An addendum has been included at the end of these minutes.

5.19 ZOLBETUXIMAB, Powder for I.V. infusion 100 mg (20 mg per mL), Vyloy®
ASTELLAS PHARMA AUSTRALIA PTY LTD

1 Purpose of submission

1.1 A Category 1 integrated codependent submission requesting Medicare Benefits Schedule (MBS) listing of immunohistochemistry (IHC) testing for Claudin 18.2 (CLDN18.2) expression and Pharmaceutical Benefits Scheme (PBS) listing of zolbetuximab with fluoropyrimidine- and platinum-containing chemotherapy for the targeted first-line treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (G/GOJ) adenocarcinoma whose tumours are CLDN18.2- positive (CLDN18.2+).

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy with no testing.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Test: Patients with locally advanced unresectable or metastatic G/GOJ adenocarcinoma. Drug: Patients with locally advanced unresectable or metastatic HER2-negative G/GOJ adenocarcinoma who are found positive after Claudin 18 testing (CLDN18.2+).
Intervention	Test: IHC testing for CLDN18.2 expression using the Ventana® CLDN18 (43-14A) RxDx Assay Drug: Zolbetuximab in combination with fluoropyrimidine and platinum-containing chemotherapy
Comparator	Test: No testing Drug: For patients without prior immune checkpoint inhibitor therapy, nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy. For patients who received nivolumab therapy for Stage II/III disease and subsequently relapsed with locally advanced unresectable/metastatic disease, chemotherapy alone.
Outcomes	Test-related outcomes: • Safety: Adverse events associated with biopsy/re-biopsy for patients with inadequate tissue for tumour testing. • Diagnostic performance: Sensitivity, specificity, assessment of extent of and implications of discordances between Australian IHC testing and clinical utility standard, test-retest reliability, evidence of stability of proteins in archival tissue, evidence of stability in CLDN18.2 status over time, test failure rate, heterogeneity within tissue samples. • Clinical validity: Positive and negative predictive values, positive and negative likelihood ratios. • Clinical utility of the test: Determine whether testing for CLDN18.2 predicts variation in the treatment effect of zolbetuximab in terms of health outcomes for patients. Drug-related outcomes: • Safety: Safety and tolerability of treatment with zolbetuximab compared to alternative treatments assessed by adverse events, physical examination, laboratory findings and vital signs. • Clinical effectiveness outcomes: ○ Objective response rate ○ Overall survival ○ Progression-free survival ○ Partial response ○ Complete response ○ Health-related quality of life • Healthcare system outcomes: ○ Cost of testing per patient and cost of associated 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.
Clinical claim	In patients with locally advanced unresectable or metastatic G/GOJ adenocarcinoma with CLDN18.2+ tumours identified by the IHC testing for CLDN18 expression, zolbetuximab in combination with chemotherapy is noninferior compared to no testing and nivolumab in combination with chemotherapy in terms of efficacy, with different but manageable safety profile

Source: Table 1-1, pp25-26 of the submission.
CLDN18 = Claudin 18; G/GOJ = gastric or gastro-oesophageal junction; HER2 = human epidermal growth factor receptor 2; IHC = Immunohistochemistry.
Italics added during evaluation based on the Table 1, p2 of the MSAC 1767 Ratified PICO Confirmation, April 2024 PASC Meeting.

2 Background

Registration status

2.1 **TGA status at time of PBAC consideration**: not registered. The submission was made under the Therapeutics Goods Administration (TGA)/ Pharmaceutical Benefits Advisory Committee (PBAC) Parallel Process. Zolbetuximab has been granted Orphan Drug Designation by the TGA, and the TGA Delegate's Overview was available at the time of PBAC consideration.

2.2 The proposed TGA indication is: 'Zolbetuximab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastro-oesophageal junction (GOJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive.'

2.3 Zolbetuximab is administered by intravenous infusion over a minimum of 2 hours. To minimise adverse reactions, it is recommended that each infusion should be started at a relatively low rate, and gradually increased as tolerated during the course of the infusion.

2.4 The use of zolbetuximab in combination with fluoropyrimidine- and platinum-containing chemotherapy (hereafter zolbetuximab + chemotherapy) for the proposed indication was recently approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). The evaluation noted that according to the EMA Product Information (PI) and FDA Prescribing Information, zolbetuximab was associated with serious adverse reactions, including hypersensitivity reactions (such as anaphylaxis and infusion-related responses), as well as severe nausea and vomiting (FDA Prescribing information for Zolbetuximab[1], EMA Product information[2]).

For more detail on PBAC's view, see section 7 PBAC outcome.

[1] FDA, Zolbetuximab prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761365s000lbl.pdf

[2] European Medicine Agency (EMA), Zolbetuximab: EPAR – Product Information, September 2024, Accessed: November 2024, https://www.ema.europa.eu/en/documents/product-information/vyloy-epar-product-information_en.pdf

3 Requested listing

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount	№.of Rpts
ZOLBETUXIMAB Injection 100 mg/20mL (vial)	$11,112.14 [Published, Private Hospital] $10,915.91 [Published, Public Hospital]	1,400 mg	0
ZOLBETUXIMAB Injection 100 mg/20mL (vial)	$8,759.85 [Published, Private Hospital] $8,596.10 [Published, Public Hospital]	1,100 mg	8
ZOLBETUXIMAB Injection 100 mg/20mL (vial)	$5,623.47 [Published, Private Hospital] $5,503.02 [Published, Public Hospital]	700 mg	12
Available brands			
Vylov zolbetuximab 100 mg injection, 1 vial			

Category / Program: Section 100 – Efficient Funding of Chemotherapy
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED)
Severity: Locally advanced unresectable or metastatic
Indication: Gastric or gastro-oesophageal junction cancer
Treatment Phase: Initial
Clinical criteria:
Patient must have/have had at the time of initiating treatment with this drug, a WHO performance status no higher than 1
AND
Clinical criteria:
The condition must have evidence of CLDN18 expression as demonstrated by immunohistochemistry in tumour material– retain this evidence on the patient's medical records; do not submit a copy of this evidence in this authority application
Clinical criteria:
Patient must be untreated (up until initiating this drug) with programmed cell death-1/ligand-1 (PD-1/PD-L1) inhibitor therapy for gastro-oesophageal cancer
Treatment criteria: Induction dose
Patient must not be undergoing treatment with this drug as a PBS benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 months from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs
AND
Patient must be undergoing treatment with this drug for the first time
Population criteria:
Conditions: gastric cancer, gastro-oesophageal junction cancer, oesophageal adenocarcinoma Concomitant therapies: chemotherapy containing at least a fluoropyrimidine drug plus a platinum drug Line of treatment: first-line drug treatment Additional clinical finding: HER2-negative
Prescribing Instructions: The treatment must be prescribed in accordance with the drug's 'Indications' section of the approved Australian Production Information with respect to each of: (i) concomitant drugs/therapies, (ii) line of therapy (i.e. prior treatments, if any)
Treatment Phase: Continuing
Clinical criteria:
The condition must not have progressed
Treatment criteria:
Patient must be undergoing current treatment with this drug through the PBS for this PBS-indication, evidenced by at least 1 PBS claim under the 'Initial treatment' phase

Prescriber Instructions:
Patient must not be undergoing treatment with this drug as a PBS benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 months from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs.

3.1 The submission did not propose an effective price for zolbetuximab as the effective price of nivolumab was unknown to the Sponsor. The Sponsor requested to enter into a Special Pricing Arrangement (SPA) similar to that of nivolumab upon receiving a recommendation from the PBAC.

3.2 The submission proposed initial and continuing criteria. For the initial criteria, the submission requested a maximum amount of 1,400 mg with no repeats. This was based on a single loading dose of 800 mg/m^2 (regardless of chemotherapy backbone) and a weighted body surface area (BSA) of 1.70 m^2 from the GLOW and SPOTLIGHT trials. For the continuing criteria, the submission requested a maximum amount of 1,100 mg with 8 repeats for the three weekly (Q3W) dose (if used with CAPOX) and 700 mg with 12 repeats for the two weekly (Q2W) dose (if used with FOLFOX). This was based on a dose of 600 mg/m^2 for the Q3W dose and 400 mg/m^2 for the Q2W dose and a weighted BSA of 1.70 m^2. The submission rounded each maximum amount to the nearest whole vial, but this was not appropriate as EFC rules for chemotherapy mean that whole vials do not need to be dispensed.

3.3 The dosing regimen proposed by the submission was consistent with the draft PI for zolbetuximab; however, the SPOTLIGHT and GLOW trials utilised maintenance doses of 600 mg/m^2 Q3W with both CAPOX and mFOLFOX6. The TGA Delegate was satisfied that the efficacy and safety of the proposed alternative dosing regimen [Q2W] is established and acceptable.

3.4 The Pre-Sub-Committee Response (PSCR) agreed to the Secretariat's proposal to include two separate continuing treatment phases, to clearly outline to prescribers the circumstances under which maximum amounts and repeats should be prescribed (i.e. different dosage regimens).

3.5 The requested restriction included patients with oesophageal adenocarcinoma (as part of the Conditions population criteria) in addition to those with G/GOJ adenocarcinoma. The evaluation noted that this was inconsistent with the proposed TGA indication for zolbetuximab. The PSCR stated that the oesophageal cancer indication was mistakenly added in the proposed population criteria.

3.6 Noting the above paragraph, the PBAC advised the population criteria that included Conditions, Concomitant therapies, Line of treatment and Additional clinical finding was unnecessary and could be removed from the proposed restriction. Additionally, the PBAC considered the Prescribing Instructions '"The treatment must be prescribed in accordance with the drug's 'Indications' section of the approved Australian Production Information with respect to each of: (i) concomitant drugs/therapies, (ii) line of therapy (i.e. prior treatments, if any)" could be removed.

3.7 The evaluation noted that the requested restriction proposed a stopping rule at 24 months from initiation, which it considered to be inappropriate. Although this was consistent with the restriction for nivolumab it was not included in the zolbetuximab PI. Additionally, the requested restriction specified that 'patient must be untreated (up until initiating this drug) with programmed cell death-1/ligand-1 (PD-1/PD-L1) inhibitor therapy for gastro-oesophageal cancer.' However, the evaluation noted that this restriction is likely not applicable to zolbetuximab. The PBAC agreed with the evaluation that both these criteria were unnecessary and could be removed.

3.8 The PSCR agreed with the Secretariat's proposed amendment to the clinical criterion in the continuing treatment phase: "The condition must not have progressed" to "The condition must not have progressed while receiving PBS-subsidised treatment with this drug for this condition."

3.9 The evaluation noted that CLDN18.2 positivity in the draft TGA Product Information and the key clinical trials was defined as ≥75% of tumour cells demonstrating moderate to strong membranous CLDN18 IHC staining, but this was not described in the requested restriction. The evaluation and the ESCs considered that excluding the threshold may lead to use in patients with <75% of tumour cells demonstrating moderate to strong membranous CLDN18 IHC staining, resulting in its use in populations where the efficacy of zolbetuximab + chemotherapy was not significantly different from chemotherapy alone (refer to paragraph 6.33 for more details). The PSCR argued for flexibility in the threshold to accommodate evolving evidence or future applications of the test, in this rapidly advancing field, noting that the approach was supported at the April 2024 PASC meeting. However, the PSCR also stated that the stringent selection of patients with CLDN18.2 positivity ≥75% ensures targeting of patients most likely to benefit from zolbetuximab therapy. The evaluation and the ESCs considered that the definition of CLDN18.2 positivity, including expression in ≥75% tumour cells, should be reflected in the requested restriction to determine eligibility for zolbetuximab, in line with the TGA PI.

3.10 The submission estimated that approximately 15 patients will transition from non-PBS to PBS-subsidised supply for zolbetuximab as grandfather patients. However, a grandfather restriction was not proposed in the submission.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 G/GOJ cancer originates in the lining of the stomach and the GOJ (the area located between the stomach and the oesophagus). Gastric cancer (GC) is the fifth most common cancer and GOJ cancer is the ninth most common cancer. In 2023, Cancer Australia estimated 2,576 new stomach cancer cases and 1,153 related deaths. Males are twice as likely to be diagnosed as females. Eastern Asia, primarily China, accounts for 60% of global gastric cancer cases and 57% of related deaths. Key risk factors

include family history, older age, tobacco use, high alcohol consumption, and dietary factors.

4.2 G/GOJ adenocarcinomas are associated with poor prognosis, with a five-year survival rate of 38%[3], which declines further in advanced stages. The mortality burden of locally advanced unresectable or metastatic G/GOJ (hereafter advanced G/GOJ) cancer is significant, with global average five-year survival rates of only 5–10% for patients with Stage IV disease.[4] G/GOJ adenocarcinomas are aggressive malignancies that significantly impact quality of life (QoL) and result in high healthcare resource utilisation.

4.3 In the current clinical management algorithm presented in the submission, patients with advanced or metastatic G/GOJ adenocarcinoma receive a combination of fluoropyrimidine- and platinum-containing chemotherapy, typically CAPOX or mFOLFOX6. For patients with HER2-positive tumours, trastuzumab is added to chemotherapy. For patients with HER2-negative tumours, nivolumab is added to chemotherapy. For the subgroup of the population with HER2-negative tumours who have relapsed after early-stage disease treatment with nivolumab or have contraindications to PD-1 inhibitors, the treatment is generally chemotherapy alone.

4.4 The submission stated that MBS listing of IHC CLDN18 testing and PBS listing of zolbetuximab will provide an additional first-line treatment option for patients with HER2-negative advanced or metastatic G/GOJ cancers. The evaluation considered that this was in line with the National Comprehensive Cancer Network (NCCN) guideline for Gastric Cancer (Version 5.2024)[5] which recommends zolbetuximab + chemotherapy for patients who are HER2-negative and tested positive for CLDN18.2 expression (≥75%) in the first-line metastatic setting.

4.5 Zolbetuximab is a genetically engineered, highly purified chimeric (mouse/human immunoglobulin G1 [IgG1]) monoclonal antibody (mAb) targeted against CLDN18.2. Upon binding, zolbetuximab induces cancer cell death through antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

4.6 The CLDN18.2 threshold for a positive result was ≥75% tumour cells showing moderate-to-strong membranous staining, while <75% indicated a negative result. This ≥75% threshold was based on evidence from SPOTLIGHT and GLOW trials. Additionally, this was supported by the FAST phase II study, which demonstrated better treatment outcomes in patients with higher CLDN18.2 expression when

[3] Cancer Australia. Stomach cancer statistics, https://www.canceraustralia.gov.au/cancer-types/stomach-cancer/statistics Accessed on 11th Nov 2024.

[4] Casamayor, M., Morlock, R., et al., (2018), 'Targeted literature review of the global burden of gastric cancer', *Ecancermedicalscience*, 12, 883, https://doi.org:10.3332/ecancer.2018.883

[5] NCCN Gastric Cancer Guidelines (Version 5.2024), https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf

zolbetuximab was added to standard chemotherapy. In the FAST study, compared to chemotherapy alone, there were significant improvements in PFS and OS in patients with CLDN18.2 expression in ≥70% of tumour cells. However, no significant differences were observed between the two arms in patients with CLDN18.2 expression ranging from 40%-69%.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated nivolumab with fluoropyrimidine- and platinum-based chemotherapy (hereafter nivolumab + chemotherapy) as the main comparator for the proposed drug. For patients who received nivolumab therapy for early-stage disease and subsequently relapsed, or who have contraindications to PD-1/PD-L1 inhibitors, chemotherapy alone was nominated as the comparator, but no economic evaluation was presented for this comparison. The main arguments provided in support of this nomination were:

- Nivolumab + chemotherapy is the standard of care for the first-line treatment of HER2-negative advanced or metastatic G/GOJ cancer, demonstrating improved overall survival (OS) in the CheckMate 649 trial.
- Nivolumab + chemotherapy was recommended for listing for the same indication at the March 2022 PBAC Meeting.
- For patients who relapse after early-stage treatment with nivolumab or have contraindications to PD-1 inhibitors, chemotherapy alone is the most appropriate treatment option, as PBS restrictions prevent the repeated use of PD-1/PD-L1 inhibitors for this condition.

5.2 The submission identified pembrolizumab, another PD-1 inhibitor, combined with chemotherapy as a near-market comparator given its similar mechanism and potential future availability. The evaluation noted that the PBAC recommended the listing of pembrolizumab in combination with chemotherapy for the first-line treatment of advanced or metastatic G/GOJ cancers in May 2022 (paragraph 14.1, pembrolizumab, Public Summary Document (PSD), November 2021 PBAC Meeting with March 2022 and May 2022 Addendums) however it is not PBS listed.

5.3 Additionally, the evaluation considered that tislelizumab, another PD-1 inhibitor, may be a relevant near market comparator. The PBAC recommended the PBS listing of tislelizumab for advanced or metastatic gastro-oesophageal cancer, noting that the

cost-effectiveness of tislelizumab in this population would be acceptable if it were cost-minimised to nivolumab[6].

5.4 The evaluation and the ESCs considered that overall, the submission's nomination of nivolumab + chemotherapy as the main comparator, and chemotherapy alone for the subgroup of patients who relapsed after early-stage nivolumab treatment or have contraindications to PD-1/PD-L1 inhibitors, appeared reasonable.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. Two clinicians supported the proposed listing, describing relevant clinical trial evidence, the natural history of the disease, rationale for the codependency, and current treatment options in the Australian setting. One clinician indicated that they may prefer zolbetuximab in patients with Claudin 18.2 positive cancers when the tumour PD-L1 expression is low (i.e. combined positive score (CPS) < 5) as these patients may be less likely to benefit from immune therapy, whereas for patients with a CPS ≥5, the decision is more complex and will take into account patient preference alongside the recognised side-effects of treatment. Both clinicians noted that the risks and side-effects of zolbetuximab are well understood, and they believed the significant associated acute adverse events such as nausea could be managed or prevented (e.g. with aggressive antiemetic regimens and changes in infusion rate).

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (1), and organisations (3) via the Consumer Comments facility on the PBS website. The comments described the poor prognosis for the proposed population and considered it valuable to have an additional treatment option for these patients.

6.3 The PBAC noted the advice received from Rare Cancers Australia (RCA) and Pancare clarifying the likely use of zolbetuximab in clinical practice. The advice included that the use of zolbetuximab may provide another treatment option for this small population of patients with advanced disease and poor prognosis. Pancare noted the improved PFS and OS compared to chemotherapy alone, which the PBAC noted was not the comparator for the submission.

[6] https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/agenda/pdf/2024/PBAC-meeting-agenda-November-2024-v6.PDF. Accessed 24 December 2024.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the zolbetuximab submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the SPOTLIGHT trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for zolbetuximab, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[7], based on a comparison with chemotherapy alone (FOLFOX), which the PBAC noted was not the comparator for the submission.

Overview of the evidence base

6.5 The approach taken in the submission was to present evidence that has been linked to support the contention that targeting CLDN18.2 expression with zolbetuximab + chemotherapy produced noninferior clinical outcomes compared to no testing for CLDN18.2 expression and nivolumab + chemotherapy for patients with HER2-negative, CLDN18.2-agnostic locally advanced or metastatic G/GOJ adenocarcinomas.

Table 2: Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence supplied		
Accuracy and performance of the test (cross-sectional accuracy)	Concordance with clinical utility standard (Jasani et al., 2024)	☒	k=1	n=15[a]
	Analytical performance and reproducibility of Ventana® CLDN18 (43-14A) RxDx IHC assay (Stratton et al., 2023)	☒	k=1	n=NR[b]
Prognostic evidence (longitudinal accuracy)	Comparison of health outcomes in patients receiving usual care (chemotherapy), conditioned on the presence or absence of biomarker-positive status	☒	k=3	n=1,058[c]
Change in patient management	Not explicitly assessed. Patients tested positive with CLDN18.2 would be eligible for treatment with zolbetuximab.	☐	k=0	n=0
Health outcomes (clinical utility)	As per treatment effect (enriched).	☒	k=2	n=1,072
Predictive effect (treatment effect variation)	No evidence presented.	☐	k=0	n=0
Treatment effect (enriched)	Two RCTs with all patients tested positive for CLDN18.2, randomised to either zolbetuximab + CAPOX/mFOLFOX6, or CAPOX/mFOLFOX6.	☒	k=2	n=1,072

Source: Table 2-6, pp57-58; Table 2-13, p78; Table 2-14, p78; Table 2-15, p78 of the submission.
CAPOX = capecitabine and oxaliplatin; CLDN18.2 = claudin 18.2; IHC = immunohistochemistry; k=number of studies; mFOLFOX6 = leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin; n = number of patients; NR = not reported; QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies; RCT = randomised controlled trial
[a] 15 resection samples were used to construct tissue microarray.
[b] 24 tissue cases were stained for repeatability analysis; 100 tissue cases were evaluated for inter- and intra-reader precision; and 28 tissue cases were stained for interlaboratory reproducibility tests (Stratton et al., 2023).
[c] n=408 in Kubota et al. (2023); n=350 in Pellino et al. (2021); n=300 in Waters et al., (2024).

[7] *Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017*

6.6 The data available to inform the comparison are summarised in Table 3.

Table 3: Data availability to inform comparisons

	Proposed treatment	Comparator treatments	
	Zolbetuximab + chemotherapy	**Chemotherapy**	**Nivolumab + chemotherapy**
Biomarker test positive	SPOTLIGHT and GLOW trials	SPOTLIGHT and GLOW trials	CheckMate 649 and ATTRACTION-4; however, the biomarker CLDN18.2 was not tested in these trials and the study participants' CLDN18.2 status was unknown.
Biomarker test negative	No evidence presented	No evidence presented	

Source: Complied during evaluation.

6.7 Notably, trials evaluating the efficacy and safety of zolbetuximab + chemotherapy exclusively included patients with CLDN18.2+ expression, while CLDN18.2 expression status was not assessed in the nivolumab + chemotherapy trials. The evaluation considered that the prognostic value of CLDN18.2 expression remains uncertain due to limitations in the evidence presented. A recent systematic review and meta-analysis by Moraes et al. (2024) found CLDN18.2 expression to be a negative prognostic indicator for overall survival in gastric cancer patients. Overall, the ESCs concluded that the available evidence suggests that expressing CLDN18.2 is possibly prognostic of poorer health outcomes in gastric cancer, but the quality and applicability of this evidence to the proposed Australian clinical population is uncertain. Additionally, no predictive evidence was provided in the submission showing a differential effect of zolbetuximab in those with CLDN18.2-positive and CLDN18.2-negative expression, which was identified using the threshold of 75%. The ESCs suggested that summarising the results of the early studies showing no effect in patients with CLDN18.2-expression would support the claim that this biomarker has a predictive effect on the effectiveness of zolbetuximab.

6.8 The evaluation noted that, the SPOTLIGHT and GLOW trials (zolbetuximab + chemotherapy) and ATTRACTION-4 (nivolumab trial) included patients with HER2-negative status, whereas the CheckMate 649 trial included patients with non-HER2-positive patients (HER2-negative or unknown HER2 status). The evaluation considered that this difference is unlikely to impact the comparison, as Janjigian et al. (2020) suggested that the majority of patients with unknown HER2 status in the CheckMate 649 trial were likely HER2-negative, based on the known incidence of HER2-overexpressing tumours in gastric/GOJ cancer. Furthermore, all trials included patients irrespective of the PD-L1 status. As part of the National Institute of Care and Excellence (NICE) evaluation of zolbetuximab, the sponsor stated that the company

was unaware of any biological mechanism by which PD-L1 expression can affect the efficacy of zolbetuximab.[8]

Clinical trials on the safety/effectiveness of zolbetuximab

6.9 No direct head-to-head comparison of zolbetuximab versus nivolumab, in combination with chemotherapy, was available. The submission was based on an indirect treatment comparison (ITC) of zolbetuximab + chemotherapy and nivolumab + chemotherapy via network-meta-analysis (NMA). While the NMA included 14 unique regimens to assess the relative treatment effect of zolbetuximab against other first-line treatments, the submission focused on the following trials:

- SPOTLIGHT trial: a global, randomised, placebo-controlled, double-blind, phase III trial comparing zolbetuximab + chemotherapy (mFOLFOX6) versus placebo + chemotherapy in patients with CLDN18.2+, HER2-negative, previously untreated, advanced G/GOJ adenocarcinoma.
- GLOW trial: a global, randomised, placebo-controlled, double-blind, phase III trial comparing zolbetuximab + chemotherapy (CAPOX) with placebo + chemotherapy in patients with CLDN18.2+, HER2-negative, locally advanced or metastatic G/GOJ adenocarcinomas.
- CheckMate 649 trial: a global, randomised, open-label, phase III study comparing nivolumab + chemotherapy (XELOX [also known as CAPOX] or mFOLFOX6) with chemotherapy alone in patients with non-HER2-positive advanced or metastatic G/GOJ, or oesophageal adenocarcinoma.
- ATTRACTION-4: a randomised, double-blind, phase III, two-part study conducted in Japan, South Korea, and Taiwan, comparing nivolumab + chemotherapy (SOX [S-1 and oxaliplatin] or CAPOX) with placebo + chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent G/GOJ cancer.

6.10 The CheckMate 649 and ATTRACTION-4 trials were previously reviewed by the PBAC as part of the nivolumab submissions in November 2021 and March 2022. While CheckMate 649 was included as the pivotal trial, the ATTRACTION-4 trial was excluded due to concerns regarding its applicability to Australian setting, including (a) trial being conducted in only Asian population; (b) the exclusion of patients with oesophageal cancer; (c) the use of a different chemotherapy regimen; and (d) differences in

[8] NICE [GID-TA11316], 'Zolbetuximab with chemotherapy for untreated claudin 18.2-positive HER2 negative unresectable advanced gastric or gastro-oesophageal junction adenocarcinoma'. Available at: https://www.nice.org.uk/guidance/gid-ta11316/documents/committee-papers

subsequent treatments (paragraph 6.8, nivolumab, PSD, November 2021 PBAC Meeting with Addendum from March 2022 PBAC Meeting).

6.11 Details of the trials presented in the submission are provided in the table below.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Zolbetuximab		
GLOW (NCT03653507)	A Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus CAPOX Compared with Placebo Plus CAPOX as First-line Treatment of Subjects with Claudin (CLDN) 18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma.	Clinical Study Report Primary CSR (Data cutoff: October 2022). Final OS CSR CSR (Data cutoff: January 2024).
	Shah, M., Shitara, K., et al. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial.	Nature Medicine 2023; 29: 2133-2141
	Lordick, F., Shah, M., et al. LBA81 Final OS CSR efficacy and safety results from phase III GLOW study evaluating VYLOY+ CAPOX as first-line (1L) treatment for patients with claudin-18 isoform 2-positive (CLDN18. 2+), HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma.	Annals of Oncology 2023; 34(S2): S1321
	Lordick, F., Shah, M., et al. 134MO Updated efficacy and safety results from phase III GLOW study evaluating zolbetuximab + CAPOX as first-line (1L) treatment for patients with claudin-18 isoform 2-positive (CLDN18.2+), HER2L, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma	Annals of Oncology 2023; 34(S4): S1524
SPOTLIGHT (NCT03504397)	A Phase 3, Global, Multicenter, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared with Placebo Plus mFOLFOX6 as First-line Treatment of Subjects with Claudin (CLDN) 18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma	Clinical Study Report Primary CSR (Data cutoff: September 2022). Final OS CSR (Data cutoff: September 2023).
	Shitara, K., Lordick, F., et al. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial	Lancet 2023; 402(10398): 290
	Shitara, K., Van Cutsem, E., et al. Final overall survival results from phase 3 SPOTLIGHT study evaluating zolbetuximab +mFOLFOX6 as first-line (1L) treatment for patients (pts) with claudin 18 isoform 2(CLDN18.2) +, HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma.	Journal of Clinical Oncology 2024, 42: 4036
	Ajani, J., Shah, M., et al. LBA82 Final OS CSR efficacy and safety results from phase III SPOTLIGHT study evaluating VYLOY+ mFOLFOX6 as first-line (1L) treatment for patients with claudin-18 isoform 2-positive (CLDN18. 2+), HER2−, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma."	Annals of Oncology 2023; 34(S4): S1525
	Ajani, J., Lordick, F., et al. 135MO Final OS CSR efficacy and safety results from phase III SPOTLIGHT study evaluating VYLOY+ FOLFOX6 as first-line (1L) treatment for patients with claudin-18 isoform 2-positive (CLDN18.2+), HER2−, locally advanced (LA) unresectable or metastatic	Annals of Oncology 2023; 34(S4): S1524-S1525.

Trial ID	Protocol title/ Publication title	Publication citation
	gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma	
Pooled analyses (GLOW and SPOTLIGHT)	Kang, Y., Shah, M., et al. 1438P First-line (1L) zolbetuximab+ chemotherapy in patients (pts) with claudin 18.2 (CLDN18. 2)+, HER2-, locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma: A pooled final analysis of SPOTLIGHT+ GLOW	Annals of Oncology 2024; 35(S2): S895.
	Shitara, K., Shah, M., et al. Zolbetuximab in Gastric or Gastroesophageal Junction Adenocarcinoma.	New England Journal of Medicine 2024; 391(12): 1159-1162.
	ESMO 2023 Presentation - Pooled HRQoL	Sponsor Database
	Lordick, F., Van Cutsem, E. et al. "1530P Health-related quality of life (hrqol) in patients with claudin-18 isoform 2-positive (CLDN18. 2+) locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mg/GEJ) adenocarcinoma: Results from SPOTLIGHT and GLOW."	Annals of Oncology 2023; 34(S2): S860-S861.
Nivolumab		
ATTRACTION-4 (NCT02746796)	Kang, Y., Chen, L., et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial.	Lancet Oncology 2022; 23(2): 234-247.
	Boku, N., Ryu. M., et al. Safety and efficacy of nivolumab in combination with S-1/capecitabine plus oxaliplatin in patients with previously untreated, unresectable, advanced, or recurrent gastric/ gastroesophageal junction cancer: interim results of a randomized, phase II trial (ATTRACTION-4).	Annals of Oncology 2019; 30(2): 250-258.
	Ryu, M., Kang, Y., et al. PP213 Three-year follow-up of the ATTRACTION-4 Korean subgroup analysis: First-line (1L) nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with previously untreated, advanced, or recurrent gastric/gastro-esophageal junction (G/GEJ) cancer.	ESMO Open 2023; 8(1S6): 14
	Boku, N., Ryu. M., et al. LBA7_PR Nivolumab plus chemotherapy versus chemotherapy alone in patients with previously untreated advanced or recurrent gastric/gastroesophageal junction (G/GEJ) cancer: ATTRACTION-4 (ONO-4538-37) study.	Annals of Oncology 2020; 31(S4): S1192.
CheckMate 649 (NCT02872116)	Janjigian, Y., Shitara, K., et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial.	Lancet 2021;398(10294): 27-40.
	Janjigian, Y., Ajani, J., et al. First-Line Nivolumab Plus Chemotherapy for Advanced Gastric, Gastroesophageal Junction, and Esophageal Adenocarcinoma: 3-Year Follow-Up of the Phase III CheckMate 649 Trial	Journal of Clinical Oncology 2024; 42(17): 2012-2020.
	Lin, D., Nguyen, H., et al. Quality-adjusted time without symptoms or toxicity analysis of nivolumab plus chemotherapy versus chemotherapy alone for the management of previously untreated patients with advanced gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma.	Gastric Cancer 2023; 26(3): 415-424.
	Liu, T., Bai, Y., et al. First-line nivolumab plus chemotherapy vs chemotherapy in patients with advanced gastric, gastroesophageal junction and esophageal adenocarcinoma: CheckMate 649 Chinese subgroup analysis.	International Journal of Cancer 2023; 152(4):749-760.
	Shitara, K., Ajani, J., et al. Nivolumab plus chemotherapy or ipilimumab	Nature (2022); 603, 942–948

Trial ID	Protocol title/ Publication title	Publication citation
	in gastro-oesophageal cancer.	(2022).
	Shen, L., Bai, Y., et al. CT184: First-Line (1L) nivolumab (NIVO) plus chemotherapy (chemo) versus chemo in patients (pts) with advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): CheckMate 649 Chinese subgroup analysis.	Cancer Research 2021; 81(S13)
	Moehler, M., Shitara, K., et al. LBA6_PR Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): First results of the CheckMate 649 study.	Annals of Oncology 2020; 31 (S4): S1191
Network meta-analyses		
Technical Study Report	Network Meta-Analysis (NMA) of First-Line Treatments for Locally Advanced or Metastatic Gastric and Gastroesophageal Junction Cancer (Attachment 04 - NMA for GC 1L Treatments - Study Report – 05312024).	Sponsor database
Shah (2024)	Shah, M., Shitara, K., et al., Network meta-analysis of global trials of 1L therapies in locally advanced (LA) unresectable or metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma.	Journal of Clinical Oncology 2024; 42: 325-325

Source: Table 2-3, pp50-52 of the submission.

6.12 The key features of the included evidence are summarised in the table below.

Table 5: Key features of the included evidence – indirect comparison

Trial	N	Design/ Median duration of follow-up for OS[a]	Patient population	Outcomes
Zolbetuximab versus chemotherapy				
SPOTLIGHT	565	R, DB, PC, MN, MC phase III 31.38-33.28 months[b]	CLDN18.2+, HER2-negative, previously untreated, locally advanced unresectable or metastatic G/GOJ adenocarcinoma.	PFS, OS, TTCD, ORR, DOR, HRQoL, Safety
GLOW	507	R, DB, PC, MN, MC phase III 31.70-32.95 months[c]	CLDN18.2+, HER2-negative, previously untreated, locally advanced unresectable or metastatic G/GOJ adenocarcinoma.	PFS, OS, TTCD, ORR, DOR, HRQoL, Safety
Nivolumab versus chemotherapy				
CheckMate 649	1,581	R, OL, MN, MC, phase III 11.1-13.1 months[d] Three-year follow-up: 47.3-47.4 months[d]	CLDN18.2 and PD-L1 agnostic, HER2-negative/unknown, previously untreated, advanced unresectable or metastatic G/GOJ or oesophageal adenocarcinoma.	PFS, OS, ORR, HRQoL, safety
ATTRACTION-4	724	R, DB, PC, MN[f], MC phase III 26.6 months[e]	CLDN18.2 and PD-L1 agnostic, HER2-negative, previously untreated, unresectable, advanced, or recurrent G/GOJ	PFS, OS, ORR DOR

Source: compiled during the evaluation

CLDN18.2 = Claudin 18.2; DB = double blind; DOR = duration of response; G/GOJ = gastric or gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; HRQoL = health-related quality of life; MC = multicentre; MN = multinational; N = total participants in the group; OL = open label; ORR = overall response rate; OS = overall survival; PC = placebo-controlled; PD-L1 = Programmed Death-Ligand 1; PFS = progression-free survival; R = randomised; TTCD = time to confirmed deterioration.

[a] Median follow-up duration is reported for OS.

[b] As at Final OS data cutoff September 8, 2023, the median follow-up duration was 33.28 months for the zolbetuximab arm and 31.38 months for the chemotherapy arm.

[c] As at Final OS data cutoff January 12, 2024, the median follow-up duration was 31.70 months for the zolbetuximab arm and 32.95 months for the chemotherapy arm.

[d] As at data cutoff May 27, 2020, the median follow-up duration was 13.1 months for the nivolumab arm and 11.1 months for the chemotherapy arm. Three-year follow-up data cutoff May 31, 2022, the median follow-up duration was 47.4 months for the nivolumab arm and 47.3 months for the chemotherapy arm.

[e] As at data cutoff January 31, 2020

[f] Japan, South Korea and Taiwan.

6.13 The included trials differed in the following eligibility criteria, which may have impacted the exchangeability of the trials for the ITC analysis:

- The SPOTLIGHT, GLOW, and ATTRACTION-4 trials included patients with G/GOJ adenocarcinoma, while the CheckMate 649 trial included both patients with oesophageal adenocarcinoma and patients with G/GOJ adenocarcinoma.
- The SPOTLIGHT and GLOW trials included patients with advanced gastric (75-86%) or GOJ (14-26%) adenocarcinoma. The CheckMate 649 trial enrolled patients with advanced or metastatic adenocarcinoma, including gastric (70%); GOJ (17%); and oesophageal (13%) cancers. The ATTRACTION-4 trial enrolled patients with gastric (65%) and GOJ (8%) adenocarcinoma, while 27% of cases had no information on the primary site of adenocarcinoma. Furthermore, 23% of participants presented with recurrent disease in the

ATTRACTION-4 trial. The evaluation noted that 7 patients (<1%) in CheckMate 649 had recurrent G/GOJ.

- The SPOTLIGHT and GLOW trials specifically included patients whose tumours expressed CLDN18.2 in ≥75% of tumour cells, while the CheckMate 649 and ATTRACTION-4 trials did not assess CLDN18.2 status.
- The CheckMate 649 trial included patients with unknown HER2 status (~ 40%), while the zolbetuximab trials enrolled only HER2-negative patients (see paragraph 6.8).

6.14 The baseline characteristics in terms of median age, gender distribution and ECOG PS of 0-1 were similar in the study populations of both zolbetuximab and nivolumab trials. The key differences in the baseline characteristics and treatments across the trials that may affect the transitivity assumptions of the ITC analysis are summarised below:

- A higher proportion of patients had GC in zolbetuximab trials (74-86%) compared to nivolumab trials (65-70%).
- While the SPOTLIGHT, GLOW and CheckMate 649 were global trials, ATTRACTION-4 was conducted in Japan, South Korea, and Taiwan. A higher proportion of patients in the GLOW trial were Asian by ancestry (62%) compared to the SPOTLIGHT (31%) and CheckMate 649 trials (25%).
- Median follow-up varied across the trials, ranging from 31.4 to 33.3 months in the GLOW and SPOTLIGHT trials, compared to a minimum of 36.2 months in the three-year follow-up of the CheckMate 649 trial and a median of 11.6 months in the ATTRACTION-4 trial.
- The proportion and type of subsequent anticancer therapies varied across the trials: 54% vs 59% in the SPOTLIGHT trial, 52% vs 60% in the GLOW trial, 38% vs 41% in CheckMate 649, and 72% vs 73% in ATTRACTION-4, in the treatment arm compared to chemotherapy arm. The evaluation and the ESCs considered that the overall impact of the differences in the proportion of patients who received subsequent therapy, and the type of subsequent therapy is unclear, but it could potentially influence the OS results.

6.15 The key characteristics of the SPOTLIGHT and GLOW trials were generally consistent with the Australian setting, with the following exceptions:

- Patients in the SPOTLIGHT trial (mean age: 59 years) and the GLOW trial (mean age: 57.6 years) were younger than the target PBS population, where the mean age at diagnosis for stomach and oesophageal cancer is approximately 70-71 years.
- In the SPOTLIGHT trial, 37% of patients were of Asian ancestry, and 63% were Caucasian. In the GLOW trial, 63% of patients were of Asian ancestry, while

37% were Caucasian. The evaluation noted that in Australia, approximately 57% of the population is Caucasian, and 18% is of Asian ancestry.

The PSCR acknowledged differences in age and ancestry between the zolbetuximab trials and the intended PBS population but stated that CLDN18.2 positivity was consistent across race and age. It highlighted zolbetuximab was effective across all subgroups, with hazard ratios favouring zolbetuximab in patients ≥65 years and both Asian and non-Asian populations. The ESCs considered that whilst applicability to the Australian setting is potentially an issue, it is largely unavoidable for small patient populations.

6.16 In both the SPOTLIGHT and GLOW trials, zolbetuximab was administered at a loading dose of 800 mg/m^2 and a maintenance dose of 600 mg/m^2 Q3W. In the GLOW trial, patients in both arms received up to 8 cycles of CAPOX, with each cycle lasting 3 weeks, covering a total of 24 weeks of treatment. After completing the 8 cycles of CAPOX, capecitabine could be continued in 3-week cycles at the investigator's discretion, until the patient met the criteria for treatment discontinuation. In the SPOTLIGHT trial, patients in both arms received up to 12 cycles of mFOLFOX6, or a modified version of mFOLFOX6 if certain components were discontinued due to toxicity. The treatment was administered on days 1, 15, and 29 of each 42-day cycle, covering a total of 24 weeks, which is equivalent to 4 cycles of 6 weeks. After completing 12 cycles of mFOLFOX6, patients could continue receiving 5-FU and folinic acid on the same 3 days of each cycle at the investigator's discretion, until the patient met the criteria for treatment discontinuation. All treatments were given as IV infusion, except for capecitabine which was administered orally. The dosage and methods of administration were consistent with the dosage and methods of administration outlined in the draft Product Information for zolbetuximab.

6.17 In the CheckMate 649 trial, nivolumab was administered at 360 mg Q3W with the CAPOX regimen and 240 mg Q2W with the mFOLFOX6 regimen. The CAPOX regimen in CheckMate 649 was similar to that in the GLOW trial, and the mFOLFOX6 regimen in CheckMate 649 was similar to that in the SPOTLIGHT trial. However, unlike the zolbetuximab trials, placebo was not given in addition to chemotherapy in the comparator arm of CheckMate 649 trial. Additionally, there was no discontinuation rule for chemotherapy in the trial. In the ATTRACTION-4 trial, nivolumab was administered at a dose of 360 mg Q3W. The CAPOX regimen used in ATTRACTION-4 was similar to that in the GLOW trial; however, the majority of patients in ATTRACTION-4 (64%) received SOX chemotherapy, which was not used in either of the zolbetuximab trials and is not considered the standard of care in Australia.

6.18 A claim of noninferior efficacy for zolbetuximab + chemotherapy over nivolumab + chemotherapy was based on OS and PFS. The submission presented an unanchored and unadjusted ITC of adverse events (AEs) to support the claim of a different but manageable safety profile.

6.19 The submission did not propose a noninferiority margin. The evaluation considered that the absence of a noninferiority margin makes it difficult to assess the noninferiority claim with certainty.

Comparative effectiveness

6.20 The results of the PFS analyses, assessed by an Independent Review Committee (IRC), are presented in Table 6.

Table 6: Results of PFS across the studies

Zolbetuximab trials	**Zolbetuximab + chemotherapy**			**Placebo + chemotherapy**			**Absolute diff. in median**	**Hazard ratio (95% CI)**
	n with event / N (%)	**Median PFS, months (95% CI)**	**Median FU time, months**	**n with event / N (%)**	**Median PFS, months (95% CI)**	**Median FU time, months**		
SPOTLIGHT[a]	159/283 (56.2%)	11.04 (9.69, 12.52)	12.94	187/282 (66.3%)	8.94 (8.21, 10.41)	12.65	2.1 months	**0.73 (0.59, 0.91)**
GLOW[b]	153/254 (60.2%)	8.21 (7.26, 8.84)	12.62[c]	182/253 (71.9%)	6.80 (6.14, 8.08)	12.09[g]	1.4 months	**0.69 (0.55, 0.86)**
Nivolumab Trials	**Nivolumab + chemotherapy**			**Placebo + chemotherapy**			**Absolute diff. in median**	**Hazard ratio (95% CI)**
	n with event / N (%)	**Median PFS, months (95% CI)**	**Median FU time, months**	**n with event / N (%)**	**Median PFS, months (95% CI)**	**Median FU time, months**		
CheckMate 649[c]	559/789 (70.8%)	7.66 (7.10, 8.54)	13.1	557/792 (70.3%)	6.93 (6.60, 7.13)	11.1	0.73 months	0.77 (0.68, 0.87)[d]
ATTRACTION-4[e]	141/362 (38.9%)	10.45 (8.44, 14.75)	11.6	184/362 (50.8%)	8.34 (6.97, 9.40)	NA	2.1 months	**0.68 (0.51, 0.90)**[f]

Source: Compiled during the evaluation from Table 2-22, p98 of the submission, and Table 4, p10 of Nivolumab PSD November 2021 PBAC Meeting; p240 of Kang et al. (2022)

CI = confidence interval; diff. = difference; FU = follow-up; m = months; n = number of participants reporting data; N = total participants in group; PFS = progression-free survival.

Bold indicates statistical significance.

Italics = added results from Nivolumab and zolbetuximab trials during evaluation.

[a] Patients received mFOLFOX6 chemotherapy in SPOTLIGHT trial.

[b] Patients received CAPOX chemotherapy in GLOW trial.

[c] Patients received mFOLFOX6 or CAPOX chemotherapy in CheckMate 649 trial.

[d] p value not tested.

[e] Patients received SOX or CAPOX chemotherapy in ATTRACTION-4 trial.

[f] 98.51% CI was presented.

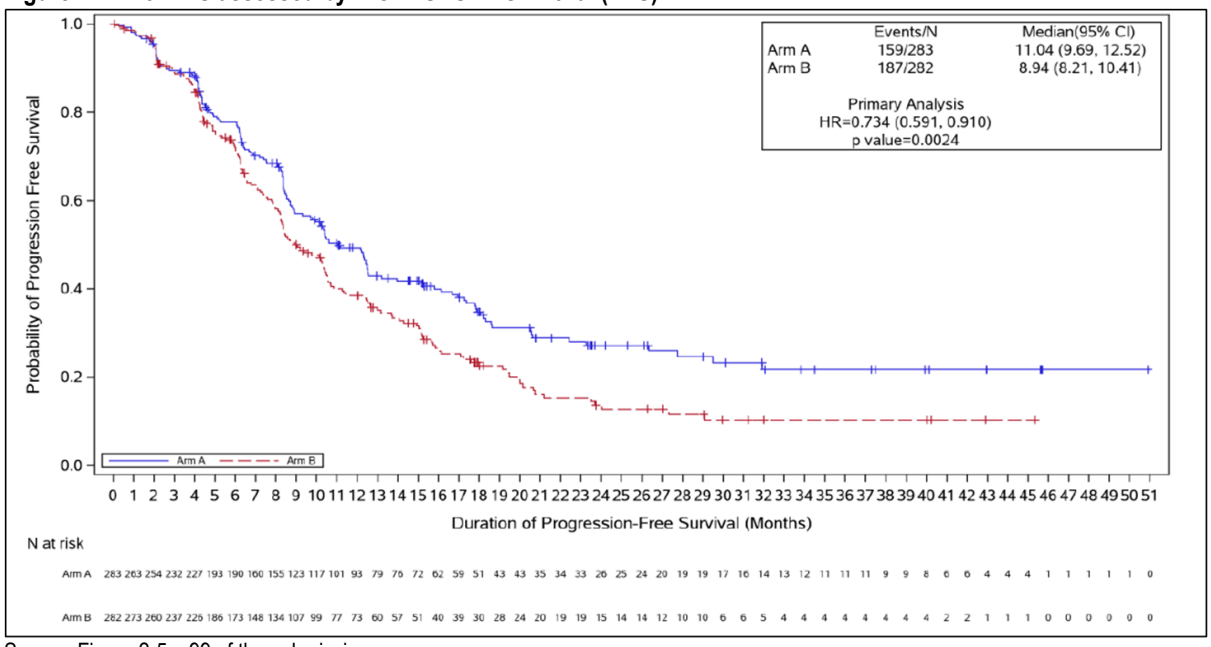
6.21 Based on the recent data cut-off, both the SPOTLIGHT and GLOW trials demonstrated statistically significant improvements in PFS with zolbetuximab + chemotherapy (median follow-up = 12.94 months SPOTLIGHT, 12.62 months GLOW) compared to placebo + chemotherapy (hereafter referred to as chemotherapy; median follow-up = 12.65 months SPOTLIGHT, 12.09 months GLOW). The difference in median PFS was 2.1 months in the SPOTLIGHT trial and 1.4 months in the GLOW trial. The prognosis of patients in the SPOTLIGHT trial was better than for those in the GLOW trial, likely due to differences in patient populations. SPOTLIGHT included more patients from Japan

and South Korea, while GLOW had a higher proportion from mainland China, where the disease course resembles that of Western patients, with generally lower overall survival[9].

6.22 The evaluation and the ESCs noted that in the CheckMate 649 trial, PFS was numerically improved in patients randomised to nivolumab + chemotherapy compared to chemotherapy alone, however, a statistical comparison was not undertaken due to the alpha spending considerations for the CheckMate 649 trial. Based on the three-year follow-up results of the CheckMate 649 trial, the PFS benefit was maintained in the overall population, with a HR of 0.79 (95% CI: 0.71, 0.89). In ATTRACTION-4 trial, treatment with nivolumab + chemotherapy compared to chemotherapy demonstrated a statistically significant improvement in PFS.

6.23 Figure 1 and Figure 2 present the Kaplan-Meier (KM) plots of PFS for the zolbetuximab trials.

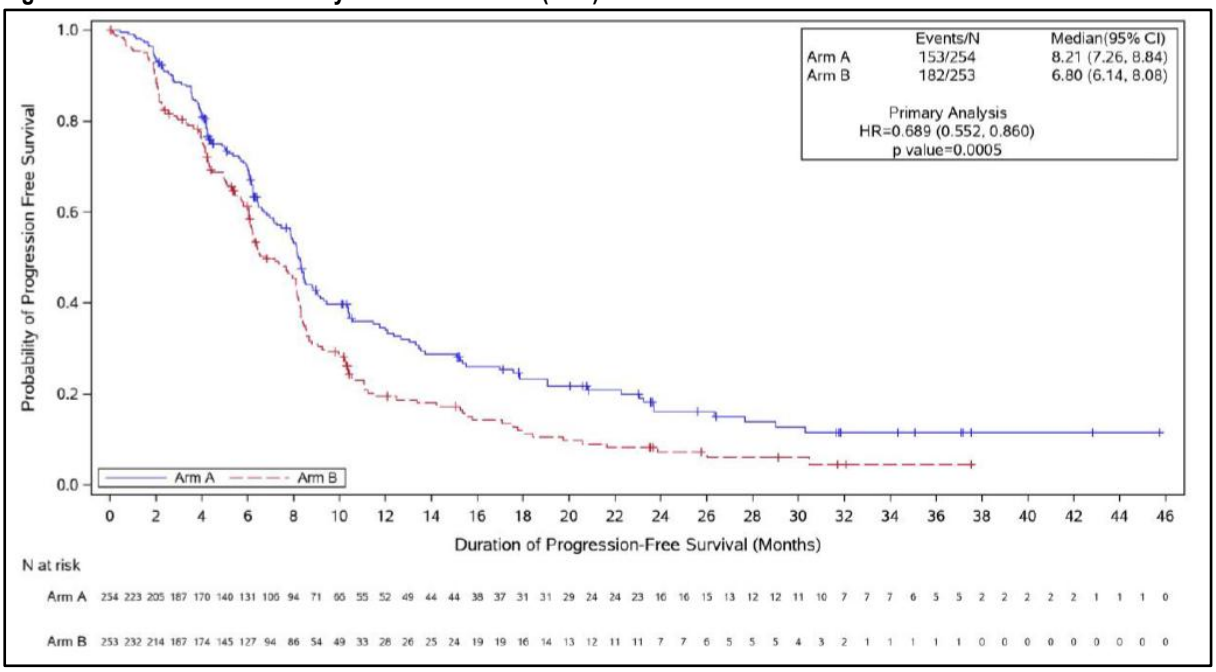
Figure 1: KM of PFS assessed by IRC in SPOTLIGHT trial (FAS)



Source: Figure 2-5, p99 of the submission.
CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IRC = Independent Review Committee; KM = Kaplan-Meier; N = total participants in group; PFS = progression-free survival.
Note: Arm A refers to zolbetuximab + mFOLFOX6 and Arm B refers to placebo + mFOLFOX6.

[9] Shah, M., Shitara, K., et al., (2023), 'Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial'. *Nat Med,* 29(8):2133-2141, https://pubmed.ncbi.nlm.nih.gov/37524953/

Figure 2: KM of PFS assessed by IRC in GLOW trial (FAS)



Source: Figure 2-6, p100 of the submission.
CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IRC = Independent Review Committee; KM = Kaplan-Meier; N = total participants in group; PFS = progression-free survival.
Note: Arm A refers to zolbetuximab + CAPOX and Arm B refers to placebo + CAPOX.

6.24 The results of the OS analyses are presented in Table 7.

Table 7: Results of OS across the studies

Zolbetuximab trials	Zolbetuximab + chemotherapy			Placebo + chemotherapy			Absolute diff. in median	Hazard ratio (95% CI)
	n with event / N (%)	Median OS, months (95% CI)	Median FU time, months	n with event / N (%)	Median OS, months (95% CI)	Median FU time, months		
SPOTLIGHT[a]	197/283 (69.6%)	18.23 (16.13, 20.63)	33.28	217/282 (77.0%)	15.57 (13.67, 16.92)	31.38	2.66 months	**0.78 (0.64, 0.95)**
GLOW[b]	180/254 (70.9%)	14.32 (12.09, 16.39)	31.70	207/253 (81.8%)	12.16 (10.28, 13.67)	32.95	2.16 months	**0.76 (0.62, 0.94)**
Nivolumab Trials	**Nivolumab + chemotherapy**			**Placebo + chemotherapy**			**Absolute diff. in median**	**Hazard ratio (95% CI)**
	n with event / N (%)	**Median OS (months)**	**Median FU time, months**	**n with event / N (%)**	**Median OS (months)**	**Median FU time, months**		
CheckMate 649[c]	544/789 (68.9%)	13.83 (12.55, 14.55)	13.1	591/792 (74.6%)	11.56 (10.87, 12.48)	11.1	2.27 months	**0.80 (0.68, 0.94)**
ATTRACTION-4[d]	230/362 (63.5%)	17.45 (15.67, 20.83)	26.6	245/362 (67.7%)	17.15 (15.18, 19.65	26.6	0.3 months	0.90 (0.75, 1.08)

Source: compiled during the evaluation from Table 2-23, p102 of the submission, and Table 4, p10 of Nivolumab PSD November 2021 PBAC Meeting; p240 of Kang et al. (2022)

CI = confidence interval; diff. = difference; FU = follow-up; n = number of participants reporting data; N = total participants in group; OS = overall survival.

Bold indicates statistical significance.

Italics added results from Nivolumab trials during evaluation.

[a] Patients received mFOLFOX6 chemotherapy in SPOTLIGHT trial.

[b] Patients received CAPOX chemotherapy in GLOW trial.

[c] Patients received mFOLFOX6 or CAPOX chemotherapy in CheckMate 649 trial.

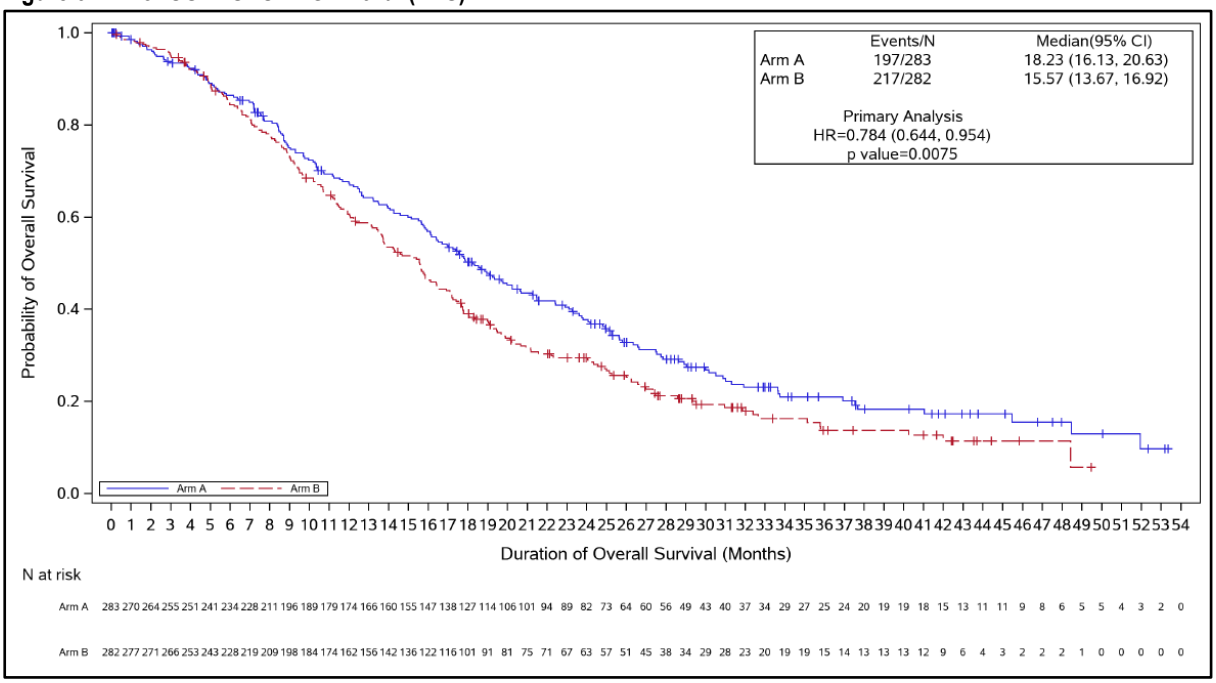
[d] Patients received SOX or CAPOX chemotherapy in ATTRACTION-4 trial.

6.25 Based on the recent data cut-offs, both the SPOTLIGHT and GLOW trials demonstrated statistically significant improvements in OS with zolbetuximab + chemotherapy (median follow-up = 33.28 months SPOTLIGHT, 31.70 months GLOW) compared to chemotherapy alone (median follow-up = 31.38 months SPOTLIGHT, 32.95 months GLOW). The difference in median OS was 2.66 months in the SPOTLIGHT trial and 2.16 months in the GLOW trial. Considering the entirety of the KM plots, the ESCs considered the OS gains associated with zolbetuximab over chemotherapy alone in each trial are modest, and noted the hazard ratios were close to one.

6.26 The evaluation noted that in both the CheckMate 649 and ATTRACTION-4 trials, OS improved with nivolumab + chemotherapy compared to chemotherapy; however, the difference was statistically significant only in the CheckMate 649 trial. Based on the three-year follow-up results of the CheckMate 649 trial, the OS benefit was maintained in the overall population, with a HR of 0.79 (95% CI: 0.71, 0.88).

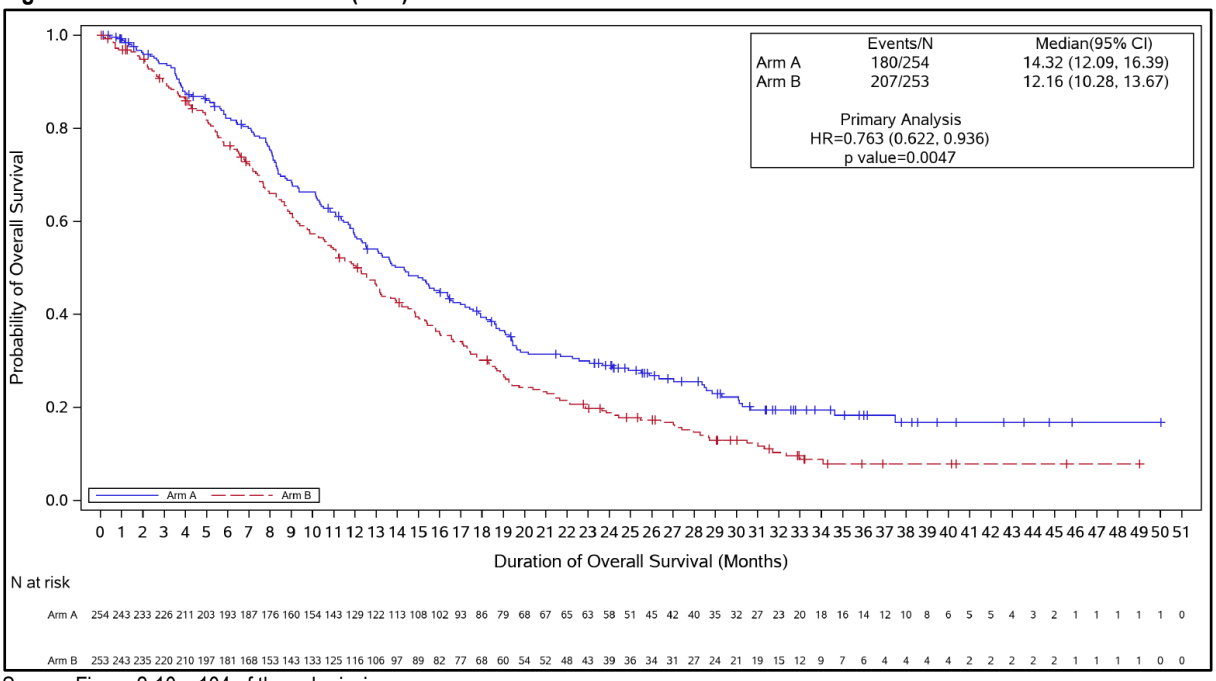
6.27 Figure 3 and Figure 4 present the KM plots of OS for the zolbetuximab trials.

Figure 3: KM of OS in SPOTLIGHT trial (FAS)



Source: Figure 2-9, p103 of the submission.
CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IRC = Independent Review Committee; KM = Kaplan-Meier; N = total participants in group; OS = overall survival.
Note: Arm A refers to zolbetuximab + mFOLFOX6 and Arm B refers to placebo + mFOLFOX6.

Figure 4: KM of OS in GLOW trial (FAS)



Source: Figure 2-10, p104 of the submission.
CI = confidence interval; FAS = full analysis set; HR = hazard ratio; IRC = Independent Review Committee; KM = Kaplan-Meier; N = total participants in group; OS = overall survival.
Note: Arm A refers to zolbetuximab + CAPOX and Arm B refers to placebo + CAPOX.

6.28 An exploratory endpoint of PFS2 was included in the zolbetuximab trials. PFS2 was defined as the time from randomisation to the earliest occurrence of progressive disease after subsequent anti-cancer therapy, death from any cause, or initiation of another anti-cancer therapy. In both trials, patients in zolbetuximab + chemotherapy demonstrated a reduced risk of progression following second-line treatment; with HR of 0.78 (95% CI: 0.64, 0.96) and 0.71 (95% CI: 0.58, 0.87) in SPOTLIGHT and GLOW trials, respectively.

6.29 While a substantial proportion of patients achieved an objective response in both arms of the SPOTLIGHT (48% vs 48%) and GLOW (43% vs 39%) trials, there was no statistically significant difference in ORR between the zolbetuximab + chemotherapy and chemotherapy arm. Similarly, no statistically significant difference was observed in the disease control rate between the treatment and chemotherapy arms in either the SPOTLIGHT (82% vs 87%) or GLOW (76% vs 76%) trials. The evaluation noted that based on the data previously presented to the PBAC, a higher proportion of patients treated with nivolumab + chemotherapy (47%) compared to chemotherapy (37%) achieved a complete or partial response in the CheckMate 649 trial (paragraph 6.18, nivolumab, PSD, November 2021 PBAC Meeting with March 2022 Addendum).

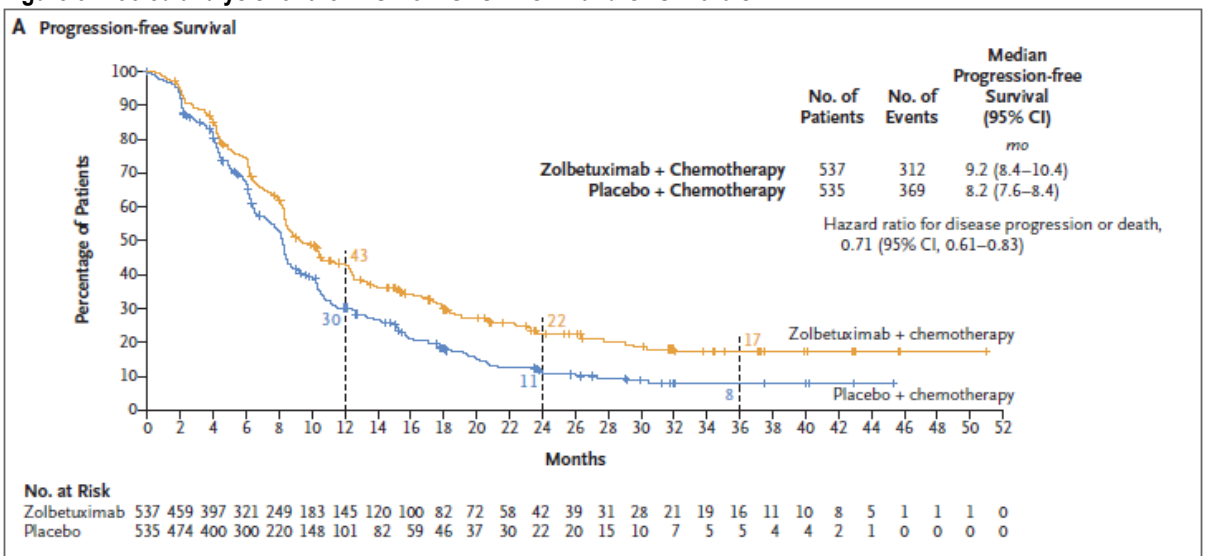
6.30 In the SPOTLIGHT trial, the median duration of response (DOR) was 9.00 months for zolbetuximab + chemotherapy and 8.11 months for chemotherapy. In the GLOW trial, the median DOR was 6.28 months for zolbetuximab + chemotherapy and 6.08 months

for chemotherapy. No statistically significant differences in DOR were observed between the groups in either trial. The evaluation noted that based on the data previously presented to the PBAC, the median DOR in the CheckMate 649 trial was 8.51 months for nivolumab + chemotherapy, compared to 6.93 months for chemotherapy alone (paragraph 6.21, nivolumab, PSD, November 2021 PBAC Meeting with March 2022 Addendum).

Pooled Analysis

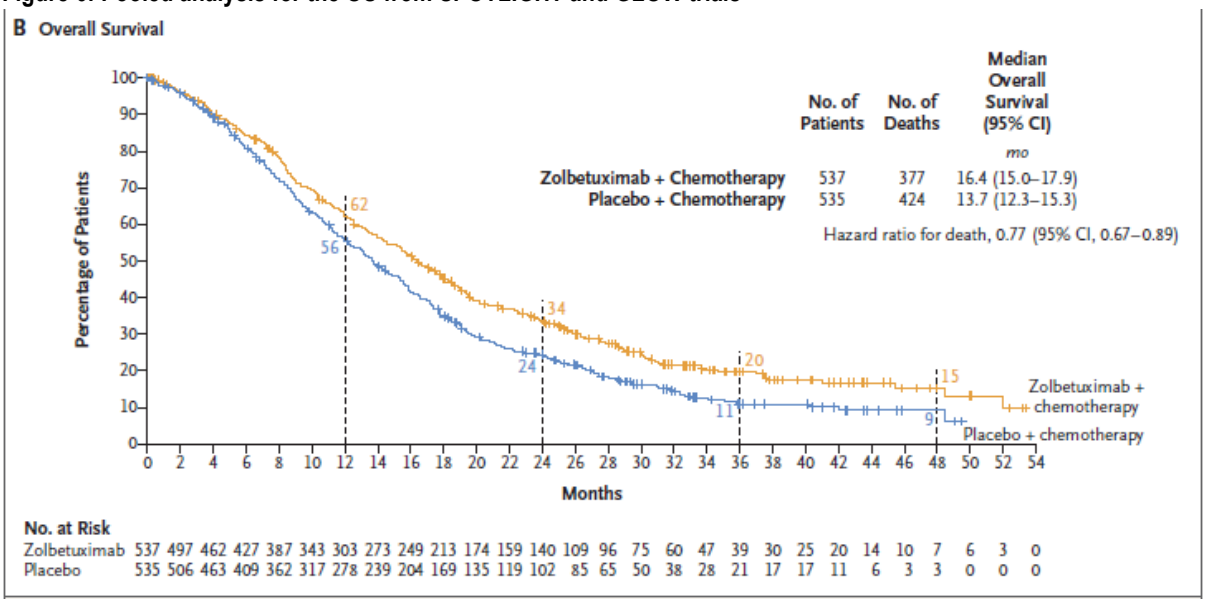
6.31 The submission presented a *post hoc* pooled analyses from the GLOW and SPOTLIGHT trials, combining data from both studies to estimate the overall treatment effect. The evaluation and the PBAC noted that the pooled analyses did not account for the heterogeneities across the trials. Figure 5 and Figure 6 summarise the pooled analysis for PFS and OS of the zolbetuximab trials.

Figure 5: Pooled analysis for the PFS from SPOTLIGHT and GLOW trials



Source: Figure 2-13, p129 of the submission.
CI = confidence interval; mo = month; PF = progression-free survival.

Figure 6: Pooled analysis for the OS from SPOTLIGHT and GLOW trials



Source: Figure 2-13, p129 of the submission.
CI = confidence interval; mo = month; OS = overall survival.

6.32 An independent search conducted by the evaluation located a meta-analysis of the SPOTLIGHT, GLOW and FAST trials evaluating zolbetuximab + chemotherapy compared to chemotherapy alone[10]. The evaluation noted that this meta-analysis demonstrated that the addition of zolbetuximab to chemotherapy was associated with a significant improvement in PFS (HR: 0.64; 95% CI: 0.49, 0.84) and OS (HR: 0.72; 95% CI: 0.62, 0.83).

6.33 The submission excluded the FAST trial due to differences in the trial setting, such as the CLDN18.2 positivity threshold (≥40% tumour cells), the chemotherapy regimen used (epirubicin + oxaliplatin + capecitabine [EOX]) and inclusion of patients with oesophageal adenocarcinoma, compared to the SPOTLIGHT and GLOW trials. The evaluation noted that the FAST trial (N=252) was a phase II study designed to assess the efficacy and tolerability of zolbetuximab in patients with advanced G/GOJ and oesophageal adenocarcinoma, who had moderate-to-strong CLDN18.2 expression in ≥40% tumour cells (Sahin et al., 2021). In patients with CLDN18.2 expression in ≥70% of tumour cells, significant improvement in PFS (HR = 0.38; 95% CI: 0.23, 0.62) and OS (HR = 0.50; 95% CI: 0.33, 0.74) was observed with zolbetuximab + chemotherapy compared to chemotherapy alone. However, patients with 40%-69% CLDN18.2 expression did not demonstrate significant differences between the two arms (PFS HR of 0.71; 95 CI: 0.32, 1.57 and OS HR of 0.78; 95% CI: 0.40, 1.49).

[10] Moraes, F.C.A et al. (2024) Efficacy and safety of Zolbetuximab plus chemotherapy for advanced CLDN18.2-positive gastric or gastro-oesophageal adenocarcinoma: a meta-analysis of randomized clinical trials. *BMC Cancer* **24**, 240 .

Network Meta-Analysis

6.34 The NMA report included in the submission presented several NMAs exploring different scenarios. The following analyses, relevant to the scope of this submission, are discussed below:

- Primary NMA: This analysis included all trials identified in the systematic review. Notably, there was no common comparator across all included trials; instead, the trials were connected through different comparators.
- Primary NMA using CAPOX and FOLFOX combined: In this analysis, CAPOX and FOLFOX were assumed to have equivalent efficacy, enhancing the stability of the network.
- Sensitivity analysis including global trials using CAPOX and FOLFOX combined: Given that results from Asian populations may not be fully generalisable to the USA or Europe, this analysis excluded trials conducted solely in Asian population.

6.35 Table 8 summarises the results of the NMA for PFS and OS between zolbetuximab and nivolumab.

Table 8: Results of the pairwise treatment comparison for PFS and OS between zolbetuximab versus nivolumab in the NMA (HR; 95% CrI)

	ZOLBE+ mFOLFOX6[a]	ZOLBE+ CAPOX[b]	ZOLBE+ mFOLFOX6/ CAPOX[a,b,c]	ZOLBE+ mFOLFOX6/CAPOX[a,b,c] (global trials only[d])
PFS				
NIVO+mFOLFOX6[e]	0.93 (0.73, 1.19)	-	-	-
NIVO+CAPOX[e,f]	-	0.88 (0.69, 1.13)	-	
NIVO+mFOLFOX6/CAPOX[c,e,f]	-	-	0.90 (0.75, 1.08)	-
NIVO+ FOLFOX6/CAPOX[e,f] (global trials only[d])	-	-	-	0.89 (0.74, 1.07)
OS				
NIVO+mFOLFOX6[e]	1.02 (0.80, 1.30)	-	-	-
NIVO+CAPOX[e,f]	-	0.94 (0.73. 1.20)	-	-
NIVO+mFOLFOX6/CAPOX[c,e,f]	-	-	0.97 (0.81, 1.16)	-
NIVO+ FOLFOX6/CAPOX[e,f] (global trials only[d])	-	-	-	0.98 (0.79,1.18)

Source: Prepared during evaluation using Table 3, pp59-60; Table 4, pp61-62; Table 5, p65; Table 6, p66; Table 7, p69; and Table 8, p70 of the 'Attachment 04 - NMA for GC 1L Treatments - Study Report – 05312024' to the submission.
CAPOX = capecitabine + oxaliplatin; CrI = credible interval; HR = hazard ratio; mFOLFOX6 = leucovorin calcium (folinic acid) + fluorouracil + oxaliplatin; NIVO = nivolumab; OS = overall survival; PFS = progression-free survival; ZOLBE = zolbetuximab.
Note: A hazard ratio <1 indicated a favourable result of the vertical treatment versus the horizontal treatment.
[a] Using data from SPOTLIGHT trial
[b] using data from GLOW trial
[c] The NMA assumed equivalent efficacy of CAPOX and mFOLFOX.
[d] The NMA included only global trials that reflected US and Europe population and assumed equivalent efficacy of CAPOX and mFOLFOX6.
[e] Using data from CheckMate 649
[f] Using data from ATTRACTION-4 trial

6.36 There were no statistically significant differences in PFS or OS for zolbetuximab versus nivolumab when used in combination with CAPOX, mFOLFOX6 or both regimens combined. The difference in PFS and OS was also not statistically significant when only global trials were included.

6.37 The independent search conducted during the evaluation identified two recently published systematic review and meta-analyses of first-line treatments for advanced G/GOJ cancer.[11,12] Zhang et al. (2024) conducted an NMA comparing immunotherapies and zolbetuximab for the first-line treatment of HER2-negative, unresectable, or metastatic gastric cancer. The analysis included eight trials with a total of 6,455 patients. The study found no statistically significant differences between zolbetuximab + chemotherapy and nivolumab + chemotherapy for OS (HR = 0.98; 95% CI: 0.91, 1.07) or PFS (HR = 0.96; 95% CI: 0.88, 1.05). Wang et al. (2023) also conducted an NMA to compare different first-line combination treatments for advanced gastric cancer. The analysis included 22 trials with a total of 10,787 patients. No significant differences were observed between nivolumab +chemotherapy and zolbetuximab + chemotherapy in terms of OS (HR = 1.13; 95% CrI: 0.84, 1.55) and PFS (HR = 0.95; 95% CrI: 0.63, 1.62), and AEs (RR = 1.19; 95% CI: 0.90, 1.57).

Comparative harms

6.38 The submission presented an unanchored and unadjusted ITC of AEs between zolbetuximab and nivolumab, comparing pooled data from the SPOTLIGHT and GLOW trials with that from the CheckMate 649 trial. The evaluation noted that safety data from the ATTRACTION-4 trial were excluded, as the chemotherapy used (SOX) differed from those in the other trials (mFOLFOX/CAPOX).

6.39 The submission compared overall safety data from the primary analysis of CheckMate 649 (with a median follow-up of 12.1 months) to pooled data from the SPOTLIGHT (22.1 months) and GLOW (17.7 months) trials. Notably, treatment-related AEs were compared using the updated three-year follow-up data from the CheckMate 649 trial (minimum follow-up of 36.2 months) for nivolumab, against pooled data from SPOTLIGHT and GLOW for zolbetuximab.

6.40 A summary of any treatment emergent AEs (TEAEs) and treatment related TEAEs of Grade ≥3 is presented in Table 9 and Table 10, respectively.

[11] Wang, G., Huang, Y., et al. (2024), 'Immunotherapy and targeted therapy as first-line treatment for advanced gastric cancer', *Critical Review in Oncology/Hematology, 198,* https://www.sciencedirect.com/science/article/pii/S1040842823002858?via%3Dihub

[12] Zhang, Z., Xie, T., et al. (2024), 'Immune checkpoint inhibitors or anti-claudin 18.2 antibodies? A network meta-analysis for the optimized first-line therapy of HER2-negative gastric cancer', *Ther Adv Med Oncol,* 16:1-10, https://journals.sagepub.com/doi/10.1177/17588359241231253

Table 9: Summary of TEAEs in the SPOTLIGHT/GLOW combined and CheckMate 649

	SPOTLIGHT/GLOW combined			CheckMate649		
	ZOLBE+chemo n with event/ N (%)	Chemo n with event/ N (%)	RD (95% CI)	NIVO+chemo n with event/ N (%)	Chemo n with event/ N (%)	RD (95% CI)
Total number of patients with at least one AE	529/533 (99.2%)	521/527 (98.9%)	0.00 (-0.01,.01)	776/782 (99.2%)	752/767 (98.0%)	0.01 (0.00, 0.02)
- Grade 3/4 AE	378/533 (70.9%)	334/527 (63.4%)	0.08 (0.03, 0.12)	540/782 (69.1%)	456/767 (59.5%)	0.10 (0.05, 0.14)
- Grade 5 AE	49/533 (9.2%)	56/527 (10.6%)	-0.01 (-0.04, 0.02)	81/782 (10.4%)	63/767 (8.2%)	0.02 (-0.01, 0.05)
AEs related to any treatment	523/533 (98.1%)	502/527 (95.3%)	0.03 (0.01, 0.05)	738/782 (94.4%)	679/767 (88.5%)	0.06 (0.03, 0.09)
- Treatment-related Grade 3/4 AE	352/533 (66.0%)	276/527 (52.4%)	0.14 (0.09, 0.19)	462/782 (59.1%)	341/767 (44.5%)	0.15 (0.10, 0.20)
- Treatment-related Grade 5 AE	11/533 (2.1%)	11/527 (2.1%)	0.00 (-0.01, 0.01)	4/782 (0.5%)	0/767 (0.0%)	0.01 (-0.00, 0.01)
SAE	245/533 (46.0%)	245/527 (46.5%)	-0.01 (-0.05, 0.04)	423/782 (54.1%)	335/767 (43.7%)	0.10 (0.05, 0.15)
Treatment-related SAE	134/533 (25.1%)	97/527 (18.4%)	0.07 (0.01, 0.08)	172/782 (22.0%)	93/767 (12.1%)	0.10 (0.06, 0.14)
AE leading to discontinuation from any study treatment	199/533 (37.3%)	169/527 (32.1%)	0.05 (-0.01, 0.08)	371/782 (47.4%)	251/767 (32.7%)	0.15 (0.10, 0.20)
Treatment-related AE leading to discontinuation from any study treatment	110/533 (20.6%)	78/527 (14.8%)	0.06 (0.01, 0.07)	284/782 (36.3%)	181/767 (23.6%)	0.13 (0.08, 0.17)

Source: Table 2-34, p135 of the submission.

AE = adverse events; chemo = chemotherapy; CI = confidence interval; n = number of participants reporting data; N = total participants in group; NIVO = nivolumab; RD = risk difference; SAE = serious adverse event; TEAE = treatment emergent adverse event; ZOLBE = zolbetuximab.

6.41 A higher proportion of Grade 3-4 TEAEs occurred in the zolbetuximab and nivolumab treatment arms compared with the chemotherapy alone arms: 70.9% vs 63.4% and 69.1% vs 59.5%, respectively. This trend was also observed for treatment related Grade 3-4 TEAE.

6.42 The addition of zolbetuximab did not increase the proportion of patients with a serious TEAEs (46.0% vs 46.5%), whereas there was an increase with the addition of nivolumab (54.1% vs 43.7%). A higher proportion of serious TEAEs were observed in the zolbetuximab and nivolumab treatment arms compared with the chemotherapy alone arms: 25.1% vs 18.4% and 22.0% vs 12.1%, respectively.

Table 10: Summary of treatment related TEAEs (≥10%) in the SPOTLIGHT/GLOW combined and CheckMate 649; Grade 3-4 occurrences only

	SPOTLIGHT/GLOW combined			CheckMate649		
	ZOLBE+chemo n with event/ N (%)	Chemo n with event/ N (%)	RD (95% CI)	NIVO+chemo n with event/ N (%)	Chemo n with event/ N (%)	RD (95% CI)
Overall	353/533 (66.2%)	279/527 (52.9%)	0.13 (0.08, 0.18)	473/782 (60.5%)	346/767 (45.1%)	0.15 (0.10, 0.20)
Nausea	62/533 (11.6%)	15/527 (2.8%)	0.09 (0.06, 0.11)	21/782 (2.7%)	19/767 (2.5%)	0.00 (-0.01, 0.02)
Vomiting	68/533 (12.8%)	15/527 (2.8%)	0.10 (0.07, 0.13)	17/782 (2.2%)	24/767 (3.1%)	-0.01 (-0.03, 0.01)
Decreased appetite	25/533 (4.7%)	7/527 (1.3%)	0.03 (0.02, 0.05)	14/782 (1.8%)	13/767 (1.7%)	0.00 (-0.01, 0.01)
Diarrhoea	21/533 (3.9%)	19/527 (3.6%)	0.00 (-0.02, 0.02)	35/782 (4.5%)	24/767 (3.1%)	0.01 (-0.01, 0.03)
Neutrophil count decreased	90/533 (16.9%)	83/527 (15.7%)	0.01 (-0.03, 0.05)	84/782 (10.7%)	67/767 (8.7%)	0.02 (-0.01, 0.05)
Peripheral sensory neuropathy	13/533 (2.4%)	20/527 (3.8%)	-0.01 (-0.03, 0.00)	34/782 (4.3%)	23/767 (3.0%)	0.01 (-0.01, 0.03)
Neutropenia	53/533 (9.9%)	37/527 (7.0%)	0.03 (0.00, 0.06)	123/782 (15.7%)	96/767 (12.5%)	0.03 (0.00, 0.07)
Anaemia	26/533 (4.9%)	24/527 (4.6%)	0.00 (-0.02, 0.02)	47/782 (6.0%)	20/767 (2.6%)	0.03 (0.01, 0.05)
Fatigue	17/533 (3.2%)	15/527 (2.8%)	0.00 (-0.01, 0.02)	30/782 (3.8%)	18/767 (2.3%)	0.00 (-0.01, 0.02)

Source: Table 2-36, p135 of the submission.

chemo = chemotherapy; CI = confidence interval; n = number of participants reporting data; N = total participants in group; NIVO = nivolumab; RD = risk difference; TEAE = treatment emergent adverse event; ZOLBE = zolbetuximab.

6.43 Zolbetuximab and nivolumab have distinct safety profiles. Compared to chemotherapy, the most common Grade 3-4 TEAEs with zolbetuximab were nausea, vomiting, neutropenia and decreased appetite, whereas for nivolumab, neutropenia, anaemia, diarrhoea, fatigue, liver enzyme elevations, and lipase increases were the most common Grade 3-4 TEAEs reported. A higher incidence of Grade 3-4 nausea and vomiting was observed with zolbetuximab, while nivolumab was associated with higher incidence of Grade 3-4 neutropenia and anaemia. The ESCs considered that the higher incidence of Grade 3-4 nausea and vomiting observed with zolbetuximab may significantly affect quality of life.

Benefits/ harms

6.44 A benefits and harms table is not presented, as the submission made a claim of noninferiority.

Clinical claim

6.45 The submission described zolbetuximab + chemotherapy as noninferior in terms of effectiveness compared to nivolumab + chemotherapy for patients with G/GOJ cancer. The evaluation and the ESCs considered that this claim was uncertain because:

- Evidence for zolbetuximab was limited to patients with CLDN18.2+ tumours, and CLDN18.2 expression status was not assessed in the nivolumab trials (CheckMate 649 and ATTRACTION-4). The PSCR argued that CLDN18.2 expression does not correlate with outcomes, and is independent from other biomarkers, and highlighted that both nivolumab trials likely included both CLDN18.2+ and CLDN18.2− patients. However, the ESCs considered that the prognostic value of CLDN18.2 expression was uncertain, potentially negatively impacting overall survival in G/GOJ patients.
- The results of the NMA may not be reliable due to potential transitivity issues between the zolbetuximab (SPOTLIGHT and GLOW) and nivolumab (CheckMate 649 and ATTRACTION-4) trials, including differences in terms of eligibility criteria, primary disease site, ancestry, follow-up duration, and subsequent anti-cancer therapies.
- The evidence base for zolbetuximab from the SPOTLIGHT and GLOW trials may have limited applicability to the intended Australian PBS population, particularly regarding differences in age at diagnosis (57.5-59 years vs 70-71 years, respectively) and ancestry (37%-63% vs 17% Asian, respectively).

Overall, the ESCs considered that the clinical claim of noninferior efficacy based on improvements in PFS and OS outcomes was uncertain but probably reasonable.

6.46 The submission described zolbetuximab as noninferior in terms of safety compared to nivolumab, with a different but manageable safety profile. The PSCR claimed that the overall safety profile of zolbetuximab, comparative assessment of key safety parameters, established management strategies for treatment-related adverse events, and positive benefit-risk assessment collectively support the claim of non-inferior safety compared to nivolumab. However, the ESCs considered that the claim remains uncertain due to the indirect nature of comparison and distinct safety profiles between zolbetuximab and nivolumab. The most common Grade 3-4 TEAEs with zolbetuximab were nausea, vomiting, neutropenia and decreased appetite, whereas neutropenia, anaemia, diarrhoea, fatigue, liver enzyme elevations, and lipase increases was the most common Grade 3-4 TEAEs reported for nivolumab. The ESCs considered that the claim of noninferior safety of zolbetuximab was not well supported by evidence, and based on the evidence provided, zolbetuximab is likely inferior to nivolumab in terms of safety.

6.47 The PBAC considered that the claim of noninferior effectiveness was not strongly supported, due to uncertainties associated with transitivity issues, unknown/unselected CLDN18.2 status in the comparator trials, and differences between trial and Australian populations, but that overall the claim was reasonable.

6.48 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data. The PBAC considered that the safety of

zolbetuximab + chemotherapy is inferior to nivolumab + chemotherapy due to the significant supper GI toxicities, likely to affect QoL.

Claim of codependence

6.49 In the trials the CLDN18.2 threshold for a positive result was ≥75% tumour cells showing moderate-to-strong membranous staining, while <75% indicated a negative result. This was supported by the FAST phase II study, which included adults with locally advanced, inoperable, recurrent, or metastatic G/GOJ cancers and CLDN18.2+ expression in ≥40% of tumour cells. In patients with CLDN18.2 expression in ≥70% of tumour cells, significant improvement in PFS and OS was observed with zolbetuximab + chemotherapy compared to chemotherapy alone. However, patients with 40%-69% CLDN18.2 expression did not demonstrate significant differences between the two arms. The improved efficacy among the subgroups of patients with high CLDN18.2 expressing tumours supports a relationship between CLDN18.2 expression and zolbetuximab. The evaluation and the ESCs considered that while the MBS item descriptor does not specify the term 'positive' or a threshold for CLDN18 expression; the threshold of ≥75% should be a requisite to determine treatment eligibility with zolbetuximab.

6.50 The submission did not present evidence for the treatment effect modification of zolbetuximab + chemotherapy for patients who tested positive for CLDN18.2 versus patients who were CLDN18.2- using the threshold of ≥75%. It was not possible to determine the variation in treatment effect attributable to CLDN18.2 positivity, isolated from its prognostic effect from the evidence presented, and acceptance of the predictive value of the test primarily relies on biological plausibility.

6.51 The PBAC considered that that the biological rationale for testing for CLDN18.2 expression as a biomarker for targeted treatment with zolbetuximab appeared to be reasonable, and aligned with international guidelines (i.e. National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines), which recommend zolbetuximab as preferred first-line treatment option for patients whose tumours are CLDN18.2+.

6.52 The PBAC considered that while there was no evidence regarding the treatment effect modification, it would be reasonable to accept the claim for codependence due to the biological rationale and results of the FAST trial.

Economic analysis

6.53 The submission presented a CMA comparing zolbetuximab + chemotherapy with CLDN18 testing, to nivolumab + chemotherapy with no testing, based on the claim of noninferior efficacy and safety. The CMA was based on the published price of nivolumab + chemotherapy.

6.54 The equi-effective doses were estimated in the submission as:

- zolbetuximab 11,574.7 mg once every three weeks (Q3W) with CAPOX is equivalent to 5,400.0 mg nivolumab Q3W with CAPOX; and
- zolbetuximab 15,659.9 mg with mFOLFOX6 once every two weeks (Q2W) is equivalent to 5,280.0 mg nivolumab Q2W with mFOLFOX6.

6.55 The PBAC noted that equi-effective doses above do not explicitly consider the duration over which the treatments are administered or the loading dose for zolbetuximab. The PBAC considered that the equi-effective doses should be revised as outlined in Section 7.

6.56 Zolbetuximab is administered intravenously (IV) with CAPOX or mFOLFOX6. For zolbetuximab + CAPOX treatment, the regimen includes a loading dose of 800 mg/m^2 and a maintenance dose of 600 mg/m^2 Q3W. For zolbetuximab + mFOLFOX6 treatment, the loading dose is 800 mg/m^2, followed by a maintenance dose of 400 mg/m^2 Q2W. As noted in paragraph 3.3, these dosing regimens are consistent with the dosing recommendations in the draft PI for zolbetuximab, however, the SPOTLIGHT and GLOW trials utilised maintenance doses of 600 mg/m^2 Q3W with both CAPOX Q2W and mFOLFOX6 Q3W. A scenario analysis was conducted by the submission, adjusting the base case to reflect the 600 mg/m^2 Q3W dosing schedule. The result showed a negligible impact on the CMA.

6.57 Nivolumab is administered as 360 mg Q3W with the CAPOX regimen and 240 mg Q2W with the mFOLFOX6 regimen for a maximum of two years. This was consistent with the approved PI for nivolumab, the dosing regimen used in CheckMate 649 trial, and the PBAC's consideration of nivolumab for the same indication.

6.58 In the base case, the submission assumed an equal split between patients receiving the CAPOX and mFOLFOX6 regimens. The submission did not provide any evidence to support this assumption. Furthermore, the derived price of zolbetuximab was sensitive to variations in the regimen split (refer to Table 13).

6.59 The mean treatment durations for zolbetuximab were based on the GLOW (7.34 months) and SPOTLIGHT (10.07 months) trials. Similarly, the mean durations for the chemotherapy components were derived from the zolbetuximab trials. For nivolumab, Janjigian et al. (2024) reported only median treatment durations; 6.80 months for nivolumab + chemotherapy and 4.90 months chemotherapy alone. The submission estimated the mean duration for nivolumab (9.81 months) and chemotherapy (7.07 months) using an exponential distribution, except for oxaliplatin. The use of oxaliplatin was assumed to be capped at 8 cycles (5.52 months) for CAPOX and 12 cycles (5.52 months) for mFOLFOX6, consistent with the regimens used in the GLOW and SPOTLIGHT trials. The evaluation and the ESCs considered that mean durations derived from exponential distributions may not be accurate. Assuming treatment duration for nivolumab and zolbetuximab resulted in a 14% decrease in the derived price of zolbetuximab. Notably, the mean number of doses calculated based

on the mean treatment duration was inappropriately rounded down to the nearest whole number for both the treatment arms in the CMA.

6.60 Relative dose intensities (RDIs) were factored into the CMA; however, they were not used in the calculation of equi-effective doses. For zolbetuximab + chemotherapy, the RDI was based on the GLOW (96.08%) and SPOTLIGHT (92.45%) trials. As the CheckMate 649 trial did not report RDIs for nivolumab + chemotherapy, the submission assumed the same RDI as for zolbetuximab.

6.61 A body surface area (BSA) of 1.70 m^2, based on the weighted average from the SPOTLIGHT and GLOW trials, was used to estimate the doses for the zolbetuximab and chemotherapy regimens. However, the inclusion of 30–60% Asian participants in these trials limits the applicability of this BSA estimate to the Australian population. The evaluation noted that Dooley et al. (2004) reported an average BSA of 1.89 m^2 for Australian male cancer patients and 1.70 m^2 for female cancer patients.[13] A scenario analysis using a BSA of 1.80 m^2 in the CMA reduced the cost of zolbetuximab by 5%, from $773.93 to $731.82.

6.62 The submission calculated the drug costs by estimating the number of vials required per patient. In the base case, the submission estimated no wastage, reflecting vial sharing in Australian clinical practice. However, the draft TGA Prescribing Information (PI) advises discarding the unused portion of single-dose vials, and the submission's proposed PBS maximum amounts were based on rounded-up, whole vials.

6.63 The CMA included the administration costs associated with the infusion of zolbetuximab + CAPOX/mFOLFOX and nivolumab + CAPOX/mFOLFOX. The administration cost per infusion was estimated as $123.05, based on MBS item code 13950. For zolbetuximab + CAPOX and nivolumab + CAPOX, the administration cost was applied every three weeks. Similarly, for zolbetuximab + mFOLFOX and nivolumab + mFOLFOX, the administration cost was applied every two weeks. The total administration cost for each treatment regimen was calculated based on their respective mean durations.

6.64 For patients receiving zolbetuximab + chemotherapy the costs of CLDN18 testing were included. The cost of CLDN18 testing was estimated using a unit cost of $112 per test and the weighted proportion (38.38%) of patients in SPOTLIGHT and GLOW trials with CLDN18.2+ expression (≥ 75% of tumour cells demonstrating moderate-to-strong membranous CLDN18 staining). Consequently, the estimated cost to detect one CLDN18.2+ patients was $291.78 ($112/38.38%). The evaluation and the ESCs considered that the actual proportion of CLDN 18.2+ expression in the Australian population remained uncertain. However, changing the proportion of patients testing

[13] Dooley, M., Singh, S., and Michael, M., (2004), 'Implications of dose rounding of chemotherapy to the nearest vial size.' *Support Care Cancer*, 12, 653–656, https://doi.org/10.1007/s00520-004-0606-5

positive for CLDN18 expression had a negligible impact on the cost of zolbetuximab (refer to Table 13).

6.65 The costs of managing AEs or monitoring for zolbetuximab and nivolumab were not included in the CMA. According to EMA and FDA guidelines, zolbetuximab is associated with serious reactions, including hypersensitivity (e.g. anaphylaxis) and severe nausea/vomiting. Pre-treatment with antiemetics, such as, Neurokinin-1 [NK-1] receptor blockers and/or 5-hydroxytryptamine receptors [5-HT3] receptor blockers (e.g. ondansetron), is recommended before each infusion to prevent these effects. Furthermore, a higher use of antiemetic medications was reported in the zolbetuximab arm compared to chemotherapy arm in both SPOTLIGHT (70% vs 63%) and GLOW (82% vs 74%) trials. The PSCR presented a sensitivity analysis to include the cost of managing zolbetuximab-related adverse events (nausea and vomiting) with ondansetron within the CMA, which had negligible impact on the derived price of zolbetuximab (reduction from $773.93 to $773.67). However, the ESCs considered that the addition of costing for ondansetron inadequately covered the costs of managing these AEs, noting the severity of grade 3-4 AEs and likely underestimation of the costs of their management.

6.66 The evaluation noted that the CMA was based on the dispensed price for maximum amount (DPMA) rather than the ex-manufacturer price (EMP); although this had a negligible impact (see Table 12).

6.67 The results of the CMA based on the published price of nivolumab + chemotherapy is presented in Table 11 and Table 12.

Table 11: Cost-minimisation approach as presented in the submission

Treatment	Mean treatment duration (months)	Relative Dose Intensity	Total number of doses	Total Admin Cost by reg. ($)	Cost per Dose based on Disp. price ($)	Total Cost by reg. based on Disp. price ($)	Total Cost by treatment based on Disp. price ($)
Zolbetuximab + CAPOX							
Zolbetuximab 800mg/m^2 (Loading dose)	7.34	96.08%	1.00	$123	$10,333	$10,333	$90,711
Zolbetuximab 600mg/m^2 Q3W (Maintenance dose)	7.34		10.00	$1,231	$7,779	$77,790	
Capecitabine 1000 mg/m^2 (Bid, 14 days) Q3W	6.98	95.04%	308.00		$1	$358	
Oxaliplatin 130mg/m^2 Q3W	3.62	82.54%	6.00		$146	$876	
Zolbetuximab + mFOLFOX6							
Zolbetuximab 800mg/m^2 (Loading dose)	10.07	92.54%	1.00	$123	$9,942	$9,942	$126,027
Zolbetuximab 400mg/m^2 Q2W (Maintenance)	10.07		21.00	$0	$5,027	$105,574	
Oxaliplatin 85mg/m^2 Q2W	4.32	86.55%	10.00	$2,830	$123	$1,229	
Leucovorin 400mg/m^2 Q2W	8.93	90.55%	20.00		$65	$1,310	
Fluorouracil (bolus) 400mg/m^2 Q2W	7.86	93.65%	18.00		$116	$2,094	
Fluorouracil (infusion) 2400mg/m^2 Q2W	10.21	93.03%	23.00		$127	$2,924	
Nivolumab + CAPOX							
Nivolumab (40 mg) 360 mg Q3W	9.81	96.08%	15.00	$1,846	$7,007	$105,111	$108,483
Nivolumab (100 mg) 360 mg Q3W	9.81		15.00				
Capecitabine 1000 mg/m^2 (Bid, 14 days) Q3W	7.07	95.04%	308.00		$1	$358	
Oxaliplatin 130 mg/m^2	5.52	82.54%	8.00		$146	$1,168	
Nivolumab + mFOLFOX6							
Nivolumab (40 mg) 240 mg Q2W	9.81	92.54%	22.00	$2,707	$4,532	$99,712	$108,838
Nivolumab (100 mg) 240 mg Q2W	9.81		22.00				
Oxaliplatin 85mg/m^2 Q2W	5.52	86.55%	12.00		$123	$1,475	
Leucovorin 400mg/m^2 Q2W	7.07	90.55%	16.00		$65	$1,048	
Fluorouracil (bolus) 400mg/m^2 Q2W	7.07	93.65%	16.00		$116	$1,862	
Fluorouracil (infusion) 2400mg/m^2 Q2W	7.07	93.03%	16.00		$127	$2,034	

Source: Table 3-10, p155 of the submission.

Bid = taken two times a day; CAPOX = capecitabine and oxaliplatin; CLDN18.2 = Claudin 18.2 positive; Disp. = Dispensed; mFOLFOX6 = fluorouracil, leucovorin, and oxaliplatin; Q2W = every two weeks; Q3W = every three weeks; reg = regimen.

Table 12: Cost minimisation results

Treatment	Split between CAPOX and mFOLFOX6	Testing Cost	Total Acquisition and Admin Cost based on dispensed price	Resulting AEMP of zolbetuximab if the cost difference is $0 based on dispensed price	Resulting AEMP of zolbetuximab if the cost difference is $0 based on AEMP
Zolbetuximab + CAPOX	50%	$292	$108,369	$773.27	$773.93
Zolbetuximab + mFOLFOX6	50%				
Nivolumab + CAPOX	50%	$0	$108,661		
Nivolumab + mFOLFOX6	50%				

Source: Table 3-11, p155 of the submission.
AEMP = approved ex-manufacturer price; CAPOX = capecitabine and oxaliplatin; DPMA = dispensed price for maximum amount; mFOLFOX6 = fluorouracil, leucovorin, and oxaliplatin.
Calculated during evaluation using the 'Attachment 10- VYLOY-CLDN Australia_Cost-min_Section 3-Final.xslx' to the submission.

6.68 Table 13 summarises the results of sensitivity analyses for the CMA conducted by the submission and during the evaluation.

Table 13: Results of univariate sensitivity analysis conducted by the submission and during the evaluation using published AEMP of nivolumab

Zolbetuximab + Testing cost	Nivolumab+ mFOLFOX/CAPOX	Incremental cost	Cost-minimised zolbetuximab AEMP (% change)
Base case based on AEMP[a]			
$102,502	$102,502	$0	-
Univariate analyses conducted by the submission			
Assuming **CAPOX /mFOLFOX6 split of 80%/20%** (base case: 50%/50%)			
$93,891	$103,822	-$9,931	11%
Assuming **CAPOX /mFOLFOX6 split of 20%/80%** (base case: 50%/50%)			
$111,114	$101,183	$9,931	-9%
Assuming **no vial sharing** (base case: no drug wastage)			
$107,304	$102,663	-$4,641	-4%
Assuming **42% of patients are CLDN18.2+** (base case: 38.38%)			
$102,477	$102,502	-$25	<1%
Assuming **35% of patients are CLDN18.2+** (base case: 38.38%)			
$102,530	$102,502	$28	<1%
Assuming **600 mg/m² Q3W dosing regimen with mFOLFOX6** (base case: 400 mg/m² Q2W)			
$102,933	$102,502	$431	<1%
Univariate analyses conducted during evaluation			
Assuming average **BSA of 1.80 m²** (base case: 1.70 m²)			
$108,253	$102,554	$5,700	-5%
Assuming the **mean treatment durations for zolbetuximab and nivolumab are identical**, based on the reported treatment duration in the SPOTLIGHT study (7.34 months) and GLOW (10.07 months) trials (base case: using mean treatment duration of zolbetuximab (SPOTLIGHT: 7.34 months and GLOW:10.07 months) and nivolumab trial (CheckMate 649: 9.81 months) [b,c]			
$102,502	$88,754	$13,748	-14%
Assuming **100% CAPOX** (base case: 50% CAPOX and 50% mFOLOFOX6)			
$88,150	$104,701	-$16,552	19%
Assuming **100% mFOLFOX6** (base case: 50% CAPOX and 50% mFOLOFOX6)			
$116,855	$100,303	$16,552	-15%
Assuming that **number of mean doses were not rounded down to the nearest whole number** (base case: mean doses were rounded down to the nearest whole number)			
$107,172	$104,018	$3,154	-3%

Source: Table 3-12, p156 of the submission and conducted during evaluation using 'Attachment 10- VYLOY-CLDN Australia_Cost-min_Section 3-Final.xslx' to the submission.

AEMP = approved ex-manufacturer price; BSA = body surface area; CAPOX = capecitabine and oxaliplatin; CLDN18.2 = Claudin 18.2; mFOLFOX6 = fluorouracil, leucovorin, and oxaliplatin; Q3W = once in three weeks.

[a] Assuming the cost difference, between zolbetuximab + chemotherapy and nivolumab + chemotherapy, becomes zero based on AEMP costs.

[b] Median duration for other components in SPOTLIGHT (4.65 months for capecitabine and 4.06 months for oxaliplatin) and GLOW (5.90 months for leucovorin, 5.30 months for fluorouracil [bolus], 6.50 months for fluorouracil [infusion] and 4.93 months for oxaliplatin) and CheckMate 649 (4.90 for all components).

[c] Mean duration for other components in SPOTLIGHT (6.98 months for capecitabine and 3.62 months for oxaliplatin) and GLOW (8.93 months for leucovorin, 7.86 months for fluorouracil [bolus], 10.21 months for fluorouracil [infusion] and 4.32 months for oxaliplatin) and CheckMate 649 (5.52 for oxaliplatin and 7.07 for all remaining components). Italics calculated during evaluation.

6.69 The evaluation and the ESCs noted that should the PBAC accept the clinical claim of overall noninferior effectiveness and safety, the cost-minimisation approach must establish that the cost per patient for treatment with zolbetuximab + chemotherapy and the CLDN18 testing would be no more than the cost per patient of nivolumab + chemotherapy. The cost per patient takes into account the mean equi-effective doses

of the new intervention and the alternative therapy, and also accounts for any difference in the mean duration of treatment. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

Drug cost/patient/course

6.70 During the evaluation, total cost per course was calculated based on costs per cycle and number of cycles and is presented in Table 14. The following difference between the drug costs as estimated using information from the zolbetuximab and nivolumab trials, in the economic model and the financial estimates were noted:

- The base case of the economic model assumed vial sharing of chemotherapy; therefore, the cost per treatment course was higher in the financial estimates which assumed no wastage; and
- EMP was calculated for zolbetuximab in the economic model whereas DMPA was used for estimating the financial costs.

Table 14: Drug cost per patient per course

	Cost per cycle[a]			Duration of treatment			Total cost per course		
	Trial[b]	Model[c] (AEMP)	Financials[d] (Weighted DPMA)	Trial	Model	Financials (Weighted DPMA)	Trial	Model (AEMP)	Financials (Weighted DPMA)
Zolbetuximab plus mFOLFOX6									
Zolbetuximab, 800 mg/m^2 (one-time cost)	$10,764	$9,735	$11,049	1 cycle[e,f]	1 cycle	0.92 cycles	$117,327	$111,953	$118,081
Zolbetuximab, 400 mg/m^2 Q2W	$5,382	$4,868	$5,584	13.2 cycle for Q3W Converted to 19.8 cycle for Q2W [e,f]	21 cycles	19.32 cycles			
Zolbetuximab plus CAPOX									
Zolbetuximab, 800 mg/m^2 (one-time cost)	$10,269	$10,118	$11,049	1 cycle[g]	1 cycle	0.96 cycles	$83,436	$85,999	$91,246
Zolbetuximab, 600 mg/m^2 Q3W	$7,702	$7,588	$8,707	9.5 cycles[g]	10 cycles	9.26 cycles			
Total (weighted; 50%/50% split between mFOLFOX6 and CAPOX)							**$100,381**	**$98,976**	**$104,663**
Nivolumab plus mFOLFOX6									
Nivolumab, 240 mg Q2W	$4,377	$4,377	$4,900	21.31 cycles	22 cycles	19.72 cycles	$96,294	$96,302	$96,618
Nivolumab plus CAPOX									
Nivolumab, 360 mg Q3W	$6,824	$6,824	$7,290	14.20 cycles	15 cycles	13.66 cycles	$102,360	$102,361	$99,593
Total (weighted; 50%/50% split between mFOLFOX6 and CAPOX)							**$99,327**	**$99,331**	**$98,106**

Source: Table 2-20, p90; 'Attachment 10- VYLOY-CLDN Australia_Cost-min_Section 3-Final.xslx' and 'Attachment 11 – VYLOY CoDep Submission S4 model_Final' to the submission.

BSA = body surface area; CAPOX = capecitabine and oxaliplatin; DPMA = dispensed price for maximum amount; mFOLFOX6 = fluorouracil, leucovorin, and oxaliplatin; Q2W = every two weeks; Q3W = every three weeks.

[a] BSA in the SPOTLIGHT trial = 1.74 m^2, GLOW trial = 1.66 m^2; Economic Model = 1.70 m^2; Financial Model = 1.70 m^2

[b] Cost per cycle in the trial was calculated as dosage × mean BSA × cost per vial ÷100

[c] Cost per cycle in the economic model was calculated as dosage × RDI × mean BSA × cost per vial ÷100

[d] Cost per cycle in the financial model was calculated as dosage × mean BSA × cost per vial ÷100

[e] This was based on the mean number of infusions in the SPOTLIGHT trial (14.2 infusions), with 1 infusion assumed to be the loading dose and remaining 13.2 infusion (Q3W) assumed to be maintenance dose for zolbetuximab.

[f] While both the economic and financial model used 400 mg/m^2, the trial used 600 mg/m^2 of zolbetuximab with mFOFLOX6.

[g] This was based on the mean number of infusions in the GLOW trial (10.5 infusions), with 1 infusion assumed to be the loading dose and remaining 9.5 infusion (Q3W) assumed to be maintenance dose for zolbetuximab.

Italics compiled during the evaluation.

Estimated PBS usage & financial implications

6.71 This submission was considered by DUSC. An epidemiological approach was used to estimate the use and costs of CLDN18 testing and zolbetuximab treatment.

6.72 The key inputs in the financial analysis are summarised in Table 15.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible population		
Incidence of GC	[redacted] in Year 1, increasing to [redacted] in Year 6; based on long-term cancer incidence projections (2024-2033) reported by AIHW.	The selected data source was appropriate. However, the AIHW database used in the submission for the annual forecast relied on 2019 data, despite the availability of more recent 2020 data, which shows a decrease of approximately 230 patients, possibly impacted by COVID. Using the updated patient numbers reduced the financial impact by 5%.
Proportion diagnosed with advanced or metastatic disease	85%; based on Wagner et al., (2010) and Nivolumab PSD March 2022 PBAC Meeting.	
Proportion with AC histology	84.08%; based on AIHW 2021 report.	
Proportion of patients with ECOG PS of 0 or 1	80%; based on reports from Ma et al. (2021) and Gómez-Ulloa et al. (2020).	This was uncertain and likely overestimated. The applicability of Ma et al. (2021) to the Australian population is limited, as the study was conducted in China. Although Gómez-Ulloa et al. (2020) included 34 patients from Australia, 70% had an ECOG performance status of 0-1 at the initiation of 2L treatment, and 26% had an unknown status. Additionally, the nivolumab March 2022 PBAC submission used a lower estimate of 74.75%.
Proportion of patients who are HER2-negative	86.10%; based on Kumarasinghe et al., (2017).	
Proportion of patients tested for CLDN18	90%; based on Sponsor's assumption.	While this approach was reasonable for estimating the number of patients who would receive treatment with zolbetuximab, it may not be appropriate for calculating the number of patients who will undergo CLDN18 testing. PASC specified that CLDN18 testing will be done in all patients with locally advanced unresectable or metastatic G/GOJ adenocarcinoma irrespective of HER2 status. (p17, MSAC Application 1767 Ratified PICO Confirmation, April 2024 PASC Meeting). DUSC considered that this input results in an unnecessary loss of patients.
Proportion of patients with ≥75% CLDN18.2 tumour expression	38.4%; weighted average of patients who tested positive for CLDN18.2 expression in SPOTLIGHT & GLOW trials.	There is inherent uncertainty regarding the proportion of patients testing positive for CLDN18.2 in Australia, as the trials were conducted internationally and the sensitivity analysis indicates that alteration of ±10% will consequently cause a ±13% change in overall estimates.
Treatment utilisation		
Uptake rate	[redacted]% in Year 1 increasing by [redacted]% each year until it reached a cap of [redacted]%; based on Sponsor's assumption.	This is likely overestimated given the modest clinical benefit, gastrointestinal AEs, and insufficient justification provided to support why clinicians would prefer zolbetuximab over nivolumab, given the claim of noninferiority. DUSC noted that the preference for zolbetuximab may increase for patients with low PD-L1 expression if PD-L1 CPS testing became routine practice in Australia as patients with low CPS values and high CLDN18.2 expression would be the optimum cohort for initiating zolbetuximab. However, the likely use of zolbetuximab would be lower for those with higher or unknown CPS scores.
Mean treatment duration for zolbetuximab	10.07 months with mFOLFOX6 in SPOTLIGHT trial and 7.34 months with CAPOX in the GLOW	

Parameter	Value applied and source	Comment
	trial.	
Mean treatment duration for nivolumab	9.8 months with both mFOLFOX6 and CAPOX based on duration of treatment in three-year follow-up of CheckMate 649 trial reported by Janjigian et al. (2024)	This was uncertain; the median duration of treatment (6.8 months) for nivolumab + chemotherapy arm was converted to mean using an exponential distribution and then applied to nivolumab.
Treatment compliance for zolbetuximab/ nivolumab + chemotherapy	92.45% with mFOLFOX6 (based on RDI reported in SPOTLIGHT. 96.08% with CAPOX (Based on RDI reported in GLOW).	The RDI for nivolumab was assumed to be same as for zolbetuximab. DUSC considered that the Australian population would likely be frailer than those in the trial resulting in a lower RDI.
Split of CAPOX between mFOLFOX6 with zolbetuximab	50%/50% based on sponsor's assumption.	DUSC noted that the estimates were sensitive to this input due to the cost offsets associated with the different treatment durations of the two protocols. DUSC noted the sensitivity analysis in the commentary which indicates a split of 20%/80% resulted in a doubling of the overall estimates.
Costs		
Zolbetuximab (cost-minimised published AEMP)	$773.27 per 100 mg vial	The cost-minimised AEMP for zolbetuximab was calculated using a zero difference between the DPMA prices, rather than the recommended AEMP.The corrected cost-minimised AEMP changed negligibly to $773.93.
Nivolumab (published AEMP)	$789.13 per 40 mg vial $1,972.83 per 100 mg vial	The effective price of nivolumab was unknown to sponsor.
CLDN18 test (MBS fee)	$112 per test	

Source: Table 4-1, p158-159; Table 4-2, p164; Table 4-3, p165 and Table 4-8, p170 of the submission.
2L = second line; AC = adenocarcinoma; AEMP = Approved Ex-Manufacturer Price; AIHW = Australian Institute of Health and Welfare; CAPOX = capecitabine and oxaliplatin; CLDN18.2 = Claudin 18.2; CPS = combined positive score; DPMA = Dispensed Price For Maximum Amount; ECOG PS = Eastern Cooperative Oncology Group Performance Status; mFOLFOX6 = fluorouracil, leucovorin, and oxaliplatin; GC = gastric cancer; GOJ = Gastric/Gastroesophageal Junction; HER2 = Human Epidermal Growth Factor Receptor 2; IHC = immunohistochemistry; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; PASC = PICO Advisory Sub-committee; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PD-L1 = Programmed Death-Ligand 1; PSD = Public Summary Document; RDI = relative dose intensity
The redacted values correspond to the following ranges:
[1] 500 to < 5,000

6.73 Table 16 presents the estimated use and financial implications in the submission.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of CLDN18 test						
Number of patients tested	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of patients likely to receive a positive test result (38.38% positivity rate)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][1]	[redacted][1]
Estimated extent of use of zolbetuximab						
Number of patients likely to be treated with proposed drug	[redacted][2a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][1]
Number of scripts dispensed[b]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications of zolbetuximab to the PBS/RPBS						
Cost to PBS/RPBS less copayments	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]
Estimated financial implications for nivolumab						
Cost to PBS/RPBS less copayments	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]	[redacted][6]
Net financial implications						
Net cost to PBS/RPBS	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net cost to MBS for CLDN18 test	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net cost to PBS/RPBS/MBS	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]

Source: Table 4-2, p164, Table 4-3, p165, Table 4-3, p165, Table 4-11, p173, Table 4-16, p176, Table 4-17, p176; and Attachment 11 – VYLOY CoDep Submission S4 model_Final' workbook to the submission.

[a] Includes <500 grandfather patients as estimated by the Sponsor's internal database.

[b] Assuming 10.22 prescriptions for zolbetuximab per year with CAPOX and 20.24 prescriptions with zolbetuximab per year with mFOFLOX6 as estimated by the submission.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *<500*

[3] *5,000 to < 10,000*

[4] *$40 million to < $50 million*

[5] *$50 million to < $60 million*

[6] *net cost saving*

[7] *$0 to < $10 million*

6.74 The total net cost to the PBS/RPBS of listing zolbetuximab was estimated in the submission to be $0 to < $10 million in Year 6, and a total of $10 million to < $20 million in the first 6 years of listing.

6.75 The evaluation noted that although zolbetuximab + chemotherapy with the CLDN18 test was cost-minimised to nivolumab + chemotherapy, it resulted in a net cost to the PBS/RPBS due to difference in number of vials used (the CMA did not account for wastage) and the effect of patient co-payments (the CMA did not include co-payments).

6.76 The evaluation considered that the utilisation/financial estimates were uncertain due to the following issues:

- The submission estimated the cost to the MBS using $291.78 cost per eligible patient for zolbetuximab, based on proposed MBS item fee for CLDN18 test ($112) and the weighted proportion of CLDN18.2+ patients from key clinical

trials (38.38%). However, the evaluation considered that this approach underestimated the actual number of patients undergoing CLDN18 testing if HER2 and CLDN18 are tested together. Instead, the MBS item fee of $112 per test should be applied to all patients with advanced or metastatic GC/GOJ who have ECOG PS of 0-1. Using this approach, the total cost to the MBS increases by 35% (assuming [redacted]% uptake rate) and 21% (assuming [redacted]% uptake rate).

- According to the updated MBS item descriptor, which included a practice note specifying that CLDN18 testing is pathologist determinable, CLDN18 testing may be performed following a negative HER2 test. The evaluation noted that financial impact to the MBS estimated during evaluation would be lower if CLDN18 tests are performed only following a negative HER2 test, resulting in a cost of $0 to < $10 million to the MBS over six years of listing, compared to $0 to < $10 million if all eligible patients with advanced G/GOJ are tested for both HER2 and CLDN18.
- The evaluation noted the inherent uncertainty about the proportion of patients testing positive for CLDN18.2 expression in Australia, as the trials were conducted internationally.
- The evaluation, the ESCs and DUSC considered that chemotherapy alone is a relevant comparator for patients who received nivolumab therapy for Stage II/III disease and subsequently relapsed. Since the cost of chemotherapy alone is lower than the combination of nivolumab and chemotherapy, the evaluation considered that cost-offsets presented in the submission may be overestimated, however noted that this cohort is likely to be small.
- Similar to the CMA, the submission estimated the mean duration of treatment for nivolumab using an exponential distribution based on the median duration observed in the nivolumab + chemotherapy arm.
- The submission claimed that use of CLDN18 testing would result in the majority of those with CLDN18.2+ expression receiving zolbetuximab + chemotherapy, but did not present sufficient justification to support the assumption of [redacted]% uptake rate for zolbetuximab in the first year, with an absolute annual increase of [redacted]% each year until it reaches a cap of [redacted]%. The DUSC and the ESCs considered this to be overestimated given the modest clinical benefit and gastrointestinal AEs associated with zolbetuximab compared to nivolumab. DUSC considered that clinical preference for zolbetuximab may increase for patients with low PD-L1 expression if PD-L1 CPS testing became routine practice in Australia, but would be lower for patients with high or unknown CPS scores.

- The submission estimated < 500 patients, based on Sponsor's internal forecast, would transition from non-PBS to PBS-subsidised supply for zolbetuximab.

6.77 Overall, DUSC considered that the financial estimates for zolbetuximab were likely to be underestimated, which was largely attributed to the lack of a prevalent population and an overestimation of cost offsets.

- DUSC considered that the poor prognosis of advanced gastric or gastroesophageal junction cancers does not preclude the proposed epidemiological model from including a prevalent population.
- DUSC considered that the larger uncertainty with regards to inappropriately applied cost offsets was due to the split between CAPOX and FOLFOX at 50%/50%. DUSC noted the sensitivity analysis in the commentary which indicates a split of 20%/80% resulted in a doubling in the overall estimates. The PBAC noted that this was in part due to the different treatment durations assumed for zolbetuximab and nivolumab.

Quality use of medicines

6.78 The submission did not present any information regarding the quality use of medicines (QUM). DUSC considered it was inappropriate for a submission with complex dosing regimens and the potential for severe adverse events such as hypersensitivity reactions, and increased rates of nausea and vomiting relative to nivolumab, to not have planned training programs for patients, carers or practitioners or planned surveillance programs. In the Pre-PBAC response the sponsor noted that a Consumer Medicines Information has been developed to help patients understand the treatment and recognise when to seek medical attention (e.g. due to hypersensitivity reactions), and identified a range of initiatives that could be undertaken to educate key stakeholders support the safe use of zolbetuximab in Australian clinical practice, including embedding information into local guidelines (e.g. EviQ), educational events, hospital in-services, presentations, and printed materials.

Financial management – risk sharing arrangements

6.79 No risk-sharing arrangements were proposed in the submission. The submission stated that only small number of patients (< 500 annually) are expected to initiate treatment with zolbetuximab, with all eligible patients confirmed by CLDN18 test, providing certainty in the financial forecast.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the listing of zolbetuximab with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (G/GOJ) adenocarcinoma whose tumours are CLDN18.2- positive (CLDN18.2+). The PBAC was of a mind to recommend zolbetuximab pending MSAC consideration of immunohistochemistry (IHC) testing for Claudin 18.2 (CLDN18.2) expression and presentation of revised restriction criteria and cost-minimisation approach (CMA). The PBAC considered that the efficacy of zolbetuximab was non-inferior compared to nivolumab, but due to the additional gastrointestinal toxicity, safety was inferior, and that this should be reflected in the CMA.

7.2 The PBAC considered that there is a moderate clinical need for new treatments for advanced G/GOJ as there are few effective treatment options for this population and the associated prognosis is poor. The PBAC accepted the sponsor's proposed clinical place for zolbetuximab, as first line treatment of locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (G/GOJ) adenocarcinoma whose tumours are CLDN18.2-positive (CLDN18.2+). However, the PBAC considered that the main place of therapy was likely to be for patients with tumours with PD-L1 CPS < 5% and contraindications to immunotherapy, given the non-inferior efficacy but inferior safety of zolbetuximab compared to nivolumab in combination with chemotherapy. The PBAC considered that while no evidence was presented in the submission to support treatment effect modification of CLDN18.2 expression, it would be reasonable to accept the claim for codependence due to the strong biological rationale and the results of the FAST trial (see paragraph 6.52), and noted the issues with generating data where it may not be ethical to expose patients to an active treatment where they are not likely to experience benefit. The PBAC considered that a requirement for at least 75% of tumour cells demonstrating moderate to strong membranous CLDN18.2 IHC staining should be included in the restriction to ensure that only patients who are likely to benefit from the addition of zolbetuximab to chemotherapy, receive zolbetuximab.

7.3 In addition to the changes to the criteria noted in paragraphs 3.6 to 3.8, the PBAC advised the following amendments to the proposed restriction criteria and requested a revised criteria be provided:

- the indication be revised to: 'Locally advanced, unresectable, or metastatic gastric or gastro-oesophageal junction cancers – first line treatment'
- it was appropriate to have an initial criteria, two separate continuing criteria (one for Q2W dosing and one for Q3W dosing) and a grandfathering criteria;

- a requirement for at least 75% CLDN18.2 expression should be specified in the relevant clinical criterion;
- with the removal of the Conditions population criteria (as discussed in paragraph 3.6) the following clinical criteria should be added: ''The treatment must be in combination with platinum-based chemotherapy plus a fluoropyrimidine drug'; and 'The condition must be human epidermal growth factor receptor 2 (HER2) negative'; and
- addition of the clinical criterion: 'Patient must be untreated for this indication' to ensure use in the first line treatment setting. With this inclusion, the criterion: 'Patient must be undergoing treatment with this drug for the first time' can be removed.

7.4 The submission nominated nivolumab + chemotherapy as the main comparator, and chemotherapy alone for the subgroup of patients who relapsed after early-stage nivolumab treatment or have contraindications to PD-1/PD-L1 inhibitors. The PBAC considered the nominated comparators were appropriate, noting that the latter subgroup of patients was likely to be small. The PBAC also noted that tislelizumab (recommended by the PBAC in November 2024) and pembrolizumab (recommended by PBAC in May 2022) are near market comparators, recommended on a cost-minimisation basis to nivolumab but not yet PBS-listed at the time of PBAC consideration.

7.5 The submission was based on an indirect treatment comparison (ITC) of zolbetuximab + chemotherapy and nivolumab + chemotherapy via network-meta-analysis (NMA), from which it focussed on two randomised, double-blind trials (SPOTLIGHT, N=565; and GLOW, N=507) comparing zolbetuximab with chemotherapy (mFOLFOX6, and CAPOX, respectively), and two randomised, double-blind trials (CheckMate 649, N= 1,581; and ATTRACTION-4, N=724) comparing nivolumab with chemotherapy (FOLFOX or CAPOX, and SOX or CAPOX, respectively). The PBAC noted potential transitivity issues between the included trials leading to uncertainty in the ITC, including differences in the primary tumour site, inclusion of patients with recurrent disease, HER2 status (negative vs unknown), CLDN18.2 expression (≥75% expression vs unknown), ancestry, follow-up duration, and subsequent anti-cancer therapies. The PBAC considered the CheckMate 649 nivolumab trial to be more applicable, noting the ATTRACTION-4 trial was excluded from the nivolumab PBAC submission due to concerns regarding its applicability to Australian setting (see paragraph 6.10).

7.6 The PBAC noted similarly modest OS improvements with zolbetuximab + chemotherapy compared to chemotherapy alone (SPOTLIGHT HR 0.78, 95% CI 0.64, 0.95; GLOW HR 0.76, 95% CI 0.62, 0.94) and nivolumab + chemotherapy compared to chemotherapy alone (CHECKMATE 649 HR 0.80, 95% CI 0.68, 0.94; ATTRACTION-4 HR 0.90, 95% CI 0.75, 1.08). The PBAC noted based on the NMA analysis included in the submission, and two additional NMAs identified during the evaluation, that the

differences in PFS and OS for zolbetuximab and nivolumab when used in combination with chemotherapy were not statistically significantly different. Although not strongly supported due to transitivity issues, the PBAC considered that the claim of noninferior effectiveness was overall reasonable.

7.7 The submission described zolbetuximab as noninferior in terms of safety compared to nivolumab, with a different but manageable safety profile. The PBAC acknowledged difficulties in assessing comparative safety, given the considerable differences in the safety profiles between zolbetuximab and nivolumab. The PBAC noted similar AE rates overall, but more Grade 3-4 upper gastrointestinal toxicity with zolbetuximab, which it considered would likely affect patient quality of life. The PBAC noted the addition of nivolumab to chemotherapy did not increase the incidence of grade 3 or 4 nausea, vomiting or decreased appetite, whereas the addition of zolbetuximab to chemotherapy increased the incidence of these events by 9%, 10% and 3%, respectively. The PBAC further noted the EMA and FDA considered zolbetuximab to be associated with serious hypersensitivity (e.g. anaphylaxis) and severe nausea/vomiting, and pre-treatment with antiemetics is recommended before each infusion. Overall, the PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the evidence, and the safety of zolbetuximab + chemotherapy is inferior to nivolumab + chemotherapy.

7.8 The submission presented a CMA of zolbetuximab + chemotherapy and nivolumab + chemotherapy. The PBAC noted separate analyses were presented for use in combination with mFOLFOX6 and with CAPOX. The PBAC further noted that different treatment durations were assumed for zolbetuximab and nivolumab, as well as the concomitant chemotherapy.

7.9 The PBAC noted that when used in combination with mFOLFOX6, the treatment duration for zolbetuximab (10.07 months based on the mean treatment duration in SPOTLIGHT) was assumed to be longer than for nivolumab (9.81 months estimated from the median treatment duration in CM649). Conversely when used in combination with CAPOX, the treatment duration for zolbetuximab (7.34 months based on the mean treatment duration in GLOW) was assumed to be shorter than for nivolumab (9.81 months estimated from the median treatment duration in CM649). Given that there is no cap on the duration of zolbetuximab treatment whereas there is a two-year cap on treatment with nivolumab, the PBAC considered that the duration of zolbetuximab treatment should not be assumed to be shorter than that for nivolumab. However, the PBAC further noted that in SPOTLIGHT and GLOW only 21% and 13% of patients, respectively, remained on treatment with zolbetuximab for longer than 72 weeks and thus considered despite no treatment cap, few patients would be treated with zolbetuximab for more than 2 years. On this basis, the PBAC considered it would be reasonable for the CMA to assume the same treatment duration for both zolbetuximab and nivolumab. The PBAC considered the average treatment duration across the SPOTLIGHT and GLOW trials (8.7 months) could be used

in the CMA, noting this was consistent with the submission's approach of assuming 50% of zolbetuximab use would be in combination with mFOLFOX6 and 50% in combination with CAPOX.

7.10 The PBAC noted that if no difference in the treatment durations is assumed in the CMA, then the cost of the chemotherapy, the cost of the administration and the relative dose intensity (RDI) can be removed from the analysis.

7.11 Based on the above the PBAC advised that the equi-effective doses would be:

- Zolbetuximab: loading dose of 800 mg/m^2 followed by maintenance doses of 600 mg/m^2 Q3W or 400 mg/m^2 Q2W for a total of 8.7 months
- Nivolumab: 360 mg Q3W or 240 mg Q2W for 8.7 months

7.12 The PBAC advised that the number of vials of zolbetuximab for the CMA should be calculated assuming an average BSA of 1.8 m^2, consistent with that expected in Australian clinical practice given the trials included a relatively high proportion of Asian participants. The PBAC also advised that the mean number of doses required should not be rounded down to the nearest whole number and wastage should be included. As per the submission's analysis, the cost of CLDN18 testing should be included in the zolbetuximab arm of the CMA assuming CLDN18.2+ expression in 38.38% of patients.

7.13 The PBAC considered the costs associated with preventing and treating gastrointestinal side effects with zolbetuximab should be included in the CMA. The PBAC noted the PSCR presented a sensitivity analysis including the cost of managing zolbetuximab-related adverse events (nausea and vomiting) with ondansetron in the CMA, however, agreed with the ESCs that the addition of costing for ondansetron inadequately accounted for the costs of managing these AEs, noting the increase in events of grade 3-4 severity. The PBAC requested a revised CMA be provided for consideration which more appropriately accounts for the costs associated with the increased toxicity with zolbetuximab. The PBAC considered the potential impact of the gastrointestinal toxicity on the patient's quality of life should also be accounted for, and in this context advised the cost per patient for zolbetuximab should be at least [redacted] % lower than for nivolumab.

7.14 The PBAC considered the financial estimates should be revised to account for (i) patients undergoing CLDN18 testing irrespective of HER2 status, (ii) likely lower uptake of zolbetuximab (likely less than 70% in year 1), (iii) the same treatment duration for zolbetuximab and nivolumab consistent with the CMA (see paragraph 7.9) and (iv) the zolbetuximab price based on the revised CMA. The PBAC noted that the DUSC considered a prevalent pool of patients should be included in the estimates, and considered that this was at least partly accounted for by the inclusion of grandfathered patients.

7.15 The PBAC considered it was appropriate for zolbetuximab to be included in the risk sharing arrangement (RSA) currently in place for nivolumab for gastro-oesophageal cancer. The PBAC considered given the listing was on a cost minimisation basis, that there should be no increase in the RSA expenditure caps with the listing of zolbetuximab.

Outcome:
Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Astellas looks forward to gaining PBS reimbursement for patients that would benefit from being prescribed Zolbetuximab. We hope to swiftly move through the final approval processes.

Addendum to the March 2025 PBAC minutes:

4.01 ZOLBETUXIMAB, Powder for I.V. infusion 100 mg (20 mg per mL), Vyloy®, ASTELLAS PHARMA AUSTRALIA PTY LTD

10 Background

10.1 At its March 2025 meeting, the PBAC deferred zolbetuximab with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (G/GOJ) adenocarcinoma whose tumours are Claudin 18.2 positive (CLDN18.2+), but was of a mind to recommend, pending MSAC consideration of immunohistochemistry (IHC) testing for CLDN18.2 expression and presentation of revised restriction criteria and cost-minimisation approach (CMA) (see paragraph 7.1).

10.2 At its 3-4 April 2025 meeting, the MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for IHC testing for CLDN18.2 expression to determine eligibility for zolbetuximab under the Pharmaceutical Benefits Scheme (PBS) in patients with locally advanced unresectable or metastatic G/GOJ adenocarcinoma. MSAC considered testing would identify patients expected to benefit from zolbetuximab and testing would have no additional safety concerns. The MSAC considered the financial impact of testing to the MBS would be relatively low, and advised that a fee between $74.50 to $112 would be appropriate (MSAC PSD, Application No. 1767 - Immunohistochemistry testing for CLDN18.2 expression in patients with gastric or gastro-oesophageal junction cancers, to determine eligibility for PBS subsidised zolbetuximab treatment, April 2025).

10.3 On 30 June 2025 the Sponsor provided a response to the PBAC deferral from March 2025, proposing an updated restriction, CMA, and financial estimates.

10.4 The PBS-listing of zolbetuximab with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-negative G/GOJ adenocarcinoma whose tumours are CLDN18.2+ was subsequently considered by the PBAC at its September 2025 meeting.

Registration status

10.5 Zolbetuximab was TGA registered on 17 March 2025: “in combination with fluoropyrimidine- and platinum-containing chemotherapy, indicated for the first-line

treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastro-oesophageal junction (GOJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive".

11 Consideration of the evidence

Economic analysis

11.1 The CMA presented in the sponsor's proposal:

- Assumed an 8.7 month treatment duration for zolbetuximab and nivolumab based on the average treatment duration across the SPOTLIGHT and GLOW trials (as requested in paragraph 7.9);
- Based the number of zolbetuximab vials on a body surface area of 1.8m^2 with no rounding down of vial numbers (as requested in paragraph 7.12);
- Removed the cost of the chemotherapy and administration, and relative dose intensity (as requested in paragraph 7.10**Error! Reference source not found.**); a nd
- Included the cost of CLDN18 testing assuming 2+ expression in 38.38% (as requested in paragraph 7.12) of patients and a cost per test of $112.

11.2 The CMA did not reduce the cost per patient by [redacted]% to account for additional gastrointestinal adverse events (AEs) associated with zolbetuximab (as requested in paragraph 7.13). The proposal stated zolbetuximab and nivolumab have similar rates of Grade ≥ 3 AE, but the type of AEs differed due to the different mechanisms of action. The proposal noted AEs for zolbetuximab are more often related to infusion reactions and gastrointestinal symptoms, and AEs for nivolumab are more often associated with immune-related reactions affecting multiple organs. The proposal argued that both treatments have manageable but significant AE rates and a different cost per patient did not seem warranted.

11.3 The CMA presented in the proposal (using the published ex-manufacturer price of nivolumab) is summarised in the table below.

Table 17: Cost-minimisation approach as presented in the proposal

	Vials per dose	Number of doses	Cost per patient
With CAPOX, every 3 weeks (50% use)			
Zolbetuximab ($594.85 per 100 mg vial) Loading dose (800 mg/m^2) Maintenance dose (600 mg/m^2)	 15 x 100 mg 11 x 100 mg	 1 12.61	 $91,433
Nivolumab (360 mg)	4 x 40 mg + 2 x 100 mg	13.61	$96,659
With mFOLFOX6, every 2 weeks (50% use)			
Zolbetuximab ($594.85 per 100 mg vial) Loading dose (800 mg/m^2) Maintenance dose (400 mg/m^2)	 15 x 100 mg 8 x 100 mg	 1 18.91	 $98,934
Nivolumab (240 mg)	1 x 40 mg + 2 x 100 mg	19.91	$94,292
Weighted cost (including testing cost)[1]			
Zolbetuximab			$95,476
Nivolumab			$95,476
Difference			-

Source: Attachment 10 VYLOY CLDN Australia Cost min PBAC v0.4.xlsm provided with proposal
mg, milligrams;
1. Test cost per patient calculated as $112/38.38%

11.4 The total number of doses per patient when used with CAPOX should be 12.61[14] (i.e., 1 loading and 11.61 maintenance doses for zolbetuximab and 12.61 doses for nivolumab) rather than 13.61. The total number of doses with mFOLFOX6 should be 18.91[15] (i.e., 1 loading and 17.91 maintenance doses for zolbetuximab and 18.91 doses for nivolumab) rather than 19.91.

11.5 The PBAC noted the CMA included the maximum test cost proposed by MSAC (see paragraph 10.2).

Estimated PBS usage & financial implications

11.6 The financial estimates presented in the proposal:

- Applied the same the duration of treatment (8.7 months) for zolbetuximab and nivolumab, consistent with the CMA;
- Assumed 100% of patients undergo CLDN18 testing; and
- Decreased uptake from 90% to 70% in Year 1 only.

11.7 Revised financial estimates are summarised below (using the published price of nivolumab).

[14] (365.25/12*8.7)/21
[15] (365.25/12*8.7)/14

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of CLDN18 test						
Number of patients tested	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of patients likely to receive a positive test result (38.38% positivity rate)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated extent of use of zolbetuximab						
Number of patients likely to be treated with proposed drug	[redacted][2,a]	[redacted][2]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications of zolbetuximab to the PBS/RPBS						
Cost to PBS/RPBS less copayments	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][6]	[redacted][6]
Estimated financial implications for nivolumab						
Cost to PBS/RPBS less copayments	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net financial implications						
Net cost to PBS/RPBS	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Net cost to MBS for CLDN18 test	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
Net cost to PBS/RPBS/MBS	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]

Source: Attachment 11 – VYLOY CoDep Submission S4 model PBAC v0.1.xls provided with proposal

[a] Includes < 500 grandfather patients

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *<500*

[3] *5,000 to < 10,000*

[4] *$30 million to < $40 million*

[5] *$40 million to < $50 million*

[6] *$50 million to < $60 million*

[7] *net cost saving*

[8] *$0 to < $10 million*

11.8 The financial estimates were based on the appropriate number of total doses (i.e., 12.61 in combination with CAPOX and 18.91 in combination with mFOLFOX6) which was inconsistent with the CMA (see paragraph 9.4) and this resulted in a small incremental cost.

12 PBAC Outcome

12.1 The PBAC recommended the Pharmaceutical Benefits Scheme (PBS) listing of zolbetuximab with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (G/GOJ) adenocarcinoma whose tumours are CLDN18.2- positive (CLDN18.2+). The PBAC considered that zolbetuximab was noninferior compared to nivolumab in terms of effectiveness, but due to the additional gastrointestinal toxicity, safety was inferior, and that this should be reflected in the cost minimisation approach (CMA). The PBAC advised zolbetuximab should be included in the risk sharing arrangement (RSA) currently in place for nivolumab for gastro-oesophageal cancers with no increase in expenditure caps.

12.2 The PBAC noted that MSAC considered testing would identify patients expected to benefit from zolbetuximab, testing would have no additional safety concerns, and that the financial impact of testing to the MBS would be relatively low.

12.3 The PBAC recalled that it had previously recommended amendments to the proposed restriction (see paragraph7.3), most of which were addressed in the updated restriction provided in the proposal. The PBAC considered that the updated restriction would be acceptable with some amendments:

- one criteria for continuing treatment and one criteria for transitioning from non-PBS to PBS-subsidised treatment (under grandfather arrangements) each incorporating the two weekly and three weekly dosing regimens would be appropriate (rather than separate criteria for two weekly and three weekly dosing as proposed in paragraph 7.3); and
- the clinical criterion 'The treatment must be in combination with platinum-based chemotherapy plus a fluoropyrimidine drug' should be changed to 'The treatment must be initiated in combination with platinum-based chemotherapy plus a fluoropyrimidine drug'. This would ensure patients are able to stop platinum-based chemotherapy and/ or fluoropyrimidine if appropriate (i.e., due to intolerance); and
- minor edits to align with standard restriction wording and formatting.

12.4 The PBAC considered the CMA presented in the proposal (based on the equi-effective doses presented in paragraph 7.11) would be reasonable with the following amendments:

- The PBAC reiterated its previous consideration that the cost per patient for zolbetuximab should be at least [redacted]% lower than for nivolumab. The PBAC noted the arguments presented in the proposal (see paragraph 11.2) but

considered the potential impact of the gastrointestinal toxicity of zolbetuximab on a patient's quality of life should also be accounted for; and

- The CMA should be based on a total of 12.61 doses in combination with CAPOX and 18.91 doses in combination with mFOLFOX6 (as discussed in paragraph 9.4).

12.5 The PBAC recalled that it previously proposed revisions to the financial estimates (see paragraph 7.14), which it noted were partly addressed in the updated financial estimates (see paragraph 11.6). The PBAC noted that the estimated number of patients undergoing CLDN18 testing irrespective of HER2 status was increased from 90% to 100%, resulting in a slightly higher number of treated patients, and the estimated uptake of zolbetuximab was reduced to 70% in Year 1, but no change in subsequent years. The PBAC considered that the estimated uptake in Year 2 to 6 (92.5% to 97.5%) remained high, given the noninferior effectiveness and inferior safety profile of zolbetuximab. The PBAC considered the revised uptake in Year 1 was reasonable (70%) but should increase by 2.5 percentage points each year consistent with the approach in the July 2025 submission (see paragraph 6.76).

12.6 The PBAC advised zolbetuximab should be included in the RSA currently in place for gastro-oesophageal cancers with no increase in expenditure caps.

12.7 The PBAC advised that the Early Supply Rule should not be applied to zolbetuximab.

12.8 The PBAC recommended that zolbetuximab should not be treated as interchangeable with any other drugs listed on the PBS.

12.9 The PBAC advised that zolbetuximab is not suitable for prescribing by nurse practitioners.

12.10 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because zolbetuximab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over nivolumab, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

12.11 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

13 Recommended listing

13.1 Add new items:

Initial

MEDICINAL PRODUCT	PBS item code	Max. Amount	№.of Rpts
ZOLBETUXIMAB Injection	NEW (Public) NEW (Private)	1,400 mg	0
Available brands			
Vyloy zolbetuximab 100 mg injection, 1 vial			
Category / Program: ☒Section 100 – Efficient Funding of Chemotherapy – Public (IP)/ Private (IV)			
Prescriber type: ☒Medical Practitioners			
Benefit type: ☒Authority Required (Streamlined) [new code]			
Prescribing rule level:			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Restriction Summary [new1] / Treatment of Concept: [new1A]			
Indication: Locally advanced, unresectable, or metastatic gastric or gastro-oesophageal junction cancers – first line treatment			
Treatment Phase: Initial treatment (loading dose)			
Clinical criteria:			
Patient must have WHO performance status no higher than 1.			
AND			
Clinical criteria:			
The condition must have evidence of Claudin 18 (CLDN18) expression of at least 75% as demonstrated by immunohistochemistry in tumour material– document this evidence in the patient's medical records.			
AND			
Clinical criteria:			
Patient must be untreated for this indication			
AND			
Clinical criteria:			
The condition must be human epidermal growth factor receptor 2 (HER2) negative.			
AND			
Clinical criteria:			
The treatment must be initiated in combination with platinum-based chemotherapy plus a fluoropyrimidine drug			

Continuing (Q3W and Q2W regimen)

MEDICINAL PRODUCT	PBS item code	Max. Amount	№.of Rpts
ZOLBETUXIMAB Injection	NEW (Public) NEW (Private)	1,050 mg	12
Available brands			
Vyloy zolbetuximab 100 mg injection, 1 vial			
Category / Program: ☒Section 100 – Efficient Funding of Chemotherapy – Public (IP)/ Private (IV)			
Prescriber type: ☒Medical Practitioners			
Benefit type: ☒Authority Required (Streamlined) [new code]			
Prescribing rule level:			
Administrative Advice:			

No increase in the maximum number of repeats may be authorised.
Restriction Summary [new2] / Treatment of Concept: [new2]
Indication: Locally advanced, unresectable, or metastatic gastric or gastro-oesophageal junction cancers – first line treatment
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria:
The condition must not have progressed while receiving PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria:
The treatment must be initiated in combination with platinum-based chemotherapy plus a fluoropyrimidine drug,
Treatment criteria:
Patient must be undergoing treatment with this drug administered at a dose of 600 mg/m^2 once every 3 weeks - prescribe up to 8 repeat prescriptions; OR
Patient must be undergoing treatment with this drug administered at a dose of 400 mg/m^2 once every 2 weeks - prescribe up to 12 repeat prescriptions.

Grandfathering (Q3W and Q2W regimen)

Restriction Summary [new3] / Treatment of Concept: [new3A]
Indication: Locally advanced, unresectable, or metastatic gastric or gastro-oesophageal junction cancers – first line treatment
Treatment Phase: Transitioning from non-PBS to PBS-subsided treatment - Grandfather arrangements
Clinical criteria:
Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [date of listing]
AND
Clinical criteria:
Patient must have had a WHO performance status score of no greater than 1 at treatment initiation with this drug
AND
Clinical criteria:
The condition must have had evidence of Claudin 18 (CLDN18) expression of at least 75% as demonstrated by immunohistochemistry in tumour material at treatment initiation with this drug– document this evidence in the patient's medical records.
AND
Clinical criteria:
Patient must have been untreated for this indication prior to initiating treatment with this drug.
AND
Clinical criteria:
The condition must be human epidermal growth factor receptor 2 (HER2) negative.
AND
Clinical criteria:
The treatment must be initiated in combination with platinum-based chemotherapy plus a fluoropyrimidine drug
AND
Clinical criteria:
The condition must not have progressed while receiving PBS-subsidised treatment with this drug for this condition.

Treatment criteria:
Patient must be undergoing treatment with this drug administered at a dose of 600 mg/m^2 once every 3 weeks - prescribe up to 8 repeat prescriptions; OR
Patient must be undergoing treatment with this drug administered at a dose of 400 mg/m^2 once every 2 weeks - prescribe up to 12 repeat prescriptions.
Prescribing Instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

14 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

15 Sponsor's Comment

Astellas welcomes the Committee's positive recommendation of zolbetuximab and looks forward to working closely with the Department to finalise the MBS and PBS restrictions, so that patients can access zolbetuximab as soon as possible. The SPOTLIGHT and GLOW studies showed no meaningful difference in patient-reported quality of life (HRQoL) between zolbetuximab plus chemotherapy and chemotherapy alone. During the clinical studies, nausea and vomiting (N&V) occurred more often during the first cycle of treatment but decreased in incidence with subsequent cycles of treatment and during clinical studies, no clinically meaningful deteriorations were observed in HRQoL scores and the early worsening of nausea/vomiting, later returned to baseline levels. Despite nausea/vomiting, no clinically meaningful differences between treatment arms were observed. No dose reduction for zolbetuximab is recommended. Adverse reactions (including N&V) for zolbetuximab are managed by infusion rate reduction, interruption, and/or discontinuation.