

## 6.10 NIVOLUMAB,

**Injection concentrate for I.V. infusion 40 mg in 4 mL**

**Injection concentrate for I.V. infusion 100 mg in 10 mL,**

**Opdivo<sup>®</sup>,**

**Bristol-Myers Squibb Australia Pty Ltd**

### 1 Purpose of submission

- 1.1 The Category 2 submission requested an Authority Required listing for nivolumab in combination with platinum-containing plus fluoropyrimidine-containing chemotherapy (henceforth nivolumab plus chemotherapy) for the treatment of non-human epidermal growth factor receptor 2 (HER-2) positive advanced or metastatic gastric cancer (GC), gastro-oesophageal junction cancer, (GOJC) or oesophageal adenocarcinoma (OAC).
- 1.2 Listing was requested on the basis of a cost utility analysis versus platinum-containing plus fluoropyrimidine-containing chemotherapy alone.
- 1.3 Table 1 presents the key components of the clinical issue addressed by the submission.

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

Component	Description
Population	Patients with non-HER2 positive advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma
Intervention	Nivolumab in combination with platinum-containing plus fluoropyrimidine-containing chemotherapy*
Comparator	Platinum-containing plus fluoropyrimidine-containing chemotherapy
Outcomes	Overall survival, progression-free survival, objective response rate, health-related quality of life, safety and tolerability
Clinical claim	Superior in terms of efficacy and inferior but manageable in terms of safety, compared with chemotherapy

Source: Table 1, p5 of the submission. HER2 = Human Epidermal Growth Factor Receptor 2

\* The dosing of nivolumab is different based on the use of either FOLFOX or XELOX. When taken with XELOX: 360 mg intravenous (IV) over 30 minutes on Day 1 of each treatment cycle, every 3 weeks. When taken with FOLFOX: 240 mg IV over 30 minutes on Day 1 of each treatment cycle, every 2 weeks.

### 2 Background

#### **Registration status**

- 2.1 TGA status at time of PBAC consideration: not registered. The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA

Delegate’s Overview was available. As this indication was assessed under Project Orbis<sup>1</sup> using the FDA Assessment Aid, no TGA clinical evaluation report was available.

- 2.2 The TGA Delegate was supportive of registration for the following indication: “in combination with fluoropyrimidine and platinum-based combination chemotherapy for the first line treatment of patients with HER2 negative advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma”. The draft TGA indication proposed in the submission did not include a reference to HER2 status in the indication.

### Previous PBAC consideration

- 2.3 At its July 2021 meeting, the PBAC recommended nivolumab for the treatment of patients with advanced or metastatic oesophageal squamous cell carcinoma who have disease progression following treatment with a fluoropyrimidine and platinum-based chemotherapy regimen.

## 3 Requested listing

- 3.1 The requested listing for nivolumab is provided below. Secretariat suggestions and additions proposed are shown in italics and deletions are in strikethrough.

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
NIVOLUMAB Injection, 100mg in 10 mL (Vial)	360mg	13 (initial and continuing)	\$7,707.38 (Published, Private Hospital)	OPDIVO, BMS
NIVOLUMAB Injection 40 mg in 4mL (Vial)			\$7,562.08 (Published, Public Hospital)	
			\$ (Effective, Private Hospital)	
			\$ (Effective, Public Hospital)	

<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
<b>Administrative Advice:</b> Special Pricing Arrangements apply.
<b>Episodicity:</b> [blank]
<b>Severity:</b> Advanced or metastatic

<sup>1</sup> A collaborative review project co-ordinated by the United States FDA.<sup>1</sup> For this submission, the regulators taking part were FDA (USA), TGA (Australia), Health Canada, and Swissmedic (Switzerland).

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<b>Condition:</b> carcinoma of the following types: (i) gastric cancer, (ii) primary adenocarcinoma of oesophagogastric junction, (iii) adenocarcinoma in situ of oesophagus
<b>Indication:</b> Advanced or metastatic non-HER2 positive carcinoma of the following types: (i) gastric cancer, (ii) gastro-oesophageal junction, cancer or oesophageal adenocarcinoma of oesophagogastric junction, (iii) adenocarcinoma of oesophagus
<b>Treatment Phase:</b> Initial treatment
<b>Clinical criteria:</b>
Patient must not have received prior PBS-subsidised treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have advanced/metastatic disease that is untreated at the time this drug is initiated
<b>AND</b>
<b>Treatment criterion:</b>
<del>The treatment must be initiated in combination with fluoropyrimidine plus platinum-based chemotherapy.</del>
Patient must be undergoing concurrent treatment with chemotherapy (capecitabine/fluorouracil + oxaliplatin, with/without folinic acid) at least at the time of treatment initiation with this drug
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have a WHO performance status of 0 or 1
Patient must have WHO performance status no higher than 1 at treatment initiation with this drug
<b>AND</b>
<b>Clinical criteria:</b>
<del>Patient must not have evidence of human epidermal growth factor receptor 2 (HER2) positive tumour.</del>
<b>Administrative Advice:</b>
In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition
<b>Treatment criterion:</b>
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
<b>AND</b>
<b>Clinical criteria:</b>
<del>Patient must have prescriber-assessed clinical benefit and must be tolerating treatment.</del>
<del>The condition must not have progressed</del>
<b>Prescriber instruction:</b>
<del>The treatment must not exceed 24 months for this PBS indication.</del>
<del>Check that the amount of drug and number of repeats on this prescription does not extend total treatment beyond 24 months. PBS subsidy duration is limited to whichever occurs first from the following: (i) disease progression, (ii) 24 months of treatment, measured from when this drug was initiated. Prescribing under this listing is a declaration that treatment obtained through this 'Continuing treatment' phase would not extend treatment beyond 24 months of treatment.</del>

- 3.2 The submission requested a special pricing arrangement, consistent with other PBS listings for nivolumab. The published dispensed price for maximum amount (DPMA) proposed was consistent with the published price of nivolumab for other PBS-listed indications.

- 3.3 The submission stated that the proposed continuation criteria were developed to align with existing PBS-listed nivolumab indications, where appropriate, and to align with circumstances of use in the pivotal CheckMate 649 trial.
- 3.4 The PBAC noted the proposed restriction included the clinical criteria “Patient must not have evidence of human epidermal growth factor receptor 2 (HER2) positive tumour”; however, the MBS item for testing HER2 (73342) only applies to patients with metastatic adenocarcinoma of the stomach [gastric cancer] or gastro-oesophageal junction in relation to meeting the PBS eligibility requirements for trastuzumab and not to patients with oesophageal cancer. The PBAC noted some ambiguity in the restriction regarding HER2 status and considered this required clarification from the Sponsor.
- 3.5 The requested restriction stated: “The treatment must be initiated in combination with fluoropyrimidine plus platinum-based chemotherapy.” The Secretariat suggested rewording to “Patient must be undergoing concurrent treatment with chemotherapy (capecitabine/fluorouracil + oxaliplatin, with/without folinic acid) at least at the time of treatment initiation with this drug “. The PBAC considered this could be simplified to “Patient must be undergoing concomitant chemotherapy with a platinum agent plus a fluoropyrimidine agent at treatment initiation with this drug”. The criterion permits use of nivolumab with cisplatin + 5-FU, FOLFOX, or XELOX/CAPOX.
- 3.6 No transitioning arrangements (i.e., ‘grandfather’ listing) were proposed in the submission. The pre-PBAC response stated that, while there is currently no formal patient access program for nivolumab plus chemotherapy in advanced or metastatic GC, GOJC or OAC, the Sponsor has granted compassionate access to < 500 patients to date, of which approximately < 500 are currently on active treatment. If nivolumab was to be listed with the Secretariat suggested edits, there would be no need for transitioning arrangements as the initial treatment restriction does not exclude such patients.

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

## **4 Population and disease**

- 4.1 Gastro-oesophageal cancer is a heterogeneous disease; tumours can appear in the oesophagus, the gastro-oesophageal junction (GOJ; the junction where the oesophagus connects to the stomach), or stomach regions of the digestive system. It is typically segmented into three distinct entities: oesophageal, which may be squamous cell carcinoma or adenocarcinoma; GOJ (cardia); and stomach (non-cardia) cancers, which are typically adenocarcinomas and usually referred to collectively as gastric cancer (GC) (Buas 2013; Gunderson 2014; Torre 2015).
- 4.2 Most patients experience disease progression within a year of beginning treatment (Hall 2020). Many patients experience a deterioration in quality of life (QoL) as the

standard of care chemotherapy regimens are often accompanied by high toxicity (Cunningham 2008; Ohtsu 2011; Van Cutsem 2006; Yamada 2015). GC (including GOJC) and OAC have a disproportionate impact on Australians with lower socioeconomic backgrounds, who were 1.4 and 1.5 times more likely to die from GC and OAC respectively in 2012-2016 than the highest socioeconomic group, with even lower survival for Indigenous Australians (AIHW, 2018).

- 4.3 The submission proposed nivolumab with chemotherapy for the first line treatment of patients with advanced or metastatic GC, GOJC or OAC who are not positive for HER-2. The MBS item for HER2 testing (MBS item 73342) is for adenocarcinoma of GC and GOJC, but not specifically for OAC. The ESC noted patients with OAC are not routinely tested for HER2 status.
- 4.4 Nivolumab is a monoclonal antibody that binds to the programmed death 1 receptor (PD-1) and blocks its interaction with the programmed death ligand 1 and 2 (PD-L1, PD-L2).

## **5 Comparator**

- 5.1 The submission nominated fluoropyrimidine- and platinum-based combination chemotherapy (henceforth chemotherapy alone) as the main comparator. The main arguments provided in support of this nomination were:
- Fluoropyrimidine- and platinum-based combination chemotherapy represents the historical 'standard of care' in these patients.
  - Real-world evidence on treatment use in Australia in advanced or metastatic gastric cancer reports combination chemotherapy with doublet or triplet regimens as the most common first-line anti-cancer drug therapy currently used, with all regimens using a combination of platinum and fluoropyrimidine-based chemotherapy (Gómez-Ulloa et al., 2020). Triplet regimens do not appear to be commonly used in Australia.
  - This aligned with Australian clinical practice, where clinicians at an advisory board confirmed platinum and fluoropyrimidine-based doublet chemotherapy is the most common treatment regimen used in Australia (Bristol-Myers Squibb Australia Pty Ltd, 2021).
  - Agents in the nominated comparator regimens are listed on the PBS as unrestricted treatments and able to be used in patients with advanced or metastatic GC, GOJC or OAC.
- 5.2 The evaluation considered it may be more appropriate to explicitly nominate the comparator as XELOX (capecitabine + oxaliplatin) or FOLFOX (5-FU + oxaliplatin + leucovorin) as the clinical evidence provided in the submission provided a comparison of nivolumab + FOLFOX/XELOX with FOLFOX/XELOX only, and no evidence for the combination or comparison with other fluoropyrimidine- and platinum-based

combination therapies such as capecitabine or 5-FU plus cisplatin were provided. The ESC considered the nominated comparator of fluoropyrimidine- and platinum-based combination chemotherapy was reasonable.

- 5.3 The PBAC noted that pembrolizumab plus chemotherapy was being considered at the same PBAC meeting for advanced or metastatic oesophageal cancer (adenocarcinoma and squamous cell carcinoma) and HER2 negative GOJ cancer. The PBAC noted the indications for nivolumab and pembrolizumab (which were based on the clinical trial populations) do not fully align; however, the PBAC considered there was likely to be significant overlap in clinical practice due to overlap in anatomical distribution of these cancers. The PBAC considered that pembrolizumab plus chemotherapy was a near term comparator.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (8) and organisations (2) via the Consumer Comments facility on the PBS website. The comments emphasised the aggressive nature of the disease, poor prognosis for patients and limited treatment options. The benefits of treatment with nivolumab included longer survival, better disease control, improved quality of life and manageable side effect profile.
- 6.3 The PBAC noted the advice received from Pancare Foundation clarifying the likely use of nivolumab in clinical practice. In addition to similar issues listed in paragraph 6.2, Pancare described oesophageal and gastric cancers as having amongst the worst 5 year survival rates of all cancers in Australia (24% and 28%, respectively). Pancare stated that a PBS listing for nivolumab would enable access to a superior first-line treatment and offer much-needed hope for Australians with gastro-oesophageal cancer. The PBAC noted that this advice was supportive of the evidence provided in the submission.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the nivolumab submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the patients with PD-L1 combined proportion score (CPS)  $\geq 5$  in the CheckMate-649 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for nivolumab, which was limited to 4 (out of a maximum of 5, where 5 and 4

represent the grades with substantial improvement)<sup>2</sup>, based on a comparison with chemotherapy.

- 6.5 The MOGA also expressed its support for the nivolumab submission on the basis of the entire cohort of patients in the CheckMate-649 trial. The PBAC noted that the MOGA presented an ESMO-MCBS for nivolumab, which was limited to 2, based on a comparison with chemotherapy.

### ***Clinical trials***

- 6.6 The submission was based on one pivotal trial, CheckMate 649 (N=1,581 in relevant arms), an ongoing, phase 3, open-label, randomised study of nivolumab plus chemotherapy or nivolumab plus ipilimumab in combination with chemotherapy compared to chemotherapy alone in patients with advanced or metastatic GC, GOJC or OAC. The ESC noted 70% of patients enrolled in CheckMate 649 were diagnosed with GC, 16% had GOJC and 13 % had OAC.
- 6.7 Details of the trials presented in the submission are provided in Table 2.

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<sup>2</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
CheckMate 649 (CM649) NCT02872116	Clinical study report - A Randomized, Multicenter, Open-Label, Phase 3 Study of Nivolumab plus Ipilimumab or Nivolumab in Combination with Oxaliplatin plus Fluoropyrimidine versus Oxaliplatin plus Fluoropyrimidine in Subjects with Previously Untreated Advanced or Metastatic Gastric or Gastroesophageal Junction Cancer Janjigian, Y. Y., et al. Checkmate 649: A randomized, multicenter, open-label, phase 3 study of nivolumab (Nivo) plus ipilimumab (Ipi) versus oxaliplatin plus fluoropyrimidine in patients (Pts) with previously untreated advanced or metastatic gastric (G) or gastroesophageal junction (GEJ) cancer. Moehler, M., et al. 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. Moehler, M. H., et al. CheckMate 649: A randomized, multicenter open-label, phase III study of nivolumab (NIVO) + ipilimumab (IPI) or nivo + chemotherapy (CTX) versus CTX alone in patients with previously untreated advanced (Adv) gastric (G) or gastroesophageal junction (GEJ) cancer. Moehler, M. H., et al. CheckMate 649: A randomized, multicenter, open-label, phase 3 study of nivolumab (nivo) + ipilimumab (ipi) or nivo + chemotherapy (CTX) vs CTX alone in pts with previously untreated advanced (adv) gastric (G) or gastroesophageal junction (GEJ) cancer.	2020  Journal of Clinical Oncology (2017). Conference 35(4 Supplement 1).  Annals of Oncology (2020). 31 (Supplement 4): S1191.  Journal of Clinical Oncology (2018). Conference 36(4 Supplement 1).  Journal of Clinical Oncology (2017). Conference 35(15 Supplement 1).

Source: Table 14, pp33-34 of the submission.

6.8 The submission excluded one trial, ATTRACTION-4 (N=724) for the following applicability reasons:

- The trial was conducted in Asian patients (from Japan, South Korea and Taiwan) with HER2 negative, unresectable advanced or recurrent GC and GOJC;
- The ATTRACTION-4 trial did not include patients with OAC (these are included in the proposed PBS indication);
- Most patients in the intervention and control arm (64.1%) in ATTRACTION-4 received SOX (S-1 + oxaliplatin) as the fluoropyrimidine plus platinum-based chemotherapy backbone in ATTRACTION-4 which is not standard of care in Australia; and
- A higher proportion of patients in ATTRACTION-4 (5.8% and 13%) compared to CheckMate 649 (0.8% and 4.0%) received subsequent (second line) immunotherapy in both the intervention and comparator arm, respectively. Second line immunotherapy is not standard of care in current Australian practice.

6.9 Overall, the evaluation considered the exclusion of ATTRACTION-4 may not be completely justified. While not completely applicable, a proportion of patients enrolled in ATTRACTION-4 may be considered representative of the requested PBS population (based on both cancer diagnosis and chemotherapy regimen) and

therefore can be considered relevant to the current submission. The ESC noted PFS (the primary endpoint) was significantly improved in ATTRACTION-4 (HR=0.68; 98.51% CI=0.51, 0.90; p=0.0007); however, there was no statistically significant differences in OS between patients treated with nivolumab + chemotherapy (SOX or XELOX) compared to chemotherapy alone (SOX or XELOX) after a median of 26.6 months follow up (OS HR = 0.90, 95% CI = 0.75, 1.08, p=0.257). The evaluation considered this suggested that there is potential for the addition of nivolumab to chemotherapy will be less effective in the proposed PBS population than reported in Checkmate 649 in patients with GC and GOJC. The ESC noted the issues raised by the evaluation but, overall, agreed with the submission and considered exclusion of ATTRACTION-4 was reasonable.

6.10 The key features of the CheckMate 649 are summarised in Table 3.

**Table 3: Key features of the included evidence**

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Nivolumab plus chemotherapy versus chemotherapy alone</b>						
CheckMate 649	1,581**	R, DB, MC 12.1 months*	Low	First line	OS, PFS, ORR, EQ-5D	Yes

Source: pp37-50 of the submission

DB = double blind; EQ-5D = EuroQol 5 dimensions; MC = multi-centre; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R = randomised.

\* Median follow-up for overall survival

\*\* CheckMate 649 also included an arm for nivolumab plus ipilimumab. Data from this arm is not included in the submission and the N value does not include these patients.

6.11 The co-primary endpoints of CheckMate 649 were overall survival (OS) and progression-free survival (PFS) in the subgroup of patients who had a PD-L1 CPS  $\geq 5$ . An alpha split using Bonferroni method between the two primary endpoints was applied, with the comparison of OS and PFS between nivolumab plus chemotherapy and chemotherapy in subjects with PD-L1 CPS  $\geq 5$  having alphas of 3% and 2%, respectively.

6.12 The outcomes relevant to the requested restriction, however, were those of the ITT population, and thus OS, PFS and ORR in the ITT population, which were secondary outcomes in CheckMate 649, were presented as the primary evidence in the submission. Using the alpha spending function, the significance level for OS in the ITT population was 0.007 (i.e. could only conclude statistically significant difference in OS in the ITT population if p-value was smaller than 0.007).

6.13 Of note, PFS in the ITT population were not considered in the alpha spending considerations for CheckMate 649. As such, no hypothesis testing of treatment effect for PFS in the ITT population could be conducted, and it was not possible to conclude whether nivolumab plus chemotherapy was superior to chemotherapy alone for the outcome of PFS in the ITT population with statistical significance.

## Comparative effectiveness

6.14 Table 4 presents a summary of the survival outcomes in CheckMate 649 in the ITT population.

**Table 4: Summary of survival outcomes in Checkmate 649, ITT population (provided in submission)**

	Nivolumab + chemotherapy	Chemotherapy	Absolute difference <sup>b</sup>	HR (95% CI) <sup>d</sup>
<b>Progression-free survival<sup>a</sup></b>				
Progressed, n/N (%)	559/789 (70.8%)	557/792 (70.3%)	-	0.77 (0.68, 0.87) (p value not tested) <sup>c</sup>
Median PFS, months (95% CI)	7.66 (7.10, 8.54)	6.93 (6.60, 7.13)	0.73	
<b>Overall survival<sup>a</sup></b>				
Deaths, n/N (%)	544/789 (68.9%)	591/792 (74.6%)	-	<b>0.80 (0.68, 0.94)</b> <b>P=0.0002</b>
Median OS, months (95% CI)	13.83 (12.55, 14.55)	11.56 (10.87, 12.48)	2.27	

Source: Table 26, p56 and Table 27, p59 of the submission.

CI = confidence interval; HR = hazard ratio.

a Based on Kaplan-Meier estimates

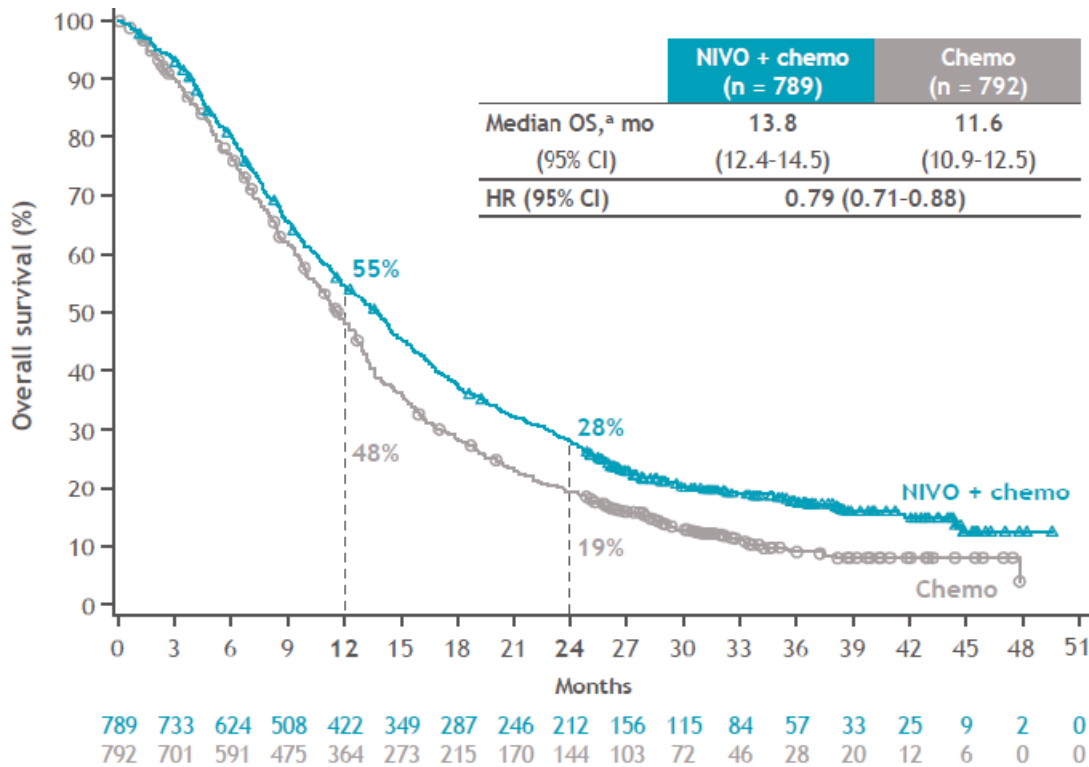
b Calculated ad hoc

c Stratified p-value and hazard ratio. Stratification factors include tumour cell PD-L1 status ( $\geq 1$  vs  $< 1\%$  [including indeterminate]), region (Asia vs North America [United States and Canada] vs ROW), ECOG PS (0 vs 1), chemotherapy (XELOX vs FOLFOX)

Values in bold indicates statistically significant differences

6.15 The results indicated a statistically significant improvement in OS (HR 0.80; CI: 0.68, 0.94) and a median OS gain of 2.27 months associated with nivolumab plus chemotherapy.

Figure 1: Kaplan-Meier plot of overall survival in CheckMate 649 updated data provided in PSCR, ITT population

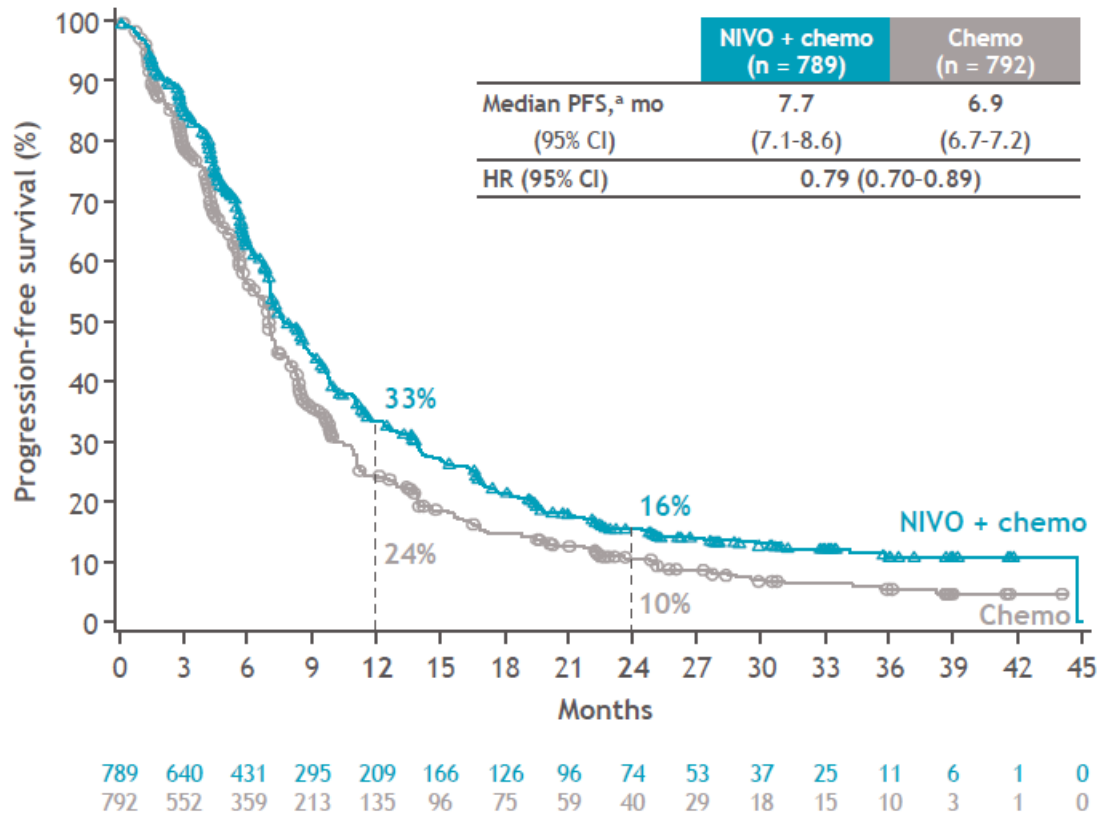


Source: Janjigian 2021, provided with PSCR

6.16 PFS appeared to be improved in patients randomised to nivolumab plus chemotherapy compared to patients randomised to chemotherapy alone as the upper confidence interval of the HR estimate was lower than 1 and the difference in median PFS was 0.73 months. However, a p value for the HR estimate could not be calculated (as described in paragraph 6.13). The Pre-Sub-Committee Response (PSCR) provided additional data for CheckMate 649 which reported a HR for PFS of 0.79 (95% CI, 0.70, 0.89) (Figure 2)<sup>3</sup>.

<sup>3</sup> Janjigian, Y., Ajani, J., Moehler, M., Garrido, M., Gallardo, C., Shen, L., & et al. (2021). Nivolumab plus chemotherapy or ipilimumab vs chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/ esophageal adenocarcinoma: CheckMate 649 study. ESMO Congress, Presentation Number LBA7

Figure 2: Kaplan-Meier plot of overall survival in CheckMate 649 updated data provided in PSCR, ITT population



Source: Janjigian 2021, provided with PSCR

6.17 Table 5 presents the results of overall response rate in CheckMate 649 in the ITT population.

**Table 5: Results of overall response rate in Checkmate 649.**

Analysis population	Nivolumab plus chemotherapy n/N (%) (95% CI) <sup>a</sup>	Chemotherapy n/N (%) (95% CI) <sup>a</sup>	Odds ratio (95% CI) <sup>b,c</sup>	RD (%) (95% CI) <sup>b, c</sup>	P-value <sup>b, d</sup>
ITT	370/789 (46.9%) (43.4, 50.4)	293/792 (37.0%) (33.6, 40.5)	<b>1.50</b> <b>(1.23, 1.83)</b>	<b>12.2%</b> <b>(7.5, 16.8)</b>	<0.0001
ITT patients with measurable disease	350/603 (58.0%) (54.0, 62.0)	280/608 (46.1%) (42.0, 50.1)	<b>1.61</b> <b>(1.28, 2.02)</b>	<b>12.8%</b> <b>(7.3, 18.2)</b>	<0.0001

Source: Table 28, p61 of the submission.

CI = confidence interval; CM649 = CheckMate 649; ITT = intention to treat; n = number of participants reporting data; N = total participants in group; RD = risk difference

a Confirmed complete response or partial response according to RECIST 1.1. CI based on the Clopper and Pearson method.

b Difference in response rate is adjusted for the stratification factors based on the DerSimonian and Laird method. Stratification factors include tumour cell PD-L1 status ( $\geq 1$  vs  $< 1\%$  [including indeterminate]), region (Asia vs North America [United States and Canada] vs ROW), ECOG PS (0 vs 1), chemotherapy (XELOX vs FOLFOX)

c Strata adjusted odds ratio (nivolumab plus chemotherapy over chemotherapy) using Mantel-Haenszel method

d Two-sided p-value from stratified Cochran-Mantel-Haenszel test

Values in bold indicates statistically significant differences

6.18 A higher proportion of patients treated with nivolumab plus chemotherapy achieved a complete or partial response compared with chemotherapy.

6.19 The submission provided descriptive results for the EQ-5D-3L and EQ-5D VAS in CheckMate 649. The submission noted:

- Baseline EQ-5D-3L and EQ-5D VAS were comparable between treatment arms;
- Patients in the nivolumab plus chemotherapy arm had improvement in mean utility index scores for EQ-5D-3L at all treatment assessments after baseline through to Week 103. For the chemotherapy arm, patients had improvements in mean utility index scores at most, but not all, on treatment assessments.
- The nivolumab plus chemotherapy arm exhibited a mean change from baseline at or above the minimal important difference (MID) of  $\geq 0.08$  points (based on a retrospective study of cancer patients by Pickard, Neary, et al., 2007) at three timepoints (Week 91, 97 and 103) compared to just one time point (Week 97) for the patients in the chemotherapy arm. The MID applied were based on a subgroup of patients (n=50) with lung cancer in Pickard, Neary, et al. 2007 (n=534). The submission did not justify why a MID from lung cancer patients were applied to patients with GC, GOJC or OAC;
- The mean EQ-5D VAS scores in all randomised patients improved over time in both arms; and
- Patients in the nivolumab plus chemotherapy arm had a mean change in EQ-5D VAS baseline scores that met or exceeded the MID ( $\geq 7$  points, also based on Pickard, Neary et al 2007) at all time points where there were  $\geq 10$  patients eligible to respond, starting at Week 85. For the chemotherapy arm, the mean change from baseline did not meet or exceed the MID. This means that patients in the nivolumab plus chemotherapy arm more regularly reported clinically meaningful

and important improvements in health related quality of life (HRQoL) than patients in the chemotherapy arm.

- 6.20 The EQ-5D-3L and EQ-5D VAS results reported by the submission do not provide robust evidence to suggest that patients treated with nivolumab plus chemotherapy experienced improvements in HRQoL compared to patients treated with chemotherapy alone, and no formal statistical testing between treatment arms was conducted to support any claims of superiority.
- 6.21 The PBAC noted that based on the data provided in the submission, the median duration of response for patients treated with nivolumab plus chemotherapy was 8.51 months compared to 6.93 months in patients treated with chemotherapy alone.
- 6.22 The submission presented a summary of OS results in patients who had a PD-L1 CPS score of  $\geq 5$ , which was the co-primary endpoint of the trial. Because the submission is requesting a restriction for a population wider than subgroup of patients which informed the primary endpoint of CheckMate 649, the survival results in the complement is presented. Table 6 presents the OS results of CheckMate 649 by CPS  $< 5$  and  $\geq 5$  subgroups.

**Table 6: Results of overall survival in CheckMate 649, randomised patients with PD-L1 CPS  $\geq 5$**

	Nivolumab plus chemotherapy		Chemotherapy		Difference in median <sup>b</sup>	Hazard ratio (95% CI) <sup>c</sup>
	n/N (%)	Median (95% CI) <sup>a</sup>	n/N (%)	Median (95% CI) <sup>a</sup>		
ITT	544/789 (68.9%)	13.83 (12.55, 14.55)	591/792 (74.6%)	11.56 (10.87, 12.48)	2.27	<b>0.80 (0.68, 0.94)</b> <b>P=0.0002</b>
CPS $\geq 5$	309/473 (65.3%)	14.39 (13.11, 16.23)	362/482 (75.1%)	11.10 (10.02, 12.09)	3.29	<b>0.71 (0.59, 0.86)</b> <b>P=&lt;0.0001</b>
CPS $< 5$	228/308 (74.0%)	12.42 (10.61, 14.26)	221/298 (74.2%)	12.25 (10.97, 13.24)	0.17	0.94 (0.78, 1.13)

Source: Table 26, p56, Table 39, p76 of the submission and Table 7.6.2-1, p118 of the CSR.

CI = confidence interval; n = number of participants reporting data; N = total participants in group; OS = overall survival

a Based on Kaplan-Meier estimates

b Calculated ad hoc

c Stratified p-value and hazard ratio. Stratification factors include tumour cell PD-L1 status ( $\geq 1$  vs  $< 1\%$  [including indeterminate]), region (Asia vs North America [United States and Canada] vs ROW), ECOG PS (0 vs 1), chemotherapy (XELOX vs FOLFOX);

Values in bold indicate statistically significant differences. Values in italics indicate extracted during evaluation.

- 6.23 A test for interaction conducted during the evaluation indicated that CPS  $< 5$  was a treatment effect modifier ( $p=0.0374$ ), providing some evidence that patients with CPS  $< 5$  and CPS  $\geq 5$  may have different response to nivolumab plus chemotherapy compared to chemotherapy alone. While it is possible that CheckMate 649 was not powered to detect differences between patients with CPS  $< 5$  and CPS  $\geq 5$ , there may be some biological plausibility to explain this relationship as higher PD-L1 expression may be correlated with higher efficacy, though it is noted that currently none of the PBS indications for nivolumab include a PD-L1 status criteria. Overall, the evaluation considered there may be a plausible clinical basis for restricting the use of nivolumab plus chemotherapy to patients with PD-L1 CPS  $\geq 5$  (which would require a codependent submission). Based on the data in Table 6, it may not be appropriate to expose patients

with CPS <5 to nivolumab plus chemotherapy, which has inferior safety, when they may not derive any clinical benefit. The PSCR stated that PD-L1 CPS may inform how well immunotherapy might work but not if it will work and the decision to treat patients with immunotherapy should not be determined by PD-L1 CPS status.

- 6.24 Additionally, no reliable PD-L1 CPS distribution in the Australian population was provided. If the proportion of patients with CPS  $\geq 5$  in the general population were lower than in CheckMate 649 (60%), then the overall OS benefit in the general population may be lower than reported in CheckMate 649. The PSCR stated there is no evidence to suggest that PD-L1 CPS distribution in Australia would be different to the ITT population seen in CheckMate 649. The PSCR stated Australian clinicians consulted by in preparing the submission agreed that the patient demographics seen in CheckMate 649 were broadly comparable to the Australian treatment landscape. The ESC noted the proportion of patients with PD-L1 CPS  $\geq 5$  in CheckMate 649 in Asian (25% of ITT population) and White (60% of ITT population) patients was consistent (60.8% and 59.7%, respectively). The ESC considered this may provide support that the distribution of CPS levels in CheckMate 649 reflects the distribution in the Australian population. The pre-PBAC response provided information on the proportion of Australian patients in CheckMate 649 that had PD-L1 CPS  $\geq 5$  and stated that because it was similar to that observed in the study, it supported that a similar OS benefit might be observed in the PBS population.

### ***Comparative harms***

- 6.25 Table 7 presents an overview of adverse events reported in CheckMate 649.

**Table 7: Overview of adverse events in CheckMate, Safety population**

Adverse event	Number of patients (%)		Risk difference (95% CI)
	Nivolumab plus chemotherapy (N=782)	Chemotherapy (N=767)	
Total number of patients with at least one AE	776 (99.2%)	752 (98.0%)	0.01 (0.00, 0.02)
Grade 3/4 AE	540 (69.1%)	456 (59.5%)	0.10 (0.05, 0.14)
Grade 5 AE*	81 (10.4%)	63 (8.2%)	0.02 (-0.01, 0.05)
AEs related to any treatment	738 (94.4%)	679 (88.5%)	0.06 (0.03, 0.09)
Treatment-related Grade 3/4 AE	462 (59.1%)	341 (44.5%)	0.15 (0.10, 0.20)
Treatment-related Grade 5 AE <sup>a</sup>	4 (0.5%)	0 (0.0%)	0.01 (-0.00, 0.01)
SAE	423 (54.1%)	335 (43.7%)	0.10 (0.05, 0.15)
Grade 3/4	281 (35.9%)	229 (29.9%)	0.06 (0.01, 0.11)
Treatment-related SAE	172 (22.0%)	93 (12.1%)	0.10 (0.06, 0.14)
Grade 3/4	131 (16.8%)	77 (10.0%)	0.07 (0.03, 0.10)
AE leading to discontinuation from any study treatment	371 (47.4%)	251 (32.7%)	0.15 (0.10, 0.20)
Grade 3/4	194 (24.8%)	113 (14.7%)	0.10 (0.06, 0.14)
Treatment-related AE leading to discontinuation from any study treatment	284 (36.3%)	181 (23.6%)	0.13 (0.08, 0.17)
Grade 3/4	132 (16.9%)	67 (8.7%)	0.08 (0.05, 0.11)
Specific AEs			
Number of patients with at least 1 AE	540 (69.1%)	456 (59.5%)	0.10 (0.05, 0.14)
Nervous system disorders	94 (12.0%)	65 (8.5%)	0.04 (0.01, 0.07)
Investigations	213 (27.2%)	150 (19.6%)	0.08 (0.03, 0.12)
Lipase increased	55 (7.0%)	28 (3.7%)	0.03 (0.01, 0.06)
Amylase increased	24 (3.1%)	3 (0.4%)	0.03 (0.01, 0.04)
Blood and lymphatic system disorders	230 (29.4%)	167 (21.8%)	0.08 (0.03, 0.12)
Anaemia	86 (11.0%)	56 (7.3%)	0.04 (0.01, 0.07)
Infections and infestations	68 (8.7%)	39 (5.1%)	0.04 (0.01, 0.06)

Source: Table 30, p66 of the submission.

AE = adverse events; CI = confidence interval; CM649 = CheckMate 649; N = total participants in group; SAE = serious adverse events

a There were 4 Grade 5 events in the nivolumab plus chemotherapy arm, 1 case each of cerebrovascular accident, febrile neutropenia, gastrointestinal inflammation and pneumonia

b Per investigator assessment, in the nivolumab plus chemotherapy 7 deaths were due to chemotherapy, 3 deaths were due to nivolumab and 2 deaths were due to nivolumab plus chemotherapy

c Per investigator assessment, in the nivolumab plus chemotherapy, 4 deaths were reported as related to nivolumab

\* The grade 5 adverse events presented in the submission could not be verified in the CSR tables.

Values in italics signify that the analyses were conducted during the evaluation.

6.26 Nivolumab plus chemotherapy was associated with higher rates of serious adverse events, severe adverse events, events leading to discontinuation, as well as several specific adverse events, including laboratory anomalies, anaemia, infections and infestations, and nervous system disorders.

### **Benefits/harms**

6.27 A summary of the comparative benefits and harms for nivolumab plus chemotherapy versus chemotherapy alone is presented in Table 8.

**Table 8: Summary of comparative benefits and harms for nivolumab plus chemotherapy versus chemotherapy**

	Nivo + chemo n/N (%) <sup>a</sup>	Chemo alone n/N (%) <sup>a</sup>	Absolute difference <sup>b</sup>		HR (95% CI) <sup>d</sup>
<b>Progression-free survival</b>					
Progressed, n (%)	559/789 (70.8%)	557/792 (70.3%)	-		0.77 (0.68, 0.87) (p value not tested) <sup>c</sup>
Median PFS, months (95% CI)	7.66 (7.10, 8.54)	6.93 (6.60, 7.13)	0.73		-
<b>Overall survival</b>					
Deaths, n/N (%)	544/789 (68.9%)	591/792 (74.6%)	-		0.80 (0.68, 0.94) P=0.0002
Median months OS (95% CI)	13.83 (12.55, 14.55)	11.56 (10.87, 12.48)	2.27		-
Proportion alive at 12 months	55%	48%	7%		-
<b>Harms</b>					
Adverse event	Number of patients (%)		Event rate/ 100 patients <sup>*</sup>		Risk difference (95% CI)
	Nivo + chemo (N=782)	Chemo alone (N=767)	Nivo + chemo	Chemo alone	
Treatment-related Grade 3/4 AE	462 (59.1%)	341 (44.5%)	59	45	0.15 (0.10, 0.20)
Nervous system disorders	94 (12.0%)	65 (8.5%)	12	9	0.04 (0.01, 0.07)
Blood and lymphatic system disorders	230 (29.4%)	167 (21.8%)	29	22	0.08 (0.03, 0.12)
Anaemia	86 (11.0%)	56 (7.3%)	11	7	0.04 (0.01, 0.07)
Infections and infestations	68 (8.7%)	39 (5.1%)	9	5	0.04 (0.01, 0.06)

Source: Table 26, p56, Table 27, p59 and Table 30, p66 of the submission.

AE = adverse events; Chemo = chemotherapy, CI= confidence interval; HR = hazard ratio; N = total participants in group; Nivo = nivolumab, SAE = serious adverse events

a Based on Kaplan-Meier estimates

b Calculated ad hoc

c Stratified p-value and hazard ratio. Stratification factors include tumour cell PD-L1 status ( $\geq 1$  vs  $< 1\%$  [including indeterminate]), region (Asia vs North America [United States and Canada] vs ROW), ECOG PS (0 vs 1), chemotherapy (XELOX vs FOLFOX)

\* Median duration of follow-up: of 12.1 months

Values in italics signify that the analyses were conducted during the evaluation.

6.28 On the basis of the CheckMate 649 trial presented by the submission, for every 100 patients treated with nivolumab plus chemotherapy instead of chemotherapy alone for a median duration of 12.1 months:

- 7 more patients were alive at 12 months.

6.29 On the basis of the CheckMate 649 trial presented by the submission, for every 100 patients treated with nivolumab plus chemotherapy in comparison with chemotherapy alone, over a median duration of follow-up of 12.1 months:

- Approximately 15 additional patients would experience a severe or life threatening or disabling adverse event (Grade 3 or 4);
- Approximately 4 additional patients would experience a nervous system disorder;
- Approximately 8 additional patients would experience a blood or lymphatic system disorder;
- Approximately 4 additional patients would experience anaemia; and

- Approximately 4 additional patients would experience an infection or infestation.

### **Clinical claim**

- 6.30 The submission described first line treatment with nivolumab in combination with chemotherapy as superior in terms of effectiveness compared with chemotherapy alone and inferior in terms of safety compared to chemotherapy alone in patients with non-HER2 positive advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma.
- 6.31 The submission also stated that treatment with nivolumab plus chemotherapy is also associated with improvements in patient reported outcomes (PROs), specifically a clinically meaningful delay in the deterioration of disease-related symptoms while maintaining health related quality of life (HRQoL) compared to chemotherapy. The PBAC noted patients treated with nivolumab plus chemotherapy had a decreased risk of time to symptom deterioration compared to the chemotherapy alone group while on treatment (HR 0.77, 95% CI: 0.63, 0.95).
- 6.32 The evaluation considered the submission's claim of superior efficacy may not be adequately supported in all patients and may require further consideration as:
- The submission is requesting a listing for all patients irrespective of PD-L1 CPS status. However, in CheckMate 649, a test for interaction conducted during the evaluation indicated that CPS  $\geq 5$  was a treatment effect modifier ( $p=0.0374$ ), with nivolumab + chemotherapy being statistically significantly more effective compared to chemotherapy in patients with CPS  $\geq 5$  (OS HR = 0.71, 95% CI 0.59, 0.86) but not in patients with CPS  $< 5$  (OS HR = 0.94, 95% CI 0.78, 1.13). While it is acknowledged that the trial may not be powered to detect such differences, consideration as to whether restricting treatment to patients with PD-L1 CPS  $\geq 5$  may be prudent. No reliable PD-L1 distribution in the Australian population has been discussed. If the proportion of patients with CPS  $\geq 5$  in the general population were lower than in CheckMate 649 (60%), then the overall OS benefit in the general population may be lower than reported in CheckMate 649; and
- 6.33 The submission's claim that nivolumab plus chemotherapy was associated with improvements in PROs may not be reasonable. These outcomes were generally exploratory outcomes, and consequently, improvements in quality of life cannot reasonably be claimed. Specifically, the basis of the claim regarding the EQ-5D-3L results (included in the model) was that there were clinically meaningful improvements from baseline to study week in question in slightly more instances with the nivolumab plus chemotherapy group compared to chemotherapy alone. This is neither statistically robust, nor an inherently valid comparison.
- 6.34 The PBAC agreed with the ESC that the submission's claim of superior effectiveness was likely to be reasonable and noted a median incremental OS benefit of 2.3 months

was clinically meaningful in view of the poor prognosis in this patient population. The PBAC considered the magnitude of the clinical benefit in the Australian population that would be treated with nivolumab is uncertain due to the proportion of patients with PD-L1 CPS <5/≥5 being unknown for the Australian population.

- 6.35 The PBAC agreed with the ESC that the submission’s claim of inferior but manageable safety was reasonable.

### **Economic analysis**

- 6.36 The submission presented a cost-utility analysis. Table 9 presents a summary of the model structure, key inputs and rationale.

**Table 9: Summary of model structure, key inputs and rationale**

<b>Component</b>	<b>Summary</b>
Treatments	Nivolumab plus chemotherapy versus chemotherapy
Time horizon	7.5 years based on a median of 12.1 months of overall survival follow up
Outcomes	LYG, QALY
Methods used to generate results	Partitioned survival model
Health states	Progression free, progressed, dead
Cycle length	1 week
Allocation to health states	Based on PFS and OS from CheckMate 649.
Extrapolation method	Parametric extrapolation was used for OS, PFS and time on treatment. OS, PFS were extrapolated using a log-logistic model for nivolumab plus chemotherapy Time on treatment was extrapolated using a Weibull model. OS, PFS and time on treatment were extrapolated using a Weibull model for chemotherapy. The Weibull model was not the best fitting model for OS and PFS in chemotherapy. Changing the selection to log-logistic (the best fitting model) increased the ICER substantially. No convergence in survival was assumed. The overall survival continues to diverge beyond KM data. The submission considered that this is reasonable based on a survival plateauing affect observed for nivolumab in other indications. 26% of incremental costs but 90% of the incremental gains occur during the extrapolated period.
Health related quality of life	Trial -based, treatment-specific utility values for progression free and progressed health states of 0.812 and 0.746, respectively, for nivolumab plus chemotherapy and of 0.798 and 0.721, respectively, for chemotherapy.
Inclusion of terminal care costs	Terminal care costs based on Langton (2016) (\$38,057.49). Estimate not specific to gastric cancer patients. May not be reflective of requested population, highly linked to extrapolation of overall survival benefit. May not be reasonable to include terminal care costs where survival is not expected to surpass the modelled time horizon.

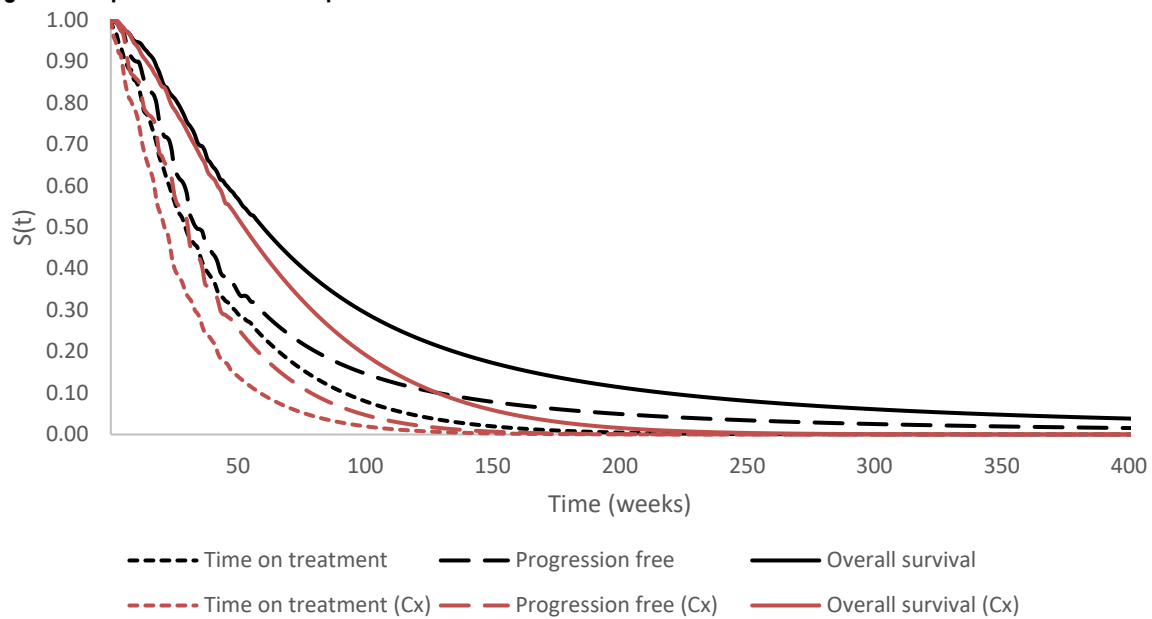
Source: pp86-112 of the submission. ICER = incremental cost-effectiveness ratio; KM= Kaplan-Meier LYG – life year gained; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year

- 6.37 The submission presented a partitioned survival model with three health states: progression free, progressed and dead. The proportion of patients in the progression free health state and the dead health state were determined by the PFS and OS curves from CheckMate 649, respectively. The post-progression/progressed disease survival health state was estimated as the difference between the PFS and OS curves.

Treatment costs were estimated separately based on the time to discontinuation (TTD) of trial interventions in CheckMate 649. The treatment costs were further adjusted by the relative dose intensity used during the trial.

- 6.38 The submission stated that the time horizon of 7.5 years was based on NICE evaluations. The submission’s advisory board considered that few patients in the requested population (10-20%) survive longer than 2 years, acknowledging that there are always outliers who survive longer, which may be due to the natural history of the disease rather than the treatment, suggesting that even a 5 year time horizon may be too long. The ESC considered a 7.5 year time horizon may be optimistic for this population. The pre-PBAC response disagreed with a 5 year time horizon as this will lead to a likely underestimation of the benefit of nivolumab and was inconsistent with previous PBAC recommendations across a number of indications (including mismatch repair deficient colorectal cancer, urothelial cancer, hepatocellular cancer, and primary mediastinal B-cell lymphoma).
- 6.39 Figure 3 presents the extrapolation applied in the model for OS, PFS and TTD for the nivolumab plus chemotherapy and chemotherapy alone arms.

Figure 3: Kaplan-Meier and Extrapolated outcomes in economic model



Source: Figure 23, p112 of the submission.

Cx = comparator

Extrapolation applied at 57 weeks for nivolumab plus chemotherapy and 48 weeks for chemotherapy alone

- 6.40 The base case chosen for the extrapolation of OS for nivolumab plus chemotherapy was the log-logistic function. Log-logistic was one of the most optimistic extrapolations for OS, estimating a higher proportion of patients surviving over time. The magnitude of the difference in both AIC and BIC for all functional forms was

relatively minor, and this was supported visually as all functional forms appeared to match the observed KM curve reasonably.

- 6.41 The submission argued that long-term OS data for nivolumab monotherapy in other cancers (melanoma, renal cell carcinoma, non-small cell lung cancer and squamous cell carcinoma of the head and neck) provides evidence that immunotherapies provide durable survival for some patients with a plateau in survival at approximately 36-48 months and significant improvements on standard of care survival rates. It may not have been reasonable to compare survival for nivolumab monotherapy in other cancers to nivolumab plus chemotherapy in GC, GOJC and OAC. The assumption of a plateau was not reflective of the trial evidence provided. Visual inspection of the OS KM curves (Figure 1) did not suggest any plateau that was not also observed in the chemotherapy arm (the tails of the KM data in both arms are also based on small patient numbers). Additionally, it may be unreasonable to assume that expected survival functions from other cancers can be applied to GC, GOJC and OAC.
- 6.42 The submission's base case modelled survival between treatment arms continued to diverge over time (this can be observed visually in Figure 3 which was not based on clinical evidence but rather an assumption that the survival curve in patients treated with nivolumab plus chemotherapy would plateau but this would not occur in patients treated with chemotherapy alone. This assumption likely overestimated the survival gain associated with nivolumab plus chemotherapy.
- 6.43 The base case chosen for the extrapolation of OS for chemotherapy alone was the Weibull function. Comparison of the extrapolated survival estimates for patients treated with chemotherapy alone at five years (0.3% remained alive) with real world data reported by the US Surveillance, Epidemiology and End Results program (SEER) for distant metastatic GC (6% five-year survival) and distant metastatic oesophageal cancer (5% five-year survival) suggested that the model substantially underestimated survival in the chemotherapy alone arm, which favoured nivolumab plus chemotherapy. Instead of the Weibull function, using a log-logistic function to extrapolate survival for chemotherapy alone resulted in a five-year survival of 4.7%, and increased the ICER by 73% from the base case. The PSCR and pre-PBAC response maintained that the application of a log-logistic extrapolation function for the chemotherapy arm is clinically implausible and does not match the known long-term survival of patients with metastatic gastric cancer treated with standard chemotherapies. The PSCR stated the impact of employing this assumption is to inappropriately bias the economic evaluation against nivolumab plus chemotherapy. The ESC noted using the best fit extrapolation for the chemotherapy treatment arm appeared to result in a more reasonable proportion of patients alive at 5 years. The PBAC agreed with the pre-PBAC response that a log-logistic extrapolation function for the chemotherapy arm may not be reasonable, that other extrapolations also fitted

- the curve, and so considered the appropriate extrapolation function remained uncertain.
- 6.44 The submission stated the model used treatment-specific utilities because the submission considered that the results of CheckMate 649 demonstrate that patients treated with nivolumab plus chemotherapy are generally healthier because the treatment is more efficacious than chemotherapy alone. As discussed in paragraphs 6.20 and 6.33, this may not have been adequately supported by the trial data. The submission also does not model disutility from adverse events separately, which may favour nivolumab plus chemotherapy as it has an inferior safety profile.
- 6.45 The incremental utility benefit applied to the nivolumab plus chemotherapy arm was independent of whether patients remained on treatment, and was simply dependent on whether they were in the nivolumab plus chemotherapy arm or chemotherapy arm, which was implausible as this suggests that patients would simply have a higher quality of life simply because nivolumab was available. Overall, it may not be reasonable to assume a differential utility based on which treatment was administered. The ESC considered the use of treatment-specific utilities was not adequately justified. The ESC noted the EQ-5D-3L and EQ-5D VAS results reported in Checkmate 649 do not provide robust evidence to suggest there would be differences in HRQoL between patients in the progression-free health state treated with nivolumab plus chemotherapy or chemotherapy alone. The ESC noted assuming the same utilities applied to both treatment arms (averaged from both treatments, 0.805 for progression free and 0.735 for progressed) increased the ICER by 7% from \$55,000 to < \$75,000/QALY to \$75,000 to < \$95,000/QALY. The pre-PBAC response stated that patients treated with nivolumab (with or without chemotherapy) have consistently shown higher preference-based QoL measures compared to chemotherapy in well controlled randomised trials. The pre-PBAC response stated this is likely due to nivolumab's ability to treat the patient's underlying cancer more effectively than chemotherapy alone, thereby reducing the burden of disease and improving nivolumab-treated patients' QoL. The pre-PBAC response maintained treatment-specific utility values were appropriate.
- 6.46 The submission applied terminal care costs of approximately \$38,058 (from Langton 2016 converted to 2021 prices) to the death state in the model. Langton 2016 was a retrospective analysis of claims data in two groups of elderly Australians diagnosed with cancer (those who died of cancer and those who died from non-cancer causes). Langton estimated that elderly patients with cancer who died of cancer accrued \$30,001 of costs in the last six months of life. Given that few patients would be expected to survive beyond 7.5 years, and there is no indication-specific clinical evidence to support that nivolumab plus chemotherapy would improve survival at such a long term, it is likely more reasonable to assume that there would be no difference in terminal care costs between the treatment arms. Moreover, it is likely

that treatment with nivolumab plus chemotherapy delays, rather than prevents, incurring terminal care costs in the proposed PBS population. The ESC noted the impact of including terminal care costs on the ICER is driven by the difference in surviving proportions at the end of the model time horizon but ultimately this cost should accrue to all patients in both treatment arms. The ESC noted the terminal care cost was based on data collected in the 6 months prior to death and considered this may result in double counting as some of these costs would have accrued in the progressed health state. Excluding terminal care costs increased the ICER by 7% from \$55,000 to < \$75,000/QALY to \$75,000 to < \$95,000/QALY. The pre-PBAC response argued the extent of double counting of terminal care costs and costs accrued in the progressed health care state is likely to be modest and can only be a maximum of ~\$1,280 (i.e. 6 months of disease management costs) or around 3.4% of the total death cost. Therefore, the ICER generated by the model (\$55,000 to < \$75,000 per QALY) is likely to be a much more precise estimate of the true ICER than an analysis where terminal care costs are entirely removed (\$75,000 to < \$95,000 per QALY). The pre-PBAC response stated the ICER generated by the base case model is likely to be a much more precise estimate of the true ICER than an analysis where terminal care costs are entirely removed and strongly believed terminal care costs should not be excluded.

6.47 Key drivers of the model are presented Table 10.

**Table 10: Key drivers of the model**

Description	Method/Value	Impact
		Base case: ██████ <sup>1</sup> /QALY gained.
Extrapolation	Use of log-logistic methods to extrapolate OS and PFS in nivolumab plus chemotherapy and Weibull for the OS and PFS of chemotherapy and time on treatment for both arms. This was applied at 57 weeks in the nivolumab plus chemotherapy arm and 48 weeks in the chemotherapy arm based on median follow -up.	High, favours nivolumab plus chemotherapy. Switching extrapolation of OS and PFS in chemotherapy arm to log-logistic increased the ICER to ██████ <sup>2</sup> /QALY gained.
Time horizon	7.5 years, extrapolated from a median trial follow up of 12.1 months for overall survival	Moderate, favours nivolumab plus chemotherapy. Shortening the time horizon to 5 years increased the ICER to ██████ <sup>3</sup>

Source: pp Source: pp86-112 of the submission.

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$115,000 to < \$135,000

<sup>3</sup> \$75,000 to < \$95,000

6.48 Results of the stepped economic analysis are presented in Table 11. The results of Step 1 could not be verified during the evaluation. Results from the evaluation attempting to verify Step 1 are presented in the table. It appeared that the 36-month time horizon in step 1 was based on the maximum treatment duration of the nivolumab plus ipilimumab arm of CheckMate 649. This was inconsistent with the KM data included in the model.

**Table 11: Results of the stepped economic evaluation**

Step and component	Nivolumab plus chemotherapy	Chemotherapy	Increment
<b>Step 1: trial-based costs and outcomes (cost per LY – 36.0-month time horizon)</b>			
Costs (\$)		\$43,714.99	
LYG	1.317	1.140	0.177
Incremental cost/extra LYG gained			
<b>Step 1: trial-based costs and outcomes (cost per LY – 36-month time horizon) -- evaluation</b>			
Costs (\$)		\$45,785.05	
LYG	1.333	1.119	0.214
Incremental cost/extra LYG gained			
<b>Step 2: time horizon extended to 7.5-year time horizon</b>			
Costs (\$)		\$47,402.05	
LYG	1.617	1.148	0.470
Incremental cost/extra LYG gained			
<b>Step 3: Transformation to QALYs</b>			
Costs (\$)		\$47,402.05	
QALY	1.276	0.881	0.395
Incremental cost/extra QALY gained			

Source: Table 62, pp114-115 of the submission.

ICER = incremental cost effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year

The redacted values correspond to the following ranges:

<sup>1</sup> \$155,000 to < \$255,000

<sup>2</sup> \$115,000 to < \$135,000

<sup>3</sup> \$55,000 to < \$75,000

6.49 The results of key sensitivity analyses of the model are summarised in Table 12.

**Table 12: Results of key sensitivity analyses of economic model**

Analyses	Incremental cost (\$)	Incremental QALY	ICER	Percent change
Base-case		0.395		-
Time horizon decreased from 7.5 to 5 years		0.317		19%
Treatment arm utility at parity		0.370		7%
Change OS function in Nivo + Chemo to Weibull - same as chemo only (base case log-logistic)		0.202		101%
Change OS function in chemo only to log-logistic – same as nivo + chemo (base case Weibull)		0.232		73%
Model run using best fit according to AIC and BIC (PFS and OS in chemotherapy arm =log-logistic)		0.222		80%
Remove terminal care costs		0.395		7%
<b>Multivariate sensitivity analyses</b>				
Model run using best fit according to AIC and BIC and remove terminal care costs and remove treatment specific utilities		0.195		111%
Model run using best fit according to AIC and BIC and remove terminal care costs, remove treatment specific utilities and time horizon 5 years		0.166		147%

Source: Table 67, pp117-119

AE = adverse events; AIC = Akaike information criterion; BIC = Bayesian information criterion; BSA = body surface area; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

<sup>2</sup> \$75,000 to < \$95,000

<sup>3</sup> \$135,000 to < \$155,000

<sup>4</sup> \$115,000 to < \$135,000

<sup>5</sup> \$155,000 to < \$255,000

- 6.50 The sensitivity analyses presented demonstrate the ICER was highly sensitive to the extrapolation method for OS. Use of different extrapolation methods resulted in an ICER which was more than double the base case ICER. Moreover, as discussed in paragraph 6.32, the survival benefit reported in the clinical trial (and applied to the economic model) may be greater than what may be experienced by the proposed PBS population which may have a lower proportion of patients with CPS  $\geq 5$ , when combined with the modest OS gain in CheckMate 649, also suggests that the OS benefit estimated by the model may be overestimated.
- 6.51 The model was also sensitive (but to a much smaller degree) to the time horizon assumption and to the assumption of differential utility between treatment arms which may not be justified.
- 6.52 The ESC noted a multivariate analysis (i) using a log-logistic extrapolation function for chemotherapy alone (ii) assuming the same utilities applied to both treatment arms (0.805 for progression free, 0.735 for progressed disease) (iii) removing terminal care and (iv) a time horizon of 5 years increased the ICER from \$55,000 to < \$75,000/ QALY to \$155,000 to < \$255,000/ QALY and considered this may be a more reasonable base case.

**Drug cost/patient/course \$ [REDACTED] to \$ [REDACTED]**

- 6.53 The submission calculated average cost per patient per course of nivolumab plus chemotherapy by calculating a cost per mg (based on weighted private/ public dispensed price) and total number of mg dispensed for each component of nivolumab plus chemotherapy (based on time on treatment frequency of dosing and dose per administration). Each component was added together and a weighted average for FOLFOX and XELOX regimens was calculated.
- 6.54 During the evaluation, drug costs were calculated as costs per cycle and number of cycles and is presented in Table 13. The following differences between the drug costs as estimated using information from the CheckMate 649 trial, in the economic model and the financial estimates were noted:
- The financial estimates and economic evaluation assumed an 80%/20% FOLFOX to XELOX split based on advice from the expert advisory board. CheckMate 649 had an approximately even split between FOLFOX and XELOX. Altering the relative use of FOLFOX to XELOX had a minimal impact on the ICER and financial estimates;
  - The base case of the economic model assumed no vial sharing of chemotherapy, therefore the doses of chemotherapy were higher than the financial estimates which used precise doses for chemotherapy; and

- Treatment duration. The cumulative dose in the trial was lower in the trial for each of the individual agents than in the economic evaluation this was a result of shorter estimated treatment duration over the trial period than the seven and a half year time horizon.

Table 13: Drug per patient drug cost of nivolumab plus chemotherapy

	Cost per cycle (\$)			Number of cycles			Total cost per course (\$)		
	Model*	CM649	Financials (weighted DPMQ)	Model **	CM-649	Financial (number of scripts)	Model	CM649	Financials
<b>Nivolumab plus chemotherapy</b>									
Nivolumab plus FOLFOX									
Nivolumab				20.6	17.17	17.74			
Oxaliplatin	\$51.89	\$115.14	\$142.82		9.37	8.85	\$1,068.67	\$1,078.86	\$1,263.96
Leucovorin	\$21.61	\$31.59	\$24.71		14.67	13.43	\$445.06	\$463.43	\$331.86
Fluorouracil	\$81.65	\$120.09	\$117.98		13.92	13.35	\$1,681.58	\$1,671.65	\$1,575.02
Fluorouracil cont.	\$95.84	\$124.61	\$128.08		15.25	15.1	\$1,973.82	\$1,900.30	\$1,933.95
Subtotal									
Nivolumab plus XELOX									
Nivolumab				13.73	11.36	12.37			
Oxaliplatin	\$80.16	\$172.71	\$158.56		6.48	6.13	\$1,100.60	\$1,119.15	\$971.98
Capecitabine	\$51.26	\$65.35	\$79.21		10.88	8.52	\$703.80	\$710.99	\$674.87
Subtotal -									
<b>Total (weighted)</b>									
<b>Chemotherapy alone</b>									
FOLFOX									
Oxaliplatin	\$72.61	\$115.14	\$142.82	13.98	9.37	8.7	\$1,015.09	\$1,078.85	\$1,242.54
Leucovorin	\$25.85	\$31.59	\$24.71		12.15	11.29	\$361.38	\$383.82	\$278.98
Fluorouracil	\$97.81	\$120.09	\$117.98		11.67	11.23	\$1,367.38	\$1,401.45	\$1,324.90
Fluorouracil cont.	\$110.38	\$124.61	\$128.08		12.32	12.22	\$1,543.11	\$1,535.19	\$1,565.09
Subtotal						\$4,286.97	\$4,399.30	\$4,411.52	
XELOX									
Oxaliplatin	\$99.52	\$172.71	\$158.56	9.32	6.7	5.38	\$927.53	\$1,157.14	\$853.06
Capecitabine	\$52.41	\$65.35	\$79.21		9.27	6.16	\$488.46	\$605.78	\$487.9336
Subtotal						\$1,415.99	\$1,762.92	\$1,340.99	
<b>Total (weighted)</b>							<b>\$3,712.77</b>	<b>\$3,158.36</b>	<b>\$3,797.41</b>

Source: Table 61, p114 of the submission, Table 6.1.1-1, pp61-63 of the CSR, attached spreadsheet of financial estimates.

DPMQ = dispensed price per maximum quantity; mg = milligram

\* Adjusted for dose intensity and relative time on treatment

\*\* Calculated by area under the curve and divided by the length of each cycle (2 weeks for FOLFOX and 3 weeks for XELOX based regimens)

FOLFOX XELOX weighting was calculated as:

80%:20% FOLFOX XELOX split in economic and financial analyses

\*\*\*53.96%:46.04% FOLFOX XELOX in the nivolumab plus chemotherapy arm of CheckMate 649

52.93%: 47.07% FOLFOX XELOX split in the chemotherapy alone arm of CheckMate 649

### Estimated PBS usage & financial implications

6.55 This submission was not be considered by DUSC. The submission took an epidemiological approach to estimating use and financial implications.

6.56 Table 14 presents key inputs applied in the utilisation and financial estimates.

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**Table 14: Key inputs applied in the utilisation and financial estimates**

Data	Value	Source	Comment
<b>Eligible population</b>			
Persons diagnosed with GC or GOJC:	2,246	AIHW 2020 estimate (Cancer Australia, 2020b)	These estimates were based on incident cases.
Persons diagnosed with OC:	1,587	AIHW 2020 estimate (Cancer Australia, 2020a)	
Population growth rate:	1.3%	(Australian Bureau of Statistics, 2020)	Data from Cancer Australia (2020) suggests that age standardised GC rates have been decreasing over several decades. Age standardised rates of OC is more difficult to generalise with an increasing trend in males and a decreasing trend in females, but a broadly consistent age-standardised rate on average. It was thus unclear if applying a population growth rate is appropriate and might have led to an overestimated incidence.
Proportion with AC histology:	GC and GOJC: 84.08% OAC: 53.53%	(Australian Institute of Health and Welfare, 2021a)	Reasonable.
Proportion diagnosed with advanced or metastatic disease	75%	Advisory board	This is essentially an assumption, with estimates in the identified literature being higher. An Australian review on management of advanced GC reported in the Western world, suggested that 80 to 90% of patients are ultimately diagnosed at an advanced stage when the tumour is inoperable (Price 2012; Wagner 2017). An audit of the South Australian Upper GI Cancer Database was conducted on patients with oesophageal cancer which also revealed 84% of patients presented with advanced or metastatic disease (Stages II, III and IV) (Nguyen 2019) The model is sensitive to this assumption, but it may not be unreasonable.
Proportion of patients who are non-HER2 positive:	86.10%	(Kumarasinghe et al., 2017) with validation from Advisory board	
Proportion of patients with ECOG performance status score of 0 or 1	74.75%	(Ma et al., 2020) and (Hall JP, Khela K, Bertwistle D, 2020) with validation from Advisory board	
Proportion of patients electing treatment:	█%	Advisory board	This may be an overestimate. The Advisors indicated between 10% to 30% of patients did not receive chemotherapy. There are some patients who were too old, had comorbidities/organ dysfunction or were too frail to receive chemotherapy. It would be expected that these patients were unlikely to have a PS of 0 or 1. However, an increase in proportion electing treatment may represent market growth due to availability of nivolumab, though not estimating market growth separately will overestimate chemotherapy substituted for and cost offsets.

Source: Table 70, p126 of the submission.

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AC = adenocarcinoma; AIHW = Australian Institute of Health and Welfare; CSR = clinical study report; DOT = duration of therapy; ECOG = Eastern Cooperative Oncology Group; GC = gastric cancer; GOJC = gastro-oesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; OAC = oesophageal adenocarcinoma; OC = oesophageal cancer; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

6.57 Table 15 presents the estimated use and financial implications in the submission.

**Table 15: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>
<b>Estimated number of scripts</b>						
<b>Nivolumab plus FOLFOX Q2W</b>						
Nivolumab 240 mg	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>
Oxaliplatin 150 mg	8,534	8,640	8,754	8,869	8,986	9,098
Folinic acid 704 mg	12,958	13,118	13,291	13,466	13,644	13,813
Fluorouracil 704 mg	12,877	13,036	13,208	13,382	13,559	13,727
Fluorouracil continuous 2,113 mg	29,134	29,494	29,883	30,278	30,677	31,058
<b>Nivolumab plus XELOX Q3W</b>						
Nivolumab 360 mg	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>
Oxaliplatin 229 mg	1,479	1,497	1,517	1,537	1,557	1,576
Capecitabine 500 mg x 120	2,054	2,079	2,107	2,135	2,163	2,190
<b>Estimated financial implications of nivolumab plus chemotherapy</b>						
Cost to PBS/RPBS less copayments, nivolumab	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>
Cost to PBS/RPBS less copayments, chemotherapy	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>4</sup>
Cost to PBS/RPBS less copayments, nivolumab plus chemotherapy	■ <sup>5</sup>	■ <sup>5</sup>	■ <sup>5</sup>	■ <sup>5</sup>	■ <sup>5</sup>	■ <sup>5</sup>
<b>Estimated financial implications for chemotherapy not used</b>						
Cost to PBS/RPBS less copayments	-■ <sup>4</sup>	-■ <sup>4</sup>	-■ <sup>4</sup>	-■ <sup>4</sup>	-■ <sup>4</sup>	-■ <sup>4</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>
Net cost to MBS	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>4</sup>	■ <sup>4</sup>
Net cost to PBS/RPBS/MBS Australia	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>3</sup>	■ <sup>5</sup>	■ <sup>5</sup>

Source: the submission.

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; Q2W = every two weeks; Q3W every three weeks; RPBS = Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 10,000 to < 20,000

<sup>3</sup> \$30 million to < \$40 million

<sup>4</sup> \$0 to < \$10 million

<sup>5</sup> \$40 million to < \$50 million

6.58 The total net cost to the PBS/RPBS of listing nivolumab plus chemotherapy was estimated to be \$30 million to < \$40 million in Year 1, increasing to \$30 million to <

\$40 million in Year 6, and a total of \$200 million to < \$300 million in the first 6 years of listing.

- 6.59 The financial estimates were sensitive to estimates of the proportion of GC, GOJC and OAC patients diagnosed with advanced or metastatic disease. The submission's assumption of 75% may be underestimated based on the literature (80-90%: Price 2012, Wagner 2017; 84%: Nguyen 2019). Overall, the evaluation considered it was difficult to provide an accurate estimate of the proportion of patients who would be diagnosed with advanced or metastatic GC, GOJC or OAC. The PSCR stated the base case financial estimates provided a balanced and appropriate approach to estimating the proportion of GC, GOJC and OAC patients diagnosed with advanced or metastatic disease. The PSCR noted that some literature sources report a lower proportion based on international data, between 59.3%-71.1% depending on cancer type (SEER, 2021b, 2021a).
- 6.60 The pre-PBAC response included the cost of an additional < 500 patients currently receiving nivolumab via compassionate access that will be grandfathered to PBS subsidised treatment. Incorporating these patients into the financial analysis (with reduced utilisation to account for treatment already received) increased the net cost to the PBS/RPBS based on the proposed effective price by \$0 to < \$10 million, to a total cost of \$40 million to < \$50 million in Year 1.
- 6.61 The PBAC noted there would be an impact on utilisation and financial estimates should pembrolizumab be recommended for PBS listing in a similar population.

### ***Quality Use of Medicines***

- 6.62 The submission stated that the Sponsor is committed to supporting the safe and effective use of nivolumab in Australia. Given the adverse effect profile of immunology agents, the Sponsor has established an extensive quality use of medicines (QUM) approach to optimise the potential benefits of treatment with nivolumab, while minimising the potential risks of this medicine for Australian patients.
- 6.63 The submission's approach includes physician education, immune-oncology preceptorship, peer to peer support, nursing and pharmacy in-services, a risk management plan, educational materials and tools, and guidance on monitoring and treating immune related adverse reactions.

### ***Financial Management – Risk Sharing Arrangements***

- 6.64 The submission stated that the Sponsor was willing to enter a risk-sharing arrangement related to expenditure in this disease state, including the potential for subsidisation caps. Such an arrangement may provide additional certainty to government regarding the potential for leakage into other patient groups.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of nivolumab in combination with chemotherapy for the treatment of treatment of advanced or metastatic non- human epidermal growth factor receptor 2 (HER-2) positive advanced or metastatic gastric cancer (GC), gastro-oesophageal junction cancer, (GOJC) or oesophageal adenocarcinoma (OAC). The PBAC noted that the clinical need for effective treatments in this therapeutic area is high, given the poor prognosis for patients and the poor efficacy and high toxicity of current treatments. The PBAC considered the evidence presented demonstrated treatment with nivolumab resulted in a clinically meaningful improvement in progression free survival (PFS) and overall survival (OS). However, the PBAC considered the incremental cost-effectiveness ratio (ICER) in this setting at the proposed price was high and moderately uncertain.
- 7.2 The PBAC noted the consumer input supported the high clinical need for additional effective treatment options for this population.
- 7.3 The submission nominated chemotherapy alone, represented by cisplatin + 5-FU-based regimens, as the comparator. The PBAC noted pembrolizumab plus chemotherapy was considered at the same PBAC meeting and considered it was a near-market comparator given the overlap in patient populations.
- 7.4 The PBAC was satisfied that nivolumab provided, for some patients, a significant improvement in efficacy over the nominated comparator.
- 7.5 The PBAC noted that the TGA indication and trial population for nivolumab reflected a subset of the full patient population likely to be considered clinically appropriate for checkpoint inhibitor treatment. The PBAC indicated its preference for an aligned, simpler restriction for checkpoint inhibitors that reflected likely clinical practice across gastric, GOJ and oesophageal cancers, while noting the different TGA indications.
- 7.6 The submission was based on one head-to-head randomised, phase 3, double-blind multi-centre trial (CheckMate 649; N=1,581 in relevant treatment arms) comparing nivolumab plus chemotherapy compared to chemotherapy alone, in patients with advanced or metastatic GC, GOJC or OAC. The PBAC noted that there was a statistically significant OS benefit associated with nivolumab (HR=0.80, 95% CI: 0.68, 0.94) with the median survival improving from 11.6 to 13.8 months and an improvement in PFS (6.9 months to 7.7 months, HR=0.77, 95% CI: 0.68, 0.87). The PBAC considered that the extent of OS benefit was clinically meaningful in the context of the poor prognosis of this patient population. The PBAC noted the OS benefit in patients treated with nivolumab plus chemotherapy compared to chemotherapy alone was supported by a higher ORR, longer duration of response and maintenance of QoL. The PBAC noted additional data with longer follow up provided in the PSCR provided further support for the clinical benefit of nivolumab.

- 7.7 While the PBAC acknowledged the clinically meaningful improvement in PFS and OS with nivolumab in the CheckMate 649 trial, it considered the magnitude of the benefit in the Australian population to be uncertain. It noted the benefit of nivolumab is less in patients with PD-L1 CPS <5 and the proportion of patients with CPS<5 in the Australian population was unknown.
- 7.8 The PBAC noted that nivolumab in combination with chemotherapy had a higher incidence of AEs than chemotherapy alone, indicating that the safety profile is inferior to that of chemotherapy. The PBAC considered that the claim of inferior safety was reasonable, and that the additional toxicity was manageable which was further supported by the maintenance of QoL.
- 7.9 The PBAC noted the base case ICER presented in the submission was \$55,000 to < \$75,000 per QALY gained. The PBAC considered this ICER to be high and moderately uncertain, with the economic model sensitive to time horizon, method of extrapolation and the inclusion of terminal care costs.
- 7.10 The time horizon in the base case economic model in the submission was 7.5 years. The PBAC considered a 7.5 year time horizon was optimistic and a 5 year time horizon would be preferable given the available data and the poor prognosis of the patient population. However, the PBAC noted it had previously recommended a 5 year time horizon in the second-line treatment setting for a similar patient population and considered a 7.5 year time horizon may be reasonable, given the earlier treatment setting, if other model assumptions were conservative.
- 7.11 The economic model in the submission extrapolated OS and PFS using KM data up to 57 weeks for nivolumab and 48 weeks for chemotherapy alone and then a log-logistic function for nivolumab and Weibull function for chemotherapy alone. The PBAC considered the use of a Weibull function for the chemotherapy alone arm underestimated the benefit of chemotherapy and overestimated the incremental survival gain for nivolumab. The PBAC noted the best fit according to AIC and BIC for OS and PFS for the chemotherapy alone arm was log-logistic function but agreed with the pre-PBAC response that this may not be reasonable and that a number of alternative extrapolations were also clinically plausible.
- 7.12 The economic model in the submission applied a terminal care cost of \$38,058 to the death health state. The PBAC noted the ESC consideration of the inclusion of terminal care costs (paragraph 6.46) and agreed with the ESC that terminal care costs should be excluded from the economic model.
- 7.13 The PBAC considered the estimated patient numbers provided with the submission (with the addition of the < 500 patients on compassionate access in the pre-PBAC response) were reasonable but noted there would be an impact on nivolumab utilisation should pembrolizumab be recommended for PBS listing in a similar population. The PBAC considered this could be further addressed in a resubmission,

noting the PBAC preference for an aligned restriction across all gastric, GOJ and oesophageal cancers (see paragraph 7.5) and the likely overlap in patient populations for checkpoint inhibitors (see paragraph 5.3).

7.14 The PBAC noted that the Sponsor is willing to enter into an RSA with the Commonwealth on sharing the costs in order to manage any risk to the overall cost to the PBS.

7.15 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for nivolumab. The PBAC also considered nivolumab addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy over any alternative therapies. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the Sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.

- Provide an economic model based on (i) a 7.5 year time horizon (ii) an appropriate extrapolation function for the chemotherapy alone treatment arm and (iii) exclusion of terminal care costs.
- Propose a price reduction to achieve an ICER of \$55,000 to < \$75,000 to \$75,000 to < \$95,000/ QALY;
- Provide revised financial estimates incorporating the revised price and addressing the issues raised in paragraph 7.13;
- Propose an appropriate RSA to manage the risk of use outside the proposed patient population included in the resubmission.

The early resolution resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the Sponsor in a simple resubmission and the early resolution timing is not acceptable, a standard re-entry pathway is available

7.16 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Not recommended

## **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**

Bristol-Myers Squibb Australia looks forward to continuing to work with the PBAC and the Department of Health to provide access to nivolumab plus chemotherapy for the first-line treatment of patients with advanced or metastatic non-HER-2-positive gastric cancer, gastroesophageal junction cancer or oesophageal adenocarcinoma.

**Addendum to the November 2021 PBAC Public Summary Document:**

**7.16 NIVOLUMAB,**

**Injection concentrate for I.V. infusion 40 mg in 4 mL**

**Injection concentrate for I.V. infusion 100 mg in**

**10 mL,**

**Opdivo<sup>®</sup>,**

**Bristol-Myers Squibb Australia Pty Ltd**

**10 Background**

- 10.1 An early resolution resubmission was provided that sought to address the PBAC's concerns from its November 2021 meeting, at which the Committee did not recommend nivolumab in combination with chemotherapy for the treatment of treatment of advanced or metastatic non- human epidermal growth factor receptor 2 (HER-2) positive advanced or metastatic gastric cancer (GC), gastro-oesophageal junction cancer, (GOJC) or oesophageal adenocarcinoma (OAC).

***Registration status***

- 10.2 Nivolumab was TGA registered on 31 January 2022 for the following indication "OPDIVO, in combination with fluoropyrimidine- and platinum-based combination chemotherapy, is indicated for the first-line treatment of patients with HER2 negative advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma".
- 10.3 Nivolumab was TGA registered on 22 February 2021 for the following indication: "OPDIVO, as monotherapy, is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior FP-based chemotherapy".

***Previous PBAC consideration***

- 10.4 In November 2021, the PBAC considered a resubmission via an early resolution pathway would be acceptable if the changes outlined in paragraph 7.15 were addressed. In summary, the resubmission was required to address the following outstanding issues:
- Propose an aligned, simple restriction across all gastric, GOJ and oesophageal cancers;

- Provide a revised economic model with a price reduction to achieve an incremental cost effectiveness ratio (ICER) of \$55,000 to < \$75,000/ QALY;
- Provide revised financial estimates; and
- Propose a risk sharing arrangement that manages the risk of use outside the proposed patient population.

10.5 In July 2021, the PBAC recommended the listing of nivolumab for the second line treatment of oesophageal squamous cell carcinoma (OSCC) (agenda item 6.05); however, the PBAC considered that the ICER was high at the proposed price and a price reduction would be required to ensure nivolumab was cost-effective in this population. The PBAC will reconsider this recommendation at the March 2022 meeting as the sponsor was unable to meet the parameters of the July 2021 recommendation.

## 11 Requested listing

11.1 The requested listing is provided below.

Name, manner of administration, form	Maximum amount	Number of repeats	Dispensed price for maximum amount	Manufacturer
NIVOLUMAB Injection 100 mg in 10 mL (vial)	480 mg	13 (initial and continuing treatment)	\$10,235.25 [Published, Private Hospital]	Bristol-Myers Squibb Australia Pty Ltd [BQ]
NIVOLUMAB Injection 40 mg in 4 mL (vial)			\$10,054.68 [Published, Public Hospital]	
	\$[REDACTED] [Effective, Private Hospital]			
	\$[REDACTED] [Effective, Public Hospital]			

<b>Restriction Type:</b> Authority Required – Streamlined
<b>Indication:</b> Advanced or metastatic carcinoma of the following types: (i) HER2-negative gastric cancer, (ii) HER2-negative gastro-oesophageal junction cancer, (iii) adenocarcinoma of the oesophagus, (iv) squamous cell carcinoma of the oesophagus
<b>Treatment Phase:</b> Initial treatment
<b>Clinical criteria:</b> Patient must not have received prior PBS-subsidised treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition. <b>AND</b> Patient must have a WHO performance status of 0 or 1.
<b>Treatment criteria:</b> Patient must be undergoing concomitant chemotherapy with a fluoropyrimidine agent plus a platinum agent at treatment initiation with this drug if they have advanced/metastatic disease that is untreated at the time this drug is initiated. <b>OR</b> Patient must be undergoing treatment with this drug as the sole PBS-subsidised therapy for this PBS indication only after having disease progression/recurrence following treatment with chemotherapy that contains at least each of a fluoropyrimidine agent plus a platinum agent if they have advanced/metastatic oesophageal squamous cell carcinoma. <b>AND</b> Patients must only receive a maximum of nivolumab 240 mg every two weeks, 360 mg every three weeks or 480 mg every four weeks, or pembrolizumab 200 mg every three weeks, under a flat dosing regimen as aligned to the TGA-approved dosing for the prescribed agent.

*Public Summary Document – November 2021 PBAC Meeting with Addendum from March 2022 PBAC Meeting*

<p><b>Prescribing Instructions:</b>                  The TGA-approved indications for OPDIVO (nivolumab) are:                  OPDIVO, in combination with fluoropyrimidine- and platinum-based combination chemotherapy, is indicated for the first-line treatment of patients with HER2 negative advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma.</p> <p>OPDIVO, as monotherapy, is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine and platinum based chemotherapy.</p> <p>The TGA-approved indication for KEYTRUDA (pembrolizumab) is:                  KEYTRUDA® (pembrolizumab), in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced or metastatic carcinoma of the oesophagus or HER2 negative gastroesophageal junction adenocarcinoma (tumour centre 1 to 5 centimetres above the gastroesophageal junction) that is not amenable to surgical resection or definitive chemoradiation.</p> <p>In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.</p>
<p><b>Administrative Advice:</b>                  Special Pricing Arrangements apply.</p> <p>Up to 17 repeats may be sought if dosing at 240 mg every 2 weeks. Where an increase is sought, the benefit is no longer a Streamlined benefit. Seek authority approval prior to issuing the prescription.</p>

<p><b>Restriction Type:</b> Authority Required – Streamlined</p>
<p><b>Indication:</b> Advanced or metastatic carcinoma of the following types: (i) HER2-negative gastric cancer, (ii) HER2-negative gastro-oesophageal junction cancer, (iii) adenocarcinoma of the oesophagus, (iv) squamous cell carcinoma of the oesophagus</p>
<p><b>Treatment Phase:</b> Continuing treatment</p>
<p><b>Clinical criteria:</b>                  Patient must have stable or responding disease.</p>
<p><b>Treatment criteria:</b>                  Patient must have previously received PBS-subsidised treatment with this drug for this condition.</p>
<p><b>AND</b>                  Patients must only receive a maximum of nivolumab 240 mg every two weeks, 360 mg every three weeks or 480 mg every four weeks, or pembrolizumab 200 mg every three weeks, under a flat dosing regimen as aligned to the TGA-approved dosing for the prescribed agent.</p>
<p><b>Prescribing Instructions:</b>                  The TGA-approved indications for OPDIVO (nivolumab) are:                  OPDIVO, in combination with fluoropyrimidine- and platinum-based combination chemotherapy, is indicated for the first-line treatment of patients with HER2 negative advanced or metastatic gastric or gastro-oesophageal junction or oesophageal adenocarcinoma.</p> <p>OPDIVO, as monotherapy, is indicated for the treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine and platinum based chemotherapy.</p> <p>The TGA-approved indication for KEYTRUDA (pembrolizumab) is:                  KEYTRUDA® (pembrolizumab), in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced or metastatic carcinoma of the oesophagus or HER2 negative gastroesophageal junction adenocarcinoma (tumour centre 1 to 5 centimetres above the gastroesophageal junction) that is not amenable to surgical resection or definitive chemoradiation.</p> <p>The treatment must not exceed 24 months for this PBS indication.</p>
<p><b>Administrative Advice:</b>                  Special Pricing Arrangements apply.</p> <p>Up to 23 repeats may be sought if dosing at 240 mg every 2 weeks. Where an increase is sought, the benefit is no longer a Streamlined benefit. Seek authority approval prior to issuing the prescription.</p>

*For more detail on PBAC’s view, see section 11 PBAC outcome.*

## 12 Consideration of the evidence

12.1 A summary of how the resubmission addressed the outstanding issues is provided in the table below.

**Table 1: Summary of changes made by the resubmission to address matters raised in the November 2021 PBAC PSD**

Parameter	Resubmission changes	Comparison with November 2021 PBAC PSD
Effective ex-manufacturer price per 100 mg vial	\$█	8% lower than proposed in previous submission (\$█)
Restriction criteria	Proposed listing for: advanced or metastatic (i) HER2-negative GC, (ii) HER2-negative GOJC, (iii) OAC, (iv) OSCC	Consistent with paragraph 7.5 Addition of OSCC patients. Proposed criteria lists TGA approved indications for nivolumab and pembrolizumab.
<b>Economic evaluation</b>		
Time horizon	7.5 years	Consistent with paragraph 7.15
Terminal care costs	Excluded	
Extrapolation function	Gompertz (OS only)	
ICER	\$55,000 to < \$75,000 per QALY	
<b>Financial estimates</b>		
Patient estimates	Consistent with previous submission for OAC, GC and GOJ with additional patients included for OSCC (first line and second line)	Consistent with paragraph 7.15
Grandfathered patients	<500 patients for OAC, GC, GOJ; <500 patients for OSCC	Previous submission stated <500 OAC, GC and GOJ patients would transition to PBS-subsidised treatment (paragraph 6.60).
RSA	Proposed a tiered cap with rebate of █% to █%, depending on expenditure above the cap.	Consistent with paragraph 7.15

GC = gastric cancer; GOJ= gastro-oesophageal junction; ICER = incremental cost effectiveness ratio; OAC = oesophageal adenocarcinoma; OS = overall survival; OSCC = oesophageal squamous cell carcinoma; QALY = quality adjusted life years; RSA = risk sharing arrangement; PSD = Public Summary Document

12.2 The table below outlines the financial implications estimated in the resubmission.

Public Summary Document – November 2021 PBAC Meeting with Addendum from March 2022 PBAC Meeting

Table 2: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Number of patients treated</b>						
GC, OAC, GOJ	1	1	1	1	1	1
- GF	2					
<b>OSCC</b>						
- First line	2	2	2	2	2	2
- Second line	2	2	2	2	2	2
- GF	2					
Total patients treated	1	1	1	1	1	1
<b>Estimated financial implications of nivolumab plus chemotherapy</b>						
Cost to PBS/RPBS less copayments, nivolumab						
GC, OAC, GOJ (\$)	3	3	3	3	3	3
First line OSCC (\$)	4	4	4	4	4	4
Second line OSCC (\$)	4	4	4	4	4	4
Total (\$)	5	5	5	5	5	5
Cost to PBS/RPBS less copayments, nivolumab plus chemotherapy						
Total (\$)	6	5	5	5	5	5
<b>Estimated financial implications for chemotherapy not used</b>						
Cost to PBS/RPBS less copayments						
Total (\$)	-4	-4	-4	-4	-4	-4
<b>Net financial implications</b>						
Net cost to PBS/RPBS (\$)	5	5	5	5	5	5
Net cost to MBS (\$)	4	4	4	4	4	4
Net cost to PBS/RPBS/ MBS (\$)	5	5	5	5	5	5
<b>Previous submission</b>						
Cost to PBS/RPBS less copayments, nivolumab <sup>a</sup> (\$)	3	3	3	3	3	3
Net cost to PBS/RPBS <sup>a</sup> (\$)	3	3	3	3	3	3

GC = gastric cancer; OAC = oesophageal adenocarcinoma; GOJ = gastro-oesophageal junction; GF = grandfathered; OSCC = oesophageal squamous cell carcinoma

Source: Table 6, Table 8 of resubmission; Table 15, PSD, November 2021 PBAC meeting.

<sup>a</sup> Excludes GF patients which were included in the pre-PBAC response (and increased net cost to \$40 million to < \$50 million in Year 1).

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> < 500

<sup>3</sup> \$30 million to < \$40 million

<sup>4</sup> \$0 million to < \$10 million

<sup>5</sup> \$40 million to < \$50 million

<sup>6</sup> \$50 million to < \$60 million

12.3 The resubmission stated that the patient estimates for GC, OAC and GOJ are consistent with those considered by the PBAC in November 2021. The revised financial estimates incorporate patients with OSCC, consistent with the proposed listing. The resubmission provided an updated estimate of the number patients that will be transitioned to PBS-subsided therapy across all indications.

- 12.4 The total net cost to the PBS/ RPBS of listing nivolumab plus chemotherapy was estimated to be \$200 million to < \$300 million over the first six years of listing (compared to \$200 million to < \$300 million in the previous submission).
- 12.5 The resubmission proposed a risk sharing arrangement with tiered rebates as outlined in the table below.

**Table 3: Proposal for tiered subsidisation cap for gastric, GOJ, and oesophageal cancers**

	Rebate payable	
Commonwealth expenditure under cap		%
Commonwealth expenditure between 100%-110% of cap		%
Commonwealth expenditure between 110%-120% of cap		%
Commonwealth expenditure above 120% of cap		%

- 12.6 The resubmission stated that if the intention was for a singular subsidisation cap for use of checkpoint inhibitors, additional work will be required in discussion with the PBAC and the Department of Health to ensure appropriate consideration of the contribution of multiple medicines across different indications within one broad PBS restriction.

*For more detail on PBAC’s view, see section 11 PBAC outcome.*

## **13 PBAC Outcome**

- 13.1 The PBAC recommended the listing of nivolumab in combination with chemotherapy for the first line treatment of advanced or metastatic gastro-oesophageal cancers as defined by the specific tumour types included in the approved TGA indications. The PBAC considered the early resolution resubmission had appropriately addressed the outstanding issues as outlined in the November 2021 PBAC Public Summary Document (PSD).
- 13.2 The PBAC’s recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of nivolumab (as a first line treatment) would be acceptable at the price proposed in the resubmission.
- 13.3 The PBAC noted the restriction criteria proposed in the resubmission addressed the Committee’s preference for an aligned restriction for patients with gastric, gastro-oesophageal junction and oesophageal cancers. However, given the significant overlap in the anatomical distribution of these cancers, the PBAC considered it would be appropriate for nivolumab (and pembrolizumab, should it be recommended) to be available for the first line treatment of advanced or metastatic ‘gastro-oesophageal cancers’ as defined by the specific tumour types included in the approved TGA Product Information document. The PBAC noted that, of the gastro-oesophageal cancers, nivolumab is currently approved by the TGA for the first line treatment of advanced or metastatic GOJ, GC and OAC.

- 13.4 The PBAC noted an early resolution resubmission for pembrolizumab is concurrently being considered. The PBAC noted that, of the gastro-oesophageal cancers, pembrolizumab is currently approved by the TGA for the first line treatment of advanced or metastatic Siewert Type 1 adenocarcinoma of the GOJ, OAC and OSCC.
- 13.5 The PBAC reiterated its view that, although the indications are not fully aligned, there was likely to be significant overlap in patients that are treated with nivolumab or pembrolizumab in clinical practice. The PBAC considered a single listing for gastro-oesophageal cancers that allows treatment choice according to the TGA approved specific tumour types for each medicine was appropriate.
- 13.6 The PBAC noted there were differences in design and patient populations across the nivolumab and pembrolizumab trials, but considered that, overall, there was unlikely to be any difference between nivolumab and pembrolizumab in clinical practice for the first line treatment of gastro-oesophageal cancers in terms of clinical benefit, tolerability and treatment duration.
- 13.7 The PBAC noted the RSA proposed in the resubmission, with tiered rebates as outlined in Table 18, and considered that appropriate rebates could be finalised with the Department. The PBAC considered the expenditure caps for the RSA should be based on the financial estimates of listing for the specific tumour types that are TGA approved. That is, for nivolumab, the financial estimates should be based on the estimated number of GC, GOJ and OAC patients treated in the first line setting. The PBAC noted that pembrolizumab is indicated for the first line treatment of OSCC and should it be recommended for PBS listing, it would be appropriate to include the financial estimates for OSCC patients in the same expenditure cap.
- 13.8 The PBAC noted nivolumab is currently TGA approved for the second line treatment of OSCC. The PBAC noted a submission to reconsider its previous recommendation to list nivolumab for the second line treatment of OSCC will be considered in March 2022 (paragraph 10.5). The PBAC foreshadowed that if nivolumab is recommended for the second line treatment of OSCC, it may be appropriate to amend the restriction (by removing reference to ‘first line’) to allow access for these patients and to include the expenditure for this population in the RSA caps.
- 13.9 The PBAC advised the following changes to the proposed restriction criteria in Section 9 would be appropriate:
- Combine the proposed initial and continuing restriction criteria into a single restriction criteria covering both treatment phases that also allows patients transitioning to PBS-subsidised treatment to access treatment.
  - Delete clinical criteria ‘Advanced or metastatic carcinoma of the following types: (i) HER2-negative gastric cancer, (ii) HER2-negative gastro-oesophageal junction cancer, (iii) adenocarcinoma of the oesophagus, (iv) squamous cell

carcinoma of the oesophagus’ and add ‘The condition must be a gastro-oesophageal cancer type as specified in the drug’s ‘Indications’ section of the approved Australian Product Information’.

- Add ‘Patient must be undergoing treatment with this drug for metastatic disease (Stage IV disease) that is untreated with drug therapy; or Patient must be undergoing treatment with this drug for locally advanced disease (Stage III disease) that is either (i) untreated with drug therapy, (ii) treated with systemic therapy in the neoadjuvant/adjuvant setting, but the cancer has recurred after more than 6 months from the last dose of systemic therapy’.
- Amend ‘Patient must have a WHO performance status of 0 or 1’ to ‘Patient must have/have had, at the time of initiating treatment, a WHO performance status no higher than 1’ to enable patients transitioning to PBS-subsided treatment to access treatment under the initial restriction criteria.
- Add clinical criteria ‘The condition must be unsuitable for each of: (i) surgical resection, (ii) chemoradiation’ to reflect the appropriate patient population.
- Change the maximum amount to 360 mg to reflect the maximum dose for the first line treatment of gastro-oesophageal cancers.
- Delete clinical criteria “Patient must have stable or responding disease” and prescribing instruction “The treatment must not exceed 24 months for this PBS indication” and add clinical criteria “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; annotate any remaining repeat prescriptions with the words ‘cancelled’ where this occurs”.
- Delete treatment criteria “Patient must be undergoing treatment with this drug as the sole PBS-subsidised therapy for this PBS indication only after having disease progression/recurrence following treatment with chemotherapy that contains at least each of a fluoropyrimidine agent plus a platinum agent if they have advanced/metastatic oesophageal squamous cell carcinoma”.

13.10 The PBAC advised that nivolumab is not suitable for prescribing by nurse practitioners as antineoplastic agents are currently out of scope for prescribing by nurse practitioners.

13.11 The PBAC recommended that the Early Supply Rule should not apply as it currently does not apply to Section 100 Efficient Funding of Chemotherapy listings.

13.12 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

13.13 The PBAC found that the criteria prescribed by the *National Health (Pharmaceutical and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for nivolumab:

- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies;
- b) The treatment is expected to address a high and urgent unmet clinical need; and
- c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

**Outcome:**

Recommended

## 14 Recommended listing

14.1 Add indication as follows:

MEDICINAL PRODUCT Form	PBS item code	Maximum amount	No. of Repeats
NIVOLUMAB Injection	New (Public) New (Private)	360 mg	13
<b>Available brands</b>			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)			
<b>Restriction Summary / Treatment of Concept: [New 1]</b>			
<b>Concept ID</b> (for internal Dept. use)	<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners		
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [New 1]		
	<b>Episodicity:</b> [blank]		
	<b>Severity:</b> Advanced or metastatic		
	<b>Condition:</b> gastro-oesophageal cancers		
New IND1	<b>Indication:</b> Advanced or metastatic gastro-oesophageal cancers		
	<b>Treatment Phase:</b> [blank]		
	<b>Clinical criteria:</b>		
New CC1	The condition must be a gastro-oesophageal cancer type as specified in the drug's 'Indications' section of the approved Australian Product Information		
	<b>AND</b>		
	<b>Clinical criteria:</b>		
New CC2	The condition must be metastatic disease (Stage IV disease) that is untreated with drug therapy at treatment initiation with this drug; or		

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New CC3	The condition must be, at treatment initiation with this drug, locally advanced disease (Stage III disease) that is either: (i) untreated with drug therapy, (ii) treated with systemic neoadjuvant/adjuvant therapy, but the cancer has recurred after more than 6 months from the last dose of systemic therapy.
	<b>AND</b>
	<b>Clinical criteria:</b>
New CC4	Patient must be undergoing concomitant treatment with chemotherapy, at least at treatment initiation with this drug, containing a minimum of: (i) a platinum agent, plus (ii) a fluoropyrimidine agent
	<b>AND</b>
	<b>Clinical criteria:</b>
New CC5	Patient must have/have had, at the time of initiating treatment with this drug, a WHO performance status no higher than 1
	<b>AND</b>
	<b>Clinical criteria:</b>
New CC6	The condition must be unsuitable for each of: (i) surgical resection, (ii) chemoradiation
	<b>AND</b>
	<b>Treatment criteria:</b>
New TC1	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; annotate any remaining repeat prescriptions with the words 'cancelled' where this occurs
New CA1	<b>CAUTION:</b> In the first few months after starting immunotherapy, a transient tumour flare may occur that may be mistaken as disease progression despite an overall positive response to treatment.
New AA2	<b>Administrative Advice:</b> The stated maximum amount in this listing is based on this drug's approved Product Information recommended dosing for specific cancer types – the drug may be prescribed in a quantity up to this amount, but need not be this amount for every cancer type. Refer to this drug's approved Product Information for the recommended dosing for the patient's particular condition.
7607	<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.
7608	<b>Administrative Advice:</b> Special Pricing Arrangements apply.

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

## 15 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.

## **16 Sponsor's Comment**

Bristol-Myers Squibb Australia looks forward to continuing to work with the PBAC and the Department of Health to provide access to nivolumab ± chemotherapy for the treatment of patients with advanced or metastatic gastro-oesophageal cancers.