MSAC Application 1787

Immunohistochemistry testing of solid tumour tissue to determine folate receptor alpha (FRα) expression status in adults with platinum resistant ovarian cancer, to determine eligibility for treatment with PBS subsidised mirvetuximab soravtansine

Applicant: AbbVie Pty Ltd

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for folate receptor alpha (FRα) expression status in adult patients diagnosed with platinum resistant high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer

Component	Description
Population	Test *If performed at confirmation of platinum resistance:* Adult patients with platinum resistant high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer. *If performed at primary diagnosis of ovarian cancer:* Adult patients with high-grade serous epithelial ovarian, fallopian tube, primary peritoneal, high-grade endometrioid, or undifferentiated epithelial ovarian cancer. Treatment Platinum resistant high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer whose tumour have a high level of folate receptor alpha (FRα) expression according to the PS2+ scoring method (i.e., ≥75% of viable tumour cells with moderate [2+] or strong [3+] staining) as determined by a validated immunohistochemistry (IHC) assay and which has been treated with no more than three lines of previous systemic therapy.
Prior tests	If performed at confirmation of platinum resistance: Test(s) to confirm high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer. If performed at primary diagnosis of ovarian cancer: Test(s) to confirm diagnosis of high-grade serous epithelial ovarian, fallopian tube, primary peritoneal, high-grade endometrioid, or undifferentiated epithelial ovarian cancer.
Intervention	Test IHC testing on solid tumour tissue to determine FRα expression based on prevalence in terms of percentage of viable tumour cells and level in terms of intensity of staining. Treatment Mirvetuximab soravtansine.
Comparator/s	Test No testing for FRα expression levels. Treatment Standard of care: non-platinum treatment (paclitaxel, topotecan, or pegylated liposomal doxorubicin) and supportive care with or without bevacizumab.

Component	Description
Reference standard	None.
Clinical utility standard	VENTANA FOLR1 (FOLR1-2.1) RxDx Assay to determine FRα expression levels.
Outcomes	<u>Test</u> **Safety outcomes**: adverse events associated with biopsy/re-biopsy for patients with inadequate tissue for tumour testing. **Diagnostic performance**: intra- and inter-reader variability; test failure rate; evidence of stability of proteins in archival tissue; heterogeneity within the same tissue sample; evidence of stability in FRα status over time with treatment and/or progression of disease; test-retest reliability. **Clinical utility of the test**: determine whether testing for FRα predicts variation in the treatment effect of mirvetuximab soravtansine in terms of health outcomes for patients. Qualitative assessment of potential risks associated with an incorrect test result or incorrect interpretation of results. Failure of the test to perform as expected or failure to correctly interpret test results may lead to improper patient management decisions. <u>Drug</u> Safety outcomes: Safety and tolerability of treatment with mirvetuximab soravtansine compared to alternative treatments assessed by adverse events, physical examination, laboratory findings and vital signs. Clinical effectiveness outcomes: • objective response rate (ORR) • overall survival (OS) • progression-free survival (PFS) • health-related quality of life (HRQoL). Healthcare system outcomes: • cost of testing per patient and cost associated with re-biopsies (e.g.: early-stage disease that has relapsed, test failure, inadequate sampling) • cost of treatment and cost of treating adverse events • financial implications: number of patients tested; number of patients treated.

Component	Description
Assessment questions	What is the safety, effectiveness, cost-effectiveness and total costs of FRα expression level testing and treatment with mirvetuximab soravtansine versus no testing and standard of care, in platinum resistant high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer? Does testing for FRα predict a treatment effect modification with mirvetuximab soravtansine? What are the potential costs and cost offsets associated with disease management arising from the listing of FRα testing?

Purpose of application

The codependent application requested:

- Medicare Benefits Schedule (MBS) listing of a test for folate receptor alpha (FRα) expression status in patients with platinum resistant ovarian cancer (PROC) for the determination of patient eligibility for mirvetuximab soravtansine.
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of mirvetuximab soravtansine for patients with platinum resistant epithelial ovarian, fallopian tube or primary peritoneal cancer.

Clinical claim:

The application claims that FRα expression status testing and mirvetuximab soravtansine results in superior health outcomes compared to no testing and standard of care therapy (non-platinum chemotherapy).

PICO criteria

Population

Test population

The population for testing FRα expression in the item descriptor proposed in the PICO Set Document (pp.7-8) is patients with PROC.

Two key Phase 3 trials (MIRASOL, FORWARD I) and one key Phase 2 study (SORAYA) were identified. Patients with ovarian cancer (including fallopian and primary peritoneal cancer) were enrolled in all studies with most patients enrolled in MIRASOL and SORAYA additionally having high grade serous epithelial and advanced disease (at least Stage III). All patients in the three studies had no more than three lines of prior therapy, likely based on the results of an early mirvetuximab soravtansine Phase 1 expansion study (IMGN853 (N=46)) that assessed the number of previous lines of treatment on mirvetuximab soravtansine efficacy (Moore, 2017). The subset of individuals enrolled in IMGN853 with one to three prior lines of therapy (n=23) demonstrated an objective response rate (ORR) of 39% and median progression free survival (PFS) of 6.7 months (compared with 13% and 3.9 months for patients with four or more prior lines, n=23) (Moore, 2017). These efficacy measures for mirvetuximab soravtansine monotherapy were comparable to those observed in the Avastin Use in Platinum Resistant Epithelial Ovarian Cancer (AURELIA; bevacizumab) trial (ORR: 31% and median PFS = 6.7 months) that led to the U.S. Food and Drug Administration (FDA) approval of bevacizumab for use alongside chemotherapy in patients with platinum resistant epithelial ovarian cancer (EOC) who have received no more than two prior therapeutic regimens (Moore, 2018).

The PICO Set Document (p.11) proposes that FRα status testing is undertaken in patients with resistance to platinum chemotherapy.

Presently there are no PBS/MBS items with a precise definition for platinum resistance. A simplistic definition of platinum resistance may be obtained from how recurrent ovarian cancer can be categorised (Lokadasan, 2016):

(i) platinum sensitive that includes those that recur after six months of completion of treatment; and
(ii) platinum refractory and resistant that includes those that progress during or recur within six months of treatment.

Platinum resistance was defined based on the number of prior lines of platinum therapy in the MIRASOL trial and SORAYA study:

- One line of platinum therapy:
  Must have received at least four cycles of initial platinum containing regimen, had a response (complete or partial), and then had disease progression between three and six months after the last dose.
- Two to three lines of platinum therapy:
  Must have had disease progression while receiving therapy or within six months after the last dose.

Platinum resistance in the FORWARD I trial was defined as progression within six months of completion of a minimum four cycles platinum-containing therapy.

The definition of platinum resistant disease also varies in the literature and continues to evolve. At the fifth Ovarian Cancer Consensus Conference (OCCC), it was noted that platinum-free interval (PFI; defined as the interval between the date of the last platinum dose and the date of relapse) has been the most widely accepted and used clinical surrogate for predicting response to treatment and prognosis and has been used to select and stratify patients in trials (Wilson, 2017). However, there was also recognition that diagnosis of relapse was influenced by the type and frequency of monitoring in trials (e.g., cancer antigen-125, computed tomography- or positron emission tomography-scan and/or clinical) that impacts on patients being categorised as 'platinum sensitive' or 'platinum resistant' (Wilson, 2017).

Wilson (2017) noted there was agreement among participants of the OCCC that response to platinum is a continuum and consensus was reached that categorisation of patients into trials be based on four subsets of PFI duration of (i) less than one month, (ii) one to six months, (iii) six to 12 months and (iv) greater than 12 months rather than the corresponding categories of platinum-refractory, platinum resistant, partially platinum sensitive and fully platinum sensitive to avoid a judgement on whether a patient would respond to platinum therapy or not. It was also agreed that where trials use PFI, that the method of diagnosing recurrence be specified (Wilson, 2017). It was also at this meeting, in recognition of increasing use of non-platinum and biological agents, that a broader term of treatment-free interval (TFI) be adopted where TFI is the TFI from last platinum dose.

Discussions at the sixth OCCC (Vergote, 2022) suggested that it was reasonable that the next line of therapy for patients with relapse within 12 weeks might be without platinum, suggesting that those with progression between three and six months may still be treated and possibly respond to platinum therapy. There is at least one ongoing mirvetuximab soravtansine trial (MIROVA) comparing mirvetuximab

soravtansine plus carboplatin versus platinum-based chemotherapy that has adopted this 12-week platinum sensitive definition (Vergote, 2022).

During the pre-PASC teleconference, the applicant's clinical experts suggested that testing at primary diagnosis would be a preferred alternative; the applicant advised that they would support FRα testing being accessible for patients upon primary ovarian cancer diagnosis. The applicant's clinical experts suggested that if testing is conducted at primary diagnosis, testing should be conducted in patients with high-grade serous epithelial ovarian, fallopian tube or primary peritoneal, high-grade endometrioid, or undifferentiated epithelial ovarian cancer as these histotypes can be difficult to distinguish.

The applicant's clinical experts indicated the following advantages of testing FRα at diagnosis:

- Most ovarian cancers require some immunohistochemistry (IHC) at diagnosis and FRα could be added as a reflex test (like human epidermal growth factor receptor (HER2) was added to estrogen receptor/progesterone receptor testing for breast cancer).
- The test would be performed or sent away for testing by the laboratory that holds the tissue samples.
- The test would likely be performed on resection or debulking sample with low failure rate and greater ability to assess heterogeneity in FRα expression levels.
- The test would be conducted while the case is being reported and has the attention of the pathologists to deliver a quick turnaround time.
- Potential to test poorly differentiated tumours as some will later prove to be high grade serous ovarian cancer (HGSOC).
- The result would be in the patient's file and be available to the clinician when the patient progresses.
- Avoids the need to specifically order the test (usually made to the oncologist's local laboratory, which has to retrieve the sample from the reporting laboratory) resulting in delays and additional MBS sample retrieval and review costs.
- Could identify if the sample is unsuitable and could order a retest early, prior to progression.
- Testing can be conducted without knowledge of patient's response to platinum.

The applicant's clinical experts indicated the following disadvantages of testing FRα at diagnosis:

- Could result in over testing of patients who are not HGSOC or who would not eventually progress.
- FRα status may change during chemotherapy.

Considerations for testing at disease progression:

- Would still need to be ordered (on diagnostic sample) for patients with current disease who were not tested at diagnosis prior to listing.
- Helpful to perform retest at progression on a new biopsy to learn if expression changes on chemotherapy.

The applicant's clinical experts suggested that although a proportion of EOC patients would be unnecessarily tested as they would not be eligible for mirvetuximab soravtansine, the associated costs of testing at primary diagnosis would still be justified by eliminating potential delays in delivering the best treatment option for eligible patients as soon as possible. Results of the FRα expression reflex test

conducted up-front, would be a part of the patients' record available exactly when a clinical decision about the next line of treatment is made. This suggestion takes into consideration the ever-evolving understanding of the nature of platinum resistance.

Another advantage discussed at the pre-PASC teleconference for the predictive biomarker test being conducted at EOC diagnosis is that its results may inform decision making about the appropriateness of mirvetuximab soravtansine treatment as patients progress through the stages of the disease. The applicant's clinical experts suggested that listing of the next generation drugs for FRα-positive EOC would involve a broader population, potentially including platinum sensitive EOC cancers. Testing at primary diagnosis may future-proof the MBS listing as several completed and ongoing trials of mirvetuximab soravtansine in combination with platinum-based chemotherapy or bevacizumab for other population subgroups, e.g., platinum sensitive (PICCOLO[1], MIROVA[2], Study-420[3], GLORIOSA[4]) or platinum-agnostic (FORWARD II[5]) EOC have been reported (Bogani, 2024).

PASC discussed the advantages and disadvantages of testing at either cancer diagnosis or at platinum resistance.

PASC noted that testing at cancer diagnosis is associated with the following benefits:

- *Lower test failure rates, as generally more tissue is available at initial resection.*
- *An opportunity for rapid re-test of failed samples.*
- *Testing the tissue sample obtained from primary tumour is in alignment with the majority of the cases of the key SORAYA study.*
- *Future-proof of item descriptor, considering the number of forthcoming clinical trials that may potentially expand the EOC population eligible for mirvetuximab soravtansine treatment. Use of the proposed item to encompass trials still underway would be restricted by the wording of the PBS restriction for the therapy.*
- *Minimise intratumour variability of FRα expression markers through multiple slice testing of larger tissue specimens obtained at diagnosis.*
- *While testing for FRα expression does not take a significant amount of time (typically a day), it can take weeks to retrieve tissue samples from a laboratory. Testing at initial diagnosis may prevent delay of starting appropriate therapy as results are already known (for those with FRα expression that meets the PBS restriction).*

PASC identified the following concerns with testing at cancer diagnosis:

- *There is limited evidence available for the stability of FRα protein over time, taking into account the stages of disease and the effects of chemotherapy. There is evidence of discordance in primary tumour specimens versus metastatic lesions indicating temporal heterogeneity of tumour (Deutschman, the*

[1] https://clinicaltrials.gov/study/NCT05041257
[2] https://clinicaltrials.gov/study/NCT04274426
[3] https://clinicaltrials.gov/study/NCT04606914
[4] https://clinicaltrials.gov/study/NCT05445778
[5] https://clinicaltrials.gov/study/NCT02606305

2024 European Congress of Pathology poster). This may place additional uncertainty on whether a re-biopsy at platinum resistance is required.

- *A larger number of patients will be tested at diagnosis compared to if testing were done at platinum resistance. This has cost implications.*
- *A patient population who have a non-informative test at initial diagnosis, or whose* FRα *expression status changes following treatment, or the current prevalent patient population who have not undergone testing will require FRα testing after developing platinum resistance. They will not be able to access the test if testing is restricted to the episode of cancer diagnosis.*

PASC considered the relative risks and benefits of both the alternative testing populations (based on timing of the test, i.e., at cancer diagnosis or at platinum resistance) should be explored in the integrated codependent submission. PASC noted that the prevalent patient population should not be excluded from accessing the test if testing is restricted to be performed at cancer diagnosis.

PASC also noted that in order to capture all patients who may potentially benefit from the drug and the reported diagnostic yield of testing, the population eligible for a biomarker test will be larger than the population that becomes eligible for the treatment.

Drug population

The proposed eligible population for mirvetuximab soravtansine is described as 'adult patients with platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer whose tumours are FRα-positive'. Details of the intended eligible PBS population were not provided in the application or PICO Set Document, however the applicant has indicated that patient eligibility will be based on the eligibility criteria of the MIRASOL trial that included patients with high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with FRα expression in ≥75% of viable tumour cells (TCs) and membrane staining at moderate and/or strong intensity levels, referred to as PS2+.

PASC noted that the proposed treatment population of patients with platinum resistance is in alignment with the key MIRASOL trial. PASC noted that for treatment eligibility within the trial, patients had to have high FRα expression (defined as ≥75% of viable tumour cells with moderate [2+] or strong [3+] staining) and no more than three lines of prior lines of therapy. PASC noted that in the key MIRASOL trial, only one in three platinum resistant patients met the eligibility criteria for FRα expression. PASC noted that eligibility criteria for FRα expression and prior lines of treatment were not well evidenced and were based on Phase 1 expansion studies (Martin, 2017 and Moore, 2017) with a limited number of patients as well as results from the Phase 3 FORWARD-I study.

Background and rationale for testing FRα

In Australia in 2023, the death rate from ovarian cancer was 4.6% of all female cancers (ACRF 2024). There are currently no recommended screening tests for ovarian cancer and the absence of definitive symptoms makes it difficult to diagnose in the early stages. Over the last 30 years, mortality rates from ovarian cancer have remained poor (Torre, 2018) with patients diagnosed with advanced disease (Stage III and IV) having

a 10-year survival rate of 10–30% (Oza, 2011; a Canadian review). In Australia, the five-year survival rate is 49%[6].

Ovarian cancer can be classified in two histological subtypes, epithelial and non-epithelial. EOC originates from ovarian surface epithelium (mesothelium) and accounts for 85-90% of all ovarian tumours. The heterogeneity of EOC, which consists of several tumour subtypes with greatly divergent clinicopathologic characteristics and behaviour, poses a major challenge to understanding the pathophysiology of the disease. HGSOC is the most common and aggressive form of EOC, which accounts for about ~70% of all EOC cases and it is the leading cause of cancer-related death among all gynaecological cancers worldwide. Less common types of EOCs include: endometrioid carcinoma, which consists of about ~20% of EOC and occurs more commonly in women with endometriosis; low-grade serous ovarian carcinoma, which is a slow-growing tumour that accounts for about 5% of EOC; mucinous carcinoma, which is more distinct and tends to be large (around 20 cm); and ovarian clear cell carcinoma accounts for approximately 5% of all ovarian carcinomas and is characterised by a high recurrence rate (Atallah, 2023).

In contrast to other common epithelial cancers, HGSOCs are initially hypersensitive to platinum chemotherapy.

Of patients with an initial response to platinum chemotherapy, 75% to 80% will eventually relapse (Cooke, 2011; Lokadasan, 2016) and nearly all patients with recurrent disease will eventually develop platinum resistance. At the pre-PASC teleconference, the applicant's clinical expert indicated that approximately 60-70% of recurrences of high grade serous cancers are platinum sensitive and even if response to one or two lines of platinum is achieved, secondary platinum resistance will occur and that there are only a small percentage of patients who don't develop resistance to one or two lines of subsequent platinum-based chemotherapy.

Folate is essential for DNA replication, methylation, and the synthesis of nucleotide precursors. Folate and FRα have an important role in the process of cancer progression. Growing evidence shows that various solid tumours (including ovarian cancer) are characterised by FRα overexpression, which can be leveraged to deliver targeted therapy (Bogani, 2024).

It was reported that 76 to 89% of EOCs have FRα overexpression, which is absent in the normal ovarian epithelium (Kalli, 2008; Moore, 2018; Scaranti, 2020). However, differential levels of FRα expression have been observed across different histological subtypes of ovarian cancer. For example, a consortium-based study drawing from 12 studies noted FRα expression in 76% of high-grade serous, 50% of low-grade serous and 32% of clear-cell ovarian cancers (Scaranti, 2020). It was suggested that FRα has emerged as an attractive candidate for targeted approaches designed to exploit its differential distribution pattern as a novel avenue of therapeutic intervention in EOC. The ability of FRα to internalise large molecules makes this receptor well suited for antibody-drug conjugate-based therapeutic approaches (Martin, 2017).

Mirvetuximab soravtansine is a FRα-directed antibody and microtubule inhibitor conjugate with a unique ability to specifically target FRα. In November 2022, the FDA granted accelerated approval to mirvetuximab soravtansine-gynx (this is assumed to be the same as mirvetuximab soravtansine in the

[6] From 2015-2019 data; https://www.canceraustralia.gov.au/cancer-types/ovarian-cancer/statistics

current request), for treatment of adult patients with FRα-positive, platinum resistant epithelial ovarian, fallopian tube or primary peritoneal cancer who have received one to three prior systemic therapies.

Estimated utilisation

Based on AIHW data, the incidence of ovarian cancer (inclusive of fallopian tube and peritoneum) is 13.5 cases per 100,000 females, which the application estimated would equate to 1,833 cases based on the 2024 population. The application also estimated that 90% of cases are epithelial and 65% are diagnosed at Stage III/IV (Cancer Council; NCI 2017 SEER data[7]). Therefore, the incidence of advanced epithelial ovarian cancer would reflect roughly 1,100 patients. The application assumed the uptake rates to be REDACTED%, REDACTED%, REDACTED% and REDACTED% in Year 1, Year 2, Year 3 and Year 4, respectively. Out of the 1,100 advanced epithelial cancer patients estimated above, approximately 70% (770) of these will go on to receive treatment (Beachler, 2020). If all these patients are assumed to have the opportunity to receive FRα testing, approximately REDACTED patients would utilise the test in Year 1 (REDACTED%). The application noted that future testing patterns for FRα are not yet well understood, given this will be a new biomarker and test within the Australian treatment landscape. Therefore, the above estimate is provided only as an indication. The applicant has advised that a detailed analysis of utilisation estimates will be provided within the integrated codependent submission, which will include sensitivity analyses and consider the impact and likelihood of testing occurring at various stages of the patient journey.

Intervention

Test

The VENTANA FOLR1 (FOLR1-2.1) RxDx Assay (henceforth referred to as 'VENTANA FOLR1') was developed for use as a companion diagnostic to aid pathologists in identifying FRα positive EOC patients. The applicant noted that VENTANA FOLR1 is a Roche Diagnostics product with current FDA approval as a companion diagnostic for mirvetuximab soravtansine. VENTANA FOLR1 was approved by the FDA for the following indication:

> "VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is a qualitative immunohistochemical assay using mouse monoclonal anti-FOLR1, clone FOLR1-2.1, intended for use in the assessment of folate receptor alpha (FOLR1) protein in formalin-fixed, paraffin-embedded epithelial ovarian, fallopian tube or primary peritoneal cancer tissue specimens by light microscopy. This assay is for use with OptiView DAB IHC Detection Kit for staining on a BenchMark ULTRA instrument. FOLR1 expression clinical cut-off is ≥75% viable tumor cells (TC) with membrane staining at moderate and/or strong intensity levels. This assay is indicated as an aid in identifying patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer who may be eligible for treatment with ELAHERE (mirvetuximab soravtansine). Test results of the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls. This product is intended for in vitro diagnostic (IVD) use". (FDA 2022, p. 1).

[7] https://seer.cancer.gov/archive/csr/1975_2017/results_merged/sect_21_ovary.pdf. Assumed to be this resource, however values cited could not be independently verified.

PASC noted that the FRα test has two dimensions: (i) prevalence - relates to the percentage of tumour cells that stained positive for FRα and (ii) level - relates to the intensity of membrane staining, assessment of which involves a degree of subjectivity.

VENTANA FOLR1 was approved by the FDA based on the Phase 2 single-arm mirvetuximab soravtansine SORAYA study enrolling patients with platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. Most of the samples tested with the VENTANA FOLR1 Assay in the study were high-grade serous EOC (86.3%; 378 of 438). Samples were either from excision/resection (75.6%; 331 of 438) or biopsy (24.4%; 107 of 438). Most samples were primary tumours (63.7%; 279 of 438) which were located in the ovary (48.6%; 213 of 438), peritoneum (10.0%; 44 of 438), and fallopian tube (3.9%; 17 of 438) (James, 2023, pp.5-6).

At the time of application, VENTANA FOLR1 was the only validated diagnostic assay for FRα status (PICO Set Document, p.4). Through communications with the Department, the applicant indicated that the assay has already been submitted for listing on the Australian Register of Therapeutic Goods (ARTG) as of late July 2024.

The current MSAC application proposed IHC testing using VENTANA FOLR1 (FOLR1-2.1) RxDx Assay for testing FRα expression status in adult patients with platinum resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer.

The application stated that in Australia, IHC testing is a well-established technique in all major pathology laboratories and that laboratories already have the platform infrastructure. The FRα antibody and reagents to perform FRα IHC testing are the only additional resource required.

The application recommended that FRα testing be conducted once a diagnosis of platinum resistant ovarian cancer has been established and ordering be restricted to gynaecologists and oncologists (i.e., a specialist or consultant physician) (PICO Set Document, p.4). The role of a certified pathologist would be limited to conducting the test and reporting of results. Delivery of this service would be provided by a pathologist with knowledge and expertise in IHC testing. The applicant also suggested that consistent with the introduction of diagnostic tests associated with access to targeted therapies, pathologist training and quality assurance programs would be developed with respect to delivery of diagnostic tests for access to PBS-listed treatment. It was proposed that FRα testing would be carried out in any pathology laboratory holding the appropriate accreditation to claim pathology services through the MBS. The application also suggested that tumour tissue specimens for the majority of target patient population will be available for testing following primary tumour debulking surgery or may be obtained as formalin-fixed paraffin-embedded (FFPE) blocks, which were archived following primary tumour debulking surgery. Retrieval and review of one or more archived FFPE block are forwarded on to the specialist molecular diagnostic laboratories who are able to analyse the tissue (PICO Set Document, p.2). Elsewhere, the application suggested that the assessment of FRα status in patients involves taking a biopsy of the tumour and performing an IHC VENTANA FOLR1 assay (PICO Set Document, p.4).

Biopsy procedures would be reserved for situations where the tumour tissue specimen is either not available or insufficient. In the FORWARD I trial protocol, Martin (2017) found that 22% of pre-treatment biopsies were not evaluable due to insufficient tumour cells. According to the applicant's clinical expert at

the pre-PASC teleconference, up to 20% of patients may require re-biopsy at recurrence if a tumour tissue specimen is unavailable or inadequate.

Under the scenario where FRα testing is conducted at diagnosis of ovarian cancer, a certified pathologist would be initiating and conducting the FRα expression test using the cancer tissue specimen from primary tumour debulking surgery. The FRα expression test would become a part of reflex testing, i.e., an approach to testing in which the pathologist handling the case is responsible for initiating and controlling testing for a set of prespecified biomarkers. It is performed automatically without the involvement of the ordering physician. Introduction of targeted therapy in the adjuvant setting has meant that biomarker testing is becoming important for clinical decision making in early-stage disease. As the number of targeted therapies increases, so will the demand for timely clinical investigation of numerous biomarkers across multiple therapeutic targets (Gosney, 2023).

Although biomarker prognostic tests have been traditionally ordered by the treating oncologist upon confirmation of an appropriate pathological diagnosis, the delay this introduces prolongs further what is already a complex, multi-stage, treatment pathway and delays the start of the systemic treatment, which is crucially informed by the results of such analysis (Gosney, 2023).

There was no information about the turnaround time of the test. This should be addressed in the integrated codependent submission. Also, as turnaround time is proposed to be less if patients are tested upon diagnosis rather than at the time of becoming platinum resistant, the integrated codependent submission should also provide evidence to support this contention.

All mirvetuximab soravtansine trials and studies conducted to date (including those in platinum sensitive and platinum agnostic populations) have assessed FRα expression with the VENTANA FOLR1 assay, with eligibility criteria set at ≥75% of TCs in most of the trials/studies. The exceptions were FORWARD II (medium/high FRα expression; ≥50%/ ≥75% of TC with PS2+ staining intensity) and Study-420 of carboplatin and mirvetuximab soravtansine, where the cut-off point was ≥25%.

The development of mirvetuximab soravtansine as a highly selective, directed therapeutic agent has necessitated reliable quantification of tumour FRα expression in order to use this measure as a response-predictive biomarker for patient selection. FDA approval of the VENTANA FOLR1 assay (FDA 2022, p.21) was made on the basis of the SORAYA Phase 2 single-arm study to evaluate the efficacy and safety of mirvetuximab soravtansine in patients with PROC, fallopian tube, or primary peritoneal cancer. Patients were permitted to receive up to three prior lines of systemic therapy. All patients were required to have received prior bevacizumab. The trial enrolled patients whose tumours were positive for FRα expression (i.e., ≥75% of viable TC demonstrated FOLR1 membrane staining at moderate and/or strong staining intensity as determined by the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay at a central site). Ideally, a validated test would present some evidence for the differential prognostic effect of positive FRα expression status in EOC. However, the single-arm SORAYA study is insufficient for establishing clinical validity of the ≥75% of TC or ≥ 2+ membrane staining cut-off for differentiating the subgroup of patients with respect to clinical efficacy of mirvetuximab soravtansine as the study did not enrol patients whose FRα expression was below 75% of TC or < 2+ membrane staining.

The rationale for (a) the target population defined as patients with high FRα expression (≥75% of TC staining, at ≥2+ staining intensity); and (b) whether the choice of this threshold for the FRα expression successfully differentiated biomarker-positive and biomarker-negative patients in their response to a targeted treatment versus standard care was explored. Only one (FORWARD I) of the three studies (MIRASOL, SORAYA, FORWARD I) reported in the PICO Set Document attempted this differentiation, albeit unsuccessfully (see below). A further Phase 1 study (IMGN853-0401) assessing the pharmacokinetics and pharmacodynamics study of mirvetuximab soravtansine in adults with ovarian cancer and other folate receptor 1 (FOLR1)-positive solid tumours was also identified.

The Phase 1 study (IMGN853-0401, NCT01609556) concluded that the recommended Phase 2 dose for single-agent mirvetuximab soravtansine administered every three weeks was to be 6.0 mg/kg (adjusted ideal body weight). The initial antitumour activity observed with mirvetuximab soravtansine monotherapy, particularly in those patients with PROC, no more than three prior lines of therapy and FRα medium or high expression per the "PS2+" scoring method [defined by 2+ intensity staining of TCs with medium ≥50% to <75% of TCs and high ≥75% of TCs] suggested the potential for a significant improvement over single-agent chemotherapy. The Phase 1 study generated a number of "expansion cohorts", possibly with overlapping patients, that were used to obtain some evidence of differential treatment effects in patients with platinum sensitive ovarian cancer (PSOC) and PROC, patients with various degrees of FRα positivity and exposure to prior lines of treatment. It appears that all "expansion cohort" investigations included a method for evaluating FRα expression consistent with VENTANA FOLR1 algorithm, in terms of calculating a percentage of cells that stained positive for FRα (the cut-off varied from ≥25% to ≥75%) together with intensity scoring method on a scale of 0 to 3, with a threshold of membrane staining intensity ≥2 set as the minimum requirement for FRα positivity (the PS2+ scoring method).

An expansion cohort study (Martin, 2017), opened as part of the Phase 1 trial of mirvetuximab soravtansine monotherapy involved 27 patients who were previously exposed to platinum-based therapy and taxane; 74% were platinum resistant. Tumour tissues were scored for FRα positivity as follows: low, 25 to 49% of TCs with ≥2+ staining intensity; medium, 50 to 74% of cells with ≥2+ intensity; and high, ≥75% of cells with ≥2+ intensity. Subgroup analysis of the outcomes by FRα expression level showed that the ORR in the cohort of patients with high FRα expression was 31% (5/16), which included two complete responses. This was compared to 20% (1/5 patients) observed in the medium cohort, and lack of any objective responses in individuals with low FRα-expressing tumours. The median PFS was 4.2 months (95% CI, 2.8 to 5.4 months) for the overall population, 5.4 months (95% CI, 2.8, not identifiable) for the high FRα cohort, 3.9 months (95% CI,2.6, 12.7) for the medium subset, and 2.8 months (95% CI,1.3, 5.4) for the low expressors. No formal statistical hypothesis was tested for the association between expression and response, however, the applicant suggested that the results from this Phase 1 study clearly demonstrated that the strongest signals of mirvetuximab soravtansine activity were associated with higher FRα expression. The small sample size, inclusion of platinum sensitive population, and confounding impact of more than 3 prior treatments in 17 of the 27 cases, limit interpretation of the results.

In the Phase 1 expansion cohort study (Moore, 2017), forty six PROC patients with FRα-positive tumours were enrolled, based on an inclusion threshold of ≥25% of cells with ≥2+ staining intensity. Patients with up to five prior lines of systemic therapy were eligible to enrol; 11 patients (24%) had received only one prior platinum regimen (i.e., primary platinum resistance), while the remaining 35 (76%) had received at

least two lines of platinum-based therapy (i.e., acquired platinum resistance). As part of the analyses, patients were sorted based on FRα positivity as follows: low (25% to 49% of tumour cells with ≥2+ staining intensity), medium (50% to 74% of cells with ≥2+ intensity), or high (≥75% of cells with ≥2+ intensity). Regardless of FRα expression, the majority of patients experienced tumour shrinkage in response to mirvetuximab soravtansine treatment. Stratification of patients based on FRα positivity failed to justify the threshold of ≥75% of tumour cells with ≥2+ intensity, possibly because of the small sample size. Small sample size and inclusion of non pre-specified subgroups limit interpretation of the results.

The findings from these ad-hoc exploratory analyses of the Phase 1 trial population were said to be instrumental in defining the target population for the FORWARD I trial, an open-label randomised controlled Phase 3 trial including patients (n=366) with one to three prior lines of therapy. Patients were randomised 2:1 to receive mirvetuximab soravtansine at 6 mg/kg adjusted ideal body weight or investigator's choice of chemotherapy (including paclitaxel, pegylated liposomal doxorubicin, or topotecan, n=109 patients). Taking into consideration the putative relationship between the level of tumour FRα expression and response, patient eligibility was expected to be based on three key eligibility criteria: platinum resistant disease, one to three prior lines of therapy and medium/high FRα (Moore 2018, p.129). The subgroups with high and moderate levels of FRα expression were pre-defined as 50 to 74% of TC staining visible at less than or equal to 10 times (≤10X) magnification (medium expressors); and ≥75% of TC staining visible at ≤10X magnification (high expressors). The focus on the subgroups indicates an intention to validate the VENTANA FOLR1 test with a threshold capable of differentiating biomarker-positive and biomarker-negative patients in their response to a targeted treatment versus standard care. However, in contrast with the Phase 1/2 studies that were performed prior, FORWARD I used the observable membranous staining at 10X microscope objective (10X scoring system) instead of the PS2 scoring method to score FRα on immunohistochemistry.

FORWARD I did not meet its primary endpoint of superior PFS in the mirvetuximab soravtansine arm in the intention to treat (ITT) population, nor in the predefined subgroup of FRα high patients. Median progression-free survival was 4.1 and 4.4 months in the mirvetuximab soravtansine and chemotherapy groups, respectively. The negative results were unexpected and were explained by the possible lack of clinical validity of the membranous staining at 10X microscope objective (10X scoring) as the method of determining FRα positivity for patient enrolment (Moore, 2021). The 10X scoring system was felt to be easier to use but ultimately was found not to correlate as vigorously with the PS2 scoring method. In fact, only 35% of FORWARD I participants would have been FRα high expressors if the PS2 scoring system was used while, with the 10X scoring system, FORWARD I classified 58% as FRα high expressors (Bogani, 2024). The authors re-analysed the data and this "Exploratory rescoring analyses using PS2+ methodology suggested that use of ≤10X scoring allowed enrolment of patients with lower than expected levels of FRα expression, thus diluting the treatment effect of mirvetuximab soravtansine, in both the ITT and high FRα populations" (Moore 2021, p.762). Looking at patients expressing high levels of FRα (expression level 75% or more determined by central testing using the anti-FOLR1 2.1 antibody (VENTANA Medical Systems, Roche Tissue Diagnostics)), median PFS was longer in patients treated with mirvetuximab soravtansine than in patients having chemotherapy (4.8 months vs 3.3 months; HR 0.69, 95% CI 0.48 to 1.00; p=0.049). However, these results were not considered statistically significant due to the Benjamini–Hochberg procedure used to control for false discovery when multiple hypothesis testing is performed (Moore, 2021).

The applicant provided a re-analysis of the FORWARD I results in order to identify sub-groups which aligned to those defined in the Phase 1 study instead (i.e., using PS2+ scoring). This analysis was presented by the authors at the European Society of Medical Oncology conference (Moore, 2019, slide 17, not previously available from published peer reviewed sources). Results of the non-preplanned analysis demonstrated that statistically significant clinical benefits were observed for high expressors (≥75% tumour cell staining at 2+ staining intensity), and non-significant benefits on all reported outcomes are observed for medium expressors (≥50 to 74% tumour cell staining at 2+ staining intensity) and for low expressors (<50% tumour cell staining at 2+ staining intensity).

It is reasonable to assume, as suggested by the applicant, that overall, the Phase 1 study findings, the non-significant results from the FORWARD I trial, and the subsequent prospective demonstration of significant clinical benefit with mirvetuximab soravtansine treatment in FRα-high expressors in SORAYA and MIRASOL all support the clinical benefits in the proposed population of patients with ≥75% tumour cell staining at 2+ staining intensity. However, since FRα-medium expressors were not enrolled in SORAYA or MIRASOL trial and no significant difference between the pre-defined subgroups of FRα-high and FRα-medium expressors was demonstrated in the FORWARD I trial, it remains uncertain, whether the exclusion of the FRα-medium expressors from mirvetuximab soravtansine treatment is justified.

Although the FORWARD I trial eventually demonstrated a significant improvement in PFS in mirvetuximab soravtansine subgroup with high FRα expression defined as ≥75% of staining, at ≥2+ intensity, this was based on an unplanned re-scoring and apparent re-classifying of the patients from high to moderate levels of FRα expression. This is not considered to be a relevant way to validate the nominated ≥75% threshold.

Concordance of the test results

The issue of concordance of the test results conducted in the archival and fresh biopsy samples is relevant to the question of eligibility for the forthcoming treatment options. The applicant summarised the findings from six studies (Martin, 2017; Rubinsak, 2018; Despierre, 2013; Kalli, 2008; Crane, 2012; Deutschman, 2024) assessing FRα expression stability over time, at different stages of the disease (e.g., before and after metastasis) and at different steps in the treatment pathway (e.g., before and after chemotherapy). It is not clear whether these six studies represent the totality of the available evidence and a thorough exploration of FRα expression stability should be presented in the integrated codependent submission.

The applicants' interpretation of the finding of the studies seems to suggest that there is sufficient evidence that the FRα expression is the same whether archival or fresh biopsy tissues are used, in addition to across samples from different anatomical sites of the patient's body or whether primary or metastatic tumour samples are assessed; and that FRα expression is maintained regardless of PFI and is not altered after chemotherapy treatment.

Only two of the presented studies used the VENTANA FOLR1 assay (Martin, 2017 and Deutschman, 2024), the other studies used unvalidated assays. Therefore, the degree to which the results obtained from different assays and scoring methods of assessment of FRα expression status are valid in the context of the integrated codependent submission remain uncertain. There are no data on concordance of the results produced by the different testing algorithms, which makes the interpretation of reported difference in scores and its statistical significance (if estimated) problematic. This is especially true if the scoring method

is limited to one of the two FRα-positivity criteria, as in Crane (2012), where FRα expression was assessed in terms of staining intensity (a 'low staining' group (score 0 or 1) and in a 'high staining' group (score 2 or 3), while omitting calculations of a proportion of TC with membrane staining.

For the purposes of establishing FRα expression stability over time, only paired (matched from the same person) samples are suitable. The size of these samples was small ranging from 24 patients (Kalli, 2008) to 59 patients (Deutschman, 2024), which undermines the applicability of the study results to the target population. Regardless of the testing method used, there is some evidence of FRα expression stability not being demonstrated in a small percentage of patients (2/15=13%), whose FRα expression changed from low in the archival tissue sample (presumably at or around the primary diagnosis) to high in the mirvetuximab soravtansine pre-treatment biopsy (Martin, 2017). The same was true in some patients (2/24 =8%) from another study (Kalli, 2008). Although it would disprove the stability assumption, transitioning from low to high level of FRα expression as EOC progresses, might be expected, however, in the Deutschman (2024) study a concordance rate of 78% was observed between primary and metastatic samples (N=59), indicating that 22% of cases were discordant. Consistent with other observations, 5% of discordant cases were assessed as negative in primary and positive in metastatic samples; and 17% of cases were assessed as positive in primary and negative in metastatic samples (Deutschman, 2024). Since cure is unlikely in platinum resistant (MIRASOL, SORAYA, and FORWARD I studies) or heavily pretreated patients (PICCOLO trial) there must be another explanation for instability in FRα expression. Although VENTANA FOLR1 is characterised by a high degree of reproducibility, it is a qualitative test and not completely free from subjective interpretation (see below). The other possible explanation may relate to tumour heterogeneity which exists spatially within the primary tumour and between the primary and the metastases and has also been shown to exist temporally, when repeat biopsies are taken at different time points during the disease course (Davis, 2014, p.627).

PASC noted that there is limited available evidence to inform the stability of the FRα marker. PASC noted that the majority of the evidence was from studies that were not directly applicable to the current application in terms of the IHC assay and test threshold used. PASC noted that FRα expression heterogeneity in the tumour can arise both temporally in different samples taken at different time points during disease/treatment, and spatially, within the same primary tissue sample due to tumour heterogeneity. PASC noted from Deutschman et al (European Congress of Pathology poster 2024), which analysed the specimens screened in the mirvetuximab soravtansine trials including MIRASOL and SORAYA, that there was high variability in FRα expression across different cores taken from the same biopsy and that there was evidence of discordance in primary tumour specimens versus metastatic lesions indicating temporal heterogeneity of tumour. PASC noted from the applicant's clinical expert that variability may be observed due to biological reasons and/or due to pre-analytical factors (e.g., loss of antigen due to prolonged fixation). The applicant's clinical experts acknowledged there is limited evidence for changes in FRα expression which prevents a full understanding of the spatial or temporal reasons for heterogeneity in the tissue sample.

<u>Method of assessing the FRα expression status</u>

EOC tissues stained with the VENTANA FOLR1 Assay display both cytoplasmic and membranous TC staining. However, only membrane staining contributes to assessment of FRα status. The assessment requires visual estimation of the percent TCs staining at a negative, weak, moderate, and strong intensity.

Specimens are considered FRα positive if 75% or more of TCs exhibit moderate and/or strong staining intensities. The scoring algorithm for the VENTANA FOLR1 Assay is specific in defining staining intensity level. It assigns a positive status for FRα expression (hence eligibility for mirvetuximab soravtansine) as ≥75% of viable tumour cells with moderate (2+) and/or strong (3+) membrane staining. Conversely, negative status is defined as <75% of viable TCs with moderate (2+) and/or strong (3+) membrane staining. A 'not evaluable' outcome is also possible. (Table 1, James, 2023; Summary of Safety and Effectiveness Data PMA P220006, FDA 2022, p.6). The FDA stated that to decrease variability of VENTANA FOLR1 for cases with %TC near the threshold of 75% [65%-85%] re-reading of the slide by one or two independent pathologists is recommended. In these cases, the patient's result with regard to FOLR1 status (positive/negative) should be obtained by either a majority rule or by consensus among the pathologists.

PASC noted from the applicant's clinical expert that according to the VENTANA protocol and manual, the majority of the cases can be clearly identified either as positive or negative, but cases at either side of a threshold can be difficult to determine (i.e., within the 65%-85% range around the 75% threshold). As scoring is subjective, these cases would require a second and even third opinion from other pathologists. Consensus is required for a conclusive outcome. The applicant's clinical experts noted that result interpretation is likely to be accurate and reliable provided the pathologists are appropriately trained and a quality assurance program is in place.

In the application, a clinical cutoff of ≥75% TCs expressing FRα on a validated IHC test is suggested as eligibility criteria for mirvetuximab soravtansine (PICO Set Document, p.2). Selection criteria in MIRASOL and SORAYA trials also included this threshold but also required a staining intensity of ≥2+. The immunohistochemical VENTANA FOLR1 (FOLR1-2.1) RxDx Assay, as presented in the application, specifically identifies FRα overexpression (FRα positivity) in quantitative terms, i.e., the percentage of viable TCs that stained positive for FRα should exceed the clinical cut-off ≥75%. However, it is less specific with respect to intensity of membrane staining, which should be assessed at moderate and/or strong intensity levels, i.e., qualitatively.

At the pre-PASC teleconference, the applicant advised that, consistent with the FDA documents and the MIRASOL trial, both criteria, for the TC proportion (≥75%) and staining intensity (≥2+) were intended to be used for mirvetuximab soravtansine eligibility. The applicant's clinical expert noted that while determining the staining intensity is relatively subjective there are guidances in assigning the intensity and that this process has been successfully and consistently performed by pathologists for over 20 years.

In response to an enquiry related to concordance of results between different FRα assays, the applicant's clinical experts expressed a conviction that it is very unlikely that an alternative test for FRα expression would emerge due to the high variation associated with in-house assays of this nature, and the high volume of resources needed to develop and validate a commercial assay.

The Department advised that MBS pathology item descriptors rarely include product names, scoring methods or scoring thresholds. Laboratories should be able to use whichever TGA approved product they choose for the test (or use an in-house IVD) provided their methods meet NPAAC accreditation/NATA standards.

In order to determine the FRα expression status, PASC considered that a laboratory may choose to use either the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay which was used in the key MIRASOL trial or an appropriately validated in house assay. PASC noted that measuring the FRα expression status with the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay, would likely limit the eligibility to mirvetuximab soravtansine to those patients fulfilling at least the 75% staining threshold (as this is the clinical cut off approved by the FDA for this device, and would likely be the same cut off if approved by the TGA). PASC noted that while the threshold proposed in the current application (≥75% of viable tumour cells with moderate [2+] or strong [3+] staining) is a clinically actionable threshold (as evidenced by the key MIRASOL and SORAYA trials), PASC considered that this may not be the optimal clinical threshold given that the key MIRASOL and SORAYA trials only treated patients who met the above stated threshold. PASC considered that while the proposed threshold is appropriate at this stage, it may change in the future if and when more data to inform other expression levels are obtained.

Treatment

Mirvetuximab soravtansine is an antibody-drug conjugate composed of an anti-FRα monoclonal antibody, a cleavable linker, and the maytansinoid DM4 payload, a potent tubulin-targeting antimitotic agent (Ab, 2015). FRα is a membrane protein that binds to and transports folate into cells. This receptor is commonly overexpressed in epithelial tumours, particularly in high-grade serous ovarian and serous endometrioid cancers, in contrast to normal adult tissues that generally exhibit more restricted FRα expression (Basal, 2009; Ledermann, 2015). A horizon-scanning report (NIHR 2023) provided the following definition: "mirvetuximab soravtansine is administered by intravenous infusion and works in two stages. First, it recognises a receptor on the cancer cells, attaches itself to the cancer cell and then enters it. When it is inside the cancer cell, the drug releases a toxic substance that kills the cancer cell and other nearby cancer cells".

Mirvetuximab soravtansine is administered at 6.0 mg/kg (adjusted ideal body weight) and administered intravenously every three weeks. The dosing regimen was established as the Phase 2 dose during a dose-escalating study (NCT01609556).

Mirvetuximab soravtansine is proposed to be used as monotherapy. However, ongoing trials assessing mirvetuximab soravtansine provide evidence of its use in combination with other drugs, albeit in PSOC or platinum agnostic populations.

Comparator(s)

Test comparator

The test comparator proposed by the applicant is no testing, as testing for FRα is not currently funded, nor available in Australia (currently under TGA review according to the applicant).

PASC confirmed that the appropriate comparator for the test is no testing for FRα expression.

Treatment comparator

For the codependent pharmaceutical mirvetuximab soravtansine, the nominated comparator is non-platinum treatment and supportive care, which are understood to be the standard of care in patients with PROC (PICO Set Document, p.6). The application indicated that non-platinum treatment and supportive care options are the standard of care in patients not eligible for platinum rechallenge due to progression on platinum-based therapy, or after a short TFI. Options for non-platinum treatment include paclitaxel, topotecan, or pegylated liposomal doxorubicin. Non-platinum chemotherapy can be given alone or with bevacizumab. The application noted that the options do not include gemcitabine, listed in combination with carboplatin, for the treatment of patients with recurrent epithelial ovarian carcinoma, who have relapsed >6 months following platinum-based therapy (PICO Set Document, p.9).

However, bevacizumab is only TGA registered for recurrent, PROC in Australia for patients who have not received bevacizumab (or any prior anti-angiogenic treatment) and have received no more than two prior chemotherapy regimens. The application stated that overall, based on current understanding, the number of patients receiving bevacizumab in a PROC setting in Australia is expected to be negligible (PICO Set Document, p.6). Bevacizumab either as a monotherapy or in combination with platinum-based agent was not suggested as a comparator.

The AURELIA trial in the bevacizumab-naïve population compared bevacizumab in combination with chemotherapy (pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan) to single-agent chemotherapy. Significant improvements in PFS (median of 6.7 months vs. 3.4 months, P<0.001) and ORR (27.3% vs. 11.8%, P = 0.001), but no benefit with respect to overall survival (OS; median of 16.6 months and 13.3 months, respectively; P<0.17) were observed (Pujade-Lauraine, 2014).

At the pre-PASC teleconference, the applicant's clinical experts considered the unrestricted listing of bevacizumab in Australia, but noted that even setting aside the TGA restrictions, there are many contraindications for prescribing bevacizumab, in particular, risk of bowel perforation, which is very common in EOC patients. Other contraindications include hypertension and deep vein thrombosis. In relation to the AURELIA trial, it was noted that 97% of patients did not receive bevacizumab as a part of first line therapy (i.e., together with platinum-based therapy), which is now a standard approach to treatment. The applicant's experts concluded that the population in the AURELIA trial is not representative of the EOC population. Although bevacizumab is re-used in subsequent lines of therapy, in the opinion of the applicant's expert, it will be displaced by the mirvetuximab soravtansine (if successfully listed).

The applicant also advised that they are seeking to understand in more detail the real-world use of bevacizumab in the PROC population in Australia. However, since the introduction of an unrestricted listing for bevacizumab in 2021, it is not possible to track whether use began to occur outside of the current TGA-approved indication.

A comprehensive consideration and justification of the appropriate comparator for mirvetuximab soravtansine should be presented in the integrated codependent submission. The appropriate treatment comparator is a matter for PBAC consideration.

PASC noted that the treatment comparator is likely to be standard of care, and that this is a matter for PBAC consideration.

PASC noted that direct evidence of the test and treatment comparator are not available from the key trials presented in the evidence base, and therefore the assessment will need to rely on indirect evidence (from any available historical data or other studies) to inform this comparison.

Clinical utility standard (for codependent investigative technologies only)

The clinical utility standard is the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay, as used in the key trials and study (MIRASOL, FORWARD I, SORAYA).

PASC confirmed that VENTANA FOLR1 (FOLR1-2.1) RxDx Assay used in the MIRASOL and SORAYA key trials represented the clinical utility standard. PASC noted from applicant correspondence that the assay is currently under TGA consideration.

The VENTANA FOLR1 FDA submission (2022) and James et al 2023 provided the following information on intra- and inter-rater concordance, reliability and reproducibility of the test.

1. In the Reader Precision study for VENTANA FOLR1 (FOLR1-2.1) RxDx Assay, within-reader and between-reader components of precision for EOC tissue reads were evaluated for FDA approval. The study included 100 unique EOC specimens (50 FOLR1 positive and 50 FOLR1 negative) that were stained with VENTANA FOLR1 (FOLR1-2.1) RxDx Assay. Specimens were blinded and randomised prior to evaluation for FOLR1 status using the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay scoring algorithm. The study included three readers (pathologists). Readers scored all samples twice, with a minimum of two-week wash-out period between reads. Each sample had six reads (two reads by each of three readers). The within-reader agreement rates ranged from 96.9% to 97%, the between-reader agreement rates ranged from 93.2% to 93.4% (Table 13, FDA 2022).
2. The Inter-laboratory Reproducibility study for the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay was conducted to evaluate reproducibility of the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay on the BenchMark ULTRA. The study included 28 EOC samples (14 FOLR1 positive and 14 FOLR1 negative) run across three BenchMark ULTRA instruments on each of five non-consecutive days at three external laboratories. Each set of five stained slides per sample per staining day was randomised and evaluated by a total of 12 readers (four readers per site). Each case had 20 results per site (60 results in total). Data showed that the performance of one of 12 readers (8.3%) was significantly different from other 11 readers. The overall agreement rate for 11 readers was 92.5% but decreased to 90.6% when the 12th (outlier) reader was added to the pool. The overall within-reader agreements were similar for 11 and 12 readers (95.8% and 95.6% respectively). The overall within-site agreement rates for 11 and 12 readers were 93.2% and 91.2% respectively) (Table 16, FDA 2022). Further information about the 12th (outlier) reader may be informative and should be addressed in the integrated codependent submission. In addition, pairwise comparison calculations were performed across three days, three sites and 12 readers. The results indicated an overall agreement of 84% between sites, 85.3% between readers and 92.6% between days.

Results of the test categorise high-grade serous epithelial PROC patients according to the FRα expression status of the TCs. Only high FRα expression patients are eligible for mirvetuximab soravtansine. Among the 2869 samples analysed from patients with HGSOC across the MIRASOL, SORAYA, and PICCOLO trials evaluating mirvetuximab soravtansine, 95% of patient samples exhibited assay-detectable FRα expression.

Approximately 36% of samples showed high FRα levels (PS2+ ≥75%), while 64% and 79% of patients had PS2+ scores of ≥50% and ≥25%, respectively. PS2+ score was calculated based on the sum of viable TCs with 2+ and 3+ staining intensity, and positivity was defined as a PS2+ score of ≥75% of viable TCs (Deutschman, 2023).

Outcomes

Test-related outcomes

Safety outcomes: adverse events associated with biopsy/re-biopsy for patients with inadequate tissue for tumour testing.

Diagnostic performance:

- intra- and inter-reader variability
- test failure rate
- evidence of stability of proteins in archival tissue
- heterogeneity within the same tissue sample
- evidence of stability in FRα status over time with treatment and/or progression of disease
- test-retest reliability.

Clinical utility of the test: determine whether testing for FRα predicts variation in the treatment effect of mirvetuximab soravtansine in terms of health outcomes for patients.

Qualitative assessment of potential risks associated with an incorrect test result or incorrect interpretation of results. Failure of the test to perform as expected or failure to correctly interpret test results may lead to improper patient management decisions.

PASC agreed with the nominated outcomes for the test, with the exception of 'sensitivity and specificity' (and by extension, the positive and negative predictive values and likelihood ratios) on the basis there is no reference standard to compare the specified test against. PASC considered that heterogeneity within the same tissue sample should be reported. PASC considered that the potential risks associated with an incorrect test result or incorrect interpretation of results to be an important outcome and considered that it should be assessed qualitatively.

Drug-related outcomes

Safety outcomes: Safety and tolerability of treatment with mirvetuximab soravtansine compared to alternative treatments assessed by adverse events, physical examination, laboratory findings and vital signs.

Clinical effectiveness outcomes:

- objective response rate (ORR)
- overall survival (OS)
- progression-free survival (PFS)
- health-related quality of life (HRQoL).

PASC noted the treatment outcomes and considered these to be a matter for PBAC consideration.

Healthcare system outcomes:

- cost of testing per patient and cost associated with re-biopsies (e.g.: early-stage disease that has relapsed, test failure, inadequate sampling)
- cost of treatment and cost of treating adverse events
- financial implications: number of patients tested; number of patients treated.

Assessment framework (for investigative technologies)

A linked evidence approach is the most appropriate as there is unlikely to be direct evidence of the impact of FRα testing on health outcomes. An assessment framework linking FRα testing to relevant health outcomes is presented in Figure 1.

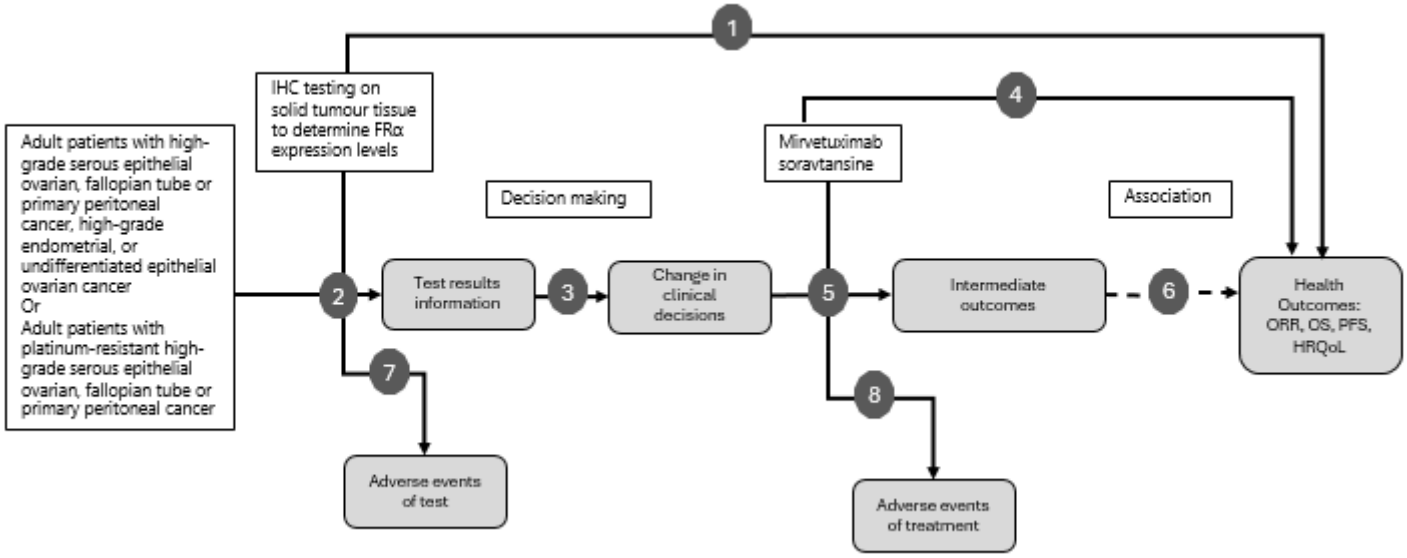

Figure 1 Generic assessment framework showing the links from the test population to health outcomes

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment
HRQoL: health-related quality of life, IHC: Immunohistochemistry, ORR: objective response rate, OS: overall survival, PFS: progression free survival

PASC confirmed that the assessment framework was appropriately described in the PICO and agreed that a linked evidence approach will be required.

Questions relevant to this assessment framework are as follows:

1. Does the use of FRα testing in place of no testing result in the claimed superior health outcomes?
2. What is the accuracy of the proposed testing?
3. Does the availability of new information (FRα status) from FRα testing lead to a change in management of the patient?

4. Do the differences in the management derived from FRα testing result in the claimed superior health outcomes (ORR, OS, PFS, HRQoL)?
5. What are the adverse events associated with FRα testing compared to a no testing strategy?
6. What are the adverse events associated with treatment with mirvetuximab soravtansine and other alternative treatments?

FRα testing to determine eligibility for mirvetuximab soravtansine is expected to lead to a change in clinical management, as patients who have high-grade serous epithelial ovarian cancer with high FRα expression will be eligible for targeted treatment. The incremental benefit (or not) of mirvetuximab soravtansine in patients not meeting this threshold cannot be informed with current data. The key trial (MIRASOL) enrolled only those who met the threshold of ≥75% of viable TCs expressing the receptor at moderate [2+] to strong [3+] staining intensity (PS2+) and subsequently randomised them to treatment with mirvetuximab soravtansine or standard of care therapy (non-platinum chemotherapy). Therefore, codependency of the test and drug combination is uncertain. Additionally, the MIRASOL trial cannot inform the clinical claim of superiority of FRα test and mirvetuximab soravtansine versus no testing and standard of care therapy (non-platinum chemotherapy).

PASC noted that the MIRASOL trial is insufficient for either establishing a codependency or justifying the ≥75% of viable tumour cells with moderate [2+] or strong [3+] staining as the optimal clinical threshold, since the trial enrolled only those who met the above criteria and subsequently randomised them to treatment with mirvetuximab soravtansine or standard of care therapy (non-platinum chemotherapy). Based on the results of the Phase 1 expansion study (Martin, 2017) and the Phase 3 FORWARD I trial, PASC noted that there is a trend towards patients with high FRα expression having more benefit with treatment with mirvetuximab soravtansine compared to patients with low/medium FRα expression. Therefore, PASC considered that codependency of the test and drug combination is likely justified. PASC noted from the Phase 3 MIRASOL key trial that patients with high FRα expression (defined in the trial as ≥75% of viable TCs expressing the receptor at moderate [2+] to strong [3+] staining intensity) treated with mirvetuximab soravtansine demonstrated a statistically significant increase in progression free survival compared to patients with high FRα expression treated with chemotherapy. However, PASC acknowledged that the incremental benefit (or lack thereof) of mirvetuximab soravtansine in patients not meeting the nominated threshold cannot be informed with these data.

PASC considered that the MIRASOL trial cannot inform the clinical claim of superiority of FRα test and mirvetuximab soravtansine versus no testing and standard of care therapy as the trial only enrolled patients who had high FRα expression and did not include any patients who were not tested for FRα expression. Therefore, as noted above, PASC considered that the clinical claim would be informed by indirect evidence.

Clinical management algorithms

Current clinical management algorithm

The application outlined the clinical management algorithm in the PICO Set Document (p.9). This text is complemented with recommendations from the latest European Society of Gynaecological Oncology (ESGO), European Society for Medical Oncology (ESMO) and European Society of Pathology (ESP)

consensus conference on ovarian cancer (Ledermann, 2024) and other sources. The gold standard for initial management of advanced EOC management is primary cytoreductive surgery, if patients are physically able to undergo surgery and complete resection, followed by systemic neoadjuvant chemotherapy. Standard chemotherapy includes platinum-based regimens such as carboplatin with paclitaxel, or alternatively with docetaxel or pegylated liposomal doxorubicin if paclitaxel is contraindicated. This can be given with or without concomitant bevacizumab. Bevacizumab added to platinum-based chemotherapy and continued as maintenance increases the tumour response rate and PFS without an OS benefit (Ledermann, 2024). Following induction of chemotherapy treatment with or without bevacizumab, poly-ADP ribose polymerase inhibitors (PARPis: olaparib, niraparib and rucaparib) are recommended for maintenance treatment in patients with *BRCA1/2* mutation or with homologous recombination deficiency (HRD+) *BRCA* wildtype (wt) tumours. Under the latest PBS restrictions, these PARPis can also be given with or without bevacizumab. PARPis significantly prolonged PFS in the recurrent setting, when given as maintenance after treatment with platinum until progression or unacceptable toxicity. This benefit was more pronounced in patients with a *BRCA1/2* mutation but still relevant in patients with *BRCA*-wt tumours regardless of HRD status (Ledermann, 2024).

In patients who are considered platinum sensitive and platinum is an option, carboplatin with paclitaxel, pegylated liposomal doxorubicin, or gemcitabine is recommended, with or without bevacizumab. Following induction treatment in this relapsed (second line) setting, bevacizumab can also be used for maintenance or alternatively, olaparib monotherapy is PBS-funded for maintenance treatment in this setting for patients who have *BRCA1/2* mutations. Of those eligible for maintenance therapy, about one-quarter of the patients initiated a maintenance regimen, and approximately 10% of those who initiated maintenance therapy completed at least 40 weeks (Johnson, 2014).

Two new classes of targeted agents have been approved for EOC therapy in the last 10 years – angiogenesis inhibitors (e.g., bevacizumab) and PARP inhibitors (e.g., olaparib) – each of which selectively impact oncogenic pathways linked to ovarian tumorigenesis. One strategy designed to improve patient outcomes involves combining targeted agents, which possess distinct mechanisms of action and favourable tolerability, with established chemotherapeutics. Validation of this approach is exemplified by use of bevacizumab alongside paclitaxel, pegylated liposomal doxorubicin or topotecan in platinum resistant, recurrent disease (Moore, 2018).

Bevacizumab (a vascular endothelial growth factor inhibitor) was first listed on PBS on 1 August 2014 initially as a restricted listing. As of 1 June 2021, bevacizumab is available on the PBS as an unrestricted benefit. The recommended dose is 10 mg/kg body weight given once every two weeks when administered in combination with one of the following agents – paclitaxel or topotecan (given weekly) or pegylated liposomal doxorubicin. Alternatively, 15 mg/kg every three weeks when administered in combination with topotecan given on days 1-5, every three weeks (TGA, 2022).

In the platinum resistant setting, treatment involves a number of non-platinum cytotoxic agents including paclitaxel, docetaxel, pegylated liposomal doxorubicin, gemcitabine and topotecan. The choice of non-platinum chemotherapy is dependent on patient characteristics, previous treatment and clinician and patient's preferences. Non-platinum chemotherapy is given alone or with bevacizumab (González-Martín,

2013; Pujade-Lauraine 2014). The PROC chemotherapies are associated with increased toxicity and response rates are below 20%, PFS of three to four months and median OS less than a year (Moore, 2018).

Each successive line of therapy in PROC is associated with progressively lower response rates. Approval of bevacizumab in combination with chemotherapy for patients with PROC was based on the AURELIA study, in which the control arm of single-agent chemotherapy was associated with an ORR of 11.8% and a median duration of response of 5.4 months. Three recent Phase 3 studies (CORAIL, NINJA, and JAVELIN Ovarian 200) conducted in patients with PROC have reported similar outcomes for non-platinum chemotherapy alone (ORR range, 4%-13%; DOR range, 3.7-13.1 months) (Gaillard, 2021; Hamanishi 2021; Pujade-Lauraine 2021).

PSOC has a median survival of 2 years, with a range of 3 months to over 10 years. PROC has a median survival of nine to 12 months and less than 15% respond to subsequent chemotherapy (Davis, 2014).

Figure 2 reproduces the current clinical management algorithm as presented in the PICO Set Document.

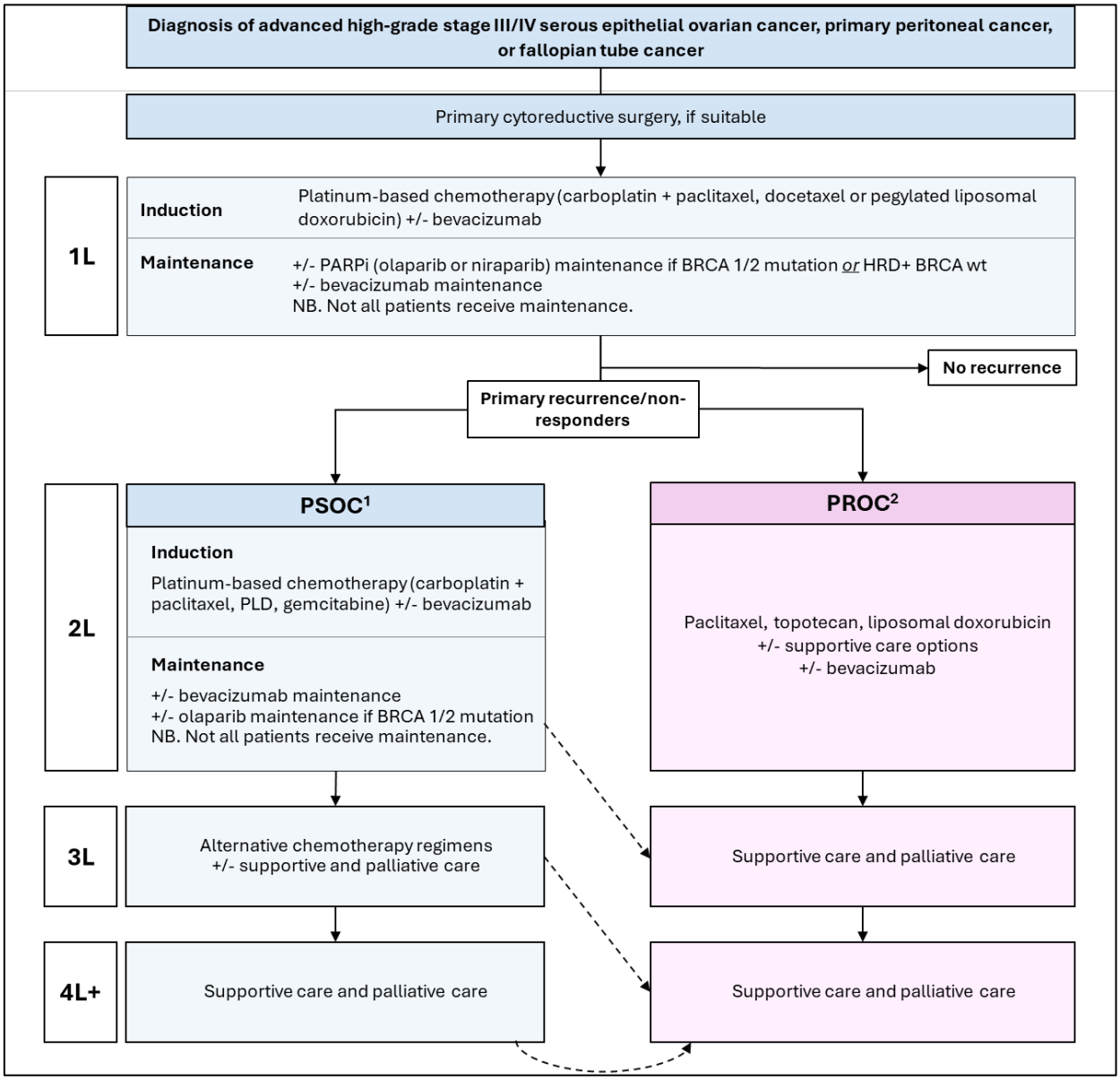

Figure 2 Current treatment algorithm for epithelial ovarian cancer

Source: PICO Set Figure 1.

Abbreviations: +, positive; +/-, with or without; BRCA, breast cancer gene; HRD, homologous recombination deficiency; PARPi, poly (ADP-ribose) polymerase inhibitor; PFI, platinum free interval until relapse; PLD, pegylated liposomal doxorubicin; PROC, platinum resistant ovarian cancer; PSOC, platinum sensitive ovarian cancer; wt, wild-type..

1. PSOC = platinum sensitive ovarian cancer. Traditionally defined as a platinum free interval before recurrence of ≥6 months. Latest guidelines by ESMO indicate this decision is driven by several patient characteristics.
2. PROC = platinum resistant ovarian cancer. Traditionally defined as a platinum free interval before recurrence of ≤6 months. Latest guidelines by ESMO (2023) indicate this decision is driven by several patient characteristics.

Dashed lines indicate how platinum sensitive patients may become platinum resistant while progressing through therapy lines.

Proposed clinical management algorithm

The application positioned mirvetuximab soravtansine in the new clinical management algorithm assuming a successful listing and a new proposed MBS item for patients with platinum resistant advanced (high-grade serous) ovarian cancer and with FRα high tumour expression. Since mirvetuximab soravtansine is

intended for the platinum resistant patient population, it could not be offered before platinum resistance is established, therefore the earliest position of mirvetuximab soravtansine is the second line of treatment, depicted in Figure 3. Mirvetuximab soravtansine (as a monotherapy) is intended as an alternative treatment option to single agent chemotherapy in PROC patients. The application also stated that patients who receive mirvetuximab soravtansine in second line or beyond may still receive other existing options in preceding or subsequent lines of therapy. The positioning of mirvetuximab soravtansine in the proposed clinical management pathway is expected to be finalised in the integrated codependent submission. The application indicated that the proposed algorithm may evolve based on clinician/expert feedback, which will be incorporated into the integrated codependent submission.

The two alternative timepoints for FRα testing are depicted in red boxes in Figure 3 where testing can either occur at platinum resistance (as proposed in the application) or at diagnosis (an alternative testing timepoint proposed by the applicant's clinical experts at the pre-PASC teleconference).

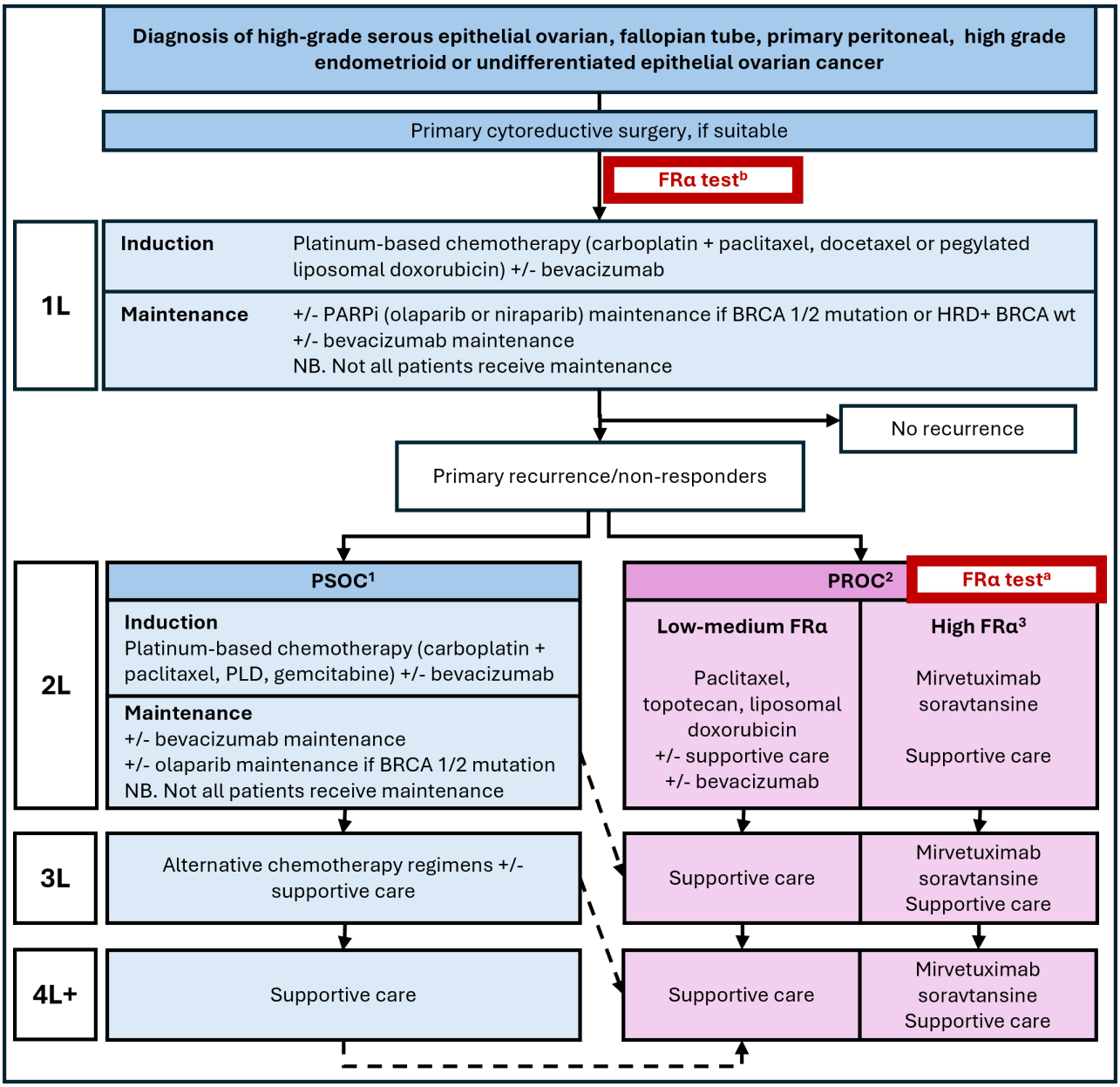

Figure 3 Proposed treatment algorithm

Source: PICO Set Figure 2 with updates to proposed patient population and FRα testing.
Abbreviations: +, positive; +/-, with or without; BRCA, breast cancer gene; FRα, folate receptor alpha; HRD, homologous recombination deficiency; PARPi, poly (ADP-ribose) polymerase inhibitor; PFI, platinum free interval until relapse; PLD, pegylated liposomal doxorubicin, PROC, platinum resistant ovarian cancer; PSOC, platinum sensitive ovarian cancer; wt, wild-type.;.
1. PSOC = platinum sensitive ovarian cancer. Traditionally defined as a platinum free interval before recurrence of ≥6 months. Latest guidelines by ESMO indicate this decision is driven by patient characteristics/not solely by 6 month time period.
2. PROC = platinum resistant ovarian cancer. Traditionally defined as a platinum free interval before recurrence of ≤6 months. Latest guidelines by ESMO (2023) indicate this decision is driven by patient characteristics/not solely by 6 month time period, e.g., this group represents all patients where "platinum is not the best option" including for patient choice/quality of life reasons.
3. High FRα expression to be determined by new MBS item - immunohistochemistry test, with ≥75% of expression on tumour cells.
Dashed lines indicate how platinum sensitive patients may become platinum resistant while progressing through therapy lines.
Red boxes indicate the two alternative timepoints for FRα testing: (a) at platinum resistance (as proposed in the application) or (b) at diagnosis (an alternative timepoint proposed by the applicant's clinical experts at the pre-PASC teleconference).

PASC accepted the current and proposed treatment algorithms. PASC considered that if testing is performed at diagnosis, it will likely be performed after the primary cytoreductive surgery (if this surgery is performed in the patient).

PASC considered that both testing timepoints (at cancer diagnosis and at platinum resistance) should be explored in the assessment so that MSAC is able to provide well informed advice regarding the time at which the test should be performed.

Proposed economic evaluation

The application claims superiority of FRα expression status testing and mirvetuximab soravtansine versus no testing and standard of care therapy (non-platinum chemotherapy). Neither the application nor the PICO Set Document provided information about relevant safety (harms) of FRα expression status testing and mirvetuximab soravtansine versus no testing and standard of care therapy.

On the basis of a claim of superior effectiveness, a cost-effectiveness (CEA), or a cost-utility analysis (CUA) would be appropriate according to Table 2.

PASC agreed that on the basis of a claim of superior effectiveness, a cost-effectiveness (CEA), or a cost-utility analysis (CUA) would be an appropriate type of economic evaluation.

Table 2 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety-	Comparative effectiveness			
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

The applicant noted that the Royal College of Pathologists of Australasia (RCPA) Cancer Advisory Committee advised that the association's position has consistently been that predictive biomarkers which determine access to therapy, such as FRα-testing, require a different MBS item rather than existing items for routine diagnostic IHCs. This is because the testing approach is more complex, including the need to

score both a proportion of cells affected and staining intensity, as well as the need for more rigorous validation, often more costly companion diagnostic assays, and the need for specific quality assurance program participation. Therefore, the applicant noted that the use of existing IHC examination MBS items (e.g., 72846) to be unsuitable for use for the current proposed test.

As stated previously, PASC considered that the integrated codependent submission should explore both testing timepoints: at cancer diagnosis and at platinum resistance. PASC noted that there are several ongoing studies related to FRα testing to determine eligibility to treatment and considered that the item descriptors should remain reasonably generic where appropriate to allow for future changes that are informed by new data.

The MBS item descriptor proposed for FRα testing at confirmation of platinum resistance is provided in Table 3. The application initially proposed a fee of $74.50 based on comparable IHC item 72814 for programmed death-ligand 1 (PD-L1) testing. Subsequently, the applicant noted that this fee does not adequately cover the costs associated with comparable IHC tests and have indicated that the fee is likely to be approximately $130.00 based on a cost build up approach.

PASC noted the application initially proposed a fee of $74.50 based on comparable IHC item 72814 for PD- L1 testing. The applicant's clinical expert suggested that the originally proposed fee is likely too low and is dependent on the cost of the test assigned by the sponsor of the test. PASC advised the applicant to present the proposed fee in the integrated codependent submission along with appropriate justification for the increased fee compared to comparable MBS items.

Table 3 Proposed item descriptor for testing at platinum resistance

Category (Category 6 – Pathology Services)
MBS item *XXXX A test of tumour tissue using immunohistochemistry for the detection of membrane FRα tumour expression, in a patient with: • platinum resistant high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancer As requested by a specialist or consultant physician, to determine eligibility for treatment with a relevant treatment under the Pharmaceutical Benefits Scheme (PBS).
Fee: TBC **Benefit:** 75% = TBC; 85% = TBC

Abbreviations: FRα, folate receptor alpha; TBC, to be confirmed.

PASC noted the evolution of understanding of platinum resistance. PASC considered the item descriptor should not define 'platinum resistant'.

Table 4 presents potential wording for an item descriptor reflecting FRα testing at the time of primary diagnosis of ovarian cancer.

Table 4 Proposed item descriptor for testing upon primary diagnosis of ovarian cancer

Category (Category 6 – Pathology Services)
MBS item *XXXX A test of tumour tissue using immunohistochemistry in a patient with high-grade serous epithelial ovarian, fallopian tube or primary peritoneal, high-grade endometrioid, or undifferentiated epithelial ovarian cancer, requested by a specialist or consultant physician to determine membrane FRα expression status for access to a relevant treatment under the Pharmaceutical Benefits Scheme (PBS). (See para PN.1.2 of explanatory notes to this Category)
Fee: TBC **Benefit:** 75% = TBC; 85% = TBC

Abbreviations: FRα, folate receptor alpha; TBC, to be confirmed.

PASC favoured the inclusion of the test methodology (i.e. immunohistochemistry) in the item descriptor as this method is able to distinguish between cytoplasmic and cell membrane FRα as opposed to other methodologies such as tumour FOLR1 *mRNA expression analyses. PASC considered that the item descriptor should specify 'membrane' FRα expression as this is considered to be the target of the drug.*

PASC noted that the key MIRASOL trial was restricted to patients with high grade serous ovarian cancer. The applicant's clinical experts noted that there is no biological rationale as to why the benefit of treatment would only be restricted to the high grade serous subgroup and that the broader epithelial ovarian cancer patient population may potentially benefit from treatment, with studies currently underway. The applicant's clinical experts further noted that in a proportion of patients there may be difficulty in distinguishing histotypes, and therefore a broader term of 'epithelial ovarian cancer' will ensure that all patients who may potentially benefit from mirvetuximab will have testing for FRα expression and those with high expression and who meet all other eligibility criteria will be able to obtain access to mirvetuximab. PASC advised that if the broader patient population is proposed, the integrated codependent submission would need to provide evidence of clinical benefit of treatment in this population. The population in the item descriptor would be updated accordingly.

PASC acknowledged the risk of a once per diagnosis strategy. The sources of uncertainty of an accurate test result include: subjectivity in interpretation of the test, which may be addressed by use of the VENTANA protocol and appropriate training; and stochastic uncertainty of whether the lesion sampled was representative of the FRα expression levels of the majority disease burden. PASC considered that the assessment should explore these different sources of uncertainty and assess whether multiple testing would reduce this uncertainty. PASC advised that a frequency of testing is not to be included in the item descriptor [at this point in time]. The amended item descriptor proposed in Table 4 does not include a frequency restrictor and would enable testing at diagnosis as well as re-testing of patients at a later stage. It would also enable testing of patients who have already been diagnosed at the time of PBS/MBS listing, should this item be supported.

PASC considered that if FRα testing is done at diagnosis, then the testing should be pathologist determinable and would need to be included in the list of pathologist-determinable services. PASC noted that in this instance, the item descriptor would not make reference to a 'certified pathologist' as the requestor, instead include a reference to the pathologist determinable practice note PN.1.2.

PASC noted the Department's advice that the PBS restriction would incorporate the testing threshold where necessary and that this would not usually be duplicated in the MBS item descriptor.

PASC noted that a quality assessment program for FRα expression testing will be required.

Summary of public consultation input

PASC noted and welcomed consultation input from two organisations. The two organisations that submitted input were:

- Rare Cancers Australia (RCA)
- Ovarian Cancer Australia (OCA)

The consultation input received was all supportive of public funding for IHC testing of solid tumour tissue to determine FRα expression status in adults with platinum resistant ovarian cancer, to determine eligibility for treatment with PBS subsidised mirvetuximab soravtansine.

Consumer Input

Ovarian Cancer Australia (OCA) input included statements from women with ovarian cancer that captured the impact on themselves and their families. The women described the anxiety surrounding the condition, living with the fear of recurrence and the challenge of holding onto hope for new drugs that are affordable and offer a positive outcome.

Rare Cancers Australia (RCA) input included patient experiences, with one woman describing a profound loss of dignity as a result of frequent medical procedures and exploratory surgeries, resulting in not having the strength to face the side effects of the medical treatment recommended. RCA also included that carers feel overwhelmed at the loss of a loved one's health and the financial strain of medical costs.

Benefits and Disadvantages

The main benefits of public funding received in the consultation input included hope for patients and the potential option for a targeted therapy in this population. Targeted therapy offers the potential to slow disease progression and improve quality of life by lessening the physical and psychological toll from non-specific treatments.

A potential disadvantage of public funding received in the consultation input was that adverse effects of the treatment could impact quality of life but appeared manageable with appropriate patient support and monitoring protocols.

Population, Comparator (current management) and Delivery

The consultation input agreed with the proposed population. RCA considered that whilst the eligibility requirement of platinum resistance for treatment was appropriate, consideration should be given to

whether patients with earlier signs of platinum resistance would also benefit from the targeted intervention.

The consultation input stated that there are no publicly funded targeted therapies currently available for patients with platinum resistant ovarian cancer that could be seen to be a comparator.

Other services identified in the consultation input as being needed to be delivered before or after the intervention included counselling and pain management support services for patients undergoing IHC testing and subsequent therapy.

MBS Item Descriptor and Fee

The consultation input partially agreed with the proposed service descriptor. RCA and OCA stated that the timing of FRα testing should be considered in the context of clinical management. OCA stated that tumour testing at recurrence is not standard of care and that testing after platinum resistance had been established may be a barrier to appropriate access to the therapy. RCA stated that testing at diagnosis should be considered to overcome potential barriers to implementation including geographic disparities in testing access. RCA advocates for pan-tumour approval pathways.

RCA stated that the MBS fee should not place undue burden on patients and that any out of pocket costs should be made transparent.

PASC noted from the consultation input that vision problems and liver toxicity are side effects of the treatment. PASC noted from the applicant's clinical expert that patients may use steroid drops, eye lubricants and dark glasses to mitigate the risks associated with the drug and that patient and clinician education on these side effects is vital. The applicant's clinical expert further raised that expert ophthalmologists would be required to review these patients and that this could raise access issues to patients especially those living in regional and rural areas with limited access to specialists. In order to circumvent issues with limited access, the applicant's clinical expert noted that optometrists could be trained to review patients and to refer to ophthalmologist only when needed.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as an Applicant Developed Assessment Report (integrated codependent submission).

Applicant Comments on Ratified PICO

The applicant had no comment.

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