

MSAC Application 1792

Immunohistochemistry testing for fibroblast growth factor receptor 2b (FGFR2b) expression in patients with unresectable locally advanced or metastatic gastric or gastro-oesophageal cancer, to determine eligibility for PBS subsidised bemarituzumab treatment

Applicant: AMGEN AUSTRALIA Ptd Ltd

PICO Confirmation

Ratified PICO Confirmation – April 2025 PASC Meeting

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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 immunohistochemistry (IHC) for FGFR2b expression in patients with unresectable locally advanced or metastatic G/GOJ adenocarcinoma

Component	Description
Population	<p>Test: Adults with unresectable locally advanced or metastatic gastric or gastro-oesophageal junction (G/GOJ) adenocarcinoma</p> <p>Treatment: Adults with unresectable locally advanced or metastatic G/GOJ adenocarcinoma that are human epidermal growth factor receptor 2 (HER2)-negative and with fibroblast growth factor receptor 2b (FGFR2b) protein overexpression</p>
Prior test(s)	None
Intervention	<p>Test: Tumour tissue testing for FGFR2b protein expression using immunohistochemistry (IHC), in parallel to current standard of care (SOC) which is HER2 testing</p> <p>Treatment^a: Bemarituzumab as part of combination therapy (chemotherapy ± nivolumab) as first-line treatment in patients with HER2-negative but FGFR2b protein overexpressed tumours</p> <p>FGFR2b protein overexpression defined as: a tumour IHC staining score of 2+ or 3+ in ≥10% of tumour cells</p>
Comparator	<p>Test: No testing for FGFR2b protein expression (i.e. current SOC with HER2 testing)</p> <p>Treatment: after current SOC determines HER2 negative status</p> <ol style="list-style-type: none"> 1. First-line treatment with nivolumab in combination with fluoropyrimidine- and platinum-based chemotherapy; or 2. Fluoropyrimidine and platinum-based chemotherapy alone (in those who previously received adjuvant programmed cell death protein 1 (PD-L1)/programmed cell death ligand 1 (PD-L1) inhibitor therapy for earlier stage disease)
Clinical utility standard	VENTANA FGFR2b (FPR2-D) Rx Dx Assay (used to assess FGFR2b expression in the FIGHT and FORTITUDE-101 trials)
Outcomes	<p>Test-related outcomes:</p> <ul style="list-style-type: none"> • Safety: adverse events (AEs) associated with biopsy, re-biopsy for tumour tissues. • Validity of the proposed cutoff point of ≥10% tumour cells with 2+/3+ staining on IHC as a biomarker for FGFR2b protein overexpression • Diagnostic performance: positive percent agreement, negative percent agreement, test-retest reliability, inter-observer concordance/reliability, test error rate.

Component	Description
	<ul style="list-style-type: none"> • Yield of testing/number needed to be tested (to identify one eligible case for bemarituzumab) • Heterogeneity of FGFR2b overexpression within tumour tissue samples • Turnaround time (to ensure timely diagnosis and access to treatment) • Rate of rebiopsy (including test failure and inadequate sample rate) <p>Clinical utility of test:</p> <ul style="list-style-type: none"> • Treatment effect modification for bemarituzumab based on FGFR2 expression (predictive validity) <p>Change in management:</p> <ul style="list-style-type: none"> • Proportion of cases eligible for bemarituzumab who would proceed to treatment in-leu of other options or considerations <p>Treatment-related outcomes</p> <ul style="list-style-type: none"> • Safety (including treatment-emergent AEs) • Overall survival (OS), progression free survival (PFS), objective response rate (ORR), duration of response (DOR), disease control rate (DCR) • Patient-reported outcomes (PROs) and health-related quality of life outcomes <p>Healthcare resources</p> <ul style="list-style-type: none"> • Cost of testing per patient (including costs of associated re-biopsies, test failure, inadequate sampling) • Cost of treatments • Cost of treating adverse events • Financial implications (including the number of patients tested and treated)
Assessment questions	<p>What is the safety, effectiveness and cost-effectiveness of FGFR2b IHC testing versus no FGFR2b testing in patients with unresectable locally advanced or metastatic G/GOJ adenocarcinoma to determine eligibility for treatment with Pharmaceutical Benefits Scheme (PBS) subsidised bemarituzumab plus chemotherapy ± nivolumab versus treatment with chemotherapy ± nivolumab in those who are HER2-negative and have FGFR2b protein overexpression?</p> <p>What is the clinical utility of IHC testing for FGFR2b (e.g. is there a treatment effect modification for bemarituzumab based on FGFR2b overexpression status?)</p>

^s Proposed new treatment as indicated in the applicant's PICO set document. Details are yet to be confirmed in the assessment report.

Purpose of application

The codependent application requested:

- Medicare Benefits Schedule (MBS) listing of immunohistochemical (IHC) testing for fibroblast growth factor receptor 2b (FGFR2b) expression for eligibility for bemarituzumab (BEMA) treatment in patients with unresectable locally advanced or metastatic gastric or gastro-oesophageal junction (G/GOJ) adenocarcinoma; and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of bemarituzumab for the treatment of unresectable locally advanced or metastatic G/GOJ adenocarcinoma.

In the initial application, bemarituzumab was proposed to be used in addition to chemotherapy (as a doublet regimen), and in the pre-PASC teleconference (19 February 2025) it was proposed that bemarituzumab may also be used in addition to chemotherapy and nivolumab (in a triplet regimen).

Clinical claim

The application stated that it was expected that, in the forthcoming codependent (MSAC/PBAC) submission, likely in early 2026, the clinical claim will be: FGFR2b protein expression testing and treatment with bemarituzumab plus chemotherapy in patients with FGFR2b protein overexpression is superior in effectiveness and non-inferior in safety, compared to no FGFR2b testing and treatment with nivolumab plus chemotherapy (or nivolumab alone in those who have had prior nivolumab for G/GOJ adenocarcinoma).

The application claimed that FGFR2b testing alone will have no impact on health outcomes. The assessment group noted that this assumed that there would not be an increase in the number of patients who required a re-biopsy for multiple biomarker testing.

In the pre-PASC teleconference (19 February 2025), the applicant stated that they are waiting on the completion of their key trial (FORTITUDE-101) prior to confirming whether they are claiming that bemarituzumab plus chemotherapy has non-inferior or superior effectiveness compared to nivolumab and chemotherapy.

The clinical claim regarding triplet therapy was: FGFR2b testing and treatment with bemarituzumab plus nivolumab and chemotherapy is superior in effectiveness and non-inferior in safety, compared to no FGFR2b testing and treatment with nivolumab plus chemotherapy.

PICO criteria

Population

The application proposed IHC testing for FGFR2b protein overexpression in adults with unresectable locally advanced or metastatic G/GOJ adenocarcinoma. The application reported that standard of care is for this population to undergo HER2 testing to determine eligibility for trastuzumab in HER2-positive patients. Those who are HER2-negative, may instead be eligible for nivolumab.

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PASC noted that the applicant's proposed test population are adults with unresectable locally advanced or metastatic G/GOJ adenocarcinoma, who constitute the majority of patients at first diagnosis with G/GOJ adenocarcinoma.

PASC considered whether there is a mismatch in the proposed MBS population for FGFR2b IHC testing and the current MBS population for HER2 ISH testing, noting the former is proposed in patients with either unresectable locally advanced or metastatic G/GOJ adenocarcinoma while the latter is currently restricted to patients with metastatic G/GOJ adenocarcinoma only (MBS item 73342). PASC noted the Department's advice that HER2 IHC testing (MBS item 72848) is the standard initial HER2 testing available for use at any disease stage and is already used to confirm HER2 negative status. HER2 ISH testing (MBS item 73342) is used to assess gene amplification in patients with evidence of HER2 overexpression, for access to trastuzumab. These patients would already have been assessed as being HER2 positive (3+) or equivocal (2+) (using IHC testing item 72848) to be eligible for item 73342.

The proposed population for treatment with bemarituzumab is patients with unresectable locally advanced or metastatic G/GOJ adenocarcinoma who are HER2-negative and have FGFR2b protein overexpression.

G/GOJ adenocarcinomas are cancers of epithelial cells lining either the stomach or GOJ (between the stomach and the oesophagus). Key risk factors for gastric cancer include being male, persistent *Helicobacter pylori* infection, high alcohol consumption, high salt intake, and low consumption of fibre (Lordick et al. 2022). Risk factors for GOJ adenocarcinoma include obesity, smoking, and gastroesophageal reflux disease (GORD) (Buas & Vaughan 2013).

Gastric cancers are the fifth most-common cancer worldwide with over 1 million new cases diagnosed in 2020. These cancers also have significant disease burden with 769,000 deaths globally in 2020 (Sung et al. 2021). Countries with the highest incidences (>20 per 100,000 in men) are China, Japan, Latin America, and Eastern Europe, and lowest incidences (<10 per 100,000 in men) are North America, parts of Africa and Northern Europe (Sung et al. 2021). In the Australian context, gastric cancers represented 1.6% of new cancer cases, and 2.2% of all cancer deaths in 2023 (Cancer Australia 2024). Estimates from the Victorian Cancer Registry reported that 82.6% of all gastric cancer cases in Victoria from 2013 to 2022 were adenocarcinoma (Cancer Council Victoria 2024).

Diagnosis of G/GOJ adenocarcinoma is confirmed through biopsy obtained via endoscopy, endoscopic mucosal resection (EnMR), endoscopic submucosal dissection (ESD) or gastrectomy. The cancer is staged according to the 8th edition of the American Joint Committee on Cancer and the International Union Against Cancer (AJCC/UICC) staging manual (Lordick et al. 2022). Additionally, G/GOJ adenocarcinoma may be categorised by the Lauren classification system. According to this system, G/GOJ adenocarcinoma is classified into three major types: intestinal, diffuse, and mixed. The intestinal type forms glands and resemble adenocarcinomas of the intestine. The diffuse type consists of poorly cohesive cells, containing signet ring cells and do not tend to form glands. Mixed types exhibit qualities of both intestinal and diffuse carcinomas. Lauren classification of G/GOJ is a prognostic factor with intestinal type being associated with greater response to neoadjuvant chemotherapy and overall survival than the other two types (van der Kaaij et al. 2017).

Early-stage G/GOJ adenocarcinoma is usually easy to treat with resection. However it is often asymptomatic at early stages, and early-stage G/GOJ adenocarcinomas are therefore rarely detected. Furthermore, even advanced stage G/GOJ adenocarcinoma often presents with non-specific symptoms such as weight loss, persistent abdominal pain, dysphagia (difficulty swallowing), hematemesis (vomiting blood), anorexia, nausea, early satiety, and dyspepsia (indigestion) (Menon, El-Nakeep & Babiker 2024). This pattern of symptoms frequently leads to patients delaying medical attention, and potential misdiagnosis from the healthcare practitioner once assistance is sought. This results in further delay in referral to a specialist. As a result, only 20% of patients with G/GOJ adenocarcinoma present with resectable disease, meaning 80% of patients will be diagnosed with locally advanced unresectable or metastatic disease (Petrillo et al. 2019). Data from the Victorian Cancer Registry reported that 20% of gastric cancer cases between January 2011 and December 2016 were detected early (Yang et al. 2021).

The prognosis of G/GOJ adenocarcinoma varies highly, based on the stage of disease. Five-year survival rates in patients with localised disease are 75%; 35% for those with regional metastasis; and 7% for distal metastasis (American Cancer Society 2024). Overall prognosis for G/GOJ adenocarcinoma remains poor with modest improvements in survival over the last 20 years. Five-year survival rates of Australian patients were 21% in 1990-1994 increasing to 38% in 2015-2019 (Cancer Australia 2024). This poor prognosis is largely driven by a greater proportion of patients diagnosed at a later stage.

Management of unresectable locally advanced or metastatic G/GOJ adenocarcinoma

Both the European Society for Medical Oncology (ESMO) (Lordick et al. 2022) and National Comprehensive Cancer Network (NCCN) (NCCN 2025) guidelines recommend a platinum-fluoropyrimidine doublet as standard first-line chemotherapy for unresectable locally advanced or metastatic G/GOJ adenocarcinoma.

Targeted treatment is also offered in addition to chemotherapy depending on the tumour's expression of HER2 biomarkers. In HER2 positive G/GOJ tumours in advanced disease, the addition of trastuzumab is recommended. This recommendation was based on the Phase III ToGA study which demonstrated higher response rates and longer OS (HR 0.74; 95% CI 0.60-0.91; $p = 0.0046$) with trastuzumab plus chemotherapy compared with chemotherapy alone. In HER2 negative G/GOJ tumours in advanced disease the addition of nivolumab is recommended. This recommendation was based on the Phase III Checkmate 649 trial which demonstrated improved OS (HR 0.71; 98.4% CI 0.59-0.86; $p < 0.0001$) and PFS (HR 0.68; 98% CI 0.56-0.81; $p < 0.0001$) for nivolumab plus chemotherapy compared with chemotherapy alone in patients with a Programmed death-ligand 1 (PD-L1) combined positive score (CPS) of ≥ 5 (minimum follow-up 12.1 months).

In Australian practice, trastuzumab is available to patients with metastatic HER2-positive G/GOJ adenocarcinoma, and nivolumab is available to advanced or metastatic HER2-negative G/GOJ adenocarcinoma patients, which aligns with global cancer guidelines. The applicant noted that the only exception is that nivolumab is available on the PBS to all HER2-negative patients, whereas NCCN guidelines recommend for those with a PD-L1 CPS score ≥ 1 (PICO Set 1792, NCCN 2025). This aligns with current PBS restrictions for nivolumab (PBAC meeting March 2022)¹. Chemotherapy regimens include: FOLFOX (folinic

¹ <https://m.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2022-03/files/nivolumab-psd-march-2021.pdf>

acid, fluorouracil, and oxaliplatin), FOLFIRI (folinic acid, fluorouracil, and irinotecan hydrochloride), or CAPOX/XELOX (capecitabine and oxaliplatin)².

The population who would be eligible for the proposed triplet regimen would be restricted to those who are untreated (up until initiating the triplet regimen) with programmed cell death-1/ligand-1 (PD-1/PD-L1) inhibitor therapy for G/GOJ, as the PBS criteria for nivolumab (a component of the triplet regimen) includes this restriction.

The role of FGFR2b in G/GOJ adenocarcinoma

FGFR2, a tyrosine kinase receptor, is a member of the FGFR protein family that is expressed in epithelial cells and drives many downstream pathways, including the mitogen-activated protein kinase (MAPK) and Akt transforming (AKT) pathways, which are essential for cell proliferation and differentiation (Sato et al. 2023).

Structural variants of FGFR2, generated by numerous alternative gene splicing events, play an important role in the regulation of FGFR2 functions (Matsuda, Ueda & Ishiwata 2012). To date, more than 20 alternative splicing variants of FGFR2 have been identified with IIIb (FGFR2b) and IIIc (FGFR2c) being the two main isoforms. Each splicing variant of FGFR2 has altered extracellular and intracellular regions with altered functions. *FGFR2* gene overexpression has been observed in breast, endometrial, cervical, lung, oesophageal, gastric, pancreatic, and colorectal cancer.

Yashiro et al. (2021) reported that all FGFR2-overexpressing gastric tumours were positive for the FGFR2b isoform and only about 14% were also positive for the FGFR2c isoform. No tumours positive for the FGFR2c isoform only were identified. Ahn et al (2016) found that the intensity of IHC staining of FGFR2b strongly correlated with *FGFR2* gene copy number changes in gastric cancer with high sensitivity and specificity. Thus, *FGFR2* gene overexpression in gastric cancer appears to be mostly driven by the overexpression of the FGFR2b isoform and IHC staining of FGFR2b is a rapid and efficient screening tool to identify G/GOJ adenocarcinoma patients with *FGFR2* gene overexpression who may benefit from FGFR2b-targeted therapy.

Tsimafeyeu and Raskin (2023) reported that one of the main problems with FGFR2 testing may be the false-negative selection of patients due to tumour heterogeneity. G/GOJ adenocarcinomas have high intra- and intertumour heterogeneity. The authors found, in a previous study, that *FGFR2* at any level of expression was detected in 47% of primary tumours and 40% metastases but the level of expression (1+, 2+, 3+) and the percentage of stained cells varied in all cases. In some cases, *FGFR2* gene expression was high in one part of the primary tumours, while no expression was detected in another part, with this leading to some lymph node metastasis without *FGFR2* gene expression, and others with strongly expressed *FGFR2* (Raskin et al. 2023).

Yashiro et al. (2021) also found that the majority (99.1%) of FGFR2-overexpressing tumours showed a variable combination of staining intensities, from 0 to 3 in different parts of the tumour. Similarly, Han et al. (2015) found that intratumoural heterogeneity and discordant FGFR2b expression in primary tumours and metastatic lymph nodes were common in gastric cancer. The authors reported that intratumour

² <https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/gastric-and-oesophageal-metastatic>
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heterogeneity was observed in 55.5% of cases and these cases also had discordant FGFR2b results between primary and metastatic lymph node samples.

Ahn et al. (2016) compared the overexpression of FGFR2b in primary versus metastatic tumour samples in 88 cases of gastric cancer, with seven cases showing overexpression, three cases were positive in both primary and metastatic samples and four cases were positive only in the metastatic lymph node samples. Additionally, when a further 32 FGFR2b-overexpression matched pairs were tested, the percentage of positive tumour cells identified in the metastatic samples was significantly higher than in the primary tumour samples (median 80% versus 35%; $p < 0.001$).

FGFR2b overexpression is associated with a poor prognosis. Ahn et al. (2016) found that FGFR2b overexpression in G/GOJ adenocarcinoma was associated with later-stage disease and poorer overall survival. Han et al. (2015) and Su et al. (2014) also found FGFR2 overexpression was associated with poor overall survival. A meta-analysis by Kim et al (2019) found that FGFR2 protein overexpression was associated with deeper tumour invasion (OR=2.63; 95% CI 1.70, 4.08; $k=6$), higher rates of lymph node metastasis (OR=1.87; 95% CI 1.31, 2.67; $k=10$), more advanced stages of disease (OR=1.78; 95% CI 1.07, 2.96; $k=7$), and worse overall survival (HR= 1.40; 95% CI 1.25, 1.587; $k=10$).

Prevalence of FGFR2b overexpression

FGFR2b overexpression (as detected by IHC) may be a better biomarker than genetic testing for *FGFR2* amplification. The frequency of FGFR2b overexpression detection by IHC ranged from 10% up to 51% whereas the frequency of *FGFR2* gene amplification, detected by IHC and confirmation by FISH, varied from 3% to 9% (Ahn et al. 2016). Similarly, Kim et al. (2019) reported that the frequencies of FGFR2 overexpression as determined by IHC varied from 2.5% to 61.4% among the 10 studies included for meta-analysis. This is likely due to varying molecular mechanisms leading to FGFR2 overexpression. *FGFR2* activating single nucleotide variants have been detected in G/GOJ adenocarcinoma samples as well as *FGFR2* gene amplification errors (Hierro et al. 2017). Additionally, the fact that the addition of bemarituzumab to chemotherapy resulted in promising clinical efficacy in patients with FGFR2b overexpression, regardless of FGFR2 amplification status, supported the selection of patients for treatment with bemarituzumab using IHC alone (Tsimafeyeu & Raskin 2023).

Overall, FGFR2b overexpression, defined as exhibiting any moderate (2+) to strong (3+) membranous IHC staining in more than 0% of tumour cells, was detected in approximately 30% of patients with HER2 negative G/GOJ adenocarcinoma prescreened for participation in the FIGHT trial (Wainberg et al. 2022). FIGHT was a randomised, double-blind, placebo-controlled, phase 2 trial investigating the safety and effectiveness of bemarituzumab in patients with FGF2b-positive G/GOJ adenocarcinoma. Rha et al. (2025) found similar results with FGFR2b protein overexpression at any % of tumour cells (greater than 0%) and $\geq 10\%$ of tumour cells, 2+/3+ overexpression was 37.8% (95% CI, 36.2 to 39.3) and 16.2% (95% CI, 15 to 17.4), respectively.

Other biomarkers associated with G/GOJ adenocarcinoma

Patients with G/GOJ may be tested for biomarkers other than FGFR2 and HER2, for the purpose of determining eligibility to other targeted therapies. This has implications for the volume of tumour tissue available for testing FGFR2 expression, and may have implications for the treatment comparator, if there is overlap between FGFR2 expression and the other biomarkers (making the patient potentially eligible for

multiple different targeted therapies). Examples of other biomarkers are discussed below and include immune checkpoint proteins, other tyrosine kinase receptors and claudin 18.2.

Immune checkpoint proteins

Immune checkpoint proteins, Programmed cell death protein 1 (PD-1) and its ligand, Programmed cell death ligand-1 (PD-L1) play a vital role in inhibiting immune responses and regulating self-tolerance of the immune system (Han, Y, Liu & Li 2020; Sharpe et al. 2007). PD-1 is a transmembrane cell surface receptor expressed on activated T, natural killer (NK) and B lymphocytes, macrophages, dendritic cells (DCs) and monocytes (Han, Y, Liu & Li 2020). PD-L1 is also a transmembrane cell surface protein expressed in many different cell types, both haematopoietic and non-haematopoietic, and its expression is often associated with ongoing inflammatory responses (Sharpe et al. 2007). When PD-L1 binds to PD-1 on CD8+ T cells, it prevents their activation and cytotoxic response. PD-L1 is also highly-expressed in many tumours, which results in tumour immune escape and ultimately, disease progression (Saito et al. 2022). Therapies targeting immune checkpoint proteins, such as nivolumab (standard of care), pembrolizumab, and tislelizumab target PD-1 and have United States Food and Drug Administration (FDA) approval to treat G/GOJ adenocarcinoma (Zhang et al. 2024). To date, nivolumab is the only anti-PD-L1 therapy available for G/GOJ adenocarcinoma that is PBS-listed (PBAC meeting March 2022). Another PD-L1 inhibitor, tislelizumab, received a positive recommendation for the treatment of advanced or metastatic GOJ cancer at the November 2024 PBAC meeting³. No molecular testing (e.g. IHC) is required for access to PBS-subsidised nivolumab.

PD-L1 overexpression is present in about 58% of G/GOJ adenocarcinoma cases (measured as a CPS of 1 or more). A pre-clinical study (Powers et al. 2016) reported that bemarituzumab increased PD-L1 expression within the G/GOJ tumour microenvironment. Overall, bemarituzumab may confer benefit by priming G/GOJ tumours for additional anti-tumour activity by PD-1/PD-L1 inhibitors. This evidence has been used to inform an additional study of bemarituzumab: FORTITUDE-102 which compares the effectiveness of bemarituzumab, nivolumab plus chemotherapy versus nivolumab plus chemotherapy.

Other tyrosine kinase receptors

HER2, epidermal growth factor receptor 1 (EGFR), mesenchymal epithelial transition factor receptor (MET) and FGFR2 are all membrane-bound receptor tyrosine kinases and overexpression of these kinases play critical roles in gastric cancer progression (Nagatsuma et al. 2015).

Overexpression of the HER2, EGFR, MET and/or FGFR2 proteins occurs in 60-80% of G/GOJ adenocarcinomas, depending on the method used to measure overexpression and the study population (Nagatsuma et al. 2015). The co-occurrence of these biomarkers varies between studies. Several studies reported that these driver mutations are largely mutually exclusive in gastric cancers, with only slight overlaps between them (Hierro et al. 2017). Su et al. (2014) reported that when high-level amplifications of HER2 and FGFR2 did co-occur the two biomarkers were detected in distinct areas of the tumour.

However, some studies reported much higher overlaps between the biomarkers. Nagatsuma et al. (2015) found that of the 22.9% of G/GOJ adenocarcinomas that overexpressed FGFR2, 24.0% were positive for overexpression of a second receptor tyrosine kinase (HER2, MET or EGFR). Yasui et al. (2022) found that

³ <https://pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2024-11/files/tislelizumab-psd-nov-2024.pdf>

25.6% of G/GOJ adenocarcinoma tumours had FGFR2 overexpression and 26.1% were HER2 positive, and that 31.1% of those that overexpressed FGFR2 were also HER2 positive. Bemarituzumab is only proposed to be used in those who are HER2 negative. It is unknown whether MET or EGFR overexpression would influence response to treatment with bemarituzumab.

Currently, trastuzumab is the only PBS-listed first-line targeted therapy against HER2 available for metastatic G/GOJ adenocarcinoma (PBAC meeting July 2015⁴). IHC (MBS Item 72848) and positive confirmation by ISH (MBS item 73342) is required prior to access to PBS-subsidised treatment.

Claudin 18.2

Another biomarker of interest is Claudin 18.2 (CLDN18.2), which is a member of the Claudin family of transmembrane proteins that form the main components of tight junctions between cells. Tight junctions mediate cell–cell adhesion and regulate selective permeability in epithelial cellular sheets (Pellino et al. 2021). The CLDN18.2 isoform is highly expressed in epithelial tight junctions of normal gastric mucosa and act as paracellular proton barriers and regulate ion-homeostasis (Kwak et al. 2024; Pellino et al. 2021).

In normal cells, CLDN18.2 is largely inaccessible to intravenous antibodies from within the confines of the tight junction. However, perturbations in gastric mucosa cell polarity and structural loss of tight junction integrity may be important for malignant transformation. Loss of tight junction integrity may allow the diffusion of nutrients and other factors necessary for the survival and growth of the tumour cells, and the decreased polarity may be important for the formation of metastases, where individual cells must leave the primary site and enter the blood vessels to reach distant sites (Morin 2005).

Loss of tight junction integrity may also result in increased exposure of CLDN18.2, making it more accessible to therapeutic antibodies (Pellino et al. 2021). When exposed, monoclonal antibodies, such as zolbetuximab, can bind to CLDN18.2 and target the G/GOJ adenocarcinoma cell for destruction by antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity (Sato et al. 2023).

Approximately 34% of G/GOJ adenocarcinomas were found to be positive for CLDN18.2 by IHC, which was defined as $\geq 75\%$ of tumour cells demonstrating moderate-to-strong membranous staining (Kwak et al. 2024). Additionally, of those G/GOJ adenocarcinomas that were FGFR2 positive, 44.2% were also positive for CLDN18.2. Thus, there is likely to be considerable overlap in G/GOJ adenocarcinomas expressing the FGFR2b and CLDN18.2 biomarkers.

A codependent application for IHC testing for CLDN18.2 to determine eligibility for treatment with zolbetuximab was considered by PBAC in March 2025 and MSAC in April 2025 (MSAC application 1767). Zolbetuximab is therefore a potential near market comparator for bemarituzumab.

Estimated size of target population (for testing)

The application assumed that all patients with newly diagnosed unresectable advanced or metastatic G/GOJC would be eligible for FGFR2b IHC testing.

The estimated number of patients eligible for testing was based solely on gastric cancer (GC). Incidence of GC was extrapolated from 2015 to 2024 data provided by the Australian Institute of Health and Welfare

⁴ <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2015-07/files/trastuzumab-gastric-cancer-psd-july-2015.pdf>

(AIHW). Over a ten year period, the AIHW reported that GC incidence increased from 2,248 in 2015 to 2,584 in 2024 (Australian Institute of Health and Welfare 2024). The proportion estimates of adenocarcinoma GC (84.08%) and advanced or metastatic disease (75%) are derived from estimates accepted by the PBAC for evaluation of nivolumab (November 2021 nivolumab PSD⁵, Table 14). Overall, it is estimated that 1,669 patients will require FGFR2b testing in 2026 (Table 2).

Table 2 Applicant's estimated number of patients meeting the proposed eligibility criteria

Year	Year 1 (2026)	Year 2 (2027)	Year 3 (2028)	Year 4 (2029)	Year 5 (2030)	Year 6 (2031)
Incident cases of GC	2,647	2,678	2,710	2,741	2,772	2,804
% with adenocarcinoma histology	84.08%	84.08%	84.08%	84.08%	84.08%	84.08%
% diagnosed with advanced or metastatic disease	75.0%	75.0%	75.0%	75.0%	75.0%	75.0%
Incidence of unresectable advanced or metastatic GC	1,669	1,689	1,709	1,728	1,748	1,768

Source: Table 1, HPP200225_FGFR2b_ESTIMATED UTILISATION

Abbreviations: GC, gastric cancer

Prior tests

No additional prior tests for the proposed FGFR2b testing.

Current standard of care (SOC) should include tests to confirm the diagnosis and staging of G/GOJ adenocarcinoma and HER2 testing.

Intervention

Test

The proposed investigative intervention is IHC testing for FGFR2 expression. The applicant requested a new MBS item for IHC testing of tumour tissue for FGFR2b expression to determine access to bemarituzumab in patients with unresectable locally advanced or metastatic G/GOJ adenocarcinoma.

FGFR2b overexpression tends to be observed in metastatic sites, particularly in the lymph nodes (Su et al. 2014) and therefore IHC testing of metastatic sites will be prioritised over the primary site.

The application states that the VENTANA FGFR2b (FPR2-D) RxDx Assay will be used to assess FGFR2b expression in the proposed population and is expected to be the only FGFR2b assay available in Australia. It is an IHC assay that uses a mouse monoclonal antibody (clone FPR2-D) to detect FGFR2b proteins on the membrane surface of the sample. The assay produces membranous staining on formalin-fixed, paraffin-embedded gastric/gastroesophageal junction adenocarcinoma⁶. The application notes that IHC staining is a common practice and can be conducted in any pathology laboratory holding the appropriate accreditation. Furthermore, most Australian laboratories already have the VENTANA BenchMark system and will be able to provide this technology without additional infrastructure and not limit the provision of FGFR2b testing. The proposed FGFR2b IHC test is not currently listed on the Australian Register of Therapeutic Goods

⁵ <https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2021-11/files/nivolumab-psd-november-2021.pdf>

⁶ <https://elabdoc-prod.roche.com/eLD/web/global/en/products/PID00000715>

(ARTG). The applicant stated at the pre-PASC meeting (19 February 2025) that an application to the Therapeutic Goods Administration (TGA) may be made in REDACTED.

The manufacturer of the assay does not provide any documentation on how the test is to be interpreted. Furthermore, there does not appear to be an accepted consensus on how FGFR2 expression status is determined. The application proposed that the threshold for a positive result is an IHC staining score of 2+ (moderate to strong) or 3+ (strong) in $\geq 10\%$ of biopsied tumour cells. This threshold was determined from a pre-specified subgroup analysis in the phase 2 FIGHT trial.

In the subgroup analysis of the FIGHT trial, the addition of bemarituzumab to chemotherapy did not result in a benefit of PFS or OS, relative to chemotherapy alone in patients who exhibited FGFR2b expression in $< 10\%$ of tumour cells. However, in patients who exhibited FGFR2b expression in $\geq 10\%$ of cells, the addition of bemarituzumab did confer a benefit in terms of PFS and OS (Table 3).

Table 3 Progression-free survival and overall survival by FGFR2b expression in Phase 2 FIGHT trial

	Tumour IHC Staining Score of 2+ or 3+ in ≥10% of Cells		Tumour IHC Staining Score of 2+ or 3+ in <10% of Cells	
	Bemarituzumab + mFOLFOX6	Placebo + mFOLFOX6	Bemarituzumab + mFOLFOX6	Placebo + mFOLFOX6
N	46	52	30	26
Progression-free survival				
Events	24 (52.2%)	41 (78.8%)	24 (80.0%)	20 (76.9%)
Median survival (95% CI)	14.0 (7.2, 19.0)	7.3 (5.4, 8.2)	8.8 (5.6, 12.9)	7.9 (5.7, 12.1)
Hazard ratio (95% CI)	0.43 (0.26, 0.73)		1.03 (0.57, 1.89)	
Overall survival				
Events	28 (60.9%)	36 (69.2%)	24 (80.0%)	18 (69.2%)
Median survival (95% CI)	24.7 (14.2, 30.1)	11.1 (8.4, 13.8)	15.1 (8.8, 22.3)	17.2 (8.9, 29.4)
Hazard ratio (95% CI)	0.52 (0.31, 0.85)		1.40 (0.76, 2.60)	

Source: FIGHT CSR (Table 14.2.1.9; Table 14.2.2.7). Sourced from applicant developed PICO set (Table 3, p4).

Abbreviations: CI = confidence interval, IHC = immunohistochemistry; mFOLFOX = modified FOLFOX regimen (leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin)

The application proposed that FGFR2b testing is to be run concurrently with standard of care, that includes HER2 testing (MBS Item 72848). The application estimated that 13.9% of those tested will be HER2 positive, based on results from a study of HER2 testing in Australia (Kumarasinghe et al. 2017). Therefore, these patients would be tested redundantly for FGFR2b.

PASC considered if the proposed FGFR2b expression testing should be restricted to patients with HER2-negative, unresectable locally advanced or metastatic G/GOJ adenocarcinoma or, to patients with unresectable locally advanced or metastatic G/GOJ adenocarcinoma irrespective of HER2 status. PASC recalled its recent consideration of IHC testing for Claudin 18 (CLDN18.2) expression in the same patient population and its acceptance that parallel HER2/CLDN18.2 testing might facilitate better timing of management decisions and was best practice for treatment considerations (MSAC application 1767, Ratified PICO Confirmation, April 2024 PASC meeting). PASC considered the same rationale for application 1767 would apply to the current application and that FGFR2b expression testing should not be restricted to those with HER2-negative tumours. PASC considered that the proposed FGFR2b protein expression testing should be conducted in parallel with HER2 testing.

PASC noted that the applicant agreed that allowing FGFR2b testing in parallel to HER2 testing is necessary to facilitate better management decisions. PASC noted the applicant's pre-PASC response that few patients have HER2 testing prior to developing locally advanced or metastatic disease, unless they are enrolled in trials or treated at centres that reflexively test all tumours.

PASC noted that it is possible that HER2 status can change, particularly following exposure to some medications (e.g. trastuzumab). The applicant was queried about whether this would necessitate a repeat biopsy to re-test a patient's HER2 status. PASC noted the applicant's pre-PASC response that repeat biopsy is rare and not done in routine practice.

PASC discussed that it is possible that due to tumour heterogeneity and the number of biomarkers that are available to be tested for patients with G/GOJ adenocarcinoma, a small number of patients would need to have a re-biopsy, as current biopsy methods may not guarantee a sufficient amount of tumour material to yield an accurate result. PASC noted that re-biopsy for this reason would occur rarely as even an endoscopic biopsy tends to sample sufficient tumour tissue for the testing of relevant biomarkers. PASC noted that tumour heterogeneity is an acknowledged issue and queried if testing of multiple biopsy samples is required. PASC noted that ASCO/NCCN guidelines recommend multiple biopsies, optimally six to eight preferred (if this is not an option, testing a cytology specimen from a fine needle aspiration cell block is acceptable). The applicant's pre-PASC response stated that the diagnostic label for FGFR2b protein expression will not include specific provisions regarding testing multiple biopsy samples and that recommendations to mitigate heterogeneity-related issues would need to be driven by external guidelines or clinical consensus rather than embedded in the diagnostic label.

PASC noted that if biomarkers were detected using the same test methodology, this may make more efficient use of tumour tissue (such as through multiplexing) than if testing methodologies differed. PASC acknowledged that biomarker testing is an evolving space (with respect to the number of biomarkers available for testing and testing methodologies available). PASC noted the changing test landscape with the possibility of ctDNA testing being available in the future.

PASC noted that the applicant's pre-PASC response stated that equivocal results are not relevant for FGFR2b IHC testing (PD-L1 and CLDN18.2 do not have equivocal scoring either). PASC noted the applicant's comments that if equivocal results do occur, a peer review or second opinion will be sought, in line with standard routine pathology practices.

PASC noted the pre-PASC response reported that all IHC-based tests involve some level of subjectivity and that the impact is minimised when the cut-offs are straightforward (e.g., any cell with 2+/3+ membrane staining). The applicant acknowledged that a cut-off of $\geq 10\%$ of tumour cells with 2+/3+ staining, as proposed for FGFR2b overexpression, introduces more subjectivity due to the requirement of differentiation between 1+ and 2+ intensity and estimation of tumour cell percentage (e.g. 9% vs. 10%). PASC considered IHC testing suboptimal for objective biomarker testing. PASC noted multiple anti-FGFR drugs are in development, many using genetic analysis rather than IHC testing to determine eligibility. PASC noted that in the randomised phase 2 FIGHT trial, patients whose tumours tested positive for FGFR2b overexpression by IHC and/or FGFR2 amplification by blood (ctDNA) were eligible to enter the trial. However, the applicant stated that FGFR2 amplification by ctDNA was not found to be predictive of treatment response to bemarituzumab. No information on the predictive validity of FGFR2 genetic variants in tumour tissue was

available. The applicant stated that FGFR2b is an isoform of FGFR2 and therefore, there is no 1:1 correlation between FGFR2b protein expression and FGFR2 gene amplification.

Treatment

The proposed treatment for those with unresectable locally advanced or metastatic G/GOJ adenocarcinoma who are HER2 negative and have FGFR2b overexpression, is bemarituzumab, at the first-line. This would be initiated together with a chemotherapy regimen with a fluoropyrimidine- and platinum-containing agent, which is reflective of clinical practice in Australia⁷ with/without nivolumab.

PASC noted that at the time of the initial application, the intervention was proposed to be a “doublet regimen” (a combination of bemarituzumab and chemotherapy). However, the applicant informed PASC that a key trial for the “triplet regimen” (a combination of bemarituzumab, nivolumab and chemotherapy) has progressed faster than expected and therefore intends to include both doublet and triplet regimen in its PBAC submission. PASC considered that if the proposed MBS population for FGFR2b testing to determine eligibility for triplet therapy remains the same as for doublet therapy, then the current PICO Confirmation would remain applicable, as the population and comparator for test would remain the same. PASC noted that the applicant would discuss any drug-related PICO issues (e.g., appropriate comparator) with the PBAC secretariat prior to formal lodgement if required as per the usual submission process.

For patients who are HER2 positive irrespective of their FGFR2b status, they can receive trastuzumab (anti-HER2 treatment) plus the same chemotherapy regimen. In patients without FGFR2b overexpression (a FGFR2b IHC score of 2+ or 3+ in ≥10% of biopsied tumour cells), and are HER2 negative, the treatment options are the same as for the comparator (chemotherapy +/- nivolumab).

Bemarituzumab is not currently TGA-registered. In the Pre-PASC meeting (19 February 2025), the applicant informed that an application to the TGA for both the test and treatment may be made in REDACTED. In April 2021, bemarituzumab was granted “breakthrough therapy” designation by the Food and Drug Administration (FDA) for patients with FGFR2b-overexpressing and HER2-negative metastatic and locally advanced gastric and gastroesophageal adenocarcinoma in combination with modified FOLFOX6 (fluoropyrimidine, leucovorin, and oxaliplatin) (The ASCO Post 2021).

REDACTED

PASC noted that the applicant’s pre-PASC response provided an update regarding their submission plan to the TGA for both the test and bemarituzumab. The applicant informed that regulatory plans are linked to the completion of the phase 3 clinical trials. Once completed and the data are available, the corresponding registration of and VENTANA FGFR2b test will begin. REDACTED

Biological rationale for targeting FGFR2 with bemarituzumab

Being a driver variant, overexpression of FGFR2b is a promising therapeutic target for G/GOJ adenocarcinomas. Inactivation of the FGFR2b receptor, preventing activation of the MAPK and AKT pathways, has downstream consequences that affect tumour cell growth and proliferation (Sato et al. 2023; Wainberg et al. 2022).

⁷ <https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/gastric-and-oesophageal-metastatic>

Bemarituzumab is a first-in-class humanised monoclonal antibody which targets the FGFR2b receptor. Bemarituzumab has two mechanisms of action in treating G/GOJ adenocarcinoma. First, the binding of bemarituzumab to the FGFR2b receptor blocks fibroblast growth factors (FGFs) from activating the FGFR2b receptor, thereby preventing downstream effects (e.g. proliferation of tumour cells). Secondly, bemarituzumab has been specifically engineered to have an increased binding affinity for natural killer cells with enhanced antibody-dependent cell-mediated cytotoxicity (Wainberg et al. 2022; Xiang et al. 2021). This was achieved by preventing fucosylation, which prevents B cell activation and enhances activation of CD16a, leading to enhanced binding to natural killer cells (Li et al. 2018).

Bemarituzumab has shown promising results in the FIGHT phase II clinical trial. The gastric cancer patients treated with bemarituzumab plus chemotherapy had a longer overall survival than those treated with placebo plus chemotherapy (HR=0.58; 95% CI 0.35, 0.95; p=0.027) (Sato et al. 2023; Wainberg et al. 2022).

Comparator(s)

Test

For patients with unresectable locally advanced or metastatic G/GOJ adenocarcinoma, there is no testing for FGFR2b expression in the current clinical management pathway. Therefore, the applicant proposed that the comparator should be 'no FGFR2b testing'. As the proposed FGFR2b IHC testing will be conducted in parallel with HER2 testing, the assessment group considers no FGFR2b testing means current standard of care (HER2 testing).

PASC noted that the proposed comparator is no FGFR2b testing which the Assessment Group considers as current standard of care, which includes HER2 testing. PASC considered that the assessment report should incorporate any near-market comparators (e.g. testing for CLDN). PASC noted that the PBAC (March 2025) deferred making a recommendation for the listing of zolbetuximab for the targeted first-line treatment of patients with locally advanced unresectable or metastatic HER2-negative G/GOJ adenocarcinoma whose tumours are CLDN18.2- positive but was of a mind to recommend zolbetuximab pending MSAC consideration (application 1767, April 2025) of IHC testing for Claudin 18.2 (CLDN18.2) expression.

Treatment

For patients with G/GOJ adenocarcinoma who are HER2 negative, the comparator is the current standard of care in Australia, which is nivolumab in combination with chemotherapy that contains at least a fluoropyrimidine drug and a platinum drug⁸.

The comparator in patients who have received nivolumab for G/GOJ adenocarcinoma previously would be chemotherapy alone. This is due to the PBS restriction for nivolumab in advanced or metastatic gastroesophageal cancer that states that patients must be untreated (up until initiating this drug) with a PD-1/PD-L1 inhibitor therapy for G/GOJ⁹. Therefore, current standard of care for those previously treated with nivolumab, is chemotherapy alone. This comparator would be inappropriate for the triplet regimen (as the population who have received prior PD-1/PD-L1 inhibitor therapy would be ineligible for the triplet regimen).

⁸ <https://www.eviq.org.au/medical-oncology/upper-gastrointestinal/gastric-and-oesophageal-metastatic>

⁹ <https://www.pbs.gov.au/medicine/item/10745m-10748q-10764m-10775d>

It was noted that a separate application for Claudin 18.2 testing/zolbetuximab treatment for G/GOJ adenocarcinoma has been submitted (MSAC 1767). Findings from Kwak et al. (2024) report that of those with gastric cancer patients (stages II-IV) who were FGFR2 positive, 44.2% (68/154) also had the Claudin 18.2 biomarker, which confers eligibility for zolbetuximab. Given this, Claudin 18.2 testing/zolbetuximab treatment has the potential to be a near-market competitor (in those patients whose tumours contain both FGFR2b and Claudin 18.2 biomarkers). IHC testing for CLDN18.2 to access zolbetuximab will be considered by at the March 2025 PBAC meeting and the April 2025 MSAC meeting.

Additionally, tislelizumab¹⁰ and pembrolizumab¹¹ (both anti-PD1) may also be considered as near-market comparators to nivolumab as it has recently been approved by the FDA for unresectable locally advanced or metastatic G/GOJ adenocarcinoma. Whilst for this indication pembrolizumab is TGA-approved and tislelizumab has a current TGA application, neither are currently PBS listed for G/GOJ adenocarcinoma. The PBAC has recommended tislelizumab listing for the treatment of locally advanced or metastatic gastro-oesophageal cancer at the November 2024 PBAC meeting¹².

PASC noted that the current comparator is standard of care being nivolumab combined with chemotherapy or chemotherapy alone if the patient has already received nivolumab for G/GOJ adenocarcinoma previously.

PASC also noted that zolbetuximab was considered by the PBAC in March 2025, and the test to determine eligibility for zolbetuximab (Claudin 18.2) was considered by MSAC in April 2025 (MSAC application 1767), and may be a near-market comparator.

PASC noted that tislelizumab and pembrolizumab (both anti-PD-1 therapies) may also be considered as near-market comparators to nivolumab. While both are TGA-registered, neither is currently PBS-listed for G/GOJ adenocarcinoma (pembrolizumab received a positive PBAC recommendation in May 2022). PASC noted the applicant commented that both tislelizumab and pembrolizumab had been claimed to be non-inferior to nivolumab.

Clinical utility standard (for codependent investigative technologies only)

The clinical utility standard is the VENTANA FGFR2b (FPR2-D) Mouse Monoclonal Antibody IHC test RxDx Assay. This test method was used in the ongoing FORTITUDE-101 trial to identify patients with FGFR2 overexpression (Rha et al. 2025). Patients were considered positive if the IHC staining score is 2+ (moderate to strong) or 3+ (strong) in at least 10% of tumour cells.

It is possible in the future that in-house IHC FGFR2b tests may be developed. If any evidence comparing these against the clinical utility standard becomes available prior to the ADAR being submitted, it should be included (in the form of concordance outcomes, positive percent agreement and negative percent agreement).

¹⁰ <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-zolbetuximab-clzb-chemotherapy-gastric-or-gastroesophageal-junction-adenocarcinoma>

¹¹ <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-chemotherapy-her2-negative-gastric-or-gastroesophageal-junction>

¹² <https://pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2024-11/files/tislelizumab-psd-nov-2024.pdf>

PASC noted that the clinical utility standard is the VENTANA FGFR2b (FPR2-D) Mouse Monoclonal Antibody IHC test RxDx Assay. REDACTED

Outcomes

Test-related outcomes

- Safety: adverse events (AEs) associated with biopsy, re-biopsy for tumour tissues.
- Diagnostic performance: positive percent agreement, negative percent agreement, test-retest reliability inter-observer concordance/reliability, test error rate.
- Yield of testing/number needed to be tested (to identify one eligible case for bemarituzumab)
- Heterogeneity of FGFR2b overexpression within tumour tissue samples
- Turnaround time (to ensure timely diagnosis and access to treatment)
- Rate of rebiopsy (including test failure and inadequate sample rate)

Clinical utility of test

- Treatment effect modification for bemarituzumab based on FGFR2 overexpression (predictive validity)

Change in management

- Proportion of cases eligible for bemarituzumab who would actually receive it

Treatment-related outcomes

- Safety (including treatment-emergent adverse events)
- Overall survival (OS), progression free survival (PFS), objective response rate (ORR), duration of response (DOR), disease control rate (DCR)
- Patient-reported outcomes (PROs) and health-related quality of life outcomes

Healthcare resources

- Cost of testing per patient (including costs of associated re-biopsies, test failure, inadequate sampling)
- Cost of treatments
- Cost of treating adverse events
- Financial implications (including the number of patients tested and treated)

PASC noted the comprehensive list of outcomes.

PASC noted that test error rate should be listed as an outcome to assess potential issues related to tumour heterogeneity.

Assessment framework

The aim of the codependent submission will be to demonstrate that IHC testing for FGFR2b overexpression and targeted treatment with bemarituzumab in combination with chemotherapy results in superior (or non-inferior) health outcomes compared to no testing and treatment with nivolumab and chemotherapy in patients with unresectable locally advanced or metastatic HER2 negative G/GOJ adenocarcinoma.

PASC advised that the codependent MSAC/PBAC submission must provide evidence to support the claim of codependency of FGFR2b protein overexpression and treatment effect with bemarituzumab, as per MSAC Guidelines for codependent technologies.

The MSAC guidelines state that in order to determine whether there is a treatment effect modifier, it must be determined whether response to treatment (versus the comparator) varies by the test result. The FIGHT trial was a biomarker stratified randomised controlled trial of bemarituzumab plus FOLFOX versus placebo plus FOLFOX. This study demonstrated that in those whose tumours were FGFR2b overexpression positive (IHC 2+ or 3+ cells proportion $\geq 10\%$, with/without cell-free circulating tumour (ct)DNA *FGFR2b* amplification), those who received bemarituzumab plus FOLFOX chemotherapy had superior PFS and OS compared to those who had placebo plus FOLFOX. Conversely, in those with tumours did not overexpress FGFR2b on IHC (but did have ctDNA *FGFR2b* amplification), there were no significant differences observed on either PFS or OS, between those who received bemarituzumab plus FOLFOX versus those who had placebo plus FOLFOX. Furthermore, FGFR2b overexpression appeared to be associated with worse prognosis, with those who had FGFR2b overexpression having poorer PFS and OS than those without FGFR2b overexpression, when receiving placebo and FOLFOX. This evidence would be reasonable for the ADAR to use to establish the predictive value of FGFR2b testing, and the codependency of FGFR2b testing with bemarituzumab. However, it was established for the comparison of bemarituzumab and chemotherapy versus chemotherapy alone, not for bemarituzumab and chemotherapy versus nivolumab and chemotherapy.

The clinical claims for the doublet regimen are based on an indirect comparison of the pivotal study (FORTITUDE-101 trial) and the Checkmate 649 trial. FORTITUDE-101 is a phase 3 double-blind, randomised control trial comparing bemarituzumab and FOLFOX chemotherapy or FOLFOX chemotherapy alone in patients with HER2 negative, FGFR2b $\geq 10\%$ 2+/3+ tumour cell (TC) staining (FGFR2b $\geq 10\%$ 2+/3+TC) G/GOI adenocarcinoma. The Checkmate 649 trial is a phase 3 open-label randomised control trial comparing nivolumab and chemotherapy to chemotherapy alone. The clinical claims for the triplet regimen are based on the FORTITUDE-102 trial, assessing the effectiveness of nivolumab plus chemotherapy in patients with FGFR2b overexpression. A summary of the data available is shown in Table 4.

Table 4 Data availability to inform comparisons between bemarituzumab plus chemotherapy and nivolumab plus chemotherapy or bemarituzumab plus nivolumab plus chemotherapy

	Bemarituzumab + chemotherapy	Chemotherapy	Nivolumab + chemotherapy	Bemarituzumab + nivolumab + chemotherapy
Biomarker test positive (FGFR2b overexpression)	FIGHT (IHC+, ctDNA +/-), FORTITUDE-101	FIGHT (IHC+, ctDNA +/-), FORTITUDE-101	FORTITUDE-102	FORTITUDE-102
Biomarker test negative (FGFR2b not overexpressed)	FIGHT (IHC-, ctDNA +)	FIGHT (IHC-, ctDNA +)	NA	NA
Biomarker not tested	NA	Checkmate 649	Checkmate 649	NA

Abbreviations: ctDNA = circulating tumour deoxyribonucleic acid determination of *FGFR2b* amplification; IHC = immunohistochemistry determined FGFR2b overexpression; NA = not available

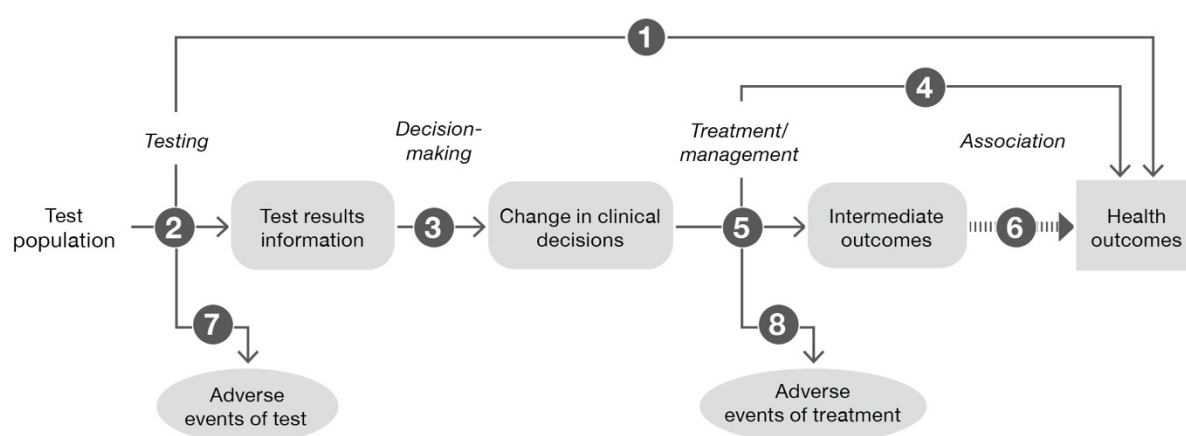


Figure 1 Generic assessment framework showing the links from the test population to health outcomes

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

Research questions mapped to the assessment framework are outlined below:

1. What is the safety, effectiveness and cost-effectiveness of FGFR2b IHC testing versus no FGFR2b testing in patients with unresectable locally advanced or metastatic G/GOJ adenocarcinoma to determine eligibility for treatment with Pharmaceutical Benefits Scheme (PBS) subsidised bemarituzumab plus chemotherapy \pm nivolumab versus treatment with chemotherapy \pm nivolumab in those who are HER2-negative with FGFR2b overexpression?
Does FGFR2b overexpression predict a treatment effect modification with bemarituzumab, distinct from any prognostic effect?
Does FGFR2b overexpression influence the prognosis of patients with unresectable locally advanced or metastatic G/GOJ adenocarcinoma receiving first-line chemotherapy \pm nivolumab?

2. What is the diagnostic yield of FGFR2b overexpression in patients with unresectable locally advanced or metastatic G/GOJ adenocarcinoma? (i.e. the number needed to test to find one patient eligible for bemarituzumab)
Are the proposed tests reliable?
3. What proportion of patients eligible for bemarituzumab based on biomarker test result, meet all other eligibility criteria, and receive treatment with bemarituzumab?
4. What is the effectiveness of bemarituzumab + chemotherapy \pm nivolumab versus chemotherapy \pm nivolumab for OS in those with unresectable locally advanced or metastatic G/GOJ adenocarcinoma at the first line and are FGFR2b positive?
5. What is the effectiveness of bemarituzumab + chemotherapy \pm nivolumab versus chemotherapy \pm nivolumab for PFS and ORR in those with unresectable locally advanced or metastatic G/GOJ adenocarcinoma at the first line and are FGFR2b positive?
6. (*if claims are based on PFS and ORR not OS*) How appropriate is PFS and ORR as surrogate outcomes for OS in patients with unresectable locally advanced or metastatic G/GOJ adenocarcinoma?
7. What is the rate of re-biopsy required due to insufficient tissue being available for testing and any adverse events associated with re-biopsy?
8. In patients with unresectable locally advanced or metastatic G/GOJ adenocarcinoma and are FGFR2b positive, what is the safety of bemarituzumab + chemotherapy \pm nivolumab versus chemotherapy \pm nivolumab?

Clinical management algorithms

Current clinical management algorithm for the identified population

For patients diagnosed with unresectable locally advanced or metastatic G/GOJ adenocarcinoma, HER2 testing is used to inform targeted treatment allocation, in addition to chemotherapy. Patients who are HER2 positive and have metastatic disease are eligible for trastuzumab, whereas those who are HER2 negative and have advanced or metastatic disease are eligible for nivolumab (Figure 2). The algorithm also allows for chemotherapy alone, as patients may have had nivolumab as an adjuvant therapy for an earlier stage of cancer, and would therefore not be eligible for nivolumab as first-line treatment for locally advanced or metastatic cancer. Figure 2 presents the current clinical management algorithm (based on the algorithm provided in the application, with the minor amendment showing the different treatment options for those with/without prior PD-1/PD-L1 inhibitor therapy).

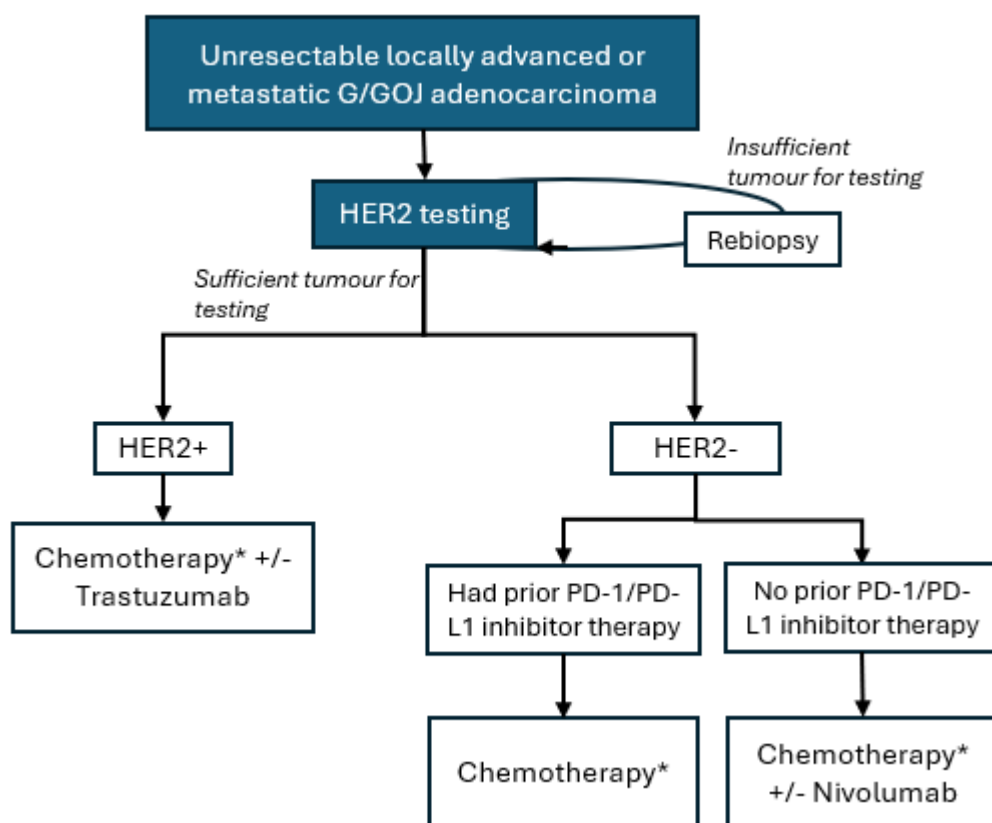


Figure 2 Current clinical management algorithm without FGFR2b testing

Source: Figure 3 PICO Set 1792 (applicant developed)

* Chemotherapy regimens containing at least a fluoropyrimidine drug and a platinum drug.

Abbreviations: G/GOJ = gastric or gastro-oesophageal; HER2 = human epidermal growth factor receptor 2.

Proposed clinical management algorithm

For patients diagnosed with unresectable locally advanced or metastatic G/GOJ adenocarcinoma, the applicant proposed concurrent HER2 and FGFR2b testing to inform the targeted therapies in treatment selection. If a patient tests HER2 positive, they are eligible for trastuzumab regardless of FGFR2b expression status. If a patient's tumour tests HER2 negative and overexpresses FGFR2b, they are eligible for bemarituzumab, and/or nivolumab (unless received as an adjuvant therapy), depending on the safety profile of the targeted therapy to the patient. If a patient tests HER2 negative and does not overexpress FGFR2b they are eligible for nivolumab (unless received as an adjuvant therapy). All patients will receive chemotherapy, regardless of targeted treatment (Figure 3). The proposed algorithm is based on the algorithm provided in the application, with the minor amendment showing the different treatment options for those with/without prior PD-1/PD-L1 inhibitor therapy, and incorporating the triplet regimen.

Triplet regimen would be required to be superior to nivolumab + mFOLFOX6 given the additional costs of bemarituzumab.

PASC noted the pre-PASC response reported that factors like relative safety and efficacy would influence the prescriber's choice of nivolumab over bemarituzumab (or vice versa), in addition to patient

comorbidities and patient preference. If immunotherapy is contraindicated, bemarituzumab will be used; and nivolumab will be favoured if ocular toxicity is a concern.

PASC noted that the proposed clinical management algorithms including doublet and triplet regimens were similar, with the exception of the option of nivolumab added to bemarituzumab and chemotherapy in the triplet algorithm.

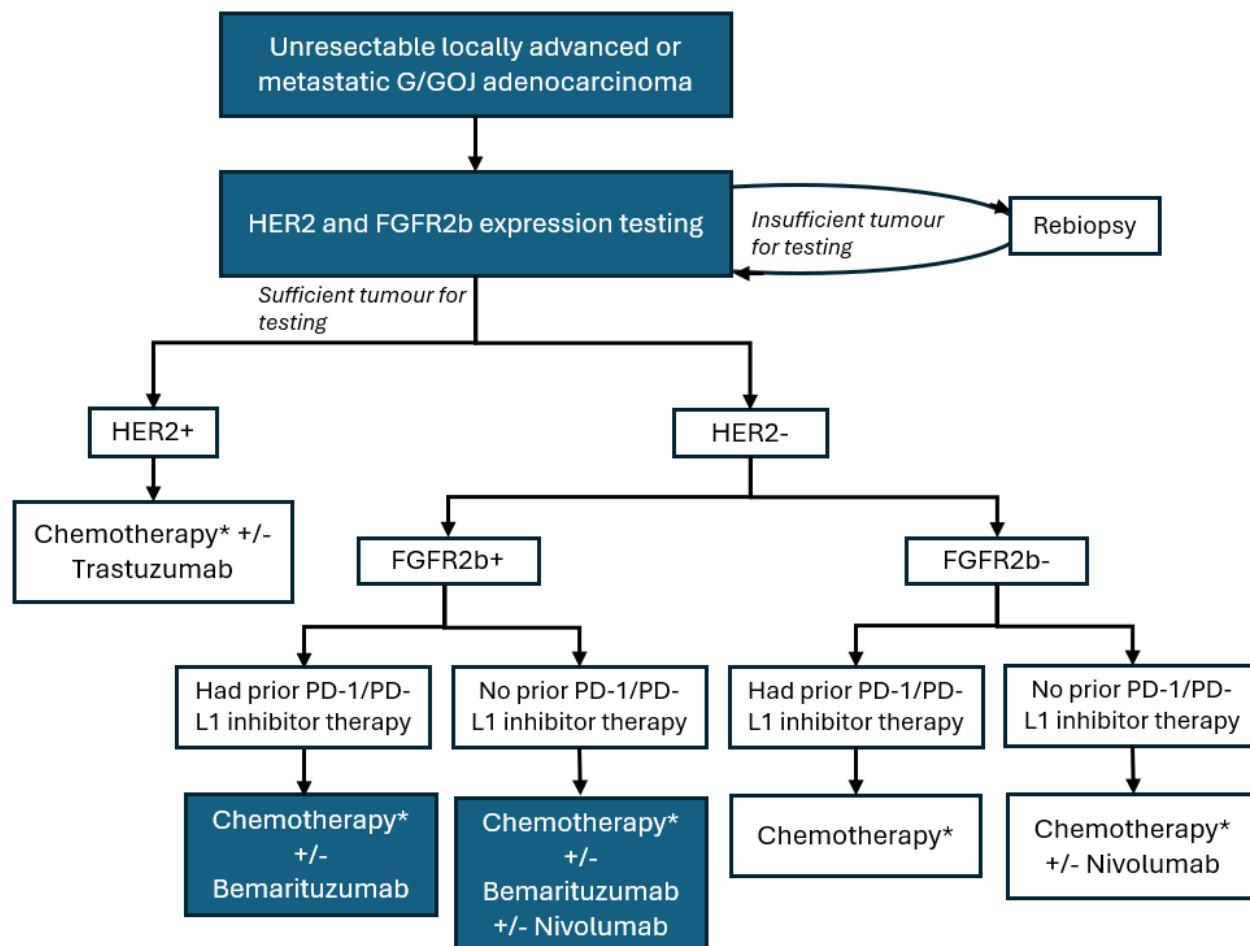


Figure 3 Proposed clinical management algorithm with FGFR2b testing

Source: Adapted from figure 4 PICO Set 1792

Note: the proposed definition of FGFR2b overexpression for bemarituzumab is an IHC staining score of 2+ or 3+ in ≥10% of cells.

* Chemotherapy regimens containing at least a fluoropyrimidine drug and a platinum drug

Abbreviations: FGFR2b = fibroblast growth factor receptor 2; G/GOJ = gastric or gastro-oesophageal junction; HER2 = human epidermal growth factor receptor 2

Proposed economic evaluation

The anticipated clinical claim is that the proposed codependent technologies (FGFR2b IHC testing and in HER2-negative and FGFR2b-overexpressing adenocarcinomas, bemarituzumab as targeted therapy) are superior in effectiveness and non-inferior in safety, compared to no FGFR2b testing and in HER2-negative patients, nivolumab in patients with unresectable locally advanced or metastatic G/GOJ adenocarcinoma. The appropriate type of economic evaluation in the assessment report would either be a cost-effective analysis (CEA) or a cost-utility analysis (CUA) (Table 5).

No clinical claim was made regarding FGFR2b IHC testing and bemarituzumab plus chemotherapy versus no FGFR2b IHC testing and chemotherapy alone, although the additional costs associated with the addition of bemarituzumab would need to be justified (such as through superior effectiveness). Likewise, the triplet regimen would be required to demonstrate superiority to nivolumab + chemotherapy given the additional costs of bemarituzumab, so the appropriate approach would have to be a CEA or CUA.

PASC noted that the appropriate form of economic analysis for a superiority claim is a cost-utility analysis.

If a claim of non-inferiority for both effectiveness and safety is made for bemarituzumab plus chemotherapy versus nivolumab plus chemotherapy, then the appropriate form of economic evaluation would be a cost-minimisation approach.

Table 5 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

Abbreviations: 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 test nominated by the applicant was the VENTANA FGFR2b (FPR2-D) RxDx Assay to assess FGFR2b expression. This is not currently listed in Australia by the Therapeutic Goods Administration (TGA), but is available for Research Use Only (RUO). However, the applicant states that most Australian laboratories have the infrastructure (Ventana BenchMark system) to conduct the assay. In the future, in-vitro diagnostics may be developed by laboratories as an alternative to the commercial kit.

The proposed new MBS item descriptor for IHC testing FGFR2b expression in patients with G/GOJ adenocarcinoma is shown in Table 6. The applicant did not reference the VENTANA FGFR2b (FPR2-D) RxDx Assay in their proposed MBS item and this was accepted by the department as being consistent with current departmental policy as agnostic branding is preferable in terms of future proofing MBS items.

Table 6 Proposed MBS item descriptor for IHC testing of FGFR2b by the applicant

Category 6 – Pathology Services	
MBS item *XXXX	Group P7 – Genetics
Immunohistochemical examination of tumour tissue from a patient with locally advanced unresectable or metastatic gastric/gastro-oesophageal junction adenocarcinoma to determine eligibility relating to fibroblast growth factor receptor 2b (FGFR2b) expression for access to treatment with bemarituzumab under the Pharmaceutical Benefits Scheme (PBS). Applicable once per lifetime.	
Fee: \$125.00 Benefit 85% = TBC 75% = TBC	

The department proposed an alternative descriptor for MSAC to consider. The alternative wording was expanded to include any relevant PBS-subsidised treatment (Table 7).

PASC noted and agreed that the proposed MBS item descriptor should be expanded to include any relevant PBS-listed treatment (Table 7).

PASC recalled its previous consideration that CLDN18.2 testing should occur in parallel to HER2 testing (MSAC 1767) and be pathologist determinable. While PASC considered that the same rationale should apply for FGFR2b testing, PASC advised that there should not be any restrictions on who can order the proposed new MBS item.

PASC noted that removal of the “Applicable once per lifetime” clause was appropriate due to rare cases in which re-testing FGFR2b status may be appropriate. PASC also noted that any reanalysis cost due to test failures would be absorbed by the first fee.

Table 7 MBS item descriptor for IHC testing of FGFR2b supported by PASC

Category 6 – Pathology Services	
MBS item *XXXX	Group P5 – Tissue Pathology
Immunohistochemical examination of tumour tissue from a patient with locally advanced unresectable or metastatic gastric/gastro-oesophageal junction adenocarcinoma to determine eligibility relating to fibroblast growth factor receptor 2b (FGFR2b) expression, to determine eligibility for a relevant treatment under the Pharmaceutical Benefits Scheme (PBS).	
Fee: \$76.30 ^a 85% = \$64.90 75% = \$57.25	

red text = added by the department, strikethrough text = deleted by the department

^aFees (exact figures to be confirmed) applicable from 1 July 2025, based on indexation of the items the proposed item is benchmarked against (MBS items 72814 and 72848).

The application proposed the testing for FGFR2b expression be requested only by gastroenterologists, gastric surgeons and oncologists once a diagnosis of unresectable locally advanced or metastatic G/GOJ adenocarcinoma has been established.

FGFR2b IHC testing is likely to be conducted in specialist laboratories who must hold the appropriate accreditation and registration for this testing procedure to receive MBS funding for the proposed item. Laboratories will need to participate in the Royal College of Pathologists of Australasia (RCPA) Quality Assurance Program (QAP), or a similar external quality assurance program. Testing must be conducted, and the results interpreted and reported by a certified and trained pathologist.

Currently, FGFR2b IHC testing is not conducted in Australia. It is expected that a patient will only be tested for FGFR2b expression in G/GOJ tumour tissue once in their lifetime. However, a patient may require an additional test in cases where insufficient tumour sample was captured during the first biopsy, especially if multiple biomarkers require parallel testing (i.e., HER2 and FGFR2b testing).

The applicant has proposed a fee of \$125, of which 100% will be covered by the MBS. The applicant has provided a justification for the fee (Table 8). The department advised that the MBS does not fund laboratory overheads and therefore, the cost breakdown should be revised omitting these costs.

Table 8 Estimated cost breakdown for the FGFR2b IHC test

Item	Description / comments	Cost per test	Source / type
Materials			
FGFR2b assay reagent	ARTG registered / IVD reagent for IHC tissue testing	\$30	Based on list price, excluding any applicable taxes
Additional testing reagents and controls	Test-specific supplies as specified in applicable instructions for use	\$10	Estimated only
Laboratory consumables	General supplies used in sample preparation and processing	\$10	Estimated only
Subtotal		\$50	-
Labour			
Test processing	Test reading / scoring, quality assurance, laboratory management, pathologist review	\$55	Estimated based on similar testing procedures
Training	Up-front and ongoing training for specific testing procedures	\$10	Estimated based on similar testing procedures
Subtotal		\$65	-
Overhead			
Depreciation	Allowance for equipment maintenance and depreciation charges	\$2	Estimated only
Accreditation and validation	Compliance and accreditation costs for laboratory	\$5	Estimated only
Other fixed costs	Allowance for other fixed overheads (including physical plant / building associated overheads)	\$3	Estimated only
Subtotal		\$10	-
Total			
Total cost		\$125	-

Source: Table 1, HPP200225_FGFR2b_COST BREAKDOWN

Abbreviations: ARTG= Australian Register of Therapeutic Goods; FGFR2b= fibroblast growth factor receptor 2b; IHC= immunohistochemistry; IVD= in vitro diagnostic.

The proposed cost appears to be substantially higher to similar items: MBS item 72848 which is used for HER2 testing (Table 9), item 72814 (Table 10) which is used for PD-L1 testing, and item 72846 which is a generic item for IHC of biopsy material (Table 11).

PASC noted that applicant's proposed fee of \$125.00 per test was substantially higher than similar items (e.g., 72848, 72814, 72846). PASC considered that the MBS Item fee should be benchmarked to similar

tests. It was noted that immunohistochemistry tests requiring objective scoring are appropriately rebated at a higher level than standard immunohistochemistry. PASC considered that the assessment report needs to provide a justification for a higher cost, noting that MBS does not fund laboratory overheads.

Table 92 MBS Item 72848 for HER2 by immunohistochemistry

Category 6 – Pathology Services	
MBS item 72848	Group P5 – Tissue Pathology
Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 of the following antibodies - oestrogen, progesterone and c-erb-B2 (HER2)	
Fee: \$74.50 Benefit 75% = \$55.90 85% = \$63.35	

Table 30 MBS Item 72814 for PD-L1 by immunohistochemistry

Category 6 – Pathology Services	
MBS item 72814	Group P5 – Tissue Pathology
Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the programmed cell death ligand 1 (PD-L1) antibody of tumour material from a patient diagnosed with:	
(a) non-small cell lung cancer; or	
(b) recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx; or	
(c) locally recurrent unresectable or metastatic triple-negative breast cancer.	
Fee: \$74.50 Benefit 75% = \$55.90 85% = \$63.35	

Table 41 MBS Item 72846 for immunohistochemistry examination of biopsy material

Category 6 – Pathology Services	
MBS item 72846	Group P5 – Tissue Pathology
Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 antibodies except those listed in 72848	
(Item is subject to rule 13)	
Fee: \$59.60 Benefit: 75% = \$44.70 85% = \$50.70	

Summary of public consultation input

PASC noted and welcomed consultation input from 2 individuals, both of whom were health professionals.

The consultation input received was supportive of public funding for IHC testing for FGFR2b expression in patients with unresectable locally advanced or metastatic gastric or gastro-oesophageal cancer, to determine eligibility for PBS subsidised bemarituzumab treatment. The consultation input raised a concern in relation to the clinical claim, noting that the claims are only appropriate as long as the pivotal trial (FORTITUDE-101) produces the expected benefits in phase 3 settings.

Benefits and Disadvantages

The main benefit of public funding received in the consultation input included providing access to FGFR2b testing for access to targeted medicines, as currently testing is not routinely available outside of clinical trials.

There were no disadvantages of public funding received in the consultation input.

Population, Comparator (current management) and Delivery

The consultation input agreed with the proposed population and comparator outlined in the application.

Other services identified in the consultation input as being needed to be delivered to provide the intervention included upskilling of pathologists to perform the IHC testing and assessment of FGFR2b.

MBS Item Descriptor and Fee

The consultation input largely agreed with the proposed service descriptor, however one health professional stated testing was appropriate only in patients that are HER2 negative.

The consultation input agreed with the proposed service fee.

Additional Comments

Both health professionals noted that FGFR testing would benefit patients with cholangiocarcinoma and other rare cancers.

PASC noted that two public consultation responses were received, and supported public funding for the proposed medical service.

Next steps

The applicant confirmed that an applicant developed assessment report (ADAR) will be prepared.

Applicant Comments on Ratified PICO

The applicant had no comment.

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Ratified PICO Confirmation – April 2025 PASC Meeting

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Application 1792 - Immunohistochemistry testing for fibroblast growth factor receptor (FGFR2b) expression in patients with unresectable locally advanced or metastatic gastric or gastro-oesophageal cancer, to determine eligibility for PBS subsidised bemarituzumab treatment

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