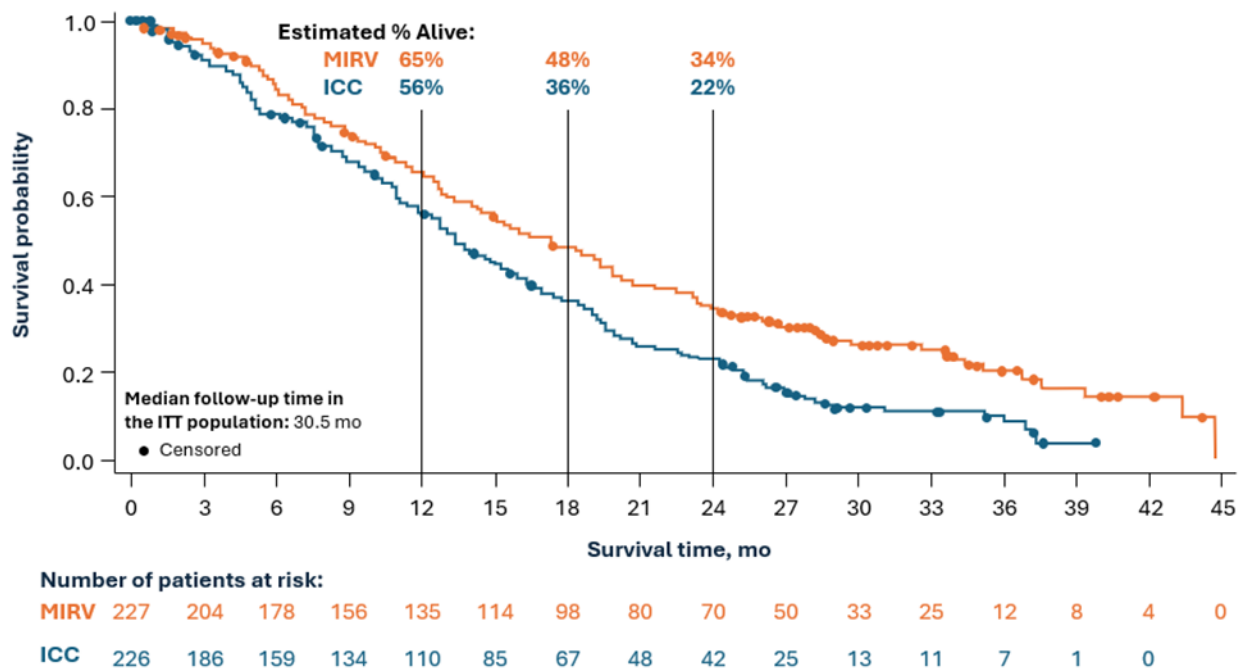
		Proportional hazards assumption assumed?	Base case distribution	Justification	Source	Reference to section in submission
OS	Mirvetuximab	No	Log-logistic	Clinical expert opinion and statistical fit	MIRASOL trial, September 2024 data cut	Section 3.3.3
	Pooled chemotherapy		Weibull	Clinical expert opinion and statistical fit		
PFS	Mirvetuximab	No	Lognormal	Statistical fit; clinical plausibility confirmed with clinical experts		Section 3.3.4
	Pooled chemotherapy		Lognormal			
DoT	Mirvetuximab	No	Exponential	Statistical fit; clinical plausibility confirmed with clinical experts		Section 3.3.5
	Paclitaxel		KM	Survival functions overestimated DoT compared with the observed data		
	Pegylated liposomal doxorubicin		KM			
	Topotecan		KM			

Abbreviations: DoT, duration of treatment; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

3.3.3. Overall survival

At the September 2024 data cut-off for MIRASOL (median follow-up time of 30.49 months for OS), median OS was 16.85 months and 13.34 months for mirvetuximab (n=227) and pooled chemotherapy (n=226), respectively (Section 2.6). The KM for OS is presented in Figure 24.

Figure 24. KM plot for OS – ITT population



Source: Data on file, MIRASOL final CSR (14).
Abbreviations: KM, Kaplan-Meier; IC Chemo, Investigator’s choice of chemotherapy; ITT, intention-to-treat; MIRV, mirvetuximab; mo, months; OS, overall survival.

As can be seen from approximately Month 24, there is substantial censoring due to the end of trial follow-up, particularly in the mirvetuximab arm. At the end of follow-up, 44 and 18 patients remained alive in the mirvetuximab and pooled chemotherapy arms and were therefore censored at end-of-study as per the trial protocol. The period in which patients are censored due to end of trial follow-up is longer than may be typically seen due to the length of the recruitment period in MIRASOL (the final patient was randomised 2.5 years after the first patient).

The final ‘drop’ in the mirvetuximab KM to zero at Month 44 (implying a 0% probability of a mirvetuximab patient being alive at Month 45) occurs when only a single patient

remains at risk, and it is therefore expected that the tail of the KM curve would change had there been additional follow-up^k.

Clinical experts consulted at the AbbVie advisory board and through follow-up clinical interviews confirmed that the end of the KM curve is not considered meaningful and should therefore be interpreted with caution. Similar observations have also been made in the methodological literature; in the context of presenting hazards for visual comparison during model selection, Palmer et al (180) state:

“...a suggestion was made to restrict figures of the plot of the hazards inherent to the trial data (observed hazard) and Kaplan-Meier estimators to a point in time when the numbers at risk are still “reasonable.”

There is no consensus regarding the definition of a “reasonable” number of patients at risk. Pocock et al (181) and Gebski et al (182) suggest alternative criteria for time points at which KM data may no longer be considered informative.

Assessment of proportional hazards

The log-cumulative hazard plot for OS is shown in Figure 25, and the Schoenfeld residuals plot is displayed in Figure 26. The test of the Schoenfeld residuals does not suggest that the PH assumption is violated ($p=0.321$), however such tests can suffer from a lack of statistical power. The proportionality of hazards for mirvetuximab and pooled chemotherapy was further explored by visual inspection of the log cumulative hazards plot. The cumulative hazards cross in several places, suggesting that the PH assumption may be inappropriate.

In addition, discussion at an AbbVie advisory board suggested that independent models may be more appropriate than dependent models, given the differing mechanisms of action between mirvetuximab and the pooled chemotherapy arms (Section 1.3.5).

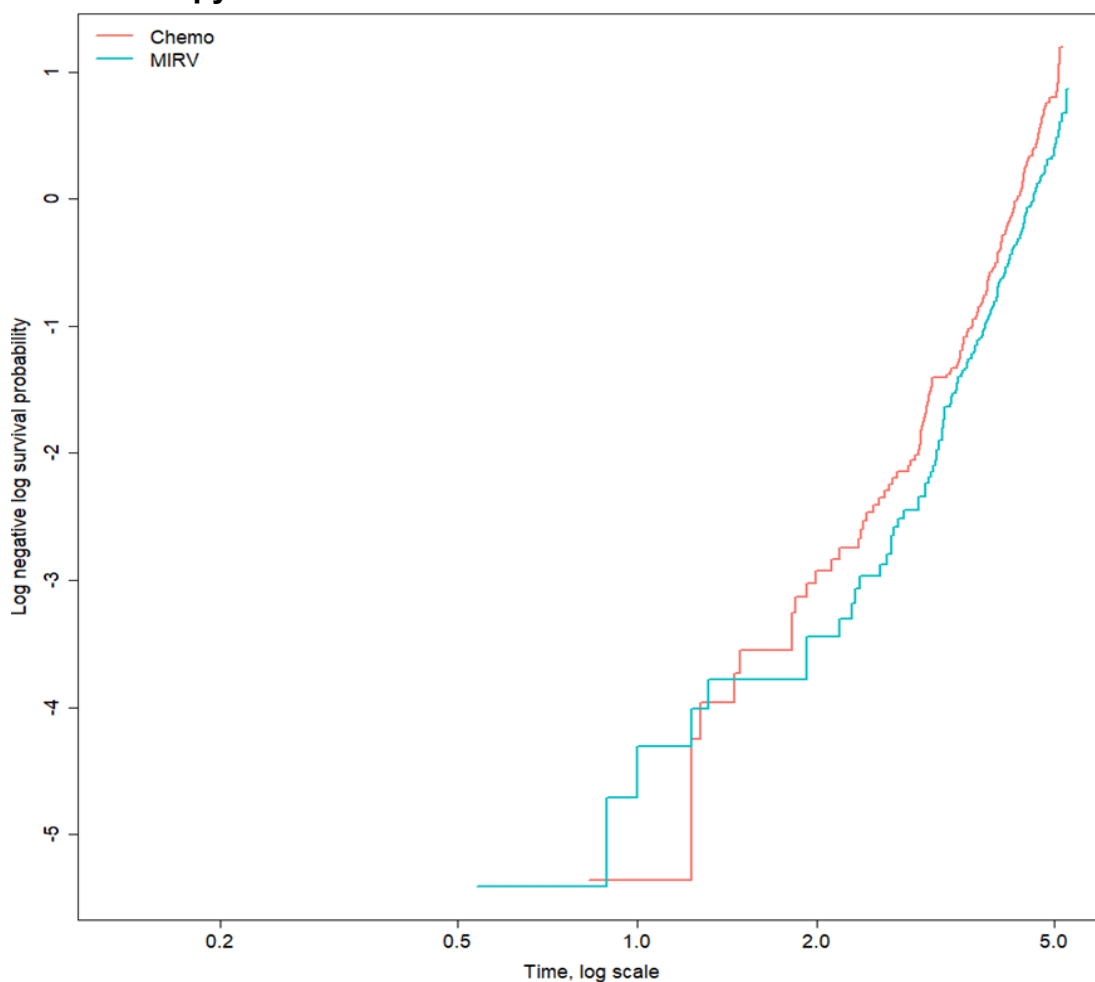
Mirvetuximab is associated with rapid and durable responses, thereby delaying progression and prolonging survival in patients with FR α positive PROC (Section 2.6.1).

^k I.e. if the survival outcomes for censored patients were observed.

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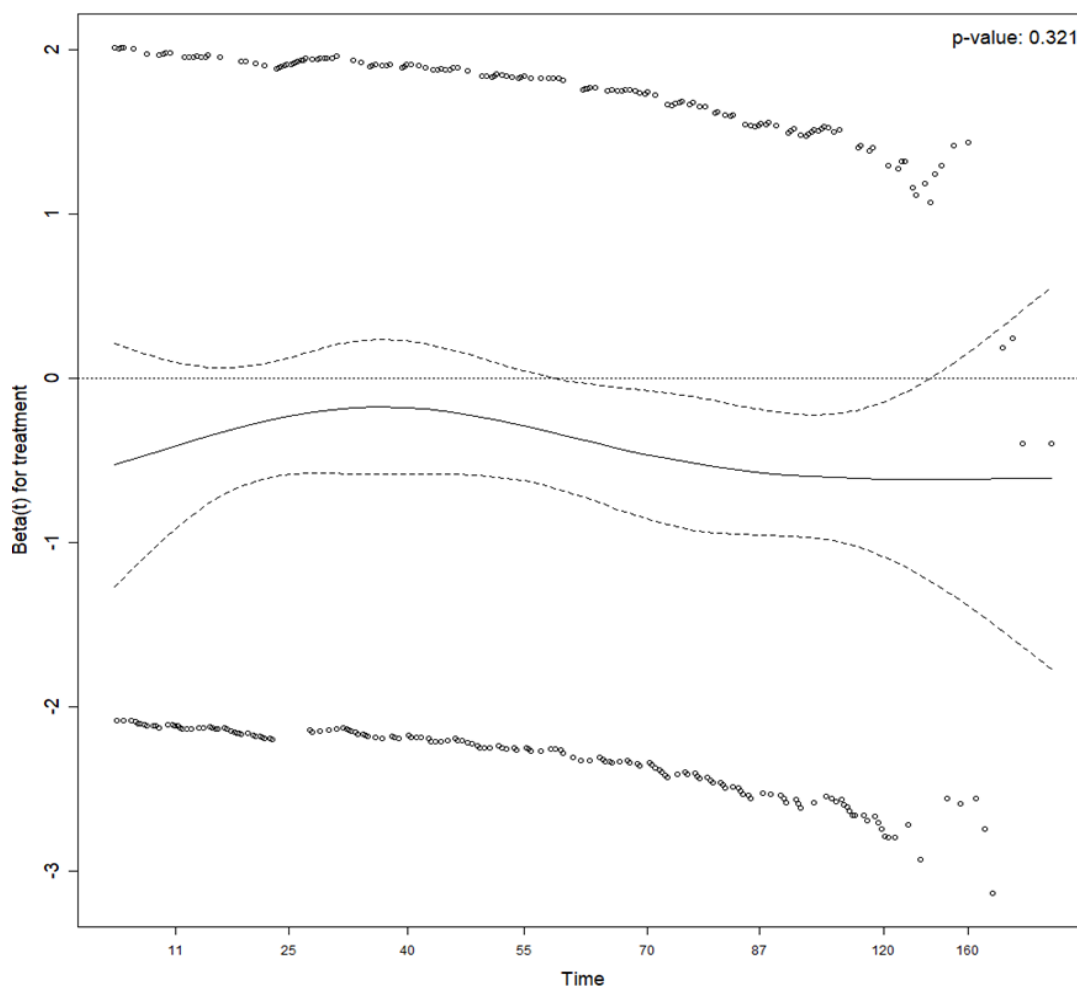
On the basis of this feedback regarding the mirvetuximab mechanism of action, inspection of the log cumulative hazard plot, and based on DSU TSD 14 (178) (which notes that when patient-level data are available it is unnecessary to rely upon the proportional hazards assumption and apply a proportional hazards modelling approach), independent models for mirvetuximab and pooled chemotherapy were used in the base case. Scenario analyses were considered using dependent models.

Figure 25. Log cumulative hazard plot for OS – mirvetuximab vs pooled chemotherapy



Abbreviations: MIRV, mirvetuximab; OS, overall survival.

Figure 26. Schoenfeld residuals plot for OS – mirvetuximab vs pooled chemotherapy



Abbreviations: OS, overall survival.

Statistical goodness of fit

Statistical goodness of fit was assessed using the AIC and BIC goodness of fit statistics. As noted in TSD 14, AIC/BIC are only useful for assessing the goodness of fit for the observed data (178).

Several distributions were associated with similarly good statistical fit based on the minimisation of AIC and BIC statistics for mirvetuximab and pooled chemotherapy (Table 23 and Table 24, respectively); there is negligible difference in goodness of fit statistics between the gamma, Weibull, log-logistic, and generalised gamma curves for mirvetuximab with distributions being within 3 and 6 points for AIC and BIC,

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respectively. For the pooled chemotherapy arm, the Weibull, gamma and generalised gamma distributions are associated with similar statistical fits.

For OS, statistical fit should be interpreted with caution given the extent to which the data were censored towards the end of MIRASOL. For reference, statistical goodness of fit based on the portion of the observed data for which the KM is considered informative/meaningful is reported in Appendix M.

Table 23. Statistical goodness of fit for OS – mirvetuximab

Parametric function	AIC	BIC
Exponential	1826.850	1830.274
Weibull	1815.392	1822.242
Log-Logistic	1817.525	1824.375
Lognormal	1825.857	1832.707
Gompertz	1820.862	1827.711
Gamma	1814.625	1821.475
Generalised Gamma	1816.571	1826.846

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

Table 24. Statistical goodness of fit for OS – pooled chemotherapy

Parametric function	AIC	BIC
Exponential	1875.726	1879.146
Weibull	1853.477	1860.318
Log-logistic	1867.257	1874.098
Lognormal	1873.860	1880.701
Gompertz	1858.912	1865.753
Gamma	1854.381	1861.222
Generalised Gamma	1855.477	1865.738

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion OS, overall survival.

Modelled OS functions and plausibility of long-term OS

The predicted OS curves associated with different parametric functions are shown for mirvetuximab and pooled chemotherapy in Figure 27 and Figure 28, respectively.

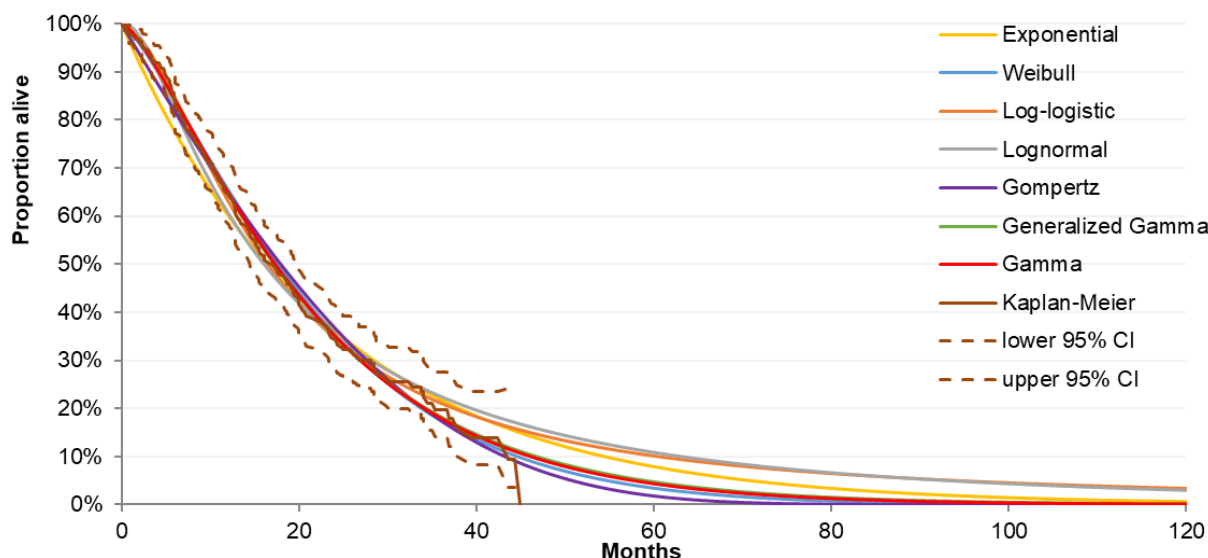
Landmark estimates for mirvetuximab and pooled chemotherapy are presented in Table 25 and Table 26, respectively. In alignment with NICE DSU TSD14, the plausibility of long-term OS extrapolations was assessed at an AbbVie advisory board and through

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clinician interviews in which extrapolations were presented to three clinicians based in England/Wales. Clinical experts noted that:

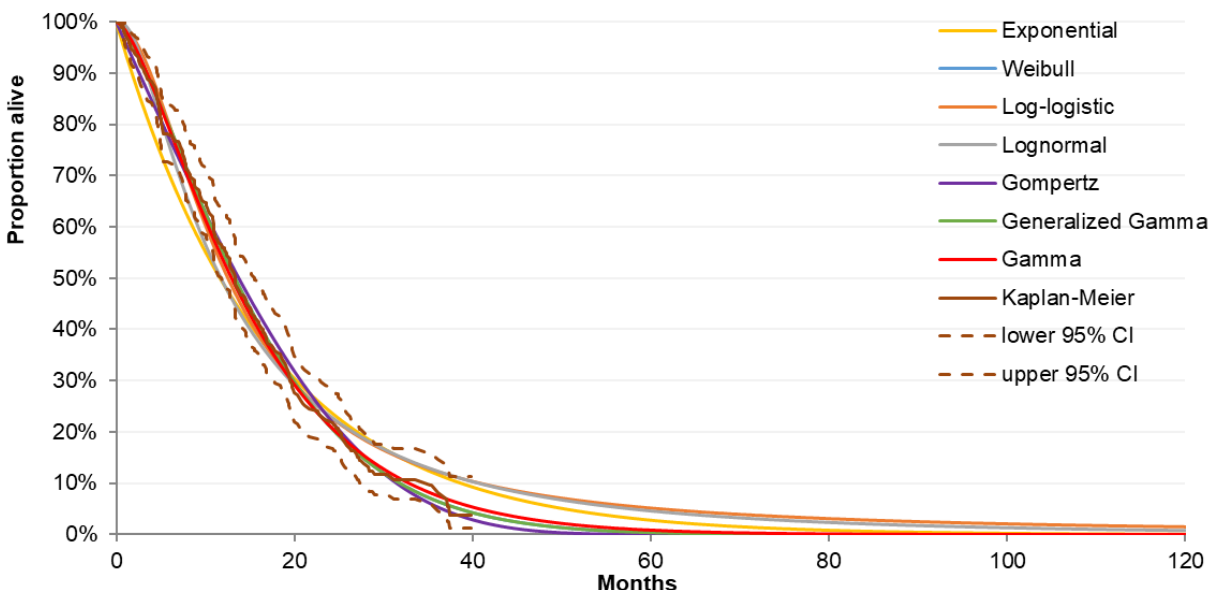
- Survival in the pooled chemotherapy arm would be expected to be 0–5% at 5 years and 0% at 10 years.
- Survival in the mirvetuximab arm would be expected to be 8–12% at 5 years and was uncertain at 10 years; it was noted that mirvetuximab has a novel mechanism of action and is not yet in routine practice, and so these patients have not been observed at 5 and 10 years in clinical practice.
- Distributions considered reasonable by clinicians for mirvetuximab included log-logistic, exponential, generalised gamma and gamma.
- For pooled chemotherapy, clinicians considered the gamma, generalised gamma, Weibull, and Gompertz distributions to be the most plausible.

Figure 27. Modelled survival functions for OS – mirvetuximab



Abbreviations: CI, confidence interval; OS, overall survival.

Figure 28. Modelled survival functions for OS – pooled chemotherapy



Abbreviations: CI, confidence interval; OS, overall survival.

Table 25. Mirvetuximab OS survival function – landmark estimates

Distribution	% alive at				
	1 year	2 years	3 years	5 years	10 years
KM	65%	35%	20%	–	–
Log-normal	61%	35%	23%	11%	3%
Log-logistic	63%	35%	21%	10%	3%
Exponential	60%	36%	22%	8%	1%
Generalised gamma	65%	35%	18%	5%	0%
Gamma	65%	35%	18%	4%	0%
Weibull	66%	36%	18%	3%	0%
Gompertz	65%	37%	18%	2%	0%

Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Table 26. Pooled chemotherapy OS survival function – landmark estimates

Distribution	% alive at				
	1 year	2 years	3 years	5 years	10 years
KM	56%	22%	10%	–	–
Log-normal	49%	23%	13%	5%	1%
Log-logistic	52%	23%	12%	5%	1%
Exponential	49%	24%	12%	3%	0%
Generalised gamma	55%	21%	7%	0%	0%
Gamma	54%	21%	8%	1%	0%
Weibull	55%	21%	7%	0%	0%
Gompertz	56%	23%	6%	0%	0%

Abbreviations: KM, Kaplan-Meier; OS, overall survival.

Base-case OS approach

For pooled chemotherapy, all distributions considered clinically plausible by clinicians (generalised gamma, gamma, Weibull, Gompertz) were associated with similar predicted OS (Table 26); given this, the Weibull distribution was selected for the base case as this was associated with the lowest AIC and BIC. All other distributions were considered in scenario analyses.

For mirvetuximab, clinicians considered the gamma, generalised gamma, exponential, and log-logistic to be potentially plausible. The exponential distribution was not considered suitable for the base case, as it has a poor statistical fit and poor visual fit to the observed data. In addition, the exponential distribution implies the strong assumption of a constant hazard, which is not reflected in the smoothed hazards for mirvetuximab presented in Figure 29; the hazard for mirvetuximab appears to rise modestly, before decreasing again up to approximately Week 120. Clinical experts have suggested that the declining hazard at later time points may reflect that relatively fitter/healthier patients with lower mortality rates remain at risk. The hazard for mirvetuximab is then seen to rise again, albeit only in the time period for which the observed data is not considered informative/meaningful. The gamma and generalised gamma distributions were similarly not considered suitable for the model base case on the basis that these distributions have monotonically increasing hazards, which again were not consistent with the observed hazard; these distributions also gave 5-year

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estimates of OS that were substantially below the clinician estimates of 8–12% (4% and 5% for gamma and generalised gamma, respectively).

The log-logistic distribution by contrast implies an increasing then decreasing hazard over time, and provides predicted survival estimates of 10% at 5 years, which was approximately in the middle of the range provided by clinical experts.

The log-logistic distribution also allows for the possibility of long-term survival in some patients, which may be expected given:

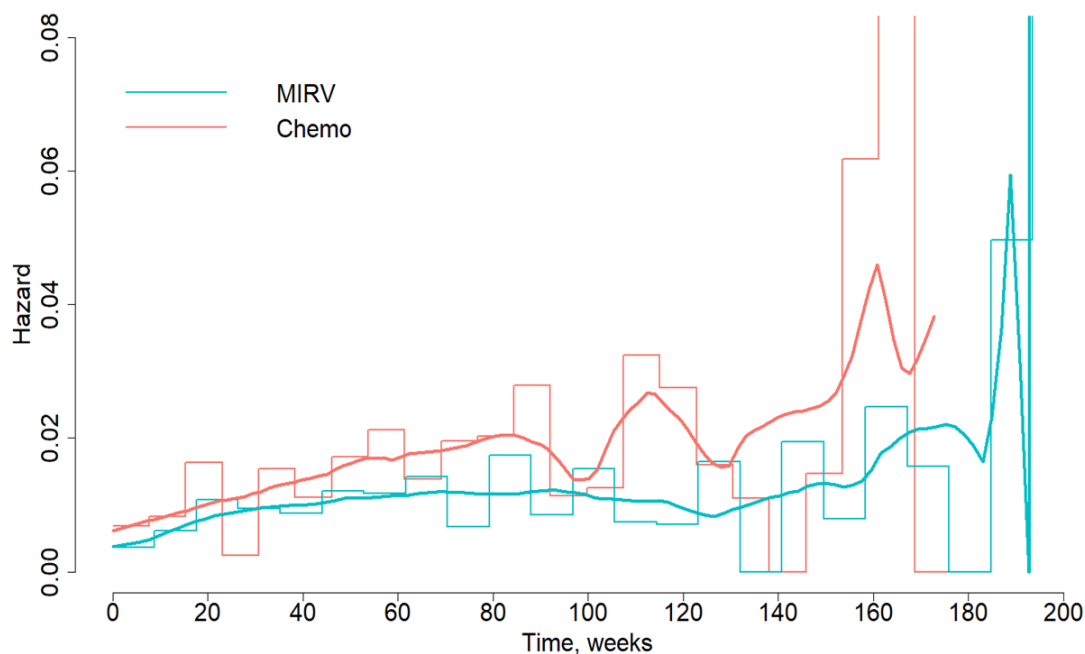
- Mirvetuximab has a mechanism of action which selectively targets FR α to deliver a highly potent and otherwise intolerable payload to induce tumour cell death. It also benefits from a bystander effect (i.e. the ability of DM4 diffusion into neighbouring tumour cells to induce further death of tumour cells). The bystander effect ensures that tumour cells without FR α expression are also killed. This is particularly beneficial where penetration into a solid tumour is limited and/or when FR α expression among the tumour cells is heterogeneous.
- The reduced tumour burden associated with mirvetuximab, as evidenced by the response rates, with tumour responses being induced in almost half the time compared with chemotherapy (1.54 vs 2.71 months median respectively), and an ORR of 41.9% was achieved with mirvetuximab, more than double the rate achieved with pooled chemotherapy (15.9%); tumour shrinkage was observed in >80% of patients with mirvetuximab, compared with 55% of patients receiving pooled chemotherapy.
- Patients in the mirvetuximab arm who were censored due to study termination (44/227, or 19.4%) were predominantly patients who had achieved either partial or complete response (29/44, or 65.9%). This shows (a) that response is prognostic as the ORR of patients censored due to study termination is higher than the full ITT population (41.9% and 15.9% for mirvetuximab and IC Chemo respectively) and (b) that since these patients were alive after at least 24 months, there is increased potential that some mirvetuximab patients survive long-term, in line with the predictions made by the log-logistic distribution.

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- Attendees at the AbbVie advisory board noted that mirvetuximab was associated with relatively low levels of myelosuppression compared with chemotherapy (such as paclitaxel or topotecan), and coupled with a break in treatment of such therapies and a period of potential recovery from the severity of these events during mirvetuximab therapy, subsequent treatment in the mirvetuximab arm may achieve better effectiveness than for patients receiving pooled chemotherapy. Evidence of this continuing benefit post-progression are found in PFS2 from MIRASOL; mirvetuximab demonstrated a greater improvement vs pooled chemotherapy, with patients receiving a balanced selection of subsequent therapies (HR of 0.59; 95% CI: 0.480, 0.728).

In summary, of the distributions suggested by clinicians, all were associated with similar statistical goodness of fit apart from the exponential distribution, but the log-logistic predicts survival at 5 years consistent with clinical expert opinion, is associated with a hazard consistent with the observed data and allows for some patients treated with mirvetuximab to experience long-term survival. On this basis, the log-logistic distribution was selected for the base-case extrapolation of mirvetuximab; all other distributions were considered in scenario analyses.

Figure 29. Smoothed hazard plot – mirvetuximab and pooled chemotherapy OS

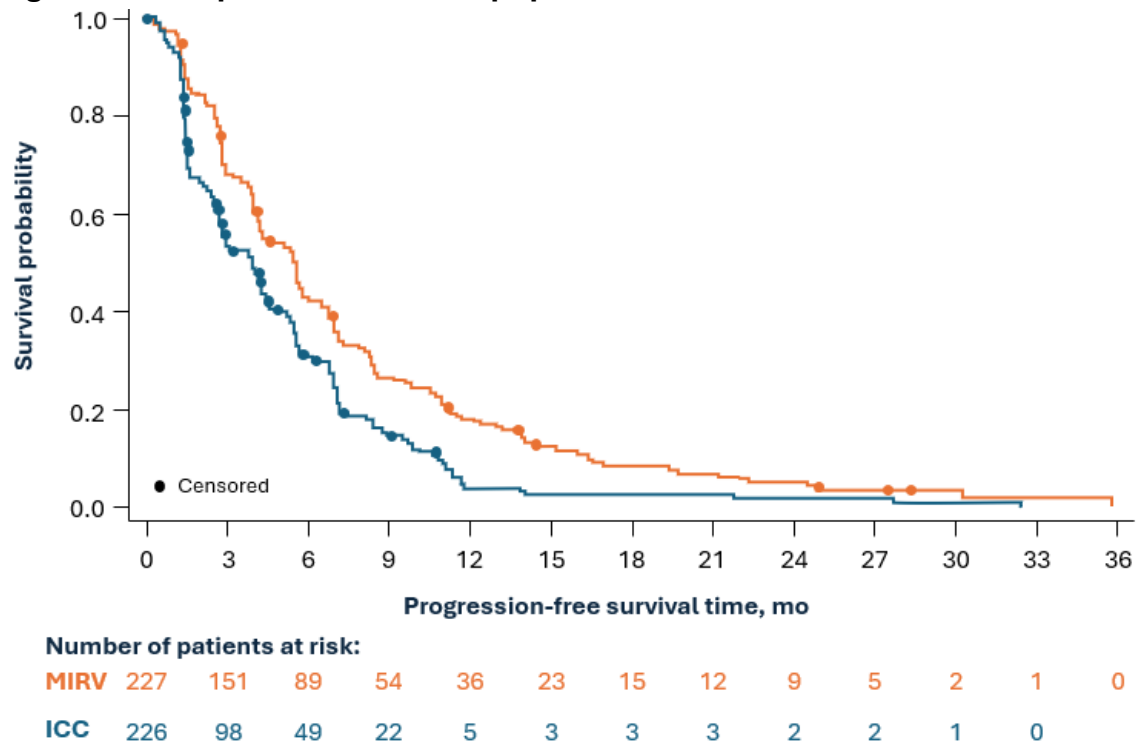


Abbreviations: MIRV, mirvetuximab; OS, overall survival.

3.3.4. Progression-free survival

At the 26th September 2024 data cut-off for MIRASOL (median follow-up time of 28.35 months for PFS), median PFS (investigator assessment) was 5.59 and 3.98 months for mirvetuximab and pooled chemotherapy, respectively (Section 2.6). The KM for PFS is presented in Figure 30; the KM estimator reaches zero for each of mirvetuximab and pooled chemotherapy.

Figure 30: KM plot for PFS – ITT population



Source: Data on file, MIRASOL final CSR (14).
Abbreviations: CSR, clinical study report; DCO, data cut-off; KM, Kaplan-Meier; ICC, Investigator’s choice of chemotherapy; ITT, intention-to-treat; MIRV, mirvetuximab; PFS_{INV}, progression-free survival per investigator.

Assessment of proportional hazards

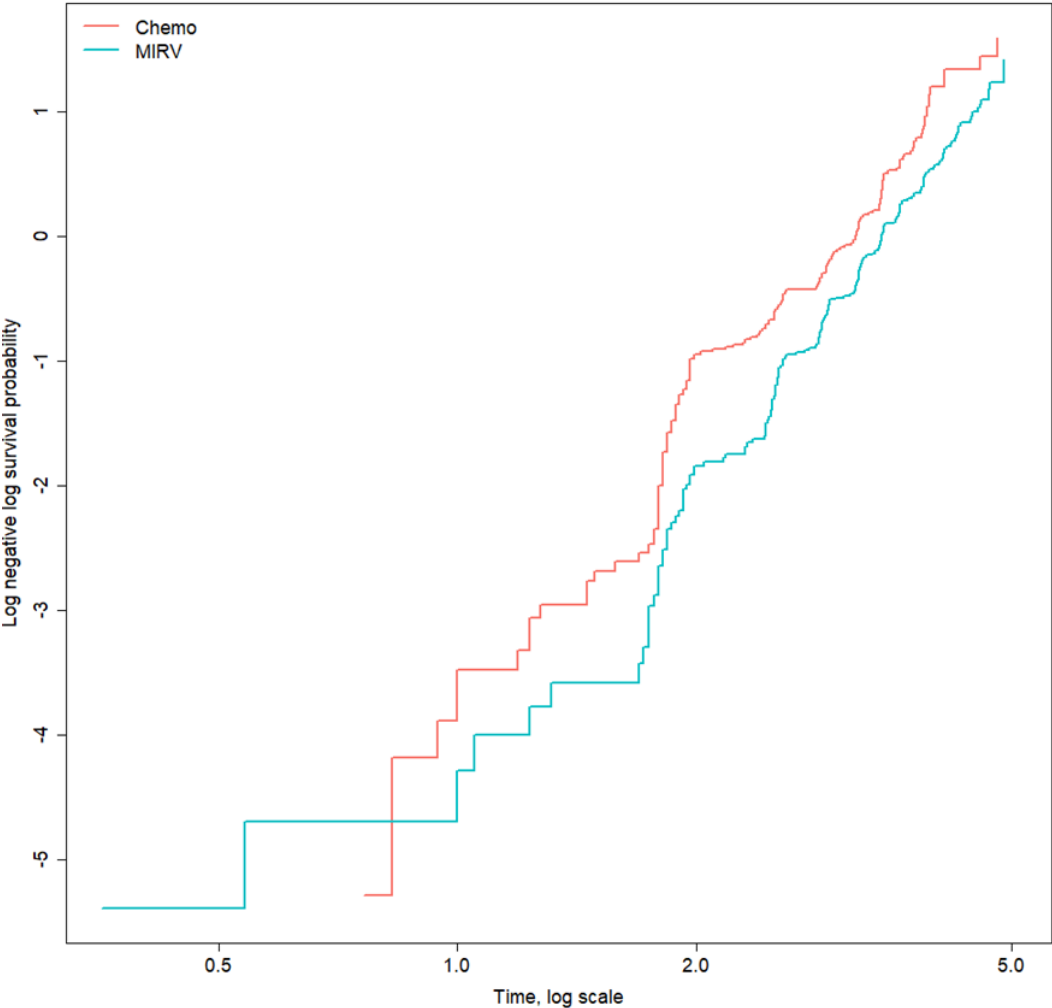
The log-cumulative hazard plot for PFS is presented in Figure 31 and the Schoenfeld residuals plot is presented in Figure 32. The log-cumulative hazard plots show one instance of curves crossing, however after initial divergence and convergence the plots become approximately parallel. Though hypothesis testing suggested that the PH assumption is not violated overall (p=0.363), visual inspection of the Schoenfeld residuals plot (Figure 32) suggests an increased treatment effect at earlier time points, indicating a possible violation of the PH assumption. In the primary publication of MIRASOL, Moore et al report the results of the supremum test for key trial outcomes, reporting that “a p value of 0.049 was observed for progression-free survival only, indicating a possible nonproportionality” (1).

Discussion at the AbbVie advisory board suggested that independent models may be more appropriate than dependent models given the differing mechanisms of action

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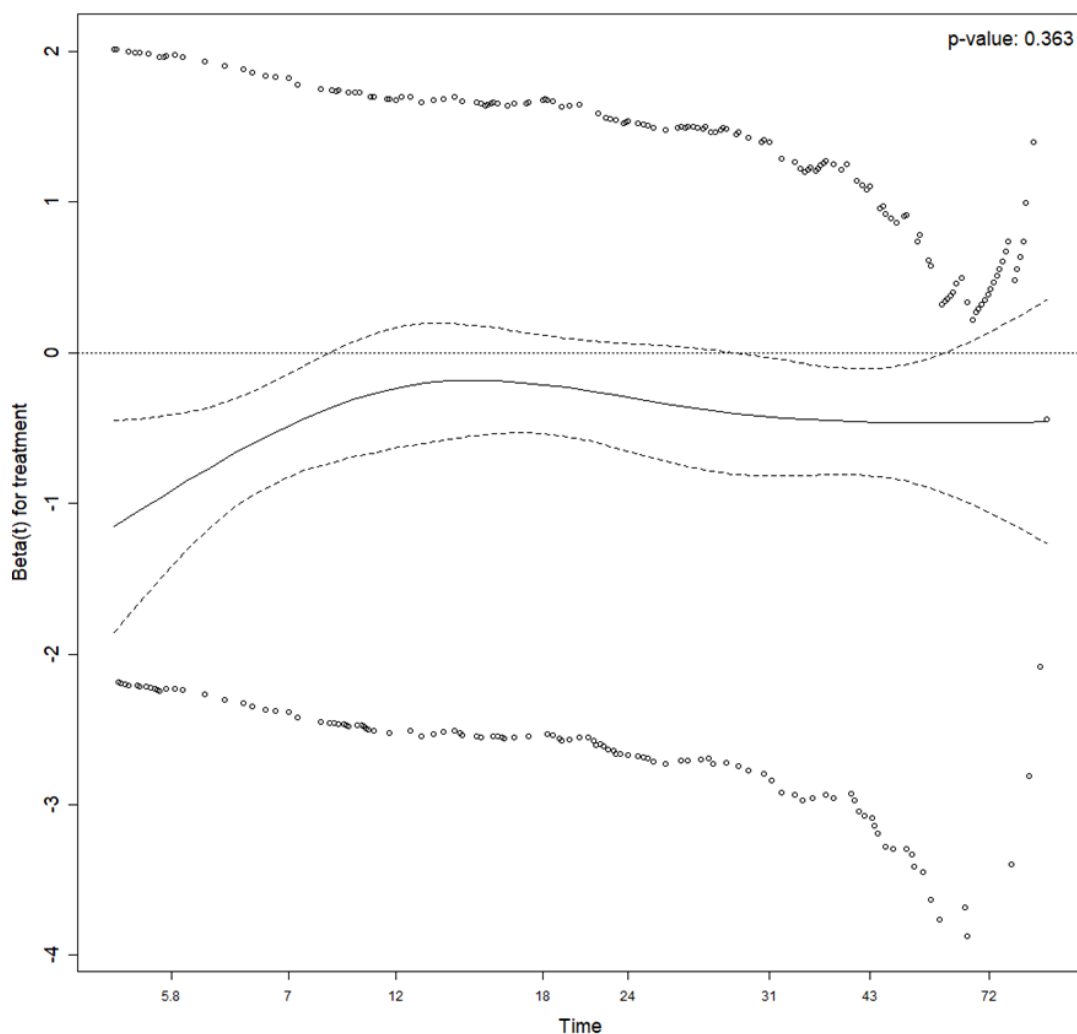
between mirvetuximab and the pooled chemotherapy arms, and potential differences in subsequent therapies (Section 3.3.3; Assessment of proportional hazards). To align with the approach taken for OS, independent models for PFS for mirvetuximab and pooled chemotherapy were considered in the base case. Scenario analyses were considered using dependent models.

Figure 31. Log cumulative hazard plot for PFS – mirvetuximab vs pooled chemotherapy



Abbreviations: MIRV, mirvetuximab; PFS, progression-free survival.

Figure 32. Schoenfeld residuals plot for PFS – mirvetuximab vs pooled chemotherapy



Abbreviations: PFS, progression-free survival.

Statistical goodness of fit

Statistical goodness of fit was assessed using the AIC and BIC goodness of fit statistics. The log-normal, log-logistic and generalised gamma distributions were associated with the best statistical fit for the mirvetuximab arm (Table 27). The log-normal and generalised gamma distributions were associated with the best statistical fit for the pooled chemotherapy arm (Table 28).

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Table 27. Statistical goodness of fit for PFS – mirvetuximab

Parametric function	AIC	BIC
Exponential	1832.650	1836.075
Weibull	1823.642	1830.491
Log-logistic	1805.801	1812.651
Lognormal	1802.668	1809.518
Gompertz	1833.948	1840.798
Gamma	1816.810	1823.660
Generalised Gamma	1804.343	1814.618

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Table 28. Statistical goodness of fit for PFS – pooled chemotherapy

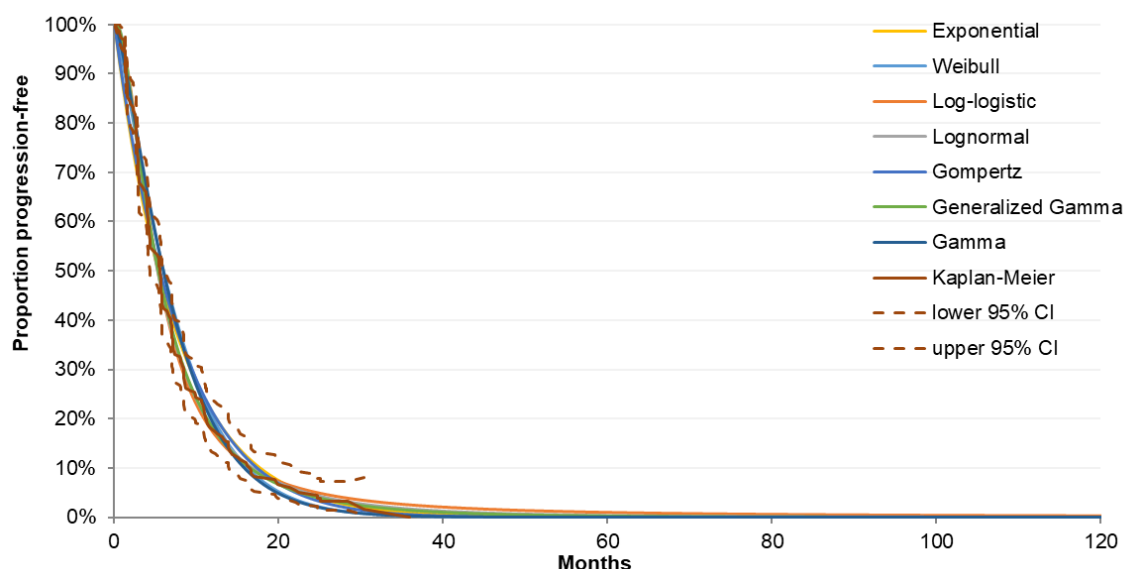
Parametric function	AIC	BIC
Exponential	1429.801	1433.222
Weibull	1419.539	1426.380
Log-Logistic	1408.009	1414.850
Lognormal	1397.088	1403.929
Gompertz	1431.005	1437.846
Gamma	1412.367	1419.208
Generalised Gamma	1398.982	1409.244

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

Modelled PFS functions

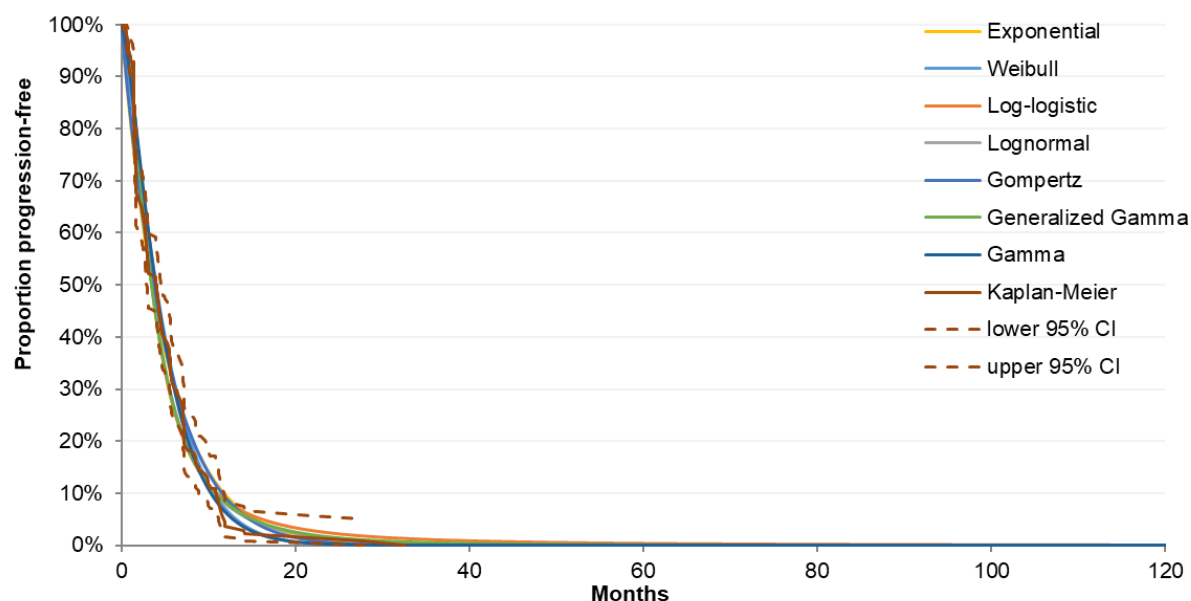
Modelled extrapolations for mirvetuximab and pooled chemotherapy are presented in Figure 33 and Figure 34, respectively. Modelled PFS functions were validated with three clinicians based in England/Wales. All experts were in alignment that the log-normal distribution for each of mirvetuximab and pooled chemotherapy provided the best estimation of PFS. Landmark estimates for the lognormal distribution for mirvetuximab and pooled chemotherapy are presented in Table 30 and Table 31.

Figure 33. Modelled survival functions for PFS – mirvetuximab



Abbreviations: CI, confidence interval; PFS, progression-free survival.

Figure 34. Modelled survival functions for PFS – pooled chemotherapy



Abbreviations: CI, confidence interval; PFS, progression-free survival.

Table 29. Mirvetuximab PFS survival function – landmark estimates

Distribution	% alive at				
	1 year	2 years	3 years	5 years	10 years
KM	18%	5%	–	–	–
Log-normal	18%	5%	2%	0%	0%
Log-logistic	17%	5%	2%	1%	0%
Exponential	21%	4%	1%	0%	0%
Generalised gamma	18%	4%	1%	0%	0%
Gamma	19%	2%	0%	0%	0%
Weibull	20%	3%	0%	0%	0%
Gompertz	21%	4%	1%	0%	0%

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Table 30. Pooled chemotherapy PFS survival function – landmark estimates

Distribution	% alive at				
	1 year	2 years	3 years	5 years	10 years
KM	4%	1%	–	–	–
Log-normal	8%	1%	0%	0%	0%
Log-logistic	9%	2%	1%	0%	0%
Exponential	10%	1%	0%	0%	0%
Generalised gamma	8%	2%	0%	0%	0%
Gamma	6%	0%	0%	0%	0%
Weibull	7%	0%	0%	0%	0%
Gompertz	9%	1%	0%	0%	0%

Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival.

Base-case PFS approach

The log-normal distribution was selected in the base case for both mirvetuximab and pooled chemotherapy based on clinical expert opinion and statistical goodness of fit. The generalised gamma and log-logistic distributions were considered in scenario analyses for mirvetuximab and the generalised gamma distribution for pooled chemotherapy due to similar statistical goodness of fit.

3.3.5. Duration of treatment

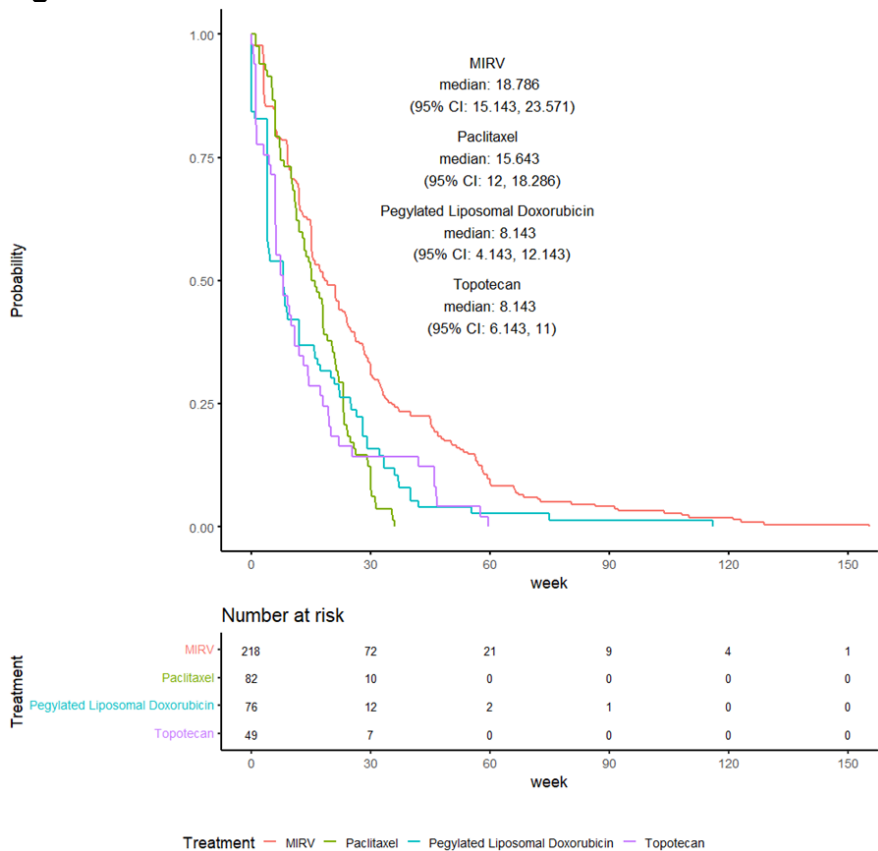
At the September 2024 data cut-off for MIRASOL, the KM estimator for DoT reaches zero for mirvetuximab and for each component of pooled chemotherapy (paclitaxel,

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pegylated liposomal doxorubicin, and topotecan). DoT data are presented in Figure 35 for mirvetuximab and pooled chemotherapy components, respectively.

DoT data from MIRASOL were analysed for the Safety Population (218 and 207 patients in the mirvetuximab and pooled chemotherapy arms, respectively); the subset of patients who received $\geq$ one dose of the assigned therapy (96%, 89%, 94% and 92% of the ITT population for mirvetuximab, paclitaxel, pegylated liposomal doxorubicin and topotecan, respectively)¹. Survival curves for DoT were therefore multiplied by the proportion of patients receiving $\geq$ one dose of the assigned therapy, to generate DoT in the ITT population for use in the model.

Figure 35. MIRASOL DoT KM



Abbreviations: CI, confidence interval; DoT, duration of treatment; KM, Kaplan-Meier; MIRV, mirvetuximab.

¹ Note that it would be challenging to fit survival curves to the DoT data for the ITT population, as none of the standard survival curves can accommodate a drop of between 4% and 11% at time zero.

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DoT was modelled separately for each of the chemotherapies administered in the trial as each of these required differing dosing regimens and cycle lengths and so would be expected to demonstrate different DoT patterns over time.

Due to the low number of patients that received topotecan on a 3-week cycle, topotecan 3-week cycle and 4-week cycle were combined as one treatment regimen for the purposes of estimating DoT. For paclitaxel, pegylated liposomal doxorubicin, and topotecan, observed KM data was used for the DoT curves in the base case as the KM estimator was complete and parametric curves overestimated the proportion of patients remaining on treatment at the tail.

Statistical goodness of fit

The exponential, Weibull, Gompertz, gamma and generalised gamma distributions were associated with the best statistical fit for mirvetuximab DoT based on the minimisation of AIC and BIC statistics (Table 31).

Table 31. Statistical goodness of fit for DoT – mirvetuximab

Parametric function	AIC	BIC
Exponential	1882.164	1885.548
Weibull	1883.061	1889.830
Log-logistic	1904.797	1911.566
Lognormal	1925.107	1931.876
Gompertz	1883.854	1890.623
Gamma	1882.889	1889.658
Generalised Gamma	1884.862	1895.016

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; DoT, duration of treatment.

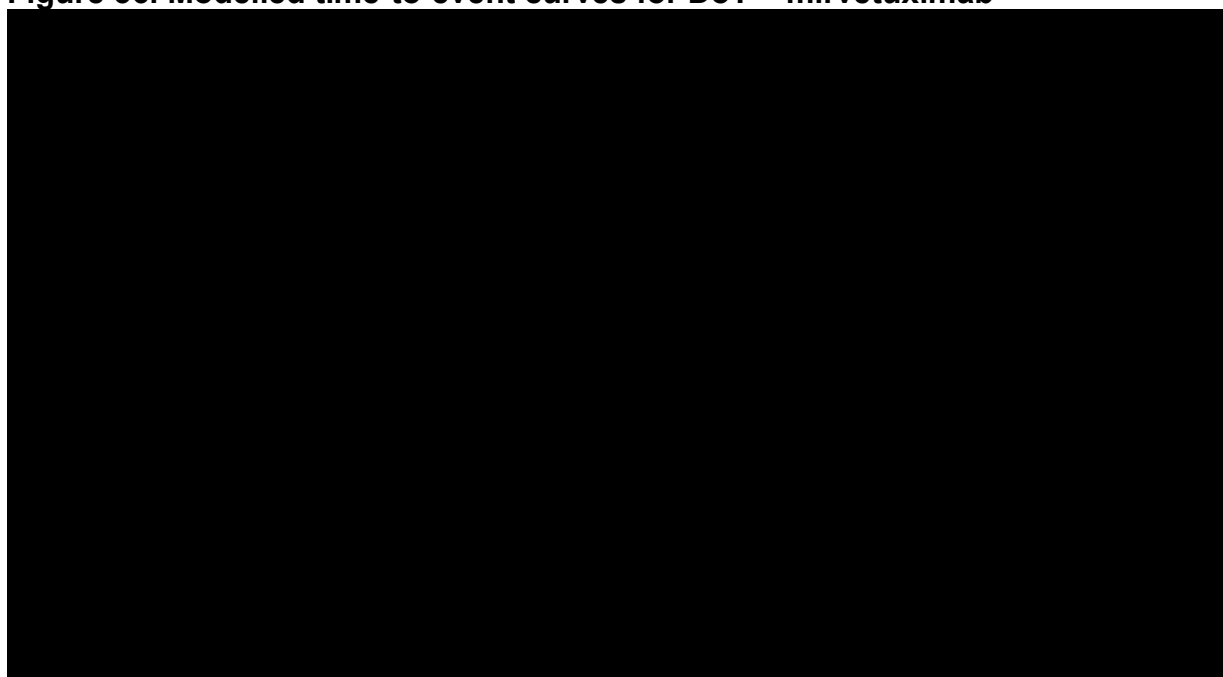
Modelled DoT functions

As the follow-up in MIRASOL was long enough to capture a complete picture of DoT for all treatments, long-term validation of alternative extrapolations was less relevant. The observed DoT curves from MIRASOL were, however, validated by three clinicians in England/Wales.

DoT KMs and modelled functions for mirvetuximab, paclitaxel, pegylated liposomal doxorubicin, and topotecan are presented in Figure 36 to Figure 39, respectively.

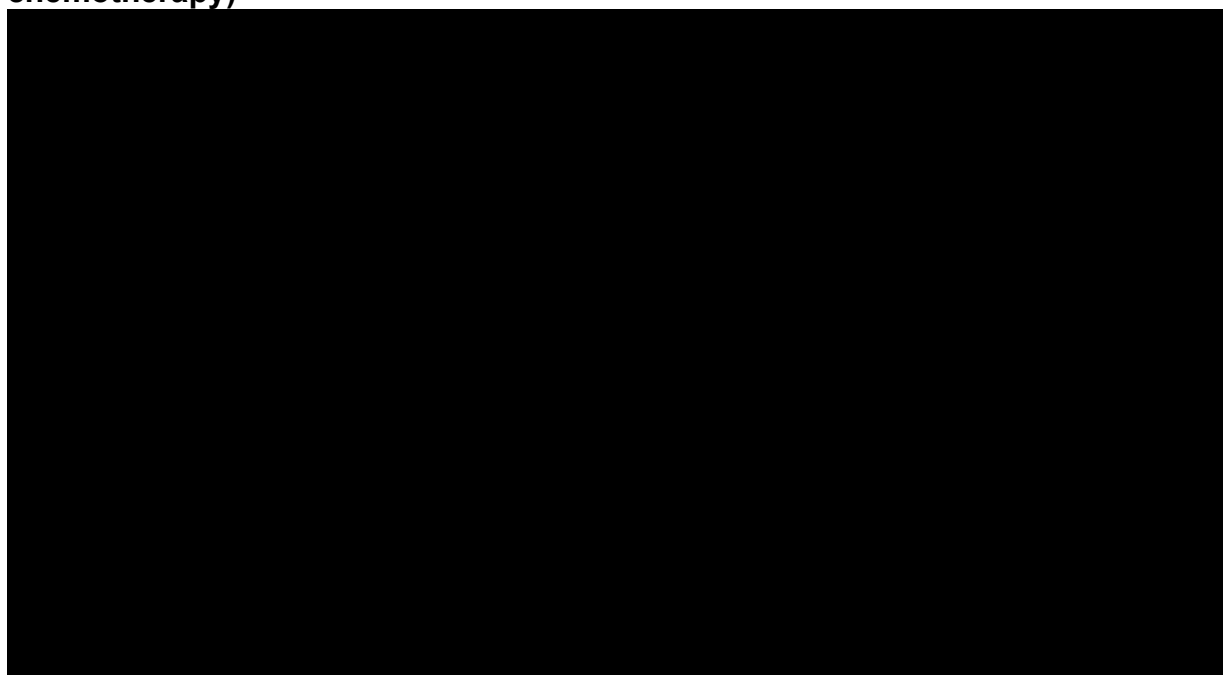
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Figure 36. Modelled time-to-event curves for DoT – mirvetuximab



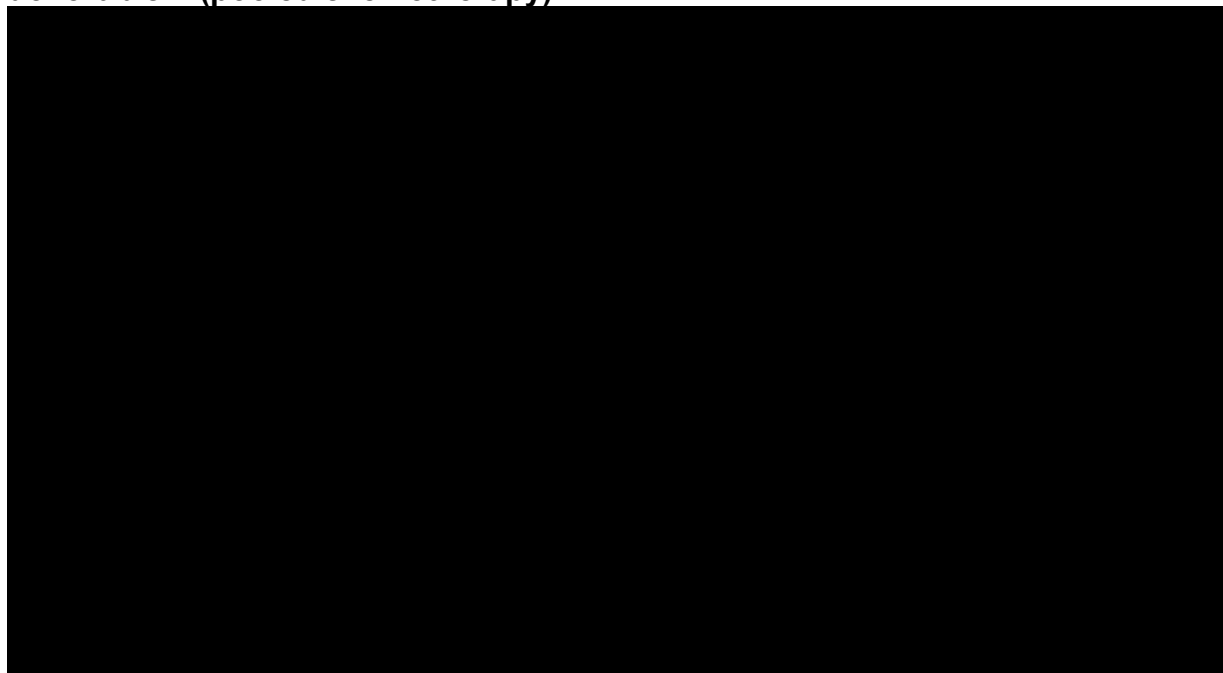
Abbreviations: CI, confidence interval; DoT, duration of treatment.

Figure 37. Modelled time-to-event curves for DoT – paclitaxel (pooled chemotherapy)



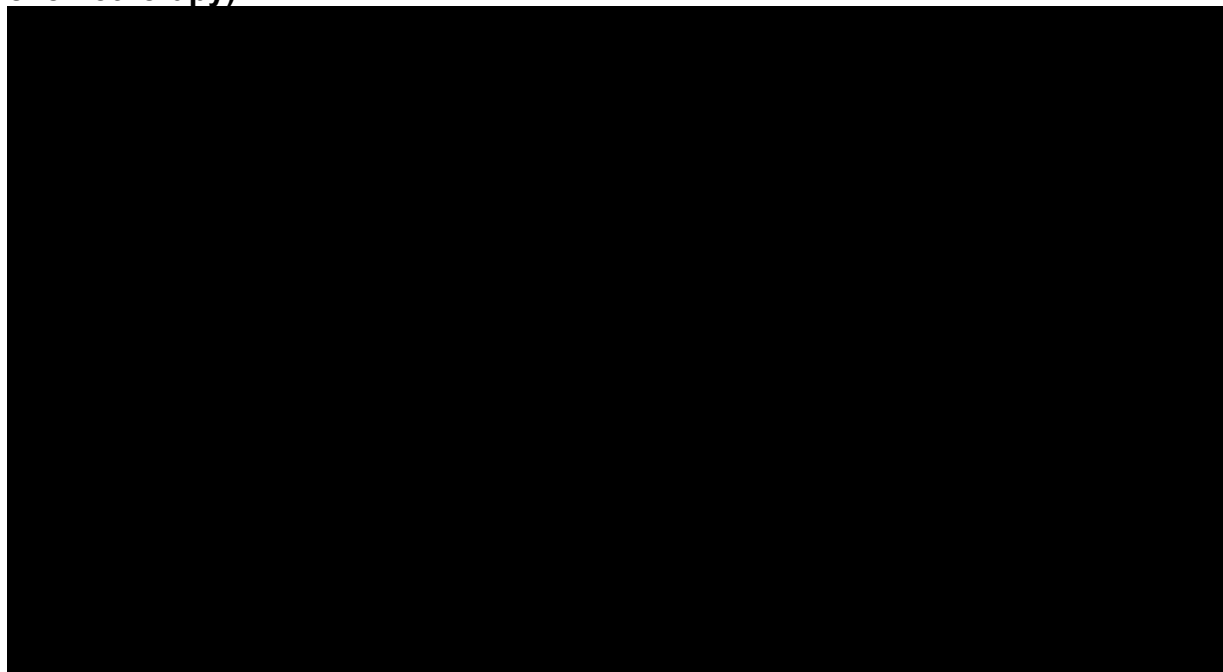
Abbreviations: CI, confidence interval; DoT, duration of treatment.

Figure 38. Modelled time-to-event curves for DoT – pegylated liposomal doxorubicin (pooled chemotherapy)



Abbreviations: CI, confidence interval; DoT, duration of treatment.

Figure 39. Modelled time-to-event curves for DoT – topotecan (pooled chemotherapy)



Abbreviations: CI, confidence interval; DoT, duration of treatment.

Base case DoT approach

In the base case, the exponential distribution was selected for mirvetuximab based on best statistical goodness of fit, given that all modelled functions were associated with similar outcomes. A scenario was undertaken with the next best fitting curve (the gamma distribution).

As the KMs were complete for the components of pooled chemotherapy from MIRASOL, and parametric curves visually overestimated DoT compared with the observed data, the KM curves were used directly to model DoT. A scenario was undertaken where extrapolated curves were used, assuming the best fitting curve of each chemotherapy treatment (paclitaxel - gompertz, PLD - gamma, topotecan - exponential).

3.3.6. General population mortality

General population mortality values were included to constrain the minimum mortality rate based on age and gender matched rates of the cohort in each model cycle^m (183). Background mortality was taken from general population life tables for England and Wales for the years 2017–2019ⁿ, as reported by the Office for National Statistics (ONS), in line with NICE guidance (170).

3.3.7. Adverse events

Modelled AEs include all those that were Grade 3–4, occurring in ≥5% of patients in either arm of the MIRASOL trial (September 2024 data cut; Safety population). The average number of AEs per patient^o were derived from MIRASOL and are presented in Table 32. The disutility (considered in a scenario analysis only) and costs associated with AEs are presented in Sections 3.4.4 and 3.5.5, respectively.

^m I.e. where the modelled probability of death falls below that of the age- and gender-matched general population, general population mortality rates are assumed to apply.

ⁿ Life tables from 2017-19 are used to ensure that estimates of general population mortality are not distorted by the COVID-19 pandemic.

^o The average number of events per patient is calculated as the total number of events in a trial arm divided the number of patients in the trial arm.

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Monitoring and treatment for the management of ocular AEs in the mirvetuximab arm were also modelled (Section 3.5.5); this is aligned with the requirements detailed in the mirvetuximab SmPC, and feedback from clinical experts at an AbbVie advisory board.

Table 32. Treatment-related Grade 3+ AEs with incidence ≥5% – MIRASOL

Adverse event	Average number of AEs per patient - MIRASOL	
	Mirvetuximab	Pooled chemotherapy
Anaemia	0.01	0.21
Cataract	0.07	0.00
Fatigue	0.02	0.05
Keratopathy	0.12	0.00
Neutropenia	0.01	0.37
Thrombocytopenia	0.03	0.11
Vision blurred	0.13	0.00

Abbreviations: AE, adverse event.

3.4. Measurement and valuation of health effects

3.4.1. Health-related quality of life data from clinical trials

EQ-5D-5L in the MIRASOL trial was collected at screening, Day 1 of every treatment cycle (3 weeks for mirvetuximab and topotecan 1.25mg, and 4 weeks for other chemotherapies) through Week 24, then every 12 weeks until documented progressive disease or start of a new anticancer therapy. After the assigned treatment ended, EQ- 5D-5L data were collected once within a week of treatment discontinuation and then approximately every 3 months during the follow-up period (19).

3.4.2. Mapping

Utility values were calculated by mapping the EQ-5D-5L responses collected from participants in the MIRASOL trial onto the EQ-5D-3L UK value set based on the recommendations in the latest TA guidance (2022), with the mapping conducted using the algorithm developed by NICE’s DSU (184, 185).

3.4.3. Health-related quality of life studies

An SLR was conducted on 4th March 2024 and updated on 20th November 2024 to identify HRQoL studies in PROC. A detailed description of the SLR methods, full results and quality assessment of the identified HRQoL data is presented in Appendix F.

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3.4.4. Adverse reactions

In the base-case analysis, AE disutilities were not applied as the impact of AEs is expected to be implicitly captured in the treatment-specific utility values used (Section 3.4.6). A scenario analysis is considered in which AE disutilities are explicitly modelled.

In these scenario analyses, patients were assumed to incur a one-off QALY loss associated with AEs (applied additively). Disutility inputs were derived from the published literature (186-188). In the absence of other data, AE durations were assumed to be 4 weeks.

Table 33 presents the AE disutilities used in the relevant scenario analyses.

Table 33. AE disutilities

Adverse event	Disutility	
	Value	Reference
Anaemia	−0.120	Shah et al, 2022 (188)
Cataract	−0.140	Brown et al, 2007 (189)
Fatigue	−0.115	Lloyd et al, 2006 (187)
Keratopathy	−0.008	Sullivan et al, 2006 (186)
Neutropenia	−0.090	Shah et al, 2022 (188)
Thrombocytopenia	−0.110	Shah et al, 2022 (188)
Vision blurred	−0.005	Sullivan et al, 2006 (186)

Abbreviations: AE, adverse event.

3.4.5. Age-based utility multiplier

The health state utility values (HSUV) detailed in Section 3.4.6 are assumed to apply at the start of the model; for every year subsequent to this, a multiplier is applied based on the ratio between the general population utility values for the current age and the starting age. General population utility values for the UK are taken from Hernandez-Alava et al, 2022^p (190).

^p General population utility values used are those reported in the Microsoft Excel file named “Expected EQ-5D-3L by age and sex and covariance matrices of the models using the HSE 2014 dataset”.

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3.4.6. Health-related quality of life data used in the cost-effectiveness analysis

As highlighted in section 2.6, mirvetuximab is linked with improved QoL for patients, compared to pooled chemotherapy. The utility differences between mirvetuximab and pooled chemotherapy as elicited from MIRASOL were noted to be relatively small (Table 36). These differences were considered to lack face validity, given feedback provided to AbbVie from individual patients on their experiences with each of chemotherapy and mirvetuximab; patient quotes are presented in Table 34, and highlight a transformative step-change in QoL when transitioning from chemotherapy to mirvetuximab.

The discrepancy between the differences reported in MIRASOL and the feedback from patients may be due to the limitations of EQ-5D in capturing key outcomes experienced by chemotherapy patients (191, 192). In addition, the timing of EQ-5D collection in MIRASOL (at the beginning of a treatment cycle) is expected to result in an underestimation of the impact of chemotherapy: Sanghera et al report that EQ-5D-5L reduced by 0.074 in the first 7 days of a treatment cycle (193). Similarly, Kristensen et al found that symptom burden was highest one week after the beginning of a treatment cycle (194).

Table 34. Patient perspectives on experience with chemotherapy and mirvetuximab

Topic	Patient quotes
Experiences with chemotherapy (including first-line platinum-based chemotherapy)	• <i>“It’s during day 3 or 4 where I really felt worse. I was dizzy, everything was spinning, my head felt muffled. I couldn’t concentrate.”</i> • <i>“Every time you get another round, all of the side effects get worse. I lost my hair, the nausea, I was having diarrhoea again, the fatigue. It was a lot...especially with chemo that they bring you so close to death without actually letting you get there because you feel like you’re going to die. It’s traumatic.”</i> • <i>“The fatigue that always accompanies you even when climbing the very few stairs to your apartment. And the hair was starting to fall out. You kind of lose your identity as well, because you look in the mirror and you don’t recognise yourself.”</i>
Experiences with mirvetuximab	• <i>“It was Elahere, which has changed my life. I got two years of living a normal life...I had no side effects coming out of the chair, which meant usually I’m very tired and I have a hard time walking because my neuropathy is quite bad, but with Elahere, nothing. I was able to live a life. I could yell at my kids and take care of my grandchildren and I could cook.</i>

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Topic	Patient quotes
	<i>I could go to the opera. I could go to Sweden and see my family without having to think about how am I going to handle the flight? Am I going to be able to walk through the airport? Am I actually be able to do anything when I'm there, visiting my sisters, my cousins, my uncle? It was life changing. It gave me my life back. I could be a person instead of a sick person."</i> • <i>"It was like a life changer. All of a sudden, I can go grocery shopping, cook dinners for the family. I can live a fairly normal life. It's 100% better with Elahere. I want to be able to see my grandchildren grow up, and I can't be healthy and do the things I want to do if I didn't have a medication like Elahere to help me.</i> • <i>"To have [MIRV] as an option and to see myself doing so well on it and feeling, you know, next to normal on it, it just gives you peace, it gives you hope...I'm able to be like out in the world and do all the things and live my life. So that's why I feel the way I do about this treatment instead of frontline because I don't have that isolation, you know, I don't feel sick constantly."</i>

Both the economic and HRQoL SLRs (Appendix E and F) were searched for relevant utility values. The economic evaluation reported by Wysham et al (164) used utility values of 0.50 and 0.40 in the progression-free and progressed states, respectively; these values were considered to reflect the poor QoL for chemotherapy patients, and were used in the model for the pooled chemotherapy arm. In the absence of other data for mirvetuximab patients, utility values were derived from the MIRASOL trial using an MMRM approach. The MMRM allows for a natural way to model repeated longitudinal observations, and assumes missing data are missing at random, as opposed to the stronger assumption of missing completely at random assumed by approaches such as generalised estimating equations.

Utility values would be expected to differ substantially between mirvetuximab and chemotherapy patients because:

- In the pre-progression state:
 - Mirvetuximab is associated with higher response rates and reduced time to response compared with pooled chemotherapy (Section 2.6); clinical experts

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- confirmed that reduced tumour volume and disease burden would translate to symptomatic improvement, and with this improved QoL.
- Statistically significant improvements were observed vs IC Chemo in the LSM analysis for the pre-specified exploratory abdominal/gastrointestinal symptom and attitude toward disease and treatment subscales (EORTC QLQ-OV28)
 - AE profiles differ between mirvetuximab and pooled chemotherapy. Mirvetuximab showed a lower frequency of Grade 3+ TEAEs and SAEs. For example, 10% of patients receiving IC Chemo experienced Grade 3+ anaemia, characterised by weakness and low energy, compared with <1% of those on mirvetuximab (Table 15).
 - In the post-progression state:
 - At the point of progression, patients who have received mirvetuximab would have a better QoL compared with pooled chemotherapy, stemming from a reduced tumour volume and disease burden; this benefit is expected to continue into the post-progression state
 - Treatment with mirvetuximab affords the opportunity of saving a chemotherapy line to a later option (14). This approach provides a period of recovery from chemotherapy side effects, whilst targeting the tumour through a different mechanistic approach.
 - Mirvetuximab is associated with improved PFS2 results compared with pooled chemotherapy, and is therefore expected to have improved outcomes and contribute to better QoL due to delayed second progression within the post-progression state.

Treatment-specific utility values have been considered in a previous NICE appraisal in OC, and were incorporated in the committee base case (106).

Base-case utilities are presented in Table 35.

Table 35. Base-case utility values

Health state	Treatment	Utility value
Pre-progression	Mirvetuximab	0.737
	Pooled chemotherapy	0.500
Post-progression	Mirvetuximab	0.655
	Pooled chemotherapy	0.400

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

Scenario analyses are considered in which utility values for both modelled arms are derived from MIRASOL. These analyses consider the following covariates:

- Progression status, treatment allocation, and the interaction between progression status and treatment allocation
- Progression status and treatment allocation
- Progression status only and adjustment for Grade 3+ AEs (with AE disutilities applied separately; see Section 3.4.4).

Utility values used in scenario analyses are presented in Table 36

Table 36. MIRASOL utility values used in scenario analyses

Source		Utility value	
		Pre-progression	Post-progression
Analysis of MIRASOL adjusting for progression status, treatment allocation and the interaction between progression status and treatment allocation	Mirvetuximab	0.732	0.675
	Pooled chemotherapy	0.712	0.596
Analysis of MIRASOL adjusting for progression status and treatment allocation	Mirvetuximab	0.737	0.655
	Pooled chemotherapy	0.706	0.625
Analysis of MIRASOL adjusting for progression status and Grade 3+ AEs		0.724	0.643

Abbreviations: AE, adverse event; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

A summary of base-case utility values is presented in Table 37.

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Table 37. Summary of base-case utility values for cost-effectiveness analysis

State	Utility value: mean (SE)	95% CI		Reference in submission (section and page number)	Justification
		Lower value	Upper value		
Health state utility values					
Pre-progression, Mirvetuximab	0.737	0.711	0.762	Section 3.4.6, page 141	Utility values for mirvetuximab have been derived from MIRASOL, in line with NICE guidance (170); utility values for pooled chemotherapy were taken from the published literature, as the reported values better reflect the quality of life experienced by chemotherapy patients (112).
Pre-progression, pooled chemotherapy	0.500	0.328	0.672		
Post-progression, Mirvetuximab	0.655	0.623	0.687		
Post-progression, pooled chemotherapy	0.400	0.238	0.562		

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

3.5. Cost and healthcare resource use identification, measurement and valuation

3.5.1. Intervention and comparators' costs and resource use

Unit costs for mirvetuximab and pooled chemotherapy are presented in Table 38. Drug acquisition costs for pooled chemotherapy were derived from the drugs and pharmaceutical electronic market information tool (eMIT) (195). Dosing schedules are presented in Section 3.2.3.

The proportions of patients in the pooled chemotherapy arm receiving each of paclitaxel, pegylated liposomal doxorubicin, and topotecan were modelled to be 40.7%, 35.8% and 23.5%, respectively, in line with the observed proportions in the MIRASOL trial (174). This ensures that the efficacy derived from MIRASOL is accurately reflected in the economic model. The proportion of topotecan-treated patients receiving the 4-week cycle dosing was modelled to be 82.0% in line with the MIRASOL trial (174).

Modelled costs were calculated both with and without vial sharing. Costs incorporating wastage (i.e. no vial sharing) were calculated using the method of moments, assuming a normal distribution around the mean BSA or AIBW (Section 3.3.1) from MIRASOL. Costs excluding wastage (i.e. 100% vial sharing) were calculated assuming the average cost per mg across different vial sizes; the only exception to this is topotecan, for which the minimum cost per mg was used^q. In the base-case analysis, it was assumed that vial sharing would occur in 50% of cases. At an AbbVie advisory board, clinical experts based in England/Wales noted that vial sharing was common for paclitaxel and pegylated liposomal doxorubicin. Additionally, during the appraisal of trastuzumab deruxtecan for treating human epidermal growth factor receptor 2 (HER2)-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 treatments, the NHS England Cancer Drugs Fund (CDF) clinical lead confirmed that vial sharing is

^q The minimum cost per mg was used to estimate costs for topotecan excluding wastage because the cost per mg differs substantially across the 1mg and 4mg vial sizes (£49.32 and £15.53, respectively) and it is expected that the 4mg vial size would be used more frequently; use of the average cost per mg results in illogical outcomes in which costs including vial sharing are higher than costs excluding vial sharing.

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encouraged by NHS England, and the committee concluded that vial sharing should be assumed to occur in 50% of cases (196). A similar degree of vial sharing might be expected for mirvetuximab and therefore the same assumption was used. Scenario analyses were performed assuming each of 100% and 0% vial sharing.

Drug acquisition costs have been adjusted using the relative dose intensities (RDI) observed in MIRASOL (Table 39)^r.

^r Note that calculations of RDI used in the model differ from those presented in the MIRASOL CSR; calculations of RDI used in the model do not exclude missed doses, but instead include these as a dose of 0 mg.

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Table 38. Drug acquisition costs

Drug		Unit size (mg)	Units per pack	Cost per pack	Reference
Mirvetuximab	List price	100	1	£4,950	AbbVie
	PAS price		1	██████	
Pooled chemotherapy	Paclitaxel	30	1	£4.79	eMIT (195)
		100	1	£12.89	
		150	1	£22.37	
	Pegylated liposomal doxorubicin	20	1	£189.46	
		50	1	£396.10	
	Topotecan	1	1	£49.32	
		4	1	£62.13	

Abbreviations: eMIT, drugs and pharmaceutical electronic market information tool; PAS, patient access scheme.

Table 39. Relative dose intensity

Drug		Relative dose intensity (%)	Standard error	Reference
Mirvetuximab		██████	██████	Patient-level analysis of MIRASOL trial (September 2024 DCO)
Pooled chemotherapy	Paclitaxel	██████	██████	
	Pegylated liposomal doxorubicin	██████	██████	
	Topotecan (4-week cycle regimen)	██████	██████	
	Topotecan (3-week cycle regimen)	██████	██████	

Abbreviations: DCO, data cut-off.

Total drug costs per administration are presented in Table 40.

Table 40. Total drug cost per administration

Drug		Dose per administration (mg)	Cost per administration
Mirvetuximab		6.00	██████
Pooled chemotherapy	Paclitaxel	80.00	£17.50
	Pegylated liposomal doxorubicin	40.00	£599.98
	Topotecan (4-week cycle regimen)	4.00	£96.11
	Topotecan (3-week cycle regimen)	1.25	£43.60

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Pre-medication costs

Pre-medication dosing schedules were obtained from the clinical trial protocol for MIRASOL and NHS sources (19, 197). The dose per administration for pre-medications is presented in Table 41. Unit costs for pre-medications are presented in Table 42, and were taken from eMIT (195) or the British National Formulary (BNF) (198). Pre-medications were assumed to not incur administration costs, as it was assumed that these would be accounted for in the administration costs already incurred each cycle.

Mirvetuximab and paclitaxel were the only treatments associated with pre-medication. Total pre-medication costs were calculated as £3.93 per drug administration for mirvetuximab, and £2.44 per drug administration for the paclitaxel regimen.

Table 41. Pre-medication dose per administration

Regimen	Pre-medication	Dose per drug administration (mg)	Reference
Mirvetuximab	Paracetamol	650	MIRASOL Trial Protocol (19), Ondansetron SmPC (199), NHS University Hospitals Sussex (200)
	Diphenhydramine	50	
	Dexamethasone (IV)	10	
	Ondansetron	80	
	Prednisolone eye drops	4.2	
	Sodium hyaluronate eye drops	16.8	
Paclitaxel	Dexamethasone (IV)	8	NHS SWAG Cancer Alliance (197)
	Chlorphenamine	10	

Abbreviations: IV, intravenous; NHS, National Health Service; SmPC, Summary of Product Characteristics; SWAG, Somerset, Wiltshire, Avon & Gloucestershire.

Table 42. Pre-medication drug acquisition unit costs

Drug	Unit size (mg)	Unit cost	Reference
Prednisolone eye drops	10	£1.82	BNF (198)
Sodium hyaluronate eye drops	10	£0.52	eMIT (2024) (195)
Paracetamol	500	£0.01	eMIT (2024) (195)
Diphenhydramine	25	£0.03	BNF† (198)
Dexamethasone	3.3	£0.31	eMIT (2024) (195)
Ondansetron	4	£0.06	eMIT (2024) (195)
Chlorphenamine	10	£1.69	eMIT (2024) (195)

†Assumed equivalent to hydroxyzine hydrochloride, in the absence of cost data for diphenhydramine.

Note: Lowest cost per mg was chosen if multiple strengths are available.

Abbreviations: BNF, British National Formulary; eMIT, drugs and pharmaceutical electronic market information tool.

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3.5.2. Administration costs

Unit administration costs were derived from the NHS reference costs 2023/24 based on the route of administration (Table 43) (201). First admittance administration costs (SB12Z, SB13Z, SB14Z) were applied on the first day of each cycle regardless of the number of components administered, and subsequent administration days in the same cycle incurred the subsequent elements administration cost (SB15Z). Note that subsequent administration costs are relevant only for the treatments with more than one day of administration per cycle.

The type of administration cost applied for each treatment was determined in line with the approach taken in NICE TA389 (108), where the selection of the relevant first attendance code was based upon the maximum infusion time recommended within the associated SmPC. For chemotherapy agents considered to require up to 60 minutes infusion time (paclitaxel and topotecan), the cost of SB12Z ('Deliver simple parenteral chemotherapy at first attendance') is applied; for agents considered to require up to 120 minutes infusion time (pegylated liposomal doxorubicin and mirvetuximab), the cost of SB13Z ('Deliver complex parenteral chemotherapy at first attendance') is applied. For subsequent cycles, for paclitaxel and topotecan, the cost of SB15Z ('Deliver subsequent elements of a chemotherapy cycle') is applied.

Table 43. Treatment administration costs

Drug		Administration type	Service	Procedure Code	Cost per administration	Reference
Mirvetuximab		Complex parenteral chemo - first attendance	Outpatient, Medical Oncology	SB13Z	£184.31	NHS reference costs 2023/24 (201)
Paclitaxel	First day	Simple parenteral chemo - first attendance	Outpatient, Medical Oncology	SB12Z	£133.39	
	Subsequent days	IV chemo - subsequent elements	Outpatient, Medical Oncology	SB15Z	£198.08	
Pegylated liposomal doxorubicin		Complex parenteral chemo - first attendance	Outpatient, Medical Oncology	SB13Z	£184.31	
Topotecan	First day	Simple parenteral chemo - first attendance	Outpatient, Medical Oncology	SB12Z	£133.39	
	Subsequent days	IV chemo - subsequent elements	Outpatient, Medical Oncology	SB15Z	£198.08	

Abbreviations: IV, intravenous; NHS, National Health Service.

3.5.3. Post-progression treatment costs

Post-progression therapies received in MIRASOL are presented in Table 44.

In the CEM, costs were included for post-progression therapies used in clinical practice in England and Wales (taxanes, topotecan, anthracyclines and gemcitabine), and for mirvetuximab, as the benefit of crossover/continued use is implicitly captured in the extrapolation of MIRASOL OS data. Experts at a UK advisory board noted the remaining treatments in Table 44 are not routinely part of clinical practice in England and Wales. Included post-progression therapies have been reweighted for use in the model (i.e. to sum to 100%; Table 45). For costing purposes, paclitaxel was assumed to be representative of taxanes, and pegylated liposomal doxorubicin was assumed to be representative of anthracyclines.

Table 44. Post-progression therapies received in MIRASOL

Type of post-progression therapy	Number of patients (%)	
	Mirvetuximab	Pooled chemotherapy
Any new anti-cancer therapy	152 (67.0)	147 (65.0)
Taxanes	80 (35.2)	59 (26.1)
Topotecan	20 (8.8)	24 (10.6)
Platinum compounds	42 (18.5)	42 (18.6)
Anthracyclines	57 (25.1)	21 (9.3)
Chemotherapy (other)	50 (22.0)	56 (24.8)
Bevacizumab	42 (18.5)	35 (15.5)
Hormonal therapy	7 (3.1)	5 (2.2)
Kinase inhibitors	12 (5.3)	10 (4.4)
Mirvetuximab soravtansine	2 (<1)	16 (7.1)
PARP inhibitors	10 (4.4)	7 (3.1)
PD-1/PD-L1 inhibitors	14 (6.2)	16 (7.1)
Gemcitabine	54 (23.8)	58 (25.7)
Other	22 (9.7)	24 (10.6)

Abbreviations: PARP, poly (adenosine diphosphate-ribose) polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

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Table 45. Modelled post-progression therapy use

Type of post-progression therapy	Number of patients in MIRASOL		Modelled proportion of patients	
	Mirvetuximab	Pooled chemotherapy	Mirvetuximab	Pooled chemotherapy
Taxanes (paclitaxel)	80	59	38%	33%
Topotecan	20	24	9%	13%
Anthracyclines (pegylated liposomal doxorubicin)	57	21	27%	12%
Mirvetuximab soravtansine	2	16	1%	9%
Gemcitabine	54	58	25%	33%

The drug acquisition and administration costs for mirvetuximab, paclitaxel, pegylated liposomal doxorubicin and topotecan are presented in Section 3.5.1; acquisition and administration costs for gemcitabine are presented in Table 46 and Table 47, respectively.

The median duration of post-progression treatment use was derived from MIRASOL for mirvetuximab, paclitaxel, pegylated liposomal doxorubicin, and topotecan use (assuming the same duration as for initial treatment in MIRASOL), and published literature for gemcitabine(174, 202-204). Median durations were converted to mean durations assuming an exponential distribution^s. For subsequent topotecan use, it was assumed the proportion of topotecan patients receiving the 4-week cycle dosing was 82.0% as per the MIRASOL trial for pre-progression treatments (Section 3.5.1) (174). A one-off post-progression treatment cost was calculated as the weekly cost of each treatment (acquisition and administration), and the mean duration of each treatment.

The dosing schedule and cost of each post-progression treatment are presented in Table 48. Mean RDI for post-progression treatments were based on those obtained from MIRASOL for mirvetuximab, paclitaxel, pegylated liposomal doxorubicin, and topotecan, and from Mutch et al, 2007 for gemcitabine (184). 50% vial sharing was

^s Mean durations were derived to reflect the average outcomes across the full considered population.

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assumed for post-progressed therapies in line with the assumptions for pre-progression therapies^t. The total one-off cost of post-progression treatment by pre-progression treatment is presented in Table 49.

^t Modelled costs were calculated both with and without vial sharing. Costs incorporating wastage were calculated using the method of moments, assuming a normal distribution around the mean BSA or AIBW from MIRASOL. Costs excluding wastage (i.e. 100% vial sharing) were calculated assuming the average cost per mg across different vial sizes; the only exceptions to this are topotecan and gemcitabine, for which the minimum cost per mg was used to prevent illogical outcomes.

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Table 46. Post-progression drug acquisition unit costs

Drug	Unit size (mg)	Unit cost	Reference
Gemcitabine	2,000	£19.74	eMIT (2024) (195)

Abbreviations: eMIT, drugs and pharmaceutical electronic market information tool.

Table 47. Post-progression drug administration costs

Drug	Administration type	Service	Procedure Code	Cost per administration	Reference
Gemcitabine	First day	Simple parenteral chemo - first attendance	Outpatient	SB12Z	£133.39
	Subsequent days	IV chemo - subsequent elements	Outpatient	SB15Z	£198.08

Abbreviations: IV, intravenous; NHS, National Health Service.

Table 48. Dosing schedule and cost of each post-progression treatment

Post-progression treatment		Dosing schedule	RDI	Total weekly cost [†]	Median treatment duration (weeks)	One-off treatment cost	Reference for treatment duration
Mirvetuximab	List price	6 mg/kg (AIBW) Q3W	████	████	18.79	████	MIRASOL (174)
	PAS price			████		████	
Taxanes (paclitaxel)		80 mg/m ² 4 days x 4-week cycle	████	£199.41	15.64	£4,500	
Anthracyclines (pegylated liposomal doxorubicin)		40 mg/m ² 1 day x 4-week cycle	████	£196.07	8.14	£2,303	
Topotecan (4-week cycle regimen)		4 mg/m ² 2 days x 4-week cycle	████	£463.12	7.71	£5,154	
Topotecan (3-week cycle regimen)		1.25 mg/m ² 4 days x 3-week cycle	████	£154.09	19.71	£4,382	
Gemcitabine		1,000 mg/m ² 3 days x 4-week cycle	90.8%	£145.06	11.74	£2,457	Mutch 2007 (184)

[†]Comprised of acquisition and administration costs

Abbreviations: AIBW, adjusted ideal body weight; Q3W, once every 3 weeks; PAS, patient access scheme; RDI, relative dose intensity.

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Table 49. Post-progression treatment costs by pre-progression treatment

Pre-progression treatment	Percentage of progressed patients receiving post-progression treatment	One-off cost	Reference
Mirvetuximab	67%	■	MIRASOL (174)
Pooled chemotherapy	65%	■	

3.5.4. Health-state unit costs and resource use

Health state resource use

The disease management cost associated with each health state included costs of visits to healthcare professionals and computed tomography (CT) scans. Unit costs of resource use were obtained from NHS reference costs and are summarised in Table 50(201). The frequencies of resource use were obtained from the NICE TA285 submission for bevacizumab for platinum-sensitive advanced OC, and are summarised for the pre-progression (Table 51) and post-progression (Table 52) health states (205).

Table 50. Unit cost of resource use

Procedures and monitoring services	Unit cost	NHS reference costs service code	Reference
Gynaecological oncology consultation	£192.39	503	NHS reference costs 2023/24 (201)
CT scan	£118.58	RD20A-RD21A, RD22Z-RD27Z (weighted average)	

Abbreviations: CT, computed tomography; NHS, National Health Service.

Table 51. Pre-progression annual resource use

Procedures and monitoring services	Annual frequency [†]	Reference	Weekly pre-progression resource use costs
Gynaecological oncology consultation	12	NICE TA285 (205)	£57.88
CT scan	6		

[†]Reflects the annual resource use frequency in all arms.

Abbreviations: CT, computed tomography; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

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Table 52. Post-progression annual resource use

Procedures and monitoring services	Annual frequency [†]	Reference	Weekly post-progression resource use costs
Gynaecological oncology consultation	4	NICE TA285 (205)	£14.75

[†]Reflects the annual resource use frequency in all arms.

Abbreviations: NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

3.5.5. Adverse reaction unit costs and resource use

Included safety-related costs were adverse event costs, and additional monitoring and treatment for ocular AEs for mirvetuximab, in line with the SmPC.

Adverse event costs

Treatment-related Grade 3+ AEs with incidence $\geq 5\%$ in any arm of the MIRASOL trial were included in the model (Section 3.3.7) (174). The unit cost of each Grade 3–4 AE was derived from the NHS reference costs 2023/24 (201) (Table 53), with the exception of fatigue, for which the unit cost was based on TA528 (107).

For neutropenia, thrombocytopenia, and anaemia, costs were derived from the NHS reference costs 2023/24 in line with currency codes used in NICE TA1007 (107). A weighted average cost was calculated based on complication and comorbidity (CC) scores of 2 or greater using unit costs from day cases, non-elective inpatient (long and short stay), and regular day or night admissions (as per NICE TA1007); CC scores of 2 or greater were assumed given that presence of ovarian cancer would indicate a minimum CC score of 1. The same approach was adopted for cataracts.

It was assumed in the model that AE costs would be incurred as a one-time cost upon model entry (Table 54).

Table 53. AE unit costs

Adverse event	Unit cost	Reference
Anaemia	£1,032.51	NHS reference costs - Year 2023/24, Total HRGs, Iron Deficiency Anaemia with CC Score 2-14+, weighted average of SA04K-G, including day case, non-elective inpatient long-stay, non-elective inpatient short-stay, regular day or night admissions (201)
Cataract	£1,425.50	NHS reference costs - Year 2023/24, Total HRGs, Phacoemulsification Cataract Extraction and Lens Implant, with CC Score 2-4+, weighted average of BZA34A-B, including day case, non-elective inpatient long-stay, non-elective inpatient short-stay, regular day or night admissions (201)
Fatigue	£447.46	TA528 (£353.06), inflated to 2023/24 using PSSRU inflation indices (107, 173)
Keratopathy	£165.15	NHS reference costs 2023/24, cost of outpatient ophthalmology visit, currency code WF01B, service code 130 (201)
Neutropenia	£1,921.57	NHS reference costs - Year 2023/24, Total HRGs, Neutropenia with CC Score 2-6+, weighted average of SA08H-G including day case, non-elective inpatient long-stay, non-elective inpatient short-stay, regular day or night admissions (201)
Thrombocytopenia	£1,257.59	NHS reference costs – Year 2023/24, Total HRGs, Thrombocytopenia with CC Score 2-8+, weighted average of SA12J-G including day case, non-elective inpatient long-stay, non-elective inpatient short-stay, regular day or night admissions (201)
Vision blurred	£165.15	NHS reference costs 2023/24, cost of outpatient ophthalmology visit, currency code WF01B, service code 130 (201)

Abbreviations: AE, adverse event; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

A summary of the total one-off AE cost for each comparator are presented in Table 54.

Table 54. Total one-off AE cost

Treatment	Total one-off AE cost
Mirvetuximab	£218.27
Pooled chemotherapy	£1,077.42

Abbreviations: AE, adverse event.

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Additional monitoring and treatment for ocular AEs for mirvetuximab

Additional monitoring and treatment for ocular AEs was included for mirvetuximab patients in line with the mirvetuximab SmPC (13), and feedback from clinical experts at the AbbVie November 2024 advisory board.

The SmPC states that:

- An ophthalmic exam including visual acuity and slit lamp exam should be conducted before the initiation of mirvetuximab, and if a patient develops any new or worsening ocular symptoms prior to the next dose.
- In patients with Grade 2+ ocular adverse reactions, additional ophthalmic exams should be conducted at a minimum of every other cycle and as clinically indicated until resolution or return to baseline.
- For patients with Grade 2+ keratopathy, secondary prophylaxis with ophthalmic topical steroids is recommended for subsequent cycles of mirvetuximab, unless the patient's eye care professional determines that the risks outweigh the benefits of such therapy.
- Patients should be instructed to use steroid eye drops on the day of infusion and through the next 7 days of each subsequent cycle of mirvetuximab.
- During treatment with ophthalmic topical steroids, the measurement of intraocular pressure and an examination with slit lamp should be carried out regularly.

Parameters used to derive the total cost of additional monitoring and treatment for ocular AEs are presented in Table 55; the total cost is calculated to be £586.73.

Table 55. Ocular event monitoring and treatment for mirvetuximab-treated patients

Component	Value	Reference
Cost per ophthalmologist visit	£165.15	National Schedule of NHS costs - Year 2023/24. Outpatient Attendances, Ophthalmology Service, consultant led (206)
Corticosteroid eye drops	–	–
Cost per unit	£1.82	BNF. Prednisolone eye drops, 10 ml (198)
Unit size (mg)	10.00	BNF. Prednisolone eye drops, 10 ml (198)
Dose per administration (mg)	4.20	Assumed equal to mirvetuximab pre-medication dose
Cost per administration	£0.76	Calculated
% of patients who require a pre-treatment ophthalmic exam	100%	All patients require an ophthalmic exam prior to the initiation of mirvetuximab. Note that an ophthalmic exam is assumed to incur the cost of one ophthalmologist visit.
Mean number of Grade 2+ ocular AEs in mirvetuximab patients	1.90	AbbVie data on file (14). Table 14.3.1.17.1. Ocular Treatment Emergent Adverse Events by Preferred Term and Maximum CTCAE Grade. Safety population
Frequency of eye drop infusions per cycle	8.00	Assumed on the day of infusion and through the next 7 days of each cycle
Duration of Grade 2+ ocular AEs (weeks)	4.00	Assumption
% of patients with Grade 2+ keratopathy	25%	AbbVie data on file (14). Table 14.3.1.17.1. Ocular Treatment Emergent Adverse Events by Preferred Term and Maximum CTCAE Grade. Safety population
Frequency of additional ophthalmologist visits per week for patients with Grade 2+ keratopathy	0.17	Assumed that patients with Grade 2+ keratopathy require ophthalmologist visits every cycle to monitor both the ocular AE and the steroid use. An additional visit is therefore required every other cycle, as patients with Grade 2+ ocular AEs are already assumed to require an ophthalmologist visit once every two cycles.
Mean duration of treatment (weeks)	30.31	AbbVie data on file (14). Table 14.2.9.1. Study Drug Exposure

Abbreviations: AE, adverse event; BNF, British National Formulary; CTCAE, Common Terminology Criteria for Adverse Events; NHS, National Health Service.

3.5.6. Miscellaneous unit costs and resource use

Testing costs

Patients receiving mirvetuximab were assumed to incur FR α testing costs at model entry. The proportion of screened patients with FR α positive expression was 32% in the MIRASOL trial; therefore, approximately three tests were required to identify one patient with FR α positive expression (1). In NICE Medtech Innovation Briefing (MIB) 135, the cost of 30–45 minutes of pathologist time to conduct a similar test was £117; inflating this value from 2018/19 to 2022/23 gives a current cost of £[REDACTED]. The cost of a kit containing [REDACTED] FR α tests is [REDACTED]; therefore, each test was calculated to cost [REDACTED]. Therefore, the estimated cost to detect one patient with FR α positive expression is estimated as [REDACTED] (Table 56).

Table 56. Testing costs

		Value	Reference
% PROC patients that test positive for FR α		32%	Moore et al, 2023 (1)
Cost per FR α test	Pathologist time	[REDACTED]	NICE MIB135 (£117), inflated from 2018/19 to 2023/24 using PSSRU indices (173, 207)
	Cost of consumables	[REDACTED]	AbbVie internal
Total cost to detect one patient with mutation		[REDACTED]	[REDACTED]

Abbreviations: FR α , folate receptor alpha; MIB, Medtech Innovation Briefing; NICE, National Institute for Health and Care Excellence; PROC, platinum-resistant ovarian cancer; PSSRU, Personal Social Services Research Unit.

Terminal care costs

In the model, patients were assumed to incur one-time terminal care costs before death to reflect palliative and hospice-related care. The terminal care cost per death was taken from the Personal Social Services Research Unit (PSSRU) 2024 (173), which reported the average cost of hospital care and social services per person in the final year of life. This also gave a breakdown by diagnostic groups, and for cancer was £13,964 for hospital and social care. This is assumed to apply to 100% of those that die, as it is an average (Table 57).

Table 57. Terminal care costs

	Value	Reference
Terminal care cost	£13,964.00	PSSRU 2024 (173)

Abbreviations: PSSRU, Personal Social Services Research Unit.

3.6. Severity

OC is a severe type of cancer, the deadliest gynaecological cancer (5) and the 6th leading cause of cancer deaths in females in the United Kingdom (UK; 2017–2019) (2). Notably, patients with PROC have a very poor prognosis and the worst survival outcomes among patients with OC, with a median OS of ≤12 months and a PFS typically 3–4 months (5), and experience a substantial symptom and QoL burden (5). In the past decade, clinical studies of many novel anti-cancer therapies have failed to make a substantial impact in the treatment of PROC, highlighting the unmet need in this population (10). Importantly, no large, randomised Phase 3 study in PROC has shown a statistically significant OS benefit (114), and in the last decade there have been five NICE appraisals in the PROC population which have been discontinued or suspended (43-47).

As noted in Section 1.3.2, most patients with PROC become increasingly symptomatic with abdominal pain due to malignant ascites, increasing tumour mass leading to bowel obstruction, an inability to tolerate medication or food, and declining performance status precluding further anticancer therapy (10). This is further evidenced by the patient experiences shared with AbbVie, where patients shared that the most challenging symptoms were:

- **Recurrent ascites** – *“having to be drained time and time again, or having a permanent drain, feeling like you’re living in a distorted body, actual draining is a very traumatic experience”.*
- **Bowel obstructions** – *“[patients] are absolutely terrified about this. If they are following low fibre diet, they feel incredibly socially isolated because suddenly they can’t go out for meals anymore or if they do, it takes extraordinary amounts of planning and looking at menus in advance”.*

Many patients also experience toxic side effects with currently available therapies, as confirmed in patient perspectives shared with AbbVie (89):

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- *“I lost probably 40 pounds. I couldn’t eat. I had to go to the hospital once a week to get fluid infusions, because I couldn’t drink, because everything came up. It was absolutely horrible. If this was going to be my life, that was the end of it. I didn’t really want to continue like that.”*
- *“The fatigue that always accompanies you even when climbing the very few stairs to your apartment. And the hair was starting to fall out. You kind of lose your identity as well, because you look in the mirror and you don’t recognise yourself.”*

Notably, these treatment-related AEs can have such a negative impact on QoL that patients with advanced OC are willing to trade meaningful PFS time in order to avoid severe AEs, highlighting the substantial treatment burden of this disease (48).

In order to determine the relevant severity modifier for this appraisal, proportional and absolute QALY shortfall were calculated in line with NICE DSU TSD 23 (208). General population utility values were derived from Hernandez-Alava et al, 2022 (190), and general population mortality values were taken from life tables published by the ONS for the years 2017-19 (183), in line with NICE DSU guidance (208). Based on a mean age at baseline of 59.2 years and a 100% female population, the expected discounted QALYs for people without OC was 12.861.

Patients treated with pooled chemotherapy would be expected to accrue 0.552 discounted QALYs, resulting in an absolute QALY shortfall of 12.309 and a proportional QALY shortfall of 96%. A severity modifier of 1.7 therefore applies.

Table 58. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Proportion female (%)	100% (Table 21)	Section 3.3.2
Starting age (years)	59.2 (Table 21)	

Abbreviations: QALY, quality-adjusted life year.

Table 59. Summary of health state benefits and utility values for QALY shortfall analysis

State	Utility value (pooled chemotherapy): mean	Undiscounted life years (pooled chemotherapy)
Pre-progression	0.5	0.427
Post-progression	0.4	0.898

Abbreviations: QALY, quality-adjusted life year.

Table 60. Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall
12.861	0.552	12.309	96%

Abbreviations: QALY, quality-adjusted life year.

3.7. Uncertainty

The MIRASOL trial was the primary clinical evidence source informing inputs in the economic model. This robust clinical trial provided a head-to-head, Phase 3, RCT of mirvetuximab and IC Chemo, the relevant comparators for this submission. Clinical experts in England and Wales confirmed the population in MIRASOL broadly aligns with UK clinical practice.

The MIRASOL trial had a median OS follow-up of 30.49 months and was associated with mature data which informed key clinical, HRQoL, and cost data for the model. PFS and DoT were mature in both arms, and median OS was reached, however OS data were subject to a high degree of censoring towards the end of the study. At the end of trial follow-up, 44 and 18 patients remained alive in the mirvetuximab and pooled chemotherapy arms, respectively; long-term outcomes for these patients therefore remain unknown. OS extrapolations for mirvetuximab and pooled chemotherapy were derived as per guidance from NICE DSU TSD14 and validated at an AbbVie advisory board by clinical experts (178). Scenario analyses were

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conducted to test the impact of alternative distributions on the incremental cost-effectiveness ratio (ICER).

Potential uncertainty associated with modelled assumptions and the robustness of the base-case analysis were explored through extensive sensitivity analysis. The impact of structural and parameter uncertainty was explored in univariate sensitivity analysis, probabilistic sensitivity analysis, and scenario analysis. Results of these analyses are presented in Section 3.11.

3.8. Managed access proposal

As noted in Section 3.7, this appraisal is informed by mature, head-to-head, randomised trial data from MIRASOL. The economic analysis is associated with low uncertainty, sensitivity analysis resulted in a probabilistic ICER that is highly congruent with the deterministic ICER, and scenario analyses estimated a range of ICERs between [REDACTED] to [REDACTED]. Therefore, the company consider that mirvetuximab is most appropriate for routine commissioning.

3.9. Summary of base-case analysis inputs and assumptions

3.9.1. Summary of base-case analysis inputs

A summary of base-case model inputs is presented in Table 61.

Table 61. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
General parameters			
Discount rate, costs	3.5%	Fixed	Section 3.2.2
Discount rate, outcomes	3.5%	Fixed	
Time horizon	40.8	Fixed	
Patient characteristics			
Starting age (years)	59.2	Fixed	Section 3.3.1
% Female	100%	Fixed	
BSA (m ²)	1.73	Fixed	
Body mass (kg)	68.84	Fixed	
AIBW (kg)	59.05	Fixed	
Survival extrapolations			

Variable		Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
OS distribution	Mirvetuximab	Loglogistic	Multivariate normal	Section 3.3.3
	Pooled chemotherapy	Weibull	Multivariate normal	
PFS distribution	Mirvetuximab	Lognormal	Multivariate normal	Section 3.3.4
	Pooled chemotherapy	Lognormal	Multivariate normal	
DoT approach	Mirvetuximab	Exponential	Multivariate normal	Section 3.3.5
	Paclitaxel	Equal to observed KM in MIRASOL	Fixed	
	Pegylated liposomal doxorubicin	Equal to observed KM in MIRASOL	Fixed	
	Topotecan	Equal to observed KM in MIRASOL	Fixed	
Adverse events				
Grade 3/4 AEs		Table 32	Beta (CI: +/- 20% around mean)	Section 3.3.7
Utility values				
Utility value (inclusive of Grade 3+ AEs)	Pre-progression, mirvetuximab	0.737	Beta (CI: 0.711-0.762)	Section 3.4.6
	Pre-progression, pooled chemotherapy	0.500	Beta (CI: 0.328 - 0.672)	
	Post-progression, mirvetuximab	0.655	Beta (CI: 0.623 – 0.687)	
	Post-progression, pooled chemotherapy	0.400	Beta (CI: 0.238 – 0.562)	
Pre-progression treatment costs				
Mirvetuximab		Table 38	Fixed	Section 3.5.1
Paclitaxel			Fixed	
Pegylated liposomal doxorubicin			Fixed	
Topotecan			Fixed	
RDI	Mirvetuximab	██████	Beta (CI: ████████)	Section 3.5.1
	Paclitaxel	██████	Beta (CI: ████████)	

Variable		Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
	Pegylated liposomal doxorubicin		Beta (CI:)	
	Topotecan (4-week cycle regimen)		Beta (CI:)	
	Topotecan (3-week cycle regimen)		Beta (CI:)	
Pre-medication drug costs	Acetaminophen	Table 42	Fixed	Section 3.5.1
	Diphenhydramine		Fixed	
	Dexamethasone		Fixed	
	Ondansetron		Fixed	
	Prednisolone eye drops		Fixed	
	Sodium hyaluronate eye drops		Fixed	
	Chlorphenamine		Fixed	
Post-progression treatment costs				
Mirvetuximab		Table 38	Fixed	Section 3.5.3
Taxanes (paclitaxel)			Fixed	
Topotecan			Fixed	
Anthracyclines (pegylated liposomal doxorubicin)			Fixed	
Gemcitabine		Table 38	Fixed	
Post-progression treatment proportions				
Mirvetuximab arm – Mirvetuximab %		Table 45	Dirichlet	Section 3.5.3
Mirvetuximab arm – Taxanes %				
Mirvetuximab arm – PLD %				
Mirvetuximab arm – Topotecan %				
Mirvetuximab arm – Gemcitabine %				
Pooled chemo arm – Mirvetuximab %				
Pooled chemo arm – Taxanes %				
Pooled chemo arm – PLD %				
Pooled chemo arm – Topotecan %				
Pooled chemo arm – Gemcitabine %				
Administration costs				
Simple parenteral chemo - first attendance		£133.39	Gamma (+/- 20% around mean)	Section 3.5.2
Complex parenteral chemo - first attendance		£184.31	Gamma (+/- 20% around mean)	

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Variable		Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
IV chemo - subsequent elements		£198.08	Gamma (+/- 20% around mean)	
AE costs				
Unit costs		Table 54	Gamma (CI: +/- 20% around mean)	Section 3.5.5
Ocular event monitoring and treatment		Table 55	Gamma (CI: +/- 20% around mean)	Section 3.5.5
Disease management costs				
Pre-progression, outpatient visit annual frequency		12	Gamma (CI: +/- 20% around mean)	Section 3.5.4
Pre-progression, CT scan annual frequency		6	Gamma (CI: +/- 20% around mean)	
Pre-progression, CT scan annual frequency		4	Gamma (CI: +/- 20% around mean)	
Outpatient visit, unit cost		£192.39	Gamma (CI: +/- 20% around mean)	
CT scan, unit cost		£118.58	Gamma (CI: +/- 20% around mean)	
Testing cost				
% PROC patients that test positive for FRα		32%	Beta (CI: +/- 20% around mean)	Section 3.5.6
Cost of FRα test	Pathologist cost	£ [REDACTED]	Gamma (CI: +/- 20% around mean)	
	Cost of consumables	£ [REDACTED]	Gamma (CI: +/- 20% around mean)	
Terminal care costs				
Terminal care cost		13,964	Gamma (CI: +/- 20% around mean)	Section 3.5.6

Abbreviations: AE, adverse event; AIBW, adjusted ideal body weight; BSA, body surface area; CI, confidence interval; CT, computerised tomography; DoT, duration of treatment; IV, intravenous; OS, overall survival; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer; RDI, relative dose intensity.

3.9.2. Assumptions

Key assumptions considered in the base case analysis are summarised in Table 62.

Table 62. Key model assumptions for the base case analysis

Assumption	Justification
The PH assumption does not apply between mirvetuximab and pooled chemotherapy for OS and PFS	The PH assumption was tested by assessing the log-log plots and the Schoenfeld residuals. These plots did not necessarily suggest that the PH assumption was violated; however, experts at an AbbVie advisory board noted that given the differing mechanisms of action between mirvetuximab and pooled chemotherapy, independent survival models may be more appropriate.
The loglogistic distribution was selected to extrapolate OS for mirvetuximab	Of the distributions suggested by clinicians, all were associated with similar statistical goodness of fit apart from the exponential distribution, but the log-logistic predicts survival at 5 years consistent with clinical expert opinion, is associated with a hazard consistent with the observed data and allows for some patients treated with mirvetuximab to experience long-term survival in line with clinical trial results.
The Weibull distribution was selected to extrapolate OS for pooled chemotherapy	The Weibull distribution is associated with the best statistical fit, assessed using the AIC and BIC statistics and considered appropriate by clinical experts in a series of validation meetings.
The lognormal distribution was selected to extrapolate PFS for mirvetuximab and pooled chemotherapy	PFS data were mature for each of mirvetuximab and pooled chemotherapy and all modelled extrapolations provided a close estimation of PFS to each other. The log-normal distribution was selected in the base case for both mirvetuximab and pooled chemotherapy based on clinical expert opinion and statistical goodness of fit.
KMs from MIRASOL were used directly to model DoT for pooled chemotherapy	DoT data for pooled chemotherapy was mature for each of paclitaxel, pegylated liposomal doxorubicin, and topotecan. The observed DoT curves were also validated by three clinicians in England/Wales.
Different sources of utilities are used for mirvetuximab and pooled chemotherapy	Utility values for mirvetuximab have been derived from MIRASOL, in line with NICE guidance (188); utility values for pooled chemotherapy were taken from the published literature, as the reported values better reflect the quality of life experienced by chemotherapy patients (113).
AE disutilities are not modelled explicitly	In the base-case analysis, AE disutilities were not modelled as the HRQoL impact of AEs was assumed to be implicitly captured within health state utility values. To assess the impact of this assumption, a scenario analysis was performed in which AE disutilities are modelled.

Assumption	Justification
DoT is capped with PFS	At an AbbVie advisory board, clinical experts agreed that they would not expect patients receiving treatment with either mirvetuximab or pooled chemotherapy to continue receiving the same treatment after experiencing disease progression.
Patients treated with mirvetuximab containing regimens were assumed to incur testing costs for FR α status	FR α status testing is required for treatment eligibility with mirvetuximab

Abbreviations: AEs, adverse event; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; DCO, data cut-off; DoT, duration of treatment; FR α , folate receptor alpha; HRQoL, health-related quality of life; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; PH, proportional hazards.

3.10. Base-case results

All results are presented with a severity modifier of 1.7 applied to the QALYs (Section 3.6); unweighted results are presented for reference in the base-case analysis only.

3.10.1. Base-case incremental cost-effectiveness analysis results

Mirvetuximab is associated with incremental QALYs of [REDACTED] and incremental costs of [REDACTED], resulting in a ICER of [REDACTED] (Table 63).

For reference, the unweighted results are presented in Table 64.

Appendix H presents the clinical outcomes and disaggregated results.

Table 63. Base-case results (deterministic) – mirvetuximab PAS price – weighted QALYs (severity modifier: 1.7)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)	NHB at £30,000
Pooled chemotherapy	██████	██████	██████	–	–	–	–	–
Mirvetuximab	██████	██████	██████	██████	██████	██████	██████	██████

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

Table 64. Base-case results (deterministic) – mirvetuximab PAS price – unweighted QALYs (no severity modifier)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)	NHB at £51,000
Pooled chemotherapy	██████	██████	██████	–	–	–	–	–
Mirvetuximab	██████	██████	██████	██████	██████	██████	██████	██████

Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years.

3.11. Exploring uncertainty

3.11.1. Probabilistic sensitivity analysis

Joint parameter uncertainty was tested through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly, using 1,000 Monte Carlo simulations.

A summary of the results of the PSA is presented in Table 65. Mirvetuximab is associated with incremental QALYs of [REDACTED] and incremental costs of [REDACTED], resulting in a ICER of [REDACTED] (Table 65). The probabilistic ICER is congruent with the deterministic ICER of [REDACTED] per QALY (Table 63). The proportion of simulations where mirvetuximab was considered to be cost-effective, considering an ICER threshold of £30,000 per QALY, was [REDACTED] %.

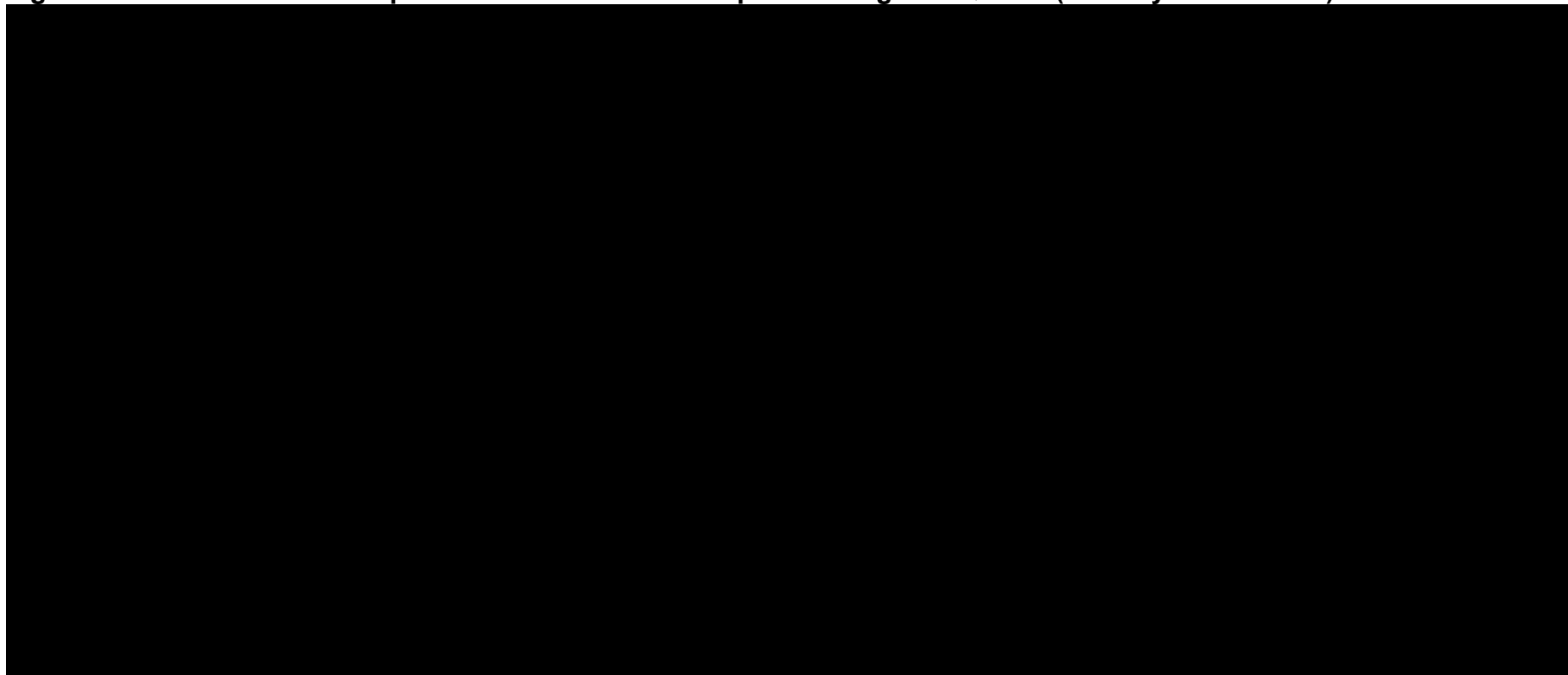
The cost-effectiveness plane and cost-effectiveness acceptability curve are presented in Figure 40 and Figure 41 below.

Table 65. Base-case results (probabilistic) – mirvetuximab PAS price – weighted QALYs (severity modifier: 1.7)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)	NHB at £30,000
Pooled chemotherapy	[REDACTED]	[REDACTED]	=	–	–	–
Mirvetuximab	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

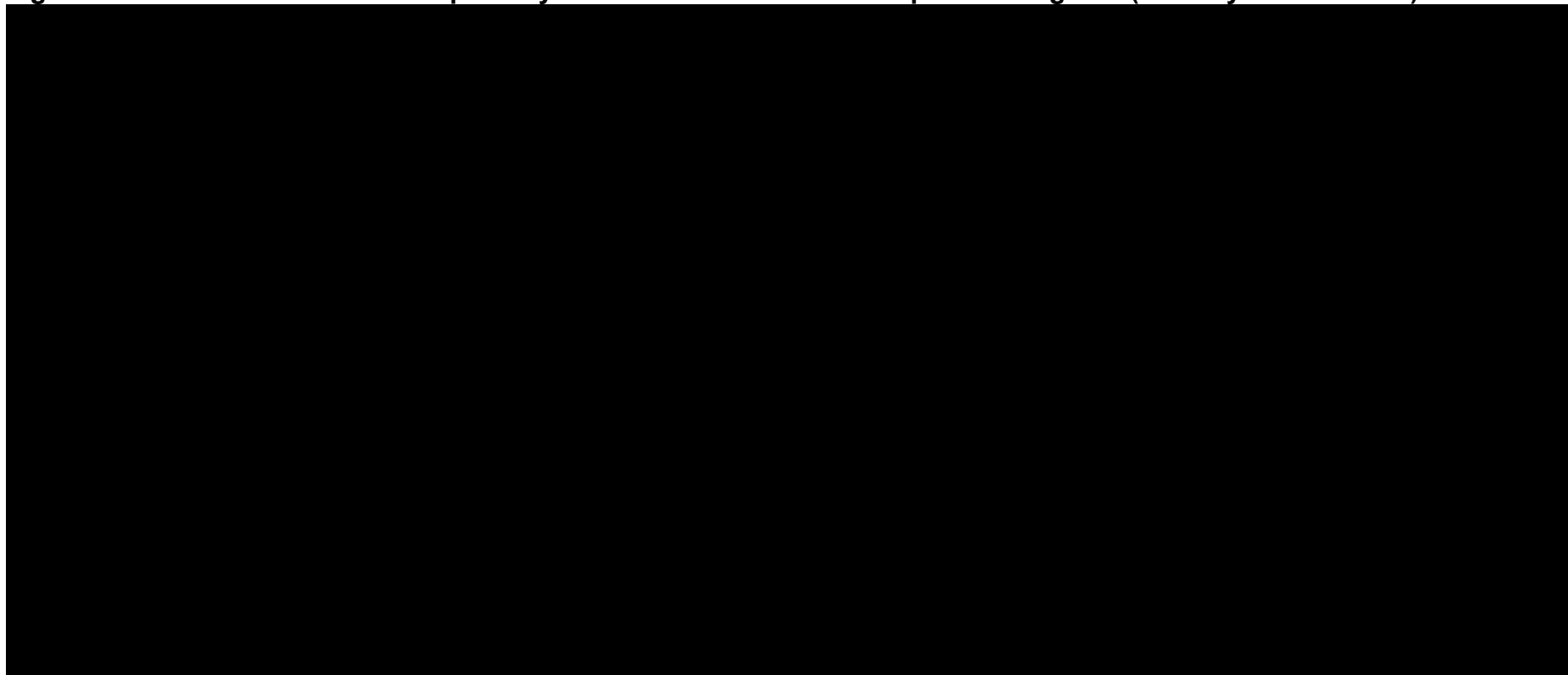
Abbreviations: ICER, incremental cost-effectiveness ratio; NHB, net health benefit; PAS, patient access scheme; QALYs, quality-adjusted life years.

Figure 40. Cost-effectiveness plane – mirvetuximab PAS price – weighted QALYs (severity modifier 1.7)



Abbreviations: PAS, patient access scheme.

Figure 41. Cost-effectiveness acceptability curve – mirvetuximab PAS price – weighted (severity modifier: 1.7)



Abbreviations: PAS, patient access scheme.

3.11.2. Deterministic sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% CI, or $\pm 20\%$ of the mean value where no estimates of precision were available.

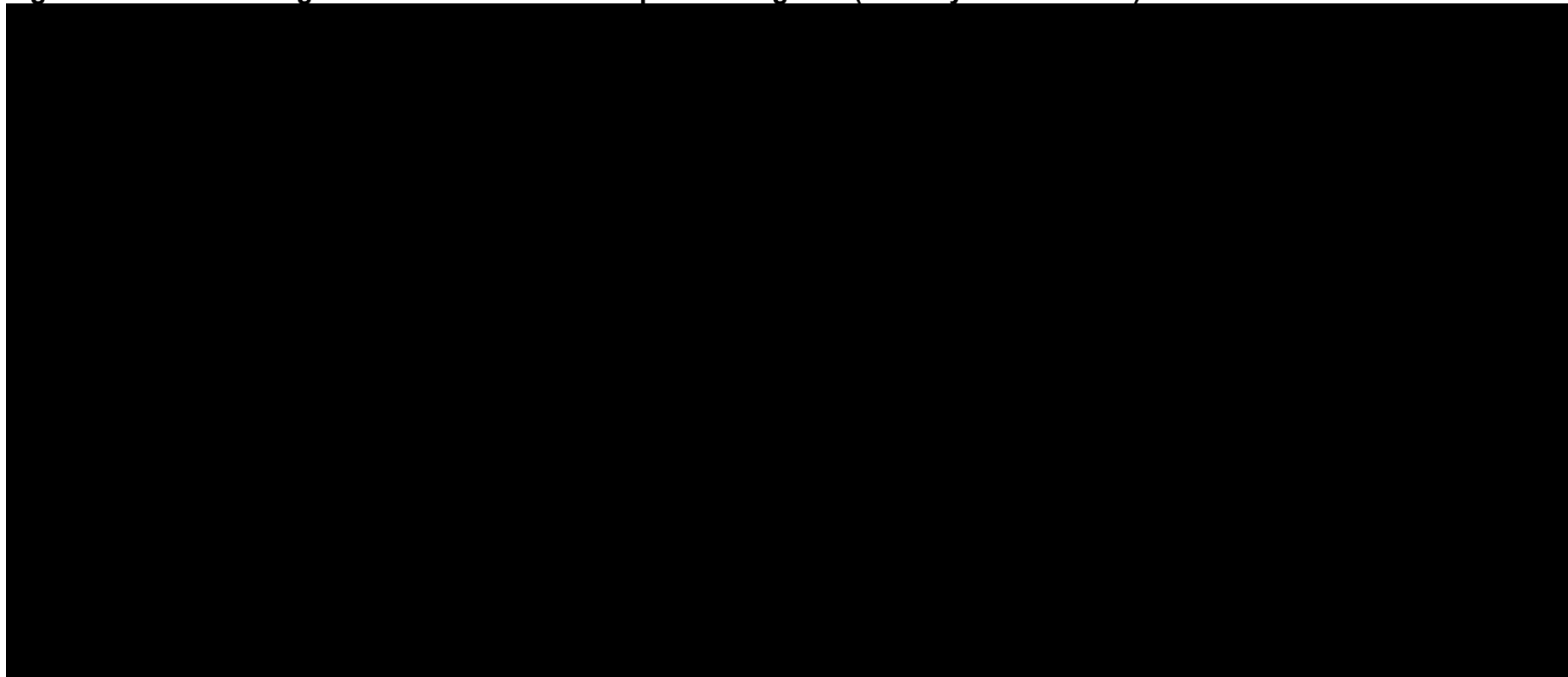
Results for the 10 most influential parameters are presented in Table 66, and the tornado diagram is presented in Figure 42. The most influential parameters were those associated with the parameters defining the OS extrapolation for mirvetuximab, and the post-progression utility value for pooled chemotherapy.

Table 66. Deterministic sensitivity analysis results – mirvetuximab PAS price

Parameter	Weighted (severity modifier: 1.7)	
	ICER at lower value of parameter	ICER at upper value of parameter
OS - Mirvetuximab - Log-Logistic - scale	██████	██████
Post-progression utility value, chemotherapy (base case)	██████	██████
OS - Mirvetuximab - Log-Logistic - shape	██████	██████
DoT - Exponential - Parameter rate - Mirvetuximab	██████	██████
Pre-progression utility value, chemotherapy (base case)	██████	██████
OS - Pooled chemotherapy - Weibull - scale	██████	██████
Post-progression utility value, mirvetuximab (base case)	██████	██████
Relative Dose Intensity - Mirvetuximab	██████	██████
Post-Prog Trt Cost - % of progressed patients receiving post-progression treatment - Pooled chemotherapy	██████	██████
Pre-progression utility value, mirvetuximab (base case)	██████	██████

Abbreviations: DoT, duration of treatment; ICER, incremental cost-effectiveness ratio; OS, overall survival; Post-prog, post progression; PAS, patient access scheme; Trt, treatment.

Figure 42. Tornado diagram – mirvetuximab PAS price - weighted (severity modifier: 1.7)



Abbreviations: PAS, patient access scheme.

3.11.3. Scenario analysis

The results of scenario analyses are presented in Table 67; all scenario analyses lay within the range of [REDACTED] to [REDACTED] per QALY. The scenarios associated with the greatest change in ICER were the OS distributions for mirvetuximab, and utility values.

Table 67. Scenario analysis – mirvetuximab PAS price

Scenario	Base case assumption	Results – weighted QALYs (severity modifier: 1.7)			
		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change from base case ICER
Base case	-	██████	██████	██████	██████
OS distribution- Joint models, Weibull (best statistical fit by AIC & BIC)	Independent models: • Mirvetuximab: loglogistic • Pooled chemotherapy: Weibull	██████	██████	██████	██████
PFS distribution - Joint models lognormal (best statistical fit by AIC & BIC)	Independent models • Mirvetuximab: lognormal • Pooled chemotherapy: lognormal	██████	██████	██████	██████
PFS distribution – mirvetuximab – log-logistic		██████	██████	██████	██████
PFS distribution – mirvetuximab – generalized gamma		██████	██████	██████	██████
PFS distribution – pooled chemotherapy – generalized gamma		██████	██████	██████	██████
OS distribution - mirvetuximab - exponential	Independent models: • Mirvetuximab: loglogistic	██████	██████	██████	██████
OS distribution - mirvetuximab - log-normal		██████	██████	██████	██████
OS distribution - mirvetuximab - Gompertz		██████	██████	██████	██████
OS distribution - mirvetuximab - gamma		██████	██████	██████	██████
OS distribution - mirvetuximab - generalized gamma		██████	██████	██████	██████
OS distribution - mirvetuximab - Weibull		██████	██████	██████	██████
OS distribution - pooled chemotherapy - exponential	Independent models: • Pooled chemotherapy: Weibull	██████	██████	██████	██████
OS distribution - pooled chemotherapy - log-logistic		██████	██████	██████	██████
OS distribution - pooled chemotherapy - log-normal		██████	██████	██████	██████
OS distribution - pooled chemotherapy - Gompertz		██████	██████	██████	██████
OS distribution - pooled chemotherapy - gamma		██████	██████	██████	██████
OS distribution - pooled chemotherapy - generalized gamma		██████	██████	██████	██████
DoT - mirvetuximab - Gamma	Exponential	██████	██████	██████	██████

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Scenario	Base case assumption	Results – weighted QALYs (severity modifier: 1.7)			
		Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change from base case ICER
DoT - pooled chemo - best fitting curves (paclitaxel - gompertz, PLD - gamma, topotecan - exponential)	Equal to observed KM's	██████	██████	██████	██████
Utility model - Progression status and treatment type (with interaction term)	MIRASOL for mirvetuximab, and published literature for chemotherapy	██████	██████	██████	██████
Utility model - Progression status and treatment type (not adjusted for AEs)		██████	██████	██████	██████
Utility model - Progression status only (adjusted for AEs)		██████	██████	██████	██████
100% vial sharing	Assumed that vial sharing would occur in 50% of cases	██████	██████	██████	██████
0% vial sharing		██████	██████	██████	██████

Abbreviations: AE, adverse event; AIC, Akaike information criterion; BIC, Bayesian information criterion; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life year.

3.12. Subgroup analysis

Not applicable.

3.13. Benefits not captured in the QALY calculation

As detailed in Section 1.4, the treatment landscape for PROC has seen no new treatments in two decades. The current landscape is associated with few treatment options, none of which are targeted therapies (1, 5-9, 27). The introduction of mirvetuximab to the treatment landscape brings a targeted therapy that is associated with improved survival and reduced AE burden compared with current standard of care (1, 14). The introduction of a new, innovative treatment into the current landscape may contribute to addressing some of the UK's ongoing health priorities (16-18): cancer, women's health, and precision medicine. Health economic models also show that precision medicine reduces unnecessary treatments and hospitalisations by ensuring that only the patients most likely to benefit from specific therapies receive them, thus lowering overall healthcare costs (128).

PROC is a severe disease and recurrent OC (including PROC) is associated with a negative impact on emotional wellbeing compared with women who are newly diagnosed (42). Alopecia, although it did not meet the threshold for inclusion as an AE within the economic model, is known to be a particularly disturbing side effect for patients (87, 88). The incidence of alopecia was lower with mirvetuximab compared with IC Chemo in MIRASOL, demonstrating a potentially positive impact on wellbeing.

The value of hope for a new treatment as expressed by patients in an area that has seen no new treatment for decades, is an important consideration that cannot be quantified as part of the QALY, and has been discussed in the literature (209, 210).

Spillover effects to other parts of society of improved health from mirvetuximab, such as on productivity are also important to mention. The treatment and management of patients with OC, including PROC, has also been shown to place considerable burden on carers (40). In one study, 55% of caregivers reported feeling moderately or extremely anxious or depressed (90). Additionally, treatment and management of patients with PROC is associated with considerable patient and caregiver time for

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travelling to or receiving treatment, with a corresponding reduction in productivity for patients and carers of a working age (92-97). The Adelphi RWE study commissioned by AbbVie in five countries, including the UK, found that caregivers for patients with PROC spend an average of 35.4 hours per week providing care, with partners/spouses spending 26.0 hours per week and children over 18 years spending 24.1 hours per week (80).

Last, the economic model only included a comparison against single-agent non-platinum chemotherapies, per NICE scope. According to the National Ovarian Cancer Audit, 27% of women with advanced OC (Stage II–IV) did not receive any form of treatment (surgery or chemotherapy) (31), and this trend continues in patients with PROC. It is plausible that a proportion of these women would instead opt for mirvetuximab, were it available on the NHS, as it is a treatment with a different and improved AE profile compared with the currently available chemotherapy options. Insights provided by AbbVie’s clinical experts suggest that untreated patients with PROC would be expected to have a very poor prognosis, with median OS of as little as 2 months. Therefore, accounting for this cohort of potential patients within the economic model could increase the expected incremental QALYs of mirvetuximab.

3.14. Validation

3.14.1. Internal validation

Quality control of the economic model was performed by the model developers and by health economists not involved in the development of the model. This included:

- Cell-by-cell checks of formulae
- Rebuilding of key sections of the model to ensure consistent outcomes
- Logical tests (for example testing extreme values such as around discounting or time horizon, tests around the clinical inputs such as setting effectiveness to be the same between arms to check outcomes are the same, and tests around utilities and costs and seeing if the change in result is what would be expected).

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3.14.2. External validation

External validation of model outcomes was performed for mirvetuximab and pooled chemotherapy. The model results were consistent with the results of the MIRASOL trial (Table 68).

Table 68. External validation – comparison of model outcomes

	Mirvetuximab		Pooled chemotherapy	
	MIRASOL result (95% CI)	Base case model result	MIRASOL result (95% CI)	Base case model result
Median OS (months)	16.85 (14.36, 19.78)	16.33	13.34 (11.37, 15.15)	13.34
Median PFS (months)	5.59 (4.34, 5.88)	5.06	3.98 (2.86, 4.47)	3.45

Abbreviations: CI, confidence interval; DoT, duration of treatment; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin.

3.14.3. Clinical validation

Expert opinion was sought to validate base-case assumptions. An advisory board was held in November 2024 and included two oncologists representing different centres in England and Wales and two independent health economists. Expert opinion was sought on the following:

- Chemotherapy dosing regimens
- Validation of long-term survival estimates, proportional hazards assumptions, and choice of base case distribution
- AE assumptions, including AE disutilities, durations, and costs
- Choice base case utility model approach
- Vial sharing assumptions
- Proportion of patients receiving subsequent therapy by treatment arm.

Further clinical opinion was sought from phone interviews with three clinical experts, who were presented with clinical data from MIRASOL to further aid in the selection of long-term survival estimates, in addition to discussion of the above topics.

3.15. Interpretation and conclusions of economic evidence

3.15.1. Strengths and limitations of the analysis

A key strength of the analysis is that the modelled population of adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens is in line with the anticipated marketing authorisation for mirvetuximab and based on the Phase 3, head-to-head MIRASOL trial compared with IC Chemo, a comparator which is reflective of therapies used in UK clinical practice.

The use of patient-level data from the MIRASOL trial allowed robust evidence for efficacy, safety, and health state utility inputs (where appropriate). Various survival extrapolation methods were explored, with the most plausible extrapolations selected following a review of model fit statistics and clinical validity. The uncertainty in survival extrapolations is expected to be modest given the maturity of data. It is noted that substantial censoring at the tail of the KM for OS has meant that it cannot be considered to be as informative as the earlier portion of the KM; however, this has been extensively explored in sensitivity analysis.

The PSM structure directly reflected the MIRASOL efficacy data and comprehensively captures the costs and health outcomes of patients over the modelled time horizon. In addition, the model was built with sufficient flexibility to allow for a range of sensitivity analyses to confirm the robustness of results.

3.15.2. Results of the cost-effectiveness analysis

At the patient access scheme (PAS) price and including a severity modifier of 1.7, mirvetuximab is associated with incremental QALYs of [REDACTED] and incremental costs of [REDACTED], resulting in an ICER of [REDACTED] per QALY. Results were robust to alternative assumptions in sensitivity and scenario analyses. Deterministic and probabilistic results were consistent, with ICERs of [REDACTED] and [REDACTED] per QALY, respectively. As the first targeted therapy in PROC via FR α expression, and the first treatment to demonstrate a statistically significant OS benefit in a Phase 3 trial in PROC vs chemotherapy, mirvetuximab offers a cost-effective treatment option vs chemotherapy for patients with PROC, thus addressing an area of high unmet need.

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3.15.3. Conclusions

For patients with FR α positive PROC, mirvetuximab presents an innovative treatment option, offering a targeted approach that drives rapid and durable responses, thereby actively reducing the volume of tumour burden, delaying disease progression, and prolonging survival in patients with FR α positive PROC. The results of the economic analyses presented in this submission demonstrate that compared with pooled chemotherapy, mirvetuximab represents a cost-effective use of NHS resources for these patients.

Furthermore, as demonstrated in the budget impact analysis, mirvetuximab being indicated for FR α positive PROC patients, is associated with a limited and a predictable budget impact.

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Appendices

- Appendix A: Summary of product characteristics (SmPC) and UK public assessment report
- Appendix B: Identification, selection and synthesis of clinical evidence
- Appendix C: Subgroup analysis
- Appendix D: Adverse reactions
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**NATIONAL INSTITUTE FOR HEALTH AND
CARE EXCELLENCE**

Single technology appraisal

**Mirvetuximab soravtansine for treating folate
receptor alpha-positive platinum-resistant
advanced epithelial ovarian, fallopian tube or
primary peritoneal cancer [ID6442]**

Summary of Information for Patients (SIP)

June 2025

File name	Version	Contains confidential information	Date
ID6442_Mirvetuximab_PROC_SIP_[no CON]	1.0	No	17/06/2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [JTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic: Mirvetuximab soravtansine

Brand name: ELAHERE™

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Mirvetuximab soravtansine (referred to as mirvetuximab throughout this document) is to be used by adult patients with high grade serous ovarian cancer (OC)[†] originating in the:

- Epithelial surface layer covering the ovaries
- Fallopian tubes (the tubes connecting ovaries to the uterus)
- Primary peritoneum (the membrane lining the abdomen)

Mirvetuximab is to be used when the cancer has returned within 6 months after being treated with a platinum-based chemotherapy (i.e. the cancer is resistant to this treatment and called platinum-resistant ovarian cancer [PROC]) and in patients who have received one to three prior systemic treatment regimens (treatments that work throughout the whole body).

Mirvetuximab is to be used in patients who are folate receptor-alpha (FR α) positive specifically i.e. whose cancer cells have high expression of a protein on the surface known as FR α . A biomarker test for FR α expression helps identify patients who will benefit most from mirvetuximab.

- To be able to receive mirvetuximab, patients must have high FR α expression. High expression is when $\geq 75\%$ of cancer cells have moderate or strong staining intensity when tested, known as 2+ intensity.

Summary of information for patients for mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

†High grade serous is the most common type of epithelial OC and describes how the cells look under a microscope. In the United Kingdom (UK) there are four Grades, from 1 to 4. The more abnormal the cells look, the higher the grade. Higher grade cancers (Grade 3+) grow more quickly than low grade cancers.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The anticipated marketing authorisation by the Medicines and Healthcare products Regulatory Agency (MHRA) for the UK is for the treatment of adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens. Please see Section 1.2 of the company submission for expected dates for MHRA approval.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AbbVie works with a range of organisations that have an interest in OC. This includes working with patient groups with lived experience of OC, to support improvements in health and care for individuals. Any collaborations that have involved funding (e.g. to support the development of information for patients and their families) are declared every year and are available at: <https://www.abbvie.co.uk/our-company/policies-disclosures.html>

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Ovarian cancer (OC) – disease course

OC is rare and diagnosed late. It develops when the abnormal cells in the ovaries, fallopian tubes and primary peritoneum grow in an uncontrolled way. Each year, approximately 7,110 people are diagnosed with OC in England (1) and 310 people in Wales (2). Symptoms of OC can include abdominal pain or bloating, urinary urgency or increased frequency, and gastrointestinal symptoms (3). As these symptoms are not specific to OC, it is not always clear that this is what is causing them. When these symptoms exist, they could be mistaken for other conditions, resulting in approximately 70% of patients having advanced disease at the time of diagnosis (meaning that the cancer has already spread beyond the pelvis) (4). Additionally, younger patients find it harder to get a diagnosis since the average age for diagnosis is skewed towards older women. Around 90% of

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all OC starts in the epithelium (the surface of the ovaries/fallopian tubes) (5), and around 70% of these are classed as high-grade serous (6).

Patients with newly diagnosed OC are typically treated with either surgery and/or platinum-based chemotherapy. While the cancer may initially respond to treatment, for the majority of patients (~80%), the cancer may reoccur (known as a relapse) after treatment (7, 8). Relapsed OC is associated with a shorter response to treatment than in the newly diagnosed phase, and eventually almost all patients will become resistant to platinum-based therapy, known as PROC (7, 9).

Platinum-resistant ovarian cancer – the focus of this submission

What are the clinical symptoms of PROC?

Patients with PROC can experience symptoms caused by the progression of their disease as the cancer spreads. This includes pain, fatigue, abdominal swelling, and being unable to perform even necessary daily activities (such as eating and taking anticancer medications) (10, 11). The most challenging symptoms for patients are bowel obstructions, recurrent ascites (when fluid builds up in the abdomen), and pleural effusions (when fluid builds up between the lungs and the chest wall).

What is the outlook for patients with PROC?

Platinum resistance influences the likely outcome of every patient with OC, and represents one of the key factors impacting survival outcomes (12). Patients with PROC have a very poor outlook and worse survival outcomes than both untreated patients and those whose cancer is still responding to platinum-based treatment, with a median overall survival (the length of time from the start of treatment that half of the patients are still alive) of 12 months or less (13).

What is the impact of PROC on quality of life?

Cancer-related symptoms and treatment side effects can have a considerable negative impact on a patient's quality of life, including the psychosocial burden this diagnosis brings. Patients with OC (including those with PROC) experience higher levels of psychological distress compared with people in the general population or people with other types of cancer (14). People with OC in the UK are almost twice as likely to experience depression and over four times more likely to experience anxiety compared with people without OC (15). OC also has a large impact on family and other personal relationships, as well as work, volunteering, and hobbies (16). Many patients report limitations in daily tasks such as moving a table, hoovering, going for a walk or bicycle ride, and climbing several flights of stairs (17). Over 50% of patients with PROC require additional support/care, help with transportation, house cleaning or maintenance, and 38% require help with shopping and preparing meals, or managing finances (18).

Patients with advanced OC (including PROC) also experience side effects caused by their treatment, which can negatively impact their quality of life (19-24). For example, patients can experience side effects from multiple rounds of cancer treatment, such as tiredness, vomiting, diarrhoea, and hair loss (19-21). Chemotherapy can also lead to blood-related side effects, such as anaemia (when the blood has a reduced ability to carry oxygen due to low levels of haemoglobin) and neutropenia (when you have too few white blood cells), which significantly impact a patient's quality of life. Anaemia for example, means patients have low energy and feel weak. In a study involving 102 patients with PROC, 73% said that they were "bothered by their treatment side effects", including feeling sick and experiencing hair loss (25). These side effects not only increase the treatment burden but can also increase the risk of patients stopping treatments early (7, 26, 27). Patient testimonies highlight the significant negative impact chemotherapy can have on their quality of life, stating that it is "traumatic", and side effects such as an inability to eat or drink meant that they "didn't really want to continue" if "that was my life", or that "in the first year [they] didn't want to go anywhere" and so "missed weddings and different life events" (28). A patient also reported the feeling of "losing [their] identity" following hair loss (28). The negative impact of PROC also extends to family members and caregivers, with 42–55% of caregivers reporting anxiety (29, 30).

Taken together, there is a clear unmet need for new therapies offering improved survival for patients with PROC, that also improve or maintain quality of life. Improving outcomes among women, and outcomes for rare and less common cancers are key areas of Government focus, along with embracing innovation (31-35).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Initial diagnosis of ovarian cancer

OC is usually diagnosed through a series of tests, including a physical examination, blood test, and an ultrasound scan. However, signs and symptoms of early-stage OC often go unreported, meaning it can take a long time for some patients to receive a diagnosis. As such, most women are diagnosed with advanced OC, which means the cancer has spread to other parts of the body beyond the pelvis (4). Moreover, younger patients encounter additional health disparities because they are frequently overlooked in ovarian cancer diagnoses, as the average age for this diagnosis is skewed toward older women. Diagnosis with platinum resistant OC, which is the focus of this appraisal, is diagnosed based on the length of time between the end of a course of platinum-based chemotherapy and the point when the cancer comes back (typically when the cancer comes back within 6 months it is considered to be platinum resistant) (36).

Additional diagnostic tests for treatment with mirvetuximab

To receive treatment with mirvetuximab, patients must test positive for high levels of a protein on the surface of tumour cells called folate receptor-alpha. This is a type of biomarker test that uses a small sample of available tumour tissue to check if a patient is positive for this protein. The test is registered with the UK regulatory body and can be used to identify patients with PROC who are eligible for treatment with mirvetuximab. As mirvetuximab requires this positive biomarker test to be confirmed before treatment can be started, it is considered a “targeted” treatment. This approach means that the treatment is tailored to individual patients and enables the identification of patients most likely to benefit from mirvetuximab.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

How is OC initially treated?

Treatment for OC generally comprises surgery and platinum/taxane based chemotherapy, depending on disease stage (26). Current first-line (initial) treatments for advanced OC are platinum-doublet based chemotherapies (patients will often receive a medicine called carboplatin or cisplatin with paclitaxel for a certain number of cycles) with the addition of bevacizumab for some patients (Figure 1).

How successful is initial treatment for OC?

While the cancer may initially respond well to platinum-based chemotherapy, most patients (~80%) eventually relapse (13, 37). The response to chemotherapy lessens with each disease relapse, rendering OC incurable and eventually becoming resistant to these treatments (Section 2a). These patients are referred to as 'platinum-resistant' and are unlikely to respond to further chemotherapies that contain platinum compounds and consequently, further treatment options become limited.

How is PROC treated?

PROC is a severe and incurable phase of OC. Therefore, the goal of treatment is to control the disease and minimise the progression of the disease, while maximising or maintaining quality of life (38-40). Treatment guidelines used in England recommend nonplatinum chemotherapies, with NICE recommending paclitaxel (Taxol®) and pegylated liposomal doxorubicin (PLD; Caelyx®) (41), and the British Gynaecological Cancer Society (BGCS) recommending paclitaxel, PLD, and topotecan (Hycamtin®) (36) (the BGCS are a medical society in the UK who are dedicated to improving the care of patients with gynaecological cancers). All three of these treatments are non-platinum, single treatments that affect the whole body (systemic treatments) and are not targeted therapies (treatments that target specific features on the cancer cells).

How successful is the treatment for PROC?

Treatment options for patients with PROC are extremely limited, with a lack of new treatments in the PROC setting in England/Wales for two decades (11). Clinical outcomes for patients treated with available therapies are poor, with patients surviving on average for less than 12 months, and average progression-free survival (how long before a patient's disease worsens) being 3–4 months (13, 42-45).

These treatments are also associated with several side effects, often without any improvement in disease-related symptoms (36). Side effects of treatment can include (but are not limited to) tiredness, vomiting and diarrhoea, blood-related side effects (e.g. anaemia and neutropenia), and hair loss, and all of these can negatively impact a patient's quality of life (19-21). Notably, around half of women undergoing chemotherapy report hair loss as the most disturbing aspect of chemotherapy treatment (46, 47). These side effects do not just increase patient burden and negatively affect quality of life, but can lead to patients stopping treatment altogether (10, 27, 48-50).

Additionally, none of the current treatment options are targeted therapies, which the BGCS has highlighted as a key area of further development as targeted treatments may lead to improved outcomes and fewer side effects (36). As such, there is a considerable unmet need in PROC for targeted treatments that are well tolerated and increase survival for patients who have exhausted platinum-based therapies.

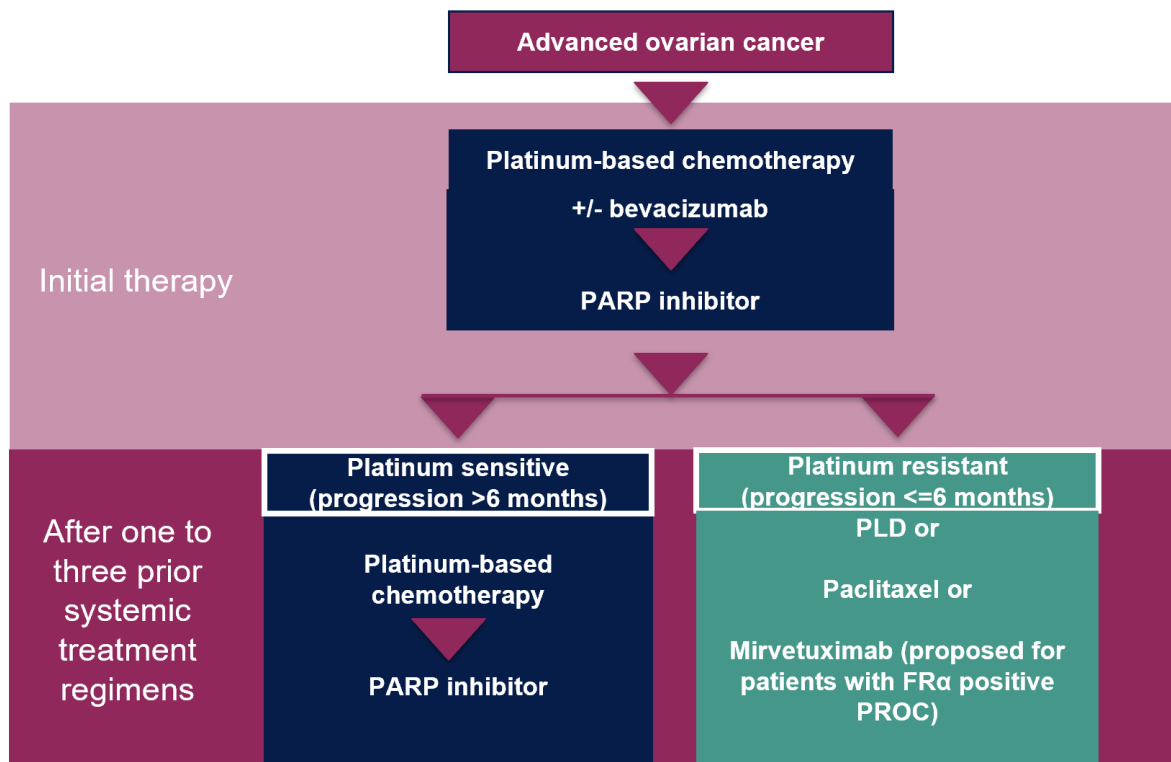
Where does mirvetuximab fit in the treatment pathway?

Mirvetuximab is expected to be used in patients with PROC who test positive for high levels of expression of a protein called folate receptor-alpha (FR α). Approximately one third of patients with PROC have a high level of FR α in their tumours (7).

The treatment pathway showing the proposed use of mirvetuximab is summarised in Figure 1: for the treatment of adult patients with FR α positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens.

Mirvetuximab is anticipated to be the first targeted therapy for the treatment of PROC via FR α expression, providing eligible patients with an alternative treatment option that improves clinical outcomes.

Figure 1: Proposed positioning of mirvetuximab the NICE treatment pathway†



†For full details of the pathway, please see Figure 4 in the company submission dossier, Section 1.3.3. Abbreviations: FR α , folate receptor alpha; NICE, National Institute for Health and Care Excellence; PARP, poly (ADP-ribose) polymerase; PLD, pegylated liposomal doxorubicin; PROC, platinum resistant ovarian cancer.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

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Patient-based evidence in the Phase 3 trial of mirvetuximab (MIRASOL)

Patient-reported quality of life measures were included as an outcome in the MIRASOL trial. Further information is reported in Section 3e of the SIP and Section 2.6 of the company evidence submission.

Patient-based evidence in the literature

Several publications in the literature describe patient-reported experiences of living with PROC. The patient-based evidence confirms that patients experience debilitating disease-related symptoms and burdensome side effects from treatment, both of which can have a substantial negative impact on quality of life (10, 17).

- In one observational study of 903 patients with OC (223 of whom had PROC), the most common and severe patient-reported symptoms at baseline included swollen stomach, bloating, stomach pain, discomfort and/or cramps, fatigue, anorexia, and anxiety (10).
- Another study looking at symptoms and quality of life of patients with PROC found that the most common disease-related symptoms were fatigue (92%), worry (89%), and trouble sleeping (76%) (25). A second study, focusing on quality of life, symptoms, and care needs in patients with persistent or recurrent PROC reported similar symptoms, but also found that 73% of patients were bothered by treatment side effects, such as nausea, skin issues, and hair loss (25). This study also reported a number of areas where patients felt they needed more support, including caregiving, mental health care, financial, illness distress, and physical health care needs (25).
- Another study of 126 patients with PROC reported that 44% of chemotherapy-treated patients experienced pain, 37% experienced fatigue, and 32% abdominal bloating/discomfort (48).
- For patients with PROC, treatment is also associated with a reduction in productivity for patients of working age, and an inability to work for patients and their caregivers due to time restraints (51-56).
- A study of 798 people with OC and 373 caregivers reported that over 42% of caregivers experience elevated anxiety (29), demonstrating the extent of the burden of this disease.
- A higher number of patients whose OC has reported limitations in daily activities such as moving a table, using a vacuum cleaner, going for a walk or a bicycle ride, and climbing stairs compared with patients whose OC had not returned (17).

Evidence from AbbVie's focus group discussion with a UK patient group

- Initial diagnosis: *"There are additional barriers to diagnosis. For every older person who's told it's menopause, there's a younger person being told you're too young for ovarian cancer."*
- Health inequalities: *"<45 years group and rarer OC group are historically poorly served because of the demographic statistically being older. They face additional health inequalities because they are going to find it harder to get a diagnosis; they have to self-advocate for specific tests they need."*
- Symptoms of PROC: *"Patients are terrified about bowel obstructions and if they are following low fibre diet, they feel incredibly socially isolated because suddenly they can't go out for meals anymore. Having to be drained repeatedly or having a permanent drain for recurrent ascites feels like you are living in a distorted body and the actual draining experience is traumatic."*
- Meaningful outcomes for patients: *"It is really about quality of life at this stage. Patients don't want to prolong life at any cost. It is not even a big bucket list. It is about being able to spend a good time with family, see their friends, enjoy their garden."*
- Experience with current treatments: *"Patients worry about the efficacy. They are aware that they are having to take a decision to do something that's going to make them feel rotten without actually knowing what the outcome is going to be."*
- Unmet need: *"Choice is the greatest unmet need. Patients find themselves in a scary place as they feel like the options are running out as they are not responding to platinum anymore."*

Evidence from UK patient groups' responses to NICE draft scope

As part of the submission process to NICE, patient groups were invited to comment on the scope of the mirvetuximab submission. Three patient groups (Ovacome, Ovarian Cancer Action, and Target Ovarian Cancer) noted that there is an urgent need for patients with PROC to be able to access effective treatment options, highlighting the lack of current treatments and negative impact PROC has on quality of life (16):

- Ovacome highlighted the lack of treatments available and the worry that patients with PROC experience, stating that *"There is an awareness among our community that there are a lack of effective treatment options for platinum resistant ovarian cancer. Being told that their cancer is platinum resistant is a source of deep distress to many of our members. They have shared their concerns that treatment options are limited and lines of treatment to control the disease will be exhausted leaving symptom control only. Being able to access effective treatment options offers a significant psychological benefit as well as physical health benefits."*
- Target Ovarian Cancer highlighted the impact OC can have on patients' quality of life, noting that *"Ovarian cancer can impact family and other personal relationships as well work volunteering and hobbies all of which can affect quality of life"*.
- One patient group from an OC charity (Ovacome) informed NICE that many people with OC find relapsing more distressing than their initial diagnosis (57).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Mechanism of action

Mirvetuximab targets specific proteins on the surface of cancer cells (folate receptor-alpha [FR α]). Mirvetuximab is a type of medicine called an antibody-drug conjugate (ADC), which is made up of a monoclonal antibody (a protein that binds to specific targets) that is chemically linked to a cancer-killing drug.

Treatment with mirvetuximab requires a patient to have high levels of expression of FR α (Figure 2) (58-60). Increased levels of FR α are related to chemotherapy resistance and poor clinical outcomes, and is therefore a good target for new treatments (61, 62). Folate receptor-alpha levels are assessed using a biomarker test on a small sample of available tumour tissue. Mirvetuximab works by binding to these proteins on the cancer cell and enters the cancer cell, where it releases a chemical that is toxic to cancer cells called DM4. This disrupts the ability of the cancer cells to grow and causes the cancer cells to die.

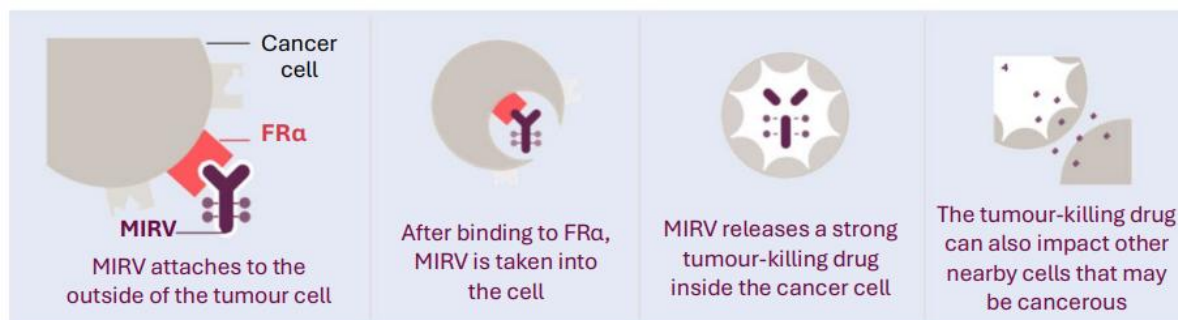
Mirvetuximab also kills nearby cancer cells that do not express FR α through a "bystander effect". Although these nearby cancer cells do not express high levels of the protein that mirvetuximab targets, mirvetuximab is toxic to surrounding cancer cells and is able to kill these cancer cells as well.

Summary of information for patients for mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Innovation

If approved, mirvetuximab would add a new, targeted treatment option to the PROC treatment pathway in the UK (11); its novel mechanism of action means it is the first available therapy which kill cancer cells by targeting FR α on the surface of tumour cells to deliver the part of the drug which kills the cells (DM4). Importantly, FR α is present in large amounts on tumour cells, but very little on healthy cells, meaning it specifically targets and kills cancer cells. By delivering cancer treatment directly to the tumour, mirvetuximab represents a substantial technical innovation and supports personalised cancer therapy for individual patients in a disease area where treatment options are limited. In addition, mirvetuximab is well tolerated, with patients reporting fewer serious side effects compared with currently used chemotherapy treatments.

Figure 2: Mirvetuximab mechanism of action



Abbreviations: FR α , folate receptor-alpha; MIRV, mirvetuximab.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Mirvetuximab is not intended to be used in combination with any other medicine.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

The recommended dose of mirvetuximab is based on a calculation of 6 mg per kg of adjusted ideal body weight (AIBW) every 3 weeks as an intravenous infusion (delivering the medicine directly into the bloodstream) until the disease gets worse or until side effects from the treatment are too severe

Summary of information for patients for mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

to be managed. Dosing based on AIBW reduces exposure variability for patients who are either under or overweight, which improves efficacy while minimising side effects.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The key clinical evidence for mirvetuximab used in this submission is data from the September 2024 data cut-off (median duration of follow-up is 28.4 months) from the completed Phase 3 trial called MIRASOL (Table 1). In this study, patients received mirvetuximab by intravenous infusion every 3 weeks at the same dose being assessed by NICE.

Table 1: Overview of the MIRASOL trial

Study name	MIRASOL (NCT04209855)
Study design	Phase 3, randomised, open-label study of mirvetuximab vs chemotherapy
Population	Adult patients with platinum-resistant, advanced high-grade serous epithelial ovarian, primary peritoneal (the membrane lining the abdomen), or fallopian tube (the tubes connecting ovaries to the uterus) cancers with high folate receptor-alpha expression ($\geq 75\%$ expression and a positive stain intensity of 2+) [†]
Location	136 global sites enrolled 453 patients (30 patients were enrolled in the UK)
Intervention	Mirvetuximab (6 mg/kg AIBW Q3W)
Comparators	Chemotherapy, as chosen by the investigator prior to randomisation (Investigators choice of chemotherapy means that clinicians chose the most appropriate treatment for each patient, from a choice of paclitaxel, PLD, and topotecan): • Paclitaxel (80 mg/m²) administered QW within a 4-week cycle (on Days 1, 8, 15, and 22) • PLD (40 mg/m²) administered Q4W • Topotecan (4 mg/m²) administered either on Days 1, 8, and 15 Q4W or for 5 consecutive days (1.25 mg/m² Days 1–5) Q3W.
Analysis	In the results section (3e), 'statistically significant' refers to the outcome of a statistical test, and means that the results are very unlikely to have happened by chance and much more likely to have happened due to a specific cause (e.g. receiving mirvetuximab)

[†]A scoring method used to assess folate receptor-alpha expression.

Abbreviations: AIBW, adjusted ideal body weight; PLD, pegylated liposomal doxorubicin; Q3W, every 3 weeks; Q4W, every 4 weeks; QW, every week; UK, United Kingdom.

Patients could take part in the MIRASOL trial if:

- They were over 18 years of age
- Had PROC
- Had high FR α expression
- Had received at least 1 but no more than 3 previous treatments.

Summary of information for patients for mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

More information on the MIRASOL trial is available in Section 2.3 of the company evidence submission.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Primary outcome: progression-free survival

- Progression-free survival measures the length of time during which the cancer is not growing or spreading, and is well established as an important outcome for clinical trials in OC (63, 64).
 - In the MIRASOL trial after 28.4 months of observation, the primary objective was met, as mirvetuximab showed a statistically significant 37% reduction in the risk of the cancer worsening or death compared with investigator's choice of chemotherapy. On average, the cancer did not progress for 5.6 months with mirvetuximab compared with 4.0 months in patients who were treated with chemotherapy.

Key secondary outcomes: overall survival and objective response rate

- Overall survival measures the length of time patients are alive after the start of treatment.
 - Mirvetuximab demonstrated a statistically significant improvement in overall survival compared with chemotherapy, representing a 32% reduction in the risk of death with mirvetuximab compared with chemotherapy. The median overall survival for patients who received mirvetuximab was approximately 3.5 months longer than with chemotherapy (16.9 months with mirvetuximab vs 13.5 months with chemotherapy).
- Objective response rate is the percentage of patients whose tumours shrink or disappear after receiving treatment. A complete response is defined as all signs of cancer having disappeared, and a partial response is when a cancer has shrunk in size but has not completely disappeared.
 - Objective response rate with mirvetuximab was more than double that with chemotherapy (41.9% compared with 15.9%, respectively). Around 6% of patients who received mirvetuximab also had a complete response, compared with 0% of patients who received chemotherapy. Additionally, 36% of patients on mirvetuximab achieved a partial response vs 16% of patients treated with chemotherapy.

Secondary outcomes

- Duration of response, which is a measure of how long the cancer stays smaller or undetectable.
 - The average duration of response in MIRASOL was statistically significantly longer in patients who were treated with mirvetuximab compared with chemotherapy (6.9 months compared with 4.4 months, respectively)
- Time to second disease progression, which measures how long a patient's cancer stays under control from the start of the first treatment through to the end of the second treatment's effectiveness

- Mirvetuximab-treated patients had a statistically significant and clinically meaningful 41% reduction in time to second disease progression compared with chemotherapy.

Detailed efficacy results are available in Section 2.6 of the company evidence submission.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQoL-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life was measured in the MIRASOL clinical trial using a number of different measures:

- EORTC QLQ-OV28: A questionnaire used to assess quality of life associated with OC including categories such as: abdominal/gastrointestinal (stomach area), peripheral neuropathy (pain or numbness in the hands or feet), sexual functioning, and attitude to disease and treatment.
 - The results of the EORTC QLQ-OV28 questionnaire demonstrated a significant improvement in the 'Abdominal/Gastrointestinal symptoms' and 'Attitude to Disease and Treatment' categories when assessing the changes from baseline to Weeks 8/9, 15/16 and 24 in patients who received mirvetuximab compared with those that received chemotherapy, while none of the categories favoured chemotherapy.
- EQ-5D-5L: A questionnaire used to assess five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
 - When assessed using the visual analogue scale (where patients mark a point on a line representing a range of values to assess their overall health), results significantly favoured the mirvetuximab arm at Weeks 8/9, Weeks 15/16, and Week 24, showing that patient's perception of overall health was maintained among patients treated with mirvetuximab while decreasing across time for IC Chemo group.
- EORTC QLQ-C30: A questionnaire used to assess quality of life associated with cancer including categories such as: global health status/quality of life, physical functioning, role functioning and fatigue symptoms.
 - The results of the EORTC QLQ-C30 questionnaire demonstrated a statistically significant improvement in the categories mentioned when assessing the changes from baseline to Weeks 8/9, 15/16 and 24 in patients who received mirvetuximab compared with those that received chemotherapy

These questionnaires were completed by patients participating in the MIRASOL clinical trial before starting treatment, and again several times during the trial. Across the patient-reported outcome measures, there was a trend towards 'meaningful improvement' or 'stability' with mirvetuximab treatment, whilst a trend towards 'deterioration' was observed with chemotherapy.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

All treatments have side effects, and the same treatment can produce different side effects in different people. In the MIRASOL trial, mirvetuximab was generally well tolerated and the majority of mirvetuximab side effects were low grade (Grades 1 and 2) and manageable.

Side effects are graded on a scale of 1–5 (65):

- Grade 1–2: mild side effects that generally do not impact patients significantly.
- Grade 3–4: serious side effects that interfere with a patient's ability to do basic things. Patients will likely need to be seen by their doctor or go to hospital.
- Grade 5: fatal side effects.

Compared with chemotherapy, mirvetuximab was associated with fewer Grade 3+ side effects (44% vs 55%, respectively).

- The most commonly reported Grade 3+ side effects by patients treated with mirvetuximab were keratopathy, blurred vision events, and cataracts.
- The most commonly reported Grade 3+ side effects by patients treated with chemotherapy were neutropenia, anaemia, and thrombocytopenia (when you have a low number of platelets, which are cells in the blood that help stop excessive bleeding).

Compared with chemotherapy, patients receiving mirvetuximab experienced fewer serious side effects (side effects which could be life-threatening or cause disability; 25% vs 33%, respectively), and fewer patients discontinued treatment due to side effects (11% vs 15%, respectively).

Known burdensome side effects associated with chemotherapy were reported less frequently with mirvetuximab, including fewer blood-related issues such as Grade 3+ anaemia (<1% vs 10%, respectively), neutropenia (<1% vs 17%, respectively), and thrombocytopenia (<1% vs 6%, respectively), and all grade hair loss (<1% vs 14%, respectively).

Although mirvetuximab treatment was associated with more eye-related side effects than chemotherapy, these were predominantly (85%) lower grade (1 and 2) and managed with supportive treatment and dose modifications (dose delays/reductions), leading to just 2% of patients discontinuing mirvetuximab treatment due to these side effects.

The most commonly reported side effects (all Grades) by patients treated with mirvetuximab were blurred vision, keratopathy (a disease affecting the cornea in the eye) and dry eye, while with chemotherapy these were anaemia (when the blood has a reduced ability to carry oxygen due to low levels of haemoglobin), neutropenia and feeling sick. Most side effects experienced by patients treated with mirvetuximab were manageable with appropriate monitoring, supportive measures (such as delaying and/or reducing treatment dose), and additional supportive medications.

Mirvetuximab provides a novel treatment option with a manageable safety profile for patients with PROC who have limited treatment options.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The PROC patient population has a high unmet need and new treatments are needed

Although surgery and platinum-based chemotherapy are effective treatments for advanced-stage epithelial OC, the cancer will reoccur after treatment for the vast majority of patients (~80%). Eventually almost all patients will become resistant to platinum-based therapy, at which point subsequent cycles of platinum-based chemotherapy are of no benefit (7, 9). Patients with PROC face worse survival outcomes than both untreated patients and those whose cancer is still responding to platinum-based treatment (13). Further treatment options are needed to improve clinical outcomes in this patient population with high unmet need.

Mirvetuximab is the first targeted treatment for patients with PROC in England and Wales

Mirvetuximab is the first treatment of its kind to target folate receptor-alpha (61, 62). Mirvetuximab is delivered to only those cells containing high levels of folate receptor-alpha, where it enters the cancer cell to release a toxic chemical that causes the cancer cells to die. Mirvetuximab is also toxic to nearby cancer cells that do not express folate receptor-alpha through a "bystander effect". This targeted approach is also anticipated to reduce treatment-related side effects, such as haematological side-effects, and hair loss (66-69) experienced by many patients treated with systemic chemotherapy, as mirvetuximab is directed specifically to the cancerous cells.

Mirvetuximab significantly improves survival and provides rapid and durable responses compared with chemotherapy in patients with PROC

Clinical outcomes for patients treated with available therapies are poor, with patients surviving on average for less than 12 months, and average progression-free survival (how long before a patient's disease worsens) being 3–4 months (13, 42-45). Mirvetuximab represents the first treatment to demonstrate a statistically significant longer survival in a Phase 3 trial in PROC compared with chemotherapy, with a statistically significant 32% reduction in risk of death.

Mirvetuximab showed a significant 37% reduction in the risk of cancer worsening or death compared with chemotherapy. Mirvetuximab was also associated with a significant and clinically meaningful 41% reduction in the risk of second progression or death compared with chemotherapy. This is important, given that the time between relapses shortens with each subsequent relapse, whilst the cumulative toxicity from further chemotherapy increases (9, 70). The extended period without disease progression offered by mirvetuximab would also offer patients a period free from traditional chemotherapy and the associated emotional and physical pain these treatments can cause (17). When asked about their experience with mirvetuximab, a patient noted that *"I can do anything, travel, see friends. I didn't do any socialising when I was on frontline chemo. I'm getting ready next week to go [on holiday]. I'm going for 13 days. I couldn't have done that with chemo."* (28). As previously mentioned, one patient group reported that many people with OC find relapsing more distressing than their initial diagnosis (71). By delaying progression, mirvetuximab treatment gives patients more time without this burden, while also leading to a longer survival time.

In addition to this, the tumour response rate was more than double with mirvetuximab compared with that of chemotherapy. This result is very important as tumour responses to non-platinum single-agent chemotherapy can often show minimal improvement in PROC. With mirvetuximab,

Summary of information for patients for mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

clinical experts commented that the tumour response rate would lead to noticeable improvements in symptoms due to the effects of tumour shrinkage.

Mirvetuximab is well tolerated with a more favourable safety profile than chemotherapy (7)

In the Phase 3 MIRASOL trial, mirvetuximab was associated with lower rates of Grade 3+ side effects, serious side effects, and fewer patients discontinuing treatment due to side effects, compared with chemotherapy. Some toxic side effects with chemotherapy are due to the treatment affecting the whole body (i.e. non-targeted treatment), including side effects related to the blood, and hair loss, which are known to also negatively affect patient quality of life. These chemotherapy-related side effects were lower with mirvetuximab due to its novel mechanism of action that selectively targets cancer cells, demonstrating the favourable safety profile of mirvetuximab compared with chemotherapy. Although mirvetuximab was associated with more eye-related side effects than chemotherapy, these were mostly low grade and resolvable.

Mirvetuximab can improve quality of life in patients with PROC

Cancer-related symptoms and the worry associated with cancer progression can have a considerable negative impact on a patient's quality of life (10, 17). Furthermore, treatment options for patients with PROC are limited, and those available often result in side effects that can further reduce quality of life (22-24). It is anticipated that mirvetuximab will improve or maintain the quality of life for patients living with PROC, as demonstrated by the results of validated quality of life measures in the MIRASOL trial. Furthermore, as detailed below, mirvetuximab is associated with a more favourable safety profile than chemotherapy, with fewer side effects that are known to negatively impact quality of life.

The MIRASOL trial reflects UK clinical practice

It should also be noted that the MIRASOL trial is considered generalisable to the UK PROC population. The Phase 3 trial provides a robust evidence base that directly evaluated mirvetuximab in a patient population that is representative of patients in the UK and compared mirvetuximab with treatments commonly used in the UK.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments.

Like most cancer treatments, mirvetuximab was associated with side effects. As described in Section 3g, mirvetuximab was associated with more eye-related side effects compared with chemotherapy; however, for most patients, eye-related side effects were mild. Patients with eye-related side effects were managed with supportive treatment and dose modifications (dose delays/reductions).

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living

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longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare services need to know whether a new medicine provides 'good value for money' compared to existing medicines. The pharmaceutical company that develops the medicines provides this information using a health economic model. The pharmaceutical company uses a health economic model to perform an analysis, which compares the benefits and costs of the new treatment (mirvetuximab) with the existing treatments or comparators. More details on the economic model and results are available in Section 3 of the company evidence submission.

How the health economic model reflects the condition

The health economic model is used to assess the benefits of treatment which a patient may experience, the impact of any side effects, and the cost to the National Health Service (NHS), through using different treatments for PROC. To simplify reality and allow an assessment to be made, the model uses health states which help to define some of these outcomes.

In this submission, these health states are based on whether patients have experienced progression of their disease. The model has three health states: 'pre-progression', 'post-progression', and 'death'. The model looks at specific time periods (called cycles). In each 1-week cycle, patients will either move to a different health state or stay in the same health state. How patients move through health states depends on the treatment they receive and is based on each treatment's clinical data.

Modelling how much a treatment extends life

People with PROC have a shorter life expectancy compared to the general population. The model uses data on survival from the MIRASOL trial to predict survival in the considered population for each of mirvetuximab and chemotherapy over time.

Modelling how much a treatment improves quality of life

The model assigns utility values to pre-progression and post-progression health states. Utility values are generally a number between 0, which represents death, and 1, which represents perfect health. These values are based on data collected during the MIRASOL clinical trial for patients who receive mirvetuximab and based on the published literature for patients who receive chemotherapy.

As patients in the pre-progression state have a higher quality of life than patients in the post-progression disease state, by slowing disease progression, those treated with mirvetuximab have a higher overall quality of life.

The overall health benefit experienced by patients is captured by quality-adjusted life years (QALYs). QALYs are a health outcome measure that consider both the length and the quality of life provided by a treatment. A year spent in perfect health (i.e. a utility score of 1) represents one QALY.

Modelling how the costs of treatment differ with the new treatment

Costs in the model come from the cost of treatments and the cost of managing the disease. Treatment costs include the cost for the NHS to buy treatments, the costs associated with administration, and any costs associated with managing side effects. Costs are also included for testing for whether a patient has high folate receptor-alpha and is eligible for treatment with mirvetuximab. Disease management costs include CT scans, hospital consultations and costs for palliative care at the end of life.

Uncertainty

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All economic modelling is associated with uncertainty. There are uncertainties around modelling the overall survival over a longer period of time than the MIRASOL trial collected. To assess the impact of the uncertainty, values for these data inputs were varied and the model calculations re-run.

Cost-effectiveness results

The cost-effectiveness results are based on calculations using a mirvetuximab price with a confidential discount that has been offered to the NHS, and the published prices of the comparators (paclitaxel, PLD, and topotecan).

Based on the results of the cost-effectiveness model, it is expected that for people with PROC, mirvetuximab is a cost-effective treatment option, when compared with investigator's choice of chemotherapy.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

There is a high unmet in PROC

Patients with PROC have a very poor prognosis and the worst survival outcomes among patients with OC, with an average overall survival of less than 12 months (13). As PROC progresses, physical symptoms, such as stomach pain or bowel obstruction, become more severe (11). Patients with PROC also experience psychological distress (e.g. anxiety or depression) (14, 29) and feelings of guilt and loss of feminine identity (71). Treatment options for patients with PROC are extremely limited (11), with current therapies consisting primarily of nonplatinum chemotherapies (13). Many patients experience toxic side effects due to currently available treatments being systemic (affecting the whole body), which negatively impacts patient quality of life and can lead to patients stopping treatment altogether (22, 23, 26, 36, 50, 72). There is a high unmet medical need in this patient population for novel targeted treatments that improve clinical outcomes and are well tolerated.

Mirvetuximab offers a new mechanism of action with a precision medicine approach

Mirvetuximab is a first-in-class therapy, offering a targeted approach for patients who have high expression of a protein called folate receptor-alpha. By targeting a specific marker, mirvetuximab offers eligible patients a higher probability of treatment response, improving outcomes and reducing certain serious side effects. This novel approach for patient selection and delivery of therapy directly to the tumour site represents a substantial technical innovation and will enable personalisation of cancer therapy for individual patients.

As the first targeted therapy in PROC via FR α expression, mirvetuximab also kills nearby cancer cells that do not express high levels of folate receptor-alpha through a "bystander effect". Although these nearby cancer cells do not express the protein that mirvetuximab targets, mirvetuximab is toxic to surrounding cancer cells and is able to kill these cancer cells as well.

Mirvetuximab demonstrates statistically significant and clinically meaningful benefits

Mirvetuximab is the first treatment to demonstrate a statistically significant and clinically meaningful overall survival benefit compared with chemotherapy in a Phase 3 trial and also has a manageable safety profile. In recognition of the efficacy and safety benefits and the novel mechanism of action, mirvetuximab has been approved by the Food and Drug Administration (FDA) and EMA (MHRA authorisation is pending); mirvetuximab is also recommended by the National Comprehensive Cancer Network (NCCN) guidelines (used by clinicians in the United States) (73-76). If approved, mirvetuximab adds a new, targeted treatment to the treatment pathway for PROC in the UK (11).

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The full quality of life benefits of mirvetuximab may not be captured

The full benefits of mirvetuximab may not be captured in the calculation of QALYs. Treatment and management of patients PROC is associated with considerable resource use including those for caregivers, as well as a reduction in productivity for patients of a working age (51-56). Additionally, the value of hope, as expressed by many patients, for a new treatment, in an area that has seen no new treatment for decades, is an important factor that cannot be quantified as part of the QALY calculations.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues [here](#)

PROC is unique amongst cancers affecting women; it is rare and severe with low survival rates and no new treatments in two decades. The equality issues stemming from this are three-fold:

1. inequalities related to the gender health gap in the UK
 2. inequalities related to the rarity of PROC
 3. inequalities related to the geographical and socioeconomic variation in UK cancer care access
- Mirvetuximab could help reduce some of these inequalities by providing a targeted therapy that improves survival and has fewer side effects than traditional chemotherapy for women with FRα positive PROC.

Inequalities related to gender health gap in the UK

Sex is a protected characteristic under the Equality Act 2010 (77). There is a recognised gender gap in UK care, with women experiencing an additional 3 years of ill health and disability compared with men (78). Gynaecology was severely impacted during the COVID-19 pandemic, with waiting lists increasing significantly. By July 2024, 46% of gynaecology patients waited longer than the NHS target of 18 weeks, and nearly 30,000 women had been waiting over a year. Long wait times lead to advanced conditions and require more complicated and costly treatments, especially in OC where delayed diagnosis is common. Targeted therapy with mirvetuximab could contribute to improving health outcomes in an area of high unmet need.

Inequalities related to the rarity of PROC

PROC is a rare cancer (79-81). Rare cancers have unique challenges, including late/incorrect diagnosis, lack of treatment options, difficulty in accessing innovative treatments, feelings of being alone, and greatly reduced quality of life (82). One-third of UK patients wait over 3 months from their first general practitioner (GP) visit for an accurate OC diagnosis, and most patients are at advanced stages when their OC is diagnosed (4, 83). Younger patients are particularly disadvantaged due to age-related diagnostic bias; they find it harder to get a diagnosis and have to self-advocate for specific tests. The delays in diagnosis and access to treatment are associated with poorer outcomes. Mirvetuximab offers a novel treatment option in the PROC setting which has not seen a new treatment in over two decades, underscoring the importance of innovative treatments especially for patients with rare cancers facing limited treatment options. Notably, improving outcomes for rare and less common cancers is also a key area of focus in the Government National Cancer Plan consultation (31).

Inequalities related to geographical and socioeconomic variation in UK cancer care access

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Not all patients in England have equal access to ovarian cancer treatments, with differences depending on where they live or their socioeconomic status. Research shows that people in deprived areas face delays and receive less surgery or chemotherapy, leading to worse outcomes. Women in the most deprived areas may face financial constraints, work commitments and caregiving responsibilities that reduce treatment uptake, especially when the benefits of treatment are small. For those with PROC, standard chemotherapies offer little improvement while causing side effects that lower quality of life and complicate treatment continuation. Mirvetuximab might help overcome these challenges by providing an effective and well-tolerated treatment option, potentially reducing health disparities across regions.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Information relating to mirvetuximab

- Published MIRASOL results: [Mirvetuximab Soravtansine in FRα-Positive, Platinum-Resistant Ovarian Cancer](#)
- MIRASOL study record: [NCT04209855](#)

Information for PROC

- Cancer Research UK information about treatments <https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/treatment/if-your-cancer-comes-back>

Information relating to OC

- Cancer Research UK information about OC: [Ovarian cancer](#)
- NHS information about OC: [Ovarian cancer](#)
- NICE guidelines for OC: [Clinical guideline 122](#)

Further information on NICE and the role of patients:

- Public involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EFPIA – Working together with patient groups: <https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>
- National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>

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4b) Glossary of terms

- **Anaemia:** A decrease in the total amount of red blood cells and therefore haemoglobin in the blood.
- **Antibody-drug conjugate:** A type of drug used to treat cancer. They are designed to target and kill cancer cells while leaving healthy cells unharmed.
- **Ascites:** When fluid builds up in the abdomen.
- **British Gynaecological Cancer Society (BGCS):** A medical society in the UK who are dedicated to improving the care of patients with gynaecological cancers
- **Chemotherapy:** A cancer treatment that uses drugs to kill cancer cells and/or relieve symptoms caused by cancer.
- **Clinical trial:** A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. They are carefully designed, reviewed, and completed, and need to be approved before they can start.
- **Computed tomography (CT) scan:** A scan using x-rays and a computer to create detailed images of the inside of the body.
- **Duration of response:** How long the cancer does not grow or is undetectable after treatment.
- **Efficacy:** The measurement of a medicine's desired effect under ideal conditions, such as in a clinical trial.
- **EQ-5D-5L:** A questionnaire used to assess five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
- **Folate receptor-alpha:** A protein that is overexpressed on some ovarian cancer cells. Folate receptor-alpha levels are assessed using a standard test in a laboratory using a small sample of tissue from a biopsy.
- **Infertility:** A condition when someone cannot get pregnant.
- **Intravenous:** The administration of medicines through a needle or tube inserted into a vein
- **Investigators choice of chemotherapy:** Clinicians chose the most appropriate treatment for each patient in a clinical trial, in this case from a choice of paclitaxel, PLD, and topotecan.
- **Keratopathy:** A disease affecting the cornea in the eye.
- **Median overall survival:** The length of time from either the date of diagnosis or the start of treatment, that half of the patients in a group of patients are still alive.
- **Medicines and Healthcare products Regulatory Agency (MHRA):** Part of the Department of Health and Social Care in the UK, which is responsible for ensuring medicines and medical devices work and are acceptably safe.
- **Monoclonal antibody:** A protein that binds to specific targets.
- **Monotherapy:** A single treatment.
- **National Institute for Health and Care Excellence (NICE):** An independent organisation set up by the UK Government to decide which drugs and treatments are available on the NHS in England.
- **Neutropenia:** When the bone marrow produces too few neutrophils, a type of white blood cell.
- **Open-label:** In open-label trials, both the researchers and people taking part know what treatment is being given.
- **Objective response rate (ORR):** The percentage of patients whose tumours shrink or disappear after receiving treatment.
- **Overall survival:** How long people live.
- **Paclitaxel:** A chemotherapy treatment used to treat ovarian cancer and platinum-resistant ovarian cancer.

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- **Pegylated liposomal doxorubicin (PLD):** A chemotherapy treatment used to treat ovarian cancer and platinum-resistant ovarian cancer.
- **Peripheral neuropathy:** Where nerves in the hands, feet, arms, or legs become damaged.
- **Platinum-resistant:** If the cancer has returned within 6 months of treatment with a platinum-based chemotherapy (either carboplatin or cisplatin), it is called platinum-resistant. In this situation it is unlikely that the cancer will respond to platinum-based chemotherapy again and different treatments are required.
- **Pleural effusions:** When fluid builds up between the lungs and the chest wall.
- **Primary endpoint:** The outcome measured to answer the key question in a clinical trial.
- **Prognosis:** A prediction of the course of the disease and the chance of recovery.
- **Progression-free survival:** The length of time during which the cancer is not growing or spreading.
- **Progressive disease:** When cancer grows, spreads, or gets worse.
- **Quality-adjusted life year (QALY):** A measure of disease burden that includes the length and quality of life.
- **Quality of life:** A measure of the overall enjoyment and happiness of life including aspects of an individual's sense of well-being and ability to carry out activities of daily living.
- **Randomised:** When people are allocated at random to one of two groups, in this case, either mirvetuximab, or investigators choice of chemotherapy.
- **Secondary endpoint:** An outcome measured to answer an additional question of interest in a clinical trial.
- **Side effect:** A side effect of a drug or other therapy. Side effects may be mild, moderate, or severe. Also referred to as 'adverse events'.
- **Statistically significant:** Refers to the outcome of a statistical test, and means that the results are very unlikely to have happened by chance and much more likely to have happened due to a specific cause
- **Systemic:** When a medicine works throughout the whole body.
- **Targeted therapy:** Treatments which target specific features of cancer cells.
- **Thrombocytopenia:** When a patient has a low number of platelets, which are cells in the blood that help stop excessive bleeding.
- **Time to second disease progression:** How long a patient's cancer stays under control from the start of the first treatment through to the end of the second treatment's effectiveness.
- **Topotecan:** A chemotherapy treatment used to treat ovarian cancer and platinum-resistant ovarian cancer.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

**Mirvetuximab soravtansine for treating folate
receptor alpha-positive platinum-resistant
advanced epithelial ovarian, fallopian tube or
primary peritoneal cancer [ID6442]**

Clarification questions

July 2025

File name	Version	Contains confidential information	Date
ID6442_Mirvetuximab_PROC_EAG_CQs_REDACTED	1	No (redacted)	July 2025

Section A: Clarification on effectiveness data

Clinical trials of mirvetuximab

A1. PRIORITY QUESTION. We believe that your rationale for excluding evidence for FORWARD-1 and SORAYA trials from the submission is:

- (a) That FORWARD-1 recruited a broader population in terms of expression of FR α and only a subgroup of participants met the criteria that would be used to determine eligibility for mirvetuximab**
- (b) That SORAYA was a Phase 2 trial and that all participants received bevacizumab, which is only relevant to a subgroup of the target population**

Please can you confirm and also respond to the following:

- You noted that data from FORWARD-1 were re-analysed to focus on the participants with high expression in line with the threshold that will be used to determine eligibility for mirvetuximab in clinical practice. Please clarify the data you have available for this target population from the FORWARD-1 trial that is relevant to the NICE scope for this appraisal and please submit methodological information for the trial and re-analysis with the relevant results with your response (i.e. using the structure set out in the NICE template for relevant clinical evidence).**
- Please clarify if SORAYA is a Phase 2 or 3 trial, as the CSR and clinical trials record list this as a Phase 3 trial**
- Please provide evidence to support your claim that previous treatment with bevacizumab in SORAYA meant that the trial was not relevant for the decision problem for this appraisal. For example, is there evidence that patients treated with previous bevacizumab would respond differently to the other first line treatments available?**

- **We have received advice that 80% of the target population for mirvetuximab will have previously received bevacizumab, and thus SORAYA would be a relevant trial of interest to the vast majority of the target population. Please submit methodological information for the trial with results for scoped outcomes with your response (i.e. using the structure set out in the NICE template for relevant clinical evidence).**

The methods and results of FORWARD-1 are presented in Appendix A. As outlined in the company submission, an exploratory re-scoring analysis was undertaken using the same method used in the MIRASOL trial, where high FR α tumour expression is defined as $\geq 75\%$ of tumour cells with moderate and/or strong membrane staining (PS2+). Note, the PS2 scoring method considers both the proportion score and the intensity of membranous FR α staining. The analysis confirmed positive efficacy findings in patients with high FR α expression, with results that aligned with MIRASOL.

As outlined in the company submission, SORAYA is not a relevant trial of interest given it is a single-arm trial with much smaller patient numbers and shorter follow-up than MIRASOL. It should be noted that SORAYA is a Phase 2 study and has been inadvertently referenced in the clinical study record (CSR) and clinicaltrials.gov as a Phase 3 study. The Matulonis 2022 manuscript correctly categorises SORAYA as Phase 2 (1). Furthermore, SORAYA was not included as part of the Medicines and Healthcare products Regulatory Agency (MHRA)/European Medicines Agency (EMA) evidence package (it was required for an accelerated approval in the United States [US]) although the results were informative for hypothesis generation for the Phase 3 trials. There were also key methodological differences between SORAYA and MIRASOL, as prior bevacizumab was **mandated** in SORAYA. Additionally, SORAYA was not powered for progression-free survival (PFS) or overall survival (OS), with no comparative survival data, making SORAYA subject to a high level of bias.

AbbVie consulted clinical experts who suggested that the percentage of prior bevacizumab use in this population is likely to range between 20–40%, rather than 100% as was the case of SORAYA. Despite this, clinical experts did not consider prior bevacizumab use as a treatment effect modifier and this is reflected in the

MIRASOL subgroup analysis which shows no significant difference in mirvetuximab efficacy based on prior bevacizumab use. As such, AbbVie are proposing that the full population be considered, regardless of prior use of bevacizumab, which would ensure the population is reflective and generalisable to UK clinical practice.

The methods and results of SORAYA are presented in Appendix A.

The MIRASOL trial was a Phase 3, randomised trial that compared mirvetuximab with comparators of interest as outlined in the National Institute for Health and Care Excellence (NICE) scope. MIRASOL is therefore considered to be the most robust and relevant study for assessment as it directly compared mirvetuximab with investigators choice of chemotherapy (IC Chemo) in the population of interest (adult patients with FRα positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens) and was the key registration-informing study.

A2. Please summarise the key issues raised by MHRA/EMA on the evidence base for mirvetuximab, including MIRASOL, FORWARD-1 and SORAYA trials.

The EMA and MHRA did not discuss the SORAYA trial as it was not considered relevant, though it led to FDA approval (as noted in response to Question A1). There was also very limited discussion on the FORWARD-1 trial, with the EMA noting that the eight amendments, including a change from 2-stage Phase 2 study to a Phase 3 study, could have affected the study integrity and results.

The main trial considered by both regulatory authorities and subsequently deemed robust enough to support granting of a marketing authorisation based on a positive risk/benefit profile, was the MIRASOL trial. Below is a summary of the key issues raised:

MHRA issues

The final report from the MHRA will not be available until approximately mid-August. As such, AbbVie cannot comment on any issues raised by the MHRA. However, as no issues were raised in the request for information (RFI) we would not expect any queries on this in the procedure.

EMA key issues

The EMA noted the requirement of patients to have an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1. The EMA highlighted that in patients with platinum-resistant ovarian cancer (PROC) who have received up to 3 prior treatment lines, it is expected that a non-negligible part would be ECOG 2. According to Roncolato et al (2), 13% of patients with PROC were ECOG ≥ 2 . However, it is well established that clinical trials often include fitter patients than would be observed in real-world practice (3). This approach was similar to other registrational Phase 3 trials in solid tumours; studies of olaparib, rucaparib, and niraparib were limited to ECOG 0–1, and trials that have included ECOG 2 rarely enrolled enough patients to assess safety in this population independently since fewer than 10% of the population have an ECOG status of 2 (4).

The safety population included patients treated with a wide range of prior cytotoxic therapies, mild to moderate renal impairment, mild hepatic impairment, and older age groups. While patients with ECOG ≥ 2 were excluded, in this broad population of patients with comorbidities commonly observed in advanced ovarian cancer, mirvetuximab has been shown to be safe and tolerable. Guidance generated from this population should be generally applicable to real-world care of ovarian cancer patients.

One of the issues raised by the EMA was regarding the open-label nature of the trial, although they did acknowledge that this was appropriate due to the interventions. Specifically, the EMA noted an uneven distribution of patients who did not receive treatment or withdrew, with patients randomised to IC Chemo leaving the trial more readily than patients in the experimental arm. As these patients have been impacted by investigator decisions, searching for further treatment options for patients randomised to IC Chemo, the EMA noted that informative censoring impacts the analysis of all time-to-event endpoints.

AbbVie acknowledges that MIRASOL, as an open-label trial, is subject to potential bias due to knowledge of treatment assignments; however, reiterates that superiority of mirvetuximab over IC Chemo has been reliably demonstrated, given the consistency of the benefit across the primary and all key secondary endpoints as well as the absolute and relative magnitude of the treatment effect on both PFS and

OS. To address the observed difference in early withdrawals between trial arms, additional stress test analyses were performed using the March 2023 and October 2023 data-cuts to assess if the advantage of mirvetuximab over IC Chemo observed in the primary PFS and key secondary OS analysis persists under a set of plausible and extreme assumptions about early censoring.

Sensitivity analyses conducted:

- Gap analysis - identical to the primary analysis, except that patients who are missing 2 or more consecutive radiological assessments (gap in radiographic assessment) were imputed as progressed diseased (PD) events on their next scheduled scan date rather than being censored on their last non-PD scan date.
- New treatment analysis - identical to the primary analysis, except that patients who are censored due to the start of a new anti-cancer therapy are being imputed as PD events on their next scheduled scan date rather than being censored on their last non-PD scan date before the start of the new therapy.
- BICR no PD analysis - identical to the primary analysis of PFS by BICR, except that patients who were PD events per investigator assessment but censored per BICR assessment (investigator event, BICR censored) are being imputed as PD events on their next scheduled scan date rather than being censored on their last non-PD (per BICR assessment) scan date.
- Investigator no PD analysis - identical to the primary analysis of PFS by investigator, except that patients who were PD events per BICR assessment but censored per investigator assessment (investigator censored, BICR event) are being imputed as PD events on their next scheduled scan date rather than being censored on their last non-PD (per investigator assessment) scan date.

The next two sensitivity analyses were interval censored analysis in which patients who had PFS events with both investigator and BICR assessments but disagreed on PD dates had the interval between the minimum and maximum of the 2 PD dates.

- Interval censored investigator analysis was otherwise identical to the primary analysis of PFS by investigator.
- Interval censored BICR analysis is otherwise identical to the primary analysis of PFS by BICR.

The results of these analyses are outlined below in **Table 1** and further support the robustness of the efficacy results observed in MIRASOL.

Table 1: Sensitivity analysis - PFS

	March 06, 2023, Data Cut	October 27, 2023, Data Cut
Analysis	HR (95% CI)	HR (95% CI)
Sensitivity analysis – gap analysis by investigator	██████████	██████████
Sensitivity analysis – gap analysis BICR	██████████	██████████
Sensitivity analysis – new treatment analysis by investigator	██████████	██████████
Sensitivity analysis – new treatment analysis BICR	██████████	██████████
Sensitivity analysis – BICR no PD	██████████	██████████
Sensitivity analysis – investigator no PD	██████████	██████████
Sensitivity analysis – interval censored investigator	██████████	██████████
Sensitivity analysis – interval censored BICR	██████████	██████████

Abbreviations: BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PD, progressed disease.

Concordance between PFS by investigator (the primary endpoint) and PFS by blinded independent central review (BICR) at the March 2023 data-cut was raised by the EMA. However, at the September 2024 data cut presented in the company submission to NICE, the sensitivity analysis by BICR was concordant with the investigator assessment primary analysis (median PFS by investigator: 5.59 months vs 3.98 months; hazard ratio [HR]: 0.63; 95% confidence interval [CI]: 0.513, 0.785;

p<0.0001; median PFS by BICR: PFS: 5.82 months vs 4.34 months, HR 0.70; 95% CI: 0.547, 0.890; p=0.0035).

Having considered the responses provided by AbbVie in response to the issues raised, the EMA concluded that the results from MIRASOL are clinically relevant to the platinum resistant ovarian cancer (PROC) population and the benefit/risk profile is positive, leading to European marketing authorisation.

Trial populations

A3. On p.26 of the CS, you state that approximately [REDACTED] patients would be eligible for mirvetuximab in the PROC population, based on an estimate of 2,144 women in England with epithelial high grade serous PROC and 32% of patients having high FR α expression. As your estimate is notably different from 32% of 2,144, please can you outline what other considerations contributed to your estimate?

Out of the 2,144 women in England with epithelial high grade serous PROC, a company assumption (based on interactions with National Health Service [NHS] experts) was made that in Year 1 of approval, [REDACTED] of eligible patients (patients with epithelial high-grade serous PROC, who have had 1-3 prior lines of systemic therapy), would be tested for FR α expression, resulting in [REDACTED] patients tested, and out of those patients 32% are found to have high FR α expression, resulting in the [REDACTED] patients. This estimate accounts for the fact that FR α testing is not currently routinely performed in the NHS in patients with PROC, and its uptake may initially be relatively slow. In the company's budget impact model, it has been assumed that testing uptake will gradually increase after the introduction of mirvetuximab to the market, reaching [REDACTED] of eligible patients being tested by Year 4.

A4. On p.28 of the CS, you state that almost all patients with PROC become increasingly symptomatic with abdominal pain due to malignant ascites, increasing tumour mass leading to bowel obstruction, and that bowel obstruction represents one of the most severe complications in the late phase of PROC, affecting up to 50% of patients. In the MIRASOL trial, 31% of mirvetuximab patients and 15% of IC chemo patients reported a TEAE of any grade for abdominal pain; for grade 3, small intestinal obstruction affected 2%

of the mirvetuximab patients and 4% of the IC chemo. Could you comment on this difference in occurrence between what you state in CS and the MIRASOL trial?

The reference to bowel complications, along with the resulting quality of life impact, has been included within the dossier predominantly to highlight the aggressive nature of PROC and the associated disease burden.

Expert feedback to the company suggests that ascites and bowel obstructions can be described as common symptoms of PROC (rather than treatment emergent AEs), which worsen with each disease progression, and the aim of treatment is to delay the onset of these symptoms for as long as possible.

The rationale for this inclusion was therefore not directed towards any comparative safety differences between treatment arms.

As demonstrated in the MIRASOL study, the expected tumour shrinkage capability of mirvetuximab (objective response rate [ORR] of 41.9% and overall tumour shrinkage of 80.1% vs 15.9% and 56.2% respectively with IC Chemo), the improved median PFS, and maintained HRQOL observations could contribute to better disease control and could delay the time to such complications arising.

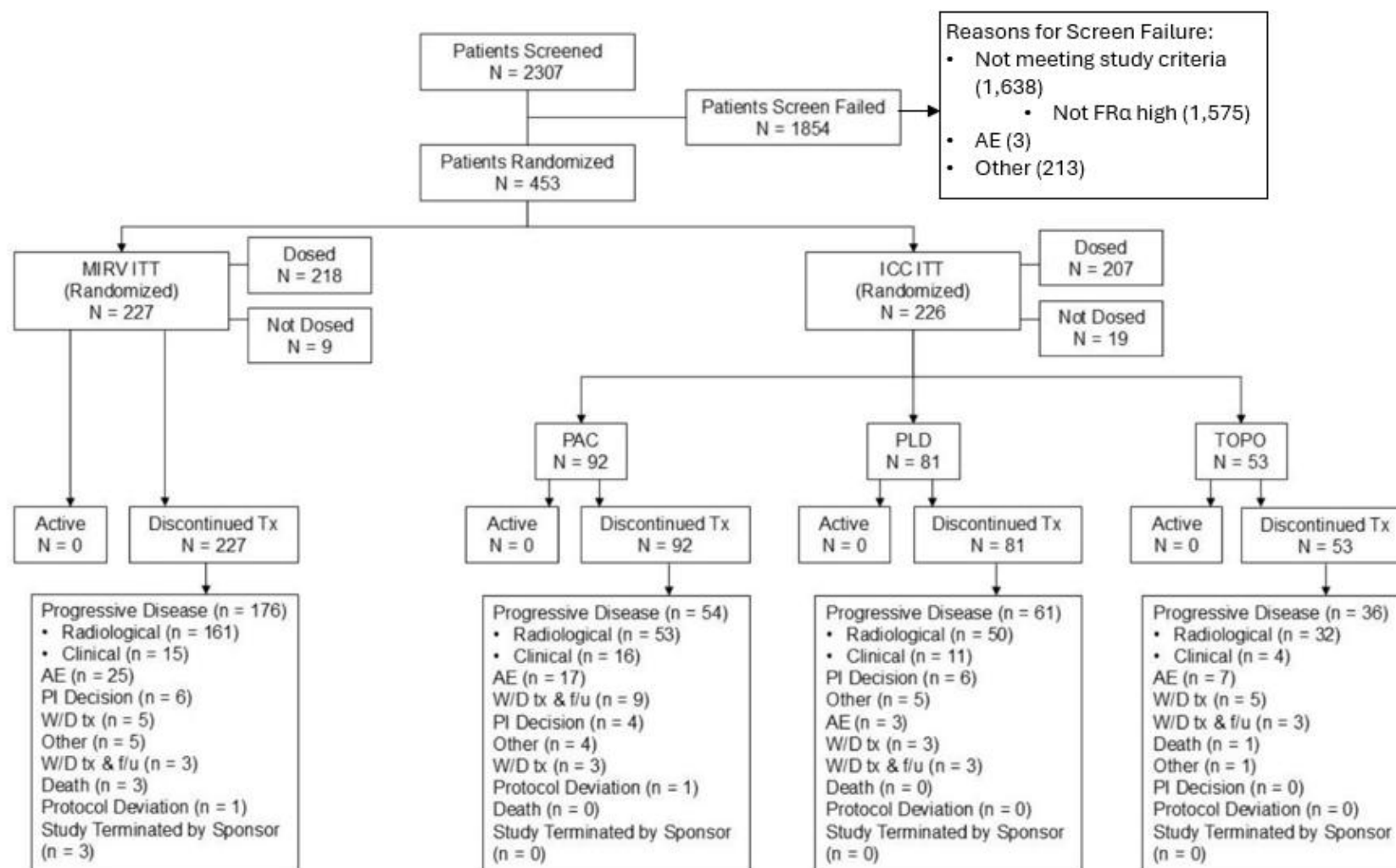
A5. The CSR defines the “Screened population” as “all patients who had signed an informed consent”. The CSR also mentions a number of “Screen Failures” and a “pre-screening informed consent form”. Please can you provide numbers completed for each of these forms in a figure, to illustrate the patient flow through the study, and include any reasons for screen failures.

The explanation is as follows:

- Pre-screening was used to pre-screen patients for FRα status before performing any additional study related tests. A pre-screening informed consent form (ICF) needed to have been completed prior to screening.
- Full patient screening was used to further screen patients who had been identified during pre-screening as eligible based on FRα expression level. A main study ICF needed to have been completed.

- Note that the patient could have consented on both pre-screening and main study ICF at the same time, and FR α testing and study-specific screening assessments could be carried out in parallel.
- The participant flow is presented in Figure 1 below. In total, 2,307 patients were screened and 1,854 failed the screen. The main reason for screen failure was not meeting the study criteria (assessed against the inclusion/exclusion criteria), and the main reason for not meeting the study criteria was not having high expression of FR α .

Figure 1. MIRASOL participant flow diagram



Source: Data on file, MIRASOL final CSR (5).

Abbreviations: AE, adverse event; f/u, follow-up; CSR, clinical study report; ICC, investigator's choice chemotherapy; ITT, intent-to-treat; MIRV, mirvetuximab; PAC, paclitaxel; PI, principal investigator; PLD, pegylated liposomal doxorubicin; TOPO, topotecan; tx, treatment; W/D, withdrawal.

A6. Please provide a breakdown of the reasons that people screened were not eligible for participation in MIRASOL

As noted in the response to Question A5, MIRASOL screened 2,307 patients. In total, 1,854 were screen failures. The most common reason was not meeting the study criteria (1,638 [71%]), which included 1,575 (68%) patients who did not have high expression FR α . A total of three patients (<1%) had an adverse event, and 213 (9%) were screen failures for other reasons.

A7. Please provide a breakdown of the reasons that people randomised to arms in MIRASOL did not receive treatment

A total of 28 patients in MIRASOL were randomised, but did not receive treatment: 9 in the mirvetuximab arm and 19 in the IC Chemo arm. The reasons that people randomised to arms in MIRASOL did not receive treatment are detailed in Table 2.

Table 2. Overview of patients who did not receive treatment

Reason	Mirvetuximab (n=9)	IC Chemo (n=19)
Physician decision	1	0
Progressive disease	1	0
Protocol deviation	1	0
Adverse event	1	2
Withdrawal of consent	0	2
Other	4	3
Withdrawal by subject	1	12

Abbreviations: IC Chemo, investigators choice of chemotherapy.

A8. Three people in the chemo arm of MIRASOL were recorded as being ECOG 2 at baseline, which we noted was contrary to the trial eligibility criteria. Can you please explain how this occurred and whether you identified their inclusion to have any impact on the trial results?

Three people in the IC Chemo arm of MIRASOL were recorded as being ECOG 2 at baseline due to the time taken between screening and dose administration (i.e. all patients with an ECOG 2 had recorded an ECOG 1 at screening and had progressed to ECOG 2 at baseline). As just three patients had ECOG 2 status at baseline, the impact on PFS and OS is expected to be minimal, as supported by the subgroup analysis data for ECOG which shows consistency of effect from the overlapping CIs.

Testing for FR α

A9. Please state how many people screened for MIRASOL did not have high expression of FR α (i.e. at the level that will be required to determine eligibility for mirvetuximab)?

As noted in response to Question A5 and A6, in total, 68% (1,575) of screened patients did not have high expression of FR α (as defined in the study eligibility criteria).

A10. We have received advice that the proportion of people who have high expression may vary across region. Can you please provide a breakdown of FR α across countries included in MIRASOL and any other evidence you have that demonstrates consistency/variation in rates of expression across settings.

The proportion of people who have high FR α expression across different European countries is [REDACTED] (based on confidential information); i.e. there were [REDACTED] (Table 3).

The proportion of patients identified at screening as expressing high FR α was consistent across both MIRASOL and SORAYA, ranging from 32% to 36% and UK clinicians indicated that this was in line with the expected proportion of PROC patients in the UK that would have positive FR α expression.

Table 3: FR α status across Europe

	Positive	Negative	Total	Prevalence	Standard error	Margin of error	Upper limit	Lower limit	Prevalence	95% CI
Belgium	■	■	■	■	■	■	■	■	■	■
Netherlands	■	■	■	■	■	■	■	■	■	■
Spain	■	■	■	■	■	■	■	■	■	■
Bulgaria	■	■	■	■	■	■	■	■	■	■
Poland	■	■	■	■	■	■	■	■	■	■
Italy	■	■	■	■	■	■	■	■	■	■
Israel	■	■	■	■	■	■	■	■	■	■
Ukraine	■	■	■	■	■	■	■	■	■	■
Portugal	■	■	■	■	■	■	■	■	■	■
France	■	■	■	■	■	■	■	■	■	■
Russia	■	■	■	■	■	■	■	■	■	■
Serbia	■	■	■	■	■	■	■	■	■	■
Czechia	■	■	■	■	■	■	■	■	■	■
Germany	■	■	■	■	■	■	■	■	■	■
United Kingdom	■	■	■	■	■	■	■	■	■	■
Total EU	■	■	■	■	■	■	■	■	■	■

A11. Please advise what diagnostic tests have been used in FORWARD-1, and SORAYA and do these align with the VENTANA test used in MIRASOL.

The MIRASOL trial is the pivotal trial used to support European Union (EU) and UK marketing authorisation. The VENTANA FOLR1 (FOLR1-2.1) CDx assay and scoring approach adopted in the MIRASOL trial is expected to be the routine test used in NHS clinical practice. SORAYA used the same VENTANA test and the same scoring approach to that adopted in MIRASOL. FORWARD-1 used the same VENTANA test, with a different scoring approach to that used in MIRASOL. FORWARD-1 was later re-scored (ad-hoc exploratory analysis) to use the same scoring approach as MIRASOL and SORAYA.

A12. Please provide diagnostic accuracy data for all tests that may be used to identify FR α expression in the NHS in order to determine eligibility for mirvetuximab.

All three studies, MIRASOL, SORAYA and FORWARD-1 used the VENTANA® FOLR1 (FOLR1-2.1) RxDx assay to determine FR α expression.

As noted in Appendix J (Section J.1.5 Validation studies) which accompanied the company submission, calculation of diagnostic sensitivity, specificity and accuracy requires a 'reference standard' or 'gold standard' benchmark test against which the results of the VENTANA® FOLR1 (FOLR1-2.1) RxDx assay can be compared. Standard assessment of analytical validity via sensitivity and specificity of the proposed test measured against a nonclinical reference standard is not relevant (or possible) for FOLR1 (FR α) as the proposed test, VENTANA® FOLR1 (FOLR1-2.1) RxDx Assay, is the evidentiary standard and the only regulatory approved test available.

Relevance of the trials to the NHS treatment pathway

A13. We have received advice that the rates of treatments received by patients in the NHS at 2nd and 3rd line may be different to the figures you have presented (cited as a UK audit, reference 22 in the CS). It appears as if reference 22 is a single slide without accompanying information about how the

figures were derived (e.g. population, methods of estimation). Can you please provide methodological details for this audit?

Methods

The Ipsos audit is a continuous, physician-based syndicated patient record form study, capturing usage of anti-cancer agents across cancer types. The submission presented data from the UK collected between August and October 2024.

Physicians were recruited if they met the following criteria: primary decision maker for anti-cancer drug therapy and seeing a minimum number of cancer patients per month; limited specialists were recruited per practice to ensure geographical distribution.

Physicians completed forms directly from reviewing patients' medical charts and were instructed to provide information on their last patients seen who are currently receiving an anti-cancer treatment.

A total of 17 physician samples were included for the NICE submission, detailing 94 patient record forms (second-line: 66; third-line: 28) for patients with Stage III–IV PROC. Criteria included: must be currently drug-treated (i.e. excludes watch and wait or surgery only patients); seen in consultation in the last 3 months; and not on a trial.

For more details, please see the accompanying file, named AbbVie. Data on file. 2024.12.23 Ipsos PROC UK Aug-Oct'24 (CQ questions) (6).

A14. We have received advice that the chemotherapies included as the comparator in MIRASOL have a different safety and efficacy profile. Subgroup analysis from MIRASOL would also suggest this trend. Can you please provide evidence that the safety and efficacy chemotherapies are not substantially different?

As the company is positioning mirvetuximab in line with its anticipated UK marketing authorisation and, given that all three IC chemo options are available in the UK, the full intention-to-treat (ITT) population from MIRASOL has been presented, rather than subgroups.

Subgroup analysis comparing to individual chemotherapy regimens is exploratory in nature and was not statistically powered to test for a difference between treatments; the result may be used for the purposes of hypothesis generation only. Exploratory analyses cannot be used to conclude that one chemotherapy regimen is statistically or clinically superior vs another. Additionally, exploratory analyses carry a risk of detecting false positive results and can lead to spurious findings, particularly if no statistical correction has been made for multiple testing. The forest plots show that the confidence intervals overlap, and the interaction tests performed for Question A29 did not identify significant differences in the type of IC Chemo.

Furthermore, as noted in the company submission, the British Gynaecological Cancer Society (BGCS) guidelines recommend non-platinum chemotherapy (e.g. weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan) administered as a single agent for the treatment of PROC (7). This recommendation aligns with the 2023 European Society for Medical Oncology (ESMO) guidelines, as well as the 2025 National Comprehensive Cancer Network (NCCN) guidelines (8, 9). These guidelines reflect the limited treatment options and note that current treatment choice is dependent on individual patient characteristics and is at the discretion of the treating clinician. Decisions are not made entirely on the relative safety/efficacy of different treatments; if so, one chemotherapy would dominate the market, which is not the case in England with the Ipsos audit demonstrating a varied range across second and third line for each available treatment.

Furthermore, in the NICE appraisal of topotecan, paclitaxel, and pegylated liposomal doxorubicin (10), the External Assessment Group (EAG) included three trials evaluating PFS in a network-meta analysis (NMA) for PROC, with results demonstrating no statistically significant differences in PFS between the three treatments, and these results were in line with results from the individual trials. This was also the case for OS, which included four trials. An education sessions paper related to the diagnosis and management of ovarian cancer notes that in patients with PROC, pegylated liposomal doxorubicin, topotecan, paclitaxel and gemcitabine have shown similar activity (11). Supporting this conclusion were the following studies:

- Ten Bokkel et al (2004). Topotecan vs paclitaxel in advanced epithelial ovarian carcinoma, no significant difference in PFS or OS (12)
- Gordon et al (2004). Pegylated liposomal doxorubicin vs topotecan in recurrent and refractory epithelial ovarian cancer, survival was similar in patients with PROC (13).

For completeness, the Kaplan-Mier curves for the individual components are presented in the response to Question A20.

Regarding the safety profile of the three chemotherapies, as noted in the CSR provided in the reference pack of the company submission (5), adverse events were broadly similar between the three chemotherapies though patients treated with paclitaxel reported more Grade 3+ study drug–related TEAEs (50% vs 17% with pegylated liposomal doxorubicin and 47% with topotecan) and study drug–related TEAEs leading to discontinuation of study drug (15% vs 0% with pegylated liposomal doxorubicin and 14% with topotecan) of any individual treatment.

A15. Two people received subsequent treatment with mirvetuximab. Can you please comment on whether re-treatment with mirvetuximab would be expected in clinical practice and in what circumstances?

Crossover was not recommended during the MIRASOL study and there were no controls placed on post-trial treatments. The commercial availability of mirvetuximab at the latter stages of the trial may have accounted for such treatment selection within a particular study country. There is no evidence available currently to guide re-treatment decision, meaning that such an approach cannot be recommended and would therefore not be anticipated in clinical practice.

A16. A relatively large number of participants in MIRASOL went on to receive subsequent treatments not typically used in the NHS. Can you please provide evidence for the impact of this on overall survival? Please refer to the latest TSD guidance on this topic.

At this stage of the disease course, there is no clear standard of care and a continuing high level of unmet need. As such, clinicians are willing to try a variety of therapies resulting in a heterogenous mix of subsequent treatments.

Clinicians informed AbbVie that other than mirvetuximab, it is not expected that any other non-NHS subsequent treatments will have a differential impact on OS, compared with treatments used routinely in the NHS. In other words, clinical experts did not expect any of these therapies, such as Kinase inhibitors, PARP inhibitors or PD-L1 inhibitors to affect patients' survival at this stage of the disease. In addition, subsequent treatments are well balanced between the mirvetuximab and IC Chemo arms.

The impact of adjusting for crossover of IC chemo patients to mirvetuximab has been formally explored and presented in the response to Question B8.

A17. Please could you demonstrate how the chemotherapy arm was pooled in your submission and provide a feasibility assessment for this.

In the MIRASOL trial, patients were assigned to one of three chemotherapy regimens based on investigators choice, prior to randomisation. The decision on which chemotherapy to use was made based on various factors such as patient clinical profile, comorbidities, and ongoing toxicity burden. In MIRASOL, no pooling was conducted, the chemotherapy arm was considered one group (IC Chemo) and as such no additional statistical methods were used to pool the data in this arm of the trial. Further to this, the use of investigators choice is standard in international clinical trials and is used to allow clinicians to use treatments relevant to their own country's practice/guidelines.

Trial outcomes and results

A19. PRIORITY QUESTION. Please provide Kaplan-Meier curves with numbers at risk and censoring for OS, PFS, time on treatment and key safety outcomes for MIRASOL, FORWARD-1 and SORAYA (ideally these could be presented in Microsoft Excel).

These data are provided in the accompanying Excel[®] files:

- Forward_ITT_PFS_OS
- Forward_SAF_DOT
- Soraya_PFS_OS

- Soraya_SAF_DOT.

A20. PRIORITY QUESTION. Please present Kaplan Meier curves including numbers at risk and censoring for PFS and OS for each individual component of the IC Chemo arm in MIRASOL compared to the pooled IC Chemo arm.

Please note that, as per response to Question A14, the MIRASOL trial was not powered to give results for individual chemotherapies and therefore these exploratory analyses carry a significant risk of detecting false positive results and can lead to spurious findings.

However, for completeness the requested data are provided in the accompanying Excel® files within the folder named: 2024-11-13 Sept24 DCO - PFS OS DoT parameters in Excel.

A21. Please can you explain the rationale for the choice of investigator assessed response as your primary outcome in MIRASOL as opposed to BICR? We note that you cite a recommendation from the Gynecologic Cancer InterGroup for this but we were unable to find a supporting rationale in the publication. We have contacted the lead author but have not yet received a response.

PFS by investigator is well established as a primary endpoint in ovarian cancer trials, having been used in many recent trials (14-18). As noted in the recommendations from the Gynecologic Cancer InterGroup (Section: Critical elements in future clinical trials) (19) *“In phase 3 trials, progression-free survival assessed **by an investigator** and overall survival are the preferred primary endpoints (although they do not necessarily have to be dual endpoints)”*. In addition, in real world clinical practice, decisions on progression would be made by the treating clinician/radiologist and not sent for a blinded review and hence investigator assessed would be more reflective of real-world outcomes. As such, PFS by investigator was the primary endpoint for MIRASOL, with OS one of the key secondary endpoints.

Furthermore, as noted in response to Question A2, at the September 2024 data cut presented in the company submission to NICE, the sensitivity analysis by BICR was concordant with the investigator assessment primary analysis (median PFS by investigator: 5.59 months vs 3.98 months; HR: 0.63; 95% CI: 0.513, 0.785;

p<0.0001; median PFS by BICR: PFS: 5.82 months vs 4.34 months, HR 0.70; 95% CI: 0.547, 0.890; p=0.0035).

A22. RECIST 1.1 states that “CT is the best currently available and reproducible method to measure lesions selected for response assessment.” Please could you provide subgroup analysis by tumor scan method (CT vs MRI).

Subgroup analysis by tumour scan method (CT vs MRI) is not available. The method of assessment was in part determined on the lesion assessment needs. To the best of our knowledge, most patients in MIRASOL were assessed by CT scan, and therefore such a subgroup analysis would not be meaningful.

A23. Please provide evidence to substantiate your rationale that a 15-point of greater change on the EORTC QLQ-OV28 was stringent and also please provide the rationale and citations for the selection of 11.1 as an alternative.

During protocol design for the MIRASOL trial, a range of scores were identified as possible thresholds for clinically meaningful change in the EORTC QLQ-OV28 Abdominal/GI symptom subscale. The most ambitious threshold of 15-point was selected for the primary patient-reported outcome analysis. The 15.0-point threshold may be viewed as stringent, as a change of 10.0 points or more has been considered a minimal clinically important difference in previous studies for a similar instrument, the QLQ-C30 (20-23).

Given the low baseline rates of Abdominal/GI symptoms in the population (mirvetuximab arm: mean score of 25.1 on a scale of 0–100; IC Chemo arm: mean score 28.0), this threshold was likely too high as many patients did not start at a baseline with enough Abdominal/GI symptoms to record an improved score of 15 or higher (20). Additionally, when looking at the change from baseline analysis of the abdominal and gastrointestinal scores, the mirvetuximab group showed a decrease in least squares (LS) mean scores from baseline indicating symptom improvement at all timepoints through to week 24. Nominally significant differences between treatments in LS mean changes were observed.

A sensitivity analysis using a threshold for meaningful change on the lower range (11-points) did find a nominally significant result (p=0.0318) with 29% of

mirvetuximab patients demonstrating a clinically meaningful and important change compared with 18% of IC Chemo patients (20).

A24. Please provide tabulated data for EQ-5D-5L VAS scores (including variance data) from MIRASOL at measured timepoints

Tabulated data for the EQ-5D-5L VAS scores are presented in Table 4.

Table 4: EQ-5D-5L VAS scores

	Mirvetuximab (N=227)	IC Chemo (N=226)
EQ-5D VAS Score		
Number of Patients Included in the Model	166	155
Estimates/Comparisons at Week 8/9		
LS Mean (SE)	2.9 (1.15)	−4.0 (1.22)
95% CI of LS Mean	(0.6, 5.1)	(−6.4, −1.6)
Difference (95% CI) in LS Mean (vs IC Chemo)	6.9 (3.6, 10.2)	
p-value	<0.0001	
Estimates/Comparisons at Week 15/16		
LS Mean (SE)	2.2 (1.12)	−4.8 (1.22)
95% CI of LS Mean	(0.0, 4.4)	(−7.2, −2.4)
Difference (95% CI) in LS Mean (vs IC Chemo)	7.0 (3.8, 10.3)	
p-value	<0.0001	
Estimates/Comparisons at Week 24		
LS Mean (SE)	1.5 (1.27)	−5.7 (1.49)
95% CI of LS Mean	(−1.0, 4.0)	(−8.6, −2.8)
Difference (95% CI) in LS Mean (vs IC Chemo)	7.2 (3.3, 11.0)	
p-value	0.0003	

Abbreviations: CI, confidence interval; IC Chemo, investigators choice of chemotherapy; LS, least square; SE, standard error; VAS, visual analogue scale.

A25. Please provide tabulated data for EORTC QLQ-C30 scores (including variance data) from MIRASOL that were described on p.73-74 of the CS

Tabulated data for the EORTC QLQ-C30 scores are presented in Table 5.

Table 5: EORTC QLQ-C30 scores

	Mirvetuximab (N=227)	IC Chemo (N=226)
Global Health Status/QoL		
Number of Subjects Included in the Model	178	159
Estimates/Comparisons at Week 8/9		
LS Mean (SE)	−0.3 (1.12)	−7.3 (1.21)
95% CI of LS Mean	(−2.5, 1.9)	(−9.7, −4.9)
Difference (95% CI) in LS Mean (vs IC Chemo)	7.0 (3.8, 10.3)	
p-value	< 0.0001	
Estimates/Comparisons at Week 15/16		
LS Mean (SE)	−0.4 (1.09)	−7.6 (1.22)
95% CI of LS Mean	(−2.5, 1.8)	(−10.0, −5.2)
Difference (95% CI) in LS Mean (vs IC Chemo)	7.2 (4.0, 10.4)	
p-value	< 0.0001	
Estimates/Comparisons at Week 24		
LS Mean (SE)	−0.6 (1.29)	−7.9 (1.56)
95% CI of LS Mean	(−3.1, 2.0)	(−11.0, −4.9)
Difference (95% CI) in LS Mean (vs IC Chemo)	7.4 (3.4, 11.4)	
p-value	0.0004	
Physical Functioning		
Number of Subjects Included in the Model	178	159
Estimates/Comparisons at Week 8/9		
LS Mean (SE)	−0.6 (1.06)	−6.9 (1.14)
95% CI of LS Mean	(−2.7, 1.5)	(−9.2, −4.7)
Difference (95% CI) in LS Mean (vs IC Chemo)	6.3 (3.3, 9.4)	
p-value	< 0.0001	
Estimates/Comparisons at Week 15/16		
LS Mean (SE)	−1.2 (1.10)	−9.1 (1.21)
95% CI of LS Mean	(−3.3, 1.0)	(−11.5, −6.8)
Difference (95% CI) in LS Mean (vs IC Chemo)	8.0 (4.7, 11.2)	
p-value	< 0.0001	
Estimates/Comparisons at Week 24		

	Mirvetuximab (N=227)	IC Chemo (N=226)
LS Mean (SE)	−1.9 (1.31)	−11.8 (1.54)
95% CI of LS Mean	(−4.5, 0.7)	(−14.9, −8.8)
Difference (95% CI) in LS Mean (vs IC Chemo)	9.9 (5.9, 13.9)	
p-value	< 0.0001	
Role Functioning		
Number of Subjects Included in the Model	176	158
Estimates/Comparisons at Week 8/9		
LS Mean (SE)	−2.2 (1.34)	−9.6 (1.45)
95% CI of LS Mean	(−4.8, 0.5)	(−12.4, −6.7)
Difference (95% CI) in LS Mean (vs IC Chemo)	7.4 (3.5, 11.3)	
p-value	0.0002	
Estimates/Comparisons at Week 15/16		
LS Mean (SE)	−3.5 (1.41)	−11.9 (1.59)
95% CI of LS Mean	(−6.3, −0.7)	(−15.0, −8.8)
Difference (95% CI) in LS Mean (vs IC Chemo)	8.4 (4.2, 12.6)	
p-value	0.0001	
Estimates/Comparisons at Week 24		
LS Mean (SE)	−5.1 (1.81)	−14.7 (2.19)
95% CI of LS Mean	(−8.7, −1.6)	(−19.0, −10.4)
Difference (95% CI) in LS Mean (vs IC Chemo)	9.6 (4.0, 15.2)	
p-value	0.0009	
Fatigue Symptoms		
Number of Subjects Included in the Model	176	158
Estimates/Comparisons at Week 8/9		
LS Mean (SE)	1.7 (1.31)	10.1 (1.40)
95% CI of LS Mean	(−0.9, 4.3)	(7.3, 12.8)
Difference (95% CI) in LS Mean (vs IC Chemo)	−8.3 (−12.1, −4.6)	
p-value	< 0.0001	
Estimates/Comparisons at Week 15/16		
LS Mean (SE)	1.7 (1.31)	11.3 (1.46)
95% CI of LS Mean	(−0.9, 4.3)	(8.4, 14.2)

	Mirvetuximab (N=227)	IC Chemo (N=226)
Difference (95% CI) in LS Mean (vs IC Chemo)	−9.6 (−13.4, −5.7)	
p-value	< 0.0001	
Estimates/Comparisons at Week 24		
LS Mean (SE)	1.7 (1.59)	12.8 (1.89)
95% CI of LS Mean	(−1.4, 4.8)	(9.0, 16.5)
Difference (95% CI) in LS Mean (vs IC Chemo)	−11.1 (−15.9, −6.2)	
p-value	< 0.0001	

Abbreviations: CI, confidence interval; IC Chemo, investigators choice of chemotherapy; LS, least square; SE, standard error.

A26. PRIORITY QUESTION. We are noting some unexpected patterns in censoring in MIRASOL. Can you please provide a breakdown of the following: Time, Censor or Event (1= event), Arm, including reasons for censoring, for OS, PFS and time on treatment. Please also include the censoring numbers alongside numbers at risk on the associated KM plots.

Time	Censor or event (1 = event)	Arm	Reasons for censoring

A breakdown of reasons for censoring in OS, PFS and DoT is provided in the accompanying Excel® file named: Survival data summary

As noted in response to Question A2, the subject of early censoring in the IC chemo arm was noted by the EMA. After considering the additional analyses and company response, marketing authorisation was granted, demonstrating that the EMA were satisfied with the clinical efficacy and safety profile of mirvetuximab.

In addition, as noted in the company submission, more patients were censored due to end of study in the mirvetuximab arm compared to the IC Chemo arm (44 vs 18 patients). The patients in the mirvetuximab arm who were censored due to study termination (44/227, or 19.4%) were predominantly patients who had achieved either

partial or complete response (29/44, or 65.9%). This implies that since these patients were alive after at least 24 months, and their response rate was higher than average, there is increased potential that some mirvetuximab patients survive long-term, in line with the predictions made by the log-logistic distribution.

A27. How many participants in MIRASOL were still responding to treatment at final follow-up and, of these, how many were in complete response?

At final follow-up, 44 patients receiving mirvetuximab and 18 patients receiving IC Chemo were still alive and thus were censored for OS at last study visit. Of these, 6 (13.6%) patients receiving mirvetuximab had achieved complete response, whereas none of the censored patients in the IC Chemo arm had achieved complete response (Table 6).

Of patients censored due to end of study, 3 of the 44 patients in the mirvetuximab arm were still on treatment with mirvetuximab (one patient discontinued due to AEs, the remainder of the 44 patients were on subsequent treatment), while all patients in the IC chemo arm had progressed and/or were on subsequent therapy. Six patients from the IC chemo arm had crossed over to the mirvetuximab arm and 2 were still being treated with subsequent mirvetuximab at last study visit.

Table 6: Best overall response in censored patients

Best overall response	Patients censored at final follow up
Mirvetuximab	n=44
Complete response	6 (13.6%)
Partial response	23 (52.4%)
Stable disease	15 (34.1%)
Progression disease	0
Not evaluable	0
IC Chemo	n=18
Complete response	0
Partial response	8 (44.4%)
Stable disease	4 (22.2%)
Progression disease	4 (22.2%)
Not evaluable	2 (11.1%)

Abbreviations: IC Chemo, investigators choice of chemotherapy.

A28. PRIORITY QUESTION. Please provide a sensitivity pairwise meta-analysis, and provide/generate a feasibility report for this comparison, for the FORWARD-1 subgroup (with the relevant threshold for FR α) and MIRASOL trials. Please provide the data points used for this analysis.

Methodology

An exploratory analysis to determine FR α -positive tumour cells using the product information-compliant PS2+ scoring method, which also takes into account the staining intensity of the tumour cell membrane, was conducted on the data from the FORWARD-1 study. The results suggested that the 10X scoring method classified the FR α expression level of some patients differently compared with the positive staining intensity ≥ 2 (PS2+) scoring method. This led to the inclusion of patients with lower FR α expression, who would not have been eligible for inclusion in the study when using the PS2+ scoring method relevant to the benefit assessment. Due to these differences in the definition of FR α positivity, the results below are presented for the patient population of the FORWARD-1 study, reclassified according to FR α expression level based on the PS2+ scoring method. The rescore was performed using digital tumour images created within FORWARD-1 prior to randomisation, based on the PS2+ rating method by an independent pathologist blinded to the treatment assignment. The product information-compliant rescore to PS2+ $\geq 75\%$ resulted in 116 patients.

Baseline characteristics for the MIRASOL and FORWARD-1 (Re-Scored) patient populations are presented in Table 7. Overall, patient demographics and disease characteristics were similar between the two trials.

Table 7: Characterisation of the study population

	MIRASOL		FORWARD-1 (Re-Scored)	
	Mirvetuximab N=227	IC Chemo N=226	Mirvetuximab N=82	IC Chemo N=34
Disease-specific characteristics				
Primary tumour site: n (%)				
Epithelial ovarian	182 (80)	182 (81)	68 (84)	31 (91)
Fallopian tubes	27 (12)	23 (10)	6 (7)	1 (3)
Primary peritoneal	2 (1)	1 (0)	1 (1)	0 (0)
FIGO				
I	4 (2)	1 (0)	0 (0)	0 (0)
II	5 (2)	8 (4)	2 (2)	0 (0)
III	137 (60)	147 (65)	52 (63)	25 (74)
IV	76 (33)	65 (29)	27 (33)	9 (26)
Missing	5 (2)	5 (2)	1 (1)	0 (0)
Any BRCA mutations				
Positive	29 (13)	34 (16)	11 (13)	3 (9)
Negative/unknown	198 (87)	190 (84)	71 (87)	31 (91)
BRCA1 mutations, n (%)				
Positive – BRCA1	24 (11)	29 (13)	8 (10)	3 (9)
Negative/unknown	203 (89)	197 (87)	74 (90)	31 (91)
BRCA2 mutations, n (%)				
Positive – BRCA2	9 (4)	7 (3)	3 (4)	0 (0)
Negative/unknown	218 (96)	219 (97)	79 (96)	34 (100)
Time from initial diagnosis to randomisation (months)				
n	208	208	73	33
Mean (SD)	33.36 (20.13)	34.93 (22.32)	27.28 (18.41)	33.98 (25.48)
Median (min, max)	28.52 (9.07, 164.24)	29.19 (8.74, 131.45)	23.89 (8.21, 128.1)	30.55 (7.2, 119.29)
Previous treatment lines, n (%)				
1	29 (13)	34 (15)	53 (65)	20 (59)
2	90 (40)	88 (39)	–	–
3	108 (48)	104 (46)	29 (35)	14 (41)
Demographic characteristics				

	MIRASOL		FORWARD-1 (Re-Scored)	
	Mirvetuximab N=227	IC Chemo N=226	Mirvetuximab N=82	IC Chemo N=34
Age (years)				
Mean (SD)	63.29 (9.85)	62.26 (9.30)	63.13 (9.42)	60.35 (12.31)
Median (Min.; Max.)	64 (32, 88)	62 (29, 87)	65 (42, 84)	62 (31, 81)
Ethnicity, n (%)				
Hispanic or Latino	12 (5)	15 (7)	4 (5)	1 (3)
Non-Hispanic or Latino	177 (78)	163 (72)	75 (91)	33 (97)
Not reported	35 (15)	45 (20)	3 (4)	0 (0)
Unknown	2 (1)	2 (1)	0 (0)	0 (0)
Missing	1 (0)	1 (0)	0 (0)	0 (0)
Race, n (%)				
White	156 (69)	145 (64)	81 (99)	31 (91)
Black or African American	8 (4)	5 (2)	0 (0)	1 (3)
Native American or Alaskan	0 (0)	0 (0)	0 (0)	0 (0)
Asian	28 (12)	25 (11)	0 (0)	2 (6)
Others	3 (1)	2 (1)	1 (1)	0 (0)
Not reported	32 (14)	49 (22)	0 (0)	0 (0)
Geographic region				
APAC	25 (11)	26 (12)	0 (0)	0 (0)
Europe	127 (56)	123 (54)	50 (61)	26 (76)
Middle East	1 (0)	8 (4)	0 (0)	0 (0)
North America	74 (33)	69 (31)	32 (39)	8 (24)
Weight (kg) at baseline				
n	213	198	79	32
Mean (SD)	68.47 (15.33)	69.24 (15.73)	71.09 (17.13)	67.83 (13.33)
Median (Min.; Max.)	65 (39, 122,7)	66.6 (39.1, 130.4)	67 (40.5, 125)	63.75 (49.2, 111)

Abbreviations: APAC, Asian-Pacific; BRCA, breast cancer susceptibility gene; FIGO, International Federation of Gynecology and Obstetrics; IC Chemo, investigators choice of chemotherapy; PARP, poly (adenosine diphosphate-ribose) polymerase; SD, standard deviation.

Feasibility assessment

A pairwise comparison was considered feasible, and results are presented in the following sections.

Efficacy results

The efficacy results of the pooled meta-analysis are presented in Table 8. The OS data uses the final MIRASOL September 2024 data-cut while PFS relies on the October 2023 data-cut from MIRASOL; for both comparisons there was only one FORWARD-1 data-cut. For both efficacy endpoints, mirvetuximab demonstrated significant benefit over IC Chemo after pooling the MIRASOL and the re-scored FRα high population of FORWARD-1.

Table 8: Meta-analysis - efficacy results

Endpoint	MIRASOL	FORWARD-1 (re-scored)	Meta-analysis
OS	HR: 0.67 [95% CI: 0.542, 0.838] p=0.0004	HR: 0.66 [95% CI: 0.401, 1.078] p=0.1043	HR: 0.67 [95% CI: 0.549, 0.818] p=0.0001
PFS (Investigator)	HR: 0.64 [95% CI: 0.519, 0.797] p=0.0001	HR: 0.65 [95% CI: 0.407, 0.1.032] p=0.0747	HR: 0.65 [95% CI: 0.538, 0.792] p<0.0001

Abbreviations: CI, confidence interval ;HR, hazard ratio; MMRM, mixed model for repeated measures; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, time to second disease progression or death; PRO, patient related outcome; QLQ, Quality of Life Questionnaire; RR, relative risk; TTR, time to response; VAS, visual analogue scale.

Safety results

The safety results of the meta-analysis reinforce those observed in the MIRASOL trial (Table 9). Patients treated with IC Chemo reported more instances of anaemia, leukopenia, thrombocytopenia, fatigue, and small intestinal obstruction, than patients treated with mirvetuximab. However, mirvetuximab-treated patients experienced more eye disorders than IC Chemo-treated patients. As noted in the company submission, the eye disorders are manageable, resolvable, and predominantly low grade. As such, the benefits of mirvetuximab outweigh the risk of eye disorders.

Table 9: Meta-analysis – safety results

	MIRASOL	FORWARD-1 (re-scored)	Meta-analysis
AESI "Eye disorder"	124 [57%] vs. 18 [9%]	39 [49%] vs. 2 [6%]	163 [55%] vs. 20 [8%]
Severe AESI "Eye disorder"	31 [14%] vs. 0	5 [6%] vs 0	36 [12%] vs. 0
Serious AESI "Eye disorder"	2 [1%] vs. 0	0 vs. 0	2 [1%] vs. 0
AESI "PNP"	81 [37%] vs. 47 [23%]	33 [42%] vs. 8 [25%]	114 [38 %] vs. 55 [23 %]
Severe AESI "PNP"	8 [4%] vs 8 [4%]	0 vs. 1 [3%]	8 [3%] vs. 9 [4%]
Serious AESI "PNP"	1 [0.5%] vs. 0		
AESI "Pneumonitis"	26 [12%] vs. 1 [0.5%]	33 [42%] vs. 11 [34%]	59 [20%] vs. 12 [5%]
Severe AESI "Pneumonitis"	3 [1%] vs. 0	5 [6%] vs. 3 [9%]	8 [3%] vs. 3 [1%]
Serious AESI "Pneumonitis"	4 [2%] vs. 0	7 [9%] vs. 4 [12%]	11 [4%] vs. 4 [2%]
Blood and lymphatic system disorders (SOC)	6 [3%] vs. 51 [25%]	4 [5%] vs. 9 [28%]	10 [3%] vs. 60 [25%]
Anaemia (PT)	2 [1%] vs. 21 [10%])	2 [3%] vs. 2 [6%]	4 [1%] vs. 23 [10%]
Leukopenia (PT)	–	1 [1%] vs. 3 [9%]	–
Neutropenia (PT)	2 [1%] vs. 36 [17%]	0 vs. 8 [25%]	2 [1%] vs. 44 [18%]
Thrombocytopenia (PT)	2 [1%] vs. 13 [6%]	–	–
Eye disorders (SOC)	31 [14%] vs. 0	11 [14%] vs. 0	42 [14%] vs. 0
Keratopathy (PT)	20 [9%] vs. 0	–	22 [7%] vs. 0
Vision blurred (PT)	18 [8%] vs. 0	–	21 [7%] vs. 0
Cataract (PT)	–	6 [8%] vs. 0	14 [5%] vs. 0
Visual Acuity reduced (PT)	9 [4%] vs. 0	–	12 [4%] vs. 0
General disorders and administration site conditions (SOC)	10 [5%] vs. 22 [11%]	4 [5%] vs. 6 [19%]	14 [5%] vs. 28 [12%]
Fatigue (PT)	5 [2%] vs. 11 [5%]	2 [3%] vs. 2 [6%]	7 [2%] vs. 13 [5%]
Investigations (SOC)	5 [2%] vs. 17 [8%])	2 [3%] vs. 2 [6%]	7 [2%] vs. 19 [8%]

	MIRASOL	FORWARD-1 (re-scored)	Meta-analysis
White blood cell count decreased (PT)	0 vs. 10 [5%]	–	–
Gastrointestinal disorders (SOC)	30 [14%] vs. 31 [15%]	13 [16%] vs. 5 [16%]	43 [14%] vs. 36 [15%]
Small intestinal Obstruction (PT)	–	0 vs. 2 [6%]	4 [1%] vs. 10 [4%]

Abbreviations: AESI, adverse event of special interest; PNP, peripheral neuropathy; PT, preferred term; SOC, system organ class.

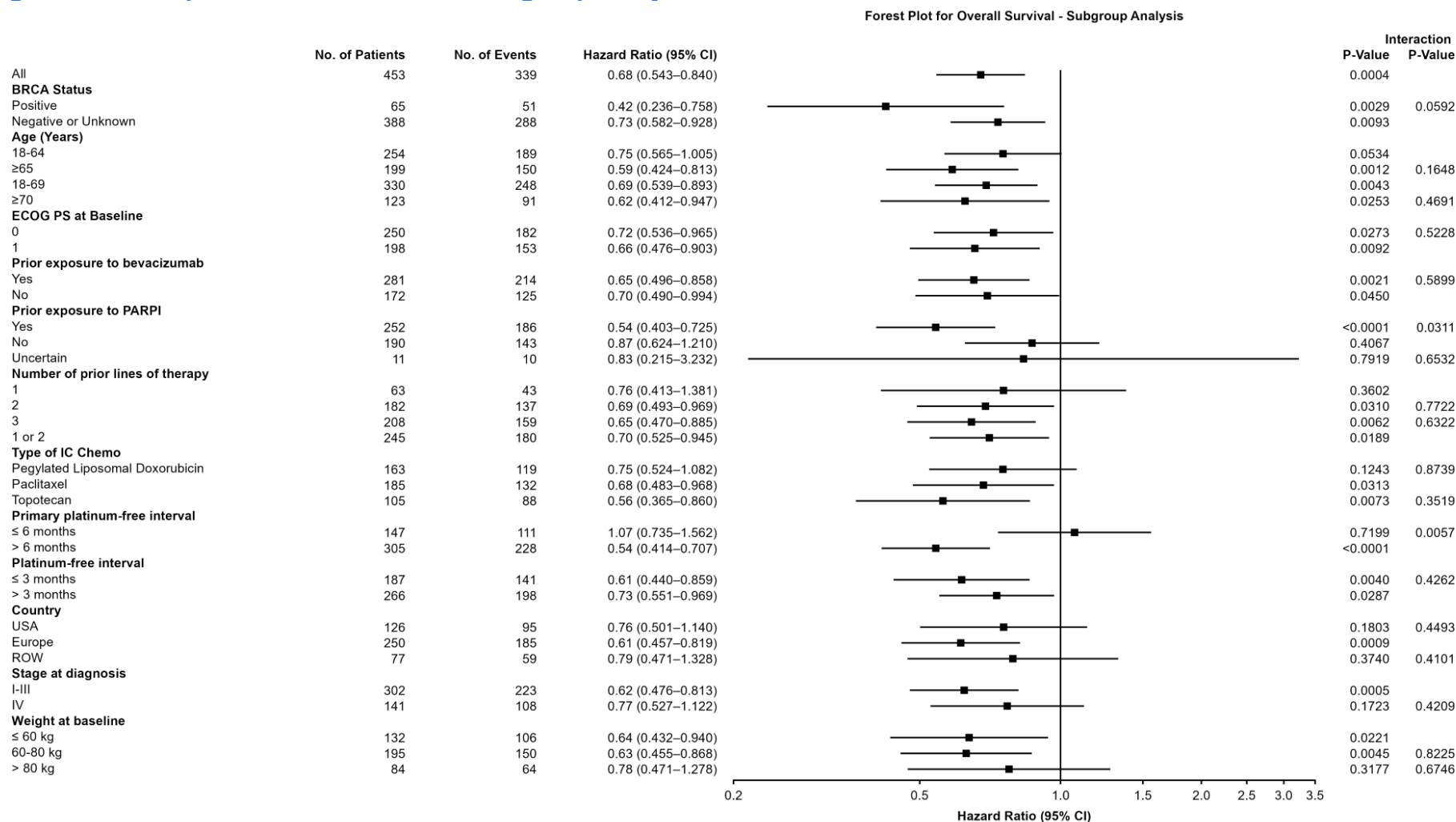
A29. For your subgroup analysis from MIRASOL:

- **Please submit the forest plot for OS and PFS to include a p-value for the treatment interaction**
- **Please separate data for Europe from Rest of World**
- **Please provide your comment on the potential difference in treatment effect according to the length of primary platinum-free interval**

As noted in section 2.8 of the company submission, although subgroup analyses were performed for PFS, ORR, OS, and PFS2 in MIRASOL, all subgroup analyses were exploratory and unstratified. The updated forest plots for OS and PFS are presented in Figure 2 and Figure 3, respectively. As requested, interaction p-values have been added to the forest plots, with results separated for Europe and Rest of the World.

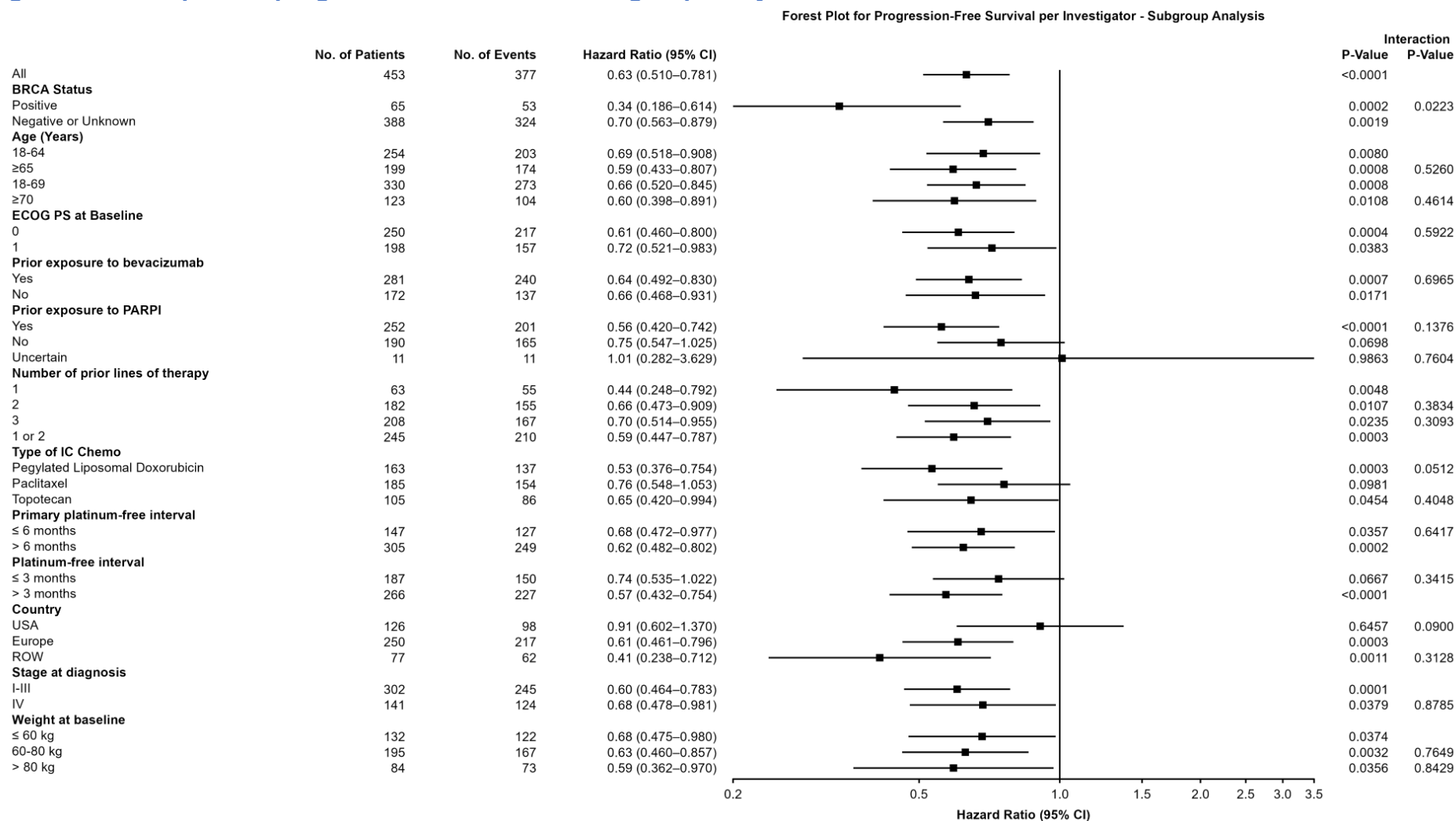
Based on the p-value for treatment effect, primary platinum-free interval was statistically significant for OS but not for PFS. Patients with PFI ≤6 months are patients who relapsed quickly following their first line (platinum) treatment for ovarian cancer. Clinical feedback to the company suggested that these patients are a group with extremely high unmet need and a very poor prognosis, as even their first cancer therapy was ineffective. Feedback also suggested that despite the HR in the forest plots, within the PROC space, they would consider patients with PFI ≤6 months as eligible for mirvetuximab, as the goal would be to give them the treatment with the best efficacy, which according to MIRASOL which compared mirvetuximab with IC Chemo, is mirvetuximab.

Figure 2. Forest plot for overall survival subgroup analysis



Abbreviations: BRCA, breast cancer gene; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IC Chemo, investigators choice of chemotherapy; PARPI, poly (ADP-ribose) polymerase inhibitors; PS, performance status; ROW, rest of world; USA, United States of America.

Figure 3. Forest plot for progression-free survival subgroup analysis



Abbreviations: BRCA, breast cancer gene; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IC Chemo, investigators choice of chemotherapy; PARPI, poly (ADP-ribose) polymerase inhibitors; PS, performance status; ROW, rest of world; USA, United States of America.

A30. From our perspective, the safety evidence for mirvetuximab presented does not clearly support your claims that mirvetuximab results in a reduced risk of ascites and bowel obstruction in comparison with chemotherapy. Please can you review these data and consider whether additional data or analysis is needed to further substantiate your claims.

As noted in the response to Question A4, bowel obstructions are typically caused by tumour growth and are not considered an adverse event from treatment itself. The tumour shrinkage observed with mirvetuximab is expected to reduce risk of bowel obstruction. Tumour shrinkage (encompassing complete and partial response, and stable disease) was observed for 80.1% of patients treated with mirvetuximab (regardless of the line of treatment, including primary platinum resistance), vs 56.2% of patients treated with IC Chemo.

Furthermore, significant improvements were observed for mirvetuximab in the mixed model for repeated measures (MMRM) change-from-baseline analysis for the abdominal/gastrointestinal symptom subscale, with reported differences in least squares mean (LSM) scores between -5.0 to -6.0 at Weeks 8/9, 15/16, and 24, all favouring mirvetuximab (nominal $p < 0.005$ at all 3-time points), demonstrating that mirvetuximab maintains abdominal symptom-related HRQOL, a crucial aspect of quality of life in this population.

Section B: Clarification on cost-effectiveness data

B1. PRIORITY QUESTION:

- a) Please explain the differences between predicted QALYs in the Zhu 2024 paper (reference 167) and the submitted economic analysis.
- b) Please also explain the drivers behind the large differences in QALYs for bevacizumab naïve and pre-treated patients.
- c) Please submit an analysis looking at the impact of bevacizumab pre-treatment on cost-effectiveness i.e. ICERs for naïve and pre-treated patients.

a)

Please note that Zhu 2024 is an independent cost-effectiveness analysis of mirvetuximab, not a company sponsored study, and therefore we do not have access to the underlying economic model or further details beyond those presented within the publication. The authors did not have access to patient level data, and the analysis was performed from the US perspective.

There are a number of differences between the submitted economic analysis and that of Zhu 2024, with regards to inputs and assumptions, which could impact estimated quality-adjusted life years (QALYs). For example, Zhu 2024 used the MIRASOL March 2023 data cut, whereas the submitted economic analysis uses the final data cut of September 2024, and adopts a shorter time horizon.

However, when comparing incremental QALYs between the analyses, Zhu 2024 reports incremental QALYs in the overall population of 0.90. The base-case company submitted analysis reports incremental QALYs, when not considering a severity modifier, of [REDACTED]. The estimated incremental QALYs associated with mirvetuximab were therefore not dissimilar.

b)

The company assumes that the question is with regards to the subgroups results from Zhu 2024. As mentioned, this is not a study affiliated with AbbVie, therefore the company has no additional detail on the methods of the study beyond those reported within the relevant publication.

Zhu 2024 reports the following OS and PFS HRs from the MIRASOL trial for mirvetuximab vs IC Chemo (March 2023 data cut; Table 10).

Table 10: Prior bevacizumab subgroup effectiveness results (Zhu 2024)

	Overall population	bevacizumab-naïve	bevacizumab-pretreated
OS	0.67	0.51	0.74
PFS	0.65	0.66	0.64

Abbreviations: OS, overall survival; PFS, progression-free survival

These show similar PFS HRs across the populations, but a better OS HR for the bevacizumab-naïve population and worse OS HR in the bevacizumab-pretreated population. Equivalent data from the September 2024 data cut are presented in Appendix C of the original submission, and summarised in Table 11, and shows a narrowing of these differences between subgroups and a reversal of the trend (OS HRs of 0.65 and 0.70 for prior exposure to bevacizumab and bevacizumab-naïve populations, respectively), therefore highlighting that prior bevacizumab treatment is not considered to modify the treatment effect of mirvetuximab. This is in line with clinical expert feedback to the company.

Table 11: Prior bevacizumab subgroup effectiveness results (MIRASOL data cut September 2024)

	Overall population	bevacizumab-naïve	bevacizumab-pretreated
OS	0.68	0.70	0.65
PFS	0.63	0.67	0.64

Abbreviations: OS, overall survival; PFS, progression-free survival

Based on the data used by Zhu 2024, it is expected that the bevacizumab-naïve population would have higher incremental QALYs compared to the overall population, and that the bevacizumab-pretreated population would have lower incremental QALYs than the overall population, as OS is a key determinant of incremental QALYs. It is uncertain from the paper what other model parameters may

be different between populations (such as whether the same distributions for extrapolating survival were used), and therefore what other drivers of results there might be.

c)

A scenario was undertaken within the submitted model, using data for the bevacizumab-naïve and bevacizumab-pretreated subgroups. Cost-effectiveness results can be seen in Table 12. Population-specific data used included: the Kaplan-Meier (KM) data, survival parameters, and baseline characteristics other than age. All other inputs and settings were kept the same as the submitted base-case.

The data for this scenario have also been included within the updated economic model.

Table 12: Prior bevacizumab subgroup cost-effectiveness results (Company model)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Submitted model					
Mirvetuximab	████	████	-	-	
Pooled chemotherapy	████	████	████	████	████
Bevacizumab-naïve population					
Mirvetuximab	████	████	-	-	
Pooled chemotherapy	████	████	████	████	████
Bevacizumab-pretreated population					
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Bevacizumab is restricted to use in the first line setting in the NHS, however, there continues to be variation in the proportion of women who receive bevacizumab for a variety of reasons such as Blueteq stipulations, and clinicians deeming patients unsuitable for bevacizumab treatment. This variability in selection is highlighted within the MIRASOL UK patient cohort (n=30) for whom only 11 patients received bevacizumab as a prior treatment regimen. As almost all patients will eventually

relapse regardless of the first-line treatment received, considering the population as a relevant whole would mean all patients at the point of PROC diagnosis would be able to benefit from the potential availability of mirvetuximab.

Survival analysis

B2. PRIORITY QUESTION: Please provide a comparison of all of the fitted parametric models to the observed smooth hazard plots. Please provide one plot per arm per outcome i.e. OS, PFS and time on treatment

The requested plots are provided in Figure 4 - Figure 11.

As mentioned within the submission, clinical experts confirmed that the end of the KM curve is not considered meaningful and should therefore be interpreted with caution. Similar observations have also been made in the methodological literature; in the context of presenting hazards for visual comparison during model selection.

In addition, the base case uses the KM's directly for time on treatment for chemotherapies, therefore the hazards presented here for chemotherapies for time on treatment are less relevant.

Figure 4: smoothed hazard vs parametric survival models (OS) – Mirvetuximab

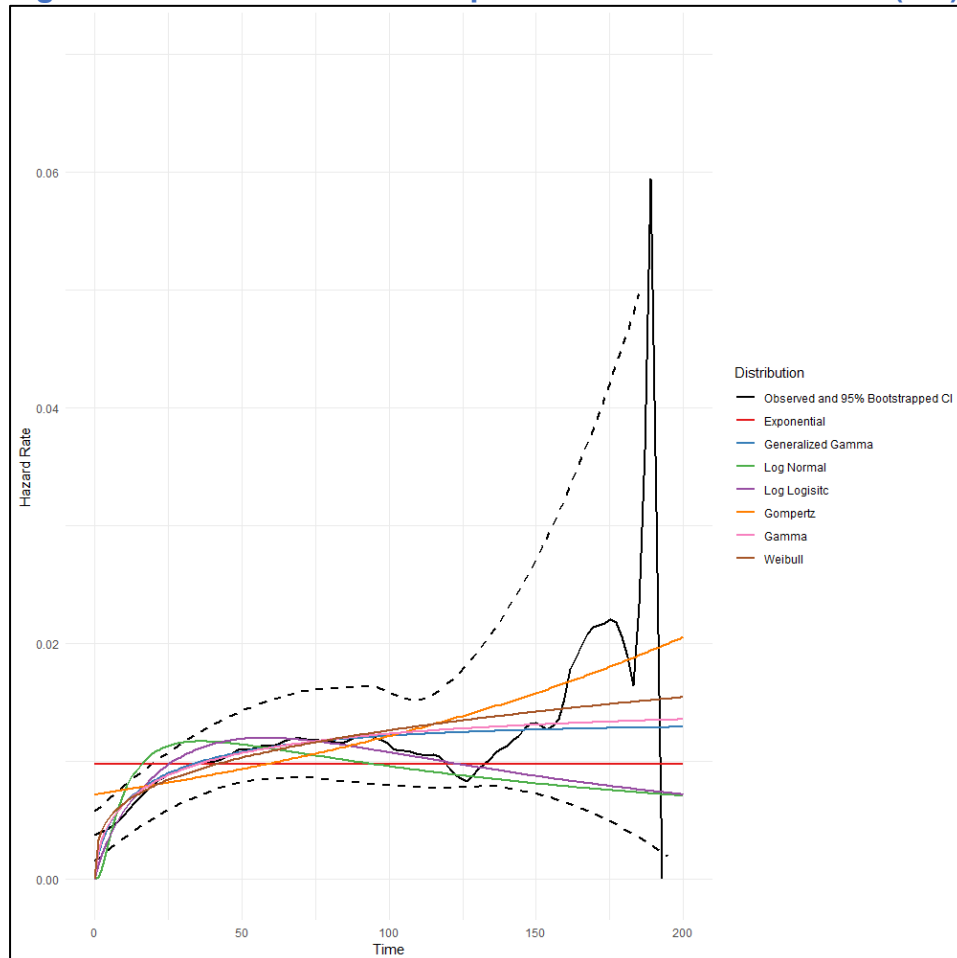


Figure 5: smoothed hazard vs parametric survival models (OS) – Chemotherapy

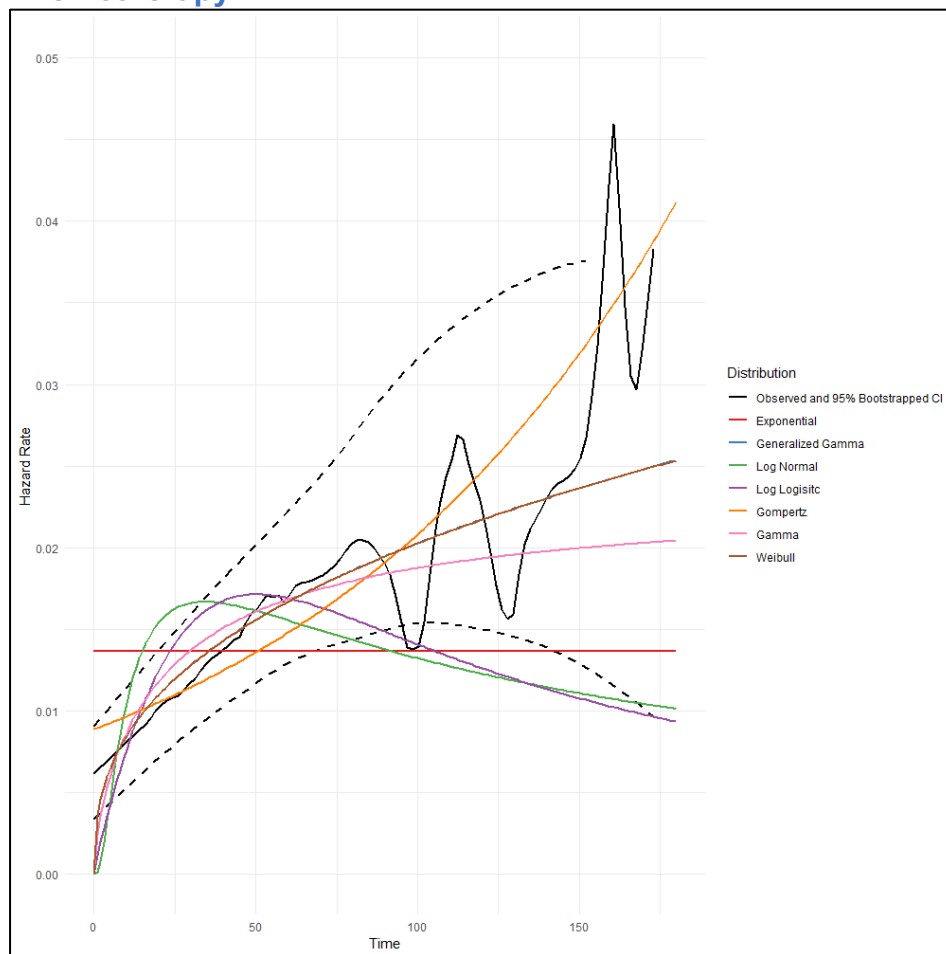


Figure 6: smoothed hazard vs parametric survival models (PFS) – Mirvetuximab

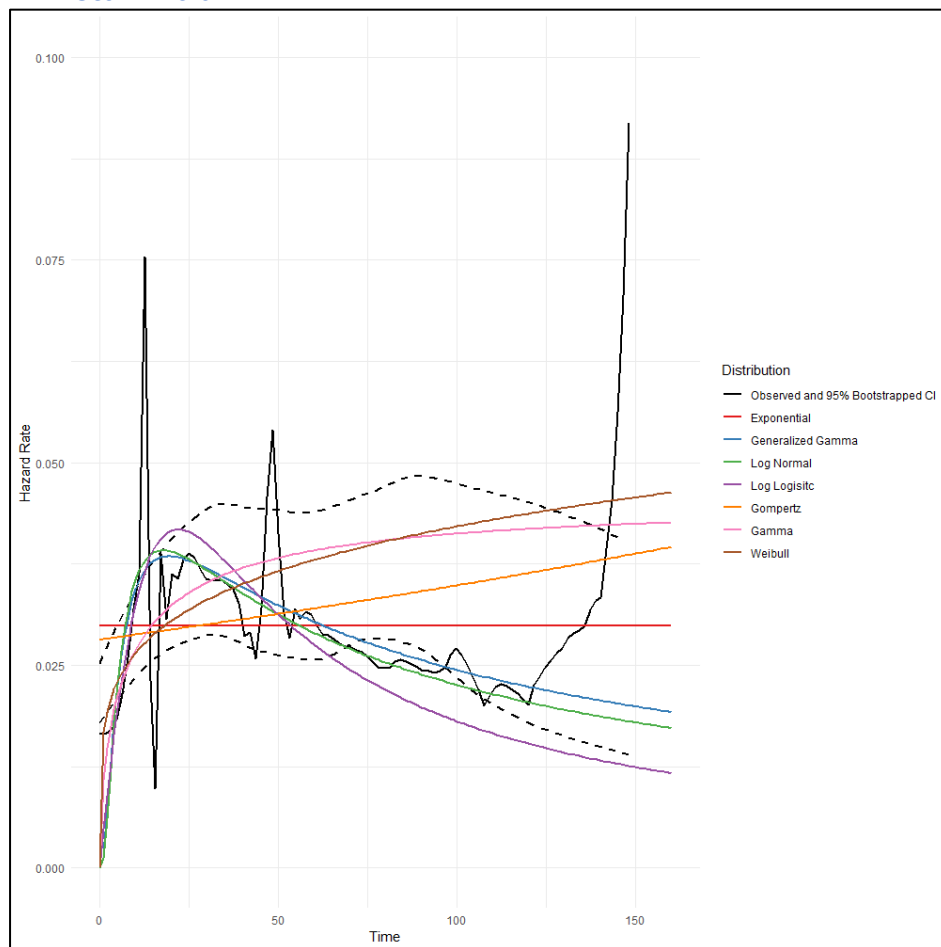


Figure 7: smoothed hazard vs parametric survival models (PFS) – Chemotherapy

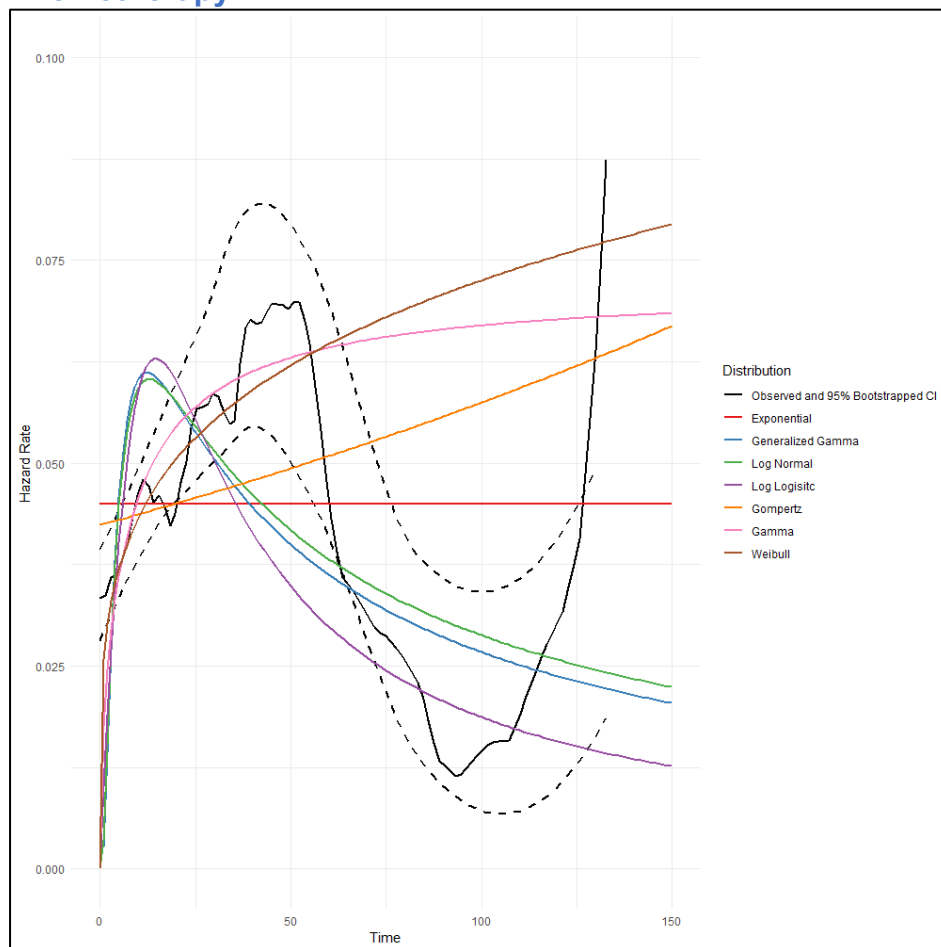


**Figure 8: smoothed hazard vs parametric survival models (time-on treatment)
– Mirvetuximab**

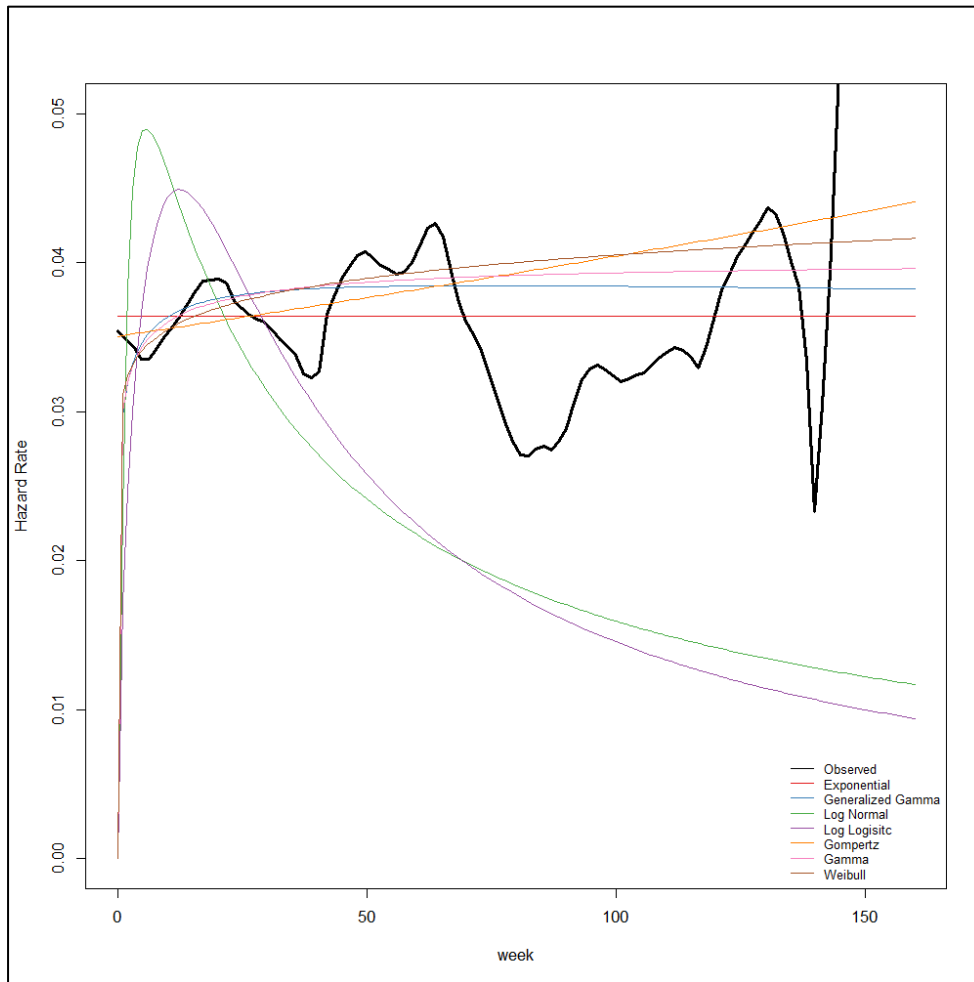


**Figure 9: smoothed hazard vs parametric survival models (time-on treatment)
– Paclitaxel**

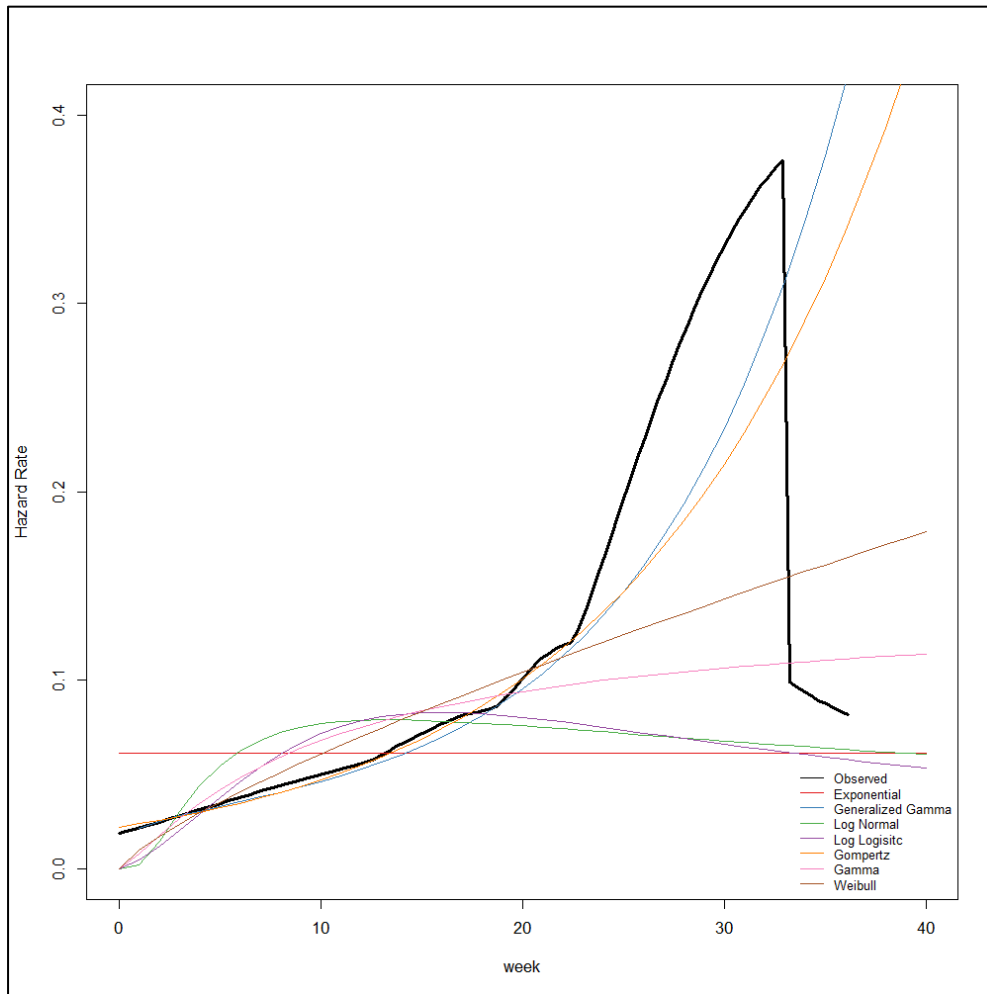


**Figure 10: smoothed hazard vs parametric survival models (time-on treatment)
– PLD**

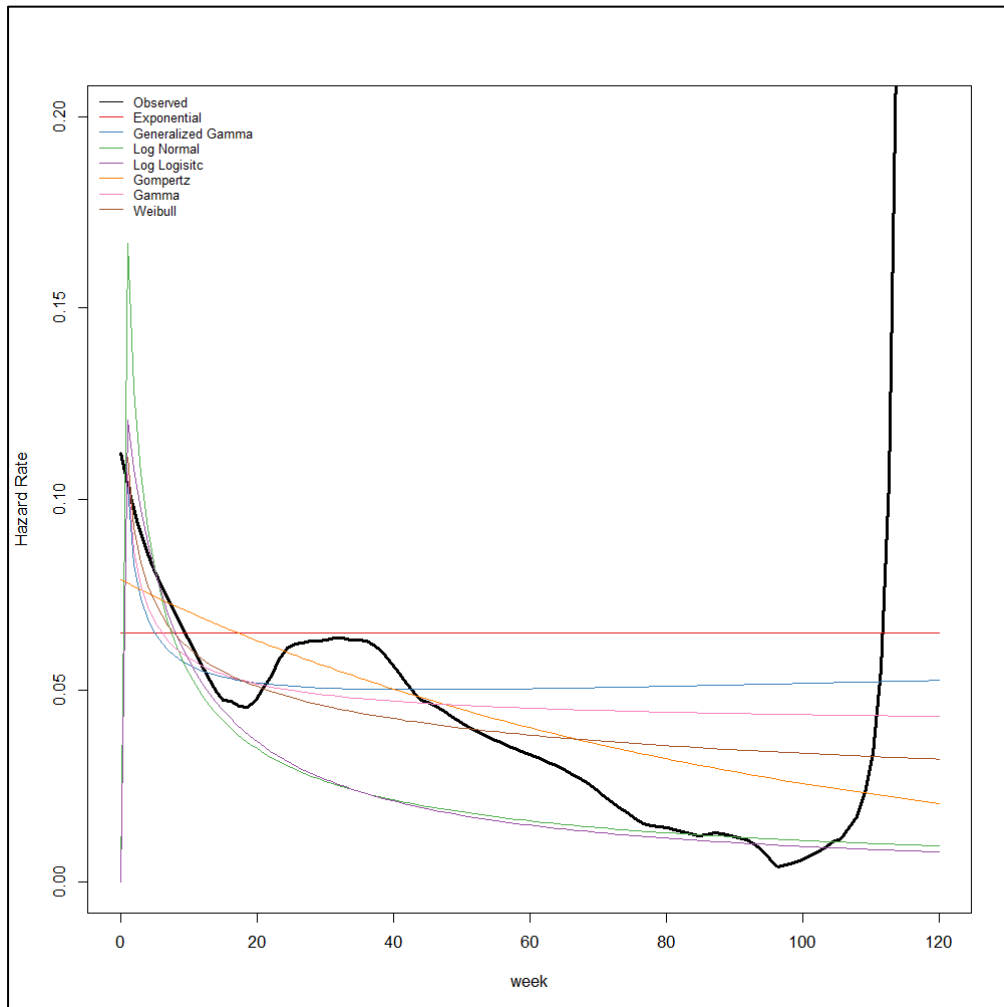
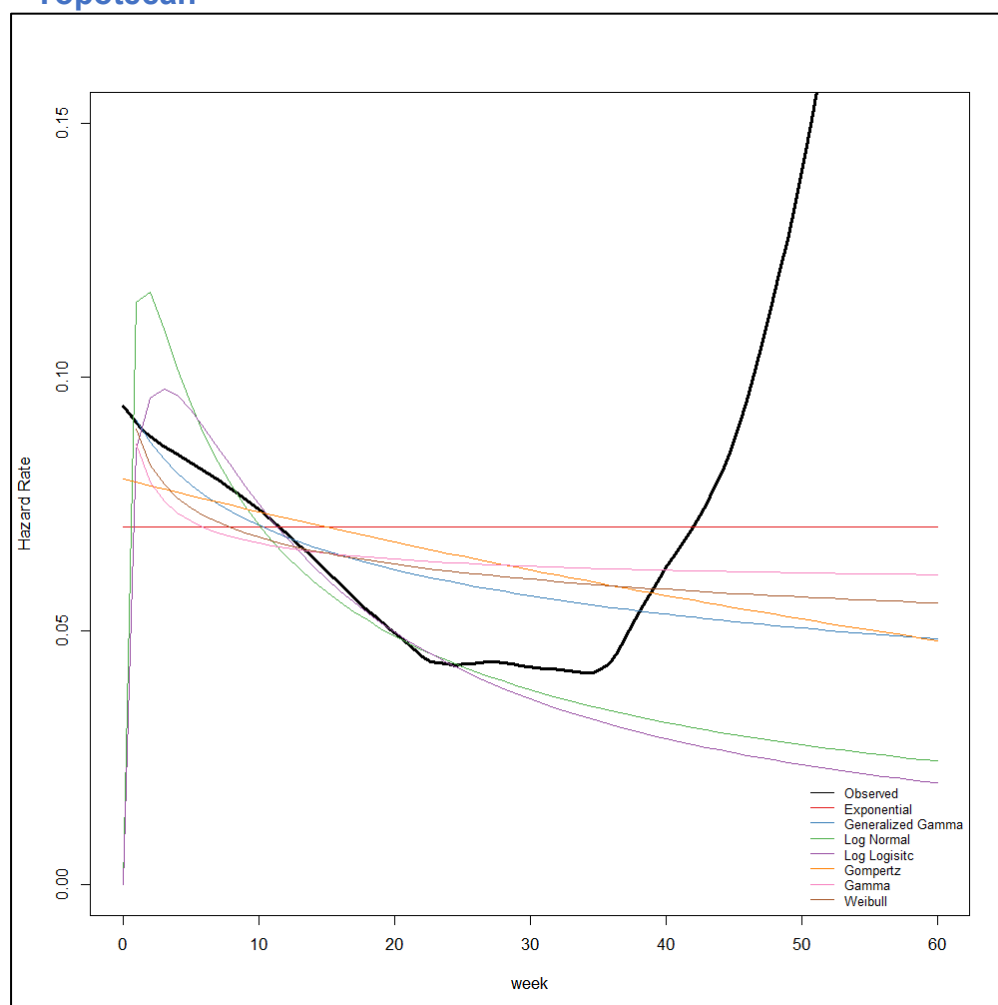


**Figure 11: smoothed hazard vs parametric survival models (time-on treatment)
– Topotecan**



B3. Please provide information on whether or not the OS, PFS and time on treatment curves cross prior to any capping adjustments being made in the base case. If so, please state at what timepoint and with what % of patients remaining without an event for each outcome?

For mirvetuximab, there is no point at which PFS is capped by OS, or duration of treatment (DoT) is capped by PFS.

For pooled chemotherapy, PFS is capped by OS from cycle 372, where there is 0.01% of people remaining progression-free at this point. For DoT, as each type of chemotherapy is considered separately, and the observed KM data is used for the DoT of the chemotherapies, rather than an extrapolated curve, then there are a small

number of points along the KMs for the chemotherapies where DoT slightly exceeds PFS, and is therefore capped from going above PFS. Notably:

- For paclitaxel; at cycles 1,5,6, 9-18, and cycle 20 (at cycle 1, 100% remain on treatment. At cycles 5 and 6, 91% and 86% remain on treatment respectively. And between cycles 9 and 20, between 73% and 37% remain on treatment).
- For pegylated liposomal doxorubicin; cycles 106 to 116 (0.01% on treatment in these cycles)
- For topotecan: cycles 39 to 46 (14% on treatment at cycle 39 and 12% on treatments at cycle 46)

Capping duration of treatment by PFS is included as an option within the model, and turning this off, leads to a slight reduction in the incremental cost-effectiveness ratio (ICER) to [REDACTED], as increased chemotherapy costs will affect the comparator arm; however the impact is minimal.

B4. The rationale provided to use KMs rather than parametric fits was: “As the KMs were complete for the components of pooled chemotherapy from MIRASOL, and parametric curves visually overestimated DoT compared with the observed data, the KM curves were used directly to model DoT”. Why then does the ICER increase rather than decrease when parametric curves are used to model chemotherapy DOT in Table 67 of the CS?

In an earlier part of the duration of treatment section of the submission (section 3.3.5), it is stated that *“For paclitaxel, pegylated liposomal doxorubicin, and topotecan, observed KM data was used for the DoT curves in the base case as the KM estimator was complete and parametric curves overestimated the proportion of patients remaining on treatment at the tail.”*

The overestimation is most apparent at the tail of the KMs, although it can also be seen for various other parts of the chemotherapy DoT KMs, and therefore in general the parametric curves were not considered to have a good visual fit to the KM data. However, for completeness, a scenario analysis was undertaken within the submission using the extrapolations, and the best fitting curves based on the goodness of fit statistics were selected. As the parametric curves provide a

smoothing of the KM curve, then on balance, this was seen to have very little impact on the ICER, increasing the ICER only by 0.1%.

Quality of life

B5. PRIORITY QUESTION:

- a) **Please justify the use of Wysham et al (164) for chemotherapy quality of life over other possible literature sources including TA389 and TAs 1007, 962 and 946 (post progression). This source appears to be using a paper from 2008 ([https://www.gynecologiconcology-online.net/article/S0090-8258\(08\)01111-6/abstract](https://www.gynecologiconcology-online.net/article/S0090-8258(08)01111-6/abstract)) that includes data from only 13 ovarian cancer patients and is using VAS which is not in line with the NICE reference case. There is also a notable difference between VAS and TTO derived utilities within the same study, suggesting internal inconsistency.**
- b) **Please provide a comparison of utility estimates for chemotherapy in all sources identified that could inform this**

a)

An alternative source for utilities for chemotherapy was used within the model, as the utility difference from MIRASOL between mirvetuximab and pooled chemotherapy was considered to lack face validity, given the feedback from individual patients on their experiences with chemotherapy and mirvetuximab. As highlighted in Section 2.6 of the submission, mirvetuximab is linked with improved quality of life (QoL) for patients, compared to pooled chemotherapy. The discrepancy between the differences reported in MIRASOL and the feedback from patients may be due to the limitations of EQ-5D in capturing key outcomes experienced by chemotherapy patients (24, 25). In addition, the timing of EQ-5D collection in MIRASOL (at the beginning of a treatment cycle) may have resulted in an underestimation of the detrimental QoL impact of chemotherapy: Sanghera et al report that EQ-5D-5L reduced by 0.074 in the first 7 days of a chemotherapy treatment cycle (26). Similarly, Kristensen et al found that symptom burden was highest one week after the beginning of a chemotherapy treatment cycle (27).

Therefore, based on findings from the economic and health-related quality of life (HRQoL) systematic literature reviews (SLRs), the utilities from Wysham, despite having limitations, were considered to best represent the poor QoL for chemotherapy patients. The values used were those from the time trade-off (TTO) analysis.

Additional reasons why mirvetuximab patients would be considered to have a substantially greater utility than chemotherapy patients, have also been reported in the main submission, and are briefly summarised here:

- In the pre-progression state:
 - Mirvetuximab is associated with higher response rates and reduced time to response compared with pooled chemotherapy; clinical experts confirmed that reduced tumour volume and disease burden would translate to symptomatic improvement, and with this improved QoL.
 - Statistically significant improvements were observed vs IC Chemo in the LSM analysis for the pre-specified exploratory abdominal/gastrointestinal symptom and attitude toward disease and treatment subscales (EORTC QLQ-OV28)
 - Adverse event (AE) profiles differ between mirvetuximab and pooled chemotherapy.
- In the post-progression state:
 - At the point of progression, patients who have received mirvetuximab would have a better QoL compared with pooled chemotherapy, stemming from a reduced tumour volume and disease burden; this benefit is expected to continue into the post-progression state
 - Treatment with mirvetuximab affords the opportunity of saving a chemotherapy line to a later option. This approach provides a period of recovery from chemotherapy side effects, whilst targeting the tumour through a different mechanistic approach.
 - Mirvetuximab is associated with improved time to second disease progression or death (PFS2) results compared with pooled chemotherapy and is therefore expected to have improved outcomes and contribute to

better QoL due to delayed second progression within the post-progression state.

b)

Sources identified that could inform the chemotherapy utilities included:

- The economic evaluations SLR (15 economic evaluations were identified, with utility values reported in 10 of these). Progression-free utilities ranged from 0.50 to 0.81. Progressed disease utilities ranged from 0.40 to 0.77.
- The HRQoL SLR (three utility studies were identified), however, none reported distinct utility values for pre- and post-progression health states.
- Finally, a targeted literature review of relevant NICE technology appraisals (TAs) was conducted to identify additional health-state specific utility values. 12 NICE TA's in ovarian cancer were identified, with utility values reported in 7 (TA962, TA946, TA908, TA784, TA389, TA284, TA285). Progression-free utilities ranged from 0.718 to 0.831. Progressed disease utilities ranged from 0.649 to 0.77.

Key outputs from these literature reviews are summarised in Table 13. The previously cited studies that did not report utility values have been excluded from the table.

The most appropriate sources were considered to be the SLR's, as they were most likely to be representative of the population in this appraisal, whereas most other NICE ovarian cancer TAs considered different populations or lines of treatment. As mentioned in response to part (a), there were a variety of reasons why there would be a larger difference between utilities in the two arms of the trial, and therefore utilities at the lower end for chemotherapy, were considered more appropriate.

Table 13: Utility inputs from noted studies

Publication, country	Population	Utility method	Utility source	Base case PF utility	Base case PD utility
Ball 2018, Canada	PRrOC	TTO	Utility elicitation study, OC: Howell 2015	0.81	0.77
Lai 2024, Taiwan	PRrOC	TTO and VAS	Utility elicitation study, OC: Havrilesky 2009 CEA of AURELIA, PRrOC: Wysham 2017	Bevbio + chemo: 0.61 Chemo: 0.50	Bevbio + chemo: 0.47 Chemo: 0.40
Luealon 2016, Thailand	PRr epithelial OC	EQ-5D	Observational study (FACT-G data)	0.766	NR
Neyt 2018, Belgium	PRrOC	EQ-5D	Adapted from utilities in HTA submissions: HTA submission, OC: NICE TA285 and NICE TA284	0.72	0.72
NICE TA389 (formally TA222) 2016, UK	Recurrent OC (platinum-resistant and sensitive analysed separately)	EQ-5D	HTA submission, PSOC: NICE TA222 (OVA-301 study)	0.718	0.649
Peters 2022, USA	PRrOC	NR	Systematic review and CEA, malignant bowel obstruction: Naghibi 2015	0.50	NR
SMC 1063/15 2015, Scotland	PRr epithelial ovarian, fallopian tube, or primary peritoneal cancer	NR	NR	0.718	0.649
Wysham 2017, USA	PRrOC	TTO	Utility elicitation study, OC: Havrilesky, 2009	Bev + chemo: 0.61 Chemo: 0.50	Bev + chemo: 0.47 Chemo: 0.40
Wallbillich 2016, USA	PRrOC	NR	Adapted from utilities in published literature	Genomic testing 0.9 SoC: 0.75	NR
Wolford 2022, USA	PRrOC	NR	NR	0.75	0.50
Zhu 2024, USA	PRrOC with high folate receptor-alpha	NR	CEA/CUA, OC: Wolford 2020	0.75	0.50
NICE TA962 2024, UK	BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after	EQ-5D-5L mapped to EQ-5D-3L	Phase 3 RCT, aOC: SOLO-1 trial	0.808	PD1: 0.756 PD2: 0.770

Publication, country	Population	Utility method	Utility source	Base case PF utility	Base case PD utility
	response to first-line platinum-based chemo				
NICE TA946 2024, UK	Advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer	EQ-5D-5L mapped to EQ-5D-3L	Phase 3 RCT, aOC: PAOLA-1 Phase 3 RCT, aOC: SOLO-1	0.750	PD1: 0.727 PD2: 0.680
NICE TA908 2023, UK	Relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer after 2 or more courses of platinum-based chemo	NR	NR	0.812	0.755
NICE TA784 2022, UK	Relapsed, platinum-sensitive ovarian, fallopian tube and peritoneal cancer	EQ-5D-5L mapped to EQ-5D-3L	Phase 3 RCT, PSOC: ENGOT-OV16/NOVA	0.831	0.762
NICE TA285 2013, UK	First recurrence of platinum-sensitive aOC	EQ-5D	HTA submission, PSOC: TA222 (OVA-301 study)	0.718	0.649
NICE TA284 2013, UK	First-line treatment of aOC	EQ-5D	Phase 3 RCT, aOC: ICON 7	Varied from weeks 0 to 54+, ranging from 0.6571 to 0.8129	0.7248

Abbreviations: AE, adverse event; aOC, advanced ovarian cancer; CEA, cost-effectiveness analysis; CI, confidence interval; EQ-5D, European Quality of Life Questionnaire – 5 Dimensions; HTA, health technology assessment; NR, not reported; NICE, National Institute for Health and Care Excellence; OC, ovarian cancer; PD, progressed disease; PF, progression free; PSOC, platinum sensitive ovarian cancer; RCT, randomised controlled trial; TA, technology appraisal; PLD, pegylated liposomal doxorubicin; PRr, platinum resistant recurrent; PRrOC, platinum resistant recurrent ovarian cancer.

B6. PRIORITY QUESTION:

- a) Please provide the statistical analysis outputs for the MMRM models fitted to EQ-5D data presented in Table 36 of the CS including variance / covariance matrices**
- b) Please provide the number and % of patients with missing data for the EQ-5D by arm, timepoint and progression status. If this proportion is high please comment on any methods used to adjust for missing data (or consider using such methods if none have been used)**

a)

MMRM models fitted to EQ-5D, adjusting for progression status, treatment allocation and the interaction between progression status and treatment allocation, can be seen in Table 14, with the variance/covariance matrix in Table 15. The progression x treatment interaction model indicates that:

- Chemotherapy patients have a significant decrement following disease progression.
- Whilst progression-free, patients treated with mirvetuximab have numerically improved utility score; however, this difference is not statistically significant
- Mirvetuximab patients have significantly improved utility score compared to chemotherapy patients post progression.
 - Mirvetuximab patients have a utility decrement of 0.057 (-0.117 [PD] + 0.060[interaction]) in the post progression state compared to when they are progression-free. In comparison the decrement is 0.117 for chemotherapy patients
 - Mirvetuximab patients have a utility benefit of 0.080 (treatment + interaction) compared to chemotherapy patients whilst in the post-progression state

Table 14: MMRM model adjusting for progression status, treatment allocation and the interaction between progression status and treatment allocation

Variable	Estimate	Standard error	t Value	Pr > t	Lower	Upper
Intercept (reference: state = PF, treatment = chemo)	0.712	0.014	51.360	<.0001	0.685	0.740
State: PD	-0.117	0.019	-6.280	<.0001	-0.153	-0.080
Treatment: Mirvetuximab	0.020	0.019	1.050	0.294	-0.017	0.057
State(PD)*treatment (mirvetuximab) interaction	0.060	0.024	2.460	0.015	0.012	0.108

Bold text indicates significant result. Abbreviations: PD, progressive disease, PF, progression-free

Table 15: Variance/covariance for MMRM model adjusting for progression status, treatment allocation and the interaction between progression status and treatment allocation

	Intercept	State	Treatment	State*treatment interaction
Intercept	0.000192	-0.00006	-0.00019	0.000060
State	-0.00006	0.000345	0.000060	-0.00034
Treatment	-0.00019	0.000060	0.000358	-0.00010
State*treatment interaction	0.000060	-0.00034	-0.00010	0.000589

MMRM models fitted to EQ-5D, adjusting for progression status and treatment allocation, can be seen in Table 16, with the variance/covariance matrix in Table 17. The progression + treatment model indicates that:

- All patients have a significant utility decrement following disease progression
- Patients treated with mirvetuximab have numerically improved utility score; however, this difference is not statistically significant

Table 16: MMRM model adjusting for progression status and treatment allocation

Variable	Estimate	Standard error	t Value	Pr > t	Lower	Upper
Intercept (reference: state = PF, treatment = chemo)	0.706	0.014	51.65	<.0001	0.679	0.733
State: PD	-0.082	0.012	-6.77	<.0001	-0.106	-0.058
Treatment: Mirv	0.030	0.018	1.64	0.101	-0.006	0.067

Bold text indicates significant result. Abbreviations: PD, progressive disease, PF, progression-free

Table 17: Variance/covariance for MMRM model adjusting for progression status and treatment allocation

	Intercept	State	Treatment
Intercept	0.000187	−0.00003	−0.00018
State	−0.00003	0.000146	2.067E-7
Treatment	−0.00018	2.067E-7	0.000342

MMRM models fitted to EQ-5D, adjusting for progression status and Grade 3+ AEs, can be seen in Table 18, with the variance/covariance matrix in Table 19. The progression and Grade 3+ AE model indicates that:

- All patients have a significant utility decrement following disease progression
- Patients who experience a Grade 3+ AE during or shortly before an EQ-5D assessment have numerically reduced utility score; however, this difference is not statistically significant

Table 18: MMRM model adjusting for progression status and Grade 3+ AEs

Variable	Estimate	Standard	t Value	Pr > t	Lower	Upper
Intercept (reference: state = PF, AE = no Grade 3+ AE)	0.724	0.010	76.040	<.0001	0.705	0.742
State: PD	−0.081	0.012	−6.690	<.0001	−0.105	−0.057
AE: Experienced Grade 3+ AE	−0.017	0.013	−1.290	0.199	−0.044	0.009

Bold text indicates significant result. Abbreviations: AE, adverse event; PD, progressive disease, PF, progression-free

Table 19: Variance/covariance for MMRM model adjusting for progression status and Grade 3+ AEs

	Intercept	State	AE
Intercept	0.000091	−0.00002	−0.00001
State	−0.00002	0.000146	−9.59E-6
AE	−0.00001	−9.59E-6	0.000182

Abbreviations: AE, adverse event

b)

please find information on coverage and missingness of EQ-5D-5L data by treatment in Table 20 to Table 24.

The percentage of coverage/missingness was computed based on the number of expected visits and the number of observed visits. In addition, given only the observed visits with a health state assigned were included in the utility analysis, the

percentage of coverage/missingness was further computed based on the number of expected visits and the number of observed visits with health states.

The analysis was conducted separately by treatment arm and stratified by on- and off-treatment periods to account for variations in the EQ-5D-5L assessment schedule based on cycle lengths and treatment status.

Please note that the current missing data analysis presents the proportion of missing data stratified by treatment arm, timepoint, and treatment discontinuation status rather than by progression status. This approach was taken because the assessment schedule is aligned with the treatment schedule. However, the proportion of missing data would be expected to be similar if stratified by progression status, as patients would discontinue treatment upon disease progression according to the protocol. As such, the current analysis should provide a reasonable representation of the overall missing data pattern.

Across all treatments, the percentage of EQ-5D-5L non-coverage/missingness during the on-treatment period reveals a variable pattern of data availability across scheduled visits. Missing data at baseline varied between 10% and 36%, but increased in the first few subsequent visits, and increased again at around weeks 24-48, likely reflecting attrition in the long term. Overall, the data did not exhibit a clear monotonic trend of increasing missingness over time. For off-treatment visits, missingness started relatively low within the first 7 days post-treatment (although still over 39%) but sharply increased to over 95% from 3 months onwards. This pattern suggests significant challenges in maintaining patient engagement and data collection during the off-treatment phase, likely due to reduced monitoring frequency or logistical barriers.

For continuous responses, linear mixed models are sometimes used to handle missingness when a series of outcomes are measured repeatedly over time (mixed-effect models for repeated measures (MMRM)). Likelihood-based methods (MMRM and GLMM) and some extended GEE (i.e. weighted GEE) models are applicable under MCAR and MAR assumptions (28).

In general, three mechanisms were considered for missing data: Missing Completely at Random (MCAR), Missing at Random (MAR), and Missing Not at Random (MNAR).

- MCAR is the ideal situation, however, it is difficult to prove that data is truly MCAR because we need to show that missingness is completely unrelated to both observed and unobserved data. Statistical tests only detect relationships with observed data, meaning they can suggest MCAR but cannot definitely prove it.
- Proving MNAR is also challenging for similar reasons, i.e. demonstrating that missingness is dependent on the missing values themselves, which are unknown.

As a result, assuming MAR is a common approach.

Table 20: Mirvetuximab EQ-5D-5L coverage/missing data

MIRV (3-week cycle)								
	Expected EQ5D visits ¹	Observed EQ5D visits with health states ²	Observed EQ5D visits without health states		% coverage	% non-coverage (i.e., % missingness)	Non-coverage due to no health state	Non-coverage due to other reasons
On treatment								
Baseline	218	182	0		83%	17%	0%	17%
Week 3	213	124	2		58%	42%	1%	41%
Week 6	209	108	0		52%	48%	0%	48%
Week 9	187	146	0		78%	22%	0%	22%
Week 12	173	95	1		55%	45%	1%	45%
Week 15	150	97	0		65%	35%	0%	35%
Week 18	135	85	1		63%	37%	1%	36%
Week 21	114	66	1		58%	42%	1%	41%
Week 24	110	53	1		48%	52%	1%	51%
Week 36	64	56	2		88%	13%	3%	9%
Week 48 ³	46	8	0		17%	83%	0%	83%
Off treatment								
Within 7 days of EoT	218	125	8		57%	43%	4%	39%
3-month post-EoT	164	4	0		2%	98%	0%	98%
6-month post-EoT	129	2	0		2%	98%	0%	98%
9-month post-EoT	107	0	0		0%	100%	0%	100%
12-month post-EoT	81	0	0		0%	100%	0%	100%

MIRV (3-week cycle)								
15-month post-EoT and after	59	0	0		0%	100%	0%	100%

Table 21: Paclitaxel EQ-5D-5L coverage/missing data

Paclitaxel 80 mg/m ² (4-week cycle)								
	Expected EQ5D visits¹	Observed EQ5D visits with health states²	Observed EQ5D visits without health states		% coverage	% non-coverage (i.e., % missingness)	Non-coverage due to no health state	Non-coverage due to other reasons
On treatment								
Baseline	82	74	3		90%	10%	4%	6%
Week 4	78	45	0		58%	42%	0%	42%
Week 8	65	50	1		77%	23%	2%	22%
Week 12	58	31	2		53%	47%	3%	43%
Week 16	50	27	0		54%	46%	0%	46%
Week 20	35	20	3		57%	43%	9%	34%
Week 24	29	11	1		38%	62%	3%	59%
Week 36	4	3	0		75%	25%	0%	25%
Week 48 ³	0	0	0		-	-	-	-
Off treatment								
Within 7 days of EoT	82	45	5		55%	45%	6%	39%
3-month post-EoT	69	1	0		1%	99%	0%	99%

Paclitaxel 80 mg/m ² (4-week cycle)								
6-month post-EoT	56	2	0		4%	96%	0%	96%
9-month post-EoT	39	1	0		3%	97%	0%	97%
12-month post-EoT	31	1	0		3%	97%	0%	97%
15-month post-EoT and after	23	1	0		4%	96%	0%	96%

Table 22: PLD EQ-5D-5L coverage/missing data

PLD 40 mg/m ² (4-week cycle)								
	Expected EQ5D visits¹	Observed EQ5D visits with health states²	Observed EQ5D visits without health states		% coverage	% non-coverage (i.e., % missingness)	Non-coverage due to no health state	Non-coverage due to other reasons
On treatment								
Baseline	76	60	2		79%	21%	3%	18%
Week 4	71	40	2		56%	44%	3%	41%
Week 8	50	29	3		58%	42%	6%	36%
Week 12	39	20	2		51%	49%	5%	44%
Week 16	28	17	1		61%	39%	4%	36%
Week 20	27	16	1		59%	41%	4%	37%
Week 24	24	13	1		54%	46%	4%	42%

PLD 40 mg/m ² (4-week cycle)								
Week 36	13	4	0		31%	69%	0%	69%
Week 48 ³	3	3	0		100%	0%	0%	0%
Off treatment								
Within 7 days of EoT	76	35	9		46%	54%	12%	42%
3-month post-EoT	52	0	1		0%	100%	2%	98%
6-month post-EoT	42	0	0		0%	100%	0%	100%
9-month post-EoT	36	0	0		0%	100%	0%	100%
12-month post-EoT	27	0	0		0%	100%	0%	100%
15-month post-EoT and after	20	0	0		0%	100%	0%	100%

Table 23: Topotecan 3 week cycle EQ-5D-5L coverage/missing data

Topotecan 1.25 mg/m ² (3-week cycle)								
	Expected EQ5D visits¹	Observed EQ5D visits with health states²	Observed EQ5D visits without health states		% coverage	% non-coverage (i.e., % missingness)	Non-coverage due to no health state	Non-coverage due to other reasons
On treatment								
Baseline	11	7	0		64%	36%	0%	36%
Week 3	10	4	0		40%	60%	0%	60%
Week 6	10	5	0		50%	50%	0%	50%

Topotecan 1.25 mg/m ² (3-week cycle)								
Week 9	6	6	0		100%	0%	0%	0%
Week 12	6	4	0		67%	33%	0%	33%
Week 15	6	4	0		67%	33%	0%	33%
Week 18	6	4	1		67%	33%	17%	17%
Week 21	6	4	0		67%	33%	0%	33%
Week 24	6	3	0		50%	50%	0%	50%
Week 36	5	5	0		100%	0%	0%	0%
Week 48 ³	5	1	0		20%	80%	0%	80%
Off treatment								
Within 7 days of EoT	11	6	0		55%	45%	0%	45%
3-month post-EoT	9	0	0		0%	100%	0%	100%
6-month post-EoT	7	0	0		0%	100%	0%	100%
9-month post-EoT	6	0	0		0%	100%	0%	100%
12-month post-EoT	5	0	0		0%	100%	0%	100%
15-month post-EoT and after	2	0	0		0%	100%	0%	100%

Table 24: Topotecan 4 week cycle EQ-5D-5L coverage/missing data

Topotecan 4 mg/m ² (4-week cycle)								
	Expected EQ5D visits ¹	Observed EQ5D visits with health states ²	Observed EQ5D visits without health states		% coverage	% non-coverage (i.e., % missingness)	Non-coverage due to no health state	Non-coverage due to other reasons
On treatment								
Baseline	38	29	1		76%	24%	3%	21%
Week 4	30	14	0		47%	53%	0%	53%
Week 8	23	16	0		70%	30%	0%	30%
Week 12	16	4	1		25%	75%	6%	69%
Week 16	10	3	0		30%	70%	0%	70%
Week 20	6	3	0		50%	50%	0%	50%
Week 24	4	0	0		0%	100%	0%	100%
Week 36	2	1	0		50%	50%	0%	50%
Week 48 ³	1	0	0		0%	100%	0%	100%
Off treatment								
Within 7 days of EoT	38	17	2		45%	55%	5%	50%
3-month post-EoT	20	0	0		0%	100%	0%	100%
6-month post-EoT	18	0	0		0%	100%	0%	100%
9-month post-EoT	13	0	0		0%	100%	0%	100%
12-month post-EoT	10	0	0		0%	100%	0%	100%

Topotecan 4 mg/m ² (4-week cycle)								
15-month post-EoT and after	8	0	0		0%	100%	0%	100%

Costing

B7. PRIORITY QUESTION:

- a) **Rather than using the RDI for mirvetuximab please model accurately the impact of missed doses and doses at a reduced level of dosing on drug costs. Please check whether there is time dependency i.e. are patients who tolerate the full dose better remaining on treatment longer?**
- b) **We are concerned that the patient weight in the model appears low for a UK population. Please provide individual patient AIBW data by geographic region**

a)

It is common amongst appraisals to consider a single value of relative dose intensity. However, for completeness, a scenario has been undertaken, based on including within the model, the per cycle;

- Proportion of people who received treatment

Thereby accounting for missed doses, as this proportion is based on 1 minus the proportion who missed doses (the proportion who missed doses being: the number who missed doses per treatment cycle divided by the number of dose records per treatment cycle). There is a low number of individuals for whom the dose was not reported (~2% of doses), and these are excluded from the number of dose records in the aforementioned calculation.

- Average RDI in those who received treatment

Taking the average dose in those with a dose reported, divided by planned dose. Therefore, separating out missed doses, so these are not being accounted for within the drug costs.

Please note this method is only being applied to the pre-progression treatment costs.

Results can be seen below in Table 25, and were found to have a minimal impact. This scenario has also been included as an option within the updated economic model.

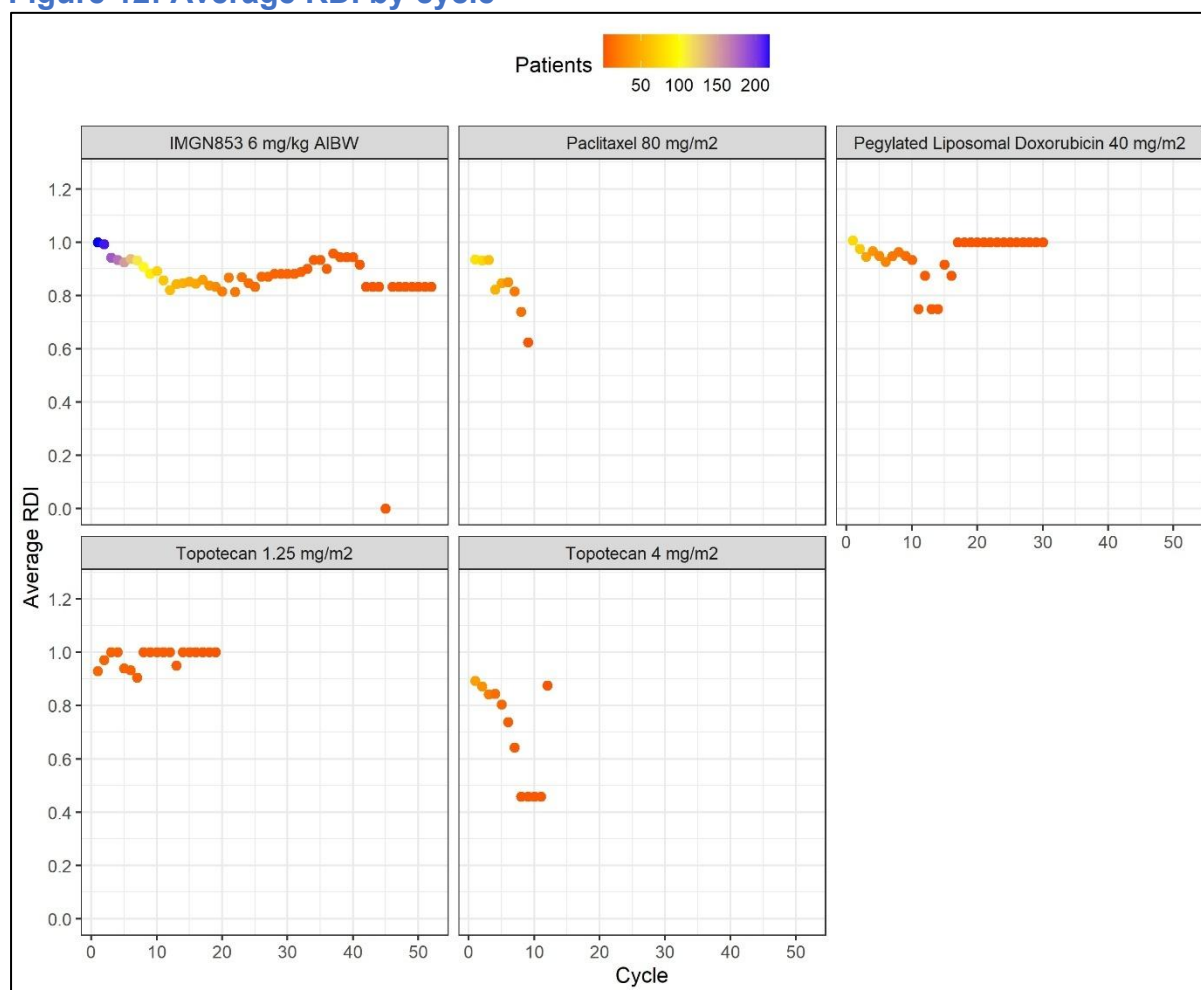
Table 25: Updated RDI approach

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Submitted model					
Mirvetuximab	████	████	-	-	
Pooled chemotherapy	████	████	████	████	████
Scenario using alternative RDI approach					
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; RDI, relative dose intensity.

Additional detail on the average RDI per cycle is shown in Figure 12; records which did not report the dose given were excluded, an RDI of 0 was given for missed doses. The plot should be interpreted with caution due to low patient numbers particularly for the individual chemotherapy components, and after cycle 20 for the mirvetuximab arm. For mirvetuximab, it is observed that RDI gradually reduces for the first 10 cycles before plateauing, after approximately cycle 20 (where there are fewer than 20 patients still receiving treatment) the RDI increases again before remaining relatively constant after cycle 40 where estimates are only based on one patient. For topotecan 1.25 mg/m², the RDI remains at or is close to 1. Topotecan 4 mg/m² and paclitaxel 80 mg/m² both display a general decreasing trend in RDI over time, though the RDI does increase in the topotecan arm when 1 patient is left on treatment. For PLD, there is a slight decreasing trend over the initial 14 cycles before increasing (though only 3 patients remain on treatment at this time).

Figure 12: Average RDI by cycle



Abbreviations: RDI, relative dose intensity. Note that IMGN853 refers to mirvetuximab.

b)

Patient AIBW by geographic region is provided in Table 26 below. This is generally consistent across regions (apart from the Middle East although that was only based on a single patient). For the 17 patients based in the UK, a mean AIBW of 60.4 was estimated which is similar to the overall AIBW.

Table 26: Summary of AIBW (kg) by region

REGION	Patients	Mean	SD	min	Q1	Median	Q3	Max
APAC	25	53.9	6.8	39.1	48.4	54.5	58.2	68.2
Europe	121	58.8	7.5	40.2	53.7	58.0	62.7	77.2
UK	17	60.4	8.9	40.2	54.6	62.2	67.8	74.5
Middle East	1	48.3	NA	48.3	48.3	48.3	48.3	48.3
North America	71	61.4	9.1	41.0	55.0	61.4	66.4	84.8
Overall	218	59.1	8.3	39.1	53.6	58.3	64.3	84.8

Abbreviations: AIBW, adjusted ideal body weight; APAC, Asia-Pacific; kg, kilograms; Q, quarter; SD, standard deviation.

B8. PRIORITY QUESTION:

- a) **Please remove the cost of mirvetuximab from the chemotherapy arm of the model as this is not appropriate (it is not currently recommended). If you wish to match costs and effectiveness consider adjusting the effectiveness of IC Chemotherapy to remove the impact of crossover, however, as the proportion is low we would not expect to see a major impact.**
- b) **Please see earlier question (A16) on the impact of other non-UK subsequent treatments on effectiveness. If a major impact was shown please use adjusted estimates in the cost-effectiveness model to ensure that costs and effects match.**

a)

Table 27 presents the results of two scenarios, firstly removing the mirvetuximab costs from the pooled chemotherapy arm as a post progression treatment, and secondly removing the mirvetuximab costs from the pooled chemotherapy arm in addition to adjusting the pooled chemotherapy OS for mirvetuximab use. The crossover analysis was undertaken using the Rank Preserving Structural Failure Time Models (RPSFTM) approach, which is a commonly used method for crossover adjustment (29). Please see Appendix C for the methodological details of this adjustment.

Within the pooled chemotherapy arm, 9% of patients received mirvetuximab post progression, and this has been distributed proportionally across the remaining treatments.

The second scenario has also been included as an option within the updated economic model.

Table 27: Chemotherapy post progression adjustments - cost-effectiveness results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Submitted model					
Mirvetuximab	████	████	-	-	
Pooled chemotherapy	████	████	████	████	████
Removal of mirvetuximab costs post progression in chemotherapy arm					
Mirvetuximab	████	████	-	-	
Pooled chemotherapy	████	████	████	████	████
Removal of mirvetuximab costs post progression in chemotherapy arm + adjusting chemotherapy OS for mirvetuximab crossover					
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

b)

In the MIRASOL trial, 22% (51/227) of patients in the MIRV arm and 29% (66/226) patients in the chemotherapy arm received 1st subsequent treatments not aligned with NHS clinical practice. A breakdown of these treatments is provided below in Table 28.

Table 28: First subsequent treatments not aligned with NHS clinical practice

Treatment	Mirvetuximab (n=227)	IC Chemo (n=226)
Targeted therapies* +/- chemotherapy	27 (12%)	27 (12%)
PD1/PD-L1 +/- chemotherapy	2 (1%)	6 (3%)
Targeted therapy + PD1/PD-L1 +/- chemotherapy	2 (1%)	2 (1%)
Mirvetuximab	0 (0%)	6 (3%)
Chemo (other) +/- platinum or Taxanes chemotherapy	20 (9%)	25 (11%)
Total	51 (22%)	66 (29%)

*Targeted therapies include bevacizumab, Kinase inhibitors, PARP inhibitors

Abbreviations: Chemo, chemotherapy; IC Chemo, investigators choice of chemotherapy; PARP, poly (ADP-ribose) polymerase; PD1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

As explained in A16, an OS adjustment analysis for these non-NHS subsequent therapies was not conducted, based on the following rationale:

- The majority of non-NHS subsequent treatments included targeted therapies with or without chemotherapy, and other chemotherapy (non-platinum, non-taxanes). These treatments were relatively balanced between the mirvetuximab and chemotherapy arms, with only 2% higher use of other chemotherapy in the chemotherapy arm. As such, the impact of adjusting would be minimal.
- The percentage of patients receiving other non-NHS subsequent therapies was low ($\leq 3\%$ for individual category), which was expected to have minimal impact on the OS. Among them, 3% (6/226) of patients in the chemotherapy arm crossed over to mirvetuximab. We performed a rank-preserving structural failure time model (RPSFTM) analysis to adjust for the cross-over effect on OS. The results showed that the adjusted OS was very similar to unadjusted OS, with adjusted HR of 0.663 (0.534, 0.822) vs. unadjusted HR of 0.674 (0.543, 0.836). This analysis supported that other non-NHS subsequent treatments, given their small numbers, are likely to have minimal impact on OS.
- AbbVie received clinical expert feedback that other than mirvetuximab, none of the other subsequent therapies could impact OS in a way that is different from the impact of treatments routinely available in the NHS.

Given these considerations, an OS adjustment for treatment switching to non-NHS subsequent therapies was not conducted, as it was unlikely to alter conclusions and deemed to be unnecessary.

**B9. Was the duration of subsequent treatment captured in the MIRASOL trial?
If so please use this in the economic model.**

The duration of subsequent treatment was captured within MIRASOL, and a scenario has been undertaken using this within the model. The median treatment durations of subsequent treatments used in the scenario is presented in Table 29. Note that some patients received more than one dose of the same subsequent

treatment at different times, e.g. one patient randomised to paclitaxel 80 mg/m² received subsequent mirvetuximab soravtansine on two occasions with a 6-week break in between.

Individual dose was not recorded, therefore the same duration for topotecan is applied to both topotecan dosing regimens.

Table 29: Subsequent treatment durations from MIRASOL

Treatment	Number completed treatment	Median (weeks)
Anthracyclines (PLD)	67	12.71
Gemcitabine	86	14.00
Mirvetuximab soravtansine	11	16.14
Taxanes	104	20.29
Topotecan	36	14.14

Abbreviations: PLD, pegylated liposomal doxorubicin

Results of the scenario analyses are presented in Table 30 with the durations from MIRASOL having little impact on the ICER.

The subsequent treatment durations from MIRASOL have been included as part of an updated model base case.

Table 30: Subsequent treatment durations from MIRASOL - cost-effectiveness results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Submitted model					
Mirvetuximab	████	████	-	-	
Pooled chemotherapy	████	████	████	████	████
Duration of subsequent treatments based on MIRASOL					
Mirvetuximab	████	████	-	-	
Pooled chemotherapy	████	████	████	████	████

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

B10. The model does not appear to align with statements in the clinical section of the CS on the level of resource intensiveness involved in treating PROC.

Please comment on the appropriateness of the inclusion of terminal care as a one off cost rather than ongoing palliative care costs during later lines of treatment.

Estimates of post-progression resource use were derived from those presented in NICE TA285 (bevacizumab for platinum-sensitive advanced OC), and are presented in Table 52 of the original submission dossier. Resource use was validated with clinicians, and was broadly in line with clinician expectations.

The mean time spent in the post progression state is considered relatively short, therefore a one-off cost as a simplification was not considered unreasonable, as this was not expected to differ between model arms. The submitted model is a three-state partitioned survival model, and as such there is no formal modelling of movements to subsequent lines of care beyond initial progression. Therefore, simplifications commonly used in models were applied, such as the application of post-progression drug costs at the point of progression, and the application of terminal care as a one-off cost incurred on death.

B11. PRIORITY QUESTION:

- a) Where did the cost of FR α tests come from and is this price guaranteed / does it cover all of the tests allowed within the draft SmPC?**
- b) We have received clinical expert feedback that in the long-term it is likely the NHS will move to testing all patients at diagnosis as biopsies are carried out at this stage rather than entry to PROC. Please amend the calculations for number of patients tested accordingly.**

a)

The cost of FR α alpha tests was derived from the manufacturer (Roche).

The only test to be utilised in the UK will be the VENTANA FOLR1 assay, and from insights obtained so far, there is no anticipation of implementation of any further validated lab-developed tests as allowed per the SmPC.

b)

Feedback was received from clinicians that it is highly unlikely the NHS would implement testing at OC diagnosis. Many patients with OC never progress to PROC; a small number are cured and some die before they become eligible for mirvetuximab. The need for testing is most critical at the point of determining eligibility for treatment. Even if testing moved to OC diagnosis, this would be adopted gradually over an extended period of time. There remains an ongoing discussion within the clinical community about the optimal timing for early testing; whether it should be conducted at first or second relapse, when patients are likely to develop platinum resistance, or at initial diagnosis to facilitate integration into the diagnostic pathology workflow. These discussions are ongoing and represent a long-term consideration that will develop over many years. Therefore, for the current submission, the company does not believe any amendments to the model are required.

Calculation of the severity modifier

B12. Please provide individual patient data for the age of patients enrolled in MIRASOL. Please also report the mean age and standard deviation.

A summary of baseline age (and uncertainty) by randomised treatment are reported in Table 31 below.

Table 31: Summary of baseline age by randomised treatment

Treatment	Patients	Mean	SD	min	Q1	Median	Q3	Max
Chemotherapy	226	62.3	9.3	29	55.25	62	69	87
Mirvetuximab	227	63.3	9.8	32	57	64	70.5	88
Overall	453	62.8	9.6	29	56	63	70	88

Abbreviations: Q, quarter; SD, standard deviation.

B13. PRIORITY QUESTION: Please use the methods presented in Lee et al. (<https://link.springer.com/article/10.1007/s40258-024-00918-9>) to account for the impact of age distribution on estimates of general population mortality and utility and recalculate the expected proportional and absolute shortfall

We acknowledge that the calculation of QALY shortfall can vary depending on the method used to represent the age distribution.

As a crude estimate of the distribution of age: The source used for mean age within the model (Parikh 2018) reports a SD around the reported age of 10.7. Using the sample size, mean age, and SD to calculate a 95% CI gives: 57.98, 60.42 (LCI, UCI). We have tested a scenario where using the upper end of the CI within the model, which did not result in a change to the calculated severity modifier.

As shown in Table 2 of the Lee (2025) paper, population QALY estimates differed by approximately -5% to +10% when alternative methods were used compared to the population mean (our current approach). We tested this full range in our model and further extended it to a more extreme scenario, assuming a 10% decrease in population QALYs (see Table 32 below). In all cases, the resulting QALY weight remained at 1.7.

Additionally, our study population resembles the ‘neoplasm’ group in the Lee paper, with patients who have platinum-resistant ovarian cancer and a mean age of around 60. As suggested in the paper, using the population mean for QALY estimation is likely a conservative approach, as an empirical age distribution would likely yield an even greater QALY shortfall.

Therefore, we believe the current QALY weight of 1.7 is reasonably robust and unlikely to be affected by the choice of methods. Finally, given that age is a protected characteristic under the equalities legislation, it would seem inappropriate to disadvantage older female patients, who may have already faced late diagnoses and treatment due to magnified challenges for rare cancers and geographic and socioeconomic variation in treatment access.

Table 32 Impact of age distribution on QALY shortfall

QALY shortfall	Base case	Population QALY decreased by 10%
General population QALYs	12.861	11.575
Absolute shortfall	12.309	11.023
Relative shortfall	96%	95%
QALY weight	1.70	1.70

Validation

B14. Please provide additional external validation of the model by comparing outcomes for chemotherapy to TA389 and TAs 1007, 962 and 946 (post progression) and by comparing modelled results to Zhu 2024 and the total modelled costs to Indukuri 2022

The company submission includes paclitaxel, PLD, and topotecan as chemotherapy comparators. In contrast, TA1007, TA962, and TA946 do not incorporate these chemotherapy agents, and their patient populations differ from that of the company submission, either because for example focusing specifically on second line treatment, or not being platinum resistant, and therefore are likely to be less severe populations. As a result, direct comparisons of chemotherapy outcomes across these sources are not considered appropriate. A summary of the populations compared across appraisals can be seen in Table 33 below.

Table 33: Overview of populations in current and previous appraisals

Appraisal	Population	Comments
Current appraisal	Adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens	The current appraisal includes a population who have had 1-3 prior lines of treatment, and therefore on average are a higher severity population. The population being considered is also platinum resistant.
TA1007	People with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy	Treatments in this appraisal are being used as maintenance treatments in a population who have responded to first line treatment. This is also not in a platinum resistant population.
TA962	Adults with BRCA-mutated advanced high-grade ovarian, fallopian tube or peritoneal cancer that have responded (completely or partially) to first-line chemotherapy without bevacizumab	Treatments in this appraisal are being used as maintenance treatments in a population who have responded to first line treatment. This is also within a specific mutation, and is not in a platinum resistant population.

Appraisal	Population	Comments
TA946	People with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer: • With complete or partial response after first-line platinum-based chemotherapy plus bevacizumab, and • Whose cancer is associated with HRD-positive status	This population is also a second line population as TA962, and is also not a platinum resistant population.
TA389	Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer. Looks at individual populations of: • platinum-sensitive disease (PFI ≥6 months) • platinum resistant/refractory disease (PFI <6 months or progression while on treatment)	Most similar population to this appraisal

Abbreviations: BRCA, breast cancer gene; FRα, folate receptor alpha; HRD, homologous recombination deficiency; PFI, platinum-free interval; TA, technology appraisal;.

TA389 does however include reported outcomes for paclitaxel, PLD, and topotecan which can be compared to the company submission. Data that were reported in TA389 from the platinum resistant/refractory population (of mean survival and QALY estimates) and data from the company submission, are compared in Table 34. Mean PFS and OS align relatively closely to the company model, and total QALYs are also similar.

Table 34: Comparison of company submission to TA389 chemotherapy outcomes

Outcomes				
Treatment	Platinum resistant/refractory network TA389		Company submission modelled outcomes	
	Mean PFS (months)	Mean OS (months)	Mean PFS (months)	Mean OS (months)
Paclitaxel	4.6	18.0	5.74	19.24
PLD	5.3	18.6		
Topotecan	5.3	18.9		
Treatment	TA389 EAG model results		Company submission model results	
	Total QALYs		Total QALYs	
Paclitaxel	0.971			
PLD	1.004			
Topotecan	1.020			

Abbreviations: OS, overall survival; QALY, quality adjusted life year; PFS, progression free survival; PLD, pegylated liposomal doxorubicin; TA, technology appraisal.

As discussed in the response to Question B1, the submitted economic analysis differs in several respects from that of Zhu 2024, particularly regarding inputs and assumptions, which could influence the estimated QALYs and costs. Additionally, the cost estimates are not directly comparable, as Zhu 2024 presents analysis based on the U.S. healthcare system. Although Zhu 2024 did not have access to patient-level data, the QALY estimates are broadly consistent with those in the company submission. For the overall population, Zhu 2024 reports incremental QALYs of 0.90, compared with [REDACTED] in the company submission (excluding the severity modifier). However, Zhu 2024 reports higher incremental life years gained, at 1.55, whereas the company submission reports [REDACTED] discounted and [REDACTED] undiscounted (not clear if Zhu 2024 is discounting life years).

Indukuri 2022 reports an average annual per-patient cost of €24,111 for PROC patients. When converted to British pounds using the XE currency converter and adjusted to 2024 values using PSSRU inflation indices, this equates to an updated average cost of £23,365. In comparison, the company's budget impact analysis estimates an average annual per-patient cost of £15,096.70 (excluding mirvetuximab), which is lower than the cost reported in Indukuri 2022. It is important to note that figures from Indukuri 2022 are derived from data across multiple countries, hence the value of this comparison may be limited.

B15. PRIORITY QUESTION:

- a) Please present a validation of model inputs (in particular utilities, resource use and cost codes selected) with TAs 1007, 962 and 946. Pay particular attention to assumptions made in that TA post progression which should align with this line of treatment**
- b) If there are areas of considerable disagreement (particularly for utilities) please update the economic model to allow use of data from previous TAs and consider updating your base case**

a)

Where reported, inputs from TA1007, TA962, and TA946 were compared with those used in the company submission, and a summary of the findings is presented in Table 35 below. The summary focuses mainly on health state utilities, and resource use and costs associated with health states.

Resource use associated with health states was found to be similar between sources, as well as costs used for resource use. The company is aware that there are differences in utilities, particularly for the chemotherapy arm (see response to B5a), and a variety of scenarios were undertaken within the submission using utilities from MIRASOL for both arms.

Table 35: Validation of model inputs

Model input	Inputs from previous TAs	Company submission input	Aligns with previous TA?	Justification
Utility				
Pre-progression HSUV	TA1007: NA TA962: 0.808 TA946: 0.750	Mirvetuximab: 0.737 Pooled chemo: 0.500	The company submission is sourced from Wysham et al. 2017 which does not align with TA1007, TA962, or TA946.	To align with patient reported experiences of chemotherapy, a lower HSUV was used for chemo.
Post-progression HSUV	TA1007: NA TA962: PD1=0.756, PD2=0.770 TA946: PD1=0.727, PD2=0.680	Mirvetuximab: 0.655 Pooled chemotherapy: 0.400	The company submission is sourced from Wysham et al. 2017 which does not align with TA1007, TA962, or TA946.	To align with patient reported experiences of mirvetuximab and chemotherapy, a lower HSUV was used for chemo.
Resource use				
CT scan cost	TA1007: £93.00 TA962: £106.22 TA946: £83.25	£118.58	In the company submission, CT scan is costed using NHS reference cost codes RD20A-RD21A, RD22Z-RD27Z which aligns with the cost codes utilised in TA946. Additionally, similar codes are used in TA1007 and TA962.	NA
CT scan frequency pre-progression	TA1007: 4 per year	6.0 per year	Pre-progression frequency for CT	Frequencies were sourced from

Model input	Inputs from previous TAs	Company submission input	Aligns with previous TA?	Justification
	TA962: 12 per year for first 2 years, 4 per year post 2 years TA946: 2 per year on trt, 1 per year off trt		scans is higher TA1007 and TA946, but lower than TA962.	TA285 submission for bevacizumab for platinum-sensitive OC and were validated by relevant clinicians.
CT scan frequency post-progression	TA1007: 0 per year TA962: 12 per year TA946: 4 per year	0.0 per year	Post-progression frequency for CT scans aligns with TA1007 and is lower than TA962 and TA946.	Frequencies were sourced from TA285 submission for bevacizumab for platinum-sensitive OC and were validated by relevant clinicians.
Gynaecological oncology consultation cost	TA1007: £158.00 TA962: £164.92 TA946: £224.55	£192.39	Gynaecological oncology consultation is costed using NHS reference cost code 503 which aligns with TA962.	NA
Gynaecological oncology consultation frequency pre-progression	TA1007: 12 per year TA962: 2 per year TA946: 16 per year on trt, 4 per year off trt	12.0	The pre-progression frequency for gynaecological oncology consultations aligns with the progression-free maintenance frequency reported in TA1007. TA962 reports a lower frequency, while TA946 reports a higher frequency than that used in the company submission.	Frequencies were sourced from TA285 submission for bevacizumab for platinum-sensitive OC and were validated by relevant clinicians.
Gynaecological oncological consultation frequency post-progression	TA1007: 4 per year TA962: 4 per year TA946: 16 per year	4.0	The post-progression frequency for gynaecological oncology consultations aligns with TA1007 and TA962. TA946 has a higher	Frequencies were sourced from TA285 submission for bevacizumab for platinum-sensitive OC, and were validated by relevant clinicians.

Model input	Inputs from previous TAs	Company submission input	Aligns with previous TA?	Justification
			progressed frequency than the company submission.	
End-of-life				
End-of-life cost	TA1007: NR TA962: £8,053.60 TA946: £8,053.60	£13,964.00	Sourced from PSSRU which is higher than TA1007, TA962, or TA946.	End-of-life cost from PSSRU has been utilised in previous recent oncology TAs.
% receiving end-of-life cost	TA1007: NR TA962: 51.28% TA946: 51.28%	100%	Sourced from PSSRU which does not align with TA1007, TA962, or TA946. All TAs utilise Guest et al. 2006 which reports 51.28% receive terminal care.	The cost is assumed to apply to 100% of those that die, as it is an average of end-of-life care for cancer patients. A more recent source was utilised than previous TA's, and the PSSRU source for the cost of death has been requested by EAG's in other appraisals (not yet published).

Abbreviations: CT, computed tomography; EAG, external assessment group; HSUV, health state utility value; NA, not applicable; NHS, National Health Service; OC, ovarian cancer; PSSRU, Personal Social Services Research Unit; TA, technology appraisal.

b)

As mentioned in response to the previous question, the company acknowledges that utilities are the area where differences exist between this submission and previous appraisals. A number of scenarios have been undertaken using utilities solely from MIRASOL, which is in line with other appraisals where utilities tend to be sourced from the trial in question.

However, for completeness, two additional scenarios have been undertaken using utilities from TA962 and TA946. Note that results are presented both at a severity modifier of 1.2. and 1.7, as using these utilities resulted in a severity modifier of 1.2 (albeit a relative shortfall of 92% and 93%, which is close to the 95% threshold). However, as mentioned in the main submission in sections 3.6 and 3.13, PROC is a severe disease, with a high unmet need given the treatment landscape has seen no

new treatments for two decades, and therefore AbbVie consider that a severity modifier of 1.7 should still be considered.

The alternative values used are summarised in Table 36, and results are summarised in Table 37. Results are broadly aligned with those of using utilities from MIRASOL.

The two scenarios are also included as alternative sources of utilities within the updated economic model.

Table 36: Alternative health state values

Health state	TA962	TA946
Progression-free	0.808	0.750
Progressed disease	0.756	0.727

Table 37: Alternative utility values – cost-effectiveness results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Submitted model					
Mirvetuximab	████	████	-	-	
Pooled chemotherapy	████	████	████	████	████
Utility scenarios using a severity modifier of 1.7					

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Utilities from TA962					
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████
Utilities from TA946					
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████
Utility scenarios using a severity modifier of 1.2					
Utilities from TA962					
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████
Utilities from TA946					
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TA, technology appraisal

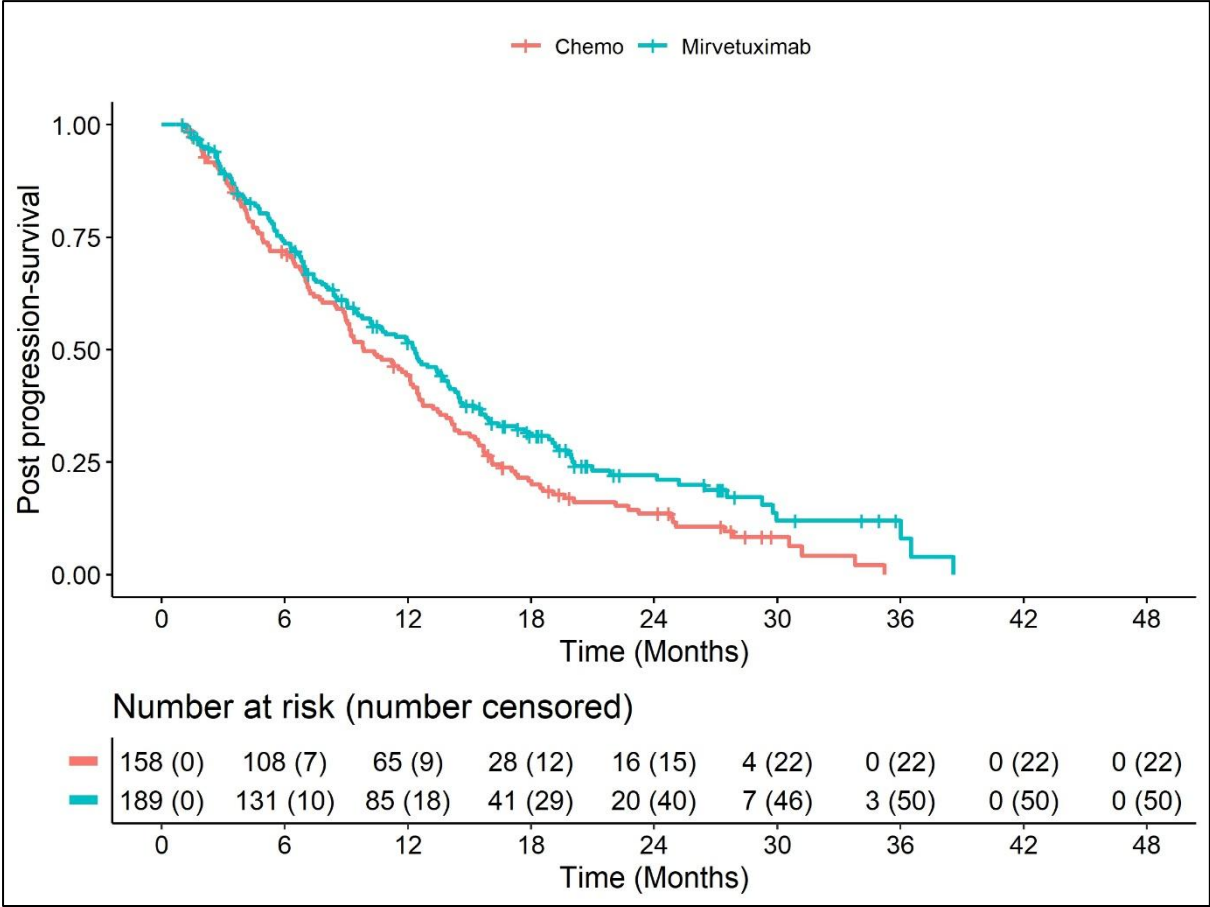
B16. PRIORITY QUESTION: the main benefit from treatment with mirvetuximab in increasing life years appears to be in the post-progression state. As subsequent treatment types and proportions are similar for both arms in the trial this would not appear to be justified. Please amend your survival curve selection or provide a clear justification for benefits post progression.

The question is correct that the main determinant of incremental benefit associated with mirvetuximab in the economic model is an increase in the number of post-progression life years compared to pooled chemotherapy. We believe this assumption is justified, as it is supported by available evidence from MIRASOL and is consistent with clinical opinion received.

Attendees at the AbbVie advisory board noted that mirvetuximab was associated with relatively low levels of myelosuppression compared with chemotherapy (such as paclitaxel or topotecan), and coupled with a break in treatment of such therapies and a period of potential recovery from the severity of these events during mirvetuximab therapy, subsequent treatment in the mirvetuximab arm may achieve better

effectiveness than for patients receiving pooled chemotherapy. Evidence of this continuing benefit post-progression are found in PFS2 from MIRASOL; mirvetuximab demonstrated a greater improvement vs pooled chemotherapy, with patients receiving a balanced selection of subsequent therapies (HR of 0.59; 95% CI: 0.480, 0.728), and also in post-progression survival (HR of 0.76; 95% CI: 0.603, 0.971) (Figure 13).

Figure 13: Post-progression survival



Other reasons to explain why longer-term survival would be possible in people on mirvetuximab, also include:

- The mechanism of action, targeted delivery of a highly potent cytotoxic payload and where particularly the bystander effect is beneficial;
- The reduced tumour burden associated with mirvetuximab as shown by the response rates;

- The fact that patients censored due to study termination were predominantly patients who had achieved either partial or complete response, showing that since these patients were alive after at least 24 months, there is increased potential that some mirvetuximab patients survive long-term. This is also reflected in the fact that there were more patients alive and censored at last study visit in the mirvetuximab arm than the IC Chemo arm (44 vs 18 patients).

Subgroups and generalisability

B17. PRIORITY QUESTION: based upon the supplied forest plots and clinical consultation the following subgroups appear to have differential effectiveness. Please amend the cost-effectiveness model to allow exploration for these subgroups

a) BRCA status

b) Primary platinum free interval

a)

Effectiveness results using data for BRCA status subgroups are reported in Table 38. The data for this scenario have also been included with the updated economic model. Population-specific data used included: KM data (for OS, PFS, DoT), survival parameters (for OS, PFS, DoT), and baseline characteristics other than age. All other inputs and settings were kept the same as the submitted base-case.

Results do not largely differ from the base case. Advice from clinicians was also that BRCA subgroups are not expected to be treatment effect modifiers, and other confounders may have played a role.

It is also important to note that subgroups in MIRASOL were non-powered and exploratory by definition and should not be over interpreted where the subgroup was not a stratification factor. The BRCA positive subgroup was also a small subgroup, as well as BRCA status was not mandated within MIRASOL, and there may also be some patients within the unknown proportion of patients who could well have been BRCA+ as this was not elucidated at baseline.

Data for this scenario have been included within the updated economic model.

Table 38: BRCA status subgroup cost-effectiveness results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Submitted model					
Mirvetuximab	██████	██████	-	-	
Pooled chemotherapy	██████	██████	██████	██████	██████
BRCA negative/unknown					
Mirvetuximab	██████	██████	-	-	
Pooled chemotherapy	██████	██████	██████	██████	██████
BRCA positive					
Mirvetuximab	██████	██████			
Pooled chemotherapy	██████	██████	██████	██████	██████

Abbreviations: BRCA, breast cancer gene; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

b)

Cost-effectiveness results using data for primary platinum free interval subgroups are reported in **Table 39**. The data for this scenario have also been included with the updated economic model. Population-specific data used included: KM data (for OS, PFS, DoT), survival parameters (for OS, PFS, DoT), and baseline characteristics other than age. All other inputs and settings were kept the same as the submitted base-case.

As previously mentioned, subgroups in MIRASOL were non-powered and exploratory by definition. As noted in the response to A29, patients with PFI ≤6 months are patients who relapsed quickly following their first line (platinum) treatment for ovarian cancer. Clinical feedback to the company suggested that these patients are a group with extremely high unmet need and a very poor prognosis, as even their first cancer therapy was ineffective.

It is also important to note the difference between primary platinum resistant (these are patients who failed 1L platinum, but some of them had further therapies before receiving mirvetuximab) vs patients with who received only 1 prior line of therapy. In

patients who received 1 prior line (who are all by definition primary platinum resistant), there is no evidence that mirvetuximab does not work as well, as there is still a numerically favourable overall survival in this group.

The data for this scenario have also been included within the updated economic model.

Table 39: Primary platinum free interval subgroup cost-effectiveness results

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Submitted model					
Mirvetuximab	██████	██████	-	-	
Pooled chemotherapy	██████	██████	██████	██████	██████
<=6 months					
Mirvetuximab	██████	██████	-	-	-
Pooled chemotherapy	██████	██████	██████	██████	██████
>6 months					
Mirvetuximab	██████	██████	-	-	-
Pooled chemotherapy	██████	██████	██████	██████	██████

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

B18. PRIORITY QUESTION: based upon EAG clinical expert input, the age of patients in the trial is lower than would be expected in UK practice. Please either supply data to the contrary or link the age in the model to effectiveness (PFS and OS) and safety to allow the exploration of the impact of this imbalance

Within the submitted economic model, the mean age used was based on real world evidence from 296 UK patients with PROC (30). This is lower than that in MIRASOL, however real-world data was considered to best represent patients who would receive treatment in practice.

Subgroup analyses for PFS and OS suggest that mirvetuximab is nominally more effective in those ≥65 compared to those aged 18-64 years (see Appendix C of Company submission), implying greater effectiveness with increasing age.

Therefore, use of a higher baseline age than observed in MIRASOL, as the EAG suggests, might suggest that the current estimates of relative efficacy implied in the economic model are conservative.

The other appraisals referred to in B15 also generally have ages lower than that of MIRASOL (ranging from 58 to 61), however it is accepted that these are not entirely comparable populations.

B19. PRIORITY QUESTION: Based upon EAG clinical expert input, the split of chemotherapy use in the IC arm in the trial is not reflective of clinical practice. We were told that current practice includes only very rare use of topotecan and that ~60% of patients use paclitaxel and ~40% PLD. Please either demonstrate equivalent outcomes across chemotherapy components for each outcome of interest or adjust for this in the model (drug and administration costs, PFS, OS, RDI, safety etc...)

UK real world evidence does show that there is some use of topotecan, for example the Adelpi study commissioned by AbbVie, which reported 7% use of topotecan, as well as the IPSOS audit mentioned in question A13. Indeed, the EAG's clinical expert also acknowledged that topotecan is used in the UK NHS, albeit to a lesser extent than other chemotherapy regimens.

The comparator arm of MIRASOL was investigators choice of chemotherapy, patients were not randomised to different chemotherapies, but were assigned a chemotherapy based on investigators opinion.

The results of subgroup analysis based on pre-assignment to the individual chemotherapy agents in MIRASOL are presented in Table 40. There is not a consistent pattern of pre-assignment to one chemotherapy in particular showing a differential effectiveness to the ITT (i.e. mirvetuximab versus IC Chemo) population across multiple outcomes. For example, for PFS2 all chemotherapies have HRs centred very close to the ITT population HR and all are significant. PLD is shown to have improved effectiveness for PFS compared to paclitaxel and topotecan, however shows less improvement for OS compared to the other chemotherapies. Therefore, there is not strong evidence on a differential effectiveness of mirvetuximab between chemotherapies. Please also see the response to Question A14.

Table 40: Results of subgroup analysis based on chemotherapy pre-assignment for selected outcomes

	OS HR (95% CI)	PFS HR (95% CI)	ORR Difference in ORR (95% CI)	PFS2 HR (95% CI)
ITT	0.68 (0.543, 0.840)	0.63 (0.513, 0.785)	25.9 (17.9, 33.9)	0.59 (0.483,0.732)
Pre-assigned subgroup				
Paclitaxel	0.68 (0.484, 0.969)	0.76 (0.552, 1.060)	8.3 (-5.4, 21.9)	0.62 (0.452, 0.861)
PLD	0.75 (0.524, 1.083)	0.54 (0.380,0.760)	43.8 (31.8, 55.9)	0.57 (0.403, 0.797)
Topotecan	0.56 (0.366, 0.861)	0.65 (0.420,0.995)	29 (14.6, 43.3)	0.62 (0.409, 0.933)

Abbreviations: ITT, intention-to-treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, time to second disease progression or death; PLD, pegylated liposomal doxorubicin.

Note: **Bold** text signifies statistical significance (confidence interval does not cross 1)

However, for completeness, a sensitivity analysis has been undertaken to exclude topotecan. This involved:

- Using adjusted survival parameters for OS, PFS, and DoT that excluded topotecan (IC chemotherapy chosen prior to randomisation was a stratification factor)
- Adjusting the proportions receiving each chemotherapy to exclude topotecan, which results in 53.20% use of paclitaxel and 46.80% use of PLD.

All other inputs/assumptions were assumed to be the same as the base case.

Results are presented in Table 41, and is shown to have minimal impact on the model results.

Table 41: Assuming pooled chemotherapy excludes topotecan

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Submitted model					
Mirvetuximab	████	████	-	-	
Pooled chemotherapy	████	████	████	████	████
Assuming pooled chemotherapy excludes topotecan					
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjust life year.

Adverse effects

B20. Based upon EAG clinical expert input, the assumptions made for adverse events have issues in terms of face validity in the following areas. Please reconsider inputs and revise the economic model accordingly:

- a) Neutropenia is included as a single category but this is too simplified as febrile neutropenia / neutropenic sepsis have major consequences and patients are not admitted outside of these
- b) The impact of vision blurring and keratopathy is underestimated – please review literature for the impact of these and clearly demonstrate the selection process used for the decrement
- c) Assuming a 4 week impact for cataracts is not realistic as there is a long wait list for surgery. Please amend the duration to use the current wait list time
- d) The suitability of a 4 week impact for other ocular toxicities is unclear. Please demonstrate how long these last for using any trial data available whether this is from MIRASOL or other studies. For example ID6211 and ID6212 consider belantamab mafodotin which results in similar types of ocular toxicities
- e) Patients are not usually admitted for anaemia or thrombocytopenia

f) Bowel obstruction, recurrent ascites, and pleural effusion are discussed as key adverse events for ovarian cancer patients in the clinical section of the CS but not appear to have been specifically captured in the economic model

Adverse events are not considered to have a large impact on the model. Consideration of the individual elements of the question are provided narratively below, with scenarios provided to explore the impact of adverse events further through:

- Doubling of all utility durations from 4 weeks to 8 weeks
- Doubling of all disutilities
- Doubling all adverse event costs

Note for the scenarios that vary adverse event disutilities, as adverse event disutilities were not included within the submitted base case, then a scenario that includes the adverse event utilities is provided in Table 42 to compare against.

Results of these scenarios are provided in Table 42. The impact of all scenarios was minimal.

Table 42: Scenarios around adverse events

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Submitted model					
Mirvetuximab	████	████	-	-	
Pooled chemotherapy	████	████	████	████	████
Submitted model (including AE disutilities – note this was not the base case)					
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████
Doubling of all utility durations from 4 weeks to 8 weeks					
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████
Doubling of all disutilities					

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████
Doubling all adverse event costs					
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Neutropenia has not been separated out within other appraisals such as those mentioned in previous questions of TA1007, TA962 and TA946.

The disutility for vision blurring and keratopathy have been taken from Sullivan et al 2006 (31), which is a commonly used UK source. The ICD code for vision disturbances was used for vision blurring with a disutility of -0.0046, and the ICD code for eye disorders NEC was used for keratopathy with a disutility of -0.0081. Several antibody drug conjugates (ADCs) can cause eye surface issues, however the corneal surface naturally regenerates every 1-2 weeks, so this layer of the cornea can often recover once the drug exposure is reduced. In the mirvetuximab pooled safety analysis, 55% of patients did not require any dose modification due to ocular AEs (32). Importantly, studies show that patients generally do not report significant differences in their quality of life whether they experience these eye symptoms or not (32).

With regards to how long ocular toxicities last, MIRASOL did not record this information, however of the patients treated with mirvetuximab who reported ocular TEAEs, 58% reported complete resolution, and an additional 34% of patients had partial improvement (defined as a decrease in severity by one or more grades from the worst grade at last follow-up). In addition, the number of doses missed can give some indication of the duration of the adverse event, as the majority of patients with ocular AEs only missed 1 dose, therefore the resolution is unlikely to have taken more than 6 weeks.

It is important to note that ocular AEs associated with ADCs vary in frequency and severity. The EAG mentions belantamab mafodotin in part (d). Based on the

belantamab SmPC, ocular AEs occur in 79%-89% of patients (depending on combination), including 57-60% Grade 3+ reduced visual acuity, 17-22% Grade 3+ blurred vision and 51-61% dry eye (all Grades) (33). Additionally, 3% of patients discontinued due to ocular AEs (33). In contrast, for mirvetuximab, ocular AEs occur in 59% of patients, with only 5% Grade 3+ keratopathy, 5% Grade 3+ blurred vision and 27% dry eye (all Grades). Only 1% of patients discontinued due to ocular AEs.

For anaemia or thrombocytopenia, these are also adverse events that are commonly costed within appraisals. Adverse events included within the model are grade 3 and above and therefore are potentially more serious.

Bowel obstruction has been discussed in detail in Question A4 and A30 and has been highlighted as a key complication of PROC, rather than an adverse event from treatment itself. The adverse events mentioned in part (f) of the question did not meet the adverse events inclusion criteria for the model of “Grade 3–4, occurring in $\geq 5\%$ of patients in either arm of the MIRASOL trial (September 2024 data cut; Safety population).”

Excel model

B.21 The model has parameters such as body surface area, adjusted ideal body weight, and weight are included in the PSA. However, since this is a cohort-based model rather than an individual patient simulation, the inclusion of these patient characteristics variables in the PSA implies that the underlying patient population varies between iterations, which is inconsistent with the model’s structure. Could you remove these parameters from the PSA and treat them as fixed inputs, please?

This has been changed in the updated version of the economic model, removing the three mentioned parameters from the PSA.

B.22 half-cycle correction is appropriate only for costs that may occur at any point during the cycle, but not for scheduled, up-front costs like drug acquisition. Could you remove half cycle correction from drug costs, please?

Thank you for pointing this out. Results from the model when remove half-cycle correction for drug costs are presented below. This slightly reduces the ICER.

This has been incorporated as part of an updated base case.

Table 43: Removing half cycle correction for drug costs

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£)
Submitted model					
Mirvetuximab	████	████	-	-	
Pooled chemotherapy	████	████	████	████	████
Removing half cycle correction for drug costs					
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjust life year.

B.23 The severity modifier used in the model appears to be hardcoded (Cell E9 in the 'Base case' sheet), rather than dynamically linked to the SM calculator ('Severity_modifier' sheet). As a result, the severity modifier is not responsive to changes in scenarios that involve alternative modelling assumptions. Please amend the model so that the dynamic severity modifier is applied to results

This has been changed in the updated version of the economic model. It has been linked from F33 on the 'Base Case' sheet.

B.24 the company's PSA isn't functioning correctly in their model. I appreciate that it's late to add a clarification question, but I imagine the company will want the opportunity to fix this in their response. Specifically, can you please ask them to amend the model so that running the PSA doesn't automatically reset all inputs to the company base case values and allows for the use of alternative input, please?

The PSA automatically resets all inputs to the default values, to avoid a user running a PSA and using different settings to the default ones, and perhaps not realising.

Use of alternative inputs for the PSA is possible, through the 'control sheet'. Column D of the control sheet lists the default inputs, and column C lists the current values, with red conditional formatting appearing in column C when the current values do not match the default values. If a user wanted to run PSA on a different set of inputs to the defaults, then they can click the button at the top of column C; "Click to update

defaults values with current values”, and this will update the default values with the users chosen current values/settings, and then PSA can be ran using these inputs. Please note if an input is changed this may also require re-specification of the parameters which determine the sampling in PSA (e.g. the standard error).

Section C: Textual clarification and additional points

C1. Please provide the format of the questions / information presented to clinicians at the meetings used to elicit landmark survival estimates for model validation?

Detail of the questions / information presented to clinicians at the meetings used to elicit landmark survival estimates for model validation are provided in the reference pack (34).

C2. Please provide the statistical analysis plan for patient-reported outcomes in MIRASOL

AbbVie has provided the statistical analysis plan for patient-reported outcomes in MIRASOL (35).

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Appendix A: SORAYA and FORWARD-1 details

2. Clinical effectiveness

2.1. Summary of methodology of the relevant clinical effectiveness evidence

2.1.1. Summary of methodology

A summary of the methodology of SORAYA and FORWARD-1 trials is provided in Table 44.

Table 44. Summary of pivotal trial methodology

Trial name	SORAYA (NCT04296890)	FORWARD-1 (NCT02631876)
Trial design	Phase 2, single arm trial	Phase 3, open-label, randomised study
Blinding	Not applicable.	Not applicable as this was an open-label study. An open-label design was used because each trial drug has a unique dose, examination schedule, and safety profile
Treatment allocation	Not applicable	Patients were randomised 2:1 into 2 groups: • Arm 1: MIRV 6 mg/kg AIBW Q3W • Arm 2: IC Chemo (weekly paclitaxel Q4W, or pegylated liposomal doxorubicin Q4W, or topotecan administered either on Days 1, 8, and 15 every 4 weeks or for 5 consecutive days Q3W) Randomisation was stratified by: • Number of prior lines of therapy (1 or 2 vs 3) • FRα levels (high expression $\geq$ 75% tumour cells with FRα membrane staining or medium expression $\geq$ 50 to < 75% tumour cells with FRα membrane staining by the Ventana IHC assay) • IC Chemo (paclitaxel, pegylated liposomal doxorubicin, or topotecan)
Eligibility criteria for participants	Key inclusion criteria • Female patients $\geq$18 years of age • Confirmed diagnosis of HGS EOC, primary peritoneal cancer, or fallopian tube cancer • Patients must have had platinum-resistant disease: ○ Patients who only had 1 line of platinum-based therapy must have received at least 4 cycles of platinum therapy, must have had a response (complete response or partial response) and then progressed between >3 months and $\leq$6	Key inclusion criteria • Female patients $\geq$18 years of age • Confirmed diagnosis of advanced EOC, primary peritoneal cancer, or fallopian tube cancer • Patients must have had platinum-resistant ovarian cancer, defined as progression within 6 months from completion of a minimum of 4 cycles of platinum-containing therapy

Trial name	SORAYA (NCT04296890)	FORWARD-1 (NCT02631876)
	months after the date of the last dose of platinum therapy ○ Patients who had received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum therapy • A patient's tumour must have high FRα expression as defined by the VENTANA® FOLR1 assay (≥75% of viable tumour cells must have exhibited level 2 and/or 3 membrane staining intensity) • Patients must have had ≥1 lesion that meets the definition of measurable disease by RECIST v1.1 • Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, including at least 1 line containing bevacizumab, and for whom single-agent therapy was appropriate as the next line of treatment • ECOG PS of 0 or 1 • Time from prior therapy: ○ Systemic antineoplastic therapy (5 half-lives or 4 weeks, whichever is shorter) ○ Focal radiation completed at least 2 weeks prior to first dose of study drug • Patients must have had stabilised or recovered (Grade 1 or baseline) from all prior therapy-related toxicities Key exclusion criteria • Patients with endometrioid, clear cell, mucinous, or sarcomatous histology, mixed tumours containing any of the above histologies, or low-grade or borderline ovarian tumour	• A patient's tumour must have medium or high FRα expression as defined by the VENTANA® FOLR1 assay (≥50% tumour staining at ≥2+ intensity) • Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy • ECOG PS of 0 or 1 • Time from prior therapy: ○ Systemic antineoplastic therapy (5 half-lives or 4 weeks, whichever is shorter) ○ Focal radiation completed at least 2 weeks prior to first dose of study drug • Patients must have had stabilised or recovered (Grade 1 or baseline) from all prior therapy-related toxicities Key exclusion criteria • Patients with clear cell, mucinous, or mixed histology with mucinous component, sarcoma, sarcomatous component, or low-grade ovarian tumour • Patients with primary platinum-refractory disease, defined as those who progressed during or within 4 weeks of completion of first-line platinum-containing chemotherapy • Patients with prior wide-field radiotherapy affecting at least 20% of the bone marrow • Patients with >Grade 1 peripheral neuropathy • Patients with active or chronic corneal disorders such as Sjogren syndrome, Fuchs corneal dystrophy (requiring treatment), history of corneal transplantation, active herpetic keratitis, active ocular conditions requiring ongoing treatment/monitoring such as uncontrolled glaucoma, wet age-related macular

Trial name	SORAYA (NCT04296890)	FORWARD-1 (NCT02631876)
	• Patients with primary platinum-refractory disease, defined as disease that did not respond to or has progressed within 3 months of the last dose of first-line platinum-containing chemotherapy • Patients with prior wide-field radiotherapy affecting at least 20% of the bone marrow • Patients with >Grade 1 peripheral neuropathy per CTCAE • Patients with active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular oedema, macular degeneration, presence of papilledema, and/or monocular vision • Patients with serious concurrent illness or clinically relevant active infection, including, but not limited to the following: active hepatitis B or C infection (whether on active antiviral therapy), HIV infection, active cytomegalovirus infection, any other concurrent infectious disease requiring IV antibiotics within 2 weeks before starting study drug • Patients with history of multiple sclerosis or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome) • Patients with clinically significant cardiac disease • Patients with a history of haemorrhagic or ischemic stroke within 6 months prior to randomisation • Patients with a history of cirrhotic liver disease	degeneration requiring intravitreal injections, active diabetic retinopathy with macular oedema, macular degeneration, presence of papilledema, and/or monocular vision. • Patients with serious concurrent illness or clinically relevant active infection, including, but not limited to the following: active hepatitis B or C infection (whether on active antiviral therapy), HIV infection, Varicella-zoster virus, active cytomegalovirus infection, any other concurrent infectious disease requiring IV antibiotics within 2 weeks before starting study drug • Patients with history of multiple sclerosis or other demyelinating disease and/or Lambert-Eaton syndrome (paraneoplastic syndrome) • Patients with clinically significant cardiac disease • Patients with a history of haemorrhagic or ischemic stroke within 6 months • Patients with a history of cirrhotic liver disease Full eligibility criteria are available in the FORWARD-1 CSR

Trial name	SORAYA (NCT04296890)	FORWARD-1 (NCT02631876)
	Patients with a previous clinical diagnosis of non-infectious ILD Full eligibility criteria are available in the SORAYA CSR	
Settings and locations where data were collected	SORAYA was conducted at 72 global sites, of which 39 sites enrolled patients across 8 countries (North America [13 sites (United States)], Europe [25 sites: Belgium-3, Germany-2, Ireland-5, Israel-2, Italy-4, Spain-9], and Asia Pacific [1 site (Australia)])	FORWARD-1 was conducted at 159 sites (including 15 satellite sites), of which 101 sites enrolled patients across 12 countries (North America [47 sites (United States-39 sites, Canada-8 sites)], Europe [51 sites: Belgium-1, Czech Republic-1, France-9, Ireland-3, Italy-9, Serbia-1, Spain-14, Ukraine-2, United Kingdom-11] and Russia [3 sites]).
Concomitant medications	All concomitant medications and supportive therapy taken within 4 weeks of C1D1 and through 30 days after the last dose of study drug were recorded in the clinical database. Antiemetic and antidiarrhoeal medications An antiemetic medication was recommended before each mirvetuximab dose; additional antiemetics and/or antidiarrhoeal medications could be used any time at the discretion of the treating physician. Folate-containing supplements Folate-containing supplements should not have been taken during the study. Antineoplastic therapy All non-study related antineoplastic therapy, including but not limited to cytotoxic, immunotherapy, and VEGF-targeted therapy, was prohibited while on study drug. Hematopoietic growth factors Patients receiving recombinant erythropoietin or darbepoetin-α before study start could continue to receive pretreatment doses. The use of erythropoietic and granulocyte growth factors in accordance with ASCO	All concomitant medications and supportive therapy taken within 4 weeks of C1D1 and through 30 days after the last dose of study drug were recorded in the clinical database. Antiemetic and antidiarrhoeal medications An antiemetic medication was recommended before each mirvetuximab dose; additional antiemetics and/or antidiarrhoeal medications could be used any time at the discretion of the treating physician. Folate-containing supplements Folate-containing supplements should not have been taken during the study. Antineoplastic therapy All non-study related antineoplastic therapy, including but not limited to cytotoxic, immunotherapy, and VEGF-targeted therapy, was prohibited while on study drug. Hematopoietic growth factors Patients receiving recombinant erythropoietin or darbepoetin-α before study start could continue to receive pretreatment doses. The use of erythropoietic and granulocyte growth factors in accordance with ASCO

Trial name	SORAYA (NCT04296890)	FORWARD-1 (NCT02631876)
	guidelines (36) could be implemented at the discretion of the treating physician. Anticoagulants The use of anticoagulant agents was allowed. Directions were provided for patients who were using apixaban and rivaroxaban due to CYP3A interaction potential. Contraception WCBP must have agreed to use highly effective contraceptive method(s) while on study drug and for at least 3 months after the last dose of mirvetuximab or at least 6 months after the last dose of paclitaxel, pegylated liposomal doxorubicin, or topotecan. Other concomitant medications Medications for the treatment of AEs or cancer symptoms (e.g. packed red blood cells and pain medications) were allowed. Prophylactic use of steroids and/or antihistamines was considered if needed. Additionally, medications (not addressed above) used to treat underlying medical conditions at study entry, including antiemetics and antidiarrheals, were allowed to continue.	guidelines (36) could be implemented at the discretion of the treating physician. Anticoagulants The use of anticoagulant agents was allowed. Directions were provided for patients who were using apixaban and rivaroxaban due to CYP3A interaction potential. Contraception WCBP must have agreed to use highly effective contraceptive method(s) while on study drug and for at least 3 months after the last dose of mirvetuximab or at least 6 months after the last dose of paclitaxel, pegylated liposomal doxorubicin, or topotecan. Other concomitant medications Medications for the treatment of AEs or cancer symptoms (e.g. packed red blood cells and pain medications) were allowed. Prophylactic use of steroids and/or antihistamines was considered if needed. Additionally, medications (not addressed above) used to treat underlying medical conditions at study entry, including antiemetics and antidiarrheals, were allowed to continue.
Trial treatments	All patients received single-agent mirvetuximab at 6 mg/kg AIBW IV administered Q3W.	Mirvetuximab arm All patients received single-agent mirvetuximab at 6 mg/kg AIBW IV administered Q3W. IC Chemo arm Patients who were randomised to paclitaxel, pegylated liposomal doxorubicin, or topotecan may have received premedication at the discretion of the investigator or according to institutional guidelines.

Trial name	SORAYA (NCT04296890)	FORWARD-1 (NCT02631876)
		• Paclitaxel was administered at 80 mg/m² as a 1-hour IV infusion on Days 1, 8, 15, and 22 of a 4-week cycle • Pegylated liposomal doxorubicin was administered at 40 mg/m² as a 1 mg/min IV infusion on Day 1 of a 4-week cycle. After Cycle 1, if tolerated, pegylated liposomal doxorubicin could be delivered as a 1-hour IV infusion • Topotecan was administered at 4 mg/m² as a 30-min IV infusion on Days 1, 8, and 15 of a 4-week cycle. Alternatively, topotecan could be administered at 1.25 mg/m² as a 30-min IV infusion on Days 1 to 5 of a 3-week cycle
Primary endpoint(s)	Objective response, including best response of complete response or partial response as assessed by the investigator	PFS, defined as the time from first dose of treatment until the time of death or PD, as assessed by the BICR • In all patients randomised to the study • In patients with high FRα expression (≥75% staining intensity)
Secondary endpoints	Key secondary endpoints • DOR, defined as the time from initial response (complete response or partial response) until investigator-assessed PD Other secondary endpoints • CA-125 response determined using the GCIG criteria (37) • PFS, defined as the time from first dose of mirvetuximab, until investigator-assessed PD or death, whichever occurred first • OS defined as the time from date of randomisation until the date of death	Key secondary endpoints • ORR per RESCIST v1.1, as assessed by BICR • OS defined as the time from date of randomisation until the date of death • PRO endpoint using the QLQ-OV28 questionnaire Other secondary endpoints • CA-125 response determined using the GCIG criteria (37) • PFS, defined as the time from first dose of mirvetuximab, until investigator-assessed PD or death, whichever occurred first

Trial name	SORAYA (NCT04296890)	FORWARD-1 (NCT02631876)
	Safety of mirvetuximab	- DOR, defined as the time from first objective response (complete response or partial response) to the time of PD among those who have achieved complete response or partial response - Patient scores on EORTC QLQ-C30, EORTC QLQ-OV28, EQ-5D-5L, and 8-item FOSI questionnaires - ADA status - Safety of mirvetuximab
Subgroup analyses	Efficacy endpoints were analysed with the following subgroups of patients: - Number of prior lines of therapy (1 vs 2 vs 3) - Prior exposure to PARP inhibitor (yes vs no vs uncertain) - ADA status	Efficacy endpoints were analysed with the following subgroups of patients: - BRCA status (yes vs no) - Age (<65 years vs ≥65 years) - Baseline ECOG PS (0 vs 1) - Number of prior lines of therapy (1 or 2 vs 3) - Prior exposure to BEV (yes vs no) - IC Chemo - Platinum-free interval (≤3 months vs >3 months) - Location of metastasis (visceral vs non-visceral) - Race (white vs non-white) - Time since initial diagnosis (≤2 years vs >2 years)

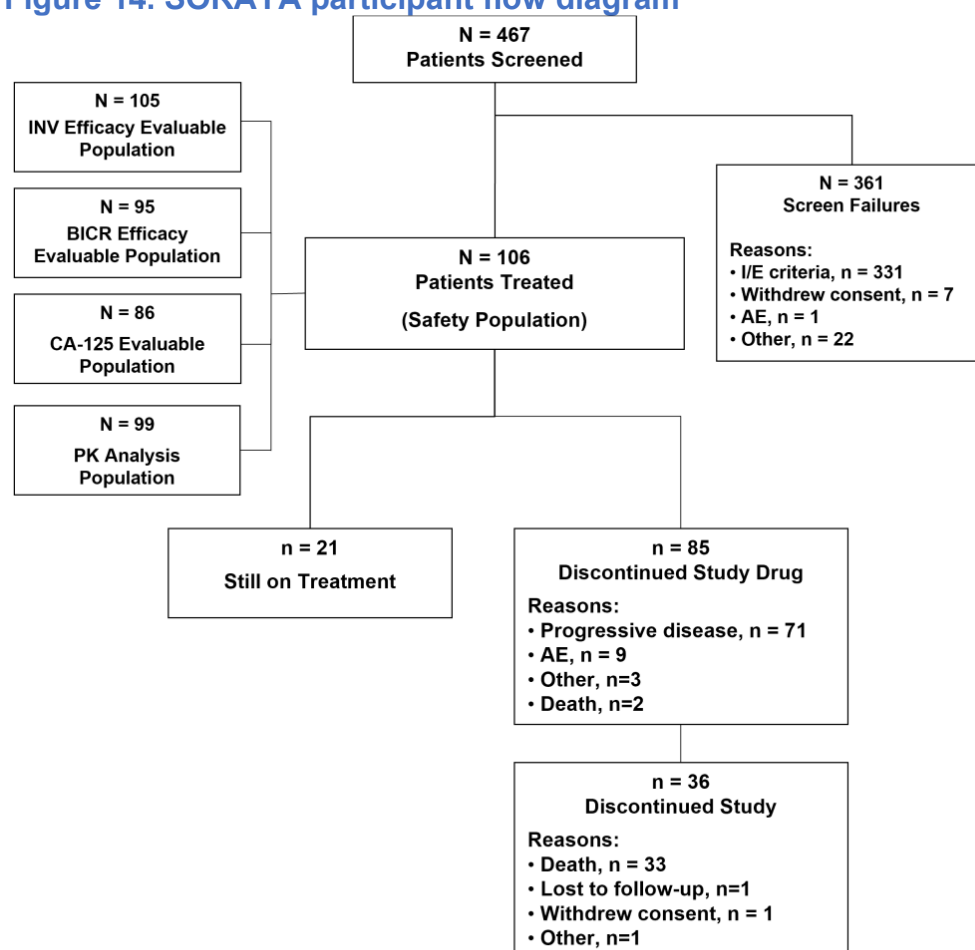
Source: Data on file, SORAYA CSR (38); Data on file, FORWARD-1 CSR (39);
Abbreviations: ADA, anti-drug antibodies; AE, adverse event; AIBW, adjusted ideal body weight; ASCO, American Society of Clinical Oncology; BEV, bevacizumab; BICR, blinded independent central review; BRCA, breast cancer gene; CA125, cancer antigen 125; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOC, epithelial ovarian cancer; EORTC, European Organisation for Research and Treatment of Cancer; FOLR1, folate receptor 1; FR α , folate receptor alpha; GCIg, Gynaecologic Cancer Intergroup; HGS, high grade serous; HIV, human immunodeficiency virus; IC Chemo, investigator's choice of chemotherapy; IHC, immunohistochemistry; ILD, interstitial lung disease; IV, intravenous; LVEF, left ventricular ejection fraction; ORR, objective response rate; OS, overall survival; PARP, poly (adenosine diphosphate-ribose) polymerase; PD, progressive disease; PFS, progression-free survival; PRO, patient reported outcome; QLQ, quality of life Questionnaire; Q3W, every 3 weeks; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; VEGF, vascular endothelial growth factor; WCBP, women of childbearing potential.

2.1.2. SORAYA - Patient disposition

Figure 14 presents the patient disposition flow diagram for all patients.

Of the 85 patients who discontinued mirvetuximab, the most common reasons for discontinuation were progressive disease (PD; 71 patients, 67%) and adverse events (9 patients, 8%). Twenty (19%) of these patients entered into response follow-up (including patients who discontinued mirvetuximab for reasons other than radiographic PD and continued with tumour assessments until documentation of radiographic PD or the start of a new anticancer therapy), and 57 (54%) entered into the survival follow-up phase. The primary reason for study discontinuation from the survival follow-up phase was death (33 patients, 31%). As of the data cutoff (16th November 2021; median follow-up time of 8.5 months), 21 patients (20%) remained on study drug.

Figure 14. SORAYA participant flow diagram



Source: Data on file, SORAYA CSR (38)

Abbreviations: AE, adverse event; BICR, blinded independent central review; CA-125, cancer antigen 125; I/E, inclusion/exclusion; INV, investigator; PK, pharmacokinetic(s); RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

2.1.3. SORAYA - Baseline characteristics

Key patient characteristics at baseline for SORAYA are presented in Table 45.

Table 45. Baseline demographic and clinical characteristics – Safety population

Characteristic	Mirvetuximab (N=106)
Age, years	
Median (range)	62 (35–85)
≥65 years, n (%)	47 (44)
Race, n (%)	
White	102 (96)
Black or African American	0
Asian	2 (2)
Not reported	2 (2)
Ethnic group, n (%)	
Hispanic or Latino	2 (2)
Not Hispanic or Latino	99 (93)
Unknown	1 (1)
Not reported	4 (4)
Primary cancer diagnosis, n (%)	
Epithelial ovarian cancer	85 (80)
Fallopian tube cancer	8 (8)
Primary peritoneal cancer	12 (11)
Other [†]	1 (1)
Stage at initial diagnosis, n (%)	
I or II	2 (2)
IIIA	6 (6)
IIIB	5 (5)
IIIC	52 (49)
IV	40 (38)
Missing data	1 (1)
ECOG performance-status score, n (%)	
ECOG PS 0	60 (57)
ECOG PS 1	46 (43)
BRCA mutation, n (%)	
Yes	21 (20)
BRCA1 positive	15 (14)

Characteristic	Mirvetuximab (N=106)
BRCA2 positive	6 (6)
Negative or unknown	85 (80)
Previous lines of systemic therapy	
1	10 (9)
2	41 (39)
3	54 (51)
>3	1 (1)
Previous exposure, n (%)	
Bevacizumab	106 (100)
PARP inhibitor	51 (48)
Taxane	103 (97)
Doxorubicin	75 (71)
Topotecan	0 (0)
Primary platinum-free interval, n (%)	
≤12 months	64 (60)
>12 months	42 (40)
Platinum-free interval, n (%)	
≤3 months	39 (37)
>3 to ≤6 months	64 (60)
>6 months [†]	3 (3)

Source: Data on file, SORAY CSR (38).

[†]One patient with primary diagnosis categorized as “other” had histopathology consistent with the inclusion/exclusion criteria (intraepithelial tubo-ovarian carcinoma); [‡]Three patients had platinum-free intervals > 6 months: Two patients had a platinum-free interval of 6.01 months; 1 patient had a platinum-free interval of 18.07 months.

Abbreviations: BRCA1, BRCA2, Breast Cancer gene 1; ECOG, Eastern Cooperative Oncology Group; IC Chemo, investigator's choice of chemotherapy; ITT, intention-to-treat; PARP, poly (adenosine diphosphate-ribose) polymerase; PS, performance score.

2.1.4. FORWARD-1 – Patient disposition

FORWARD-1 used the 10x method to determine FR α expression ($\geq 50\%$ of tumour cells with any FR α membrane staining visible at $\leq \times 10$ microscope objective; 50–74% and 75% representing medium and high expression, respectively), with 366 patients included. In contrast, MIRASOL used the PS2+ scoring method and only included patients with high FR α expression. Although the FORWARD-1 CSR presents results for the FR α high population, these may not be accurate due to differences in the scoring methods which led to the inclusion of patients with lower FR α expression (i.e. some patients with medium FR α expression were included as high FR α patients), who would not have been eligible for inclusion in the study when using the PS2+ scoring method relevant to the benefit assessment.

An exploratory re-scoring analysis was therefore undertaken to determine FR α positive tumour cells using the product information-compliant PS2+ scoring method, which also takes into account the staining intensity of the tumour cell membrane on the data from the FORWARD-1 study. The rescore was performed using digital tumour images created within FORWARD-1 prior to randomisation, based on the PS2+ rating method by an independent pathologist blinded to the treatment assignment. The product information-compliant rescore to PS2+ $\geq 75\%$ resulted in 116 patients.

Where possible, results are presented for the re-scored population. However, for additional endpoints, please see the CSR for the original high FR α population, though note that these may not be fully accurate.

2.1.5. FORWARD-1 – Baseline characteristics (re-scored population)

Baseline characteristics for the re-scored FORWARD-1 patient population are presented in Table 46. Overall, patient demographics and disease characteristics were similar between the two arms.

Table 46: Characterisation of the re-scored study population

	FORWARD-1 (re-scored)	
	Mirvetuximab N=82	IC Chemo N=34
Disease-specific characteristics		
Primary tumour site: n (%)		
Epithelial ovarian	68 (84)	31 (91)
Fallopian tubes	6 (7)	1 (3)
Primary peritoneal	1 (1)	2 (6)
FIGO		
I	0 (0)	0 (0)
II	2 (2)	0 (0)
III	52 (63)	25 (74)
IV	27 (33)	9 (26)
Missing	1 (1)	0 (0)
Any BRCA mutations		
Positive	11 (13)	3 (9)
Negative/unknown	71 (87)	31 (91)
BRCA1 mutations, n (%)		
Positive – BRCA1	8 (10)	3 (9)
Negative/unknown	74 (90)	31 (91)
BRCA2 mutations, n (%)		
Positive – BRCA2	3 (4)	0 (0)
Negative/unknown	79 (96)	34 (100)
Time from initial diagnosis to randomisation (months)		
n	73	33
Mean (SD)	27.28 (18.41)	33.98 (25.48)
Median (min, max)	23.89 (8.21, 128.1)	30.55 (7.2, 119.29)
Previous treatment lines, n (%)		
1	53 (65)	20 (59)
2	–	–
3	29 (35)	14 (41)
Demographic characteristics		
Age (years)		
Mean (SD)	63.13 (9.42)	60.35 (12.31)
Median (Min.; Max.)	65 (42, 84)	62 (31, 81)

	FORWARD-1 (re-scored)	
Ethnicity, n (%)		
Hispanic or Latino	4 (5)	1 (3)
Non-Hispanic or Latino	75 (91)	33 (97)
Not reported	3 (4)	0 (0)
Unknown	0 (0)	0 (0)
Missing	0 (0)	0 (0)
Race, n (%)		
White	81 (99)	31 (91)
Black or African American	0 (0)	1 (3)
Native American or Alaskan	0 (0)	0 (0)
Asian	0 (0)	2 (6)
Others	1 (1)	0 (0)
Not reported	0 (0)	0 (0)
Geographic region		
APAC	0 (0)	0 (0)
Europe	50 (61)	26 (76)
Middle East	0 (0)	0 (0)
North America	32 (39)	8 (24)
Weight (kg) at baseline		
n	79	32
Mean (SD)	71.09 (17.13)	67.83 (13.33)
Median (Min.; Max.)	67 (40.5, 125)	63.75 (49.2, 111)

Source: Data on file, FORWARD-1 CSR (39)

Abbreviations: APAC, Asia-Pacific; BRCA, breast cancer gene; FIGO, International Federation of Gynecology and Obstetrics; PARP, poly ADP ribose polymerase; SD, standard deviation.

2.2. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.2.1. SORAYA - Analysis populations

All patients who received at least one dose of mirvetuximab were included in the Safety population.

The Efficacy Evaluable population was the primary dataset for all efficacy analyses. The Efficacy Evaluable population was defined as all patients in the Safety population who had measurable disease at Baseline.

2.2.2. SORAYA - Summary of statistical analyses

A summary of the statistical analyses undertaken in SORAYA is provided in Table 47.

Table 47. Summary of statistical analyses

Trial	SORAYA
Hypothesis objective	Primary objective: To determine the efficacy of mirvetuximab in patients with PROC and high FR α expression
Statistical analysis of primary endpoint	The primary endpoint of ORR was calculated based on the Efficacy Evaluable population and its 95% exact CI was estimated using the Clopper-Pearson method.
Statistical analysis of secondary endpoints	Key secondary endpoints • DOR was summarized in patients with a confirmed BOR of CR or PR only. Secondary endpoints • PFS and OS were summarised using the Efficacy Evaluable population. Their distribution was estimated using the Kaplan-Meier method. PFS and OS rates were reported at 3-month intervals (e.g. 3 months, 6 months, etc). • TTR was summarised in patients with a confirmed BOR of complete response or partial response only with the simple summary statistics.
Statistical analysis of safety endpoints	• The main safety summary tables used data from the Safety population.
Sample size and power calculation	The primary endpoint of this study was ORR as assessed by the investigator. The study was designed to test the null hypothesis that the ORR is 12%. A sample size of 105 efficacy evaluable patients achieved 90% power to detect a difference in ORR of 12% (24% vs 12%) using a 1-sided binomial test. The target significance level (1-sided α level) was 0.025. The actual significance level achieved by this test was 0.0242. These results assumed that the ORR is 12% under the null hypothesis and 24% under the alternative hypothesis. For the primary endpoint of ORR, the null hypothesis that ORR is 12% was tested against 1-sided Type I error (α) of 0.025. This study rejects the null hypothesis if the lower bound of 95% (2-sided) CI for ORR is greater than 12%.

Trial	SORAYA
Data management and patient withdrawal	Partial dates were allowed in the clinical database for subsequent anticancer therapy start date, AE onset and resolution dates, concomitant medication start and stop dates, and concomitant procedure dates. An entry for the year was required in the clinical database for each of these dates. Only the month and day may have been entered as unknown. Prior anticancer systemic therapy start and stop dates and subsequent anticancer therapy stop date allowed for unknown dates in the clinical database. Dates from these forms were reported in listings as collected.

Source: Data on file, SORAYA CSR (38)

Abbreviations: AE, adverse event; BOR, best objective response; CI, confidence interval; CR, complete response; CSR, clinical study report; DOR, duration of response; FR α , folate receptor alpha; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; PROC, platinum-resistant ovarian cancer; TTR, time to response.

2.2.3. FORWARD-1 – Analysis populations

All patients who received at least 1 dose of mirvetuximab were included in the Safety population.

The intention-to-treat (ITT) population was the primary dataset for all efficacy analyses. The ITT population was defined as all patients randomised in the Phase 3 portion of the study.

2.2.4. FORWARD-1 Summary of statistical analyses

A summary of the statistical analyses undertaken in FORWARD-1 is provided in Table 48.

Table 48. Summary of statistical analyses

Trial	FORWARD-1
Hypothesis objective	Primary objective: To compare the PFS of patients randomised to mirvetuximab vs IC Chemo
Statistical analysis of primary endpoint	The primary endpoint of PFS by BICR was estimated using the Kaplan-Meier method
Statistical analysis of secondary endpoints	Key secondary endpoints • ORR was estimated along with a 95% CI. The ORR of the mirvetuximab arm and that of the IC Chemo arm were compared using appropriate statistics tests. Secondary endpoints • OS, DOR, and PFS by investigator were estimated using the Kaplan-Meier method
Statistical analysis of safety endpoints	• The main safety summary tables used data from the Safety population.

Trial	FORWARD-1
Sample size and power calculation	The study had 91% power to detect a hazard ratio of 0.583 in the FRα-high expression subgroup and 96% power in all randomised patients at a study-wise alpha level of 5%; the study had a 39% probability of stopping for futility at the interim analysis under the null hypothesis. Sample size and power were determined by simulations using SAS® software with the following assumptions: • Median PFS for the IC Chemo arm is 3.5 months. • Median PFS for the mirvetuximab arm is 6 months. • Exponential distribution for both event and censoring processes. • Ratio of FRα high to FRα medium is 2:1. • Annual censoring rate is 20% in both arms.
Data management and patient withdrawal	For efficacy analyses, 1 patient had partial date of death (day was missing but both month and year were reported) which has been imputed as the last day of the month. All other data were reported as they are collected. No imputation methods were used to replace missing data for efficacy analyses.

Source: Data on file, FORWARD-1 CSR (39)

Abbreviations: BICR, blinded independent central review; CI, confidence interval; CSR, clinical study report; DOR, duration of response; FR α , folate receptor alpha; IC Chemo, Investigator's choice of chemotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

2.3. Clinical effectiveness results of the relevant studies

2.3.1. SORAYA

Primary endpoint: ORR

The confirmed ORR per RECIST v1.1 as assessed by investigator was 32.4% (34 patients) (95% confidence interval [CI]: 23.6%, 42.2%; Table 49). Five patients had a confirmed response of complete response (CR); 29 patients had a confirmed response of partial response (PR).

Table 49. Summary of ORR – INV Efficacy Evaluable population

	Mirvetuximab (N=105)
Confirmed ORR, n (%)	34 (32.4)
95 % CI	23.6, 42.2
Confirmed BOR, n (%)	
CR	5 (4.8)
PR	29 (27.6)
SD	48 (45.7)
PD	20 (19.0)
No evaluable	3 (2.9)

Source: Data on file, SORAYA CSR (38)

Abbreviations: CI, confidence interval; CR, complete response; CSR, clinical study report; ORR, objective response rate; PD, progressed disease; PR, partial response; SD, stable disease.

Key secondary endpoint: Duration of response

Among the 34 patients in the Efficacy Evaluable population with a confirmed CR or PR, the median duration of response (DOR) per RECIST was 5.9 months (95% CI: 5.6, 7.7 months; Table 50 and Figure 15).

The median time to response (TTR) was 1.5 months (range: 1.0, 5.6 months). At the time of the protocol-specified primary analysis, 15 of the responders remained on mirvetuximab without disease progression and were censored in the DOR analysis.

Table 50. Summary of DOR – INV Efficacy Evaluable population

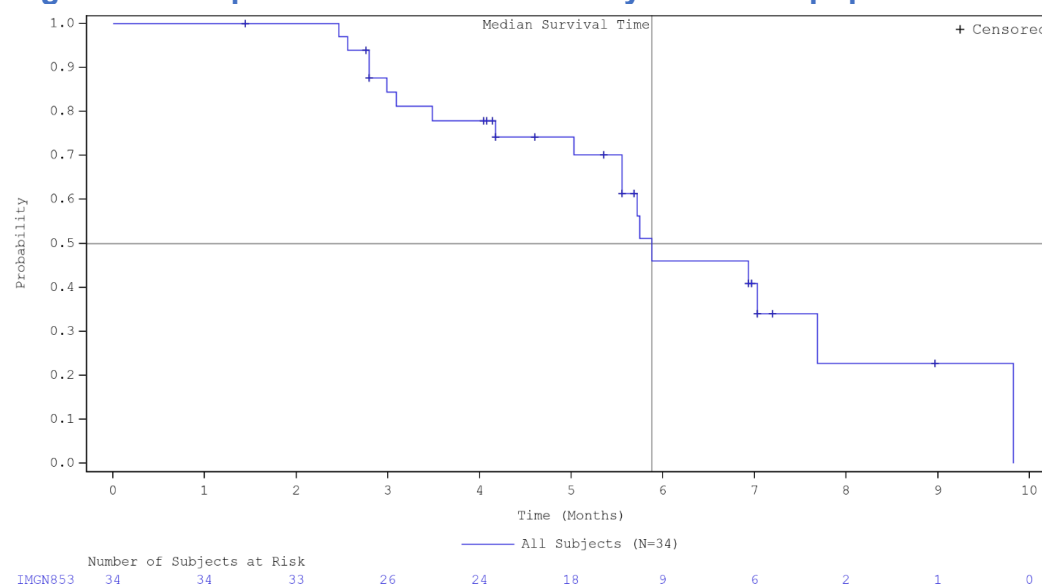
	All responders (N=34)
DOR events, n (%)	
Radiological progression	18 (52.9)
Death without documented progression	0
Censored, n (%)	
New anticancer therapy prior to progression or death	1 (2.9)
No death or progression	15 (44.1)
Progression or death after missing 2 or more consecutive radiological assessments	0
Kaplan-Meier estimates for DOR (months)	
Median (95% CI)	5.9 (5.6, 7.7)
1st quartile (95% CI)	4.2 (2.8, 5.7)
3rd quartile (95% CI)	7.7 (6.9, NR)
Range	1.4+, 9.8

Source: Data on file, SORAYA CSR (38)

+, censored

Abbreviations: CI, confidence interval; CSR, clinical study report; DOR, duration of response.

Figure 15. KM plot for DOR – INV Efficacy Evaluable population



Source: Data on file, SORAYA CSR (38)

Abbreviations: CSR, clinical study report; DOR, duration of response; KM, Kaplan-Meier.

Secondary endpoint: PFS

Table 50 presents the summary of progression-free survival (PFS) as assessed by investigator. The median PFS in the Efficacy Evaluable population was 4.3 months (95% CI: 3.7, 5.1 months). The Kaplan-Meier plot for PFS is presented in Figure 16.

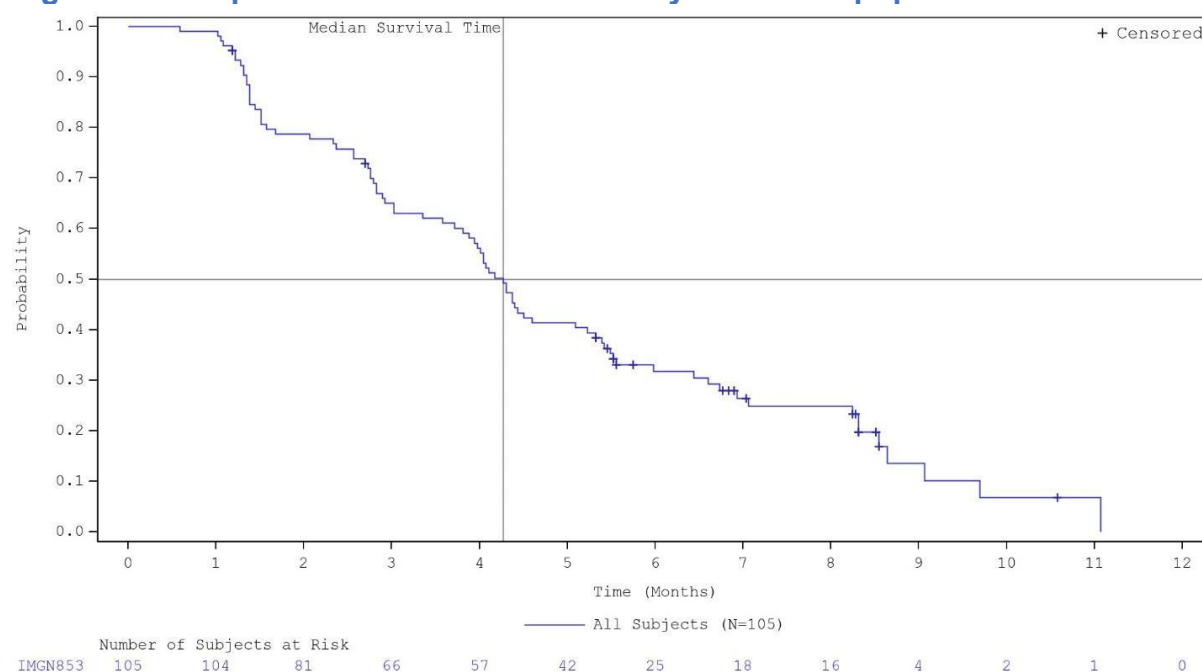
Table 51. Summary of PFS – INV Efficacy Evaluable population

Measure	Efficacy Evaluable Population (N=105)
PFS_{INV} events, n (%)	
Radiological progression	72 (68.6)
Death without documented progression	10 (9.5)
Censored, n (%)	
No postbaseline radiological assessments and patient did not die within 105 days of first dose	0
New anticancer therapy prior to progression or death	2 (1.9)
No death or progression	19 (18.1)
Progression or death after missing 2 or more consecutive radiological assessments	2 (1.9)
Kaplan-Meier estimates for PFS_{INV} (months)	
Median (95% CI)	4.3 (3.7, 5.1)
1st quartile (95% CI)	2.6 (1.4, 2.9)
3rd quartile (95% CI)	7.1 (5.6, 8.6)
Range	0.6, 11.1

Source: Data on file, SORAYA CSR (38)

Abbreviations: CI, confidence interval; CSR, clinical study report; PFS_{INV}, progression-free survival assessed by investigator.

Figure 16. KM plot for PFSINV – INV Efficacy Evaluable population



Source: Data on file, SORAYA CSR (38)

Abbreviations: CSR, clinical study report; KM, Kaplan-Meier; PFS, progression-free survival

Secondary endpoint: Overall survival

Table 52 shows overall survival (OS) data. With a median follow-up of 8.5 months, 31% of patients had died, and median OS was not reached. The Kaplan-Meier plot for OS is presented in Figure 17.

Table 52. Summary of OSINV – INV Efficacy Evaluable population

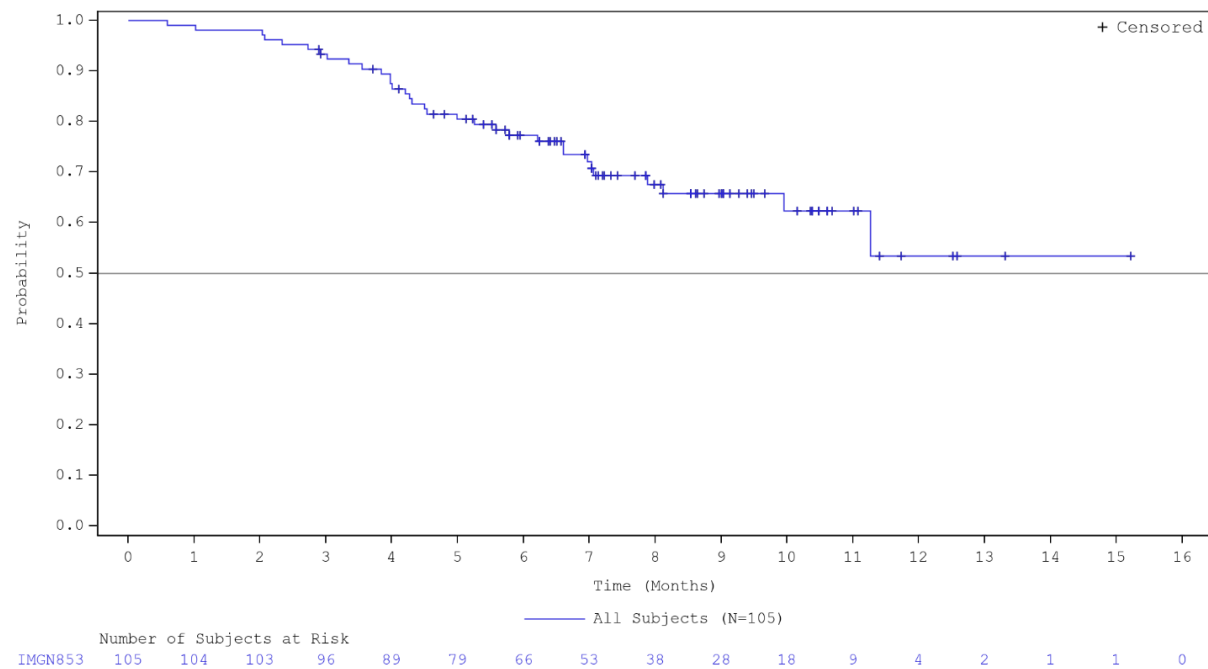
Measure	Efficacy Evaluable Population (N=105)
OSINV events, n (%)	
Death	33 (31.4)
Censored, n (%)	
Alive	71 (67.6)
Lost to follow-up	1 (1.0)
Kaplan-Meier estimates for OS (months)	
Median (95% CI)	NR (10.0, NR)
1 st quartile (95% CI)	6.6 (4.3, 8.1)
3 rd quartile (95% CI)	NR (NR, NR)
Range	0.6, 15.2+
Kaplan-Meier estimates for OS rate (95% CI)	
At 3 months	0.93 (0.87, 0.97)
At 6 months	0.77 (0.68, 0.84)
At 9 months	0.66 (0.54, 0.75)
At 12 months	0.53 (0.33, 0.70)
At 15 months	0.53 (0.33, 0.70)
RMST for OS (months) (95% CI)	
At 3 months	2.9 (2.9, 3.0)
At 6 months	5.5 (5.2, 5.7)
At 9 months	7.6 (7.1, 8.0)
At 12 months	9.4 (8.7, 10.1)
At 15 months	11.0 (9.8, 12.2)
Median follow-up time for OS (months) (95% CI)[†]	8.5 (7.3, 9.0)

Source: Data on file, SORAYA CSR (38)

+, censored; [†]OS median follow-up time and its 95% CI are estimated using reverse Kaplan-Meier method.

Abbreviations: CI, confidence interval; CSR, clinical study report; OS, overall survival.

Figure 17. KM plot for OSINV – INV Efficacy Evaluable population



Source: Data on file, SORAYA CSR (38)

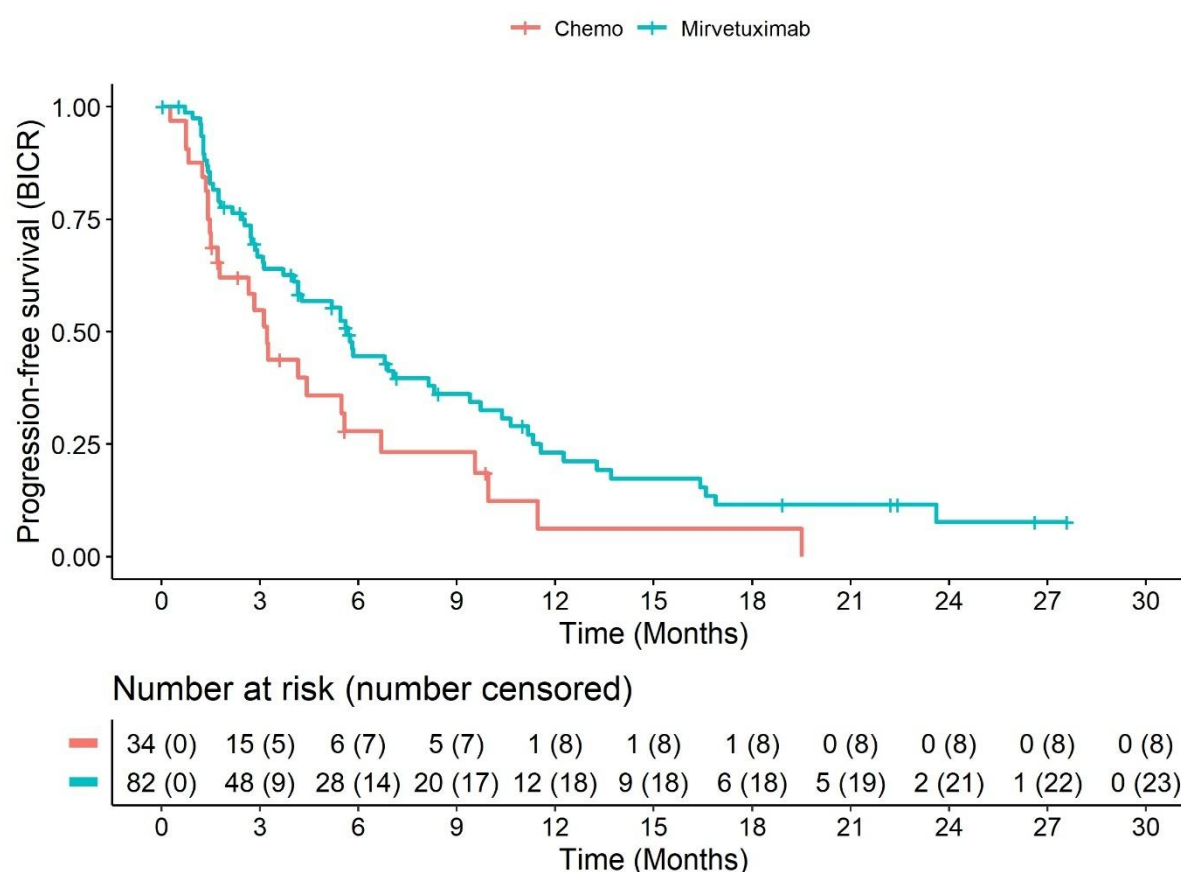
Abbreviations: CSR, clinical study report; KM, Kaplan-Meier; OS, overall survival.

2.3.2. FORWARD-1

Primary endpoint: PFS by BICR

The Kaplan-Meier for PFS by BICR is presented in Figure 18. In mirvetuximab-treated patients, the median PFS was 5.68 months, compared with 3.22 months in IC Chemo-treated patients (HR: 0.588; 95% CI: 0.368, 0.940; $p=0.0267$).

Figure 18: KM plot for PFS by BICR – ITT population



Abbreviations: BICR, blinded independent central review; ITT, intention-to-treat; Kaplan-Meier; PFS, progression-free survival.

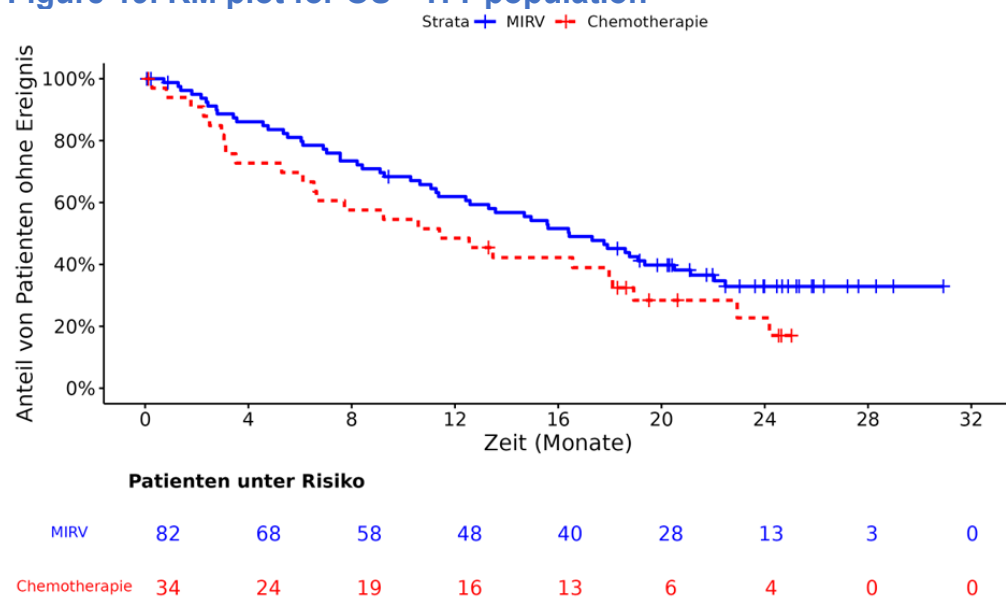
Key secondary endpoint: ORR

A re-scored analysis of ORR is not available. Please see the FORWARD-1 CSR for the analysis of ORR in the original FR α high population, although please note that these results may not be accurate.

Key secondary endpoint: OS

The Kaplan-Meier for OS is presented in Figure 19. In mirvetuximab-treated patients, the median OS was 16.4 months, compared with 11.4 months in IC Chemo-treated patients (HR: 0.678; 95% CI: 0.410, 1.119; p=0.126).

Figure 19. KM plot for OS – ITT population

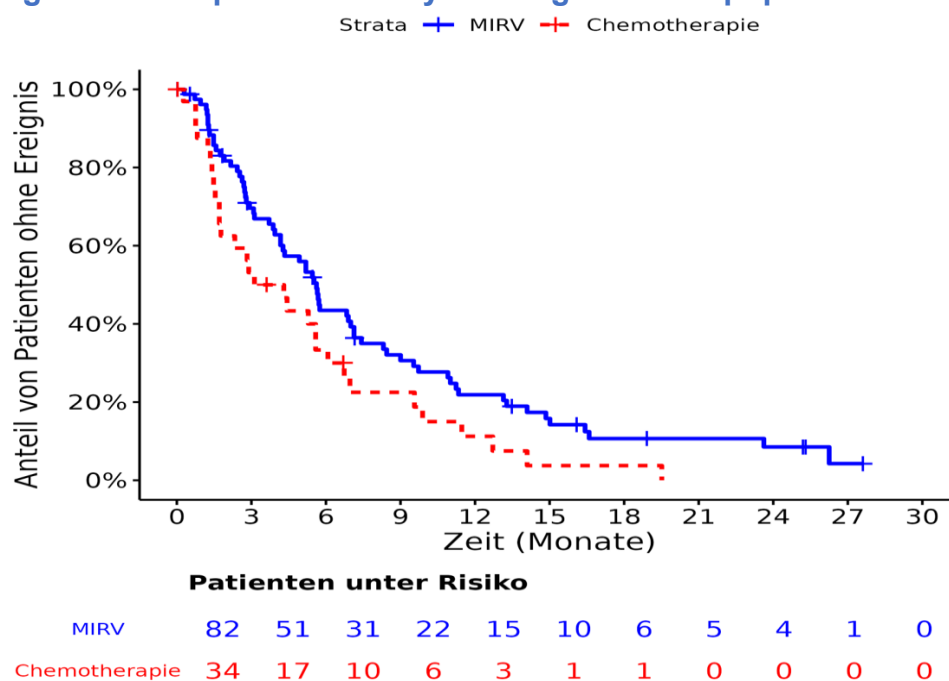


Abbreviations: HR, hazard ratio; IC Chemo, Investigator's choice of chemotherapy; ITT, intention-to-treat; KM, Kaplan-Meier; mOS, median overall survival; OS, overall survival.

Secondary endpoint: PFS by investigator

The KM for PFS by investigator is presented in Figure 20. Median PFS by investigator was 5.62 months in mirvetuximab treated patients, vs 3.71 months in IC Chemo treated patients (HR: 0.65; 95% CI: 0.407, 1.032; p=0.0747).

Figure 20. KM plot for PFS by investigator – ITT population



Abbreviations: HR, hazard ratio; IC Chemo, Investigator's choice of chemotherapy; ITT, intention-to-treat; PFS, progression-free survival.

2.4. Subgroup analysis

2.4.1. SORAYA

Subgroup analysis of ORR and DOR are presented in Table 53 and Table 54, respectively.

Results of the subgroup analyses suggest the response rate observed in patients with 3 prior lines of therapy was consistent with the rates observed in patients with 1 or 2 prior lines of therapy and the overall Efficacy Evaluable population. Similarly, the response rate in patients with prior PARP inhibitor exposure was consistent with the response rates in patients with no prior PARP inhibitor exposure and the overall Efficacy Evaluable population.

As with ORR, results for the individual subgroups for DOR were consistent across categories and with the overall Efficacy Evaluable population.

Table 53. Objective response rate by Investigator – subgroup analysis

Clinical Parameter Subgroup	N	ORR, n (%)	95% CI
Efficacy Evaluable Population	105	34 (32.4)	23.6, 42.2
Number of prior lines of therapy			
1 or 2	51	18 (35.3)	22.4, 49.9
3	53	16 (30.2)	18.3, 44.3
Prior exposure to PARPi			
Yes	50	19 (38.0)	24.7, 52.8
No	51	14 (27.5)	15.9, 41.7

Abbreviations: CI, confidence interval; ORR, objective response rate; PARPi, poly (ADP-ribose) polymerase inhibitor.

Table 54. Duration of response by Investigator - subgroup analysis

Clinical Parameter Subgroup	N	Events (%)	Median (95% CI) (months)
Efficacy Evaluable Population	34	18 (52.9)	5.9 (5.6, 7.7)
Number of prior lines of therapy			
1 or 2	18	8 (44.4)	5.9 (4.2, NR)
3	16	10 (62.5)	7.0 (3.5, NR)
Prior exposure to PARPi			
Yes	19	11 (57.9)	5.7 (3.5, NR)
No	14	7 (50.0)	5.9 (2.8, NR)

Abbreviations: CI, confidence interval; PARPi, poly (ADP-ribose) polymerase inhibitor.

2.4.2. FORWARD-1

Subgroup analysis on the re-scored population was not conducted. Please see the CSR for subgroup analysis of the original population.

2.5. Adverse reactions

2.5.1. SORAYA

Overview of adverse events

A summary of overall safety is presented in Table 55.

Table 55. Overview of TEAEs until the data cut-off date – Safety population

Adverse event, n (%)	N=106
TEAE	
All grades	105 (99)
Grades 3+	53 (50)
Study drug-related TEAE	
All grades	91 (86)
Grades 3+	31 (29)
Serious TEAE	
All grades	33 (31)
Grades 3+	25 (24)
Serious drug-related TEAE	
All grades	11 (10)
Grades 3+	8 (8)
TEAE leading to study drug discontinuation	
All grades	12 (11)
Study drug-related TEAE leading to study drug discontinuation	
All grades	7 (7)
TEAE leading to death	2 (2)
Study drug-related TEAE leading to death	1 (1)

Source: Data on file, SORAYA CSR (38)

Abbreviations: CSR, clinical study report; DCO, data cut-off; TEAE, treatment emergent adverse event.

Overview of treatment-emergent adverse events

A total of 105 (99%) patients experienced ≥ 1 treatment-emergent adverse event (TEAE), with 86% experiencing ≥ 1 study drug–related TEAE. Most TEAEs observed (91%) in the study were $\leq$ Grade 2 in severity. Thirty-three patients (31%) reported ≥ 1 serious adverse event (SAE). Most TEAEs were manageable as demonstrated by the low rates of patients who discontinued due to any TEAE (11%) or a study drug–related TEAE (7%).

Two patients each had 1 TEAE with a maximum severity of Grade 4 (intestinal perforation and keratopathy). One of these events (keratopathy) was assessed as related to mirvetuximab; the TEAE of Grade 4 keratopathy reflected a visual acuity change and was accompanied by nonconfluent corneal deposits, led to permanent discontinuation of study drug, and resolved within 15 days by ophthalmic examination.

Two patients had fatal TEAEs (small intestinal obstruction and respiratory failure), including one patient with a Grade 5 study drug–related TEAE (respiratory failure [possibly related, without evidence of drug reaction on autopsy showing metastatic ovarian cancer in lungs, with diffuse alveolar damage in background of fibrosis with recent bronchopneumonia]).

Common treatment-emergent adverse events

The most common TEAEs ($\geq 20\%$ incidence) were blurred vision (46%), nausea (40%), keratopathy ([grouped term] 37%), abdominal pain ([grouped term] 33%), diarrhoea (31%), constipation (30%), fatigue (30%), dry eye ([grouped term] 27%), peripheral neuropathy ([grouped term] 27%), and asthenia (21%) (Table 56).

Anaemia, neutropenia, and thrombocytopenia were reported in 13%, 11%, and 5%, respectively.

Table 56. Treatment-Emergent Adverse events reported by preferred term by $\geq 10\%$ of patients – Safety population

Preferred term	N=106, n (%)	
	All grades	Grade 3+
Patients with any event	105 (99)	53 (50)
Vision blurred	49 (46)	7 (7)
Nausea	42 (40)	0
Keratopathy	39 (37)	10 (9)
Abdominal pain	35 (33)	7 (7)
Diarrhoea	33 (31)	3 (3)
Constipation	32 (30)	1 (1)
Fatigue	32 (30)	2 (2)
Dry eye	29 (27)	2 (2)
Peripheral neuropathy	29 (27)	2 (2)
Asthenia	22 (21)	1 (1)
Vomiting	20 (19)	0
Cataract	19 (18)	3 (3)
Decreased appetite	19 (18)	1 (1)
Arthralgia	18 (17)	0
Photophobia	18 (17)	0
Aspartate aminotransferase increased	16 (15)	2 (2)
Anaemia	14 (13)	2 (2)
Gamma-glutamyltransferase increased	13 (12)	5 (5)

Preferred term	N=106, n (%)	
	All grades	Grade 3+
Abdominal distension	12 (11)	0
Alanine aminotransferase increased	12 (11)	1 (1)
Blood alkaline phosphatase increased	12 (11)	2 (2)
Neutropenia	12 (11)	1 (1)
Dyspnoea	11 (10)	0
Eye pain	11 (10)	0
Hypokalaemia	11 (10)	2 (2)
Hypomagnesaemia	11 (10)	0
Myalgia	11 (10)	0

Source: Data on file, SORAYA CSR (38)

The most common ($\geq 20\%$ incidence) study drug-related TEAEs were blurred vision (41%), keratopathy ([grouped term] 36%), nausea (29%), dry eye ([grouped term] 23%), fatigue (23%), diarrhoea (22%), and peripheral neuropathy ([grouped term] 21%).

Adverse events of interest

The SORAYA trial did not specify any all-grade grouped-term AEs of special interest (AESI). However, certain TEAEs are highly relevant to patients and clinicians, namely ocular TEAEs, peripheral neuropathy, and pneumonitis. A summary of AEs of interest is presented in Table 57.

Table 57. Summary of adverse events of interest – Safety population

Adverse event, n (%)	N=106
Ocular TEAES	55 (52)
No action taken	48 (45)
Dose delayed/not given	22 (21)
Dose reduced	11 (10)
Permanent discontinuation	1 (1)
Peripheral neuropathy TEAES	29 (27)
No action taken	28 (26)
Dose delayed/not given	0 (0)
Dose reduced	2 (2)
Permanent discontinuation	1 (1)
Pneumonitis TEAES	8 (8)
No action taken	5 (5)
Dose delayed/not given	2 (2)
Dose reduced	1 (1)
Permanent discontinuation	0 (0)

Source: Data on file, SORAYA CSR (38)

Abbreviations: TEAE, treatment-emergent adverse event.

2.5.2. FORWARD-1

An overview of rescored safety results is presented in Table 58. For more details, please see the original population presented in the CSR.

Table 58. Safety outcome – rescored population

	Re-scored population N=116	
	Mirvetuximab N=82	IC Chemo N=34
Blood and lymphatic system disorders (SOC)	4 (5%)	9 (28%)
Anaemia (PT)	2 (3%)	2 (6%)
Leukopenia (PT)	1 (1%)	3 (9%)
Neutropenia (PT)	0	8 (25%)
Eye disorders (SOC)	11 (14%)	0
Cataract (PT)	6 (8%)	0
General disorders and administration site conditions (SOC)	4 (5%)	6 (19%)
Fatigue (PT)	2 (3%)	2 (6%)
Investigations (SOC)	2 (3%)	2 (6%)
Gastrointestinal disorders (SOC)	13 (16%)	5 (16%)
Small intestinal Obstruction (PT)	0	2 (6%)

Abbreviations: IC Chemo, investigators choice of chemotherapy; PT, preferred term; SOC, system organ class.

Appendix B

1. Scenarios explored as part of EAG requests

Table 59: Scenarios explored as part of EAG requests (using a severity modifier of 1.7 unless otherwise specified)

	Include in updated company base case	Included as scenarios in updated model	Incremental costs	Incremental QALYs	ICER	Impact on ICER
Submitted company base case	-		████	████	████	-
B1c - Bevacizumab-naïve population ¹	No	Yes	████	████	████	Increase
B1c - Bevacizumab-pretreated population ¹	No	Yes	████	████	████	Decrease
B7a – updated RDI approach ³	No	Yes	████	████	████	Increase
B8a - Removal of mirvetuximab costs post progression in chemotherapy arm	No	No	████	████	████	Increase
B8a - Removal of mirvetuximab costs post progression in chemotherapy arm + adjusting chemotherapy OS for mirvetuximab crossover ²	No	Yes	████	████	████	Increase
B9 – MIRASOL duration of subsequent treatment	Yes	NA	████	████	████	Increase
B15b - Utilities from TA962 ⁴	No	Yes	████	████ (1.2 modifier = █████)	████ (1.2 modifier = █████)	Increase
B15b - Utilities from TA946 ⁴	No	Yes	████	████ (1.2 modifier = █████)	████ (1.2 modifier = █████)	Increase
B17a – BRCA negative/unknown ¹	No	Yes	████	████	████	Increase

	Include in updated company base case	Included as scenarios in updated model	Incremental costs	Incremental QALYs	ICER	Impact on ICER
B17a – BRCA positive ¹	No	Yes	████	████	████	Decrease
B17b - Primary platinum free interval ≤6 months ¹	No	Yes	████	████	████	Increase
B17b - Primary platinum free interval > 6 months ¹	No	Yes	████	████	████	Decrease
B19 - Pooled chemotherapy excludes topotecan	No	No	████	████	████	Increase
B20 - Doubling of all utility durations from 4 weeks to 8 weeks	No	No	████	████	████	None
B20 - Doubling of all disutilities	No	No	████	████	████	None
B20 - Doubling all adverse event costs	No	No	████	████	████	Decrease
B22 - Removing half cycle correction for drug costs	Yes	NA	████	████	████	Decrease
Updated company base case	-		████	████	████	

Notes;

1. Alternative populations can be selected on the 'Settings' sheet. But please note only deterministic inputs are included for subgroups other than the ITT population, due to time constraints. Therefore sensitivity analyses, including PSA, cannot be undertaken for these subgroups.
2. The option for using the crossover analysis (which also removes mirvetuximab from the post-progression costs for chemotherapy) can be found in I43 on the 'Effectiveness' sheet.
3. Using the per cycle RDI option can be selected on the 'Duration of treatment' sheet cell E10.
4. Options for two additional utility sources have been added to the 'Utility' sheet.

Abbreviations: BRCA, breast cancer gene; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year, NA, not applicable

Note that for the updated model, changes have also been made based on B21 and B23 (removing certain characteristics from PSA, and linking up the severity modifier).

2. Updated company base case incremental cost-effectiveness analysis results

Results from the updated base case can be seen below in Table 60. Note that these results are still based on a severity modifier of 1.7 applied to the QALYs.

Table 60: Updated company base case results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	Incremental ICER (£/QALY)
Mirvetuximab	████	████	████				
Pooled chemotherapy	████	████	████	████	████	████	████

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life years gained; QALY, quality adjusted life years

3. Probabilistic sensitivity analysis

Probabilistic results are presented in Table 61.

Table 61: Updated company base case results (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Incremental ICER (£/QALY)
Mirvetuximab	████	████			
Pooled chemotherapy	████	████	████	████	████

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life years

The cost-effectiveness plane and cost-effectiveness acceptability curve are presented in Figure 21 and Figure 22.

Figure 21. Cost-effectiveness plane for updated base case

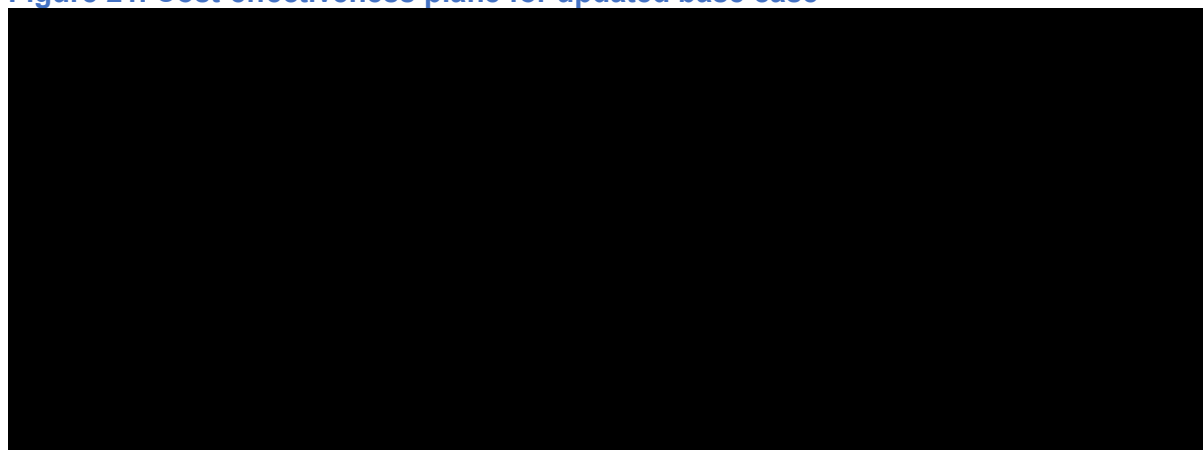
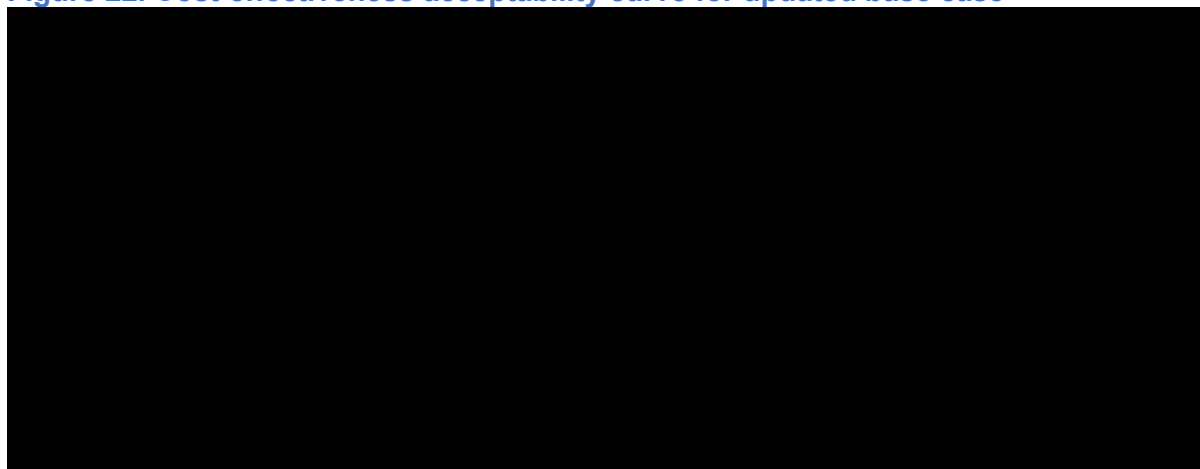


Figure 22. Cost-effectiveness acceptability curve for updated base case



4. Deterministic sensitivity analysis

Results for the 10 most influential parameters are presented in Table 62 and the tornado diagram is presented in Figure 23. The most influential parameters were those associated with the parameters defining the OS extrapolation and DoT extrapolation for mirvetuximab, and pooled chemotherapy utilities.

The results can be seen in a tornado diagram in Figure 23.

Table 62. Deterministic sensitivity analysis results

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS - Mirvetuximab - Log-Logistic - scale	██████	██████
OS - Mirvetuximab - Log-Logistic - shape	██████	██████
DoT - Exponential - Parameter rate - Mirvetuximab	██████	██████
Post-progression utility value, chemotherapy (base case)*	██████	██████
Pre-progression utility value, chemotherapy (base case)*	██████	██████
OS - Pooled chemotherapy - Weibull - scale	██████	██████
Post-progression utility value, mirvetuximab (base case)	██████	██████
Relative Dose Intensity - Mirvetuximab	██████	██████
Post-Prog Trt Cost - % of progressed patients receiving post-progression treatment - Pooled chemotherapy	██████	██████

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
Pre-progression utility value, mirvetuximab (base case)	■	■

Abbreviations: DoT, duration of treatment; ICER, incremental cost-effectiveness ratio; OS, overall survival; Post-prog, post progression; PAS, patient access scheme; Trt, treatment.

*For pre-progression chemotherapy utility the lower CI has been capped at the base case value of the post progression chemotherapy utility (0.4), and for post-progression, the upper confidence interval has been capped at the base case value of the pre progression chemotherapy utility (0.5), so as not to provide illogical results that do not have face validity.

Figure 23: Tornado diagram

5. Scenario analysis

Scenario analyses are presented in Table 63. The scenarios associated with the greatest change in the ICER were the OS distributions for mirvetuximab, and utility values.

Table 63. Scenario analysis

Scenario	Weighted severity modifier of 1.7 (unless otherwise specified)			
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change from base case ICER
Base case	████	████	████	████
OS distribution- Joint models, Weibull (best statistical fit by AIC & BIC)	████	████	████	████
PFS distribution - Joint models lognormal (best statistical fit by AIC & BIC)	████	████	████	████
PFS distribution – mirvetuximab – log-logistic	████	████	████	████
PFS distribution – mirvetuximab – generalized gamma	████	████	████	████
PFS distribution – pooled chemotherapy – generalized gamma	████	████	████	████
OS distribution - mirvetuximab - exponential	████	████	████	████
OS distribution - mirvetuximab - log-normal	████	████	████	████
OS distribution - mirvetuximab - Gompertz	████	████	████	████
OS distribution - mirvetuximab - gamma	████	████	████	████
OS distribution - mirvetuximab - generalized gamma	████	████	████	████
OS distribution - mirvetuximab - Weibull	████	████	████	████
OS distribution - pooled chemotherapy - exponential	████	████	████	████
OS distribution - pooled chemotherapy - log-logistic	████	████	████	████

Scenario	Weighted severity modifier of 1.7 (unless otherwise specified)			
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	% change from base case ICER
OS distribution - pooled chemotherapy - log-normal	████	████	████	████
OS distribution - pooled chemotherapy - Gompertz	████	████	████	████
OS distribution - pooled chemotherapy - gamma	████	████	████	████
OS distribution - pooled chemotherapy - generalized gamma	████	████	████	████
DoT - mirvetuximab - Gamma	████	████	████	████
DoT - pooled chemo - best fitting curves (paclitaxel - gompertz, PLD - gamma, topotecan - exponential)	████	████	████	████
Utility model - Progression status and treatment type (with interaction term)	████	████	████	████
Utility model - Progression status and treatment type (not adjusted for AEs)	████	████	████	████
Utility model - Progression status only (adjusted for AEs)	████	████	████	████
100% vial sharing	████	████	████	████
0% vial sharing	████	████	████	████

Abbreviations: AE, adverse event; AIC, Akaike information criterion; BIC, Bayesian information criterion; DoT, duration on treatment; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; QALY, quality-adjusted life year.

*Using a severity modifier of 1.2 applied to the QALYs.

Appendix C: Methods of analysis adjusting for crossover to mirvetuximab

In the MIRASOL trial, treatment crossover occurred when patients randomized to chemotherapy switched onto mirvetuximab. Specifically, 7.1% of patients in the chemotherapy group switched to mirvetuximab, with 75.0% of these switches occurring after disease progression and 25.0% occurring without progression, potentially biasing the ITT OS estimates and underestimating the survival benefits of mirvetuximab. For regulatory and Health Technology Assessment (HTA) decision-making, unbiased OS estimates that represent the counterfactual scenario in which no treatment crossover occurred are required.

In this study, a feasibility assessment was first conducted to assess the suitable approach for crossover adjustment. Based on the feasibility assessment results, post-hoc analyses of the MIRASOL trial were conducted to evaluate the impact of crossover from the chemotherapy group to mirvetuximab treatment on OS following crossover and to estimate OS under the counterfactual scenario in which no crossover occurred.

Methods

Analytic sample

This post-hoc analysis of OS focused on 453 patients enrolled in the MIRASOL trial. Analyses were based on the September 2024, data cutoff of MIRASOL.

Definition of treatment crossover

- Treatment crossover was defined in two ways:
 - **All crossover:** Patients who were initially randomised to the chemotherapy group but subsequently received mirvetuximab at any point during the study.
 - **Direct crossover:** A subset of “all crossover,” consisting of patients who received mirvetuximab immediately following chemotherapy, without receiving any other intervening treatment.

- **No crossover:** Patients who were randomised to the chemotherapy group and did not receive mirvetuximab at any point during the study.

Feasibility assessment

A hierarchy of candidate methods including naïve approaches and advanced statistical methods recommended by NICE was reviewed to adjust for chemotherapy-to-MIRV crossover and assess their suitability based on MIRASOL data availability and methodological assumptions. RPSFTM was deemed to be the most appropriate method.

RPSFTM

RPSFTM is a randomization-based approach used to adjust for treatment crossover in trials with survival outcomes. It is commonly applied in oncology trials where patients in the control group may crossover to receive the experimental treatment, as was the case in MIRASOL. In this context, RPSFTM estimates what survival outcomes would have been observed for patients who switched from chemotherapy to mirvetuximab, had they instead remained on chemotherapy without switching to mirvetuximab. The method assumes a common treatment effect, meaning the effect of mirvetuximab on survival is constant regardless of when it is received.

Under these assumptions, each switcher's counterfactual survival time—that is, the time they would have survived had they not received mirvetuximab—is reconstructed based on their treatment history. Specifically, the counterfactual time for patient i is defined as

$$T_i^*(\psi) = T_{obs,off,i} + T_{obs,on,i} e^{-\psi},$$

where $T_{obs,off,i}$ is the time accrued while the patient was not receiving mirvetuximab (i.e. prior to crossover), $T_{obs,on,i}$ is the time accrued while on mirvetuximab, and ψ is the log-acceleration factor representing the treatment effect of mirvetuximab vs. chemotherapy.

The value of ψ was estimated using both nonparametric and parametric implementations of the RPSFTM. A log-rank based g-estimation procedure was used to search over a grid of ψ values and identify the value that minimized survival

differences between the mirvetuximab and chemotherapy groups after counterfactual adjustment. In parallel, a parametric Weibull model was used to compute the test statistics of ψ (instead of a log-rank test) that represents the difference between the mirvetuximab and chemotherapy groups after counterfactual adjustment. Kaplan–Meier (KM) curves for the two treatment groups, after counterfactual adjustment, were also examined to evaluate the adequacy of balance.

Survival analyses following crossover adjustment

After counterfactual survival times for switchers were derived using the RPSFTM, adjusted OS outcomes were evaluated through KM curves and Cox proportional-hazards modeling. KM curves for the mirvetuximab group (using observed data) and adjusted KM curves for the chemotherapy group were generated under three scenarios: (i) ITT (no adjustment for crossover), (ii) adjustment for any switching from chemotherapy to mirvetuximab (“all crossover”), and (iii) adjustment for direct switching from chemotherapy to mirvetuximab at any time (“direct crossover”). Cox proportional-hazards models, with randomized treatment as the sole covariate, were fitted to each of these adjusted datasets to estimate crossover-adjusted HRs and corresponding 95% CIs. Wald tests provided nominal p -values. These analyses, conducted without additional covariate adjustment or re-censoring, enable a quantitative comparison of survival outcomes between mirvetuximab and chemotherapy groups following adjustment for crossover, and facilitate interpretation relative to the original ITT results.

Single Technology Appraisal

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

NHS organisation submission (ICBs and NHS England)

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	British Gynaecological Cancer Society
3. Job title or position	

Commissioning organisation submission

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

4. Are you (please select Yes or No):	Commissioning services for an ICB or NHS England in general? No Commissioning services for an ICB or NHS England for the condition for which NICE is considering this technology? No Responsible for quality of service delivery in an ICB (for example, medical director, public health director, director of nursing) No An expert in treating the condition for which NICE is considering this technology? Yes An expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? Yes (not specifically for Mirvetuximab) Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Gynaecological Cancer Society is a professional organization dedicated to advancing the science and practice of gynaecological oncology for public benefit. Its membership comprises medical practitioners, clinical nurse specialists, and allied professionals, including scientists, all focused on gynaecological cancers. It is funded by members' fees and it has a charitable status
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

Current treatment of the condition in the NHS

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines , ESMO and ASCO guidelines as well as BGCS guidelines
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care for platinum resistant ovaria cancer is well defined however the treatment may differ depending on when the resistance develops. Some patients develop platinum resistance after the first line treatment and others will receive several courses of chemotherapy before platinum resistance develops. There are very few drugs effective in this condition and most clinicians will opt for either liposomal doxorubicin or weekly paclitaxel with or without bevacizumab (bevacizumab is not available in NHS setting). Platinum resistant ovarian cancer is an unmet need for patients with ovarian cancer and new treatments are urgently needed. Once it develops , life expectancy is in the range of months , usually less than 12.
8. What impact would the technology have on the current pathway of care?	Access to Mirvetuximab would make a big difference for patients with platinum resistance . It would be the first drug that offers survival advantage in this setting and it would give hope to hundreds of patients who suffer from this condition

The use of the technology

9. To what extent and in which population(s) is the technology being used in your local health economy?	Currently not available
10. Will the technology be used (or is it already used) in the same way	N/A

as current care in NHS clinical practice?	
10a. How does healthcare resource use differ between the technology and current care?	Most patients would receive palliative chemotherapy for symptom control but would have no survival gain, the new drug is the first one to offer overall survival benefit. Current standard of care chemotherapy can be effective but very short lasting and most patients develop progression whilst either on treatment or shortly after completing chemotherapy
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This drug would only be used in a cancer centre setting /specialised services setting
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	It will require tumour testing for foliate receptor alpha (FR α) and this will be an additional cost
10d. If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	The response assessment would be by CT scan as per standard of care , before and after treatment
11. What is the outcome of any evaluations or audits of the use of the technology?	Clinical trial data – MIRASOL trial

Equality

12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
12b. Consider whether these issues are different from issues with current care and why.	N/A

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Patient Organisation Submission

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You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]																		
2. Name of organisation	Ovacom Ovarian Cancer Charity																		
3. Job title or position	[REDACTED]																		
4a. Brief description of the organisation (including who funds it). How many members does it have?	Ovacom is the national UK ovarian cancer charity focused on providing support and information to anyone affected by ovarian cancer. This includes people who have either been diagnosed with the disease or think that they might be at risk, as well as their friends and family and healthcare professionals. We currently have over 5000 members and 18 members of staff. We are funded through charitable donations, trusts and foundations donations, community fundraising donations and earned income.																		
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company,	From 1 February 2024 to 1 February 2025 <table border="1"> <thead> <tr> <th>Company</th> <th>Amount Received</th> <th>Date received money</th> <th>Funding for:</th> </tr> </thead> <tbody> <tr> <td>GSK</td> <td>£1,130.10</td> <td>15/04/2024</td> <td>Participation in a patient panel at GSK UK Annual Conference on 20 March 2024 + mileage + travel time</td> </tr> <tr> <td>GSK</td> <td>£560.00</td> <td>15/04/2024</td> <td>Patient recruitment for an Advisory Board</td> </tr> <tr> <td>GSK</td> <td>£2,560.00</td> <td>06/06/2024</td> <td>Disease awareness campaign - Give Us Time - 1st payment</td> </tr> </tbody> </table>			Company	Amount Received	Date received money	Funding for:	GSK	£1,130.10	15/04/2024	Participation in a patient panel at GSK UK Annual Conference on 20 March 2024 + mileage + travel time	GSK	£560.00	15/04/2024	Patient recruitment for an Advisory Board	GSK	£2,560.00	06/06/2024	Disease awareness campaign - Give Us Time - 1st payment
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amount, and purpose of funding.	GSK	£1,050.00	06/06/2024	Disease awareness campaign - Give Us Time - 2nd payment
	GSK	£915.00	07/06/2024	Patients as Partners (Europe) Conference
	GSK	£600.00	09/08/2024	Patient Advisory Board - UK Ovarian Cancer Patient Council
	MSD	£83,509.30	22/08/2024	Grant towards Health Equality work
	MSD	£83,509.30	01/10/2024	Grant towards Health Equality work
	GSK	£520.00	13/11/2024	UK Ovarian Cancer Patient Panel
	Pharma&	£9,060.00	06/12/2024	Donation
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.			
5. How did you gather information about the experiences of patients and carers to include in your submission?	Knowledge and experience from 29 years providing support to those affected by ovarian cancer. Feedback and discussions through My Ovacom online forum.			

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Ovarian cancer has a significant impact on quality of life. The majority of people are diagnosed at Stage III when it has already spread outside of the pelvis. This means they can experience significant symptoms impacting their health and quality of life, such as ascites. They are often told at diagnosis of advanced disease that this will mean recurrences of their cancer. Treatment is therefore aimed at minimising the burden of the disease and maximising periods of wellness between treatments. The surgery undertaken is most usually a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Some patients may have maximal cyto-reductive surgery at recurrence. Surgical procedures can have long term effects on abdominal organs and particularly the bowel with associated continence issues. This may mean having manage a stoma, either short or long term. Removal of both ovaries results in immediate surgical menopause. Associated issues include fatigue, possible chronic pain and changes to body image and function affecting sexuality. Long-term effects of chemotherapy treatment can include peripheral neuropathy which can limit both walking mobility and ability to drive. These physically and psychologically debilitating side effects can impact relationships, work and caring roles permanently. Living with ovarian cancer can be very isolating for patients and carers. Due to its comparative rarity they may not meet anyone else with the same condition or facing the same issues of managing their cancer as a chronic condition rather than aiming for a cure. Those diagnosed and their friends and family live with the anxiety of possible recurrence. As treatment lines are exhausted, they dread being told there is no more treatment available to manage the ovarian cancer. They are aware platinum chemotherapy has been the main chemotherapy treatment for many years and live with the fear being told they are resistant to this long-established treatment.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Our members express concerns regarding limited choices and availability of treatment for ovarian cancer which does not respond to platinum treatment. These include; • concerns about the availability of effective treatments for platinum resistant disease • concerns that platinum sensitivity is criterion for accessing PARP maintenance therapies and so these targeted maintenance therapies are unavailable for those with already limited treatment options • concerns that treatment options are limited and lines of treatment to control the disease will be exhausted leaving palliative care only
8. Is there an unmet need for patients with this condition?	There is currently no treatment specifically for platinum-resistant ovarian cancer. People who have platinum-resistance are offered other chemotherapies; the MIRASOL trial demonstrated mirvetuximab soravtansine offers “significant benefits with respect to progression-free survival, objective response, and overall survival” compared to chemotherapy. (https://www.nejm.org/doi/full/10.1056/NEJMoa2309169)
9. Is the scoring method used by the company for categorising FRα positive cancer appropriate (at least 75% of viable tumour cells showing moderate and/or strong levels of membrane staining)?	We are unable to comment on this.

Advantages of the technology

10. What do patients or carers think are the advantages of the technology?	Please note the comments from members quoted below includes those not based in the UK and those on trials with platinum sensitive disease. Some of the comments are from the same person, but separated out for clarity. <i>They think it is an effective treatment with manageable side-effects, offering hope to those with platinum resistant disease who have fewer treatment choices. Quotes from our forum members include:</i> “I believe Mirv[etuximab] should be available to patients because although it wasn’t the magic solution I had hoped, it gave me more relatively healthy time. I did have low platelets on several occasions but I generally did well. I have an aggressive cancer, so it was a godsend to me.” “It’s a good option for platinum resistant people.” “the best hope for platinum resistant people.” “giving hope to us all.” “the effectiveness of the Elahere is really encouraging.” “Access to additional therapeutics already in existence gives another option to ladies waiting for places on a trial.” “It worked magically in the beginning.” “quality of life [on treatment] was good” “I found it much much kinder than chemotherapy” “I’ve no idea where I’m heading, but I have felt reasonably well at least, and it does seem there are options [...] I had begun to feel options were running out.”

	"Once the carboplatin stopped working I wondered if anything could tame my rampaging cancer -- now I'm feeling genuinely hopeful!"

Disadvantages of the technology

11. What do patients or carers think are the disadvantages of the technology?	<i>They are aware there are side effects – broadly grouped into digestive and visual effects in the comments below - but these are generally found to be manageable:</i> <i>Digestive side effects</i> “The side effects aren't bad, mainly fatigue and diarrhoea.” “I had very bad side effects with my first dose. I had terrible diarrhoea, nausea, lack of appetite and fatigue. Thankfully no vision issues yet. I am now taking Imodium immediately after infusion and so far no diarrhoea.” “During the treatments I was also diagnosed with steroid induced diabetes and started on insulin [...] I'm now and taking Metformin which is providing better control. It is my opinion that the Insulin reaction combined with the Elahere side effects created a perfect storm that caused my increased difficulties.” “My CA125 is lower than it's been in years and my tumor burden shrunk on CT and is now stable. I developed chemo induced colitis, finally developed neuropathy [...] and have very dry eyes and blurry vision. With the exception of the dry eyes/blurry vision it would be unfair to blame the side effects entirely on Elahere necessarily as this may just be the "straw that broke the camel's back" as far as the colitis and neuropathy.” <i>Visual side effects</i> “I did have a reaction with my eyes. They didn't feel dry but they were and I ended up with Keratitis [...] Using preservative free tears every hour and ointment at night and sometimes during the day really helped. I have also been experiencing some neuropathy too. I have been on a break but will be restarting the treatment soon. [...] I have responded very well to the drug. My CA125 [has fallen] [...] and my tumors are shrinking as well. All that after only 2 treatments!” “I had a problem at one point with blurry vision from side effects but lasted about 2 weeks. You have to take a regime of eye drops while on the trial and have eye checks regularly. I had peripheral neuropathy in feet and

	hands but was treated with gabapentin. Other than that no other side effects. No sickness, no tiredness, no pain, was nothing like traditional chemo which I think was great.” “You have to be very religious about following the eyedrop schedule before, and after Elahere treatment to preserve your eye health... I did get some abdominal cramping after the first infusion, but not too much after that... Nine days after my second infusion, I did get significant eye issues, incredible light sensitivity, and blurry vision... My eye doctor tells me that Elahere causes corneal oedema which leads to the blurry vision, and the only way to calm this down is to take preservative free eyedrops pretty regularly and to hold off on the next infusion until your eyes calm down... Additionally, the doctors dose reduce your Elahere if you do have eye issues [...] other than some central blurriness and light sensitivity, I feel really good and I’m hopeful that this will do the trick.” <i>They are aware it may not work but still want it available as a treatment choice:</i> “Although it only worked for 5 months I feel it was worth doing.” “I was on it as a trial drug last year, for seven weeks until they realised the cancer was progressing and the Elahere was not slowing it down. The side effects were fairly mild and manageable [...] In our situation anything is worth trying and it wouldn't put me off future trials.” “unfortunately, did not do well on Elahere. I had horrible diarrhoea, no appetite and some nausea the first two treatments. [...] I just had my second scan and there is more growth. I will say that I may be the exception because I hear that others have done very well with little to no side effects. I am just recounting my experience.”

Patient population

12. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

13. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We know that some people with ovarian cancer can struggle to access treatments if they don't fully understand treatment options and choices. This may include people with learning disabilities, people who have English as a second language or who have low levels of literacy. It is important that all patients have equal access to this treatment option where clinically appropriate, and that includes detailed understanding of risk-benefits. It is essential that all patients' information and support needs are assessed on an individual basis and that risk-benefit conversations take place in an appropriate and accessible manner. These should take into consideration patient preferences such as preferred language and preference for face to face, or over the phone appointments.

Other issues

14. Are there any other issues that you would like the committee to consider?	

Key messages

In up to 5 bullet points, please summarise the key messages of your submission.	• Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding the choice treatments for this group of patients is vital. • People with platinum-resistant disease live with the fear of being told there is no more treatment available to manage their ovarian cancer. Mirvetuximab soravtansine offers an effective treatment and hope for this group of patients who have fewer treatment options (including maintenance therapies) than those with platinum sensitive disease. • For patients with advanced ovarian cancer knowing from diagnosis that their cancer is likely to recur and could become resistant to platinum treatment, having an option available for platinum-resistant disease offers significant ongoing psychological as well as health benefits. • Our forum members comments demonstrate the treatment's side effects are broadly manageable and good quality of life is possible while on treatment. • For patients (particularly those who may have barriers to accessing information) it is essential that information and support needs are assessed on an individual basis and that risk-benefit conversations take place in an appropriate and accessible manner.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Patient organisation submission

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Your privacy

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Please select YES if you would like to receive information about other NICE topics - **YES** or NO

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- Your response should not be longer than 10 pages.

About you

1. Your name	██████████
2. Name of organisation	Ovarian Cancer Action
3. Job title or position	██████████████████
4a. Brief description of the organisation (including who funds it). How many members does it have?	Ovarian Cancer Action is the UK's ovarian cancer research charity. Ovarian Cancer Action funds research into early detection and better treatments, raises awareness of risk and symptoms to improve prevention and early diagnosis, and gives a voice to all those affected by ovarian cancer. Since 2006, Ovarian Cancer Action has funded over £12 million in research projects and launched the first ever dedicated centre of ovarian cancer research in Europe. Research is focussed on early detection and treatment of ovarian cancer to transform how long and how well women live after an ovarian cancer diagnosis. The charity raises funds through a variety of sources, the majority through individual public giving, philanthropic donations and charitable trusts and foundations. A small % is raised from gifts from corporate organisations including pharmaceuticals. It is not a membership organisation.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months?	None
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

Patient organisation submission

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5. How did you gather information about the experiences of patients and carers to include in your submission?	Significant experience of day-to-day interactions with patients, their families and healthcare professionals. Consultation through email, phone, virtual meetings and surveys with patients and family members who volunteered to tell us about their experiences with ovarian cancer and its treatment. This included members of our Research Network. Previous direct consultation of patients for other NICE and SMC reviews. Quotes include those from patients not taking this medication, but who have given us insight into what living with ovarian cancer is like and their opinions on medications.

Living with the condition 6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of ovarian cancer can be devastating, significantly affecting the quality of life of patients and their families. Supporters tell us about the huge impact on the physical and mental health of the woman diagnosed, but also of the practical, financial and emotional impacts on the whole family. Patients tell us: <i>"I didn't sleep for months after being told I had advanced ovarian cancer."</i> <i>"It was like being hit by a tornado"</i> <i>"Living with ovarian cancer is a total nightmare. My life is in two stages: BC and AC before and after cancer"</i> <i>"Ovarian cancer has taken away everything that makes me a woman"</i> <i>"Being diagnosed with and living with cancer is like a roller coaster. Telling my family was the worst as I have two daughters. It was a very emotional time"</i> <i>"Catastrophic. It was devastating when I was diagnosed particularly knowing the survival rate and the fact that there is no absolute cure"</i> <i>"I'd had to have so much time off work, I had to take early medical retirement which was crushing to me. This was really difficult. I was incredibly lonely and isolated. This disease stopped my whole life".</i> Ovarian cancer affects every aspect of a woman's life – their relationships, work, family life and social life. There can be additional challenges cultural insensitivity and feelings of isolation. Furthermore, family members and carers are also impacted by all of these issues: <i>"[my diagnosis] has had a huge impact on my family. From being someone who never had a day's sick leave in 25 years of working to being someone who initially needed help to get upstairs and at times was in a wheelchair it was a very difficult time for all of us."</i> The husband of a lady who sadly died from the disease in 2017 said: <i>"Life for both the patient and carer becomes totally consumed by the disease – when the next hospital appointment will be, managing side effects, organising childcare, sleepless nights – it is a vicious circle that never seems to end."</i> Another patient told us: <i>"I saw the impact of what it did to me on my family because that ripple effect is huge and it's not really talked about enough."</i> Many women diagnosed are in their 50s/60s, leading active lives with work and dependent family to deal with. Ovarian cancer

	impacts women's lives totally and completely, even once they are well: <i>"Fortunately I am currently in remission. That said, I had to take medical retirement from my full-time job as a university lecturer due to the after effects (physical, mental and emotional) of a cancer diagnosis and treatment."</i> A patient who first developed ovarian cancer at the age of 37 and is currently being treated for platinum resistant recurrence said: <i>"When you have ovarian cancer you are not yourself - life revolves around the disease and in the very worst moments you have no interest in your family, friends and general life outside of the disease and what it is putting your body and mind through."</i> Even after a seemingly successful course of treatment there is still fear and anxiety due to the possibility of a recurrence, as recurrence rates for ovarian cancer are around 70%. This has a significant impact emotionally with patients and their families experiencing high levels of fear and anxiety: <i>"As soon as my mum was diagnosed, I was in a fight or flight state constantly, waiting for a phone call that it had returned. I can't emphasise this enough- I was in this state for 3 years."</i> <i>"Although I have recovered physically from my treatment the fear of a recurrence plagues me."</i> <i>"Even when I've been NED, I've worried a lot about recurrence. Every twinge is a worry. For a long time I couldn't sleep, I was getting two hours a night and I had to beg for sleeping tablets as I couldn't function. What if I'm living my life and the cancer's growing?"</i> <i>"You're told we've done a good job you don't have any cancer at the moment but most likely story is it'll come back."</i> <i>"You have the trauma of knowing it is most likely coming back and you access all the support you can. Then you learn to live in a new way"</i> <i>"Constant stress in the background lurking you're just waiting for it to come back, stats tell you it will."</i> <i>"It's like a constant shadow over your life. You never stop thinking about it and how long you have left. You carry this around with you and don't really share it with anyone for fear of upsetting family."</i> <i>"Once a cancer patient, always a cancer patient. I may not have active disease at the moment but there is always the mental health side of things of "is it going to come back" or what's that niggle?"</i> <i>"Once treatment ends, what it's left behind leaves an indelible mark on your emotions and on your brain."</i> The disease may become platinum-resistant even if it was initially sensitive to platinum therapy. Women are aware of this and of this happening to friends they've made through their journeys. This creates a sense of uncertainty about the future and this is

	difficult for many women to live with: <i>"You live with the uncertainty of cancer reoccurring all the time and in the knowledge that if it comes back too quick there are very few treatment options available to you."</i> For women who have been found to be platinum resistant, this concern is multiplied. There is worry over what options will be and whether they will be left with no choices. <i>"When my cancer returned, it knocked me for six."</i> <i>"Details on the internet about the likely incurable nature of the disease and the massive shortening of life expectancy, was a very heavy weight to bear."</i> <i>"It felt like a death sentence and I was told that it was incurable."</i>

Current treatment of the condition in the NHS 7. What do patients or carers think of current treatments and care available on the NHS?	Concerns raised by patients and carers include: -Anxiety over the likelihood of recurrence, and having to repeat chemotherapy, and experience its side effects, again and again. -The availability of treatments and whether their options will change. -The feeling that certain maintenance options are only available if your cancer comes back- options being available at first line take away the trauma of waiting on a recurrence to be allowed a drug that they believe would give them more time -Variations in care across the country -Increasing knowledge of different treatment options available in other countries, which creates concern that England is behind. Some patients have described their initial surgery to us: <i>"Horrendous. Key hole surgery turned into open surgery due to the size of the tumour that had grown in 4 days."</i> <i>"I had 30 staples in my stomach from sternum to pelvis. Following the operation I was unable to walk more than to the end of my bed, I had to be held up by nurses, I lost 3 stone in weight in 10 days as I couldn't eat as I was in so much pain."</i> Some women struggle greatly post-surgery: <i>"It was PTSD. I have flashbacks and I have a very difficult time in even trying to remember that period because of how difficult that became because I came home and I'd look at my scar, I couldn't even look at it. I just felt mutilated."</i> Supporters told us about their experiences with chemotherapy: <i>"[Chemo] filled me with dread but I was in such a bad way, it was my only option."</i> <i>"Feeling sick, extreme tiredness, low moods, hair loss, lack of appetite, the embarrassment of others staring when out in public."</i> <i>"They started me on the Carboplatin protocol. I developed neuro peripheral neuropathy, which I still have to this day and from the tests that they've recently been doing, it looks like it's going to be a permanent disability."</i> <i>"Looking back I coped well with chemotherapy compared to my sisters and my daughter (who was treated for breast cancer). My treatment was excellent and I paced myself to ensure I got through it. I was not great for the first week of treatment but improved in the next two weeks"</i> <i>"I had 6 cycles of chemotherapy, with two drugs (carboplatin and taxol). I was given the taxol weekly, so had treatment every week for 18 weeks. I had an extreme reaction to chemotherapy, including twice taken to hospital by ambulance to stop me vomiting. The experience was completely exhausting."</i>

"I had severe skin reaction to the chemotherapy, but couldn't find resources showing this side effect on skin the colour of my skin".

Patients also described their treatment journey in general:

"I had such an awful time and my treatment journey wasn't wasn't very good. I had very little options. I suffered very badly from side effects. And with all of that, I reached a really dark place. Physically it bashed me but it nearly broke me mentally as well and emotionally, to the point where I wanted it all to end. I wanted life to end.."

A patient who has been having treatment over the course of the last seven years said *"Quality of life is poor – reasonable at best when on treatment. There is a desire to cram as much into life as possible due to not knowing what is going to happen next, but being bound by the horrific side effects such as complete exhaustion, severe pain, nausea and vomiting and mouth ulcers that make it almost impossible to eat."*

"The standard current treatment for ovarian cancer is debilitating. Many women like me are left with chronic bowel pain and disturbance (or a stoma) after surgery and the chemotherapy leaves women with multiple long-term effects including peripheral neuropathy, joint pains and fatigue, and many understandably suffer from a degree of post-traumatic stress disorder."

"Looking back, [my wife] was ravaged by cancer but the treatment had absolutely destroyed her."

"There were points where I couldn't even get up and go to the bathroom. I'm a really independent person and all of a sudden my daughters are bathing me and I'm having to be carried to the bathroom."

"I found the whole treatment for ovarian cancer extremely arduous and devastating both physically and emotionally."

Even once treatment is over, women tell us that one of their concerns about recurrence is whether they can cope with going through it again:

"For me personally after the initial diagnosis and first lot of treatment I thought there is just no way I can do that again. Chemotherapy is so tough."

"Chemo is gruelling . Blood tests, needles, steroids etc. Once is ok but going through it all again ... It's that feeling that this is the only option and how many times can I put my body through this."

For many, the fact they have exhausted their options is terrifying:

"For me I had ultra radical debunking and chemo then nothing- the awful news there's nothing else for you until it returns. I begged for something to keep it at bay."

	One of the remaining options for a woman who is platinum resistant is to take the chemotherapy pegylated liposomal doxorubicin hydrochloride (Caelyx). Patients tell us: <i>"I was on Caelyx for my second round of chemo. It really was like being hit with a sledge hammer which was not going to let you get up for a few days. If I could have slept through those days it would have been wonderful. It was removed from treatment after four rounds but it is just 'flattening'."</i> <i>"I found Caelyx to be hard to get through during the first few days."</i> <i>"I have had three rounds of chemo and Caelyx was in the third cycle. I found the combination with carboplatin to be particularly tough on side effects - extreme debilitating nausea."</i> <i>"I had more chemotherapy, this time it was Carbo/Caelyx which surprisingly I had fewer side effects with than Carbo/Taxol. I took all the advice for preventative self-care like using a certain mouthwash and it seemed to work."</i>

8. Is there an unmet need for patients with this condition?	-There is an unmet need for all ovarian cancer patients, of treatments that allow women to have a good quality of life with their families and friends. -There is also a huge unmet need for women with platinum resistant disease, as their options are so limited. This creates a mental burden for women and their families. -Patients tell us that have seen the introduction of PARP inhibitors in other groups of patients and have seen little progress for women like them. -There is also concern in the patient population around becoming platinum resistant. <i>"There is a huge unmet need: We need treatments that stop it coming back. We need more alternatives to chemotherapy which is so gruelling."</i> <i>"An unmet need is the treatment options available on the NHS. I do not think the treatment options available to patients includes recent advancements in extending life expectancy and outcomes for patients with OC"</i> <i>"Yes there is an unmet need - we feel like the poor relation."</i> <i>"We need diversity of drugs and tailored treatment options, plus improved chemo effectiveness"</i> <i>"[There is a] lack of treatments for all types of OC, particularly rare types."</i> <i>"When you have no opportunities there is a lack of hope."</i> <i>"[We need] choice of treatment options rather than just being told which treatment you are being put on."</i>
9. Is the scoring method used by the company for categorising FRα positive cancer appropriate (at least 75% of viable tumour cells showing moderate and/or strong levels of membrane staining)?	We understand around a third of platinum resistant patients to be in this category. We appreciate the need to focus on the patient group where efficacy would be greatest. However, we would also be supportive of further research into efficacy in people with lower level of FRα expression. This would offer hope to more patients and their families.

Advantages of the technology 10. What do patients or carers think are the advantages of the technology?	Due to the limited access thus far, there are not many patients in the population to offer their experiences of the drug. However, we were able to ask patients and their families what they thought of the medication in principle, and whether they'd want access to it. Several patients expressed that they had heard of this, and other, medications for ovarian cancer being available in the United States of America or Europe, and with that came concern that England is behind. This understandably causes frustration and worry, because it shouldn't matter where you live as to whether you get life-saving treatment. <i>"It's profoundly demoralising to know that treatment options exist but are not available to me because they are not available on the NHS."</i> Other patients expressed that they would be willing to try this or other possible treatments if it was their only option: <i>"I have read about this drug. If it was offered to me I would seriously consider taking it."</i> <i>"Even if there were side effects, I would want to try. I'd rather try and fail than not try."</i> <i>"If is proven to work, then of course I would take it if ultimately it was going to save my from an untimely and horrible death"</i> <i>"If this was the most appropriate treatment, of course, I would take it. There are relatively few options available."</i> <i>"If my disease came back and there was a new treatment available to me, I think I would try it regardless of the side effects. I'd rather try and fail, I'd try anything."</i> <i>"I have heard of some types of ovarian cancer having access to this drug. Surely it's best to give someone any kind of cancer treatment with the best possible chance of success and the best possible chance of reducing side effects or complications from the treatment."</i> Others believe that there is a benefit for there to simply be more choices available: <i>"I can't be the only one who has pre-existing conditions that can complicate treatment, so the more options there are, the more chance of someone not having to choose between certain death and likely death"</i> <i>"[more choice would make a] huge amount of difference. I don't dwell on it but never want to hear that I have come to the end of the line in terms of treatment and drug availability. I just don't allow myself to go there."</i> <i>"It's hard to impress the importance of options. I personally get excited when I hear of a new treatment and my mood improves."</i> <i>"To try various drugs to see if something works and the balance with the side effects is manageable would be great."</i>

	<i>"The discovery of novel treatments give me hope that my survival may be extended if I relapse"</i> <i>"Knowing that there are more choices available if I should relapse gives me some comfort."</i> <i>"I like to have options, so more treatment choices would be wonderful. I like to think "what's plan A? If that doesn't work, what's plan B, C etc"</i> It's vital to consider the positive mental health impact of having another treatment option, either for people who are still platinum sensitive who may be concerned about the future, and for people who find themselves in the position of no longer responding to platinum chemotherapy: <i>"Well, it's a question of surviving or not surviving. And I just don't mean physically surviving, but mentally surviving. Because it's all about hope and hope is what sustains you. Because nothing much has changed in ovarian cancer in 30 years. And this is what you hope for because you think is this it? Everybody's looking for hope. And if somebody can give you some hope, then it sort of recharges your batteries and you're off again."</i> Giving a woman hope, through access to a drug offering greater progression-free survival gives her whole family, and friends, hope too. Access would allow women more, and better, quality time with friends and family, with better mental health due to reduced anxiety. <i>"As I've had two recurrences, progression free survival is of utmost importance to me."</i> Patients on a different maintenance treatment described the impact of being able to take a drug that gave them more time: <i>"I went from absolutely no hope to some hope. And now to every hope."</i> <i>"I live a wonderful, manageable life. I can do the things to lead a great life. I still have to manage the fatigue, and stress of living with cancer, but I am able to celebrate important life events of my children. Build more memories with my children. Try and become a better person".</i> Ovarian Cancer Action supports new options being made available that can give women more good quality time with their families and friends. In order to improve survival rates we must ensure that more patients have access to the best available treatment, and at the earliest opportunity. These new options are life-changing for the patients we see every day, offering hope for the future

Disadvantages of the technology 11. What do patients or carers think are the disadvantages of the technology?	It is imperative that quality of life is assessed as a priority, which should include mental health as well as physical health. We understand that overall, side effects of this drug are comparable, or milder, than the chemotherapy options. However, of concern to patients is the probability of ocular side effects that have been reported in the research. Although many of the ocular issues seen were low grade, we understand that not all optical side effects will return to normal if the drug is discontinued. Patients tell us that one of the biggest issues with certain treatment side effects, is having to stop driving. Blurred vision, and other ocular problems, could cause huge issues with a woman's day to day activities, work and social life, independence and also ability to attend medical appointments, particularly in rural areas. This has a profound impact on the woman's mental health as well as practically speaking, for the whole family. For example, a patient who had to stop driving due to cyber-knife treatment for brain metastases explained it was one of the worst aspects of her journey: <i>"I had to lose my driving license during the treatment and two years afterwards. It was the absolute worse punishment ever. I have three children, one had just started uni and two were still at secondary school at the time so it really was hugely inconvenient. It affected me greatly."</i> We understand that there will be close monitoring of these issues, direct interventions to reduce ocular side effects and options to modify the dose if necessary. Within this should be consideration that for some women, the idea of reducing the dose of a medication is concerning, as there is a question of efficacy at a lower dose in the patient's mind. Anecdotally we have heard from patients on PARP inhibitors who are scared to tell their clinical teams about side effects they are experiencing for fear of being taken off the maintenance treatment they are on. We would suggest ensuring detailed information and reassurance for patients within this process to ensure they are still confident in their treatment plan.
Patient population 12. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality 13. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The health literacy of patients should be taken into consideration, ensuring plain English, and where technical language is used this is explained. Any literature needs to be accessible so that patients with visual impairments or different language needs can still get the information they need in a way that suits them.
Other issues 14. Are there any other issues that you would like the committee to consider?	Whilst an understandable focus is on cost and efficacy data, it's important to consider the person at the centre of this (and their family/loved ones too). We appreciate that the committee take into account the input from patient groups such as Ovarian Cancer Action and similar organisations and hope that every element of discussion returns at some point to the person at the centre of this. One supporter reminded us: <i>"Remember that there is a real person with some real emotions there, we are not just the diagnosis."</i> Another patient told us: <i>"What is sorely needed is for the medical system to treat the patient as a real, whole person. Take into account not only the one specialty, but also other health issues, their current home and work set up and support system. I was very lucky that the team who treated me did this, and it made such a difference to my recovery."</i>

Key messages In up to 5 bullet points, please summarise the key messages of your submission.	• Ovarian cancer is a devastating disease for both patients and their families/ friends, with a poor prognosis for the many women diagnosed at a late stage. • Patients and their families face a great deal of anxiety over treatment itself, and whether the disease will recur (which it does for most). This is compounded when a woman is (or becomes) platinum resistant. • There is an unmet need for treatments for women who become platinum sensitive. • It is vital that quality of life whilst on treatment, and after, is considered when assessing treatments, and plans put in place to manage any negative effects. • Ovarian Cancer Action supports new options being made available that can give women more good quality time with their families and friends. In order to improve survival rates we must ensure that more patients have access to the best available treatment, and at the earliest opportunity. These new options are life-changing for the patients we see every day, offering hope for the future.

Thank you for your time.

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Single Technology Appraisal

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	██████████
2. Name of organisation	Target Ovarian Cancer
3. Job title or position	████████████████████
4a. Brief description of the organisation (including who funds it). How many members does it have?	Target Ovarian Cancer is the UK's leading ovarian cancer charity. We work to: • improve early diagnosis • fund life-saving research • provide much needed support to women with ovarian cancer We are the only national charity fighting ovarian cancer on all three of these fronts, across all four nations of the UK. We are the authority on ovarian cancer. We work with women, family members, and health professionals to ensure we target the areas that matter most for those living and working with Target Ovarian Cancer is funded through voluntary donations and in the last 12 months we have received some limited funding from pharmaceutical companies outlined below
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant	Target Ovarian Cancer has received a pledge of a donation £10,000 from AbbVie to support our support events in March 2025. The donation is subject to a contract which is in the process of being signed.

Patient organisation submission

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	• Patient survey on experience of platinum resistant ovarian cancer • Anecdotal feedback from patients and their families. • Calls to the Target Ovarian Cancer support line and questions and comments on our online communities

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Around 6,900 women are diagnosed with ovarian cancer in England each year and two thirds are diagnosed at a late stage (stage III or IV) when the cancer is more difficult to treat. Survival rates for ovarian cancer trail those for many other cancers. Around 70 per cent will experience a recurrence and once the disease as recurred within 6 months of treatment with platinum-based chemotherapy it will be considered platinum-resistant which greatly reduces treatment options and treatment efficacy leading to a poor prognosis. Those living with platinum-resistant disease tell us that they live with the fear of running out of treatment options, the knowledge of the poor prognosis of the disease can cast a shadow over their lives and in addition to the sometimes debilitating side effects from standard chemotherapy from previous treatments. <i>'It's a brutal disease, and so many women are left with few or no options once standard chemotherapy stops working. Support for patients dealing with the long-term side effects of treatment, including heart complications and chronic fatigue, is also crucial. It's not just about prolonging life but also about ensuring those extra months or years are worth living.</i> Woman with platinum-resistant ovarian cancer <i>'Fear that due to recurrences being close and unstable cancer there are less options and worse prognosis'</i> Woman with platinum-resistant ovarian cancer

7. What do patients or carers think of current treatments and care available on the NHS?	Patients with platinum-resistant ovarian cancer tells us that the main challenges with current treatment and care is the lack of treatment options. They are often aware of the poor outcomes associated with platinum-resistant disease which impacts quality of life and mental health. <i>'The biggest challenge is the limited treatment options available. Knowing that standard platinum-based chemotherapy is no longer effective makes it feel like the clock is ticking faster. The side effects from repeated treatments, including fatigue, breathlessness, and heart complications, make everyday life more difficult. Insomnia, anxiety, and the emotional toll of living with a terminal illness add another layer of struggle. There's also the constant worry about how my family will cope as my condition worsens.'</i> Woman with platinum-resistant ovarian cancer <i>'My main challenges are running out of options as I have tried chemo'</i> Woman with platinum-resistant ovarian cancer <i>'Shortage of treatments to go on and little faith in them working'</i> Woman with platinum-resistant ovarian cancer <i>'Standard treatments do not work. Access to others such as immunotherapy or newer ADC treatments impossible and cost prohibitive. Having any kind of rarer cancer stops you from accessing drugs as there are no NICE protocols for you so everything is off license.'</i> Woman with platinum-resistant ovarian cancer <i>'The limited treatment possibilities and the knowledge that available treatments that such treatments are unlikely to be effective'</i> Woman with platinum-resistant ovarian cancer

8. Is there an unmet need for patients with this condition?	Yes patients with platinum-resistant ovarian cancer do not currently have access to effective treatment options.
9. Is the scoring method used by the company for categorising FRα positive cancer appropriate (at least 75% of viable tumour cells showing moderate and/or strong levels of membrane staining)?	We are unable to comment on this

Current treatment of the condition in the NHS

Advantages of the technology

10. What do patients or carers think are the advantages of the technology?	Best possible care – patients are aware of the poor outcomes associated with platinum -resistant ovarian cancer. By accessing a new treatment like Mirvetuximab soravtansine many feel they are giving themselves the best possible chance of prolonging their life, <i>'It would provide me with a lifeline. It may not cure me but it might offer me more time to get things in order before I die. Or more time so that I'm still alive when even more treatments become available to keep me going. It would reduce my anxiety and fear that I currently have. It would make being on death row more bearable'</i> Woman with platinum-resistant ovarian cancer <i>'It would be another opportunity to be able to bring the disease under control where previous treatments have not been successful'</i> Woman with platinum-resistant ovarian cancer Emotional/mental health an new effective treatment for platinum-resistant ovarian cancer will have a positive impact on mental health allowing patients valuable time to potentially live their lives as fully as possible. Many patients also told us how important having hope that there may be a treatment available for them is for their mental health. <i>'It would mean hope. The possibility of extending my life while maintaining some quality of it is everything. A treatment that is less toxic but still effective would allow me to spend more time with my loved ones without being completely debilitated by side effects. It would also provide reassurance that there are still options left, rather than feeling like I've run out of chances.'</i> Woman with platinum-resistant ovarian cancer Choice - Many women welcome the opportunity to be involved in making decisions about their care and treatments they receive, and feel they are able to take some control at what is a very uncertain time a new treatment would be mean greater choice <i>'Potentially extend my life and give me more time to spend with family making memories'</i> Woman with platinum-resistant ovarian cancer

Disadvantages of the technology

11. What do patients or carers think are the disadvantages of the technology?	Side effects - some women will find these more difficult to tolerate, depending upon the side-effect and its severity but are best managed in discussions between patient and clinicians

Patient population

12. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

13. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

14. Are there any other issues that you would like the committee to consider?	

Key messages

In up to 5 bullet points, please summarise the key messages of your submission.	Quality of life impact: Knowledge of the extremely limited treatment options for platinum-resistant ovarian cancer looms large over patients' lives. The emotional, practical and physical implications for patients and their loved ones are significant. This makes it hard for women to plan events and activities that would have a positive impact on their quality of life. Access to the best possible treatment patients with platinum-resistant ovarian cancer deserve access to the best possible treatment. Given the limitations of current treatment options, a new treatment for the condition which could extend life is extremely valuable Choice: Many women welcome the opportunity to be involved in making decisions about their care and treatments they receive, and feel they are able to take some control at what is a very uncertain time

Thank you for your time.

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Single Technology Appraisal

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Clinical expert statement

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Monday 6th October 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Part 1: Treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Prof Jonathan A Ledermann
2. Name of organisation	UCL Cancer Institute, University College London and UCLH Hospitals NHS Trust, London
3. Job title or position	Professor of Medical Oncology and Hon Consultant in Medical Oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer? ☐ A specialist in the clinical evidence base for folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)

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6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of treatment is to prolong survival with secondary aims to improve symptoms of the disease and to extend the time before disease progression occurs.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	The main outcome benefit from treating 'platinum-resistant' ovarian cancer is to prolong the survival time of patients. Currently this is poor, usually around 12 months depending on the clinical characteristics of the patient entering this phase of treatment. Many of these patients have a tumour burden that results in significant symptoms. The response rate and duration of response with current standard treatments is modest, so an improvement in tumour response rate would represent a very useful clinical benefit. Historical data of response rates needs to be interpreted with caution; they depend on the clinical characteristics of the patient when entering a non-platinum-based clinical trial. Generally, it is around 10-15% with the highest reported at 32% with weekly paclitaxel in the AURELIA trial Poveda et al 2015. A greater proportion of patients responding to treatment translates into better symptom control and consequently an increase in the progression-free survival. Such beneficial effects may increase survival although previous trials of treatment for platinum-resistant disease have not led to any significant improvement in survival.
10. In your view, is there an unmet need for patients and healthcare professionals in folate receptor alpha-	Currently treatment options for this phase of the disease are limited, particularly so in England and Wales, where there is no approval for the most active

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positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer ?	regimen, namely weekly paclitaxel and bevacizumab (available in Scotland and most of Europe). With the current NICE-approved drugs the expected median progression-free survival is around 4 months and the median overall survival is about 12 months. Current drugs provide short-term palliation, and the most active and commonly used NICE-approved drug is weekly paclitaxel (weekly infusions for up to 24 weeks or less if progression occurs). There is currently no biomarker to select patients who might benefit from one of the NICE-approved drugs during this phase of treatment. The use of biomarker directed therapy provides a much more efficient use of a drug for treating this phase of the disease. Real World data analysis has shown that about one third of patients with high grade ovarian cancer have high expression of the folate alpha receptor Bax et al 2025, and for these patients Mirvetuximab soravtansine (MIRV) provides a treatment that has been shown in clinical trials to improve the tumour response rate, prolong progression-free and overall survival in patients relapsing with a treatment-free interval of less than 6 months.
11. How is folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Currently within this group of 'platinum-resistant' patients there is no selection of treatment based on any biomarker. All patients who need and agree to treatment are treated similarly. • Treatment selection is based on Clinical Guidelines. In Europe, the most respected guidelines are published in the ESMO (European Society of Medical Oncology) Clinic Practice Guidelines and Ovarian Cancer Consensus Statements developed jointly by ESMO, ESGO (European Society of Gynaecological Oncology) and ESP (European Society of Pathology) (See ESMO Ovarian Cancer CPG , ESMO-ESGO-ESP Ovarian Cancer Consensus). A brief section in the British Gynaecological Cancer Society's Guidelines also refers to platinum-resistant ovarian cancer BGCS Ovarian Cancer Guidelines .

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	• The pathway for treating with non-platinum drugs is well defined and clearly delineated in the ESMO Ovarian Cancer CPG. It should be noted that over the last few years there has been a move away from defining platinum-resistance as being disease progression/relapse with an interval of less than 6 months, to a situation where platinum-based drugs, the most active chemotherapy, is unlikely to work. Nevertheless, the 'less than 6 months' and 'greater than 6 months' (platinum-sensitive) definition continue to be used for commercial trial design and regulators. It is a convenient stratification factor. Clearly this time division is arbitrary; not only is it dependent on when clinical imaging is performed but many patients relapsing after 6 months have a tumour that is resistant to platinum. It should also be noted that there are no randomised trials comparing platinum-based therapy to non-platinum-based drugs in the 'less than 6 month' [platinum-resistant] group. The adoption of using re-using platinum-based drugs in this less than 6-month group is slowly gaining traction within the oncology community. However, it should be noted that the number of patients in this category is small and that all patients relapsing after an interval of less than 6 months will eventually become truly platinum-resistant. To summarise, whatever current treatment is considered in this less than 6-month group, the duration of response is short, and these patients need better treatments. • Currently PARP inhibitors are the only biologically-directed therapy for ovarian cancer. Their use in biologically-selected tumours has made a big impact on outcome, and treatment selection based on the biology of a tumour is a scientifically sound approach. Identifying the approximately one third of patients with high tumour expression of the alpha folate receptor provides an opportunity to tailor therapy which has been shown a randomised trial to provide a superior tumour response rate, progression-free and overall survival compared to standard

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	chemotherapy. Testing of the tumour is by a simple immunohistochemical test, like the many other immunohistochemical tests currently undertaken to diagnose and categorise the tumour subtype. As more than 70% of all patients with advanced ovarian cancer relapse, and many of these receive further chemotherapy for relapse, most patients who are being considered for further treatment would be eligible to be tested. Being aware of the biological status of the tumour would allow the introduction of MIRV at a time when a further treatment is considered in patients with a less than 6 month treatment-free interval.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	• In England, the most commonly used non-platinum drug in this less than 6 month (platinum-resistant group) is weekly paclitaxel. This is given weekly, or sometimes weekly for 3 out of 4 weeks, usually for 24 weeks, or shorter depending on response and toxicity. Pegylated liposomal doxorubicin may be used if it has not been previously given with carboplatin for platinum-sensitive recurrent disease. Topotecan, the third drug reviewed in NICE TA389 (2016) and is rarely used. These three drugs were used as part of the AURELIA trial (chemotherapy with/without bevacizumab), but not compared directly. The tumour response rates in this trial ranged from 30.2% paclitaxel, 7.8% PLD and 0% topotecan Poveda et al (2015). (It should be noted that favourable clinical characteristics for trial entry were more stringently controlled in AURELIA compared to MIRASOL (MIRV) trial. • The introduction of MIRV would bring in a once every three-week treatment, and, in comparison with weekly paclitaxel, this would reduce day care hospital time and associated blood testing. However, the unique ocular toxicity of Antibody Drug Conjugate (ADC) therapy requires the establishment of links to Ophthalmology support services to review and treat any ocular toxicity. • Gynaecological Cancer Treatments in England are given in designated hospitals within the context of Cancer Centre Multi-disciplinary care. MIRV

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	therapy would be given in the same location as all other systemic treatments for this group of patients. There is an associated cost of 1) the testing for alpha folate receptor and 2) Ophthalmology support. The former is a simple immunohistochemical test that could be performed either locally by a pathologist specialising in gynaecological malignancies, or through a more centralised service. There has been an increase in biology diagnostic use across all gynaecological cancer pathology and the addition of this test to ovarian cancer is a simple addition. The Ophthalmology pathway would need to be set up at a local level with review/treatment in accordance with the licensed recommendations.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	- The published results of the MIRASOL trial showed that the median overall survival with MIRV was approximately 4 months longer than with standard treatment, with the Kaplan-Meier survival curves remaining separated beyond the median. Similar survival benefits of MIRV were seen in the subgroup analyses of different control arm chemotherapy. The behaviour of the control arm was similar to the expected median overall survival with the standard non-platinum-based chemotherapy drugs used in other trials. - The Quality of Life results of the MIRASOL trial were published this year (Van Gorp et al (2025)). No significant improvement or detriment was seen between the two groups with the instruments used. However, there was a numerical superiority (not statistically significant) in the QLQ-OV28 abdominal and gastrointestinal scores favouring MIRV. From a clinical perspective, it is noteworthy that the responses in the MIRV arm were higher than in the control arm (ORR 42.3% versus 15.9%) and that these responses occurred early. As many patients have symptomatic disease, an early response to treatment is the best way of alleviating symptoms- these may not necessarily be captured in the classical QoL instruments.

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14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This technology is only likely to be beneficial in patients with ovarian cancers that have high expression of the alpha folate receptor and is best suited to those with relapsing or progressing disease after a treatment-free interval of less than 6 months
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Whilst the use of daycare facilities will be less (compared to the most commonly used weekly paclitaxel regimen) there will need to be an increase in Ophthalmology service support. This is largely review for visual assessment and presence of ocular keratitis and its treatment with topical applications.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Guidelines are being drawn up- an update of the ESMO Clinical Practice Guidelines incorporating the indications for the use of MIRV has been submitted for publication. Pathways for Folate alpha testing but immunohistochemistry will need to be established either locally or centrally with clarity about when it would be most efficient to undertake this. The costs may be less testing all patients with advanced disease at the outset as these patients already undergo many immunohistochemical tests on their tumours and 70 % of these patients will relapse and many will become eligible for treatment if they have high alpha folate expressing tumour. Alternatively testing could be done at the time of first relapse, but here may be additional costs retrieving samples and cutting new sections before testing. This pathway is best evaluated locally. Treatment would start in tumour-positive patients when treatment is clinically necessary in a group who have a progression/relapse-free interval of less than 6 months

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	Monitoring of tumour response is according to standard practice with discontinuation of treatment for either tumour progression or unmanageable toxicity.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The QoL data show no benefit or detriment of MIRV although in some domains (eg GI) there is a trend in favour of benefit. Recent work in this patient groups suggest that Patient Reported Outcome measures are more useful than the standard QoL instruments GCIG MOST scale; King et al 2018. These were not done in this trial so interpretation of the QoL results is difficult. As stated in section 13, there was a large difference in response rate in favour of MIRV which is of clinical importance regarding symptom control. Also, there was much less classical haematological toxicity (anaemia, neutropenia and thrombocytopenia) with MIRV compared with standard chemotherapy. The 'knock-on' effects of these, management of haematological toxicity etc may not be picked up by the QALY assessments. Similarly, a reduction in hair loss may not be picked up by QoL instruments. As stated previously the most used standard regimen is weekly paclitaxel and this has a higher resource-use than 3-weekly MIRV. However, the cost-effects of Ophthalmological support for MIRV will need to be considered.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	No previously conducted phase III trial in this group of patients has shown a survival benefit. Thus, this biomarker-directed therapy leading to an overall survival benefit represents a step-change in the management of this group of patients with recurrent ovarian cancer. The significant extension in survival addresses an important need for this group of patients.

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19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Comparative analysis of the side effects identified less haematological toxicity than standard chemotherapy, and less alopecia than with paclitaxel. However, both MIRV and paclitaxel have similar degrees of neurotoxicity and GI toxicity. 9% patients discontinued MIRV due to toxicity compared to 16% in the chemotherapy group. Ophthalmic symptoms are a specific side-effect for MIRV, however only 2% of patients stopped treatment because of this toxicity (supplement Moore et al NEJM 2023).
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, the results are applicable to UK practice, particularly as bevacizumab with paclitaxel is not available. Thus, the comparator arms in the MIRASOL trial are relevant to UK practice. The most important outcome is overall survival and was measured in this trial
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	At ASCO 2024 there was a poster presentation of the outcome of patients in the 'long-term' survivor group from pooled trials (SORYA Phase II, FORWARD1 and MIRASOL phase III trials), those alive at 15 months (230 patients). This provides information about the tail of the survival curve beyond 15 months in this grouping of patients. O'Malley et al ASCO 2024 [poster]
23. How do data on real-world experience compare with the trial data?	I am not aware of any data as MIRV has only recently been licensed for clinical use.
24. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this	No inequality issues. Treatment of patients with ovarian cancer in England fall under a centralised multidisciplinary practice with designated treatment centres for systemic treatment. The treatment is no more difficult to administer than any

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treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics.

Please state if you think this evaluation could

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

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other, and monitoring requires the usual education of staff for new treatments and the appropriate linkage to Ophthalmology services.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- MIRV is the first biomarker-directed therapy for patients with recurrent ovarian cancer relapsing or progressing after an interval of less than 6 months from previous chemotherapy
- The phase III trial results are the first to demonstrate a treatment with a survival benefit in this group of patients
- The extension of survival coupled with an increase in tumour response rate with MIRV represents a valuable new treatment for a selected biomarker-defined subgroup of patients with ovarian cancer
- MIRV is generally well tolerated with fewer patients withdrawing from treatment due to toxicity compared to standard treatment
- It has a unique ocular toxicity, often found with ADC therapies which can be successfully managed in the majority of affected patients but requires a service input from Ophthalmology.

Thank you for your time.

Your privacy

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☐ **Please tick this box** if you would like to receive information about other NICE topics.

Clinical expert statement

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Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Single Technology Appraisal

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on 3 October 2025**.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Agnieszka Michael
2. Name of organisation	British Gynaecological Cancer Society
3. Job title or position	Consultant Medical Oncologist , Professor of Oncology
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with Ovarian cancer ☒ A specialist in the clinical evidence base for Ovarian cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Advisory role and educational grants–BMS, Ipsen, GSK, Astra-Zeneca, Research Grants –MERCK

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8. What is the main aim of treatment for platinum resistant ovarian cancer ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve symptoms, improve quality of life and survival
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in patients' symptoms and longevity of response , current treatment has a very short duration of response and no impact of survival
10. In your view, is there an unmet need for patients and healthcare professionals in platinum resistant ovarian cancer ? ?	Yes , all women with ovarian cancer develop platinum-resistant ovarian cancer and multiple symptoms that come with it. Most of the symptoms i.e. malignant bowel obstruction are very difficult to treat and extremely distressing for patients. Current standard of care -weekly paclitaxel or liposomal doxorubicin, have low response rate and a very short duration of response. Patients often progress almost immediately after the chemotherapy has finished. There is no impact of overall survival at all
11. How is platinum resistant ovarian cancer ? currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The following guidelines are used : BGCS Ovarian cancer guidelines - Guidelines and Recent Publications - British Gynaecological Cancer Society ESMO ovarian cancer guidelines (https://doi.org/10.1016/j.annonc.2023.07.011833) The difference in UK is that patients in Scotland are able to access bevacizumab with weekly paclitaxel and patients in England and Wales are only able to access weekly paclitaxel on NHS. Apart from that there is little choice in terms of drugs as only a couple of options available. Approval of the technology would dramatically change the outlook for patients who express folate receptors, it would form an effective line of treatment that has an impact on PFS and OS.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	No, this will form an additional line of treatment and the first targeted therapy ; no current access to this drug in NHS It will be used in specialist cancer centres Testing for alpha folate receptor will be a new requirement , immunohistochemistry
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes , as explained above , this is a platinum resistant stage of the disease where current standard of care has a relatively minor effect and the PFS is very short, in addition there is no gain in OS
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients need to have alpha folate receptor expression
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient	As long as testing for folate receptor is implement , there will be no difference in how easy or difficult the use of this drug is

acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No, the testing will be the same as for any other chemotherapy treatment and will include CT scan at the beginning as a baseline, half way through the course of treatment and at the end ; this is a standard of care
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes , symptom control in patients with platinum resistant ovarian cancer , increased OS
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	It is a targeted therapy and it forms an important step forward in individualised approach to cancer treatment , it will be more precise than trying any approved chemotherapy and it will benefit those patients who are likely to benefit rather than a blind approach currently used
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Most of the side effects that are seen with this drug are very similar to side effects of any chemotherapy except for the ocular toxicities, which are not seen with standard of care chemotherapy. Ocular toxicity will need an input from ophthalmology. The reports from the trial are that this toxicity is rare , around 5%.
20. Do the clinical trials on the technology reflect current UK clinical practice?	The clinical trials do reflect standard UK practice and no further data will be required . We will need to implement folate receptor testing and have access to ophthalmology review if required

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• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance	no
23. How do data on real-world experience compare with the trial data?	I have not see it/ no access to real world data as yet
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could	Not aware

Clinical expert statement

- exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation
- lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population
- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Platinum resistant ovarian cancer is an unmet need that has a devastating impact on women with ovarian cancer

Currently there are very few effective treatments and none of them have an impact on overall survival and only a moderate effect on PFS, the response rate is poor

Mirvetuximab is a targeted therapy that prolongs overall survival in platinum resistant ovarian cancer, and it is the first agent that showed this in clinical trials

Mirvetuximab is a targeted therapy, and it will therefore be only offered to women who are likely to respond to this treatment

Mirvetuximab has an acceptable toxicity profile that can be managed by oncologists with little support required from other specialties

Thank you for your time.

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Clinical expert statement

ID6442

Single Technology Appraisal

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer or caring for a patient with folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

Thank you for your time.

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Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Part 1: Living with this condition or caring for a patient with folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer

Table 1 About you, folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer, current treatments and equality

1. Your name	Rachel Downing
2. Are you (please tick all that apply)	☐ A patient with folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer ? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Target Ovarian Cancer
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing

Patient expert statement

5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer ? If you are a carer (for someone with folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer) please share your experience of caring for them	
7a. What do you think of the current treatments and care available for folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of current NHS treatments for folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer (for	

Patient expert statement

example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer over current treatments on the NHS please describe these. For example, are there any risks with folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	

Patient expert statement

11. Are there any groups of patients who might benefit more from folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer and folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer ? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	

Patient expert statement

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

13. Are there any other issues that you would like the committee to consider?	

Patient expert statement

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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Patient expert statement

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

Patient expert call: ID6442 Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer

Background

The patient expert was unable to attend the committee meeting. To ensure their insights could be considered in the appraisal, the patient expert met virtually with two members of the NICE technical team, the lay lead on the appraisal, a member of the Patient and Communities Team (PaCT) and a patient group representative. The virtual meeting took place on 29th October 2025 and this document is a summary of the insight provided by the patient expert. The patient expert had platinum-resistant high grade serous epithelial ovarian cancer and is currently having mirvetuximab soravtansine as part of a clinical trial.

Questions and responses

The NICE technical team presented the 'patient perspective' slide that had been prepared for the committee meeting.

Question 1. Is there anything you would like to add that is not captured on the slide or anything that does not reflect your experience?

Response: The patient expert said that they had nothing to add and that the slide summarises the patient experience well.

Question 2: 1. For people having chemotherapy (pegylated liposomal doxorubicin or paclitaxel), would you expect quality of life to be different at the start of each treatment cycle compared to the end of each treatment cycle? If yes, what would the difference be?

Response:

- The patient expert said that they were currently having mirvetuximab but had previously had two lines of chemotherapy, including paclitaxel.
- The patient expert explained that when they started treatment with chemotherapy, they experienced a severe negative impact to their quality of life. They worked full time and often had to call in sick. They lost their senses of taste and smell and experienced a low appetite as a result. They lost their hair which made them feel miserable and very isolated. They said that they felt very low.
- The patient expert explained that they experienced pain in the first cycle, and that this was managed with painkillers in subsequent cycles. The patient expert said that they felt very tired all the time and that this was difficult to manage. They had to take 6 months off work after surgery.
- The patient expert said that preparing for the next cycle of chemotherapy felt debilitating because it meant anticipating the negative experience they would inevitably have.

*Question 3: For people with disease that has **not progressed**, would you expect there to be a difference in quality of life for people having mirvetuximab soravtansine compared with people having chemotherapy? If yes, how big is the difference in quality of life and what causes this?*

Response:

- The patient expert explained that they have experienced a significant positive difference in how they feel in themselves with mirvetuximab compared with chemotherapy.
- Their disease has not progressed since starting treatment with mirvetuximab and they recalled feeling relieved when they found out that the treatment was actually working.
- They have not experienced any side effects and are now able to live a relatively normal life.
- In addition to not experiencing any side effects with mirvetuximab, they feel much less depressed and anxious.
- The patient expert explained that the side effects of chemotherapy had such a negative impact on their quality of life that if they had been offered chemotherapy again instead of mirvetuximab, they would have questioned whether to continue with treatment.

*Question 4: For people with disease that **has progressed**, would you expect there to be a difference in quality of life for people who had mirvetuximab soravtansine before progression compared with people who had chemotherapy before progression? If yes, how big is the difference in quality of life and what causes this?*

Response:

- The patient expert felt that this question was difficult for them to answer because their disease has not progressed since starting treatment with mirvetuximab.

Question 5: Have you experienced any eye-related side effects whilst having treatment with mirvetuximab soravtansine (for example, cataracts, blurry vision or keratopathy)? If so, what impact has this had on your quality of life?

Response:

- The patient expert explained that they have not experienced any eye-related side effects. They did have a routine eye examination before starting treatment to assess their eye health because they wear glasses and have an astigmatism. They have eye drops to avoid problems associated with dry eyes. However, they have not noticed any deterioration in their eyesight.

Question 6: Is there anything else you would like to share with us?

Response:

- The patient expert said they feel extremely passionate about the availability of the drug as it offers lots of hope. They said that they currently need to travel around 2.5 hours to receive the drug in hospital, which not everybody with this disease is able to do. They are excited and hopeful that it could be made more widely available soon.
- The patient expert also said: "I only wish it was easy to express in words how much of a difference the drug has made to my mental health as well as its physical benefit. To be able to feel positive/confident that I will be able to continue working so not have financial worries and more importantly not feel a burden to family or dependent upon state benefits enables me to hold my head up high and concentrate on enjoying life to the full whilst living with this dreadful disease."



Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]:

External Assessment Group (EAG) Report

Produced by	Peninsula Technology Assessment Group (PenTAG) University of Exeter Medical School
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University
of Exeter

Author contributions

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<i>Ahmed Abdelsabour</i>	Critical appraisal of the company submission and economic analyses, conduct of economic analyses, drafted sections of the report
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Abbreviations

ADA	anti-drug antibodies
AE	adverse event
AIBW	adjusted ideal body weight
AIC	akaike information criterion
Bev	bevacizumab
BGCS	British Gynaecological Cancer Society
BIC	bayesian information criterion
BICR	blinded independent central review
BNF	British National Formulary
BRCA	BReast CAncer gene
CDx	companion diagnostic
CI	confidence interval
cPAS	comparator patient access scheme
CQ	clarification questions
CS	company submission
CSR	clinical study report
CT	computed tomography
DNA	deoxyribonucleic acid
DoT	duration of treatment
DSU	decision support unit
EAG	External Assessment Group
ECOG	Electrocorticography and Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EOC	epithelial ovarian cancer
EORTC-QLQ-OV28	European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-OV28
EORTC-QLQ-OV30	European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-OV30
EQ-5D	EuroQol five dimension
FR α	folate receptor alpha
HCRU	healthcare resource use
hgs	high grade serous

HR	hazard ratio
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
HSUV	health-state utility value
HTA	health technology assessment
IC Chemo	Investigator's choice of chemotherapy
ICER	incremental cost-effectiveness ratio
IHC	immunohistochemistry
IPCU	inverse probability of censoring weighting
IPD	individual patient data
ITT	Intention-to-treat
IV	intravenously
KM	kaplan meier
MAR	missing at random
MCID	minimal clinically important difference
MHRA	Medicines and Healthcare products Regulatory Agency
MIRV	mirvetuximab
MRI	magnetic resonance imaging
MMRM	mixed models for repeated measures
NA	not applicable
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
OC	ovarian cancer
ORR	objective response rate
OS	overall survival
OWSA	one-way sensitivity analysis
PAC	paclitaxel
PARP	poly (ADP-ribose) polymerase
PPFI	platinum free interval
PFS	progression-free survival
PFS _{BICR}	progression free survival per blinded independent central review
PFS _{INV}	progression free survival per investigator assessment
PFS2	time to second disease progression

PGIS	patient global impression of severity
PH	proportional hazards
PLD	pegylated liposomal doxorubicin
PN	peripheral neuropathy
PRO	patient-reported outcome
PROC	platinum resistant ovarian cancer
PS	performance score
PSS	Personal Social Services
PSA	probabilistic sensitivity analysis
QA	quality assessment
QALY	quality adjusted life year
QoL	quality of life
Q3W	every 3 weeks
RCT	randomised controlled trial
RDI	relative dosing intensity
RECIST	response evaluation criteria in solid tumors
RPSFTM	rank preserving structural failure time model
SD	standard deviation
SLR	systematic literature review
SmPC	Summary of Product Characteristics
TA	technology Appraisal
TEAE	treatment-emergent adverse event
TOPO	topotecan
TSD	technical support document
Trt	treatment
TTCD	time to confirmed clinically meaningful deterioration
TTDD	time to definitive clinically meaningful deterioration
TTO	time trade-off
UK	United Kingdom
US	United States
vs	versus
WTP	willingness to pay

1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 explains the key issues in more detail. Secondary issues identified by the EAG are explored in section 1.4. No modelling errors impacting the deterministic base case were identified. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in its appraisal of the company submission (CS) is provided in Table 1. Further details of the issues are provided in Section 1.3.

No key issues related to the clinical effectiveness evidence were identified. In terms of cost effectiveness issues, firstly the EAG noted that the company base case used utility values for the chemotherapy arm from a non-reference case source that had design limitations rather than using EQ-5D data collected in the company's pivotal trial (MIRASOL). This may underestimate the quality of life of patients receiving chemotherapy. Secondly, the EAG noted that the overall survival curve selected in the company base case likely overestimated survival in patients treated with mirvetuximab, with the majority of survival gain coming from the post progression state. This was considered clinically implausible and inconsistent with statistical and visual fit to the trial data.

Table 1: Summary of key issues

ID	Summary of issue	Impact on results	Report sections
1	Health state utilities	High	4.2.6 and 3.3.6
2	Choice of distribution for extrapolating overall survival for mirvetuximab	High	4.2.5.1

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
Quality of life	MIRASOL utilities for mirvetuximab and literature-based utilities for chemotherapy	MIRASOL utilities used for both arms	4.2.6
Overall survival	mirvetuximab	Gamma for both arms	4.2.5.1
Duration on Treatment	Exponential curve for MIRV	KM up to week 120 followed by exponential extrapolation	4.2.5.4
Subsequent therapy	MIRASOL based subsequent therapy	Removal of mirvetuximab costs post progression in both treatment arms + adjusting chemotherapy OS for mirvetuximab crossover	4.2.8
Pooled chemotherapy	MIRASOL based distribution of chemotherapy agents	Pooled chemotherapy excludes topotecan. Adjustment only for cost impact.	4.2.4
Wastage	Mean RDI applied	Cycle-specific RDI (more accurate accounting for wastage)	4.2.8.1
Vial sharing	50% vial sharing in both arms	No vial sharing for MIRV and 50% vial sharing in the chemotherapy arm	4.2.8.2
Health state costs	Equal annual frequencies of resource use in post-progression state	Adjust resource use frequencies to reflect on or off treatment status	4.2.8.5
Adverse events cost	Average of HRG reported in NHS reference costs	Anaemia and neutropenia managed as day case and exclude the cost of fatigue	4.2.8.6

Abbreviations: EAG, External Assessment Group; HRG, Healthcare Resource Group; MIRV, mirvetuximab; OS, overall survival; RDI, relative dosing intensity

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology was modelled to affect QALYs by:

- Increasing overall survival: this increased QALY gains for mirvetuximab - large ICER impact
- Increasing progression free survival: this increased QALY gains for mirvetuximab through delayed progression - moderate ICER impact
- Using different utility values by treatment arm resulting in x1.7 severity weight: this led to a large increase in QALYs for mirvetuximab - large ICER impact

Overall, the technology was modelled to affect costs by:

- Higher drug acquisition costs for mirvetuximab compared to chemotherapy: this significantly increased total costs in the mirvetuximab arm - large ICER impact
- Reduced costs in the post-progression stage due to delayed progression: this reduced downstream costs for the mirvetuximab arm - small ICER impact
- Increased testing, administration and monitoring costs: a small net increase in mirvetuximab costs which had a minimal upward effect on the ICER (less than £1,000 per QALY)
- Reduced adverse events related costs: in the company base case, mirvetuximab adverse events (AEs) were associated with lower costs than chemotherapy AEs, leading to a small decrease in the ICER (less than £1,000 per QALY)
- Reduced terminal care costs: as identical costs were applied to both arms and all patients were assumed to die by the end of the time horizon, the impact was balanced. However, because patients in the chemotherapy arm were modelled to die earlier, their terminal care costs were subject to less discounting, resulting in slightly higher costs. The overall effect on the ICER was minimal (less than £500 decrease).

The modelling assumptions that had the greatest effect on the ICER were:

- The use of a different source of health state utilities for mirvetuximab and chemotherapy
- The choice of distribution for extrapolating overall survival for mirvetuximab
- The application of the severity modifier (1.7 vs 1.2)

1.3. The EAG's key issues

Key Issue 1: Health state utilities

Report sections	4.2.6
Description of issue and why the EAG has identified it as important	The company used utility values from a 2008 TTO study for pooled chemotherapy that lacked face validity instead of EQ-5D data collected in MIRASOL. This was important as the use of different utility sources did not only result in reduced QALYs in the chemotherapy arm but also resulted in mirvetuximab being assigned a higher severity weight.
What alternative approach has the EAG suggested?	Using quality of life data collected in the MIRASOL trial for both arms, as this aligned with NICE's reference case and had greater face validity.
What is the expected effect on the cost-effectiveness estimates?	This reduced the estimated incremental QALY gain for mirvetuximab, and resulted in a lower severity modifier (1.2 instead of 1.7) and higher estimated QALY gain in the chemotherapy arm. This had a significant impact on the ICER increasing it from [REDACTED] to [REDACTED] per QALY
Could any additional evidence or analyses be provided to resolve this key issue?	Validation against the FORWARD-1 re-scored population may be of some interest, however, questionnaires were collected on day 1 of the chemotherapy cycle similar to MIRASOL. Validation against wider literature in the PROC population has been conducted using the data sources provided by the company, however, given issues with reporting of the SLR (e.g. relevant sources either not identified or excluded) the EAG could not rule out other data sources being available that may be of use.

Abbreviations: EAG, External Assessment Group; TTO, time trade-off; QALY, quality-adjusted life-year

Key Issue 2: Choice of distribution for extrapolating overall survival for mirvetuximab

Report sections	4.2.5.1
Description of issue and why the EAG has identified it as important	The company selected a log-logistic distribution for extrapolating overall survival for mirvetuximab. The EAG considered this inappropriate as it produced long-term survival projections that were not clinically plausible and had worse statistical and visual fit.
What alternative approach has the EAG suggested?	The EAG preferred to use the gamma distribution
What is the expected effect on the cost-effectiveness estimates?	Using the gamma distribution resulted in lower OS for mirvetuximab, thus increasing the ICER from the company base case [REDACTED] to [REDACTED] per QALY.
Could any additional evidence or analyses be provided to resolve this key issue?	Additional trial follow-up data could help validate long-term survival projections, although this was not expected within the timeframe of this appraisal.

Abbreviations: EAG, External Assessment Group; ICER, incremental cost effectiveness ratio; OS, overall survival

1.4. Secondary issues identified by the EAG

- **Testing for folate receptor alpha (FR α) expression** was required to determine eligibility for mirvetuximab. At the time of appraisal, the only test licensed for use within the NHS was Roche's Ventana assay. However, the diagnostic accuracy of this test was uncertain due to the absence of a universally accepted gold standard for assessing FR α expression. Clinical trials (MIRASOL, FORWARD-1 and SORAYA) evaluating the efficacy and safety of mirvetuximab used the Ventana test to determine eligibility. Therefore, if an alternative assay were adopted for identifying FR α expression within the NHS, there would be a risk that the population deemed eligible for mirvetuximab treatment could differ from the population studied in the clinical trials. This discrepancy could impact the generalisability and applicability of the trial outcomes to clinical practice. The way in which testing would be implemented in the NHS could also affect outcomes. For example, the EAG received advice from two clinical experts that FR α testing could move to diagnosis, which would increase the number of people who would be tested and thus would increase the ICER for mirvetuximab (although testing at diagnosis may lead to benefits elsewhere in the treatment pathway if knowledge of FR α expression could be useful for informing treatment use at other lines; see Section 2.1.2).
- **The median age of participants in the clinical trials** of mirvetuximab was likely to be younger than the target population in NHS practice. As younger age at diagnosis was associated with improved prognosis for PROC, this affected the generalisability of the evidence to the target population (see Section 3.2.2.2). In addition, the model used a younger starting age than was observed in the clinical trial evidence (MIRASOL). This impacted the calculation of the severity modifier (a starting age of 65 years or above implied a lower severity modifier, a UK observational study implies a mean age of 68¹).
- **Duration of treatment:** the EAG used the Kaplan-Meier (KM) curve for duration of treatment (DoT) up to week 120, followed by exponential extrapolation. This avoided early underestimation of DoT and accounted for the fact that some participants (3/227) were still receiving mirvetuximab at the end of the trial (Section 4.2.5.4).
- **Subsequent therapy:** the EAG considered the company's inclusion of mirvetuximab as a subsequent treatment to be inappropriate. A crossover-adjusted scenario using rank preserving structural failure time model (RPSFTM) and exclusion of mirvetuximab post-progression was included in the EAG base case (Section 4.2.8).

- **The distribution of chemotherapy agents** in the MIRASOL arm did not align with NHS practice or the NICE scope for this appraisal (Section 4.2.4). The EAG excluded topotecan from the EAG base case by adjusting the costs of treatment. Appraisal of clinical efficacy and safety data for the different chemotherapies did not identify meaningful differences in effectiveness or safety outcomes, and therefore these outcomes were not adjusted. This was consistent with the view of the EAG's clinical expert, who confirmed that they would expect similar outcomes across regimens.
- **Wastage:** the EAG base case used cycle-specific relative dose intensity, instead of a single average value, and no vial sharing for mirvetuximab (Section 4.2.8.1). This accounted more accurately for missed doses, dose reduction and time dependency. No vial sharing was assumed for mirvetuximab in line with previous technology assessments in ovarian cancer and because the EAG clinical experts were less certain if a vial sharing assumption would apply. For chemotherapy, the clinical experts agreed that chemotherapy agents were commonly used in a number of indications and so it was reasonable to assume vial sharing.
- **Subgroup analysis:** a scenario analysis was conducted based on the length of the primary platinum free interval as clinical experts suggested that this was a prognostic factor. The EAG considered subgroup data from the trial to be inconclusive. Despite this a scenario analysis incorporating length of the primary platinum free interval as a prognostic resulted in a notable change to the ICER (see section 4.2.10).

Company's modelling errors identified by the EAG

Some minor errors identified by the EAG, such as the inclusion of patient characteristics in the probabilistic sensitivity analysis (PSA) and application of cycle correction to drug costs, were addressed by the company during the appraisal and incorporated into the company base case. As the company promptly resolved these issues during the clarification process, no further corrections were required.

1.5. Summary of EAG's preferred assumptions and resulting ICER

Table 3: Summary of EAG's preferred assumptions and ICER

Scenario	Incremental cost	Incremental QALYs	ICER	Change from company base case
Company's deterministic base case after clarifications (x1.7 severity weight)				
Cycle-specific Relative Dose Intensity				
Removal of mirvetuximab from post-progression				
No vial sharing for mirvetuximab and 50% vial sharing for chemotherapy				
Removal of topotecan from pooled chemotherapy				
Mirvetuximab OS curve: gamma distribution				
Mirvetuximab DoT: KM followed by exponential extrapolation at 120 weeks				
Chemotherapy OS: gamma				
Age from MIRASOL				
Utilities from MIRASOL trial				
(x1.2 severity weight)				
Include disutilities from AEs				
Increase duration of ocular AEs and increased frequency of ophthalmologist visits				
Adjust AEs costs				
Adjust health states cost				
Adjust OS for crossover				
EAG's preferred base case deterministic				
(x1.2 severity weight)				

Abbreviations: AE, adverse event; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality adjusted life year; DoT, Duration of Treatment. Note: Weighted severity modifier of 1.7 (unless otherwise specified)

2. BACKGROUND

This report critiques the company submission (CS) for mirvetuximab soravtansine (hereafter referred to as mirvetuximab) for the treatment of adult patients with folate receptor-alpha (FR α) positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens.

2.1. Critique of the company's description of the underlying health problem

2.1.1. Platinum-resistant ovarian cancer, fallopian tube and primary peritoneal cancer

The company described Platinum-Resistant Ovarian Cancer (PROC) in CS Section B.1.3 of the CS. They described platinum-resistant high grade serous (HGS) ovarian, fallopian tube, or primary peritoneal cancer collectively as PROC throughout the submission. The EAG considered the company's description to be predominantly accurate.

The company described ovarian cancer which includes fallopian tube and peritoneal cancer, the indications are typically grouped together due to their similar tissue origins and treatment strategies^{3,4}. Some of the company evidence was specific to ovarian cancer only, though overall the EAG considered that this could be reasonably generalised across the target population.

The company identified prevalence estimates based on clinician input and the national annual incidence of ovarian cancer and suggested that around 2,144 women in England develop epithelial HGS PROC each year. Consistent with this, the EAG found that, in 2022, 2,918 women were diagnosed with stage 3 or 4 epithelial ovarian cancer⁵ in England.

The company described PROC as having a markedly poor prognosis, worse than platinum-sensitive disease. Development of platinum resistance was identified as one of the strongest prognostic factors in ovarian cancer and a major driver of mortality in HGS histology. People with PROC typically experienced substantially worse survival outcomes, and outcomes worsened with each recurrence and subsequent line of treatment. This was consistent with clinical advice received by the EAG. Additionally, age was recognised as a prognostic factor, with younger people generally having better prognosis. Clinical experts to the EAG concurred with the company that PROC primarily affected those aged 65 to 70 years and older. The EAG also agreed with risk factors for PROC reported by the company: the risk of OC has been

shown to increase with age, family history of OC, and inherited mutations in the BRCA1 or BRCA2 genes⁶.

2.1.2. Folate receptor alpha expression and testing

The licence for mirvetuximab⁷ was for the treatment of people with platinum-resistant HGS ovarian, fallopian tube, or primary peritoneal cancer who express high levels of FR α . FR α is a protein that plays a significant role in DNA synthesis, cell proliferation, DNA repair, and intracellular signalling, all of which are essential for tumourigenesis⁸. FR α was thought to be overexpressed in 90% of ovarian tumour cells, including peritoneal and epithelial, compared to non-malignant ovarian cells⁸⁻¹⁰. Clinical experts to the EAG explained that FR α -positive cancer cells tend to be more resistant to standard chemotherapy. These cells are more likely to survive initial treatment and may contribute to chemotherapy-resistant disease in later stages. This supported the company's rationale for targeting FR α in treatment. Mirvetuximab relies on binding to the FR α receptor to be effective, selecting people whose tumours express high levels of FR α therefore increases the likelihood of treatment success.

For the purposes of the licence⁷ for mirvetuximab, FR α positivity was defined as $\geq 75\%$ of tumour cells with moderate and/or strong membrane staining (PS2+). At the time of the appraisal, testing for FR α was not standard practice in the NHS. While several tests for FR α were available, in response to clarification (A12) the company stated that Roche's VENTANA[®] FOLR1 (FOLR-2.1) companion diagnostic (CDx) assay was the only test licensed for use in the NHS. This was the test used in the clinical trials of mirvetuximab and the company stated that it had demonstrated high repeatability and consistency between readers¹¹. At clarification (A12), the EAG requested that the company submit diagnostic accuracy data for the Ventana test, however the company stated that as there was no reference standard for assessing FR α , it was not possible to produce such data. The EAG therefore considered that the extent to which the test accurately classifies FR α was uncertain. The interchangeability of different tests was unclear, and the eligible population for mirvetuximab could vary depending on the assay used. This could impact the generalisability and applicability of the trial outcomes to clinical practice. However, at clarification, the company confirmed that VENTANA FOLR1 assay is the only regulatory approved test, and the only test to be utilised in the UK, therefore the EAG consider this to be in line with, and generalisable to, UK practice at the time of decision-making. The EAG further noted that if an alternative assay were adopted for identifying FR α expression within the

NHS, there would be a risk that the population deemed eligible for mirvetuximab could differ from the population studied in the clinical trials.

In addition to this, the way in which testing would be implemented in the NHS, such as the timing of testing, was also considered to plausibly affect treatment outcomes. Clinical trials evaluating mirvetuximab included participants with tumours tested from both archived and recent biopsies. The optimal timing for FR α testing was not yet known; i.e. whether new samples would be needed or samples taken historically during diagnosis could be tested. The EAG received advice from two clinical experts that FR α testing could move to diagnosis, which would increase the number of people who would be tested and thus would increase the ICER for mirvetuximab (Section 4.2.8.4). The EAG was aware that research about FR α expression in PROC was ongoing and it was therefore plausible that testing at diagnosis may lead to benefits elsewhere in the treatment pathway if knowledge of FR α expression could be used to inform treatment decisions at other treatment lines.

The Ventana FOLR1 assay was an immunohistochemical assay developed to detect FR α in cut slide specimens of formalin-fixed, paraffin-embedded (FFPE) epithelial ovarian cancer tissue stained on the BenchMark ULTRA automated staining instrument using the Ventana OptiView DAB IHC Detection Kit. As noted above, in both the MIRASOL and FORWARD-1 trials, testing for FR α expression used both archival tumour tissue and new biopsy tissue for enrolment into the study, though the proportion of each method was not reported by the company. In UK practice it was expected that the vast majority of FR α testing would be undertaken on archival samples taken during the patient's initial surgery. It was unclear to the EAG whether FR α expression changes throughout the treatment pathway, therefore this has an unquantifiable impact on the generalisability of these results.

Clinical experts to the EAG stated that understanding of the prevalence of FR α in people with PROC was not yet known. One expert reported a lower positivity rate (10–20%) in their local population compared to the approximately 40% positivity rate reported for high-grade serous ovarian cancer patients in a previous clinical trial they were involved with. However, another expert was unsure whether FR α expression varied across geographic regions. One real-world study found that 89.3% of tumours had some degree of FR α expression, and a third (36.3 %) exhibited high FR α expression levels when using the same array and scoring system as the MIRASOL trial¹². This aligned with the company-supplied data from the MIRASOL trial, demonstrating consistent FR α positivity rates across different geographic regions. At

clarification (A10), the EAG asked the company whether they had evidence about prevalence rates of FR α expression levels across geographic areas. The company stated that the proportion of individuals with high FR α expression was [REDACTED]. The FR α status across Europe table included some non-European countries, however [REDACTED]. [REDACTED] The reported FR α expression levels were [REDACTED] than those observed in the MIRASOL trial [REDACTED] though the difference was not statistically significant. Overall, the EAG considered that there was some uncertainty over the prevalence of high FR α expression given that research is still ongoing, however there was no evidence that the prevalence estimated by the company would differ from the target population in clinical practice.

The EAG's clinical experts also stated that the association between FR α expression and cancer progression was unknown. Although cancer cells can evolve, there was no clear evidence that this affected FR α expression in PROC. One expert noted that there were no data indicating that FR α status directly impacts tumour behaviour, viewing it primarily as a surface marker. However, she also explained that there was a rationale to expect increased FR α expression further along treatment lines. Since FR α -positive cells tend to be relatively resistant to chemotherapy, treatment preferentially kills off the more sensitive FR α -negative cells, resulting in a higher proportion of FR α -positive cells over time. This would suggest that levels of FR α may vary across the disease course. This contributes to uncertainty about the way that testing for FR α is implemented in clinical practice and its impact on the generalisability of the trial evidence.

Overall, while the evidence base was considered relevant for decision-making, the EAG identified uncertainties regarding the prevalence of high FR α expression, the accuracy of the companion diagnostic assay, and potential impact of using alternative assays in NHS practice. Further research about FR α and optimum testing approaches could affect both the generalisability of trial results and, potentially, the cost-effectiveness of mirvetuximab in real-world settings. This issue was identified as a Secondary Key Issue by the EAG (Section 1.4).

2.2. Critique of the company's overview of current service provision

The company's overview of the current care pathway for the target population was described in the CS, Section 1.3.

The comparator to mirvetuximab in the NICE scope was chemotherapy, either paclitaxel or pegylated liposomal doxorubicin (PLD). The evidence base for mirvetuximab used a slightly broader comparator arm, comprised of investigator's choice of paclitaxel, PLD and topotecan. The CS stated that market research data collected by AbbVie between August–October 2024 about people with PROC showed that, at second-line, 14% of people with PROC received paclitaxel, 45% received PLD, and 9% received topotecan; and at third-line, 25% of people with PROC receive paclitaxel, 36% receive PLD, and 4% receive topotecan¹³. The reported percentages did not sum to 100%, indicating that patients used other treatments as well though these were not described. In general, clinical experts to the EAG advised that, in the NHS, the target population would receive paclitaxel (approximately 60%) or PLD (approximately 40%). While topotecan was still used by some clinicians, its use had become less common due to concerns about toxicity and patient preferences for different treatment regimens. The EAG also noted that topotecan was not recommended within the TA389 appraisal¹⁴, raising questions about its inclusion in the IC chemo arm. Therefore, the trial evidence provided by the company only partially aligned with expectations for the use of chemotherapy in clinical practice (Section 3.2.4). However, the EAG appraisal did not identify major differences in efficacy and safety of topotecan in the company's pivotal trial of mirvetuximab.

As mirvetuximab was only licenced for use in people with high expression of FR α , it would only be used to treat a subgroup of people who would be treated with chemotherapy at this treatment line. The EAG was not aware of any reason why people with high expression of FR α would be more likely to receive one chemotherapy over another in clinical practice.

2.3. Critique of company's definition of decision problem

Overall, the EAG considered that the CS was consistent with the NICE scope for the appraisal. As discussed in Section 2.2, comparative trial evidence compared outcomes for mirvetuximab to a pooled chemotherapy arm that included topotecan, which was rarely used in the target population in the NHS. However, as discussed in Section 3.3, the EAG did not identify differences in the efficacy and safety of topotecan in the trials that were considered to undermine the generalisability of the evidence to clinical practice. The company's decision problem, along with the EAG's critique is shown in Table 4.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with FR α -positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer	Adult patients with FR α positive, platinum-resistant high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens	As mentioned in the response to the draft scope and decision problem form, the target population addressed in this submission is in line with the anticipated licensed indication.	The description of the target population was appropriately aligned with the anticipated licensed indication and the MIRASOL trial.
Intervention	Mirvetuximab soravtansine	Mirvetuximab soravtansine	N/A	The clinical trial evidence was consistent with the licence.
Comparator(s)	• Paclitaxel monotherapy • Pegylated liposomal doxorubicin hydrochloride monotherapy	Pooled chemotherapy, including • Paclitaxel monotherapy • Pegylated liposomal doxorubicin hydrochloride monotherapy	The comparators are in line with the NICE scope and best represented by the pooled chemotherapy arm of the MIRASOL trial which included clinician's choice between paclitaxel, PLD, and topotecan, modelled as a single 'pooled chemotherapy' arm in line with the MIRASOL trial. These chemotherapies are the recommended therapies in PROC as per the BGCS guidelines ¹⁵ and are reflected in UK market research data ¹³ .	The comparator population evaluated by the company was broader than that in the NICE scope. In the MIRASOL trial, the chemotherapy arm included clinician's choice of paclitaxel, PLD, or topotecan. Topotecan was not commonly used in routine NHS practice and was not recommended by NICE. Clinical experts to the EAG expected a different safety profile for topotecan but similar clinical effectiveness.

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]:A Single Technology Appraisal

Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	N/A	The outcomes reported were consistent with the NICE scope.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention,	In line with scope		The analysis used utilities for the chemotherapy arm that included non-reference case sources. The economic model included the cost of diagnostic testing and the cost associated with number of patients tested to identify one potential patient with FR-alpha positive mutation. However, no scenario analysis excluded the cost of diagnostic testing. Otherwise, the analysis was in line with the NICE reference case and final scope.

comparator and subsequent treatment technologies will be taken into account.

The availability and cost of biosimilar and generic products should be taken into account.

The use of mirvetuximab soravtansine is conditional on having folate receptor alpha-positive ovarian cancer. In the pivotal trial for mirvetuximab soravtansine, a tumour sample was considered FR α positive if at least 75% of viable tumour cells showed moderate and/or strong levels of membrane staining.

The economic modelling should include the costs associated with testing for folate receptor alpha expression in people with ovarian cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]:A Single Technology Appraisal

	cost of the diagnostic test			
Subgroups	• Number of previous lines of therapy • PARP inhibitor treatment • Previous bevacizumab • BRCA status	N/A	Subgroup analysis was conducted for the clinical data (presented for the suggested subgroups). These analyses were exploratory only and therefore are not included in the economic model.	Subgroup analyses for BRCA and prior bevacizumab use were submitted in response to clarification (B1 and B17). Other subgroups were presented in the CS.
Special considerations including issues related to equity or equality		As a result of gender inequalities, magnified challenges for rare cancers and geographic and socioeconomic variation in treatment access, patients with OC (including PROC) are subject to health inequality concerns ¹⁶⁻²² . The benefits of mirvetuximab may contribute to reducing inequalities through earlier diagnosis of eligible patients, increasing treatment options and choice in an underserved, rare, disease area which affects women.	OC is a cancer affecting the female reproductive system. In the UK, there is a clear gender health gap in which women experience an additional 3 years of ill health and disability compared with men ²⁰, underscoring the urgent need to improve women's health outcomes ²⁰. OC is the most lethal gynaecological cancer in the UK ²³ and patients with PROC experience the poorest outcomes ⁶. OC is rare and severe, posing unique challenges such as delayed screening, late/incorrect diagnosis, lack of treatment options, feelings of isolation, and reduced QoL. Therefore, health inequalities remain a	It is not clear to the EAG how introducing a new drug treatment (i.e., mirvetuximab) alone reduces inequalities through earlier diagnosis of eligible patients. The company did not present evidence or rationale to demonstrate that mirvetuximab would lead to earlier detection of eligible patients. Mirvetuximab was considered to be innovative specifically for those with Fra high expression. However, it was not applicable to other patients with PROC.

major barrier to care for patients living with rare cancers.

Not all patients in England have equal access to ovarian cancer treatments. Research has shown that there are geographic and socioeconomic variations in terms of treatment access, hence leading to variations in health outcomes.

Gender inequalities, challenges of rare cancer and disparities in treatment access create inequalities for patients with PROC.

Mirvetuximab aims to contribute to addressing these challenges in patients with FR α positive PROC through its innovative, targeted medicine approach, offering significant survival benefits, a manageable safety profile, and preservation of QoL compared with chemotherapy.

Abbreviations BGCS, British Gynaecological Cancer Society; BRCA, BRCA1/2 gene; EAG, External Assessment Group; FR α , folate receptor-alpha; NICE, National Institute for Health and Care Excellence; OC, ovarian cancer; PARP, Poly (ADP-ribose) polymerase; PLD, Pegylated liposomal doxorubicin; PROC, Platinum Resistant Ovarian Cancer; QoL, quality of life.

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to assess the clinical effectiveness (efficacy and safety) of all currently available therapies used to treat people with previously treated, platinum-resistant/refractory epithelial ovarian, primary peritoneal, or fallopian tube cancers. An appraisal of the methods used by the company is presented in Table 5.

Table 5: Summary of the EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix B. 1.1	The searches were well conducted and clearly presented with a good range of sources used. The company chose to use the Scottish Intercollegiate Guidelines Network (SIGN)²⁴ clinical studies filter but to change some of the terms in the filter to make it broader (to include conference abstracts), instead of using the Cochrane RCT filter²⁵ which is the gold standard and does not exclude conference abstracts. However, this was unlikely to have materially affected the search results. The company did not include subject heading searches for drug resistance, fallopian tube cancer or peritoneal cancer in their searches (although keyword searches for this were used); it is possible that this could have resulted in missing some relevant records, although the EAG did not test this.
Inclusion criteria	Appendix B.1.2.1	The inclusion/exclusion criteria were generally appropriate but excluded real-world evidence and single-arm clinical trials which may have been relevant to this appraisal. The post-hoc criteria were used to de-prioritise studies that, although relevant in an international context, were not conducted in the UK and therefore did not meet the geographic requirements of the NICE submission. This approach was considered to be appropriate to the NICE appraisal.
Study selection	Appendix B.1.2.2	Study selection was conducted to an appropriate standard. Both title/abstract and full-text screenings were conducted independently by two reviewers based on predefined eligibility criteria. Discrepancies were resolved through discussion, with a third reviewer available for arbitration when necessary.
Data extraction	Appendix B 1.2.3	Data extraction was conducted to an appropriate standard. It was performed by one reviewer and validated by a second independent reviewer to verify data accuracy. Details of how discrepancies were resolved were not clear.
Quality assessment	Appendix B 1.2.4	The company used the Cochrane Risk of Bias 2 tool to assess MIRASOL and FORWARD-1. No quality assessment was performed for SORAYA, as it was a single-arm study not included in the clinical effectiveness SLR. The assessment was stated to be conducted by one reviewer and quality

Evidence synthesis	Section 3.3.11	checked by a second independent reviewer. The EAG considered the choice of tool to be appropriate, however, only study-level ratings were reported, without consideration of outcome-level bias. This could, for example, overlook limitations in outcomes with high attrition or subjective outcomes affected by the lack of blinding. The EAG focused its appraisal of the overall study rating calculated by the tool algorithm, as opposed to the rating of the researcher, which deviated from the tool methods. The company did not report a pooled analysis in the CS. At clarification, the company presented a pairwise meta-analysis including the MIRASOL trial and the relevant, re-scored high-FRα population from FORWARD-1. The EAG considered the meta-analysis to be generally appropriate, however it was not well described in terms of the methodology used, which would have allowed a more thorough appraisal by the EAG. It was also not clear to the EAG why the results from this analysis were not considered for use in the model. However, given the similarity to the results from the MIRASOL trial, this was not expected to make a difference to the economic analysis.

Abbreviations: CS, Company submission; EAG, External Assessment Group; FR α , folate receptor alpha; RCT, randomised controlled trial

3.2. Critique of the methods of the trials of the technology of interest

An overview of the clinical evidence for mirvetuximab is provided in Table 6.

The CS largely focussed on evidence from the company's pivotal trial (MIRASOL) of mirvetuximab vs. chemotherapy. Two other trials evaluating mirvetuximab, FORWARD-1 and SORAYA, were noted in the CS but full details were not presented. At clarification (A1), the EAG asked the company to confirm its rationale for excluding these studies and to present evidence for these trials for appraisal by the EAG. The company stated that FORWARD-1 was not presented in the CS due to the original trial population being based on a broader range of FR α expression than is now required by the licence for mirvetuximab. Data relevant to the licence from this study were based on a post-hoc subgroup analysis in which they had re-scored the data to include only those participants who met the licensed threshold requirement of FR α (now referred to as the 're-scored' population'). Despite the limitations of using a post-hoc analysis, the EAG considered that evidence for the re-scored population from FORWARD-1 was relevant to the decision problem and should have been presented in the CS. In response to a request at clarification, the company submitted data for the re-scored high-FR α subgroup from FORWARD-1, although not all outcomes were available for this subgroup. Where necessary, the EAG referred to an original subgroup analysis in the trial that included people with high FR α expression using a different threshold.

The company stated that SORAYA was not presented in the CS on account of it being a Phase 2, single arm trial where all participants were required to have previously received bevacizumab. The EAG noted that Phase 2, single-arm trials are not automatically excluded from relevance in NICE submissions and that this rationale was therefore not sufficient to exclude the evidence, even if it may be of lower evidential quality than evidence from RCTs. The EAG also received advice from clinical experts that indicated that in UK practice, the majority of ovarian cancer patients with PROC would receive prior treatment with bevacizumab, and therefore this trial would be representative of many people in the target population. The EAG therefore considered that evidence from SORAYA should also have been presented in the CS.

As evidence for FORWARD-1 and SORAYA were submitted at clarification, due to time constraints, the restricted population and evidence quality of SORAYA, the EAG chose to focus its report on evidence from the two RCTs (MIRASOL and FORWARD-1) as they were considered to be most probative for decision making. However, as part of its appraisal, it did compare results between the RCT evidence and evidence from SORAYA and this report includes discussion of the comparability of evidence between trials, where indicated.

Table 6: Clinical effectiveness studies of technology of interest

	MIRASOL²⁶	FORWARD-1²⁷	SORAYA²⁸
Role in this evaluation	Clinical effectiveness, safety, used in the company's economic analysis.	Clinical effectiveness and safety. Relevant evidence is in the re-scored FRα expression subgroup.	Clinical effectiveness and safety evidence – appraised by the EAG but not extensively reported in the EAG report. Comparability with MIRASOL and FORWARD-1 highlighted by the EAG, where pertinent.
Study type	Phase 3, randomised, open-label	Phase 3, randomised, open-label	Phase 2, single-arm, open-label
Patient group	Adults aged ≥18 years with platinum-resistant HGS ovarian, primary peritoneal, or fallopian tube cancers, high FRα expression, and 1–3 prior lines of systemic therapy.	Adults aged ≥18 years with histologically confirmed epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer that was platinum-resistant, with 1–3 prior lines of therapy.	Adults aged ≥18 years with a confirmed diagnosis of high-grade serous ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. had received 1–3 prior therapies including bevacizumab.
FRα expression determination	Patients had to have met the minimum requirement of FRα positivity on archival tumour samples by immunohistochemistry (IHC; ≥ 75% of tumour staining at ≥ PS2+ intensity). Patients with less than 25% expression were not eligible.	Confirmation of threshold FRα positivity by IHC (Re-scored population: ≥ 75% of cells to stain at intensity ≥ PS2+ intensity, High expression subgroup: ≥ 75% of tumour cells with any FRα membrane staining visible at ≤ 10X microscope objective).	High FRα tumour expression was assessed by the Ventana FOLR1 assay, defined as ≥75% of viable tumour cells exhibiting ≥PS2+ membrane staining intensity by immunohistochemistry.
Subgroups	BRCA status; age; Baseline ECOG; number of prior lines of therapy; prior exposure to BEV; prior exposure to PARP inhibitor; primary platinum-free interval; most recent platinum-free interval; country; cancer stage at diagnosis; weight at baseline	No subgroup analyses were performed in the re-scored FRα population. Subgroup analyses were available in the original FRα-high population: age; BRCA status; ECOG, prior exposure to BEV; number of prior lines of therapy; type of chemotherapy; platinum-free interval; location of metastasis; race; and time since initial diagnosis.	Number of prior lines of therapy; prior exposure to PARP inhibitor; and ADA status.

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Key exclusion criteria	Patients with primary platinum-refractory disease defined as disease that did not respond to complete response or partial response or had progressed within 3 months of the last dose of first-line platinum containing chemotherapy Patients with > Grade 1 peripheral neuropathy Patients with active or chronic corneal disorders or active ocular conditions requiring ongoing treatment/monitoring Patients with clinically significant cardiac disease, history of haemorrhagic or ischemic stroke within 6 months prior, history of cirrhotic liver disease (Child-Pugh Class B or C) or non-infectious interstitial lung disease (ILD), including non-infectious pneumonitis, or history of other malignancy within 3 years prior.	Patients with primary platinum-refractory disease as defined by those who progressed during or within 4 weeks of completion of first platinum-based chemotherapy Patients with uncontrolled bleeding disorders or inadequate coagulation parameters Patients with > Grade 1 peripheral neuropathy. Active or chronic corneal disorders, including conditions requiring ongoing treatment/monitoring History of haemorrhagic or ischemic stroke within the last 6 months, history of cirrhotic liver disease, previous clinical diagnosis of non-infectious interstitial lung disease, including non-infectious pneumonitis, or history of other malignancy within 3 years prior.	Patients with primary platinum-refractory disease, defined as disease that did not respond to complete response or partial response or had progressed within 3 months of the last dose of first-line platinum containing chemotherapy Patients with > Grade 1 peripheral neuropathy Patients with active or chronic corneal disorders or active ocular conditions requiring ongoing treatment/monitoring Patients with clinically significant cardiac disease, history of haemorrhagic or ischemic stroke within 6 months prior, history of cirrhotic liver disease (Child-Pugh Class B or C) or non-infectious interstitial lung disease (ILD), including non-infectious pneumonitis, or history of other malignancy within 3 years prior.
Intervention	Mirvetuximab 6 mg/kg AIBW Q3W	Mirvetuximab 6 mg/kg AIBW Q3W	Mirvetuximab 6 mg/kg AIBW Q3W
Comparator	Investigator choice of chemotherapy, determined prior to randomisation: •Paclitaxel (80 mg/m²) administered on Days 1, 8, 15, and 22 of a 4-week cycle •PLD (40 mg/m²) administered on Day 1 of a 4-week cycle •Topotecan either 4 mg/m² administered on Days 1, 8, and 15 of a 4 week cycle, or 1.25 mg/m²	Investigator choice of chemotherapy, determined prior to randomisation: • Paclitaxel administered at 80 mg/m² as a 1-hour IV infusion on Days 1, 8, 15, and 22 of a 4-week cycle • PLD administered at 40 mg/m² on Day 1 of a 4-week cycle. • Topotecan administered at 4 mg/m² over 30 minutes on Days 1, 8, and 15 of a	No comparator

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	administered on Days 1 to 5 of a 3-week cycle	4-week cycle or at 1.25 mg/m ² over 30 minutes on Days 1 to 5 of a 3-week cycle	
Median follow-up	28.35 months (Sept 2024 cut off)	12.45 months	13.4 months
Location	Multicentre, international study across 201 locations, including: the US, Canada, and the UK.	Multicentre, international study across 131 locations, including: the US, Canada, and the UK.	Multicentre, international study across 89 locations, including: US, Australia, and Spain.

Abbreviations: ADA Status, anti-drug antibodies; AIBW, adjusted ideal body weight; BEV, Bevacizumab; BRCA, BReast CAncer gene; EAG, External Assessment Group; ECOG, Electrocardiography and Eastern Cooperative Oncology Group performance status; FR α , Folate receptor alpha; HGS, High Grade Serous; IHC, immunohistochemistry; PARP inhibitor, poly (ADP-ribose) polymerase inhibitor; Q3W, every 3 weeks.

3.2.1. Study design

3.2.1.1. MIRASOL

MIRASOL²⁶ was an open-label multi-centre Phase 3 randomised trial. There were two arms: mirvetuximab vs. investigator's choice (IC) of PAC, PLD or topotecan chemotherapy. Hereafter this 'pooled' IC chemotherapy arm will be referred to collectively as 'chemotherapy'. Participants were randomised 1:1, stratified by prior therapy lines (1, 2, or 3) and chosen chemotherapy type. The company stated that analysis data cuts were available at 6th March 2023 and 26th September 2024. The EAG appraisal focussed on the final data cut-off, with reference to the interim data cut, where pertinent.

The EAG noted that the trial was sufficiently powered to the PFS outcome. The final analysis was conducted when at least [REDACTED] had been observed. The study had 90% power to detect a hazard ratio of 0.7 at a two-sided α level of 0.05. [REDACTED]

[REDACTED] The EAG considered that these methods were appropriate, as it maintained the integrity of the trial's statistical design while minimising participants' exposure to potentially ineffective treatment.

3.2.1.2. FORWARD-1

Like MIRASOL, FORWARD-1²⁷ was an open-label, Phase 3 randomised trial comparing mirvetuximab with IC of PAC, PLD, or topotecan. The doses of treatments were consistent with MIRASOL (Table 9). Participants were randomised 2:1, stratified by prior therapy lines (1, 2, or 3), chosen chemotherapy, and FR α expression level (high: $\geq 75\%$ tumour cells; medium: 50– $<75\%$ tumour cells).

As the threshold of high FR α expression used in the trial was not aligned with the licence for mirvetuximab, for this appraisal, participants in the FR α -high expression subgroup (MIRV = 147, chemotherapy = 71) were re-scored using digital tumour images prior to randomisation, to align with the licence (membrane staining intensity level PS2+ in $\geq 75\%$ viable tumour cells). The re-score was performed using digital tumour images created within FORWARD-1 prior to randomisation, based on the PS2+ rating $\geq 75\%$ method by an independent pathologist blinded to the treatment assignment. The EAG agreed with this approach. This resulted in 116 relevant participants (MIRV = 82; chemotherapy = 34). The EAG appraisal focussed on this re-scored

FR α -high expression subgroup, as this aligned with the licence for mirvetuximab, though drew upon evidence for the original high expression subgroup where data were not available.

The study had 85% to 91% power to detect a hazard ratio of 0.583 in the original FR α -high expression subgroup at a study-wise alpha level of 5%; [REDACTED]

[REDACTED] However, this was a different subgroup to the re-scored subgroup used in the meta-analysis. Given the change in group definition and size, it is unclear whether the trial was adequately powered to address the decision problem.

3.2.1.3. SORAYA

SORAYA was an open-label, Phase 2, single-arm study designed to evaluate the efficacy and safety of mirvetuximab in people who had previously received bevacizumab. Participants had to have high FR α expression, as defined using the threshold specific in the MHRA licence for mirvetuximab. The primary efficacy endpoint was ORR as assessed by investigator. Key secondary endpoints included PFS, defined as the time from first dose of mirvetuximab until investigator assessed radiological PD or death, and OS. Censoring rules for SORAYA aligned with the MIRASOL trial for PFS_{INV} and OS (Table 13). A comparison with FORWARD-1 was not possible as the company did not provide the statistical analysis plan.

3.2.2. Population

In this section, the EAG presents its appraisal of the eligibility criteria and baseline characteristics in the trials of mirvetuximab presented by the company.

3.2.2.1. Trial eligibility criteria

The eligibility criteria for the MIRASOL and FORWARD-1 trials are summarised in Table 7. The EAG considered the criteria for the two trials to be comparable, except for the criteria for high FR α expression (which was no longer a consideration when outcomes were evaluated in the re-scored population). Results in the 'high FR α ' subgroup from the original trial protocol (presented when re-scored data were not available), were not directly applicable to the licence as they used membrane staining visible at $\leq 10\times$ microscope objective rather than cells to stain at intensity $\geq$ PS2+ intensity, which meant that some participants classified as 'high FR α ' may have only weak, low-intensity expression and may not derive the same clinical benefit observed in the licensed population.

As part of the MIRASOL trial, participants with an ECOG performance status of two, corneal disorders and pneumonitis/lung disorders were excluded, even though such participants would not be precluded from receiving mirvetuximab in clinical practice. Clinical advice provided to the EAG highlighted that excluding people with an ECOG performance status of two may pose a generalisability issue, as a considerable proportion of the PROC population exhibit this level of functional status. Similarly, as corneal and lung disorders were identified as being a safety risk of mirvetuximab, the exclusion of people with pre-existing vulnerability to these effects could underestimate the adverse event risks of mirvetuximab.

However, in general the trial populations were similar across other characteristics, and therefore the EAG did not consider the issue to have a meaningful impact on outcomes.

The EAG also considered MIRASOL and SORAYA to be comparable, other than for the criteria for all participants to have had prior use of bevacizumab in SORAYA. Bevacizumab was used by most of the population in clinical practice, and therefore the evidence base may have been relevant to the majority of the target population.

Table 7: Key eligibility criteria MIRASOL and FORWARD-1

MIRASOL²⁶

Female patients ≥ 18 years of age

Confirmed diagnosis of high-grade serous EOC, primary peritoneal cancer, or fallopian tube cancer

Patients must have had platinum-resistant disease:

Patients who only had 1 line of platinum-based therapy must have received at least 4 cycles of platinum, must have had a response (complete response or partial response) and then progressed between > 3 months and ≤ 6 months after the date of the last dose of platinum

Patients who had received 2 or 3 lines of platinum therapy must have progressed on or within 6 months after the date of the last dose of platinum Note: Progression was calculated from the date of the last administered dose of platinum therapy to the date of the radiographic imaging showing progression

Note: Patients who were platinum refractory during frontline treatment were excluded

Patient's tumour must have been positive for FRα expression as defined by the Ventana FOLR1 assay (membrane staining intensity level PS2+ in ≥ 75% viable tumour cells)

Testing for FRα expression is required for all patients using the Ventana FOLR1 assay in archival or fresh biopsy tumour sample.

Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy, and for whom single-agent therapy was appropriate as the next line of treatment:

FORWARD-1²⁷

Female patients ≥18 years of age

Confirmed diagnosis of advanced EOC, primary peritoneal cancer, or fallopian tube cancer

Patients must have had platinum-resistant ovarian cancer, defined as progression within 6 months from completion of a minimum of 4 cycles of platinum-containing therapy.

The required minimum FRα expression level allowed was ≥ 50% of tumour cells with any FRα membrane staining visible at 10X microscope magnification. A stratification cutoff of ≥ 75% of tumour cells with any FRα membrane staining visible at 10X magnification was also implemented to evaluate antitumour activity of MIRV based on higher levels of FRα expression, as defined by the VENTANA® FOLR1 assay. The rescored population was defined as ≥ 75% of cells to stain at intensity ≥ PS2+ intensity.

Testing for FRα expression is required for all patients using the Ventana FOLR1 assay in archival or fresh biopsy tumour sample.

Patients must have received at least 1 but no more than 3 prior systemic lines of anticancer therapy and for whom single-agent chemotherapy is appropriate as the next line of treatment.

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Adjuvant ± neoadjuvant was considered 1 line of therapy

Maintenance therapy (e.g., bevacizumab, PARP inhibitors) was considered as part of the preceding line of therapy (i.e., not counted independently)

Therapy changed due to toxicity in the absence of progression was considered as part of the same line (i.e., not counted independently)

Hormonal therapy was counted as a separate line of therapy unless it was given as maintenance

ECOG PS of 0 or 1

Time from prior therapy:

Systemic antineoplastic therapy (5 half-lives or 4 weeks, whichever is shorter)

Focal radiation completed at least 2 weeks prior to first dose of study drug

Patients must have had stabilised or recovered (Grade 1 or baseline) from all prior therapy-related toxicities

Adjuvant ± neoadjuvant was considered as 1 line of therapy.

Maintenance therapy (eg, bevacizumab or poly [ADP-ribose] polymerase [PARP] inhibitors) were considered as part of the preceding line of therapy (ie, not counted independently).

ECOG PS of 0 or 1

Time from prior therapy:

Systemic antineoplastic therapy (5 half-lives or 4 weeks, whichever is shorter)

Focal radiation completed at least 2 weeks prior to first dose of study drug

Patients must have had stabilised or recovered (Grade 1 or baseline) from all prior therapy-related toxicities

Abbreviations: ALT, alanine aminotransferase; AST, Aspartate aminotransferase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOC, epithelial ovarian cancer; IV, intravenously; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; PRBC, packed red blood cell; Topo, topotecan; ULN, upper limit of normal; WBC, white blood cell; WCBP, Women of childbearing potential. Shading indicates variation across trials.

3.2.2.2. Baseline characteristics

Baseline characteristics for the MIRASOL²⁶ and FORWARD-1²⁷ trials (FR α -high population, re-scored) are shown below in Table 8.

Clinical advice to the EAG was that the baseline characteristics in the MIRASOL and FORWARD-1 trials were generally relevant to a UK clinical practice context. However, clinical experts to the EAG advised that the age of trial participants appeared younger than the typical age of the target population in UK practice. A UK-based study¹ of the demographics of people with PROC using data from the National Cancer Registration and Analysis Service (NCRAS) reported that the median age of people at diagnosis was 68 (56 – 77), which would support the conclusion that participants in MIRASOL and FORWARD-1 (who were several years from initial OC diagnosis) were younger than the UK population. Younger, fitter populations are typically recruited into clinical trials, often due to eligibility criteria for overall health and comorbidities. In the context of this appraisal, younger people diagnosed with PROC may have improved prognosis, including longer expected survival, due to improved health and ability to receive more (intensive) therapies. The EAG therefore noted this as an uncertainty in the generalisability of evidence from the trials to clinical practice. Age was also a consideration for the company's economic analysis, which used a younger starting age than was observed in MIRASOL. This impacted on the calculation of the severity modifier (a higher starting age implied a lower severity modifier; see Section 5.3.1) and thus had a significant impact on the ICER. This was identified as a secondary issue by the EAG (Section 1.4) and is discussed further in Section 4.2.3.

One clinical expert noted that the percentage of BRCA positive participants may be higher than typically expected in UK clinical practice, although the second clinical expert considered this to be a reasonable representation. Reported prevalence of BRCA mutations in ovarian cancer varies across the literature, with estimates ranging from around 13–16% in large UK studies²⁹⁻³¹, although estimates across different cohorts range from 5.8% to 24.8%³². This may have affected the generalisability of the trial results to clinical practice, as people who are BRCA positive tend to be more chemotherapy sensitive. This is discussed later in Section 3.3.8.

In addition, one clinical expert noted that prior treatment with PARP inhibitors was likely to be underrepresented in the MIRASOL trial, although the EAG was uncertain by what extent. Some data suggested that most people eligible for second-line maintenance therapy would already have received a PARP inhibitor as part of first-line treatment³³. Underrepresentation of prior

PARP use may limit the generalisability of the trial findings to UK clinical practice as prior treatment with PARP inhibitors can reduce sensitivity to subsequent chemotherapy, and thus the trial results may overestimate the potential benefit of chemotherapy. Across all countries, increased use of PARP inhibitor monotherapy was observed over time, with a decrease in the use of anti-angiogenic monotherapy as first-line maintenance.

Trial arms were considered comparable in the MIRASOL trial, with balanced patient characteristics. While fewer baseline characteristics were reported for the re-scored population in FORWARD-1, those characteristics reported were comparable between arms.

Table 8: Key baseline characteristics MIRASOL trial – ITT population

Characteristic	MIRASOL ²⁶		FORWARD-1 ²⁷ (FR α - high population, re-scored)	
	Mirvetuximab (N=227)	Chemotherapy (N=226)	Mirvetuximab (N=82)	Chemotherapy (N=34)
Age, years				
Median (range)	64 (32–88)	62 (29–87)	65 (42, 84)	62 (31, 81)
Mean	63.3 (9.85)	62.3 (9.30)	63.13 (9.42)	60.35 (12.31)
≥65 years, n (%)	107 (47.1)	92 (40.7)	-	-
Primary cancer diagnosis, n (%)				
Epithelial ovarian cancer	182 (80.2)	182 (80.5)	68 (84)	31 (91)
Fallopian tube cancer	27 (11.9)	23 (10.2)	6 (7)	1 (3)
Primary peritoneal cancer	16 (7.0)	20 (8.8)	1 (1)	2 (6)
Other	2 (0.9)	1 (0.4)	-	-
Missing data	5 (2.2)	5 (2.2)	-	-
ECOG performance-status score, n (%) [§]				
ECOG PS 0	130 (57.3)	120 (53.1)	NR	NR
ECOG PS 1	97 (42.7)	101 (44.7)	NR	NR
ECOG PS 2	0	3 (1.3)	NR	NR
Missing data	0	2 (0.9)	NR	NR
BRCA mutation, n (%)				
BRCA1 positive	24 (10.6)	29 (12.8)	8 (10)	3 (9)
BRCA2 positive	9 (4.0)	7 (3.1)	3 (4)	0 (0)
Negative or unknown	198 (87.2)	190 (84.1)	-	-
Previous lines of systemic therapy				
1	29 (12.8)	34 (15.0)	53 (65)	20 (59)
2	90 (39.6)	88 (38.9)	-	-
3	108 (47.6)	104 (46.0)	29 (35)	14 (41)
Previous exposure, n (%)				

Characteristic	MIRASOL ²⁶		FORWARD-1 ²⁷ (FR α - high population, re-scored)	
	Mirvetuximab (N=227)	Chemotherapy (N=226)	Mirvetuximab (N=82)	Chemotherapy (N=34)
Bevacizumab	138 (60.8)	143 (63.3)	NR	NR
PARP inhibitor	124 (54.6)	128 (57)	NR	NR
Taxane	227 (100)	224 (99.1)	NR	NR
Doxorubicin or PLD	130 (57.3)	134 (59)	NR	NR
Topotecan	1 (0.4)	2 (0.9)	NR	NR
Primary platinum-free interval, n (%) ^{††}				
≤12 months	144 (64)	142 (62.8)	NR	NR
>12 months	81 (36)	84 (37.2)	NR	NR
Missing data	1 (0.4)	0	NR	NR
Platinum-free interval, n (%) ^{‡‡}				
≤3 months	88 (38.8)	99 (43.8)	NR	NR
>3 to ≤6 months	138 (60.8)	124 (54.9)	NR	NR
>6 months	1 (0.4)	3 (1.3)	NR	NR

Abbreviations: BRCA1, BReast CAncer gene 1; ECOG, Eastern Cooperative Oncology Group; IC Chemo, investigator's choice of chemotherapy; ITT, intention-to-treat; PARP, poly (adenosine diphosphate-ribose) polymerase; PS, performance score.

Source: Data on file, MIRASOL final CSR³⁴; Moore et al, 2023²⁶.

Notes: †Percentages may not total 100 because of rounding; §ECOG PS scores are assessed on a scale of 0 to 5, with higher scores indicating greater disability; ††Primary platinum-free interval was defined as the time from last dose of first-line platinum therapy to the date of disease progression or relapse after first-line therapy; ‡‡Platinum-free interval was defined as the time from last dose of the latest line of platinum therapy to the date of disease progression or relapse after that line of therapy.

3.2.3. Intervention

The intervention in MIRASOL²⁶ was mirvetuximab 6 mg/kg adjusted ideal body weight, which was intravenously administered every 3 weeks. Participants continued to receive the study drug until disease progression, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminated the study (whichever came first). This was assessed via CT/MRI scans, which were performed at screening and subsequently every 6 weeks ($\pm$ 1 week) from cycle 1 day 1 (for all regimens) for the first 36 weeks, and then every 12 weeks ($\pm$ 3 weeks).

Patterns of subsequent treatments in the company's trials of mirvetuximab are discussed in Section 3.3.7. Overall, these treatments were broadly similar between mirvetuximab and chemotherapy groups, with taxanes, anthracyclines, and gemcitabine being the most common. Similarly, anthracyclines, taxanes and other chemotherapies were the most common in FORWARD-1. Clinical advice to the EAG was that, following on from 2nd or 3rd line treatment, clinicians typically administered the chemotherapy agent not previously used (i.e., PLD as 3rd line following paclitaxel 2nd line). They emphasised a general reluctance to offer conventional chemotherapy after failure of two prior regimens. In practice, people who had undergone four or five lines of therapy were usually informed of the low likelihood of benefit, and most subsequently chose not to pursue further treatment.

The intervention in FORWARD-1²⁷ was also mirvetuximab 6 mg/kg adjusted ideal body weight, which was intravenously administered every 3 weeks. Tumour assessments, including radiologic assessments by CT or MRI scans were performed at screening and subsequently every 6 weeks for the first 36 weeks, then every 12 weeks until disease progression per RECIST v1.1, death, or the initiation of subsequent anti-cancer therapy, whichever occurred first. All participants who discontinued study treatment for any reason were followed for survival after disease progression as per BICR, or after start of anti-cancer therapy. All participants were followed for survival every 3 months ($\pm$ 2 weeks) until death, lost to follow-up, withdrawal of consent for survival follow-up, or until end of study, whichever came first.

3.2.4. Comparator

The comparator arm in the MIRASOL trial included clinician's choice of chemotherapy between paclitaxel (n = 92), PLD (n = 81) and topotecan (n = 53), which were combined in a single 'pooled' chemotherapy arm. The dose and schedule of chemotherapy used in the MIRASOL trial is available in Table 9. At the time of appraisal, these chemotherapies were recommended

therapies for treating PROC as per the BGCS guidelines.³⁵ although, as discussed in Section 2.2, the EAG was advised that topotecan was rarely used in UK practice.

The comparator arm in the FORWARD- 1 trial (FR α -high population) included IC of chemotherapy before randomisation; in the original high expression subgroup, participants received paclitaxel (n = ■), PLD (n = ■), or topotecan (n = ■). At clarification, the EAG asked the company for a feasibility report and accompanying meta-analysis using the high FR α expression re-scored subgroup in the FORWARD-1 trial and the MIRASOL trial. The company presented baseline characteristics and an accompanying meta-analysis for a re-scored FR α -high population from FORWARD-1, which is available in Section 3.3.11. The company did not provide the breakdown of baseline characteristics by chemotherapy type in the re-scored comparator arm. This has an unknown impact on the generalisability of the results and introduces uncertainty about the comparability of outcomes across trials, particularly regarding the potential influence of different chemotherapy types in the comparator arm.

The dosing and schedule of study drugs are outlined in Table 9. The EAG was advised that the official licensed dose of PLD is 50 mg/m², however in clinical practice PLD was often administered at 40 mg/m², as people experience less toxicity and similar efficacy, and therefore display increased tolerance for the regime. This was supported in the literature³⁶⁻³⁹. The trials used a dose of 40 mg/m² in line with this (Table 9).

NICE guidance for second-line therapy with paclitaxel is a dosing schedule of 175 mg/m² every three weeks, over three hours. However, the dose used in the MIRASOL trial did not align to the product licence or to UK practice. Clinical expert advice to the EAG was that across a 4-weekly cycle, PAC was often administered on day 1, 8 and 15, followed by a week off treatment due to bone marrow suppression. In the trial, PAC was received on day 1, 8, 15, and 22 of a 4-week cycle; this involved one fewer administration than the MIRASOL regimen (Table 9).

Topotecan administration was licensed for five consecutive days every three weeks. However, reduced doses, and weekly schedules, had been found to be associated with similar efficacy and an improved toxicity profile^{14,40,41}. Clinical advice to the EAG was that the reduced doses and weekly schedules were relevant to clinical practice as topotecan was usually delivered on day 1 and 5 of a three-week cycle only, on account of bone marrow suppression. This latter advice aligns with the dosing schedules in the trials (Table 9).

Table 9: Dose and schedule of study drugs (MIRASOL and FORWARD-1)

Group	Drug	Trial Dose	Dosing schedule (trials)	Licensed dose
Arm 1	MIRV	6mg/kg AIBW IV	Day 1 of a 3-week cycle	6mg/kg AIBW IV
Arm 2	Pac	80 mg/m ² IV	Day 1, 8, 15, and 22 of a 4-week cycle	175 mg/m ² every 3 weeks over 3 hours
	PLD	40 mg/m ² IV	Day 1 of a 4-week cycle	50 mg/m ² every 28-days
	Topo	4 mg/m ² IV	Days 1, 8, and 15 of a 4-week cycle	1.5 mg/m ² /day, administered on Days 1 to 5 of a 3-week schedule
	Topo	1.25 mg/m ² IV	Days 1 to 5 of a 3-week cycle	1.5 mg/m ² /day, administered on Days 1 to 5 of a 3-week schedule

Abbreviations: AIBW, adjusted ideal body weight; IV, intravenously; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan

3.2.5. Outcomes

The outcomes reported in the MIRASOL²⁶ and FORWARD-1²⁷ (FR α -high population and re-scored FR α -high population) trials are summarised in Table 10.

Table 10: Outcomes reported in the included trials of the technology

	MIRASOL ²⁶	FORWARD-1 ²⁷ (high FR α population)	FORWARD-1 ²⁷ (re- scored high FR α population)
PFS	✓	✓	✓
PFS2	✓	✓	✓
OS	✓	✓	✓
EORTC QLQ-OV28 Abdominal/GI subscale scores	✓	✓	✗
EORTC QLQ-C30 Abdominal/GI subscale scores	✓	✗	✗
EQ-5D-5L	✓	✓ [*]	✗
PGIS	✓	✗	✗
Subsequent therapies	✓	✓	✗
Duration of treatment (DoT)	✓	✓	✗
ORR	✓	✓	✗
Safety	✓	✓	✓ [†]

Abbreviations: HRQoL, health-related quality of life; PFS, progression free survival; OS, overall survival; ORR, objective response rate; DOT, duration of treatment; PFS2, time to second disease progression; HRQoL, health-related quality of life; European Organisation for Research and Treatment of Cancer (EORTC)-Quality of Life Questionnaire (QLQ)-OV28; PGIS, Patient Global Impression of Severity.

Notes: ^{*}The EAG reviewed the trial CSR but the data tables containing EQ-5D data were not provided by the company. [†] partial

3.2.5.1. Clinical efficacy outcomes

MIRASOL

Efficacy outcomes for the MIRASOL²⁶ trial are defined in Table 11. Key methods for handling missing data in efficacy analyses are outlined in Table 12.

Table 11: Efficacy outcome definitions (MIRASOL)

Outcome	Definition	Population
PFS _{INV} (Primary outcome)	The time from date of randomisation until investigator-assessed progressive disease or death, whichever occurs first based on radiological assessments. Investigator assessed in the primary analysis.	ITT
PFS _{BICR}	The time from date of randomisation until investigator-assessed progressive disease or death, whichever occurs first based on radiological assessments. Assessed by blinded independent central review in sensitivity analysis.	ITT

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OS	The time from date of randomisation until the date of death. Patients alive at the time of analysis were censored at the last known date known to be alive.	ITT
ORR	Best response of complete response (CR) or partial response (PR) as assessed by the investigator in the first instance. Response was assessed per RECIST 1.1 criteria. Assessed by investigator (primary analysis) and BICR (sensitivity).	ITT
DoT	The time participants continued to receive the study drug until disease progression, unacceptable toxicity, withdrawal of consent, death, or until the sponsor terminated the study in the safety population. Duration of dosing (weeks) is (date of last dose - date of first dose + 21) / 7. This calculation includes an additional cycle after discontinuation, to ensure the full exposure to study drug is captured.	Safety
PFS2	The time from date of randomisation until second disease progression, end of next line of therapy, or death (whichever comes first), regardless of whether the patient received new anti-cancer treatment. Investigator assessed only.	ITT

Abbreviations: DoT, Duration of treatment; ITT, intention to treat; OS, overall survival; ORR, overall response rate; PFS_{INV}, progression free survival per investigator assessment; PFS_{BICR}, progression free survival per blinded independent central review; PFS2, second progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors. Shading indicates primary trial outcome.

The company also presented stress tests for PFS on account of the EMA's observation that informative censoring influences time-to-event outcomes (CQ A2). This is presented in Section 3.3.1.

Distributions for PFS_{INV}, PFS_{BICR}, PFS2_{INV}, OS, were estimated using the Kaplan-Meier method and differences between groups were assessed via the log-rank test stratified by the randomisation stratification factors (see Section 3.2.1). Hazard ratios with 95% confidence intervals were estimated using a stratified cox PH model.

The company presented scaled Schoenfeld residuals and a visual check via a log cumulative hazard plot, to check whether proportional hazards (PH) assumption was met for OS and PFS. The EAG noted that the Schoenfeld tests presented in the CS did not suggest that the PH assumption was violated for OS ($p=0.321$) or PFS ($p = 0.363$), however the supremum test (described in the CSR) suggested that the PH assumption was violated ($p = 0.049$) for progression-free survival²⁶. Upon visual inspection of the log cumulative hazard plot and advice from the AbbVie advisory board, the company determined that the PH could not be assumed for PFS and OS. The EAG noted that despite the PH assumption not being met, the company

presented HRs from the cox PH model in their primary analysis. However, the company further presented stratified, restricted mean survival time at 3-month intervals, with a 12-month interval used for comparison between treatments in the CSR, which the EAG considered a reasonable way of handling non-PH and showed the same direction of effect. Implications of the PH assumption violation for the economic model are discussed in Section 4.2.5.1.

DoT was modelled separately for each of the chemotherapies administered in the trial with those receiving topotecan on a 3-week cycle or 4-week cycle combined as one treatment regimen. The EAG agreed with this approach on account of low sample size in the topotecan arm (n=53).

ORR was analysed using a Cochran-Mantel-Haenszel test stratified by the randomisation stratification factors (Section 3.2.1). P-value and 95% CIs for ORR was provided, alongside an odds ratio and its 95% CI. The EAG considered these methods acceptable and interpretable.

Table 12: Handling missing data MIRASOL²⁶

Missing data issue	Method
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Censoring rules for PFS_{INV} are available in Table 13. Censoring for subsequent treatment was not in line with the economic model, which assigned subsequent treatment costs on progression (see Section 4.2.8.3). Twenty patients (8.9%) were censored in the chemotherapy arm vs eight (3.5%) participants in the mirvetuximab arm because they received subsequent treatment; all censoring took place in the first 12-month interval. The EAG considered the impact of this to be minimal given the low rate of censoring.

Table 13: Censoring rules for PFS_{INV}

Situation	Date of PFS Event or Censoring	Outcome
[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: PD, disease progression; PFS, progression free survival.

The EAG considered that these methods were robust and suitable for decision making.

FORWARD-1

Efficacy outcomes for the FORWARD-1²⁷ trial are defined in Table 14. [REDACTED]

[REDACTED]

Table 14: Efficacy outcome definitions (FORWARD-1²⁷ high FR α population)

Outcome	Definition	Population
PFS _{INV}	The time from date of randomisation until PD or death, whichever occurred first. Investigator assessed in sensitivity analysis.	Re-scored FR α -high
PFS _{BICR}	The time from the date of randomisation until the time of death or PD. Assessed by blinded independent central review in the primary analysis.	FR α -high

(Primary outcome)		
OS	The time from the date of randomisation until the date of death. Participants who did not experience the event of death were to be censored at their last date known to be alive.	Re-scored FR α -high
ORR	Best response of complete response (CR) or partial response (PR). Response was assessed per RECIST 1.1 criteria. Assessed by blinded independent central review (primary analysis) and by investigator (sensitivity).	FR α -high
DoT	At clarification, the company defined DoT as follows: duration of dosing (weeks) was (date of last dose - date of first dose + 21) / 7". This calculation included an additional cycle after discontinuation, to ensure the full exposure to study drug was captured. The EAG assumed the same definition was used in FORWARD-1 but this was not clear.	FR α -high subset of safety population
PFS2	The time from date of randomisation until second PD or death, whichever occurred first. Investigator assessed only.	FR α -high

Abbreviations: DoT, Duration of treatment; PFS_{INV}, progression free survival per investigator assessment; PFS_{BICR}, progression free survival per blinded independent central review; OS, overall survival; ORR, overall response rate; PFS2, second progression free survival; ITT, intention to treat; RECIST, Response Evaluation Criteria in Solid Tumors. Shading indicates primary trial outcome.

The primary outcome, PFS_{BICR}, distribution was estimated using the [REDACTED] and differences between groups were assessed via the [REDACTED] stratified by the [REDACTED]

[REDACTED] The secondary endpoints of OS, PFS2, and PFS_{INV} were estimated using the [REDACTED] Comparison between treatment arms was conducted using the [REDACTED]

It was not clear to the EAG why PFS per investigator was favoured over PFS per BICR as the primary outcome in the MIRASOL trial²⁶, and this was at odds with the FORWARD-1 primary outcome²⁷. This is discussed in Section 3.2.6.1. Nevertheless, the EAG considered that these methods were robust and suitable for decision making.

3.2.5.2. Health Related Quality of Life

MIRASOL

The following patient-reported outcomes (PRO) measures were collected in the MIRASOL²⁶ trial: EORTC QLQ-C30 (a generic cancer questionnaire to assess the symptoms and

functioning of cancer patients), EORTC QLQOV28 (a disease-specific module to supplement the QLQ-C30 to assess the quality of life of patients with ovarian cancer), EQ-5D-5L (an international, standardised, generic instrument for describing and valuing HRQoL), and the PGIS (a single-item, overall patient assessment of the severity of ovarian cancer symptoms over the past week). In the CS, the primary PRO assessment was defined as the number of participants achieving at least 15 point absolute improvement at Week 8 or Week 9 in the abdominal/GI scale of EORTC QLQ-OV28.

PROs were completed on day 1 of each cycle, which the company stated may not reflect the experience of participants midway through a treatment cycle. The EAG agreed that completing PROs only on day 1 of each cycle may not fully capture the patient experience, particularly symptom burden that arises midway through the treatment cycle. However, as noted in the PRO report⁴² submitted for MIRASOL by the company, mirvetuximab had a 3-week cycle whereas chemo had a 4-week cycle (apart from those who received topotecan). This difference in cycle length means that PRO assessments for mirvetuximab may have occurred relatively closer to the prior dose, potentially capturing patients at a different point in their recovery compared to those on chemotherapy. However, it is unclear whether this timing difference would systematically favour mirvetuximab, especially as patients in that arm may have received more frequent dosing over the same follow-up period, potentially increasing cumulative toxicity. Differences in EORTC QLQ-OV28 were analysed using a Cochran-Mantel-Haenszel test stratified by the randomisation stratification factors (Section 3.2.1). P-value and 95% CIs were provided. The EAG considered that these methods were acceptable and interpretable.

A pre-specified sensitivity analysis was conducted by the company on the abdominal/gastrointestinal subscale using an 11.11-point threshold, on the basis that the primary threshold of 15 points was 'stringent'. At clarification, the company stated the rationale for the 11.11 threshold was due to the belief that patients in the trial already experienced baseline GI/abdominal symptoms, and thus had limited scope for large improvements. They argued that a lower threshold would better capture meaningful changes in this population; however, given the randomised design and similar baseline scores between arms (25.1 vs 28.0), this rationale may be of limited validity. While the sensitivity analysis using the 11.11-point MCID showed a statistically significant difference between MIRV (29.0%) and IC chemotherapy (18.0%) at Week 8/9 ($p = 0.0325$), the strength of this result depends on the acceptance of the lower threshold. The EAG expressed caution when interpreting this result as the strength of this result depends on the acceptance of the lower threshold and further noted that the EORTC

QLQ-C30 and the EORTC QLQ-OV28 questionnaires differ in their structure and symptom focus.

Analyses included descriptive statistics, longitudinal modelling using mixed models for repeated measures (MMRM), responder analyses, and time-to-event analyses. While the EAG considered the MMRM approach appropriate under the missing at random (MAR) assumption, it is unclear whether this assumption was adequately tested or justified in this case. The EAG noted that sensitivity analyses to assess how sensitive the results were to violations of the missing at random assumption were not pre-planned or available in the CS. The company's responder analysis included a comparison between the proportion of participants with a MCID at week 8/9 for key domains of the EORTC QLQ-C30, EORTC QLQ-OV28, and EQ-5D-5L. A Cochran-Mantel-Haenszel (CMH) test stratified by the randomisation stratification factors to test for differences between mirvetuximab and IC Chemotherapy was performed. The time-to-event analysis of time to confirmed clinically meaningful deterioration (TTCD) and time to definitive clinically meaningful deterioration (TTDD).

Distribution was estimated using the Kaplan-Meier method and differences between groups were assessed via the log-rank test stratified by the randomisation stratification factors. A hazard ratio was estimated using a stratified cox PH model.

3.2.5.3. Adverse events

For MIRASOL²⁶, adverse event data were reported in the CS for the safety population at the final follow-up (September 2024). The company stated (p.78 of the CS) that the safety results were consistent with the previous data cut of MIRASOL and the SORAYA²⁸ and FORWARD-1²⁷ trials.

Adverse event outcomes were reported by the company in the CS (for MIRASOL) and at clarification (for FORWARD-1 and SORAYA). The level of detail reported by the company for the overall safety of treatments in FORWARD-1 was minimal: while the data were based on the re-scored population, the nature of the outcomes reported were unclear: in Table 58 of the company's clarification response it was unclear if events were treatment-emergent or treatment-related, whether they consisted of any grade of event, or whether they were limited to a particular prevalence.

In response to clarification (A28, Table 9), the company submitted a pairwise meta-analysis of specific adverse events using pooled data from MIRASOL and the re-scored population from

FORWARD-1. While the company stated that the analysis was feasible, some outcomes were not pooled and the rationale was not stated.

For the comparative trials (MIRASOL and FORWARD-1), safety data were presented for the pooled chemotherapy arm (i.e. not split separately according to the type of chemotherapy received) with data for only two selected outcomes reported by the company at clarification (A14). However, the EAG was able to access these data from the trial CSRs.

Table 15: Adverse event outcomes reported in MIRASOL, FORWARD-1 and SORAYA

	MIRASOL ²⁶	FORWARD-1 ²⁷ (N=116)	SORAYA ²⁸
Median follow-up	28.35 months	12.45 months	13.4 months 15.80 months
	Any TEAE Drug-related TEAE Serious TEAE Serious drug-related TEAE TEAE leading to discontinuation Drug-related TEAE leading to discontinuation TEAE leading to death Drug-related TEAE leading to death Grade 3+ TEAEs reported by ≥5% of either arm Most common serious TEAE TEAEs reported by ≥10% of either arm TEAEs of special interest*	Blood and lymphatic system disorders, eye disorders, general and administration site disorders, fatigue, investigations, gastrointestinal disorders – class and nature unknown	Any TEAE Drug-related TEAE Serious TEAE Serious drug-related TEAE TEAE leading to discontinuation Drug-related TEAE leading to discontinuation TEAE leading to death Drug-related TEAE leading to death TEAEs reported by ≥10% of either arm TEAEs of special interest*

Abbreviations: TEAE, treatment-emergent adverse event

Note: *not defined in the study protocol and selected post hoc (criteria not described)

3.2.6. Critical appraisal of the design of the studies

3.2.6.1. MIRASOL

In general, the EAG agreed with the use of the Cochrane risk of bias tool v2 algorithm's assessment of MIRASOL²⁶; i.e. that there were 'some concerns' but most domains of the tool were at low risk of bias. The EAG noted that the open-label nature of the trial was a risk of bias as this may influence participant retention (note that more people chose to withdraw from the chemotherapy arm after treatment allocation), the treatments received by people in the trial and the way in which outcomes were assessed. The latter was a particular concern for outcomes that require subjective judgement, such as HRQoL.

The assessment also noted that the primary outcome was investigator-assessed (rather than BICR). In the CS and at clarification (A21), the company stated that the choice of investigator-assessed response as the primary trial outcome was consistent with the way that the treatment would be used in clinical practice and was consistent with consensus recommendations from the Gynecologic Cancer InterGroup⁴³. The EAG consulted these consensus recommendations but these did not report a rationale for the preference for investigator-assessed response (either in the main publication or in the supplementary appendix). The EAG contacted the lead author but did not receive a response during the appraisal. At clarification (A2), the company stated that the EMA had flagged discrepancies between the investigator- and BICR-assessed response results, but that the two outcomes were consistent at the final follow-up. Overall, the EAG considered that the choice of investigator-assessed response was a risk of bias within an open-label trial,⁴⁴ but that it was unlikely to meaningfully affect the results within this submission.

The EAG also noted that both computed tomography (CT) and magnetic resonance imaging (MRI) scans were used in the MIRASOL to assess tumour response, while CT⁴³ was considered to be the best available method. At clarification (A22), the EAG asked the company to provide a subgroup analysis by tumour scan method, however the company stated that this was not available and that as most participants in MIRASOL were assessed by CT scan, they did not consider that this would be meaningful. As the company did not provide the number of participants who were assessed using MRI and their breakdown across trial arms, it was not possible for the EAG to determine whether this was a concern but did not expect this to have a major influence on the results.

3.2.6.2. FORWARD-1

The company assessment was that FORWARD-1²⁷ was at low risk of bias across all domains of the tool. The EAG disagreed with this assessment and considered it to be at odds with the assessment of MIRASOL, given that both trials were open-label and this was highlighted as a risk of bias for MIRASOL. As with MIRASOL, the open-label nature of the trial may have undermined the robustness of the evaluation, with particular issues for subjective outcomes. The EAG also noted that the re-scoring of the trial population to match an alternative definition of FR α expression was also a concern: while baseline characteristics for the re-scored treatment arms did not show evidence of an imbalance, there was less information in the CS about the flow of participants through the trial and whether there were differences in the receipt of treatment (e.g. whether participants attrition varied according to treatment allocation).

3.3. Critique of the results of the trials of the technology of interest

The EAG selected the outcomes most relevant to the NICE scope and economic modelling for critique in this section. The MIRASOL²⁶ and FORWARD-1 (re-scored FR α -high population or FR α -high population)²⁷ trials are presented side by side to highlight similarities and differences between the trial results. The company provided a meta-analysis at clarification stage (A28), pooling the duration of treatment (DoT), PFS_{INV}, and OS outcomes respectively in the MIRASOL, and re-scored FR α -high population from FORWARD-1, which is described later in Section 3.3.11.

To aid comparison of results across the clinical trials of mirvetuximab (MIRASOL, the re-scored population from FORWARD-1, and SORAYA²⁸), the EAG created KM curves including evidence from all trials using individual patient data provided by the company at clarification for the following outcomes: PFS_{INV}, and OS. These are also presented in this section.

3.3.1. Progression free survival

MIRASOL²⁶

The company reported PFS data from the latest data cut of the MIRASOL trial (September 2024) with a median duration of follow up of 28.35 months (95% confidence interval [CI]: 24.97, not reached [NR]).

For PFS assessed by investigator (PFS_{INV}), mirvetuximab showed a reduction (37%) in the risk of tumour progression or death compared to chemotherapy (HR of 0.63 (95% CI: 0.513, 0.785;

$p < 0.0001$). In the ITT population, median PFS_{INV} was 5.59 months (95% CI: 4.34, 5.88) vs 3.98 months (95% CI: 2.86, 4.47) for mirvetuximab and chemotherapy, respectively. KM curves showed separation earlier than ten weeks after randomisation (Figure 1).

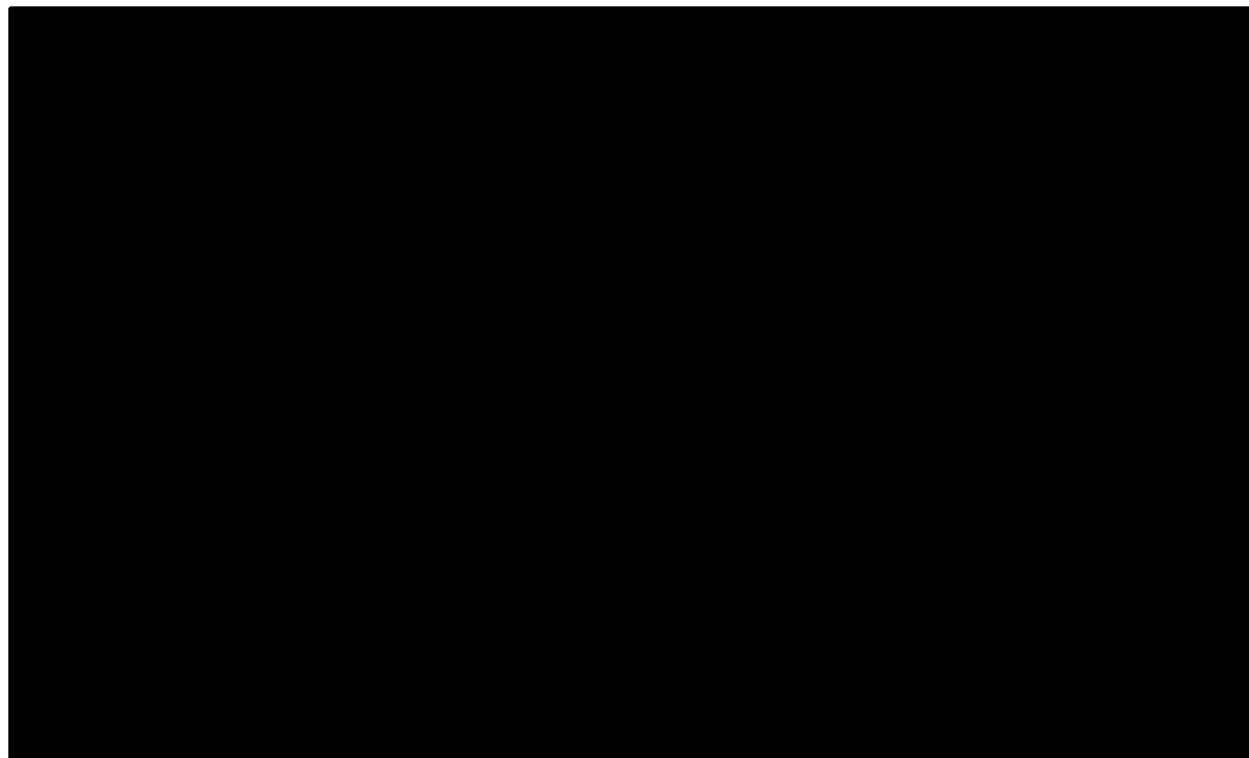
The results for PFS_{BICR} in the ITT population were generally consistent with PFS_{INV}, though more conservative. These showed a reduction of █% in the risk of tumour progression or death compared to chemotherapy █. Median PFS_{BICR} was █ months (95% CI: █) vs █ months (95% CI: █) for mirvetuximab and chemotherapy, respectively.

The company provided additional 'stress tests' for informative censoring provided at the clarification stage (A2) for both the March 2023 and October 2023 data cuts for PFS. These were conducted in response to the EMA's observation that informative censoring influenced time-to-event outcomes. These analyses, based on the October 2023 data cut, resulted in a hazard ratio ranging from 0.608 (95% CI: 0.495, 0.746) to 0.713 (95% CI: 0.560, 0.908). The EAG considered the pooled HR and consistency across outcomes to be a good indication of the benefits of mirvetuximab over chemotherapy, and it was plausible that the treatment effect lay within this range.

Comparability across chemotherapies (MIRASOL)

The EAG produced Figure 1 using PFS_{INV} IPD data from the MIRASOL trial. Participants in the mirvetuximab arm were split according to the chemotherapy they would have received if they had been allocated to the chemotherapy arm (i.e. 'MIRVpac', 'MIRVpld', and 'MIRVtopo'). Those receiving topotecan in the trial ('topo') showed the shortest PFS, with █ remaining progression-free beyond █ followed by the paclitaxel arm ('PAC'), with only █ extending PFS beyond █. All chemotherapy arms displayed overlapping survival curves, suggesting that these treatments offered similar PFS outcomes, without a clear advantage over one another in terms of long-term progression control.

Figure 1: KM comparison of PFS_{INV} across pre-assigned chemotherapy (MIRASOL²⁶)



Abbreviations: KM, Kaplan-Meier; MIRV, mirvetuximab; MIRVpac, mirvetuximab pre-assigned paclitaxel; MIRVpld, mirvetuximab pre-assigned PLD; MIRVtopo, mirvetuximab pre-assigned topotecan; PAC, paclitaxel; PLD, pegylated liposomal doxorubicin; topo, topotecan; trt, treatment.

FORWARD-1²⁷

PFS_{BICR} for mirvetuximab in the FR α -high rescored population showed a reduction (41%) in the risk of tumour progression or death compared to chemotherapy (HR: 0.588; 95% CI: 0.368, 0.940; p=0.0267). Median PFS_{BICR} for mirvetuximab was 5.68 months (n = 82) vs chemotherapy 3.22 months (n = 34).

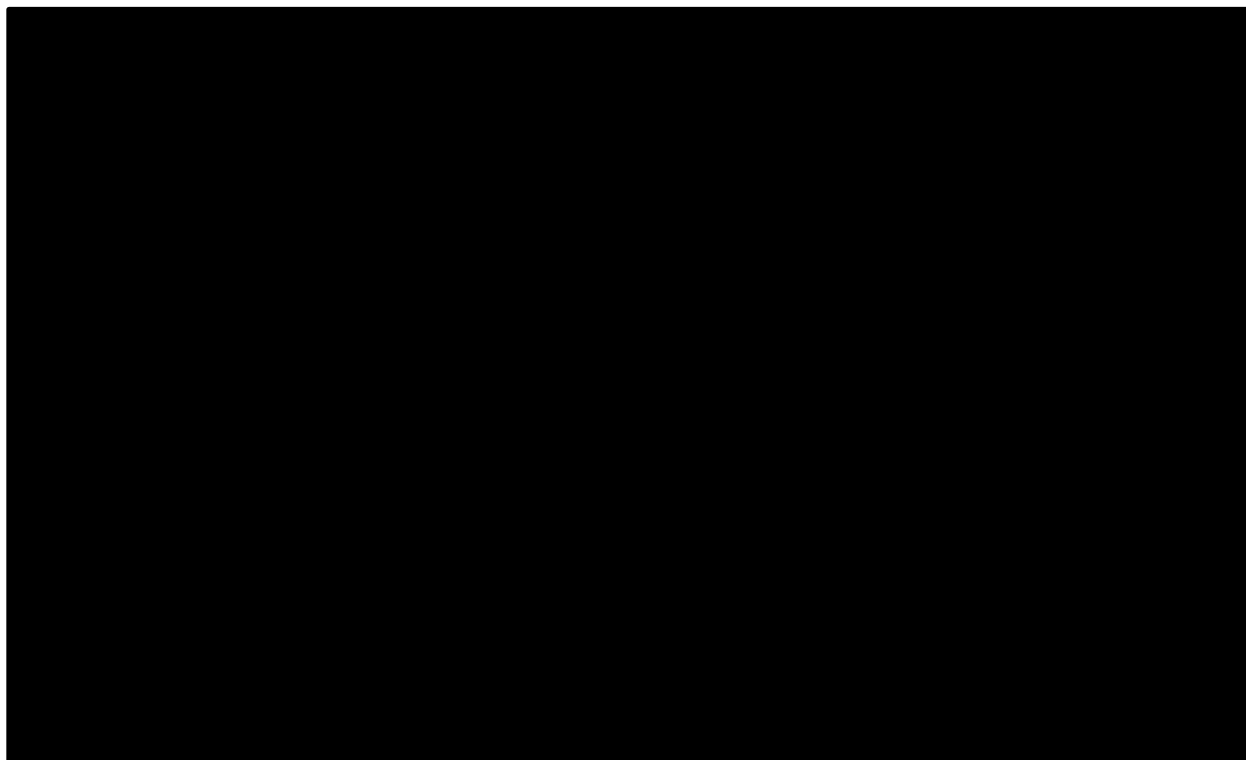
PFS_{INV} for mirvetuximab in the re-scored FR α -high population showed a reduction (35%) in the risk of tumour progression or death compared to chemotherapy (HR: 0.65; 95% CI: 0.407, 1.032; p=0.0747). Median PFS_{INV} for mirvetuximab was 5.62 months (n = 82) vs chemotherapy 3.71 months (n = 34). KM curves showed separation earlier than ten weeks after randomisation (Figure 2).

SORAYA²⁸

In the efficacy population (n = 105), median PFS_{INV} was 4.3 months (95% CI: 3.7, 5.1).

Comparability across trials

Figure 2: Comparison of PFS_{INV} across all clinical trials of mirvetuximab (ITT population)



Abbreviations: CHEMO, chemotherapy; FWD, FORWARD-1; KM, Kaplan-Meier; ITT, intention-to-treat; MIRV, mirvetuximab; PFS_{INV}, progression-free survival per investigator; SRY, SORAYA; trt, treatment.

Figure 2 shows the KM curves for PFS across MIRASOL, FORWARD-1 (re-scored FR α -high population), and SORAYA. The chemotherapy arms in the FORWARD-1 and MIRASOL trials overlapped, as did the mirvetuximab arms, suggesting similar PFS outcomes between the same treatments in the two trials. The mirvetuximab arm in SORAYA did not overlap with that of FORWARD-1 or MIRASOL, instead overlapping with the chemotherapy arms of FORWARD-1 and MIRASOL. As SORAYA was not a controlled trial, it was not possible to investigate whether the relative efficacy of mirvetuximab varied in SORAYA from the other trials. Within its appraisal, the EAG was unable to identify a reason why PFS was poorer in SORAYA, but ruled out differences in censoring rules and reasons for discontinuation, based on information provided by the company at clarification.

3.3.2. Second progression-free survival

MIRASOL²⁶

PFS2 was assessed by investigator only. In the ITT population, the benefit of mirvetuximab showed greater benefit beyond first progression, into next line of therapy or death. There was a statistically significant 41% reduction in the risk of second progression or death compared with chemotherapy (HR: 0.59; 95% CI: 0.480, 0.728). Median time to secondary progression was 11.01 vs 7.59 months for mirvetuximab and chemotherapy, respectively ($p < 0.0001$).

FORWARD-1²⁷

PFS2 was assessed by investigator only and was not available in the re-scored FR α -high population. In the original FR α -high trial population, mirvetuximab showed greater benefit beyond first progression, into next line of therapy or death. There was a [REDACTED] the risk of second progression or death compared with chemotherapy (HR: [REDACTED]). Median time to PFS2 was [REDACTED] months (95% CI: [REDACTED] vs. [REDACTED] (95% CI: [REDACTED]) for patients randomised to mirvetuximab and chemotherapy, respectively.

3.3.3. Overall survival

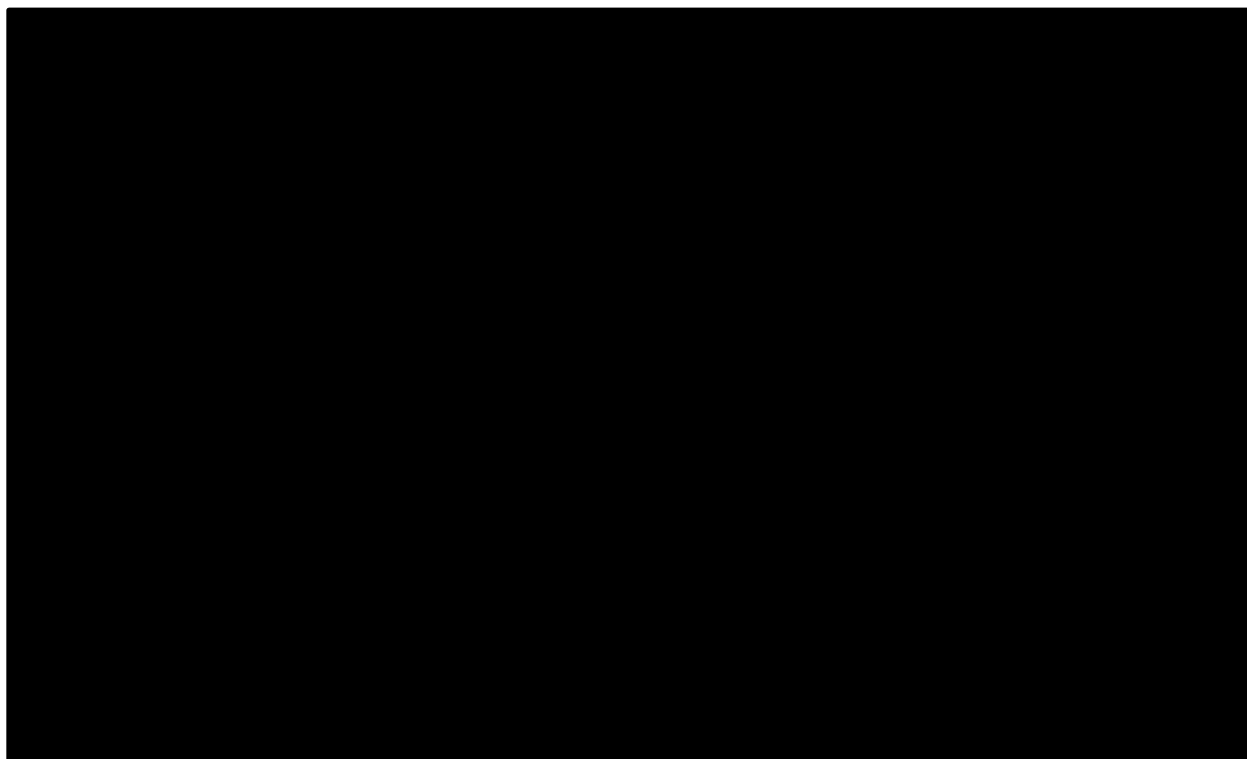
MIRASOL²⁶

The company used OS data from the latest data cut of the MIRASOL trial (September 2024). In the ITT population, the results for OS showed a 32% reduction in the risk of death in participants randomised to mirvetuximab (HR: 0.68; 95% CI: 0.54, 0.84; $p = 0.0004$). The median OS for mirvetuximab was 16.85 months (95% CI: 14.36, 19.78) vs 13.34 (95% CI: 11.37, 15.15) months for chemotherapy. KM curves showed separation earlier than ten weeks after randomisation (Figure 3). At the time of study closure, there were still 44 participants alive in the mirvetuximab arm, vs 18 participants alive in the chemotherapy arm.

Comparability across chemotherapies (MIRASOL)

The EAG produced Figure 3 using OS_{INV} IPD data from the MIRASOL²⁶ trial. As per the previous figures, the mirvetuximab arm was split according to the chemotherapy participants would have received if they were randomised to the chemotherapy arm. The three chemotherapy arms showed similar OS curves, with notable overlap. [REDACTED] of the patients in the chemotherapy arms remained at risk beyond [REDACTED] weeks.

Figure 3: KM comparison of OSINV across pre-assigned chemotherapy (MIRASOL)



Abbreviations: KM, Kaplan-Meier; MIRV, mirvetuximab; trt, treatment; MIRVpac, mirvetuximab pre-assigned paclitaxel; MIRVpld, mirvetuximab pre-assigned PLD; MIRVtopo, mirvetuximab pre-assigned topotecan; PAC, paclitaxel; PLD, pegylated liposomal doxorubicin; topo, topotecan.

FORWARD-1²⁷

In the FR α -high re-scored population, results for OS showed a 32% reduction in the risk of death in participants randomised to mirvetuximab (HR: 0.678; 95% CI: 0.410, 1.119; p=0.126). The median OS for mirvetuximab was 16.4 months vs 11.4 months for chemotherapy (variance data not reported by the company). KM curves showed separation immediately after randomisation (Figure 3).

SORAYA²⁸

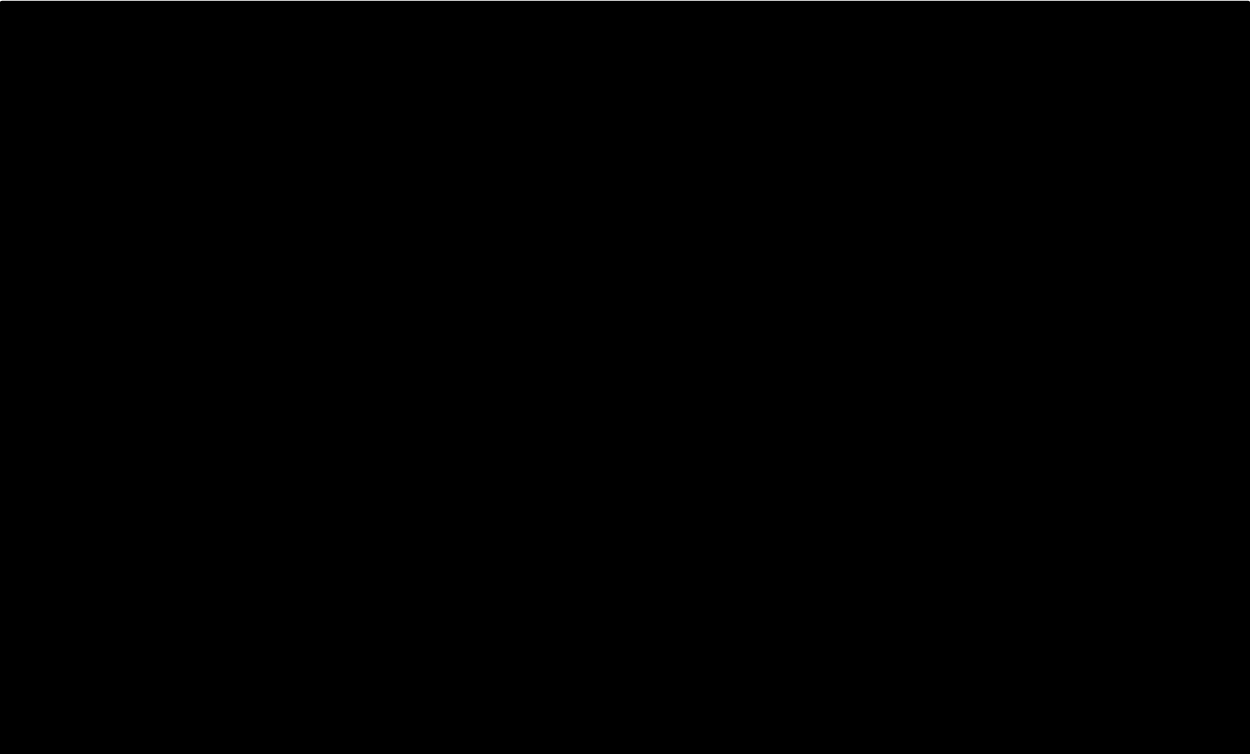
Median OS was not reached in the efficacy population ($n = \blacksquare$). The median follow-up time was $\blacksquare$ months $\blacksquare$ at which point, $\blacksquare$ of participants had died.

Comparability across trials

Figure 4 demonstrates the KM curves for OS across MIRASOL, FORWARD-1 (re-scored FR α -high population), and SORAYA. The chemotherapy arms in the FORWARD-1 and MIRASOL trials overlapped, suggesting similar OS outcomes. The mirvetuximab arms in the FORWARD-1

and MIRASOL trials also overlapped suggesting similar OS outcomes. The mirvetuximab arm in SORAYA overlapped with that of FORWARD-1 and MIRASOL up until week 110, indicating similar trends in OS. All trials consistently suggest an OS advantage for mirvetuximab compared to chemotherapy.

Figure 4: Comparison of OS_{INV} across all clinical trials of mirvetuximab (ITT population)



Abbreviations: CHEMO, chemotherapy; FWD, FORWARD-1; ITT, intention-to-treat; KM, Kaplan-Meier; MIRV, mirvetuximab; PFS_{INV}, progression-free survival per investigator; SRY, SORAYA; trt, treatment

3.3.4. Duration of Treatment

MIRASOL²⁶

In the safety population (mirvetuximab *n* = 218; chemotherapy *n* = 207), the median DoT was [REDACTED] weeks in the mirvetuximab arm (95% CI: [REDACTED]). For individual chemotherapies, the median duration of the assigned treatment was [REDACTED] weeks (95% CI: [REDACTED]) for paclitaxel, [REDACTED] for PLD, [REDACTED] weeks (95% CI: [REDACTED]) for topotecan. This was available in Figure 35 in the CS. Treatment durations are summarised in Table 16.

Table 16: Duration of treatments received in MIRASOL

Drug	Cycle and duration

Mirvetuximab	7.0 cycles (mean: 9.2; range: 1 to 51 cycles); median duration: 4.98 months
Pooled Chemotherapy	3.0 cycles (mean: 4.5; range: 1 to 30 cycles); median duration: 2.96 months
Paclitaxel	4.0 cycles (mean: 4.5; range: 1 to 9 cycles); median duration: 3.80 months
Pegylated liposomal doxorubicin	3.0 cycles (mean: 4.6; range: 1 to 30 cycles); median duration: 2.76 months
Topotecan	1.25 mg/m ² : 6.0 cycles (mean: 9.1; range: 1 to 19 cycles); median duration: 5.01 months
Topotecan	4.0 mg/m ² : 2.0 cycles (mean: 3.2; range: 1 to 12 cycles); median duration: 2.10 months

FORWARD-1²⁷

In the FR α -high population (mirvetuximab $n = 142$; chemotherapy $n = 64$), the mirvetuximab arm received a median of [REDACTED] weeks of treatment (range: [REDACTED]); participants in the chemotherapy arm received [REDACTED] weeks (range: [REDACTED] weeks) paclitaxel, [REDACTED] weeks (range: [REDACTED]) PLD, and [REDACTED] weeks (range: [REDACTED] weeks) topotecan. The EAG noted that the company did not present the summary statistics or baseline characteristics at clarification (A28) for the re-scored safety population (mirvetuximab $n =$ [REDACTED]; chemotherapy $n =$ [REDACTED]) and so it was not possible to compare the similarity of the re-scored safety population and the FR α -high population. Although given the small discrepancy in sample size from the re-scored FR α -high ITT population (mirvetuximab $n =$ [REDACTED]; chemotherapy $n =$ [REDACTED]), the EAG noted that the baseline characteristics were likely to be similar.

SORAYA²⁸

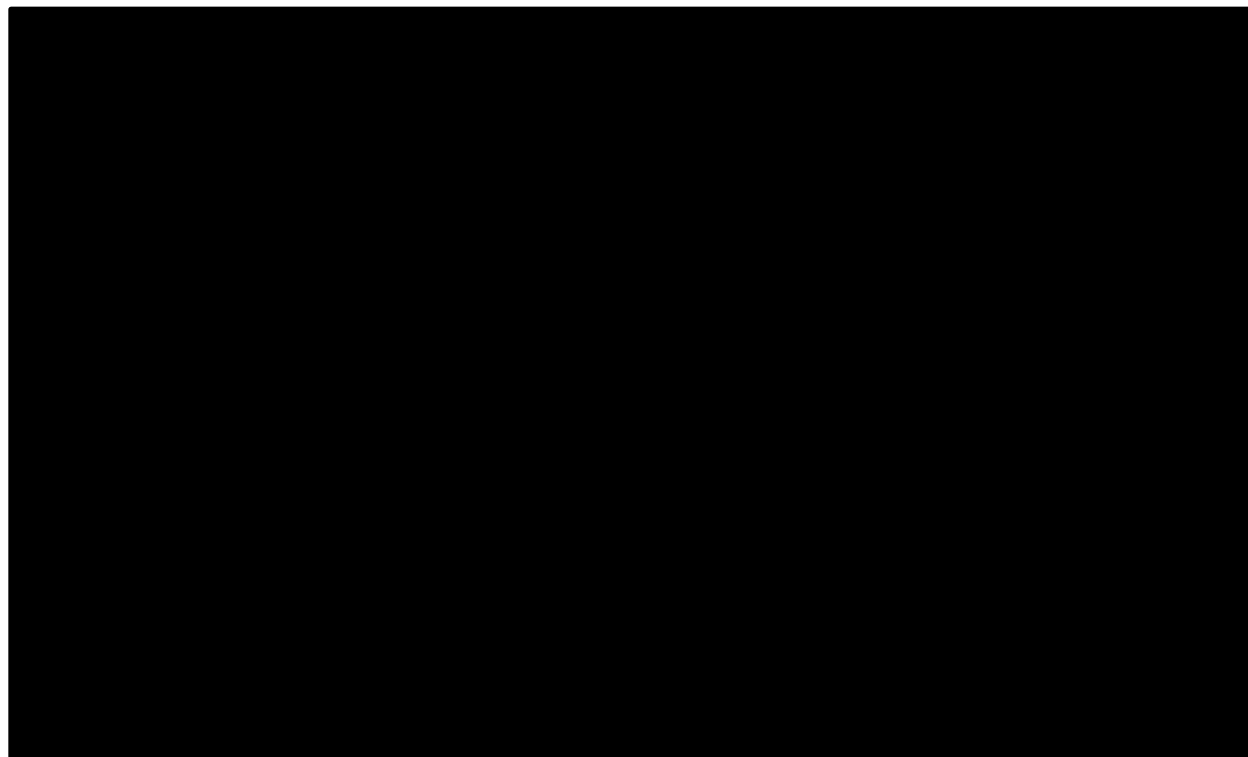
The company did not present summary statistics for the DoT at clarification. The IPD was provided by the company and the EAG plotted this in Figure 5, alongside the MIRASOL and FORWARD-1 trials.

Comparability across trials

Figure 5 demonstrates the KM curves for DoT across MIRASOL, FORWARD-1 (re-scored FR α -high population), and SORAYA. KM curves for mirvetuximab and chemotherapy separate early in the MIRASOL and FORWARD-1 trials. The respective chemotherapy and mirvetuximab arms

in MIRASOL and FORWARD-1 overlapped, indicating similar patterns of treatment duration in these studies. Although the chemotherapy arm in FORWARD-1 showed the shortest treatment duration, with no participants remaining on treatment by week 60, all trials suggested a longer DoT for mirvetuximab compared to chemotherapy.

Figure 5: Duration of treatment (safety populations) MIRASOL, SORAYA, re-scored FRα-



high population FORWARD-1

Abbreviations: CEMO, chemotherapy; FWD, FORWARD-1; ICC, Investigator's choice of chemotherapy; ITT, intention-to-treat; KM, Kaplan-Meier; MIRV, mirvetuximab; SRY, SORAYA; trt, treatment.

3.3.5. Overall Response Rate

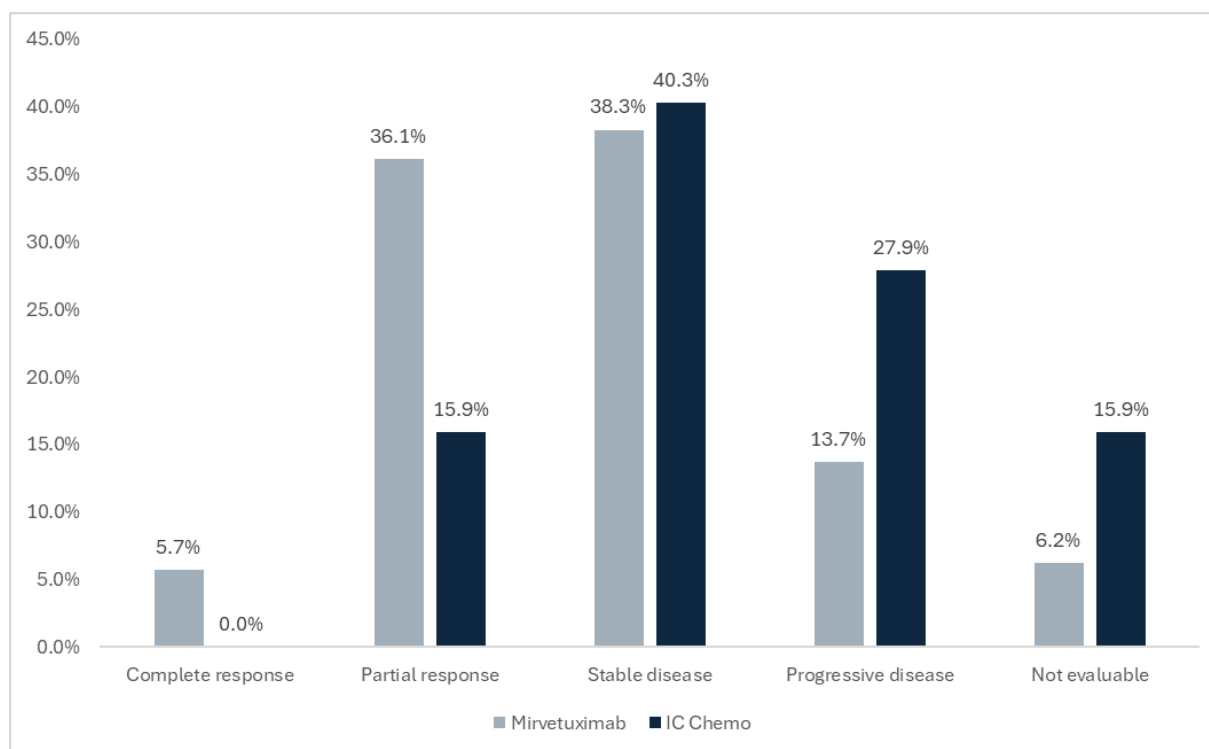
MIRASOL²⁶

The company reported ORR data from the latest data cut of the MIRASOL trial (September 2024). In the ITT population, ORR_{INV} in participants treated with mirvetuximab was 41.9% (95% CI: 35.4, 48.6) vs chemotherapy 15.9% (95% CI: 11.4, 21.4) (odds ratio: 3.75; 95% CI: 2.40, 5.85; p<0.0001). In the mirvetuximab group, 5.7% of participants achieved a complete response vs 0% in the chemotherapy arm (Figure 6). Tumour shrinkage (encompassing complete and partial response, and stable disease) was observed for 80.1% of patients treated with mirvetuximab vs. 56.2% in the chemotherapy arm.

ORR_{BICR} was evaluated as a sensitivity analysis. In the ITT population, ORR_{BICR} was [REDACTED] for mirvetuximab vs [REDACTED] for chemotherapy; OR: [REDACTED]

The EAG noted that no patients in the chemotherapy group and 13 patients in the mirvetuximab group achieved a complete response. The majority of responses being made up of partial response or stable disease in both groups (Figure 6). The EAG received expert advice relating to diminished chances for a complete response as PROC progresses, as people become less sensitive to treatments, which aligned with these findings.

Figure 6: Summary of best overall response – ITT population (September 2024 DCO)



Source: Data on file, MIRASOL final CSR ³⁴.

Abbreviations: CI, confidence interval; CSR, clinical study report; DCO, data cut-off; IC Chemo, Investigator's choice of chemotherapy; ITT, intention-to-treat.

FORWARD-1²⁷

ORR_{BICR} in the FRα-high population was [REDACTED] for mirvetuximab vs. [REDACTED] chemotherapy [REDACTED] ORR_{INV} in participants treated with mirvetuximab was [REDACTED] vs. chemotherapy [REDACTED]. The company did not present summary statistics for ORR in the re-scored FRα high population.

SORAYA²⁸

ORR_{INV} was 32.4% (95% CI: 23.6%, 42.2%) for mirvetuximab. Five participants had a confirmed complete response; 29 patients had a confirmed partial response.

3.3.6. Health-related quality of life (HRQoL)

For the PROs, MCIDs for the EORTC QLQ-C30 were set at 16.67 for Global Health Status/QoL, 13.33 for Physical Functioning, 33.33 for Role Functioning, 16.67 for Emotional Functioning, and 22.22 for Fatigue. They also set a pre-specified sensitivity analysis MCID at 11.11 for Abdominal/GI symptoms. For the EORTC QLQ-OV28, MCIDs were defined as 16.67 for Abdominal/GI symptoms, 22.22 for Peripheral Neuropathy and Attitude to Disease and Treatment, and either 33.33 or 16.67 for Sexual Function, depending on the number of items completed. For the EQ-5D-5L VAS, the company applied a threshold of a 10-point increase from baseline to indicate clinically meaningful improvement. The company's rationale for the MCIDs selected was not provided in the documents supplied by the company. Overall, the MCIDs applied for the EORTC QLQ-C30 were generally higher than the commonly referenced 5 to 10 point range supported by previous research, raising questions about their appropriateness and emphasising the need for a clear justification for these larger thresholds⁴⁵. For the EQ-5D-5L, a change of 7–12 points has been considered clinically meaningful⁴⁶. The MCID used by the company for the EQ-5D-5L VAS therefore fell within the evidence-based range.

MIRASOL

PROs were collected at multiple timepoints but completion rates dropped to about 56% by week 24 across most outcomes. Adjusted rates (i.e., calculated as the number of patients with minimum requirements for scoring divided by the number of patients with PRO assessments expected) were lower than expected, and the chemotherapy group had more missing data. The MMRM method assumed data were missing at random (MAR), but no justification for this assumption was given. Week 24 exhibits high levels of missing data, however, the company did not perform sensitivity analyses to explore the impact of this missingness. Consequently, it remains unclear to the EAG whether the MMRM model is appropriate under the MAR assumption.

Patients treated with mirvetuximab generally maintained or improved HRQoL compared to those receiving investigator's choice chemotherapy, which showed more deterioration across

questionnaires. However, the extent of clinically meaningful change varied by measure and symptom domain. While improvements for the EORTC QLQ-OV28 in fatigue and some ovarian cancer-specific symptoms favoured mirvetuximab, differences in peripheral neuropathy and sexual function were lower and not statistically significant. Similarly, time to event analyses for the EORTC QLQ-C30 and the EORTC QLQ-OV28 found HRs largely favoured mirvetuximab over chemotherapy for TTCD and TTDD in all domains except GHS/QoL for TTCD, however TTCD found no statistically significant differences for GHS/QoL and Attitude to Disease and Treatment domain. Chemotherapy was favoured in PN and SF domains, however HRs did not reach statistical significance. This suggests that mirvetuximab generally preserves or improves HRQoL compared to chemotherapy, with statistically significant benefits in some domains; however, these benefits were not consistent across all measures.

FORWARD-1

The company did not present summary statistics for HRQoL in the re-scored high FR α population. The FORWARD-1²⁷ CSR provided by the company at clarification provided limited data on PROs for the high FR α population, in comparison to MIRASOL. The CSR only provided information for EORTC QLQ-OV28, in the abdominal/GI Symptom domain. Mirvetuximab showed a [REDACTED] [REDACTED] After excluding early progressors, this improvement [REDACTED] [REDACTED]

3.3.7. Subsequent treatment

The CS presented MIRASOL data showing that 67% of patients treated with mirvetuximab received subsequent therapies. These treatments were broadly similar between mirvetuximab and chemotherapy groups, with taxanes, anthracyclines, and gemcitabine being the most common. Crossover was not recommended during MIRASOL and there were no controls placed on post-trial treatments.

At clarification, the company provided data relating to *first* subsequent treatments received by patients in the MIRASOL trial which were not aligned with NHS clinical practice. This corresponded to 22% (51/227) of patients in the mirvetuximab arm, and 29% (66/226) patients in the chemotherapy arm. A breakdown of these treatments is provided below in Table 17. The

EAG received advice from clinical experts that this was not expected to impact clinical effectiveness as none of these treatments have shown a benefit (except for mirvetuximab).

Table 17: First subsequent treatments not aligned with NHS clinical practice

Treatment	Mirvetuximab (n=227)	IC Chemo (n=226)
Targeted therapies* +/- chemotherapy	27 (12%)	27 (12%)
PD1/PD-L1 +/- chemotherapy	2 (1%)	6 (3%)
Targeted therapy + PD1/PD-L1 +/- chemotherapy	2 (1%)	2 (1%)
Mirvetuximab	0 (0%)	6 (3%)
Chemo (other) +/- platinum or Taxanes chemotherapy	20 (9%)	25 (11%)
Total	51 (22%)	66 (29%)

Abbreviations: Chemo, chemotherapy; IC Chemo, investigators choice of chemotherapy; PARP, poly (ADP-ribose) polymerase; PD1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

Notes: *Targeted therapies include bevacizumab, Kinase inhibitors, PARP inhibitors

Mirvetuximab was received as a subsequent treatment for 7% (n = 16) of participants in the chemotherapy arm, and re-treatment in <1% (n = 2) of participants in the mirvetuximab arm. Given the low rate of subsequent mirvetuximab use in the chemotherapy arm, the impact on overall survival was likely to be minimal. However, the company used a Rank Preserving Structural Failure Time Models (RPSFTM) to adjust for subsequent use of mirvetuximab in the chemotherapy arm. The EAG considered that this was an appropriate method on account of its ability to estimate the counterfactual survival outcomes had subsequent treatment with mirvetuximab not occurred, thereby preserving the treatment effect as observed under the original randomisation. Additional sensitivity analyses using IPCW or censoring at subsequent treatment points would have improved confidence in the results. At clarification, the company confirmed that there is no clinical evidence to support re-treatment with mirvetuximab (A15) meaning that such an approach cannot be recommended and would therefore not be anticipated in clinical practice. Section 4.2.8.3 discusses the effect on the economic analysis of removing the costs of subsequent mirvetuximab and adjusting for the impact on effectiveness in the chemotherapy arm.

In FORWARD-1, 75% of patients treated with mirvetuximab received subsequent therapies in the FR α -high group. Similarly, anthracyclines, taxanes and other chemotherapies were the most common subsequent treatments. While allowing crossover was initially considered in FORWARD-1, it was removed from the design before any patients were eligible for the crossover, to reduce the potential confounding effect of mirvetuximab on OS when comparing

mirvetuximab to chemotherapy. This was in line with NHS clinical practice as mirvetuximab was not available as a post-progression treatment option within the NHS for this population.

3.3.8. Subgroup analyses

Subgroup analyses were performed in the ITT population for PFS_{INV}, PFS2, OS and ORR_{INV} in the MIRASOL²⁶ trial, these were unstratified, exploratory, and were explored in scenario analysis in the economic model (Section 4.2.10). The subgroups included: age (18-64 years, ≥ 65 years, 19-69 years, ≥ 70 years), BRCA mutation status (positive, negative/ unknown), Eastern Cooperative Oncology Group (ECOG) status (0, 1), number of prior lines of therapy (1, 2, 3, 1 or 2), prior exposure to PARP inhibitor maintenance (yes, no, uncertain), prior exposure to bevacizumab (yes, no), stage of diagnosis (I-III, IV), *primary* platinum free interval (≤ 6 months, > 6 months), platinum-free interval (≤ 3 months, > 3 months), country (USA, rest of world), type of chemotherapy (PLD, paclitaxel, topotecan), and weight at baseline (≤ 60kg, 60-80kg, > 80kg).

The company did not present summary statistics for subgroups in the re-scored FRα high population in FORWARD-1²⁷. Instead, subgroup analyses were performed in the FRα-high population for PFS_{BICR}, OS, ORR_{BICR}. The subgroups included: age (< 65 years, ≥ 65 years), BRCA mutations (yes, no), Baseline Eastern Cooperative Oncology Group (ECOG) status (0, 1), prior exposure to bevacizumab (yes, no), number of prior lines of therapy (1 or 2, 3), type of chemotherapy (PLD, paclitaxel, topotecan), platinum-free interval (≤ 3 months, > 3 months), location of metastasis (visceral, non-/ line visceral), race (white, non-white), time since initial diagnosis ≤ 2 years, >2 years).

The EAG noted that results were highly uncertain due to limited statistical power to detect meaningful differences, and trends in the data should be interpreted with appropriate caution. The EAG present results from subgroups which indicated a statistically significant effect might be plausible, for the outcomes most aligned with the decision problem.

The EAG noted that the impact of platinum free interval was inconsistent in the clinical data. In OS data, a primary platinum-free interval of > 6 months in the MIRASOL trial (n=305) yielded a more favourable HR for mirvetuximab vs. chemotherapy (HR: 0.54; 95% CI: 0.415, 0.707) whereas there was no difference between mirvetuximab and chemotherapy for those with a primary platinum free interval ≤ 6 months (n = 147; HR 1.07 (95% CI: 0.735, 1.562). At clarification (A29) the company submitted additional detail for the subgroup analyses in the

MIRASOL trial, which included interaction effects for OS ($p=0.0057$), which suggested a statistically significant effect of the primary platinum free interval on the treatment effect on OS.

Conversely, in the MIRASOL trial, PFS_{INV} results were comparable between subgroups according to primary platinum-free interval: those with an interval of > 6 months ($n = 305$), showed a PFS_{INV} HR of 0.62 (95% CI: 0.482, 0.802) and those with a primary platinum free interval ≤ 6 months ($n = 147$) had a HR of 0.68 (95% CI: 0.472, 0.977); the interaction effect was $p=0.6417$.

Primary platinum-free interval (≤ 6 months, > 6 months) was not measured in the FORWARD-1 trial. The subgroup analysis of platinum-free interval (≤ 3 months, > 3 months) in the FR α high population from FORWARD-1 suggested there was [REDACTED] effect on OS or PFS_{BICR} .

Clinical advice to the EAG indicated that it was plausible that a longer platinum free interval would lead to a better response to treatment. Noting that a shorter primary platinum-free interval suggests the disease was chemotherapy resistant, and people may therefore have a poorer response to any treatment. Nevertheless, given the inconsistency in the data and lack of adjustment at the alpha level for multiple comparisons, the EAG considered the impact of primary platinum free interval to be unclear at this stage and should be interpreted with caution.

In the economic analysis, the subgroup analysis results for people with a primary platinum-free interval of > 6 months had a large impact on estimates of cost-effectiveness ([REDACTED] [REDACTED]). See Section 5.2.4.1 for details.

Positive BRCA status in the MIRASOL trial yielded a more favourable hazard ratio of OS for mirvetuximab (HR: 0.42, 95% CI: 0.237, 0.759) vs. chemotherapy. Whereas in the negative or unknown BRCA status group, the HR was 0.73 (95% CI: 0.582, 0.928); although the EAG noted that sample size was low ($n = 65$ positive; $n = 388$ negative or unknown). The EAG's clinical expert advised that people who are BRCA positive tend to be more chemotherapy-sensitive due to the role of BRCA in DNA repair pathways and tend to have a better prognosis, which may explain this trend in the data. The interaction effect suggested that this effect was borderline ($p=0.0592$) for OS (clarification A29). Whereas the interaction effect for PFS_{INV} was statistically significant ($p=0.0223$), suggesting that BRCA status may indeed modify the treatment effect of mirvetuximab versus chemotherapy (clarification A29). However, the EAG expressed caution in

interpreting these results on account of the small sample size and lack of adjustment at the alpha level for multiple comparisons. Positive BRCA status was not measured in the FORWARD-1 trial so the EAG could not determine the pattern of results across trials. Economic analysis demonstrated that using the subgrouping according to BRCA status had limited impact on the economic analysis (clarification B17).

3.3.9. Adverse effects

Overall, the safety data reported by the company for the three trials showed a similar overall risk of adverse events for mirvetuximab and the pooled chemotherapy arms. In MIRASOL²⁶, the vast majority of participants in both arms experienced at least one adverse event related to the study drug (88% receiving mirvetuximab and 81% receiving chemotherapy). Close to a third of people in each arm experienced at least one adverse event related to the study drug that was Grade 3 or above (27% receiving mirvetuximab and 37% receiving chemotherapy), though in only a minority of participants were these considered to be serious (8% in both arms). A similar number of people in both arms discontinued treatment due to adverse events related to treatment (9% and 8% in the mirvetuximab and chemotherapy arms, respectively). No one in the mirvetuximab arm was reported to have died from an adverse event related to treatment compared to one person in the chemotherapy arm (reason for death not reported). However, the MHRA assessment⁷ highlighted that pneumonitis was a risk of treatment with mirvetuximab and that two people in the trial died due to respiratory failure (one with grade 1 pneumonitis and one without pneumonitis).

As stated in Section 3.2.5, overall safety data from FORWARD-1²⁷ for the re-scored population wasn't reported in a comparable way to the data from MIRASOL. However, comparison with overall safety data for the high FR α expression population reported in the FORWARD-1 CSR showed comparable findings. The results of the company's pairwise meta-analysis (Section 3.3.11) showed comparable risk across various categories and types of adverse events between the two trials. The risk of adverse events with mirvetuximab in SORAYA (as reported in the company's clarification response) was also comparable.

As stated by the company, the evidence submitted demonstrated that mirvetuximab was associated with an increased risk of eye disorders, while chemotherapy was associated with an increased risk of haematological events. Clinical expert advice to the EAG was that oncologists were experienced in dealing with haematological adverse events associated with chemotherapy and they would expect there to be a learning curve for handling eye disorders if mirvetuximab

was accepted. Guidance on the use of mirvetuximab by the MHRA⁷ recommends assessments for eye conditions before and during treatment with mirvetuximab, in addition to the routine use of eye drops in all patients. The MHRA guidance also specifies that people should be monitored for pulmonary signs of pneumonitis and peripheral neuropathy

The CS stated that mirvetuximab was associated with a reduced risk of ascites and bowel obstructions in comparison with chemotherapy. The EAG did not consider that the safety evidence in the CS was clearly in support of this statement and, at clarification (A30), offered the company the opportunity to provide further evidence or rationale for this claim. The company response stated that a reduced risk of bowel obstruction may be experienced indirectly through a reduction in tumour size. They also cited data for the abdominal/gastrointestinal symptom subscale of the EORTC QLQ-OV28. The EAG wasn't convinced by this evidence: firstly, safety evidence did not show a difference in the risk of bowel obstruction with mirvetuximab compared to chemotherapy. Secondly, there was no clinically meaningful difference in scores on the abdominal/gastrointestinal symptom subscale EORTC QLQ-OV28 when using the standard MCID (as opposed to the 'less stringent' threshold selected by the company). Overall, while there were some limitations in the evidence base, the EAG did not consider there to be convincing evidence that mirvetuximab resulted in a reduced risk of bowel obstruction or ascites.

The EAG examined the risk of adverse events associated with each of the chemotherapies pooled in MIRASOL using the separated data provided in the CSR. The EAG was aware of evidence⁴⁷ that has identified a different safety profile for these chemotherapies. Evidence for MIRASOL did not demonstrate a major difference in the risk of adverse events between chemotherapies; PLD appeared to have an improved safety profile compared to paclitaxel and topotecan, which compared similarly. However, there was inconsistency in this across AE outcomes and between trials and so, overall, the EAG did not identify any consistent difference in safety between the chemotherapies that would have a major impact on the generalisability of the trial results to clinical practice. This was the case even when considering that participants who received topotecan in the trial would, in the NHS, likely receive paclitaxel or PLD.

3.3.10. Real-world evidence

The company did not present any real-world evidence for the clinical effectiveness of mirvetuximab or its comparators. Real-world evidence was excluded from the company's SLR.

3.3.11. Pairwise meta-analyses

In response to clarification, the company presented a pairwise meta-analysis combining results for OS, PFS and safety outcomes from MIRASOL²⁶ and the re-scored population (FRα expression level based on the PS2+ scoring method) from FORWARD-1²⁷. The company stated that it considered the analysis to be feasible though did not report any detail of the methods used to determine this and whether any differences in study methods or results were noted between trials. The EAG would have preferred to see a feasibility report detailing the random and/ or fixed effects model used, assessments of heterogeneity between and/ or within the trials, and consistency in outcome measures across trials.

The OS analysis used the final MIRASOL September 2024 data-cut while PFS relied on the October 2023 data-cut from MIRASOL (this aligned with the data-cut used in the 'stress test' analyses for PFS). For both comparisons there was only one FORWARD-1 data-cut. The EAG noted inconsistency in the reporting of the re-scored FORWARD-1 OS outcome between Table 8 of the CQ response and 2.3.2 of the CQ response, which led to uncertainty in the data used in the analysis.

For the pooled PFS_{INV} outcome, mirvetuximab showed a statistically significant [REDACTED] reduction in the risk of tumour progression or death compared to chemotherapy with a HR of [REDACTED]

[REDACTED] Pooled OS showed a statistically significant, [REDACTED] reduction in the risk of death in participants randomised to mirvetuximab with a HR of [REDACTED]

[REDACTED] The EAG noted that this indicated a similar direction and magnitude of effect and a stable trend toward improved OS and PFS across studies in favour of mirvetuximab.

It was difficult for the EAG to determine whether the results of the pairwise meta-analysis were robust given poor reporting of the methods used and the data inconsistency identified. The EAG was unclear why pooled data from the trials were not reported in full in the original CS, nor why these were not considered for inclusion in the company's economic model.

3.4. Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

An indirect treatment comparison was not presented by the company as direct evidence for the comparison of interest was available.

3.5. Critique of the indirect comparison or multiple treatment comparison.

Not applicable.

3.6. Additional work on clinical effectiveness done by the EAG

The EAG created KM curves to display the relative effectiveness of mirvetuximab and chemotherapy side by side for all three clinical trials using IPD data provided by the company at clarification; and using MIRASOL IPD the comparative effects of pre-assigned chemotherapy in the mirvetuximab arm vs the three chemotherapy regimes. These curves are reported in Section 3.3 to support the discussion of the trial results.

3.7. Conclusions of the clinical effectiveness section

The EAG considered that the company's SLR was of reasonable quality and likely to have identified all key mirvetuximab and comparator studies within the eligibility criteria that the company used. Overall, the EAG considered that the company submission was consistent with the NICE scope for the appraisal, although questioned the exclusion of the FORWARD-1 (re-scored population) and SORAYA trials from the CS.

The EAG generally considered MIRASOL to be a well-conducted RCT, although highlighted some uncertainties related to the generalisability of the trial to clinical practice. In particular, the EAG considered that the median age of participants in MIRASOL was likely to be younger than the target population and excluded some people who may have poorer treatment response (ECOG2) or an increased risk of side effects with mirvetuximab (ocular and lung disorders).

The EAG also recognised that research into FR α expression and ways of testing for this in clinical practice is ongoing. At the time of the appraisal, there was no diagnostic accuracy data to understand how accurate the Ventana assay test was for identifying people who would be eligible for treatment with mirvetuximab. Without this, if an alternative assay were adopted for identifying FR α expression within the NHS, there would be a risk that the population deemed eligible for mirvetuximab treatment could differ from the population studied in the clinical trials. Moreover, the preferred timing for testing for FR α was uncertain and could influence the number of people who would be tested or could meet the threshold for treatment (if FR α expression changes over the disease course). The EAG considered these to be secondary issues to this appraisal.

MIRASOL also included participants who received chemotherapy in the trial and went on to receive subsequent treatment with mirvetuximab (7.1%). This was not in line with clinical practice, however, the EAG were satisfied that the impact of subsequent treatment did not significantly impact the results as the company used appropriate modelling (RPSFTM) to adjust for subsequent use of mirvetuximab in the chemotherapy arm.

The EAG also received clinical advice that topotecan was rarely given in UK clinical practice on account of its toxicity and burdensome regime, yet 53 (23.5%) participants received topotecan in the MIRASOL trial. Despite this, the EAG found topotecan to have similar effectiveness and safety compared to the chemotherapies in the trials and therefore are satisfied this does not undermine the generalisability of the evidence to UK clinical practice.

Mirvetuximab was more beneficial vs chemotherapy in PFS and OS after a follow-up of two to three years. This was in spite of very few participants (5.7%) in MIRASOL or chemotherapy (0.0%) experiencing a complete response to treatment. The benefits of mirvetuximab were consistent across MIRASOL and FORWARD-1 (re-scored high FR α population). The results for SORAYA, whilst a single arm trial, appeared to show the same pattern of effect for mirvetuximab. In MIRASOL, the median time to progression with mirvetuximab was 5.59 months vs 3.98 with chemotherapy (investigator-assessed). While the EAG considered this difference to be small, it did convey a survival benefit, with a median of three additional months of life (median OS 16.85 months for mirvetuximab and 13.34 months chemotherapy). The EAG was unsure to what extent treatment with mirvetuximab had a clinical benefit for patients' quality of life; while there was a trend for mirvetuximab to be associated with an improvement in HRQoL across some domains of the tools used, these were not always over the MCID and/or statistically significant. Mirvetuximab had a comparable risk of AEs to chemotherapy, however the types of AEs experienced by participants were different to those typically experienced during treatment with chemotherapy. Clinical advice to the EAG was that oncologists would need to become accustomed to monitoring and managing these AEs.

4. COST-EFFECTIVENESS

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission (CS). Section 4.1 focuses on the company's review of the cost-effectiveness evidence and Section 4.2 focuses on the company's economic evaluation.

4.1. Critique of the review of cost-effectiveness evidence

The company undertook three systematic literature reviews (SLRs) to assess the cost effectiveness of all currently available therapies used to treat patients with previously treated, platinum-resistant/refractory epithelial ovarian, primary peritoneal, or fallopian tube cancers. The first SLR was for cost effectiveness (see Table 16); the second was for health-related quality of life (Table 17) and the third SLR was for costs and resources (see Table 18).

Overall, the searches conducted for the three SLRs appeared to be reasonable and the methods described as being used in the selection and extraction of evidence appeared robust. However, the EAG identified multiple issues with the way that studies were selected for inclusion (e.g. studies not identified that would reasonably have been expected to according to the methods used) and a lack of coherent or justifiable rationale for the way that studies were selected for inclusion in the company's model. This meant that the EAG lacked confidence that the company had selected the most appropriate evidence for inclusion in the model.

The company's search for published economic evaluations identified 15 studies; only one of these was considered to be of relevance to the decision problem by the EAG: Zhu 2024⁴⁸, which evaluated the cost-effectiveness of mirvetuximab vs IC chemo in a US setting. This independent evaluation used an earlier datacut of MIRASOL²⁶ (March 2023 vs. Sept 2024 in the CS) and a US perspective, but nevertheless estimated similar incremental QALYs when the severity modifier was removed (0.90 vs ■■■). None of the evaluations identified looking at PROC more broadly were in a UK setting.

Only three studies were identified in the SLR for health-state utility values (HSUVs), none of which were used by the company in the economic model. To justify their exclusion, the company referenced two studies^{49,50}, though these were not identified by the SLR and their provenance was unclear. The study chosen by the company for inclusion in the economic model (Wysham 2017⁵¹) was instead taken from the SLR of economic evaluations, which was not a primary utility study. The data used in this evaluation came from a primary study

(Havrilesky 2009)⁵², which was not identified by the company's HSUV SLR. The company did not provide a rationale as to why the original study was not identified. In general, the company did not draw upon the SLR on economic evaluations to identify utility data that had been used in previous models, which would have been useful to identify further studies that may have been missed. Table 13 in the company's clarification response provided a comparison of utility data from a subset of papers identified in the SLRs for utilities, economic evaluations and a separate review of previous TAs; however, not all papers identified in these searches were presented in the table. Overall, the results of the SLR created uncertainty in the robustness of the methods used by the company to identify HSUV for the model. Furthermore, the method used by the company to determine which quality of life studies to consider for inclusion in the economic analysis was also unclear.

No previous NICE evaluations were identified in the company's searches for economic evaluations or HSUVs, which would appear to be a major omission. It was unclear why this was the case as the company list relevant HTA websites as having been searched. The CS drew on TA389 for precedent in a number of areas within the economic evaluation. TA389 investigated topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer and is therefore of high relevance as it is the TA under which the comparators in this appraisal were appraised. In addition, there are a number of earlier-line TAs which could inform evaluation of HSUVs (e.g. recently TAs 1007, 962 and 946).

Nine studies were prioritised for providing healthcare resource use (HCRU) data, from the original 112 identified. UK studies were prioritised for inclusion; which the EAG agreed with. The studies identified included the HTA reports for TA389⁵³, TA389¹⁴, TA946⁵⁴, TA673⁵⁵ and TA962⁵⁶. None of the other studies reported relevant information on HCRU (many looked at HCRU related to initial surgery following diagnosis). TA1007⁵⁷ was not included, the reason for this was unclear as it was published within the date range for the update search (20 November 2024). The results of the search were not referenced in the CS and the company instead sporadically selected references to support their HCRU assumptions (vial sharing from an appraisal in breast cancer [TA862⁵⁸], TA285⁵⁹ which was an appraisal from 2013 in platinum-sensitive OC for HCRU, TA389¹⁴ for administration cost codes, TA1007⁵⁷ for AE cost codes). This led to the need for the EAG to conduct additional checks with clinical experts around HCRU inputs.

Table 18: Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness evidence

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix E. 1.1	The searches were clearly presented with a good range of sources used. The company used a range of cost effectiveness search terms but it was not clear whether this was a tested search filter. It did not appear to be the one from SIGN²⁴ or from Canada's Drug Agency.⁶⁰ The company searched for HTA reports in a range of sources; it is unclear why these reports were not identified during screening. The company did not include subject heading searches for drug resistance, fallopian tube cancer or peritoneal cancer in their searches (although keyword searches for this were used); it is possible that this could have resulted in missing some relevant records, although the EAG have not tested this.
Inclusion criteria	Appendix E.1.2.1	The inclusion/exclusion criteria were generally appropriate.
Screening	Appendix E.1.2.3	The CS stated that both title/abstract and full-text screenings were conducted independently by two reviewers based on predefined eligibility criteria. Discrepancies were resolved through discussion, with a third reviewer available for arbitration when necessary.
Data extraction	Appendix E.1.2.4	Data extraction was conducted appropriately using MS Excel. It was performed by one reviewer and validated by a second independent reviewer to verify data accuracy. Details of how discrepancies were resolved were not clear.
QA of included studies	Appendix E.1.2.5	The company used the Drummond checklist ⁶¹ . Quality assessment was performed by one reviewer and quality checked by a second independent reviewer.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment

Table 19: Summary of EAG's critique of the methods implemented by the company to identify health related quality of life data

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix F. 1.1	The searches were well conducted and clearly presented with a good range of sources used. The company used a range of cost effectiveness search

		terms but it was not clear whether this was a tested search filter. It did not appear to be the one from Canada's Drug Agency.⁶⁰ The company searched for HTA reports in a range of sources; it is unclear why these reports were not identified during screening. The company did not include subject heading searches for drug resistance, fallopian tube cancer or peritoneal cancer in their searches (although keyword searches for this were used); it was possible that this could have resulted in missing some relevant records, although the EAG did not test this.
Inclusion criteria	Appendix F.1.2.1	The inclusion/exclusion criteria were generally appropriate.
Screening	Appendix F.1.2.2	The CS stated that both title/abstract and full-text screenings were conducted independently by two reviewers based on predefined eligibility criteria. Discrepancies were resolved through discussion, with a third reviewer available for arbitration when necessary. The primary utility study used in the economic model⁵² was not included in either the included or excluded studies list, which was a major omission and raised doubt as to the quality of the SLR.
Data extraction	Appendix F.1.2.3	Data extraction was conducted appropriately for primary utility studies using MS Excel. It was performed by one reviewer and validated by a second independent reviewer to verify data accuracy. Details of how discrepancies were resolved were not clear. Data extraction was not performed for economic evaluations that included utility estimates, and the primary references used within these were not checked. This was a major omission.
QA of included studies		Not reported.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment; SLR, systematic literature review

Table 20: Summary of EAG's critique of the methods implemented by the company to identify healthcare resource use and costs

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix G. 1.1	The searches were well conducted and clearly presented with a good range of sources used. The company searched for HTA reports in a range of sources; it is unclear why these reports were not identified during screening.

		The company did not include subject heading searches for drug resistance, fallopian tube cancer or peritoneal cancer in their searches (although keyword searches for this were used); it was possible that this could have resulted in missing some relevant records, although the EAG did not test this.
Inclusion criteria	Appendix G. 1.2.1	The inclusion/exclusion criteria were generally appropriate.
Screening	Appendix G. 1.2.2	Both title/abstract and full-text screenings were conducted independently by two reviewers based on predefined eligibility criteria. Discrepancies were resolved through discussion, with a third reviewer available for arbitration when necessary. TA1007 was missing from the writeup of the SLR. The reason for this was unclear.
Data extraction	Appendix G. 1.2.3	Data extraction was conducted appropriately using MS Excel. It was performed by one reviewer and validated by a second independent reviewer to verify data accuracy. Details of how discrepancies were resolved were not clear.
QA of included studies	Appendix	Not reported.

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; QA, quality assessment; SLR, systematic literature review

4.2. Critique of the submitted economic evaluation

4.2.1. NICE reference case checklist

Table 21: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	Direct health effects for patients only, which was appropriate for this condition
Perspective on costs	NHS and Personal Social Services	In line with reference case
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	In line with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	40.8 years. At this point, fewer than ■ of patients remained alive in both arms
Synthesis of evidence on health effects	Based on systematic review	Additional relevant data on HRQoL shared during the clarification stage. The company did not provide a clear rationale for excluding some relevant

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]: A Single Technology Appraisal

		evidence (e.g. the FORWARD-1 ²⁷ re-scored population) or for selecting certain health-related quality of life data over other available sources. Overall, the company's approach lacked a systematic and transparent justification for the inclusion or exclusion of evidence.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	EQ-5D-5L data from the MIRASOL ²⁶ trial were mapped to EQ-5D-3L for the mirvetuximab arm. For the chemotherapy arm, utility values were sourced from the literature. However, these values lacked face validity, and the source ⁵² used was not consistent with the NICE reference case
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	In line with reference case for data taken from MIRASOL. For Havrilesky 2009, ⁵² utilities were derived from a time trade-off exercise using vignette-based health states valued by a mixed sample of patients and members of the general public
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	In line with the reference case for utilities from MIRASOL used for mirvetuximab as EQ-5D-5L responses collected from participants were mapped onto the EQ-5D-3L UK value set. However, utility values used in the chemotherapy arm weren't representative of the UK population
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the people having the health benefit, except in specific circumstances	In line with the reference case
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Broadly in line with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	In line with reference case

Abbreviations: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

4.2.2. Model structure

The company used a partitioned survival analysis (PartSA) structure that extrapolated DoT, PFS and OS independently. Given the high level of maturity of the observed data, this was considered appropriate by the EAG. The company stated that a key reason for the selection was the ability to incorporate time-dependency in the post-progression state in a straightforward manner. The EAG noted that a PartSA did not directly model survival in the post-progression state; instead relying on the OS and PFS extrapolations selected to inform post-progression. As noted in Section 4.2.5.3, the distributions chosen by the company led to assumptions that were not considered credible by the EAG's clinical experts in terms of post-progression survival gain.

The company extrapolated outcomes for pooled IC chemotherapy for PFS and OS but predicted separate DoT for each of the components of the chemotherapy comparator arm, given the differences in administration frequency.

The impact of AEs was only captured pre-progression. The omission of AEs post progression was considered unlikely to have a major impact on results as the same types of treatments were expected to be received after mirvetuximab and chemotherapy in practice and differences in AE frequency had limited impact on modelled outcomes pre-progression [REDACTED] QALY loss associated with AEs for mirvetuximab and pooled chemotherapy, respectively.

The company used a 1-week cycle length and applied a half-cycle correction for OS and PFS.

4.2.3. Population

The population included in the economic model was taken from the MIRASOL trial and aligned with the licensed population in the SmPC⁷.

As noted in Section 3.2.2, there were some areas where the MIRASOL trial may not be considered generalisable to UK practice. In particular, participants in MIRASOL were younger than would be expected, people with ECOG 2 were excluded, one clinical expert suggested there was a higher proportion of participants who were BRCA positive than typically expected in UK clinical practice, and more patients in clinical practice would be expected to have been previously treated with PARP inhibitors. Overall, the EAG judged that OS in MIRASOL may be somewhat optimistic compared to the target population. However, the forest plot supplied by the company at clarification indicated that the impact of this issue on relative effectiveness may be limited (Figure 2 and Figure 3 in CQs). Accordingly, the impact on cost-effectiveness estimates

was not expected to be large (although it was noted that the bias was in favour of mirvetuximab). However, the company base case assumed a starting age of 59.2 years, which was younger than the MIRASOL population (62.8 years), and younger still than that seen in routine NHS practice. To ensure consistency with the source of clinical effectiveness data, the EAG used the MIRASOL mean age in its base case but also explored an older starting age in scenario analysis.

4.2.4. Interventions and comparators

The intervention considered in the analysis was mirvetuximab 6 mg/kg (AIBW) intravenous (IV) infusion on Day 1 of each treatment cycle Q3W until disease progression or unacceptable toxicity. This was in line with MIRASOL and the draft SmPC.

The economic analysis assumed that the split of chemotherapies received aligned with the MIRASOL trial:

- 40.7% of patients receive paclitaxel
- 35.8% of patients receive PLD
- 23.5% of patients receive topotecan

Discussion relating to the appropriateness of the dosing schedule for these chemotherapies is available in Section 3.2.4. One clinical expert estimated that in practice, approximately 60% of patients would receive paclitaxel vs. approximately 40% receiving PLD. Another clinical expert expected more patients to receive PLD than paclitaxel due to administration being less frequent and patients not losing their hair with PLD, whereas they do with paclitaxel. The EAG was advised that patients now rarely receive topotecan on account of its toxicity and burdensome regime (Section 3.2.4). The impact on effectiveness of using different proportions of chemotherapies than would be expected in the target population was unknown; clinical expert advice to the EAG was that this would not be expected to be large in this indication, considering that chemotherapy treatments have limited effectiveness.

The EAG base case assumed that 46.8% of patients would receive PLD and 53.2% paclitaxel (3 weeks out of 4) with no impact on effectiveness.

The cost per 4-weekly cycle for PLD was somewhat higher than for the two other chemotherapy regimens (£604 for 4 weeks vs £81 for paclitaxel and £225 for topotecan (5 days Q3W); all prices at list price excluding wastage and missed doses).

4.2.5. Treatment effectiveness and extrapolation

4.2.5.1. Overall Survival

The company used OS data from the latest data cut of the MIRASOL²⁶ trial (September 2024), with median follow-up of 30.5 months. At this cut-off, median OS was 16.9 months for mirvetuximab (n=227) and 13.3 months for pooled chemotherapy (n=226). The KM curves demonstrated increasing censoring beyond month 24, especially in the mirvetuximab arm. The company noted that the final drop in the KM curve to zero for mirvetuximab at month 44 was driven by a single patient remaining at risk. The EAG agreed that the KM tail should be interpreted with caution due to limited numbers at risk in later time points. The company presented AIC/ BIC data for the entire population in their base case, and within an appendix presented AIC/BIC for a subset of the population before heavy censoring. The EAG did not agree with the use of AICs/BICs presented for only a subset of the data in the appendices, as these statistics should be based on the full dataset to ensure robust model selection. Assessing fit based on a selected part of the data could bias model selection in favour of those distributions that perform better in this restricted part of the data but give less plausible projections beyond observed data.

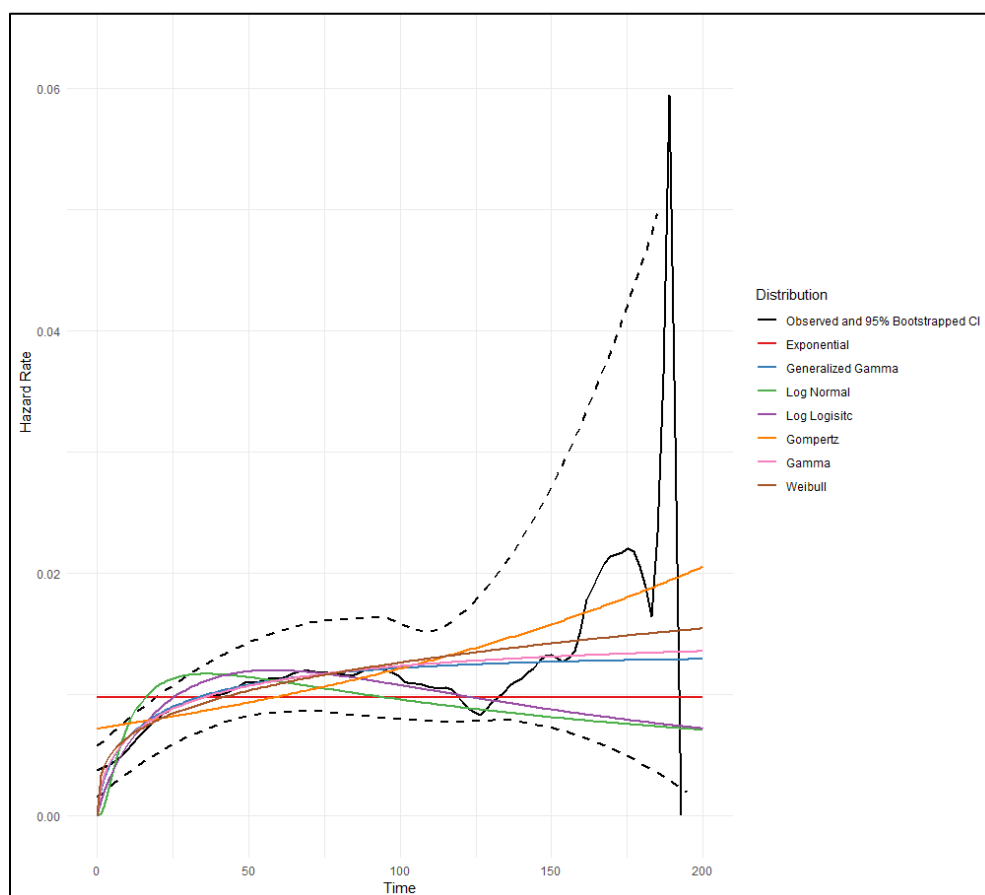
The company considered that proportional hazards could not be assumed, supporting the use of independent models (see Section 3.2.5.1 for further details). The EAG agreed with this conclusion and considered the use of independent models for OS to be consistent with TSD 14 guidance⁶², recommending that when log-cumulative hazard plots are not parallel, proportional hazards cannot be assumed and independent curves should be fitted.

The company fitted the following parametric models to both arms: exponential, Weibull, log-normal, log-logistic, Gompertz, gamma, and generalised gamma. Model selection was based on statistical fit (AIC/BIC), visual inspection, and input from clinical experts consulted by the company. For mirvetuximab, the log-logistic distribution was selected for the base case. The company argued that this distribution implied a hazard function consistent with the observed smoothed hazard (initially increasing then decreasing hazard) and predicted 10% survival at 5-years within the 8 -12% range provided by their expert. The exponential, gamma, and

generalised gamma distributions were ruled out due to implausible hazard shapes. No details were provided on whether this was obtained using robust and structured expert elicitation methods.

The EAG disagreed with the company's exclusion of the gamma and generalised gamma models, noting that both provided better statistical and visual fit to the observed data, including when compared with the smoothed hazard plot (Figure 7). The company's clinical expert also considered both distributions to be clinically plausible. Moreover, their long-term extrapolations aligned with the EAG's clinical experts' opinion that no patients would be expected to survive beyond 10 years in either the mirvetuximab or chemotherapy arms. The EAG considered the Gompertz and Weibull to be plausible models and tested them in a scenario analysis.

Figure 7: Smoothed hazard vs parametric survival models (OS) – mirvetuximab

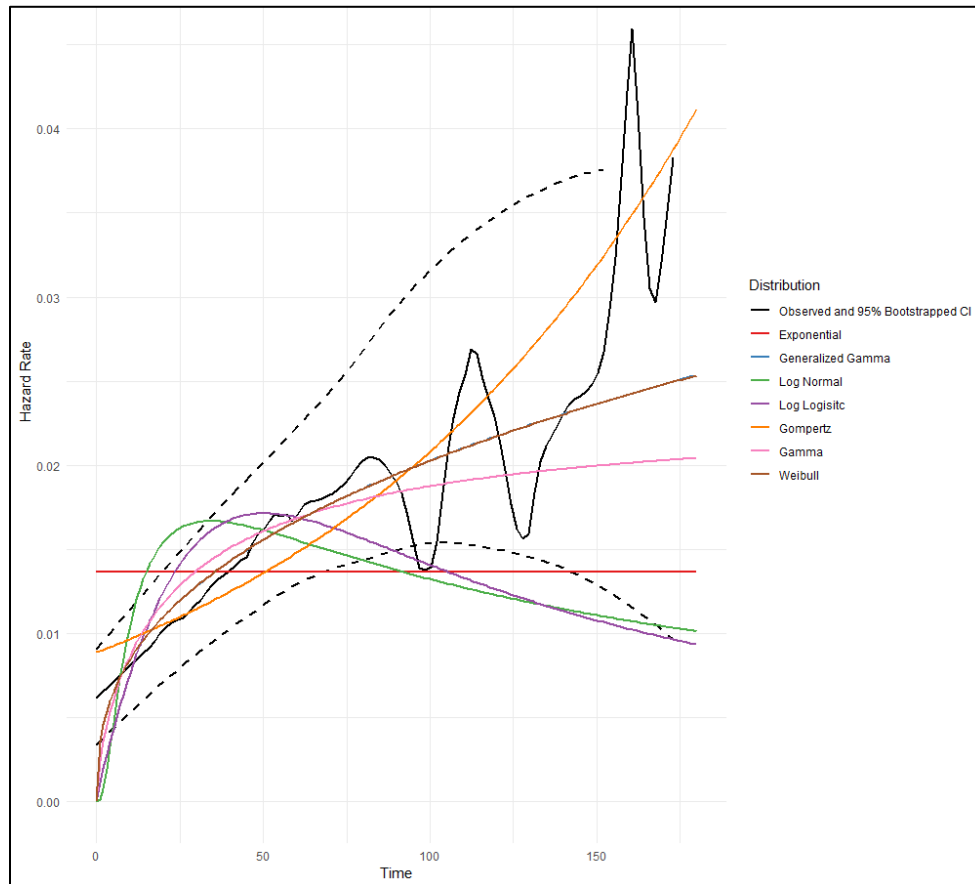


For pooled chemotherapy, the company selected the Weibull model based on the lowest AIC and BIC among distributions that were also considered clinically plausible (generalised gamma,

gamma, Weibull, and Gompertz). The Weibull distribution was also consistent with what the company's clinical expert expected, that long-term survival for chemotherapy patients would be 0-5% at 5 years and 0% at 10 years.

The EAG selected the gamma distribution as its base-case for pooled chemotherapy as it provided a good visual fit to the smoothed hazard plot (Figure 8) and generated survival estimates consistent with the company's and EAG's clinical expert estimation (1-5% at 5 years and 0% at 10 years). The log-normal and log-logistic distributions were tested in scenario analyses to explore the upper end of the expert range but were not favoured for the base case due to poor visual fit. Although the Weibull distribution did not align with the EAG clinical expert estimate of 1-5%, instead predicting that 0% would be alive at 5 years, it was still considered plausible and therefore explored in a scenario analysis. The EAG base case also incorporated adjusted RPSFTM-OS to mitigate the potential bias introduced by patients in the chemotherapy arm switching to mirvetuximab after progression.

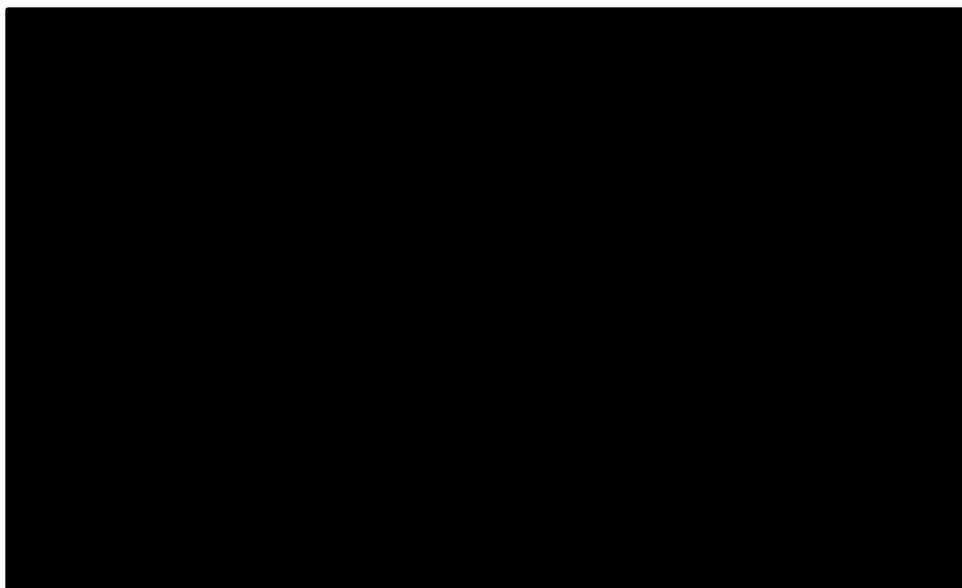
Figure 8: Smoothed hazard vs parametric survival models (OS) – chemotherapy



Note: generalised gamma distribution line is visually indistinguishable from the gamma distribution line in this plot, as both occupy the same position

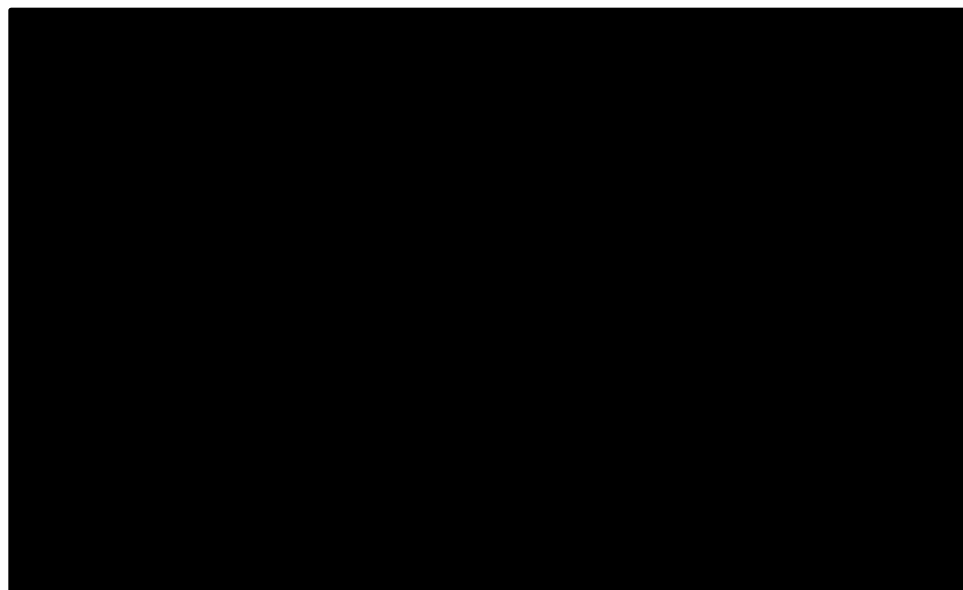
The company's base case assumed a continued improvement in the hazard ratio favouring mirvetuximab over time (Figure 9). The EAG considered that this assumption was implausible. Instead, the EAG's base case curve selection results in a HR initially decreasing before stabilizing to a constant HR between mirvetuximab and chemotherapy, which was considered more clinically plausible (Figure 10).

Figure 9: Treatment effect over time: company base case



Note: Figure and data can be found in Effectiveness_Calc sheet of the company's model.

Figure 10: Treatment effect over time: EAG base case, uses RPSFTM adjusted data



4.2.5.2. Progression Free Survival

The company used PFS data from the MIRASOL²⁶ trial (data cut-off: 26 September 2024), with a median follow-up of 28.4 months. Median PFS was 5.6 months in the mirvetuximab arm and 4.0 months in the pooled chemotherapy arm. The KM curves reached zero in both arms, suggesting complete event capture over the trial horizon.

As for OS, the company considered that proportional hazards could not be assumed (see Section 3.2.5.1 for further details). The company therefore adopted independent models for the base case, citing clinical differences between treatment mechanisms and aligning with the OS approach. The EAG agreed that the use of independent models for PFS was appropriate.

The company fitted exponential, Weibull, log-normal, log-logistic, gamma, generalised gamma, and Gompertz distributions to each arm. Statistical fit was assessed using AIC and BIC. For mirvetuximab, the log-normal distribution was associated with the best statistical fit, closely followed by the log-logistic and generalised gamma distributions. For pooled chemotherapy, the log-normal and generalised gamma distributions also had the best statistical fit. This was supported by the company's clinical experts, who agreed on the use of the log-normal distribution in both arms. Given that the KM curves reached zero in both arms, the EAG found this appropriate and validated those results with the EAG clinical experts but also tested the use of KM data directly in the model in scenario analysis given the almost complete PFS KM data.

4.2.5.3. Post Progression Survival

The EAG noticed that the majority of life year gains associated with mirvetuximab were concentrated in the post-progression stage, despite both trial arms receiving relatively similar subsequent therapies. In response to clarification questions, the company provided a rationale that lower tumour burden and improved tolerability during initial treatment with mirvetuximab could lead to improved post-progression outcomes. The EAG consulted two oncologists on this point, who had conflicting views on this point. The first expert considered that lower myelosuppression with mirvetuximab in pre-progression may reduce treatment breaks and improve tolerance of post-progression chemotherapy, potentially delaying further recurrence. The bystander effect was considered plausible (the release of the cytotoxic payload in alpha FR-positive cells potentially killing adjacent tumour cells lacking alpha FR expression), however they noted that the magnitude of any post-progression benefit from these assumed mechanisms was uncertain. The second expert considered it unlikely that this would meaningfully alter post-progression outcomes. The company also presented a statistical analysis showing a hazard ratio of 0.76 (95% CI: 0.603-0.971) for post-progression survival in patients initially randomised to mirvetuximab versus chemotherapy, supporting a post progression survival advantage.

While the EAG accepted that some post-progression benefit from prior treatment with mirvetuximab may be plausible, it was not convinced that this could explain close to [REDACTED] the incremental gains in PPS ([REDACTED]) compared to the PFS benefit ([REDACTED]). This

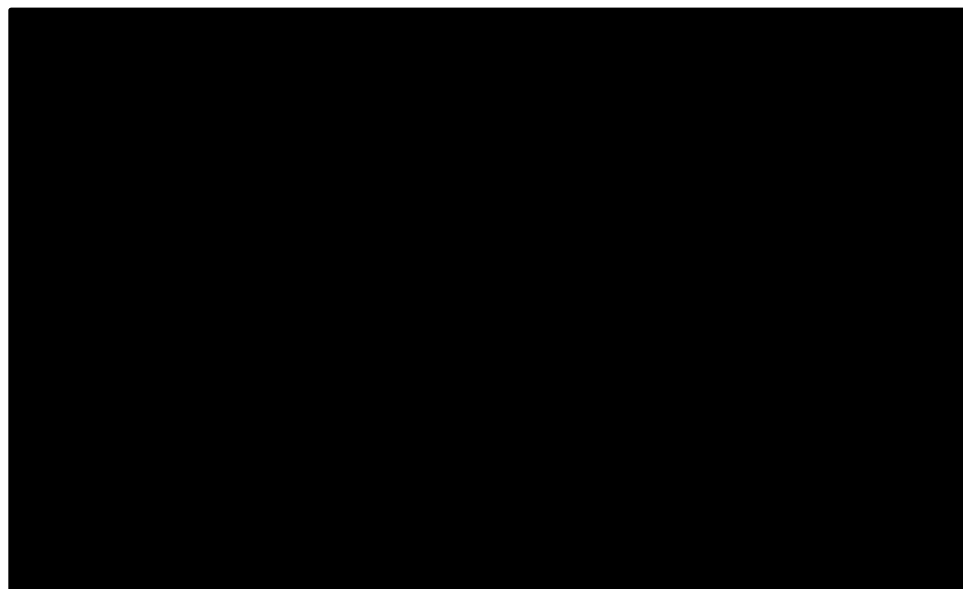
raised concerns that the model may be overestimating the true impact of mirvetuximab on survival. The EAG's base case estimated smaller incremental gains in PPS (■■■■■■■■■■), reflecting a more conservative assumption about post progression survival gains.

4.2.5.4. Duration of Treatment

DoT was based on KM curves from the MIRASOL safety population, adjusted by the proportion of patients receiving at least one dose to reflect the ITT population. This meant that patients who didn't receive any doses in MIRASOL had zero drug costs. The EAG also noted a difference between the median duration of treatment for mirvetuximab reported in the MIRASOL CSR and that presented in the company submission. Following clarification, the company explained that the way the CSR figures were calculated included an additional cycle after discontinuation to capture full drug exposure, while the figures in the submission did not. Instead, the economic model used treatment durations derived from IPD for the safety population. The EAG found this appropriate. The KM curves reached zero for all three chemotherapy agents, indicating complete follow-up. This resulted in the company using observed KM curves in the base case, which the EAG considered appropriate given the completeness of follow-up.

For mirvetuximab, the company selected an exponential distribution based on statistical fit. However, the EAG considered that this approach underestimated DoT, especially in the earlier part of the KM curve. The EAG therefore preferred an alternative approach that used the observed KM data up to 120 weeks, followed by exponential extrapolation. This avoided early underestimation of DoT and accounted for the fact that some patients in the mirvetuximab arm remained on treatment at the end of the trial. This is showed in Figure 11 below.

Figure 11: DoT by approach used



4.2.6. Health-related quality of life

EQ-5D-5L was collected in the MIRASOL²⁶ trial and mapped to EQ-5D-3L using the NICE DSU crosswalk algorithm. Utilities were estimated using a mixed-effects model with repeated measures. Treatment-specific values were applied in the company's base case: 0.737 and 0.655 for mirvetuximab in the pre- and post-progression states, and 0.500 and 0.400 for pooled chemotherapy, respectively. These values were drawn from MIRASOL (mirvetuximab arm) and partly from literature (chemotherapy arm).

The EAG had several concerns with the company's approach. First, the utilities assigned to post-progression survival for patients treated with mirvetuximab (0.655) exceeded those assigned to the pre-progression period for chemotherapy (0.500), which the EAG considered implausible and lacking face validity. Second, the assumption of a large difference in post-progression utilities (0.255) by treatment arm was not supported by clinical logic or the EAG's clinical expert advisors, as most patients would receive similar treatments after progression. Third, the source⁵² of the utility values used in the chemotherapy arm was based on a time trade-off exercise using vignette-based health states valued by a mixed sample of patients and members of the general public. These values lacked face validity compared with EQ-5D-5L and showed inconsistencies in results (e.g. higher utility for patients experiencing grade 3-4 AEs than for grade 1-2).

The company argued that utility values from the literature provided greater face validity in patients receiving chemotherapy as values from MIRASOL may have overestimated the quality of life of participants receiving chemotherapy because the EQ-5D questionnaire was administered at the start of each treatment cycle and so may not capture the impact of chemotherapy-related side effects. However, the EAG compared utilities from MIRASOL with those from trial OVA-301 (used in TA389¹⁴ to model the utilities for PLD for treating recurrent ovarian cancer), where EQ-5D was collected both at the start and end of each cycle and should therefore have captured the impact of chemotherapy on quality of life. Despite this, the pre- and post-progression utility values reported in TA389 (0.718 and 0.649, respectively) were similar to those from the chemotherapy arm in MIRASOL (0.706 and 0.625), suggesting that the timing of EQ-5D administration was not a meaningful source of bias. Given this, the EAG considered that treatment-specific utility values from MIRASOL were appropriate for the base case. These values showed a difference in quality of life between mirvetuximab and chemotherapy within health state that was considered more plausible. The MMRM adjusting for progression status and treatment allocation only (and not the model including the interaction between the two) was chosen for the EAG base case as, although goodness of fit statistics were not provided by the company, the direction of results in the model including interaction was unexpected (bigger benefit for mirvetuximab following progression), which may have been influenced by low sample size and high levels of missingness post progression. To test the impact of alternative plausible assumptions, values from TA389 were used in sensitivity analysis (Table 22).

As the EAG noted previously in Section 3.3.6, there was a substantial amount of missing EQ-5D data at later time points in MIRASOL. However, the proportion of missing questionnaires based on expected completions was similar across arms, reducing the risk of bias between the two arms. The similarity of values from TA389 and MIRASOL also supports that this was unlikely to be a major source of bias, and that MIRASOL trial data were the most appropriate source of utilities for the base case.

Table 22: Health state utilities used

Health state	Treatment arm	Company base case (mirv: MIRASOL, chemo: Havrilesky 2009 vignette)	EAG base case (MIRASOL)	EAG scenario (TA389)
Pre-progression	Mirvetuximab	0.737	0.737	0.718
	Pooled chemotherapy	0.500	0.706	0.718
Post-progression	Mirvetuximab	0.655	0.655	0.649
	Pooled chemotherapy	0.400	0.625	0.649

Abbreviations: EAG, External Assessment Group

4.2.7. Adverse events

The EAG included both the cost and disutility of adverse events, compared with the company's inclusion of costs only. Both base cases used Grade 3/4 adverse events occurring in $\geq 5\%$ of patients, based on the average number of events per person. The EAG considered the company's assumption of a 4-week duration for ocular adverse events to lack face validity. Clinical experts confirmed that events such as cataract, blurry vision, and keratopathy were unlikely to resolve within 4 weeks, given the need for referral to ophthalmology and associated waiting times, unlike anaemia or thrombocytopenia which oncologists commonly manage without referral. Therefore, the EAG doubled the assumed duration of ocular adverse events to 8 weeks.

The EAG also considered the company's disutility estimates for ocular adverse events to be inconsistent with clinical expectations. For example, the company assumed disutilities of 0.008 for keratopathy, 0.005 for blurry vision, and 0.14 for cataract. Clinical expert advice to the EAG was that cataracts would not be fixed until surgery, which often incurs a long wait list, and that vision blurring / keratopathy can be painful and would have more of an impact and be more difficult to resolve. The EAG therefore explored in a scenario analysis using a disutility of 0.16 for ocular adverse events, consistent with the value used in a previous submission (NICE ID6212). The EAG acknowledged that the original source of this value was the mean utility loss in severe dry eye reported by Schiffman 2003⁶³. This source was relatively old, meaning that

treatment patterns may have changed since publication, and the scores were elicited using TTO from 57 patients with the condition rather than from a representative sample of the general public valuing health states. The EAG therefore considered that this value was likely to overestimate the impact. The true value was therefore likely to lie somewhere between the company's estimates and the 0.16 value used in the scenario analysis.

The EAG recognised the potential for double counting when applying the company AE disutilities on top of values from MIRASOL, as some AE impact may already be captured in the treatment covariate. However, this risk was likely mitigated in MIRASOL due to the substantial amount of missing EQ-5D data, which was plausibly correlated with severe AEs.

4.2.8. Resources and costs

The company included a range of direct medical costs in the economic model, including drug acquisition, administration, health state resource use, adverse event management, monitoring, and end-of-life care. BNF and eMIT list prices were used unless otherwise stated. All oral treatments were appropriately costed on a per pack basis, consistent with NICE guidance.

Drug acquisition costs were based on publicly available BNF and eMIT list prices. The mirvetuximab patient access scheme discount was applied for the base case. Confidential prices did not apply for any of the other treatments considered in the model, and therefore no cPAS appendix was required to accompany this report. Clinical experts advised that paclitaxel was often administered on days 1, 8, and 15 of a 28-day cycle, followed by a treatment break to allow for bone marrow recovery, meaning it may be used less frequently in practice. However, the total cost of paclitaxel (including drug acquisition and administration) over the full treatment duration was [REDACTED] representing only [REDACTED] of the [REDACTED] incremental cost in the model. Given the relatively small cost impact and uncertainty around any effect on clinical outcomes, no adjustment was made to the model to account for this.

4.2.8.1. Relative dose intensity and wastage

The EAG preferred the use of a cycle-specific relative dose intensity (RDI) approach, which separately accounted for the proportion of patients receiving treatment each cycle and the average RDI among those treated. This allowed for a more accurate estimation of drug usage and wastage by explicitly incorporating missed doses, reduced dosing and time dependency. While the overall impact on results was limited, the EAG considered this more appropriate than using a single average RDI value.

4.2.8.2. Vial sharing

The EAG assumed no vial sharing for mirvetuximab, consistent with previous submissions for novel therapies in this disease area. Clinical experts to the EAG were uncertain about how plausible it would be to use vial sharing for mirvetuximab, particularly for smaller units as it would not be reasonable to delay treatment so that vials could be shared.

For chemotherapy, clinical experts advised that these agents were used across multiple indications with varying doses, making vial sharing more feasible. They advised that treatments were often provided pre-made and dose banded for the most commonly used doses. The EAG therefore assumed 50% vial sharing for chemotherapy agents.

4.2.8.3. Subsequent therapy

The company included mirvetuximab as a subsequent treatment for 9% of patients in the chemotherapy arm who received a subsequent therapy, based on crossover in MIRASOL²⁶ (see Section 3.3.7 for details). However, the EAG considered that this was inappropriate, as mirvetuximab was not available as a post-progression treatment option within the NHS for this population. The company then provided a scenario analysis using the RPSFTM to adjust for crossover, which showed a small QALY difference versus the company base case (■■■■■). The EAG considered that this was appropriate (see Section 3.3.7) and excluded the cost of mirvetuximab post progression in both arms and incorporated RPSFTM-adjusted survival in its base case.

4.2.8.4. Cost of testing

The company assumed that all patients receiving mirvetuximab would incur FRα testing costs at model entry. Based on MIRASOL data showing a 32% positive rate for eligible patients, approximately ■■■■■ tests were required to identify one eligible patient. Using inflated costs for pathologist time ■■■■■ and consumables ■■■■■ the total cost per positive patient was estimated at ■■■■■.

The EAG considered that the company's FRα testing cost assumptions were reasonable for the base case. However, feedback from oncologists and testing experts indicated that testing at diagnosis would be beneficial, as it would allow FRα-targeted treatment opportunities to be identified early and that this could be implemented within the next 2-3 years. The EAG therefore included a scenario moving testing to diagnosis, as well as a scenario removing testing costs, in line with the NICE reference case.

4.2.8.5. Health state costs

The company included disease management costs for each health state, covering gynaecological oncology consultations and CT scans. Unit costs were sourced from NHS reference costs (2023/24)⁶⁴, and resource use frequencies were taken from NICE TA285 (2013)⁶⁵ for bevacizumab in platinum-sensitive advanced ovarian cancer, applied equally across arms.

The EAG initially had concerns about using frequencies from a relatively old source. Verifying this with clinical experts indicated that visit frequency depended on whether a patient was on or off treatment. Typically, they would see someone once monthly whilst on treatment and once every three months when off treatment. They also expected a CT scan once every three months if the person was on treatment, regardless of the line of treatment. This meant that the company's pre-progression frequency was broadly consistent with this expectation; however, post-progression frequencies required adjustment. To reflect clinical practice more accurately, the EAG assumed on-treatment frequencies for the average duration of post-progression chemotherapy and off-treatment frequencies for the remainder of post-progression survival.

4.2.8.6. Adverse events

The company included Grade 3+ AEs with $\geq 5\%$ incidence in MIRASOL²⁶, costed using NHS Reference Costs 2023/24⁶⁴ (fatigue from TA528⁶⁶, inflated). Costs for haematological AEs and cataract were weighted averages assuming CC score ≥ 2 and applied as one-off costs at model entry.

Additional ocular AE costs for mirvetuximab included pre-treatment exams, ophthalmologist visits, and steroid eye drops, assuming a 4-week duration for Grade ≥ 2 events and ophthalmologist visits every other cycle. The EAG retained the company's overall approach but made two changes to the ocular AE assumptions in the mirvetuximab arm. First, the duration of Grade ≥ 2 ocular AEs was doubled from 4 to 8 weeks, reflecting clinical expert opinion that events such as cataract, keratopathy, and blurred vision typically require longer to resolve. Second, the frequency of ophthalmologist visits for these events was increased from 0.17 per week (one visit every 6 weeks) to one every three weeks in line with the assumption for moderate keratopathy AE in ID6212.

The EAG also heard from oncologists that the company's costs for managing anaemia and neutropenia likely overestimated real-world costs. Anaemia was usually managed as a day

case, and neutropenia was also typically dealt with on a day-case basis, with hospitalisation required only in the uncommon scenario of febrile neutropenia or sepsis. Clinical experts further noted that fatigue was generally not managed with parenteral nutrition; instead, patients were encouraged to self-manage, with occasional referrals to occupational therapy and/or physiotherapy. Accordingly, the EAG revised the costs of anaemia and neutropenia to reflect day-case management and excluded the cost of fatigue.

4.2.9. Uncertainty

The company conducted both probabilistic and deterministic sensitivity analyses for most model parameters. Where available, standard errors were derived from source data; otherwise, a default range of $\pm 20\%$ of the base-case value was applied. Probabilities were modelled using beta distributions and costs using gamma distributions. The EAG considered that the company's approach was generally acceptable for characterising parameter uncertainty.

However, one limitation was identified: parameters related to patient characteristics were included in the PSA. As the model was cohort-based rather than an individual patient simulation, varying patients characteristics across PSA iterations implies that the underlying patient population changes between iterations, which was inconsistent with the model's structure. In its response to clarification, the company excluded those parameters from the PSA based on the EAG request.

4.2.10. Subgroups

As part of the scenario analyses, the company explored cost-effectiveness by primary platinum-free interval (PFI ≤ 6 months vs > 6 months), using subgroup-specific KM data and survival parameters (OS, PFS, DoT). All other model inputs were kept consistent with the base case. The company noted that subgroups from the MIRASOL trial were not powered and exploratory, and so results should be interpreted with caution. The EAG agreed with this; however, there was a clinical rationale for different prognosis in these groups, which some of the trial data supported (see Section 3.3.8), and a notable impact on the ICER, so the EAG included this in the scenario analysis.

The company also explored scenarios modelling BRCA and prior bevacizumab subgroups. Both scenarios had a relatively small impact on the ICER, with results broadly consistent with the overall population.

5. COST-EFFECTIVENESS RESULTS

The results presented in this report incorporate the PAS discount for mirvetuximab and eMIT or BNF prices for all other treatments. No other treatments have confidential cPAS

5.1. Company's cost-effectiveness results

5.1.1. Company's base case

The results reported by the company post-clarification are shown in Table 23 and Table 24. These assumed a 1.7x severity weighting. The deterministic and probabilistic results resulted in incremental cost-effectiveness ratios (ICERs) of £[REDACTED] and £[REDACTED] per QALY gained respectively. Excluding severity weighting resulted in an ICER of £[REDACTED] per QALY gained.

Table 23: Company's deterministic base-case cost-effectiveness results with and without severity weighting (x1.7) at clarification

	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs (x 1.7 weighting)	ICER (£/QALY) (x 1.7 weighting)
Mirvetuximab	[REDACTED]	[REDACTED]			-
Pooled chemotherapy	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Mirvetuximab	[REDACTED]	[REDACTED]			
Pooled chemotherapy	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years

Note: The company considered that a disease severity modifier of 1.7 was appropriate.

Table 24: Company's probabilistic base-case cost-effectiveness results with severity weighting (x1.7)

	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs (X1.7 weighting)	ICER (£/QALY) (x1.7 weighting)
Mirvetuximab	[REDACTED]	[REDACTED]			
Pooled chemotherapy	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years

Note: The company considered that a disease severity modifier of 1.7 was appropriate.

5.1.2. Company's sensitivity and scenario analyses

5.1.2.1. One way sensitivity analysis

The company varied model parameters using one way sensitivity analysis (OWSA; Table 25). The most influential parameters were those associated with the parameters defining the OS extrapolation and DoT extrapolation for mirvetuximab and pooled chemotherapy utilities. These results were based on the company's clarification base case. The EAG noted that correlated parameters (e.g. OS shape/scale) were varied independently, which misrepresents true parameter uncertainty.

Table 25: Company one way sensitivity analyses

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS - mirvetuximab - Log-Logistic - scale	████	████
OS - mirvetuximab - Log-Logistic - shape	████	████
DoT - Exponential - Parameter rate - mirvetuximab	████	████
Post-progression utility value, chemotherapy (base case)*	████	████
Pre-progression utility value, chemotherapy (base case)*	████	████
OS - Pooled chemotherapy - Weibull - scale	████	████
Post-progression utility value, mirvetuximab (base case)	████	████
Relative Dose Intensity - mirvetuximab	████	████
Post-Prog Trt Cost - % of progressed patients receiving post-progression treatment - Pooled chemotherapy	████	████
Pre-progression utility value, mirvetuximab (base case)	████	████

Abbreviations: DoT, duration of treatment; ICER, incremental cost effectiveness ratio; OS, overall survival; Trt, treatment

* The upper bound for the post-progression utility value was truncated by the mean for the pre-progression utility value and the lower bound for the pre-progression utility value was truncated by the mean for the post-progression utility value

5.1.2.2. Scenario analysis

Scenario analyses were based on the company clarification response and run from the clarification base case. The ICERs ranged from ██████████/QALY (Table 26). The greatest impact came from alternative OS distributions for mirvetuximab and utility values. Across most scenarios, the difference in ICERs between the original company submission and the new post clarification scenario analysis was minimal, typically within a █████ range. The only

notable exception was the “OS distribution - pooled chemotherapy - log-logistic” scenario, in which the ICER increased from █████ in the original submission to █████ in the updated analysis. This was explained by the severity weight of 1.7 being held constant in the original model, whereas the company’s model submitted during clarification was responsive to changes in chemotherapy arm and so resulted in 1.2 severity weight in this scenario.

Table 26:Company scenario analysis

Scenario	Weighted severity modifier of 1.7 (unless otherwise specified)	
	ICER (£/QALY)	% change from base case ICER
Base case	████	1
OS distribution- Joint models, Weibull (best statistical fit by AIC & BIC)	████	████
PFS distribution - Joint models lognormal (best statistical fit by AIC & BIC)	████	████
PFS distribution – mirvetuximab – log-logistic	████	████
PFS distribution – mirvetuximab – generalised gamma	████	████
PFS distribution – pooled chemotherapy – generalised gamma	████	████
OS distribution - mirvetuximab - exponential	████	████
OS distribution - mirvetuximab - log-normal	████	████
OS distribution - mirvetuximab - Gompertz	████	████
OS distribution - mirvetuximab - gamma	████	████
OS distribution - mirvetuximab - generalised gamma	████	████
OS distribution - mirvetuximab - Weibull	████	████
OS distribution - pooled chemotherapy - exponential	████	████
OS distribution - pooled chemotherapy - log-logistic	████	████
OS distribution - pooled chemotherapy - log-normal	████	████
OS distribution - pooled chemotherapy - Gompertz	████	████
OS distribution - pooled chemotherapy - gamma	████	████
OS distribution - pooled chemotherapy - generalised gamma	████	████
DoT - mirvetuximab - Gamma	████	████
DoT - pooled chemo - best fitting curves (paclitaxel - gompertz, PLD - gamma, topotecan - exponential)	████	████

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Utility model - Progression status and treatment type (with interaction term)	████	████
Utility model - Progression status and treatment type (not adjusted for AEs)	████	████
Utility model - Progression status only (adjusted for AEs)	████	████
100% vial sharing	████	████
0% vial sharing	████	████

Abbreviations: AE, adverse event; AIC, Akaike information criterion; BIC, Bayesian information criterion; DoT, duration on treatment; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; QALY, quality-adjusted life year.

Notes: *Using a severity modifier of 1.2 applied to the QALYs.

Table 27: Scenarios explored by the company in response to EAG requests at clarification

	Incremental costs	Incremental QALYs	ICER
Submitted company base case	████	████	████
B1c - Bevacizumab-naïve population	████	████	████
B1c - Bevacizumab-pretreated population	████	████	████
B7a – updated RDI approach	████	████	████
B8a - Removal of mirvetuximab costs post progression in chemotherapy arm	████	████	████
B8a - Removal of mirvetuximab costs post progression in chemotherapy arm + adjusting chemotherapy OS for mirvetuximab crossover	████	████	████
B9 – MIRASOL duration of subsequent treatment	████	████	████
B15b - Utilities from TA962	████	████ (1.2 modifier = █████)	████(1.2 modifier = █████)
B15b - Utilities from TA946	████	████ (1.2 modifier = █████)	████(1.2 modifier = █████)
B17a – BRCA negative/unknown	████	████	████
B17a – BRCA positive	████	████	████
B17b - Primary platinum free interval <=6 months	████	████	████

	Incremental costs	Incremental QALYs	ICER
B17b - Primary platinum free interval > 6 months	■	■	■
B19 - Pooled chemotherapy excludes topotecan	■	■	■
B20 - Doubling of all utility durations from 4 weeks to 8 weeks	■	■	■
B20 - Doubling of all disutilities	■	■	■
B20 - Doubling all adverse event costs	■	■	■
B22 - Removing half cycle correction for drug costs	■	■	■
Updated company base case	■	■	■

Abbreviations: BRCA, breast cancer gene; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year, NA, not applicable

5.1.2.3. Probabilistic sensitivity analysis

The model showed good convergence after approximately 390 iterations. The PSA shows mirvetuximab was consistently more effective and more costly (with all iterations in the northeast quadrant). At a willingness to pay threshold of £30,000/QALY, mirvetuximab had the highest net monetary benefit in ■ of simulations and chemotherapy had the highest net monetary benefits in ■. This distribution of results reflected the probabilistic ICER ■ per QALY threshold, consistent with the deterministic ICER ■.

5.2. EAG's additional analyses

5.2.1. Model validation and face validity check

The EAG identified a number of limitations within the company's base case and explored the impact of parameter values and assumptions that the EAG believed were more plausible.

This section is organised as follows:

- **Section 5.2.2:** Summary of the EAG's preferred assumptions and results, which reflect the most plausible and methodologically appropriate approach to cost-effectiveness analysis, based on NICE's reference case.
- **Section 5.2.3:** Results of the probabilistic sensitivity analysis conducted using the EAG's preferred assumptions.
- **Section 5.2.4:** Scenario analyses exploring uncertainty around the EAG base case.

Results are presented deterministically for each adjustment made by the EAG due to the slow speed of the PSA in the executable model. PSA is presented for the EAG base case only.

5.2.2. EAG's preferred assumptions

The EAG's preferred base case was implemented in the post-clarification version of the company model. Adjustments were made to: align model inputs with clinical practice in the NHS; reflect the MIRASOL trial population; incorporate clinical expert advice; and apply survival curves and utility values considered most appropriate for decision-making. A list of the assumptions used in the EAG base case alongside the section of the report where these are discussed is presented in Table 28. The impact on the economic analysis of applying the EAG base case assumptions is shown in Table 29.

Table 28: EAG base case assumptions

No.	EAG preferred assumption	Rationale	Section of the report	Direction of ICER impact
1	Cycle-specific relative dose intensity	To reflect actual dosing intensity over time.	4.2.8.1	Small increase
2	Remove cost of mirvetuximab from post-progression	To be more consistent with the use of mirvetuximab in the NHS	4.2.8.3	Small increase
3	No vial sharing for mirvetuximab and 50% vial sharing for chemotherapy	Reflect clinical experts' opinion on expected and current NHS practice	4.2.8.2	Small Increase
4	Remove topotecan from pooled chemotherapy	Not commonly used in UK clinical practice	4.2.4	Small Increase
5	Mirvetuximab OS: gamma	Best visual/statistical fit and consistent with clinical advice	4.2.5.1	Significant increase
6	Mirvetuximab DoT: KM followed by exponential extrapolation at 120 weeks	Better reflected observed DoT	4.2.5.4	Small Increase
7	Chemotherapy OS: gamma	Good visual fit and aligned with clinical expectations.	4.2.5.1	Small increase

No.	EAG preferred assumption	Rationale	Section of the report	Direction of ICER impact
8	Age from MIRASOL	Aligned with trial population and source of effectiveness	4.2.3	Small increase
9	Utilities from MIRASOL	Higher validity and relevance to the appraisal population and NICE reference case	4.2.6	Significant increase
10	Include AE disutilities	Reflects quality-of-life impact of AEs	4.2.7	Small decrease
11	Increase duration of ocular AEs and increased frequency of ophthalmologist visits	Clinical advice indicated longer resolution times.	4.2.7	Small increase
12	Adjust AE costs	Aligns with oncologists' description of how AEs were managed in the NHS	4.2.8.6	Small increase
13	Adjust health state costs	Reflected clinical advice on resource use frequency	4.2.8.5	Small decrease
14	Adjust OS for subsequent mirvetuximab use	Corrected for the effect of treatment switching in MIRASOL.	4.2.8.3	Small decrease

Abbreviations: AE, adverse event; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; MIRV, mirvetuximab soravtansine; OS, overall survival; QALY, quality-adjusted life year; RDI, relative dose intensity; DoT; duration of treatment.

Table 29: EAG Results using the EAG's preferred model assumptions

Preferred assumption	Intervention	1.7 weighting unless otherwise specified					
		Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY	Cumulative ICER
Company's base case	Chemotherapy	████	████	█	█	█	█
	Mirvetuximab	████	████	████	████	████	████
Cycle-specific relative dose intensity	Chemotherapy	████	████	█	█	█	█
	Mirvetuximab	████	████	████	████	████	████
Remove cost of mirvetuximab from post progression	Chemotherapy	████	████	█	█	█	█
	Mirvetuximab	████	████	████	████	████	████
No vial sharing for mirvetuximab and 50% vial sharing for chemotherapy	Chemotherapy	████	████	█	█	█	█
	Mirvetuximab	████	████	████	████	████	████
Remove topotecan from pooled chemotherapy	Chemotherapy	████	████	█	█	█	█
	Mirvetuximab	████	████	████	████	████	████
Mirvetuximab OS: gamma	Chemotherapy	████	████	█	█	█	█
	Mirvetuximab	████	████	████	████	████	████
Mirvetuximab DoT: KM followed by exponential extrapolation at 120 weeks	Chemotherapy	████	████	█	█	█	█
	Mirvetuximab	████	████	████	████	████	████
Chemotherapy OS: gamma	Chemotherapy	████	████	█	█	█	█
	Mirvetuximab	████	████	████	████	████	████
Age from MIRASOL	Chemotherapy	████	████	█	█	█	█
	Mirvetuximab	████	████	████	████	████	████
Utilities from MIRASOL	Chemotherapy	████	████	█	█	█	█
	Mirvetuximab	████	████	████	████ (1.2)	████	████
Include AEs disutilities	Chemotherapy	████	████	█	█	█	█

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Preferred assumption	Intervention	1.7 weighting unless otherwise specified					
		Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £/QALY	Cumulative ICER
	Mirvetuximab						
Increase duration of ocular AEs and increased frequency of ophthalmologist visits	Chemotherapy						
	Mirvetuximab						
Adjust AEs costs	Chemotherapy						
	Mirvetuximab						
Adjust health state costs	Chemotherapy						
	Mirvetuximab						
Adjust OS for subsequent mirvetuximab use	Chemotherapy						
	Mirvetuximab						
EAG base case cumulative impact, severity weight 1.2	Chemotherapy						
	Mirvetuximab						
EAG base case without severity weighting	Chemotherapy						
	Mirvetuximab						

Abbreviations: AE, adverse event; EAG, External Assessment Group; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; MIRV, mirvetuximab soravtansine; OS, overall survival; QALY, quality-adjusted life year; RDI, relative dose intensity; DoT; duration of treatment.

5.2.3. EAG probabilistic analysis

The EAG ran 1,000 simulations using the EAG base case (Table 30). Scenario analyses were not run probabilistically due to the computation time required (approximately 25 minutes per PSA run). Results were consistent with the deterministic base case: mirvetuximab was associated with an incremental cost of [REDACTED], an incremental QALY gain of [REDACTED], and an ICER of [REDACTED] per QALY gained. Chemotherapy had the highest net monetary benefit in [REDACTED] of simulations, showing strong evidence that it is the cost-effective option at the conventional threshold of £30,000 per QALY.

Table 30: EAG probabilistic analysis

Intervention	Total costs	Total QALYs	Incremental costs	Incremental QALY	ICER
Chemotherapy	[REDACTED]	[REDACTED]			
Mirvetuximab	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year

Figure 12: PSA Results (EAG Base Case)

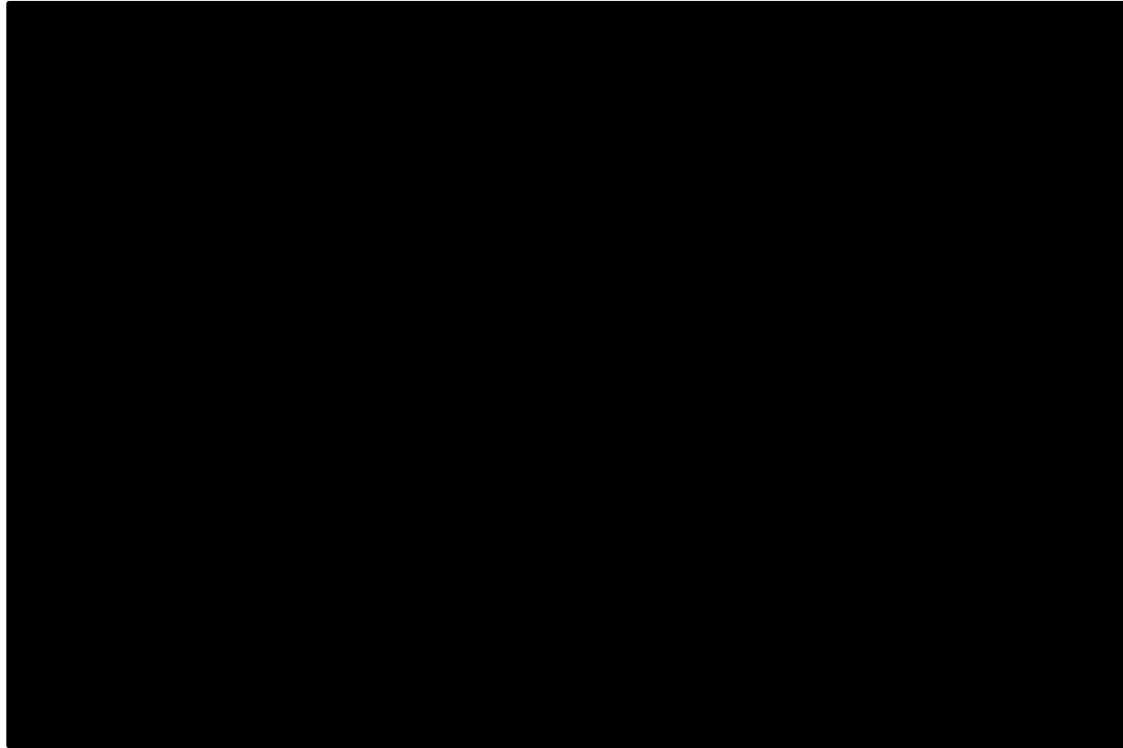
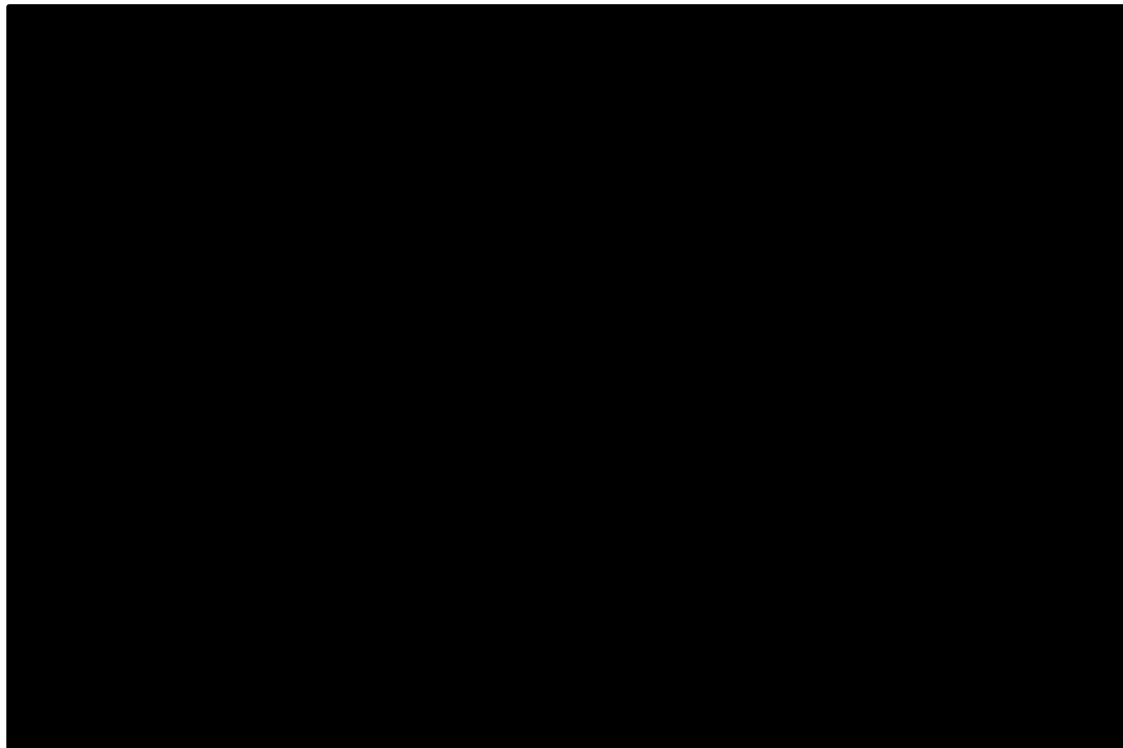


Figure 13: Cost-Effectiveness Acceptability Curve (CEAC) - EAG Base Case



5.2.4. Scenario analyses using EAG's preferred assumptions

The EAG explored areas of uncertainty through scenario analyses, all of which were run deterministically. Each scenario varied a single assumption while holding all other EAG base-case inputs constant. Table 31 lists the scenarios explored, and Table 32 presents the results, showing changes from the EAG base case.

Scenarios that had a major impact on the EAG base case were:

- The PPFI subgroup analysis: the subgroup of patients with PPFI less than or equal to 6-months resulted in an ICER of [REDACTED]
- The choice of OS curve for chemotherapy: some of the more optimistic extrapolations increased the ICER by [REDACTED]

The subsections below provide a detailed description of the results of each scenario.

Table 31: Summary of EAG's scenario analyses using EAG's preferred assumptions

EAG's base-case assumption	EAG's scenario	Section of the report
Mirvetuximab OS curve: gamma	Mirvetuximab OS curve: gen gamma Mirvetuximab OS curve: Gompertz Mirvetuximab OS curve: Weibull	4.2.5.1
Chemotherapy OS curve: gamma	Chemotherapy OS: lognormal Chemotherapy OS: log-logistic Chemotherapy OS: gen gamma Chemotherapy OS: Weibull	4.2.5.1
Age from MIRASOL	Age from Pickwell-Smith ¹ study	4.2.3
Utilities from MIRASOL	Utilities from TA389 Utilities from TA946 Utilities from TA962	4.2.6
PFS using lognormal	Use KM for chemotherapy arm	4.2.5.2
32% of PROC patients test positive for FR-alpha	Removing the cost of testing Testing at diagnosis	4.2.8.4
ITT population	Subgroups PPFI ≤6 months PPFI >6 months	4.2.10

Abbreviations: DoT, duration of treatment; FRα, folate receptor alpha; ITT, intention to treat; KM, Kaplan–Meier; MIRV, mirvetuximab soravtansine; OS, overall survival; PPFI, platinum-free interval; PROC, platinum-resistant ovarian cancer; TA, technology appraisal

Table 32: Results of EAG's scenario analyses using EAG's preferred assumptions

Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs (x1.2 weighting)	ICER £/QALY	Change from the EAG base case ICER
EAG base case	██████	██████	██████	█
MIRV OS: gen gamma	██████	██████	██████	██████
MIRV OS: Gompertz	██████	██████	██████	██████
MIRV OS: Weibull	██████	██████	██████	██████
Utilities from TA389	██████	██████	██████	██████
Utilities from TA946	██████	██████	██████	██████
Utilities from TA962	██████	██████	██████	██████
PPFI less than or equal 6 months	██████	██████	██████	██████
PPFI above 6 months	██████	██████	██████	██████
Chemotherapy OS: lognormal	██████	██████	██████	██████
Chemotherapy OS: log-logistic	██████	██████	██████	██████
Chemotherapy OS: exponential	██████	██████	██████	██████
Chemotherapy OS: Weibull	██████	██████	██████	██████
Use KM for chemo PFS	██████	██████	██████	██████
Removing the cost of testing FR alpha	██████	██████	██████	██████
Testing at diagnosis	██████	██████	██████	██████

Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs (x1.2 weighting)	ICER £/QALY	Change from the EAG base case ICER
Age from Pickwell-Smith study				

Abbreviations: DoT, duration of treatment; FR α , folate receptor alpha; ITT, intention to treat; KM, Kaplan–Meier; MIRV, mirvetuximab soravtansine; OS, overall survival; PPFI, platinum-free interval; PROC, platinum-resistant ovarian cancer; TA, technology appraisal

5.2.4.1. Subgroup by primary platinum-free interval

The EAG explored cost-effectiveness by PPFI subgroup, informed by MIRASOL trial KM showing differential OS by PPFI. In patients with PPFI >6 months, mirvetuximab showed greater benefit, resulting in an ICER of [REDACTED]. In equal or <6-month subgroup, the ICER rose sharply to [REDACTED]. This reflected the very small incremental QALY gain [REDACTED] in the later subgroup, as chemotherapy provided a slight advantage in life-years gain but mirvetuximab was associated with higher utility values, still leading to the small incremental QALY.

This suggested that applying a subgroup specific OS could lead to a substantial difference in results. However, as discussed before in Section 3.3.8, the subgroup analysis was post hoc so the EAG interpreted these results with caution.

5.2.4.2. Overall survival extrapolation pooled chemotherapy

The EAG explored alternative OS curves for pooled chemotherapy to assess uncertainty in long-term survival projections. Weibull was explored as it provided a good visual fit to the smoothed hazard plot. However, it predicted 0% survival at 5 years, which lay outside the 1-5% range predicted by clinical experts. Log-normal and log-logistic were also explored, despite poorer visual fit, as their 5-year survival predictions aligned with the upper limit of expert opinion. The Weibull scenario produced the lowest ICER, [REDACTED]. While, lognormal and log-logistic led to ICERs of [REDACTED] and [REDACTED], respectively, reflecting longer survival predictions in the chemotherapy arm and, as a result, higher ICERs.

5.2.4.3. Overall survival mirvetuximab

The EAG explored the impact of alternative OS extrapolations for mirvetuximab, as this was a key area of uncertainty. Scenarios using gen gamma and Weibull were explored as they provided a good visual fit to the smoothed hazard. The Gompertz distribution was tested as a

potential worst-case scenario; although it had poorer visual fit, it is also the only curve associated with lower incremental gains in post-progression survival [REDACTED] relative to gains in PFS [REDACTED]. This scenario resulted in the least favourable ICER [REDACTED]. In comparison, gamma and Weibull resulted in ICERs of [REDACTED] and [REDACTED] respectively.

5.2.4.4. Utilities

As health state utility was a major driver of the ICER in the model, the EAG explored using utility values from previous TAs in ovarian cancer. All utility values tested in scenario analysis were derived using EQ-5D.

Table 33: Utilities from previous TAs

Source	PFS Utility	PPS Utility
TA389	0.718	0.649
TA946	0.750	0.727
TA962	0.808	0.756

Abbreviations; PFS, progression free survival; PPS, post-progression survival; TA, technology appraisal

TA389 possibly represented the closest population match, comprising a mixed population of platinum-sensitive and platinum-resistant ovarian cancer in the same treatment line as patients who received one of the chemotherapy agents included in the pooled comparator arm of this appraisal. TA946 and TA962 were based on populations treated in the first-line maintenance setting following response to platinum-based chemotherapy (TA946: high-grade epithelial ovarian cancer; TA962: BRCA mutation-positive advanced ovarian cancer).

Given that a substantial proportion of life years gained with mirvetuximab were in PPS, it was unsurprising that TA389 (associated with the lowest PPS utility 0.649) resulted in the highest ICER [REDACTED], followed by TA946 [REDACTED]. TA962, which had the highest utility values, led to a slightly lower ICER than the EAG base case [REDACTED]

5.2.4.5. Testing

As discussed before in Section 4.2.8.4, the EAG explored two scenarios related to FRα testing: (1) moving the cost of testing to the point of diagnosis and (2) removing the cost of testing, in line with the NICE reference case.

For the scenario in which testing was assumed to occur at diagnosis, the EAG estimated the proportion of patients who would test positive and be eligible for mirvetuximab as follows:

$$\text{Positive rate at diagnosis} = \left(\frac{2144}{7110} \right) \times \blacksquare \times 32\% = \blacksquare$$

Where:

- 7,110 = Annual number of women diagnosed with ovarian cancer in England
- 2,144 = Annual number of women in England with epithelial high-grade serous PROC
- $\blacksquare$ = Proportion with 1-3 prior lines of therapy (company assumption based on clinical input)
- 32% = Proportion with high FR α expression (from MIRASOL)

This implied that approximately $\blacksquare$ patients would need to be tested to identify one eligible patient, compared with $\blacksquare$ patients in the base case. As a result of this, the ICER increased to $\blacksquare$ when testing was moved to diagnosis. Removing the cost of testing resulted in a small reduction in the ICER $\blacksquare$.

5.2.4.6. Age

A scenario analysis using a mean age of 68 years from Pickwill-Smith 2025¹. was also explored. This study included 9,572 UK patients with ovarian cancer from 2016-2017 and represented a close estimate of age in NHS practice. Applying this scenario on top of the EAG base case had negligible impact $\blacksquare$ as the EAG base case already assumed x1.2 severity weighing. By comparison, the impact was clear when applied to the company base case, increasing the ICER from $\blacksquare$ to $\blacksquare$ due to the change in severity weight from 1.7 to 1.2.

5.3. Decision modifiers

5.3.1. QALY weighting for severity

The company presented a case for applying a severity modifier based on QALY shortfall calculations using pooled chemotherapy outcomes as the standard of care. The analysis followed NICE DSU TSD 23 and used utility values of 0.5 (pre-progression) and 0.4 (post-progression), with a starting age of 59.2 years and a 100% female population. General population utility values were taken from Hernandez-Alava et al (2022)⁶⁷, and mortality from ONS life tables (2017-2019)⁶⁸. This resulted in a proportional QALY shortfall of $\blacksquare$ and an

absolute shortfall of [REDACTED] QALYs, justifying the use of a severity modifier of 1.7 in the company's base case.

The EAG did not consider the company's severity modifier of 1.7 to be appropriate. The values used by the company to calculate shortfall were inconsistent with the utility values derived from the MIRASOL trial, which the EAG considered a more robust and relevant source of health-related quality of life values for patients on chemotherapy (Section 4.2.6). Therefore, in line with NICE methods, the EAG base case applied a severity modifier of 1.2.

Although using the mean age of participants in MIRASOL (62.8 years) didn't change the severity weight used in the company base case alone, the EAG noted that small changes around the starting age of the cohort had a substantial impact on the ICER. This was because severity weighting is sensitive to age. For example, applying a starting age of 65 years results in a lower severity weight (x1.2) and increases the ICER to [REDACTED]. Some clinical experts consulted by the EAG noted that patients in MIRASOL appeared younger than those typically seen in NHS practice¹.

Table 34 presents the differences between the EAG and the company's assumptions regarding the general population. Table 35 outlines differences in assumptions related to standard care. Table 36 shows the impact of these assumptions on the severity weight applied in each of their respective base cases.

Table 34: Summary of company's and EAG's preferred assumptions for general population QALY shortfall estimates

Factor	Company	EAG
Sex distribution	100% Female	100% Female
Starting age	59.2	62.8
Expected years of life	ONS life tables (2017–2019) ⁶⁸	ONS life tables (2017–2019) ⁶⁸
Quality of life by age	Hernandez-Alava et al. (2022) ⁶⁷	Hernandez-Alava et al. (2022) ⁶⁷
Discount rate	3.5%	3.5%

Abbreviations: EAG, external assessment group; ONS, Office of National Statistics; QALY, quality-adjusted life year

Table 35: Summary of company's and EAG's preferred assumptions for standard-care QALY shortfall estimates

Modelled input	Company's preferred assumptions for standard-care	EAG's preferred assumptions for standard-care	Rationale or justification
Parametric function for modelling PFS	Log-normal	Log-normal	4.2.5.2
Parametric function for modelling OS	Weibull	Gamma	4.2.5.1
Adverse events disutilities	Disutilities from AEs not included	MIRASOL ²⁶ AE incidence, disutilities from published literature (used by the company in a scenario analysis) ⁶⁹⁻⁷¹	4.2.6
Health state utility values	Literature-based utilities	MIRASOL based utilities	4.2.6
Age-related disutility	Hernandez-Alava et al. (2022) ⁶⁷	Hernandez-Alava et al. (2022) ⁶⁷	NICE reference

Abbreviations: AE, adverse event; EAG, external assessment group; OS, overall survival; PFS, progression-free survival

Table 36: Summary of company's and EAG's base-case QALY shortfall analyses and preferred QALY weighting

	Expected total QALYs for the general population	Expected total QALYs for people living with a condition on current treatment	Absolute QALY shortfall	Proportional QALY shortfall	Preferred QALY weight
Company's base case	12.861 93.0%	0.552	12.309	95.7%	1.7
EAG's base case	11.644	0.819	10.826	93.0%	1.2

Abbreviations: EAG, external assessment group; QALY, quality-adjusted life year

5.3.2. Uncaptured benefits

The EAG considered that the drug's tolerability and innovative nature were already reflected in the modelled QALY gains, while the scale of productivity and caregiver effects were uncertain. Furthermore, the "value of hope" is not quantifiable within the NICE framework.

5.3.3. Health inequalities

The company stated that mirvetuximab had the potential to address health inequalities through improving health outcomes for women, providing a treatment option for a rare condition where there have been no new treatments for 20 years, and by addressing barriers to treatment that they may disproportionately be experienced by people with PROC in more deprived areas of the country. The EAG did not consider the latter argument to have merit, based on the argument presented by the company: it was not clear to the EAG how the availability of mirvetuximab would lead to better treatment access specifically in deprived areas. However, the EAG agreed that the availability of an alternative to chemotherapy for an advanced stage of this condition would offer value to people with PROC.

5.4. Conclusions of the cost-effectiveness section

In the company's base case, mirvetuximab could be considered to be cost-effective compared with chemotherapy, with an ICER of [REDACTED]

In the EAG base case, the deterministic ICER was [REDACTED] per QALY. This considerably exceeded typical NICE willingness-to-pay thresholds of £20,000 - £30,000 per QALY, even with a x1.2 severity weighting applied. The most impactful differences from the company base case were the choice of parametric survival models for OS and the use of MIRASOL based utilities. The PSA analysis showed that [REDACTED]

The EAG's scenario analyses showed that the model was sensitive to OS extrapolation choices for the chemotherapy arm. Using lognormal or log-logistic OS curves for chemotherapy increased ICERs to [REDACTED] and [REDACTED] per QALY. Changes to OS modelling for mirvetuximab resulted in ICERs ranging from [REDACTED] (generalised gamma) to [REDACTED] (gompertz). Utility source also affected results, with ICERs rising to [REDACTED] using TA389 utilities and falling slightly to [REDACTED] using TA962 utilities.

Removing the cost of FR-alpha testing had minimal impact on the ICER in the EAG base case (reduction of less than [REDACTED]), while moving testing to the point of diagnosis increased the ICER to [REDACTED] per QALY. Restricting the analysis to the PFI ≤6 months subgroup markedly worsened cost-effectiveness (ICER £[REDACTED] per QALY) due to the poor prognosis of this group. By comparison, the PFI >6 months subgroup had a relatively lower ICER of [REDACTED] per QALY. None of the EAG scenarios had an ICER below £30,000 per QALY.

Given these results, the EAG considers it reasonably certain that mirvetuximab would not be cost-effective compared to chemotherapy at a threshold of £30,000 per QALY.

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Single Technology Appraisal

Mirvetuximab soravtansine for treating folate receptor alpha-positive platinum-resistant advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [ID6442]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 1st September 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **confidential** should be highlighted in turquoise and all information submitted as **depersonalised data** in pink.

Issue 1 Incorrect model implementation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Table 32, Page 110, on Page 113 and Page 117, the EAG presented an ICER of [REDACTED] using utility values from TA389. The company were not able to replicate this result when implementing this scenario as it was described in Table 22 (Page 95).	The company request this value be updated to [REDACTED]	Amending incorrect results presented in the EAG report.	Thank you for spotting this. The scenario in the model was implementing the same utility both pre and post progression for both arms from TA389. The reporting of the scenario in Table 22 of the report was incorrect and has now been updated.
In cell W27 of the 'Disease Management Costs' sheet, the cost of a CT scan is multiplied by 0.25 (i.e. assumed to apply once every 4 weeks). However, on page 97 of the EAG report, it states that clinicians "expected a CT scan once every three months if the person was on treatment, regardless of the line of treatment"	The company request this is amended in the model to reflect 3-monthly CT scans while on treatment, as confirmed by the EAG's clinical experts	Inconsistency between model and report.	Thank you for spotting this. We have updated to align costs in post progression while on treatment exactly with the cost in pre progression on treatment, in line with the report. We did not amend to be every 3 months as this does not align with the company assumption pre progression (6 times per year) and EAG clinical expert advice was

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			not considered to strongly disagree on this point. This made a minor difference to the results.

Issue 2 Incorrect reporting of results

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In Table 28, page 105 of the EAG report, the direction of ICER impact of the EAG's preferred assumption 'Adjust health state costs' is described as leading to a 'small increase'.	The company suggest this is amended to: "small decrease"	For accuracy. As demonstrated in the following table (Table 29) presenting the results, adjusting the health state costs leads to a reduced ICER.	Amended thank you.
On page 18, in Table 3, a scenario analysis is labelled 'No vial sharing'	The company suggest this is amended to "No vial sharing for mirvetuximab"	Potential for misinterpretation without the additional context: elsewhere in the report, the EAG base case is described as no vial sharing for mirvetuximab and 50% vial sharing for other comparators.	Agree. This has been amended to align with how this scenario is reported in the other tables.
On page 85, the costs per cycle of the three	The company suggest the text be updated as follows:	It is not clear whether the cost for topotecan is the weighted	The topotecan price was calculated as 5 *

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
chemotherapies are being compared, however there appears to be an error in the calculation for the topotecan costs per cycle.	“The cost per 4-weekly cycle for PLD was somewhat higher than for the two other chemotherapy regimens (£604 for 4 weeks vs £81 for paclitaxel and ~~£225~~ £295 for topotecan; all prices at list price excluding wastage and missed doses)”	cost across both possible dosing frequencies of topotecan, as the company are unable to match the cost of £225 reported. Assuming the cost without wastage, and calculating costs per cycle (for the Q4W regimen this would be an initial dose and then two additional days for the subsequent doses, and then for the Q3W dosing regimen this would be an initial dose and then 4 additional doses for the subsequent doses) and weighting by the distribution across the two dosing frequencies gives a cost of £295.	£33.68 * 4/3 using the Q3W regimen cost (5 days at 1.25mg / m ²). This has been clarified in the report. This aligns with the clinical expert advice to the EAG that in the rare instances topotecan is used it is used for the 3 weekly cycle.
On page 96, the report states “The company then provided a scenario analysis using the RPSFTM to adjust for crossover, which showed a small QALY difference (████).”	The company suggest the sentence be amended to: “The company then provided a scenario analysis using the RPSFTM to adjust for crossover, which showed a small QALY difference versus the company base case (████).”	In the original statement, the value quoted is incorrect, and it is unclear whether the QALY difference is between treatment arms or versus the company base case.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 101, in Table 26, in the row labelled “OS distribution – pooled chemotherapy – log-logistic” does not include an asterisk next to the ICER to indicate that a severity modifier of 1.2 applies	Please add an asterisk to this row.	To clarify that this result is based on QALYs with a 1.2 multiplier applied.	Added
On page 109, the report states: “The PPFI subgroup analysis: the subgroup of patients with PPFI less than or equal to 6-months resulted in an ICER of [REDACTED] as the HR for OS was >1”	The company propose this is amended to: “The PPFI subgroup analysis: the subgroup of patients with PPFI less than or equal to 6-months resulted in an ICER of [REDACTED] as the OS subgroup results for this group showed the HR for OS was >1 ”	The value of [REDACTED] reflects the change from the EAG base-case ICER rather than the ICER itself for the specified scenario. The statement on the HR is unclear, as it implies a HR was applied to the chemotherapy arm, whereas the company believes the HR is referring to the subgroup results from the submitted appendix.	Amended
On page 100, the report states “The ICERs ranged from [REDACTED] [REDACTED]/QALY (Table 26)”	Please amend to: “The ICERs ranged from [REDACTED]/QALY (Table 26)”	To reflect the highest and lowest ICERs presented in Table 26.	Amended

Issue 3 Incorrect/unclear statements: Economic

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 12, the report states “the EAG noted that the overall survival curve selected in the company base case overestimated survival in patients treated with mirvetuximab, with the majority of survival gain coming from the post progression state. This was considered clinically implausible and inconsistent with statistical and visual fit to the trial data”	The company suggest this is amended to “the EAG noted that the overall survival curve selected in the company base case may overestimate survival in patients treated with mirvetuximab, with the majority of survival gain coming from the post progression state. This was considered clinically implausible and inconsistent with statistical and visual fit to the trial data”	The original wording suggests that the true overall survival is known. Clinical expert feedback provided to the company suggested that the log-logistic distribution fell within a plausible range. Additionally, statistical and visual fit are not reasons to discard the company base case survival estimate. This is particularly the case when considering the data for which the KM is considered informative/meaningful (page 118 and Appendix M of Company submission).	Amended to state: “company base case likely overestimated” as this accurately reflects the EAG’s position based upon the available data and expert advice received. The EAG note that the company do not provide comment on the main point of this sentence i.e. the majority of survival gain coming from the post progression state.
On page 83, the report states: “As noted in Section 4.2.5.3, the distributions chosen by the company led to assumptions that were not considered credible in	The company suggest this is amended to “As noted in Section 4.2.5.3, the distributions chosen by the company led to assumptions that were not considered credible by the EAG in terms of post-progression survival gain.”	It is not clear from the original statement that the assessment of credibility has been made by the EAG, rather than clinical experts.	Amended to state by the EAG’s clinical experts. The EAG consulted clinical experts to inform our opinion.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
terms of post-progression survival gain.”			
On page 85, the report states: “The company presented AIC/ BIC data for a subset of the population before heavy censoring in their base case. However, the EAG did not agree with the use of AICs/BICs presented for only a subset of the data in the appendices, as these statistics should be based on the full dataset to ensure robust model selection. Assessing fit based on a selected part of the data could bias model selection in favour of those distributions that perform better in this restricted part of the data but give less plausible projections beyond observed data.”	The company suggest this is amended to; “The company presented AIC/ BIC data for the entire population in their base case, and within an appendix, presented AIC/BIC based on the portion of the observed data for which the KM is considered informative/meaningful. Assessing fit based on a selected part of the data could lead to distributions that perform better in this restricted part of the data but give less plausible projections beyond observed data.”	It is incorrect that the company base case based the AIC/BIC on a subset of the population. The impact of basing fit on selected part of the data in terms of any potential bias is unclear.	The EAG have implemented the amendments to clarify the company base case. The EAG do not consider the wording suggested for the second sentence to be an improvement.
On page 88, the report states “the EAG’s base case assumed a constant	The company suggest this is amended to “the EAG’s base case curve selection results in a HR initially decreasing	The use of the term ‘constant HR’ by the EAG is misleading, as it implies a proportional	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
hazard ratio between mirvetuximab and chemotherapy, which was considered more clinically plausible (Figure 10)”	before stabilizing to a constant HR between mirvetuximab and chemotherapy, which was considered more clinically plausible (Figure 10)”	hazards approach that uses a constant HR applied to chemotherapy.	
On page 2, the report states: “This was important as the use of different utility sources did not only underestimate QALYs in the chemotherapy arm but also resulted in mirvetuximab being assigned a higher severity weight.”	The company suggest this is amended to: “This was important as the use of different utility sources may have underestimated QALYs in the chemotherapy arm and also resulted in mirvetuximab being assigned a higher severity weight”.	It is not known whether the company approach underestimates QALYs in the chemotherapy arm.	Amended to “This was important as the use of different utility sources did not only result in reduced QALYs in the chemotherapy arm” as this better reflects the facts.
On page 94, the report states that “the company assumed disutilities of [REDACTED] for keratopathy, [REDACTED] for blurry vision, and [REDACTED] for cataract”	The company suggest this is amended to “the company assumed disutilities of [REDACTED] for keratopathy, [REDACTED] for blurry vision, and [REDACTED] for cataract”	The company submission used a disutility of [REDACTED] for cataract.	Amended and CIC marking removed as this is available unmarked in Table 33 of the CS.
On page 67, the report states “The MMRM method assumed data were missing at random (MAR), but no justification for this assumption was given”.	The company suggest this is amended to “The MMRM method assumed data were missing at random (MAR) ~~but no justification for this assumption was given~~ ”	The original wording implies that the assumption of missing at random was not discussed in the company submission. However, the company submission discussed that the assumption of MAR is less strong than the assumption of	Not a factual inaccuracy. The assumption of missing at random is still reasonably strong and is not justified.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		missing completely at random assumed by approaches such as generalised estimating equations.	
On page 13, in row 7 of Table 2, the label states 'Wastage', but subsequent columns discuss both RDI and vial sharing; there is also a row below describing assumptions for vial sharing, which are slightly different.	The company request the label for row 7 to be corrected to 'RDI' and remove reference to vial sharing.	For clarity.	Reference to vial sharing removed. Relationship between cycle-specific RDIs and wastage has now been clarified.
On page 95, Section 4.2.8.1 has the heading 'Wastage'	The company suggest this heading is amended to ' Relative dose intensity '	Section 4.2.8.1 discusses relative dose intensity; the following section discusses wastage/vial sharing.	Clarified the link between RDI and wastage in the text and heading.
On page 97, the report states that "The EAG assumed no vial sharing for mirvetuximab, consistent with previous submissions for novel therapies in this disease area"	The company suggest this is amended to "The EAG assumed no vial sharing for mirvetuximab, consistent with previous submissions for novel therapies in this disease area, with the exception of TA1055, for which vial sharing was implemented for bevacizumab. "	Vial sharing was implemented in a previous NICE appraisal in ovarian cancer.	No amendment made. TA1055 is an appraisal for rucaparib and was published in April 2025. Bevacizumab was a comparator in this submission and available as a biosimilar across

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			multiple indications so is not relevant to assessing whether vial sharing is expected for a new novel therapy.
On page 98, the report states that “a default standard error of 20% of the base-case value was applied”	The company suggest this is amended to “ a range of +/-20% of the base-case value was applied”	For accuracy of reporting, as applying a standard error of 20% of the base case would result in different upper and lower bounds than were used in the company model.	Amended
On page 83, the report states that “differences in AE frequency had limited impact on modelled outcomes pre-progression ([REDACTED])”	The company suggest this is amended to “differences in AE frequency had limited impact on modelled outcomes pre-progression [REDACTED] QALY loss associated with AEs for mirvetuximab and pooled chemotherapy, respectively). ”	It is not clear from the original statement that the values reflect QALY losses associated with AEs, and which of the two treatment arms each value relates to.	Amended
On page 105, Table 28, row 11 “Increase duration of ocular AEs” And	The company suggest this is amended to “Increase duration of ocular AEs and increased frequency of ophthalmologist visits ” to clarify that this model change also includes changing the frequency of ophthalmologist visits.	To clarify all changes that are made as part of this scenario analysis.	Amended in both tables and also Table 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 107, Table 29 “Increase duration of ocular AEs”			
On page 15, in row 4 of the table for Key Issue 1, the report states “This reduced the estimated QALY gain for mirvetuximab, and resulted in a lower severity modifier (1.2 instead of 1.7) and higher estimated QALY gain in the chemotherapy arm”	The company suggest this is amended to: “This increased the total QALYs in the chemotherapy arm, resulting in a lower severity modifier (1.2 instead of 1.7) and a reduced QALY gain for mirvetuximab compared with chemotherapy”	For clarity. The QALY gain is referred to for both mirvetuximab and chemotherapy, but in one case is comparative and in the other case is absolute.	Added the word incremental to clarify. Other amends are not considered to be required as the first part now reads: “result in reduced QALYs in the chemotherapy arm”
On page 41, the report states that “a higher starting age implied a lower severity modifier”	The company suggest this is amended to “a higher starting age (68 years) implied a lower severity modifier”	The original wording implies that the age used in the EAG base case results in a lower severity modifier.	Amended and clarified the source of the 68 years
On page 84, the report states “There was a higher proportion of participants who were BRCA positive than typically expected in UK clinical practice”	The company suggest this is amended to “ Clinical experts suggested there was a higher proportion of participants who were BRCA positive than typically expected in UK clinical practice, although this is not necessarily reflected in the literature”	The current wording implies it is from the literature, rather than clinical opinion, which may be misleading. For instance, within UK literature BRCA mutation rates are quoted to be found in approx. 16% of ovarian cancer cases (1, 2) while the British Gynaecological Cancer Society	Amended and added the information available from literature to Section 3.2.2.2 which this paragraph references.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		states that BRCA1/2 are present in up to 20% of patients (3)	

Issue 4 Incorrect/unclear statements: Clinical

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 16, the EAG note that “Younger age at diagnosis was associated with improved prognosis”. The company would like to clarify that it is not entirely certain that younger patients have better prognosis, as this is affected by multiple factors. The CS also notes that younger patients may be subject to age-related diagnostic bias, according to feedback from patients received by the company. In the same paragraph, the EAG reference section 3.2.2.2, where they offer a more nuanced description of	The company propose amending the sentence on page 16 to “Younger age at diagnosis may be associated with improved prognosis, unless patients become subject to age-related diagnostic bias”	To clarify that that the company did not make a definitive statement around the impact of age on survival, and that younger patients also face severe unmet need.	Thank you for raising this. The EAG disagrees that this needs to be mentioned here, as that is not the point we are making. We have however signposted to that, stating “As younger age at diagnosis was associated with improved prognosis for PROC, this affected the generalisability of the evidence to the target population (see Section Error! Reference source not found. for further detail on differences in age affecting prognosis).”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
how age may be related to prognosis.			
On page 19 the EAG note that “age was recognised as a prognostic factor, with younger people generally having better prognosis.” The CS did not make a definitive statement around the relationship between age and survival in patients with PROC. The CS also notes that younger patients may be subject to age-related diagnostic bias, according to feedback from patients received by the company.	The company would propose amending to “ According to the EAG’s clinical experts , younger people may have better prognosis”	The EAG have not provided any data to support this statement; therefore it would be more accurate to align with the language in Section 3.2.2.2 of the EAG report, which notes the possibility of better prognosis in younger patients, but does not make definitive statements. It would also clarify that the company have not stated that younger patients have better prognosis.	Thank you for highlighting this point. The EAG agrees to make a change to “According to the EAG’s clinical experts, younger people have better prognosis”.
On page 35, table 6, and on page 55, table 15, the EAG report that the follow up time for FORWARD-1 is “35.56 months”, and the follow-up time for SORAYA is “15.80 months”.	The company suggest that for FORWARD-1, this is changed to “ median follow up: 12.45 months ” and for SORAYA, this is changed to “ median follow up: 13.4 months ”	For accuracy, as the number 35.56 does not appear in the FORWARD-1 CSR or the company submission, while 15.80 does not appear in the SORAYA CSR or the company submission.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 74, the EAG noted inconsistency in the reporting of the re-scored FORWARD-1 OS outcome between Table 8 of the CQ response and 2.3.2 of the CQ response. They also noted that “It was difficult for the EAG to determine whether the results of the pairwise meta-analysis were robust given poor reporting of the methods used and the data inconsistency identified”	The value of 0.678 presented in Section 2.3.2 of the CQ response was based on an outdated version of the meta-analysis. The data in Table 8 of the CQ response is the most up-to-date and the company can confirm that no other inconsistencies have been identified. The company would propose amending the statement to “It was difficult for the EAG to determine whether the results of the pairwise meta-analysis were robust given poor reporting of the methods used ~~and the data inconsistency identified~~”	The company acknowledge and apologise for the inconsistency in the reporting and can confirm the data in Table 8 is correct. The amendment would highlight that the issue was with the reporting, and not with the data itself.	Thank you for acknowledging this. The statement as written is correct, as there was an inconsistency in the data reported. As this is therefore an accurate representation of our consideration during the appraisal, we have not changed the wording.
On page 16, the report states “if an alternative assay were adopted for identifying FRα expression within the NHS...” This is repeated on page 21 “The EAG further noted that if an alternative assay were adopted for identifying FRα expression within the NHS, there would be a risk that the population deemed eligible for mirvetuximab could differ	Currently there is only one assay available, so it is inappropriate to theorise the risk of an alternative assay. As such, the company requests these statements are removed.	Authorisation wording clearly states that eligible patients should have FRα tumour status defined as $\geq 75\%$ viable tumour cells demonstrating moderate (2+) and/or strong (3+) membrane staining by immunohistochemistry (IHC), assessed by a CE-marked <i>in vitro</i> diagnostic (IVD) with the corresponding intended purpose. If a CE-marked IVD is	We acknowledge that there is only one assay available to assess for FRα tumour status within the NHS at the time of the appraisal, which was the same test used in the clinical trials of mirvetuximab. However, as the results of this test are used to determine

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
from the population studied in the clinical trials. “ And page 75 “if an alternative assay were adopted for identifying FRα expression within the NHS, there would be a risk that the population deemed eligible for mirvetuximab treatment could differ from the population studied in the clinical trials.”		not available, an alternative validated test should be used.	eligibility for mirvetuximab, it is appropriate to comment on the importance of using that test when considering the use of mirvetuximab. This is not a factual inaccuracy and no change has been made.
On page 16, the report states “EAG received advice from two clinical experts that FRα testing could move to diagnosis” And on page 21, the report notes “testing could move to diagnosis, which would increase the number of people who would be tested and thus would increase the ICER for mirvetuximab”	The company propose this is amended to “testing could move to diagnosis, which would increase the number of people who would be tested. The impact on the ICER for mirvetuximab is unknown”	The current statement is factually inaccurate as no formal assessment has been made on the impact on the ICER. For example earlier diagnosis of patients with FRα, could improve relative survival and negate the impact of increased FRα costs such that the ICER for mirvetuximab reduces.	Thank you for your comment. If testing for FRα tumour status moved to diagnosis, this would increase the number of people with PROC who would be tested. This would increase the costs for mirvetuximab in the economic model, thus increasing the ICER. Given that no other treatments are available, which would use the result to guide

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			treatment decisions, an impact on effectiveness is considered unlikely. The statement is correct and has not been amended.
On page 38, the report states “Bevacizumab was used by most of the population in clinical practice”	The company propose this is amended to “ According to the EAG’s clinical experts, bevacizumab was used by most of the population in clinical practice. However, advice received by the company from their own clinical experts indicated lower use, at 30–40%. ”	To add clarity and provide balance to the report, highlighting the difference in opinion of the clinical experts. Furthermore, on page 32, the report states “The EAG also received advice from clinical experts that indicated that in UK practice, the majority of ovarian cancer patients with PROC would receive prior treatment with bevacizumab, and therefore this trial would be representative of many people in the target population”, highlighting that this statement requires additional context.	The EAG acknowledges this, however, will only be reporting on what our clinical experts said, as the company’s clinical expert views have been presented elsewhere.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 37, Section 3.2.1.3, the EAG note that “A comparison with FORWARD-1 was not possible as the company did not provide the statistical analysis plan.”	The company propose this sentence is moved to the last sentence of Section 3.2.1.2	For accuracy of reporting, as it is currently below the SORAYA trial, which may be confusing.	Thank you for highlighting this. We acknowledge the point raised; however, we believe that the current information presented is sufficient for the intended purpose.
On page 54, the EAG state “The company stated (p.78 of the CS) that the safety results were consistent with the previous data cut of MIRASOL (data not reported) and the SORAYA²⁷ and FORWARD-1²⁶ trials.” Although the company did not provide the safety data from the previous data cut of MIRASOL, in the company submission this statement was accompanied by references to the published data (1. Moore KN, Angelergues A, Konecny GE, Garcia Y, Banerjee S, Lorusso D, et al.	The company propose to amend the sentence to “The company stated (p.78 of the CS) that the safety results were consistent with the previous data cut of MIRASOL (~~data not reported~~), and the SORAYA²⁷ and FORWARD-1²⁶ trials.”	For accuracy of reporting, as it currently reads that the company did not provide the MIRASOL safety data, which is not wholly accurate as the data was provided in the reference pack.	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Mirvetuximab Soravtansine in FRalpha-Positive, Platinum-Resistant Ovarian Cancer. N Engl J Med. 2023;389(23):2162-74.), which were supplied in the reference pack to the EAG. Further, the EAG did not request any additional information on this data cut at clarification questions.			
On page 46, the EAG state “The comparator arm in the FORWARD- 1 trial (FRα-high population” and “The company did not provide the breakdown of baseline characteristics by chemotherapy type in the comparator arm”	Please clarify if this is referring to the rescored arm of the FORWARD-1 study or the original population	To add clarity.	Thank you, we have clarified this
On page 66, the report states “The EAG noted that the rate of complete response was low in both groups” This wording implies that both chemotherapy and	The company propose to amend this sentence to “The EAG noted that no patients in the chemotherapy group and 13 patients in the mirvetuximab group achieved a complete response.”	For clarity and accuracy. The EAG argues that obtaining CR decreases with subsequent line of therapy, so it is important to be clear that for MIRASOL at the line of treatments patients received, that no patients	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
mirvetuximab had low levels of CR, whereas no patients achieved CR with chemotherapy, and only patients treated with mirvetuximab achieved CR		achieved CR with chemotherapy vs 5.7% with mirvetuximab	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 73, the report states “The CS stated that mirvetuximab was associated with a reduced risk of ascites and bowel obstructions in comparison with chemotherapy. The company provided no further information to the clarification query regarding its claim that mirvetuximab results in a lower risk of ascites.” However, at clarification the company noted that inclusion was not directed towards any comparative study and that the expected tumour shrinkage capability of mirvetuximab, improved PFS and maintained HRQoL observations could contribute to better disease control and positively contribute in delaying the time to such complications arising.”	The company propose to amend this sentence to “The CS stated that mirvetuximab was associated with a reduced risk of ascites and bowel obstructions in comparison with chemotherapy. ~~The company provided no further information to the clarification query regarding its claim that mirvetuximab results in a lower risk of ascites”~~	For accuracy. The company does not claim that mirvetuximab was associated with a reduced risk or ascites and bowel obstructions.	Amended.
On page 12, the report states “..design limitations rather	The company suggests rephrasing to“..design limitations rather than	The addition of the word ‘may’ makes the language more	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
than using EQ-5D data collected in the company's pivotal trial (MIRASOL). This underestimated the quality of life of patients receiving chemotherapy."	using EQ-5D data collected in the company's pivotal trial (MIRASOL). This may underestimate the quality of life of patients receiving chemotherapy."	neutral rather than definitive, better reflecting that this is the opinion of the EAG. Insights received from patients report chemotherapy treatment has a significant impact on quality of life, and it would be inappropriate to use definitive wording to conclude that the lower utility values from literature are an underestimate.	
On page 16, the report states "Some participants were still receiving mirvetuximab at the end of the trial"	The company suggests to amend to "Some participants (3/227) were still receiving mirvetuximab at the end of the trial"	For clarity and accuracy.	Amended
On page 19, the report states that "The company description mainly described ovarian cancer, which accounted for the vast majority of cases in the target population. Fallopian tube and primary peritoneal cancers were considered distinct from ovarian cancer"	The company suggests to amend to " The company described ovarian cancer which includes fallopian tube and peritoneal cancer. "	It is not clear from the original statement that ovarian, fallopian tube and peritoneal cancer are grouped together, as the risk factors and symptoms are the same and they are treated in the same way and ovarian cancer is the accepted term used to describe them. As written, the current statements could be interpreted as the company claiming that	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		these are three distinct patient populations.	
On page 19, the report states “The company described PROC as having a markedly poor prognosis compared with platinum-sensitive disease.”	The company suggests to rephrase to “The company described PROC as having a markedly poor prognosis, worse than platinum-sensitive disease. ”	The current wording suggests the company presented evidence comparing PROC to PSOC. As this could lead to confusion, we suggest amending.	Amended
On page 41, the report states “(who were several years from diagnosis)”	The company suggests to amend to “(who were several years from initial OC diagnosis)”	To add clarity to the sentence and avoid misunderstandings	Amended
On page 38, the report states “A key exclusion criterion for FORWARD-1 was disease progression occurring within 4 weeks of the last platinum dose, in contrast to MIRASOL and SORAYA, which used a 3-month threshold. By applying a stricter definition FORWARD-1, the trial may have excluded participants who would have been eligible for MIRASOL and SORAYA, potentially selecting for a population with more platinum-resistant disease	The company proposes that this is amended to “A key exclusion criterion for FORWARD-1 was disease progression occurring within 4 weeks of the last platinum dose, in contrast to MIRASOL and SORAYA, which used a 3-month threshold. By applying a stricter definition FORWARD-1, the trial may have included participants who not would have been eligible for MIRASOL and SORAYA, potentially selecting for a population with more platinum-	The shorter criteria for disease progression applied in FORWARD-1 means that patients would have been eligible for this trial who would be excluded from MIRASOL and SORAYA.	Thank you for identifying this. The EAG have replaced the test to improve as follows: “A key exclusion criterion for FORWARD-1 was disease progression occurring within 4 weeks of the last platinum dose, whereas MIRASOL and SORAYA excluded patients who progressed within 3 months. This meant that FORWARD-1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
and affecting cross-trial comparisons.”	resistant disease and affecting cross-trial comparisons.”		included patients who progressed between 5 weeks and 3 months after platinum, a group that would not have been eligible for MIRASOL or SORAYA. As a result, FORWARD-1 may have included a broader population with more platinum-resistant disease, which could affect cross-trial comparisons.”

Issue 5 Incorrect/unclear statements: SLRs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 30, Table 5, row 6, the EAG note that “No quality assessment was performed for SORAYA.”	Please amend to “No quality assessment was performed for SORAYA, as it was single-arm study not included in the clinical effectiveness SLR ”.	For accuracy of reporting, as it currently reads as if the company did not conduct a quality assessment without a specified reason.	Amended
On page 31, Table 5, row 6, the EAG claim that “The assessment was also not accompanied with any explanation of the ratings made by the company.” However, in the company submission (Section 2.5, page 60, 61) we state: “However, the assessor-based evaluation indicated a low risk of bias, as investigator-assessed PFS is considered the most robust analysis for PFS, as supported by the GCIG (144). Additionally, the investigator-assessed results, including PFS, were	The company suggest the sentence “The assessment was also not accompanied with any explanation of the ratings made by the company” is removed.	For accuracy of reporting, explanations of the rating were provided. The EAG also did not request further information of the explanations at the clarification stage.	Amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
consistent with results based on a blinded independent central review (BICR) (14). MIRASOL is therefore considered to have a low risk of bias. Other outcomes, such as OS, are not prone to open-label biases (145, 146).” And in Section 2.13.2, page 92, 91), we note “Another possible limitation of the evidence is that MIRASOL was an open-label trial. Blinding was not feasible because each drug had a unique dose, examination schedule, and safety profile. Consequently, the RoB2 tool identified 'some concerns' in the outcome measurement domain. However, consistent results are seen in investigator-assessed and BICR analyses. The robustness of the efficacy results observed in MIRASOL is also supported by outcomes			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
such as OS, which is not prone to open-label biases, with studies showing similar effects for PROs (145, 146).”			
On page 78, the report states: “Table 13 in the company’s clarification response provided a comparison of utility data from a subset of papers identified in the SLRs for utilities, economic evaluations and a separate review of previous TAs; however, not all papers identified in these searches were presented in the table.”	Please amend to: “Table 13 in the company’s clarification response provided a comparison of all utility data identified in the SLRs for utilities, economic evaluations and a separate review of previous TAs”	As noted in the clarification response, “the previously cited studies that did not report utility values have been excluded from the table”; all available utility data were therefore reported.	There are only 17 studies included in Table 13, whereas the company state in the bullets above this that there were 10 economic evaluations reporting utility values, 3 HRQoL studies and 7 NICE TAs reporting utility values. The EAG does not therefore consider this table comprehensive. The EAG is unclear which 3 studies are missing. Nor does the table provide the primary reference for utility data for the NICE TAs or economic evaluations.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 78, the report states “The results of the search were not referenced in the CS and the company instead sporadically selected references to support their HCRU assumptions” On page 79, the report states “The results of the search were not referenced in the CS and the company instead sporadically selected references to support their HCRU assumptions (vial sharing from an appraisal in breast cancer [TA862(4)], TA285(5) which was an appraisal from 2013 in platinum-sensitive OC for HCRU, TA389(6) for administration cost codes, TA1007(7) for AE cost codes).”	Please amend to “The company selected resource use costs where available due to limited relevant information and validated these with clinical experts.”	To maintain neutral wording, and to clarify the approach. Please note that: • TA862 was cited as a recent example of expert clinical input on the use of vial sharing in the NHS; vial sharing was less relevant in many recent appraisals in ovarian cancer as many of therapies used flat dosing. • TA285 was selected for healthcare resource use; it is acknowledged that other sources may be equally valid. • TA389 was selected for administration costs as this source gave a decision rule for assigning administration types to the treatments included as comparators	Thank you for providing some additional detail on how sources were selected in this response. The wording in the EAG report has not been amended as no link was provided in the CS between the literature searches and the sources selected for each of these examples.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		in the current submission. TA1007 was selected for AE costs as the most recent NICE appraisal at the time of the development of the model.	
On page 79, the report states; “No previous NICE evaluations were identified in the company’s searches for economic evaluations or HSUVs, which would appear to be a major omission.”	The company suggests this sentence be reworded to “No previous NICE evaluations in PROC were identified in the company’s SLR searches for economic evaluations or HSUV ⁷ ~~which would appear to be a major omission~~	TAs 1007, 962, 946, and 673 were identified during handsearching, however they were deemed not relevant to the NICE submission due to not being in the PROC population. In question B5b of the clarification questions, the company reported the TAs identified through a targeted literature review of relevant NICE TAs that was conducted to identify additional health state utility values, which included TA962 and TA946. We acknowledge that this was not completely clear in the company submission and request, however the statement	Thank you for providing some additional detail on how sources were selected in this response. TA389 was in PROC and the EAG is unclear why this was not included in the HSUV search results. Also post progression HSUVs in the earlier line TAs could have data relevant to PROC. Therefore, the wording in the EAG report has not been amended.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		in the report is factually inaccurate and potentially misleading as the specific population of this appraisal (PROC) has not had a NICE evaluation in two decades, hence the very high unmet need. The TA's mentioned by the EAG (1007, 962, 946, and 673) are all in OC not PROC. Therefore, the EAG could clarify that it is their preference to extend the HSUV searches to OC as a whole in the absence of PROC data, rather than framing it as an omission by the company.	

Issue 6 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Misspelt company name “Abbvie” on page 2	Please correct to “AbbVie”	For the avoidance of doubt and correction of company name	Amended
Misspelt “heretoeafter” on page 19	Please amend to either “hereafter” of “hereinafter”	For clarity and to aid ease of understanding	Amended
US spelling of “signaling” on page 20	Please correct to “signalling”	For clarity	Amended
US spelling of “tumor” on pages 21, 22, 33, 36, 39, 45, 50, 51	Please correct to “tumour”	For clarity	Amended
On page 21, the reports states “ Although the EAG was aware that research about FR α expression in PROC was ongoing and it was therefore plausible that testing at diagnosis may lead to benefits elsewhere in the treatment pathway if knowledge of FR α expression could be used to inform treatment decisions at other treatment lines”	Please remove “although” from the start of the sentence	For clarity and to aid ease of understanding	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
US spelling of “behavior” on page 22	Please correct to “behaviour”	For clarity	Amended
Duplicated text on page 23 “However, the EAG appraisal did not identify major differences in efficacy and safety of topotecan in the company’s pivotal trial of mirvetuximab in the company’s pivotal trial of mirvetuximab ”	Please amend the sentence removing the duplicated text to “However, the EAG appraisal did not identify major differences in efficacy and safety of topotecan in the company’s pivotal trial of mirvetuximab”	For clarity and to aid ease of understanding	Amended
Duplicated text on page 31 “This could, for example, overlook limitations in outcomes with high attrition or subjective outcomes affected by the lack of blinding blinding ”	Please correct to “This could, for example, overlook limitations in outcomes with high attrition or subjective outcomes affected by the lack of blinding”	For clarity and to aid ease of understanding	Amended
On page 31, the report states “The company stated that FORWARD-1 was not presented in the CS due to the original trial population being based on a broader range of FR α expression	Please replace the bolded “ that ” with “than”	For clarity	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
that is now required by the licence for mirvetuximab.			
On page 32, the EAG state “this report includes discussion of the comparability of evidence between trials in its report , where indicated”	Please amend the duplicated text to “this report includes discussion of the comparability of evidence between trials, where indicated”	For clarity and to aid ease of understanding	Amended
On page 33, the report states “Patients with less than 25 expression were not eligible.”	Please amend to “Patients with less than 25% expression were not eligible.”	For clarity	Amended
On pages 33, 38 and 39, the report states “intensity $\geq$ 2+ intensity”	Please correct to “ $\geq$ PS2+”	For clarity	Amended
US spelling of “hemorrhagic” on page 34	Please correct to “haemorrhagic”	For clarity	Amended
US spelling of “multicenter” on page 35	Please correct to “multicentre”	For clarity	Amended
On page 37, the report states “ Although this was a different subgroup to the re-	Please replace “although” with “ however ”	For clarity	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
scored sub-group used in the meta-analysis”			

On page 37, the cross reference to table 13 has an error within the field code, meaning that it is followed by additional incorrect text “Censoring rules for SORAYA aligned with the MIRASOL trial for PFSINV and OS (Table 13 Censoring rules for PFSINV are available in Table 13. Censoring for subsequent treatment was not in line with the economic model, which assigned subsequent treatment costs on progression (see Section 4.2.8.3). Twenty patients (8.9%) were censored in the chemotherapy arm vs eight (3.5%) participants in the mirvetuximab arm because they received subsequent treatment; all censoring took place in the first 12-month interval. The EAG considered the impact of this to be minimal given the low rate of censoring.	Please correct the sentence to read “Censoring rules for SORAYA aligned with the MIRASOL trial for PFSINV and OS (Table 13).	For clarity and to aid ease of understanding	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table).			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 46, there is an unnecessary addition of UK, at the start of the sentence “ UK NICE guidance for second-line therapy...”	Please amend to “NICE guidance for second-line therapy...”	The addition of UK is redundant and potentially confusing	Amended
Inconsistent use of PLD or pegylated liposomal doxorubicin throughout	Please amend to either pegylated liposomal doxorubicin throughout, or pegylated liposomal doxorubicin on the first instance and abbreviate to PLD throughout	For clarity and to avoid confusion	Amended
On page 56, there appears to be a missing word in the following text “As the company did not provide the numbers who were assessed using MRI and their breakdown across trial arms”	Please amend to “As the company did not provide the number of participants who were assessed using MRI and their breakdown across trial arms”	For clarity and to aid ease of understanding	Amended
US spelling of “favored” on page 68	Please correct to “favoured”	For clarity	Amended

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 77, the report states “This mean that the EAG lacked confidence that the company had selected the most appropriate evidence for inclusion in the model.”	Please correct to ‘meant’	For clarity	Amended
Misspelt “positivie” on page 96	Please correct to “positive”	For clarity	Amended
On page 110, Table 25, the EAG have included an asterisk on rows “Post-progression utility value, chemotherapy (base case)*” and “Pre-progression utility value, chemotherapy (base case)*”. However, the footnote of the table does not signify what this asterisk is referring to.	Please add a footnote detailing the reason for the asterisk below Table 25	For clarity and to aid ease of understanding	Added

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 100, there is a missing full stop at the end of the following sentence: “Scenario analyses were based on the company clarification response and run from the clarification base case”	Please amend to include a full stop	For clarity	Added
On page 100, there is duplicate text “(Table 26Table 26).”	Please amend to “(Table 26).”	For clarity	Amended
Misspelt “Aligeds” on page 105	Please amend to “Aligns”	For clarity	Amended

References

1. George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, et al. Implementing rapid, robust, cost-effective, patient-centred, routine genetic testing in ovarian cancer patients. *Sci Rep*. 2016;6:29506.
2. Eccleston A, Bentley A, Dyer M, Strydom A, Vereecken W, George A, et al. A Cost-Effectiveness Evaluation of Germline BRCA1 and BRCA2 Testing in UK Women with Ovarian Cancer. *Value Health*. 2017;20(4):567-76.
3. Moss E, Taylor A, Andreou A, Ang C, Arora R, Attygalle A, et al. British Gynaecological Cancer Society (BGCS) ovarian, tubal and primary peritoneal cancer guidelines: Recommendations for practice update 2024. *Eur J Obstet Gynecol Reprod Biol*. 2024;300:69-123.
4. National Institute for Health and Care Excellence (NICE). NICE guidance TA862. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 treatments. Available at: <https://www.nice.org.uk/guidance/ta862/resources/trastuzumab-deruxtecan-for-treating-her2positive-unresectable-or-metastatic-breast-cancer-after-1-or-more-antiher2-treatments-pdf-82613609326789> (accessed February 2025). 2023.
5. National Institute for Health and Care Excellence. Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer [TA285]. <https://www.nice.org.uk/guidance/ta285/documents/ovarian-fallopian-tube-and-primary-peritoneal-cancer-recurrent-advanced-platinumsensitive-partially-platinumsensitive-bevacizumab-roche2>. (accessed February 2025). 2013.
6. National Institute for Health and Care Excellence (NICE). NICE guidance TA389. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer. Available at: <https://www.nice.org.uk/guidance/ta389/resources/topotecan-pegylated-liposomal-doxorubicin-hydrochloride-paclitaxel-trabectedin-and-gemcitabine-for-treating-recurrent-ovarian-cancer-pdf-82602858104773> (accessed February 2025). 2016.
7. National Institute for Health and Care Excellence (NICE). NICE guidance TA1007. Rucaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer. Available at: <https://www.nice.org.uk/guidance/ta1007/resources/rucaparib-for-maintenance-treatment-of-relapsed-platinumsensitive-ovarian-fallopian-tube-or-peritoneal-cancer-pdf-2973528218334661> (accessed February 2025). 2024.