

**7.12 NIVOLUMAB,
Injection concentrate for I.V. infusion
40 mg in 4 mL,
Injection concentrate for I.V. infusion
100 mg in 10 mL,
Opdivo[®],
Bristol-Myers Squibb Australia Pty Ltd**

1 Purpose

- 1.1 The early re-entry resubmission requested a Section 100 (Efficient Funding of Chemotherapy Program) Authority Required listing (Telephone/Online) for the adjuvant treatment of patients with oesophageal cancer (OC) or gastroesophageal junction cancer (GOJC) who have received platinum-based chemoradiotherapy and surgery.
- 1.2 The resubmission was in response to the PBAC recommendation from July 2022. The resubmission has partially addressed the issues raised by the PBAC (Table 1).

Table 1: Summary of key matters to be addressed

Matter of concern	Proposed in resubmission	Addressed?
Requested listing		
<ul style="list-style-type: none"> • Amendment to the restriction as outlined in paragraphs 7.3-7.4 (paragraph 7.14, July 2022 PBAC PSD). <p>The PBAC nominated the following issues to be addressed in July 2022:</p> <ul style="list-style-type: none"> • Inclusion of suggestions and additions to the restriction proposed by the Secretariat. • Inclusion of a time restriction for treatment initiation post-surgical resection that is aligned with the Checkmate 577 trial (16 weeks). • The prescriber instruction for a confirmatory scan, taken at least 4 weeks after progression/transient tumour flare, was not considered relevant to a PBS listing in the adjuvant setting and the PBAC advised that it be removed from the restriction. • Immunotherapy restricted to one course of treatment per lifetime for OC and GOJC. 	<ul style="list-style-type: none"> • Suggestions and additions to the restriction proposed by the Secretariat were accepted. • Inclusion of a time restriction for treatment initiation post-surgical resection (16 weeks). • The prescriber instruction for a confirmatory scan was removed. • Wording to limit treatment to once per lifetime was not considered necessary, as adjuvant treatment is the earliest immunotherapy setting for OC and GOJC. The submission stated it would work with the Department to include wording in the advanced and metastatic treatment setting. 	<p>Yes, however wording to limit treatment to once per lifetime was not included in the restriction for adjuvant treatment. The PBAC considered the proposed restriction acceptable.</p>
Economic model		

Public Summary Document – November 2022 PBAC Meeting

Matter of concern	Proposed in resubmission	Addressed?
<ul style="list-style-type: none"> Amendment to the economic model as specified in paragraph 7.11 and propose a price that results in an ICER of \$30,000/QALY gained or less (paragraph 7.14, July 2022 PBAC PSD). Paragraph 7.11 stated: The PBAC noted that, despite excluding the operability to model convergence, the evaluation was able to approximate convergence of the survival curves in the economic model by changing extrapolation functions and the time at which cure occurs... The PBAC noted that this adjustment to the economic model did not specifically address the issues regarding the time horizon and subsequent use of immunotherapy...but considered it provided a conservative basis to assess the cost effectiveness of nivolumab in this treatment setting. 	<ul style="list-style-type: none"> The updated economic model was consistent with adjustments made in the evaluation to approximate overall survival convergence. Subsequent therapy costs were updated to reflect a restriction of immunotherapy to once per patient lifetime. This change to the economic model was not specified in the July 2022 PSD. The pre-PBAC response maintained that it is appropriate to restrict immunotherapy to once per patient lifetime in the economic model. Ex-manufacturer price (EMP) for each 100 mg vial reduced from \$█ to \$█; for each 40 mg vial from \$█ to \$█. Base case ICER = \$█¹. 	<p>Partially.</p> <p>Additional amendments to the model were made that were not specified in paragraph 7.11 (i.e., inclusion of subsequent immunotherapy costs, change to cost of subsequent chemotherapy, change to split of Q2W and Q4W dosing).</p>
Financial estimates		
<ul style="list-style-type: none"> Provide revised financial estimates incorporating: <ul style="list-style-type: none"> a new proposed price; and reduced use of immunotherapy in the advanced / metastatic treatment setting (paragraph 7.14, July 2022 PBAC PSD). 	<ul style="list-style-type: none"> Ex-manufacturer price (EMP) for each 100 mg vial was reduced from \$█ to \$█; for each 40 mg vial was reduced from \$█ to \$█. Reduced use of immunotherapy in the advanced/metastatic setting was not included in the financial estimates. 	<p>Partially.</p>
Financial Management		
<ul style="list-style-type: none"> Proposal of an RSA that addresses issues raised in paragraph 7.13 (paragraph 7.14, July 2022 PBAC PSD). <p>The PBAC considered in July 2022 it would be reasonable for use to be included in the RSA recommended in the advanced / metastatic setting with the expenditure caps revised to account for the estimated financial impact (after accounting for offsets associated with reduced use in the advanced / metastatic setting).</p>	<ul style="list-style-type: none"> An update to the current risk share arrangement for nivolumab in the advanced / metastatic setting (GC/GOJC/OAC) was provided. Consistent with the financial estimates, expenditure caps in the advanced / metastatic setting were not revised to account for reduced use. 	<p>Partially.</p>

Source: Section 7, nivolumab PBAC PSD, July 2022 PBAC meeting and the resubmission.
EMP = ex-manufacturer price; GC = gastric cancer; GOJC = gastroesophageal junction cancer; ICER = incremental cost-effectiveness ratio; LYG = life years gained; OAC = oesophageal adenocarcinoma; OC = oesophageal cancer; RSA = risk share arrangement; PSD = Public Summary Document.

The redacted values correspond to the following ranges:
¹ \$25,000 to < \$35,000

2 Background

Registration status

- 2.1 Nivolumab was TGA registered on 29 November 2021 for the following indication:
- as monotherapy, for the adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer in patients who have received neoadjuvant chemoradiotherapy.
- 2.2 Nivolumab is also TGA approved for (i) use 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 and (ii) as monotherapy, for the treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine and platinum-based chemotherapy.

Previous consideration

- 2.3 The PBAC did not recommend nivolumab for the adjuvant treatment of patients with OC or GOJC at its July 2022 meeting. The PBAC considered that nivolumab provided moderate clinical benefit over ‘watch and wait’ surveillance in terms of disease-free survival (DFS), however it was uncertain if it provided an overall survival benefit as clinical data for this outcome was unavailable (paragraphs 7.6-7.7, nivolumab PBAC Public Summary Document (PSD), July 2022). Clinical data for overall survival (OS) were not provided in the resubmission.
- 2.4 The PBAC considered the outstanding issues could be resolved in a simple resubmission for nivolumab using the early re-entry pathway, based on the following (paragraph 7.14, nivolumab PBAC PSD, July 2022):
- Amend the restriction to include a 16-week time restriction for treatment initiation post-surgical resection, remove the prescriber instruction for a confirmatory scan and restrict immunotherapy to one course of treatment per lifetime for OC and GOJC.
 - Revision to the economic model to model convergence (which the PBAC considered would provide a conservative basis for assessing the cost-effectiveness of nivolumab in this treatment setting).
 - A revised price that reflects an incremental cost-effectiveness ratio (ICER) of \$30,000/QALY gained or less using the economic model incorporating convergence.
 - Revised financial estimates incorporating the new price and accounting for reduced use of immunotherapy in the advanced / metastatic setting.
 - Propose a risk-share arrangement that accounted for reduced use of immunotherapy in the advanced / metastatic setting.

2.5 From 1 October 2022, nivolumab was listed on the PBS for advanced or metastatic gastro-oesophageal cancers as specified in the 'Indications' section of the approved Australian Product Information (see paragraph 2.2).

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Requested listing

3.1 The proposed restriction presented in the resubmission is shown below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough. The Pre-PBAC response considered the proposed changes appropriate.

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
			\$9,731.26	
NIVOLUAB Injection 100 mg in 10 mL (vial)	480mg	3 (initial treatment)	[Published, Private Hospital] \$9,557.05	Opdivo® Bristol-Myers Squibb Australia Pty Ltd [BQ]
NIVOLUMAB Injection 40 mg in 4 mL (vial)		8 (continuing treatment)	[\$] [Effective, Private Hospital] [\$] [Effective, Public Hospital]	

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: No increase in the maximum amount or number of units may be authorised.
Administrative Advice: Up to an additional 4 repeat prescriptions (7 in total) may be sought only where dosing is on a 2-weekly schedule. This listing's stated number of repeat prescriptions is based on 4-weekly dosing.
Indication: Adjuvant treatment of stage II or III oesophageal carcinoma or gastro-oesophageal carcinoma
Treatment Phase: Initial treatment
Clinical criteria: The condition must have histological evidence confirming a diagnosis of a least one of: (i) adenocarcinoma, (ii) squamous cell carcinoma; document this evidence in the patient's medical records
AND
Clinical criteria: The condition must have been treated with <i>neoadjuvant</i> platinum-based chemoradiotherapy
AND

Public Summary Document – November 2022 PBAC Meeting

Clinical criteria:
The treatment must be for the purposes of adjuvant use following complete surgical resection <i>that occurred within 16 weeks prior to initiating this drug</i>
AND
Clinical criteria:
The treatment must have commenced within 16 weeks of complete resection.
AND
Clinical criteria:
The condition must have evidence, through resected specimen, that residual disease <i>meets the Tumour Nodes Metastases (TNM) staging system (that published by the Union for International Cancer Control) is present to the extent of either: (i) at least ypT1, (ii) at least ypN1; document this evidence in the patient's medical records</i>
AND
Clinical criteria:
Patient must be in a state that they either: (i) have a current WHO performance status of no higher than 1 at treatment initiation, (ii) had a WHO performance status no higher than 1 where treatment was initiated as non-PBS subsidised supply
AND
Clinical criteria:
Patient must not have experienced disease recurrence
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Treatment criteria:
Patient must be undergoing treatment with a dosing regimen as set out in the drug's approved Australian Product Information
AND
Treatment criteria:
Patient must not receive more than 12 months total treatment duration of combined PBS subsidised and non-PBS subsidised adjuvant therapy. Patient must not be undergoing PBS subsidised treatment with this drug where this prescription extends treatment beyond whichever comes first: (i) 12 months from treatment initiation, irrespective of whether initial treatment was PBS-subsidised/non-PBS subsidised, (ii) the residual disease progressing despite treatment with this drug
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Indication: Adjuvant treatment of stage II or III oesophageal carcinoma or gastro-oesophageal carcinoma
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received PBS subsidised treatment with this drug for this condition.
AND
Clinical criteria:
Patient must not have experienced disease recurrence.
AND
Clinical criteria:

The treatment must be the sole PBS-subsidised therapy for this condition.
AND
Clinical criteria:
The treatment must be for the purposes of adjuvant use following complete surgical resection
Treatment criteria:
Patient must be undergoing treatment with a dosing regimen as set out in the drug's approved Australian Product Information
AND
Treatment criteria:
Patient must not receive more than 12 months total treatment duration of combined PBS-subsidised and non-PBS-subsidised adjuvant therapy.

- 3.2 The resubmission reduced the ex-manufacturer price (EMP) for each 100 mg vial of nivolumab by 39% from \$|to \$|.
- 3.3 Given that adjuvant treatment is the earliest immunotherapy treatment setting for OC and GOJC, the resubmission considered that wording to limit treatment to once per lifetime was not required. The resubmission proposed the following eligibility criterion be included in the initial treatment restrictions for drugs that are indicated for the treatment of locally advanced / metastatic oesophageal or gastro-oesophageal junction cancer: “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 oesophageal or gastro-oesophageal junction cancer.” The PBAC considered it would be appropriate to refer to “gastro-oesophageal cancer” rather than “oesophageal or gastro-oesophageal junction cancer” to reflect the intention of one treatment course per lifetime for the broader condition.
- 3.4 The PBAC considered it would be reasonable to specify the listed number of repeats to be 5 which would allow 24 weeks of treatment per script (at a dose of 480 mg every 4 weeks). The PBAC considered it would also be reasonable to permit increases in repeat prescriptions to 7 for patients prescribed 240 mg every 2 weeks (i.e. permit an additional 2 repeat prescriptions). The PBAC noted these changes would allow prescribers to align to the trial dosing of 240 mg every 2 weeks for the first 16 weeks, followed by 480 mg every 4 weeks for the remainder of the 12 month treatment duration.
- 3.5 The PBAC considered the treatment criteria that includes “(ii) the residual disease progressing despite treatment with this drug” should state “(ii) disease recurrence despite treatment with this drug” to more appropriately reflect the adjuvant treatment setting.

For more detail on PBAC’s view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item.

Consumer comments

- 4.2 The PBAC noted and welcomed the input from one organisation, the Medical Oncology Group of Australia (MOGA) via the Consumer Comments facility on the PBS website. The MOGA 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 Checkmate 577 trial. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for nivolumab, which was a Grade A, the highest grade (on a scale from A to C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies).¹
- 4.3 The PBAC recalled the input from individuals (1), health care professionals (1) and organisations (2) received previously (paragraph 6.2, nivolumab PBAC PSD, July 2022).

Comparative effectiveness

- 4.4 The July 2022 consideration of nivolumab for the adjuvant treatment of patients with OC or GOJC was based on one randomised, double-blind trial comparing nivolumab (n=532) and placebo (representing standard of care) (n=262) (Checkmate 577). At the July 2022 meeting, the PBAC was satisfied that nivolumab was superior to standard care (the nominated comparator) in improving DFS with a hazard ratio of 0.67 (95% CI: 0.55, 0.81) and a median DFS of approximately 22 months compared to 10 months in the standard care arm. However, the PBAC was uncertain if nivolumab provided an overall survival benefit as clinical data for this outcome was unavailable (paragraphs 7.1 and 7.7, nivolumab PBAC PSD, July 2022).
- 4.5 The PBAC previously noted that there was an approximate 8% increase in grade 3 or 4 treatment related AEs associated with nivolumab compared with placebo in the Checkmate 577 trial. However, the PBAC considered the overall safety associated with nivolumab treatment in the adjuvant setting was acceptable (paragraph 7.8, nivolumab PBAC PSD, July 2022).
- 4.6 No additional clinical data were presented in the resubmission.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

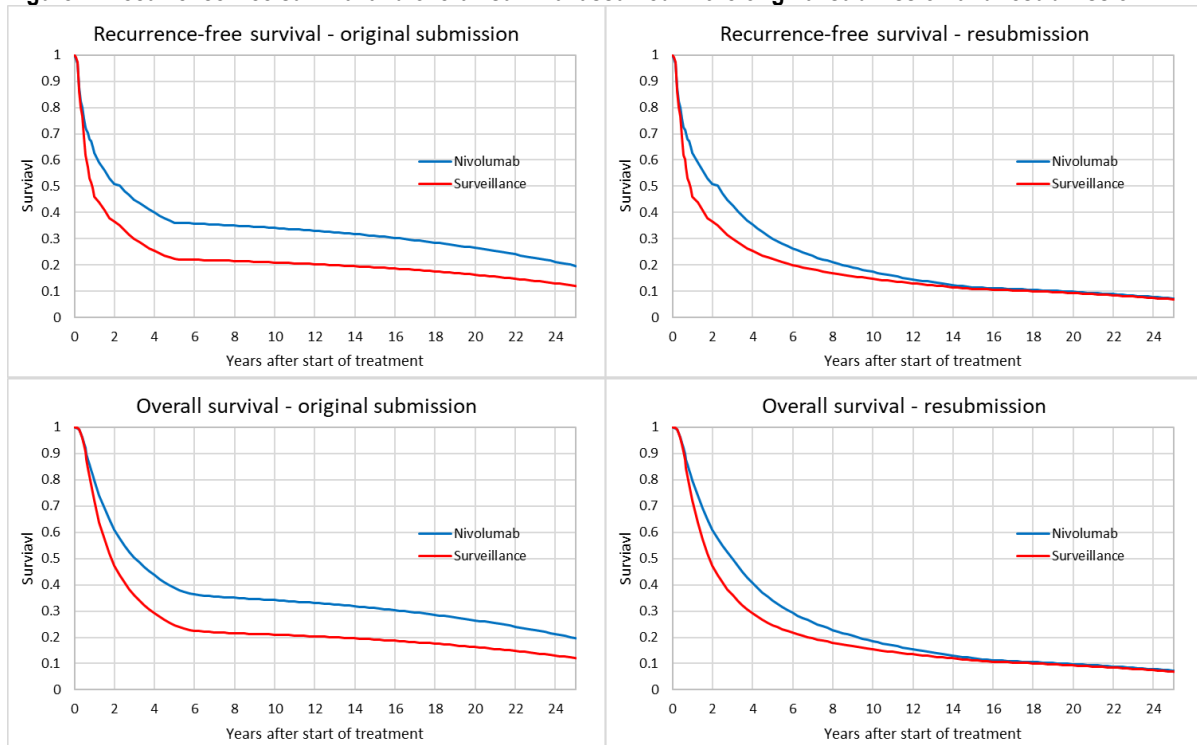
Clinical claim

- 4.7 In July 2022, the PBAC considered that the claim of superior comparative effectiveness was reasonable (paragraph 6.30, nivolumab PBAC PSD, July 2022).
- 4.8 In July 2022, the PBAC considered that the claim of inferior comparative safety was reasonable (paragraph 6.31, nivolumab PBAC PSD, July 2022).

Economic analysis

- 4.9 As an early re-entry resubmission, the economic analysis has not been independently evaluated.
- 4.10 In accordance with the PBAC's advice, the economic model was adjusted to reduce the extrapolated clinical benefit associated with adjuvant nivolumab. The resubmission applied the same adjustments made in the evaluation to approximate overall survival convergence (paragraph 6.42, July 2022 nivolumab PBAC PSD), including:
- a log logistic parametric extrapolation for time to recurrence (TTR) in the nivolumab arm (base case of the original submission was a generalised gamma function); and
 - a cured fraction from 15 years (base case of the original submission was 5 years).
- 4.11 The impact of these revisions to the recurrence-free survival and overall survival in the economic model is shown in Figure 1.

Figure 1: Recurrence-free survival and overall survival assumed in the original submission and resubmission



4.12 The resubmission stated that to ensure alignment with both the intent of the restriction and the financial estimates, in which the sponsor accepts that immunotherapy is restricted to once in a lifetime, the sponsor included the cost of subsequent therapy in the standard of care ('surveillance') arm to be reflective of what will happen in clinical practice. The early re-entry pathway nominated at the July 2022 PBAC meeting did not require the economic model to amend the approach to subsequent treatments and the PBAC considered the economic model approximating convergence (as outlined in paragraph 7.11 and 7.16 of the PBAC PSD) provided a conservative basis to estimate the cost effectiveness of nivolumab in this treatment setting without further amendment. The PBAC noted the ICER increased from \$25,000/QALY to < \$35,000 per QALY gained to \$55,000/QALY to <\$75,000 per QALY gained when subsequent immunotherapy therapy costs in the standard of care arm were removed from the economic model.

4.13 The base case economic model in the original submission assumed a cost per recurrence of \$6,005 for both treatment arms. The original submission assumed that adjuvant nivolumab would not preclude use of immunotherapy in the metastatic setting (assumed to be pembrolizumab plus chemotherapy), and a sensitivity analysis applied a one-off cost of \$88,668 (including administration costs) to transitions of recurrence in both arms of the economic model (paragraph 6.48, July 2022 nivolumab PBAC PSD). The resubmission adjusted the cost of subsequent immunotherapy in the economic model and applied only to transitions to recurrence in the standard care arm to reflect one treatment course per lifetime.

4.14 The approach to calculating the cost of subsequent immunotherapy and chemotherapy in the resubmission is outlined in Table 2 and Table 3.

Table 2: Immunotherapy costs in the advanced and metastatic setting

	GOJC and OAC patient population	OSCC patient population
Immunotherapy		
Nivolumab, 100mg vial (\$)		
Dose	360 mg q3w	240 mg q2w
DPMA, per dose (\$)		
Doses per treatment course	12.37	15.40
Total (DPMA) (\$)		
Patient distribution	63.2%	36.8%
Total weighted price (\$)		
Infusion		
Cost	\$114.20	\$114.20
Infusions per treatment course	12.37	15.40
Total	\$1,412.65	\$1,758.68
Patient distribution	63.2%	36.8%
Total weighted price	\$1,539.88	

Source: p10 of the submission, 'Subsequent treatment derivation' spreadsheet of 'Attachment 1 Updated Economic Evaluation Workbook Adj OC and GOJC.xlsm'

DPMA = dispensed price per maximum amount; GOJC = gastroesophageal junction carcinoma; mg = milligram; OAC = oesophageal adenocarcinoma; OSCC = oesophageal squamous cell carcinoma; q2w = every 2 weeks; q3w = every 3 weeks

4.15 The submission stated that dosing and mean durations of treatment are different across the GOJC, oesophageal adenocarcinoma (OAC) and oesophageal squamous cell carcinoma (OSCC) indications. In order to weight the total treatment cost according to dose and treatment duration, patient numbers from previous PBAC considerations were used to calculate the percentage split of each indication. The submission estimated the proportion of patients in the advanced / metastatic setting with GOJC / OAC was 63.2% and with OSCC was 36.8%.

4.16 In the advanced / metastatic setting, nivolumab is administered in combination with chemotherapy. The submission assumed the chemotherapy administered in the CM-648 clinical trial (the pivotal trial for OSCC – not previously considered by the PBAC), which consisted of fluorouracil 800 mg/m²/day as an intravenous continuous infusion on Day 1 through Day 5 and cisplatin 80 mg/m² as a 30- to 120-minute infusion on Day 1 of a 4-week cycle, as a proxy for chemotherapy administered in the advanced / metastatic setting in the economic model (Table 3). The resubmission stated that, for simplicity, the model assumed the same cost for chemotherapy alone in the resubmission as for add on chemotherapy to nivolumab.

Table 3: Chemotherapy costs in the advanced and metastatic setting

	Cisplatin	Fluorouracil
Dose	80mg/m ² = 141 mg	4000mg/m ² = 7044 mg
Maximum amount, mg	150	7500
DPMA, per dose	\$144.78	\$168.50
Doses per treatment course	5.1	6.6
Total (DPMA)	\$738.40	\$1,112.12
TOTAL	\$1,850.51	

Source: p11 of the submission, 'Subsequent treatment cost' spreadsheet of 'Attachment 1 Updated Economic Evaluation Workbook Adj OC and GOJC.xlsm'

DPMA = dispensed price per maximum amount; mg = milligram

Note: Assumed body surface area = 1.761m²

4.17 A summary of the subsequent therapy costs applied to the updated economic model is shown in Table 4. All patients in the standard of care arm of the economic model that experience disease recurrence are assumed to receive immunotherapy + chemotherapy at a total treatment cost of \$1,850.51. For those patients who receive nivolumab in the adjuvant treatment setting, upon disease recurrence they are all assumed to receive chemotherapy at a total treatment cost of \$2,479.

Table 4: Summary of total subsequent treatment costs used in the updated economic evaluation

Resource	Cost
Immunotherapy + chemotherapy	
Immunotherapy (\$)	
Infusion	\$1,539.88
Chemotherapy	\$1,850.51
Total (\$)	
Chemotherapy alone	
Chemotherapy	\$1,850.51
Infusion	\$628.10
Total	\$2,478.61

Source: p11 of the submission, 'Subsequent treatment cost' spreadsheet of 'Attachment 1 Updated Economic Evaluation Workbook Adj OC and GOJC.xlsm'

4.18 Results of the updated economic evaluation are presented in Table 5.

Table 5: Results of the updated economic evaluation*

	Nivolumab	Standard of care	Increment
Costs (\$)		\$46,806	
QALY	3.727	3.113	0.614
Incremental cost/ QALY gained			1

Source: 'Model' spreadsheet of 'Attachment 1 Updated Economic Evaluation Workbook Adj OC and GOJC.xlsm'

QALY = quality adjusted life year

*Including updated fees and associated charges that took effect 1 July 2022 and an updated MBS item fee for item 13950

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000/QALY

4.19 The economic model in the original submission assumed the average nivolumab treatment course included 7.07 infusions of 240 mg every two weeks and 5.23 infusions of 480 mg every 4 weeks. The economic model in the resubmission assumed all infusions were 480 mg taken every four weeks from treatment initiation (see Table 6).

- 4.20 The PBAC noted the economic model assumed approximately 84% of patients in the surveillance arm would recur (Year 1: 49%, Year 2: 21%, Year 3: 7%, Year 4: 4%, Year 5: 3%) and all patients (i.e., 100%) would receive immunotherapy in the advanced / metastatic treatment setting in the first 5 years.
- 4.21 The PBAC considered it unlikely that 100% of patients that recur would receive immunotherapy (due to declining performance status) and 80% was a more clinically reasonable estimate. The PBAC noted assuming 80% of recurrent patients are treated with immunotherapy increased the ICER from \$25,000/QALY to < \$35,000 per QALY gained to \$35,000/QALY to < \$45,000 per QALY gained.

Drug cost/patient/course

Table 6: Nivolumab cost per patient / course

	Economics		Financials		Total
	Nivolumab 240 mg every 2 weeks over first 16 weeks	Nivolumab 480 mg every 4 weeks for remainder of 1 year of treatment	Nivolumab 240 mg every 2 weeks over first 16 weeks	Nivolumab 480 mg every 4 weeks for remainder of 1 year of treatment	
Infusions per treatment course	-	8.8	7.07	5.23	12.3
DPMA per infusion (\$)	-				
Drug cost/patient/course (\$)	-				

Source: 'Model' spreadsheet of 'Attachment 1 Updated Economic Evaluation Workbook Adj OC and GOJC.xlsm'
 DPMA = dispensed price per maximum amount; mg = milligram

- 4.22 The drug cost associated with one treatment course of adjuvant nivolumab per patient reduced from \$| to \$| in the resubmission.
- 4.23 The financial estimates assumed patients received 7.07 infusions at a dose of 240 mg every 2 weeks and 5.23 infusions at a dose of 480 mg every 4 weeks. This is consistent with the assumptions used in the financial estimates and economic model in the previous submission. However, the economic model in the resubmission assumed all infusions were 480 mg taken every four weeks from treatment initiation. The PBAC noted assuming all patients receive 480 mg every 4 weeks was likely to have minimal impact on the ICER.

Estimated PBS usage and financial implications

- 4.24 The PBAC considered the number of patients likely to be treated with adjuvant nivolumab estimated in the July 2022 submission was reasonable, however noted that the financial estimates did not account for a reduction in use of immunotherapy in the advanced / metastatic setting (paragraph 7.12, nivolumab PBAC PSD, July 2022). The resubmission stated that the financial estimates for nivolumab in the advanced / metastatic setting only included patients with an initial diagnosis of advanced metastatic disease and did not include patients who progress from an early stage of disease. The resubmission considered it was not appropriate to include a cost offset for subsequent therapy for the adjuvant patient group. The PBAC considered this was

not reasonable as there was overlap in the estimated incident patient populations and stage at diagnosis between the advanced / metastatic submission and the adjuvant submission.

4.25 The updated workbook included an additional < 500 treated patients in the first year of listing, that were reflective of a prevalent pool of patients. This is consistent with PBAC consideration that it would be reasonable for 40% of the incident patients projected in year 1 to be used as an estimate for the prevalent population (paragraph 6.66, nivolumab PBAC PSD, July 2022).

4.26 The estimated use and financial implications provided in the resubmission are presented in Table 7. At year 6, the estimated number of treated patients was < 500 and the cost to the PBS / RPBS (less co-payments) was \$10 million to < \$20 million, this is compared to \$20 million to < \$30 million estimated in the original submission.

Table 7: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	1	2	2	2	2	2
Number of patients treated – previous submission	2	2	2	2	2	2
Number of infusions Q2W ^a	1	1	1	1	1	1
Number of infusions Q4W ^b	1	1	1	1	1	1
Estimated financial implications of nivolumab						
Cost to PBS/RPBS less co-payments (\$)	3	3	3	3	3	3
Cost to PBS/RPBS less co-payments – previous submission (\$)	4	4	4	4	4	4
Net financial implications						
Net cost to PBS/RPBS (\$)	3	3	3	3	3	3
Net cost to MBS (\$)	5	5	5	5	5	5
Net cost to PBS/RPBS/MBS (\$)	3	3	3	3	3	3
Net cost to PBS/RPBS/MBS – previous submission (\$)	4	4	4	4	4	4

Source: 'Attachment 2 Updated Budget Impact Model Price \$[redacted].xlsx' workbook. Table 16, July 2022 PBAC Public Summary Document. Note: Correction made to calculation errors made in the methods and assumptions section on '3a. Scripts – proposed' spreadsheet, 'Attachment 2 Updated Budget Impact Model Price \$[redacted].xlsx' workbook. Cells F188:K188 updated to reflect total number of patients electing treatment with nivolumab. Cells F192:K192 and cells F196:K196 updated to reflect total number of infusions.

^a Assuming 7.07 infusions per year as estimated by the submission.

^b Assuming 5.23 infusions per year as estimated by the submission

Shaded cells from previous consideration

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

³ \$10 million to < \$20 million

⁴ \$20 million to < \$30 million

⁵ \$0 to < \$10 million

Financial management – Risk Sharing Arrangements

- 4.27 The resubmission proposed amending the current risk share arrangement for nivolumab in the advanced / metastatic setting (GC/GOJC/OAC/OSCC) (Table 8), increasing the subsidisation caps to include utilisation in the adjuvant setting.
- 4.28 This proposed update maintains the existing tiered rebate for nivolumab in the advanced / metastatic setting (GC/GOJC/OAC/OSCC) with an 1% rebate for expenditure between 100-120% of the cap and a 2% rebate for expenditure beyond 120% for nivolumab in the adjuvant setting (OC/GOJC).

Table 8: Proposed update to risk share arrangement for nivolumab in gastro-oesophageal cancers

	Rebate tier	Patient population	Year 1	Year 2	Year 3	Year 4	Year 5
Existing advanced / metastatic subsidisation cap	Tier 1 (1% rebate)	Advanced metastatic GC/GOJC/OAC/second line OSCC	1	1	1	1	1
	Tier 2 (2% rebate)		2	2	2	2	2
Net cost to PBS / RPBS	N/A	Adjuvant OC/GOJC	3	3	3	3	3
Proposed subsidisation cap for gastro-oesophageal cancers ^a	Tier 1 (1% rebate)	Adjuvant OC/GOJC + advanced/metastatic	5	2	2	2	2
	Tier 2 (2% rebate)	GC/GOJC/OAC/second line OSCC	6	5	5	5	5

Source: p16 of the submission

GC = gastric cancer; GOJC = gastro-oesophageal junction cancer; OAC = oesophageal adenocarcinoma; OSCC = oesophageal squamous cell carcinoma

The redacted values correspond to the following ranges:

¹ \$30 million to < \$40 million

² \$40 million to < \$50 million

³ \$10 million to < \$20 million

⁴ \$20 million to < \$30 million

⁵ \$50 million to < \$60 million

⁶ \$60 million to < \$70 million

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy Program) Authority Required listing of nivolumab for the adjuvant treatment of patients with oesophageal cancer (OC) or gastroesophageal junction cancer (GOJC) who have received platinum-based chemoradiotherapy and surgery. The resubmission provided a revised economic model and financial estimates in response to previous concerns raised by the PBAC. The PBAC noted that additional revisions were made to the economic model that were not included in the early re-entry

pathway nominated at the July 2022 PBAC meeting and noted that the additional changes favoured nivolumab. The PBAC therefore considered the incremental cost-effectiveness ratio was underestimated and a further price reduction would be required to achieve a cost-effective listing for adjuvant nivolumab. The PBAC advised the net cost of listing nivolumab in the adjuvant treatment setting should be revised to account for the reduced use of immunotherapies in the advanced / metastatic treatment setting.

- 5.2 The PBAC recalled the poor prognosis of patients with OC and GOJC, the need for effective new adjuvant therapies and the quality of life benefits gained by reducing the burden associated with cancer recurrence (paragraph 7.2, nivolumab PBAC PSD, July 2022 meeting).
- 5.3 The PBAC recalled it had previously been satisfied that nivolumab was superior to the nominated comparator in improving disease free survival (DFS) with a hazard ratio of 0.67 (95% CI: 0.55, 0.81) and a median DFS of approximately 22 months compared to 10 months in the standard of care arm (paragraph 7.7, nivolumab PSD, July 2022). The PBAC noted no overall survival data were included in the July 22 submission or the resubmission.
- 5.4 The PBAC recalled it had previously considered that nivolumab was inferior to placebo in terms of comparative safety (paragraph 7.8, nivolumab PBAC PSD, July 2022).
- 5.5 The PBAC considered the restriction proposed by the Secretariat and accepted by the sponsor (see Section 3) was acceptable with the additional amendments outlined in paragraphs 3.4 and 3.5.
- 5.6 The PBAC noted a flow on change would be required to all immunotherapies listed in the advanced / metastatic treatment setting to include the treatment criteria: “Patient must be untreated with programmed cell death-1/ligand-1 (PD-1/PD-L1) inhibitor therapy for gastro-oesophageal cancer” to limit the use of immunotherapies to one course of treatment per patient per lifetime.
- 5.7 The PBAC noted the base case ICER presented in the resubmission was less than \$30,000 per QALY gained and that the updated economic model converged the overall survival curves using the approach as recommended in the July 2022 PBAC PSD. However, the PBAC also noted that additional revisions were made to the economic model to incorporate the cost of subsequent immunotherapy in the standard care arm. Although this revision was consistent with treatment with immunotherapy being restricted to one course per patient per lifetime and the PBS listing of nivolumab for advanced / metastatic gastro-oesophageal cancers, the PBAC noted that it was a deviation from the model scenario outlined for the early re-entry pathway, and it had a substantial impact on the incremental cost and the ICER. Further, the PBAC noted it was assumed that 100% of standard care patients with recurrence would receive immunotherapy and considered this to be an overestimate. The PBAC noted that the ICER increased from \$25,000/QALY to < \$35,000/QALY to \$55,000/QALY to < \$75,000 per QALY gained when the subsequent immunotherapy therapy costs in the standard

of care arm were removed and hence the model scenario outlined for the early re-entry submission was implemented (paragraph 7.14, nivolumab PBAC PSD, July 2022). The PBAC considered the lower estimate of the ICER (\$25,000/QALY to < \$35,000 per QALY gained) to be unreliable; and the upper estimate (\$55,000/QALY to < \$75,000 per QALY gained), although possibly an overestimate of the ICER, indicated that nivolumab was not cost-effective at the price proposed in the resubmission.

- 5.8 The PBAC noted that using the price recommended in the advanced / metastatic treatment setting for gastro-oesophageal cancers (\$1 per 100 mg vial), the ICER for the early re-entry model scenario decreased from \$55,000/QALY to < \$75,000/QALY to \$45,000/QALY to < \$55,000/QALY per QALY gained. The PBAC noted this exceeded the \$30,000 per QALY gained threshold stated in the July 2022 PBAC PSD, but acknowledged it was potentially an overestimate of the ICER, and, although based on a model that had not been evaluated, if more than 55% of recurrent patients in the standard of care arm received subsequent immunotherapy, the ICER would potentially be less than \$30,000/QALY. Overall, noting the poor prognosis and clinical need in this patient population, the PBAC considered that, on balance, nivolumab is likely to be cost-effective in the adjuvant treatment setting at the same vial price as the advanced / metastatic treatment setting.
- 5.9 The PBAC considered the estimated number of patients likely to be treated with nivolumab presented in the resubmission (500 to <5,000 in Year 1 to 500 to <5,000 in Year 6) and the methodology for calculating the financial implications of listing nivolumab was reasonable. However, the PBAC considered the net cost to the PBS/RPBS was overestimated as the financial estimates did not account for reduced use of immunotherapy in the advanced / metastatic treatment setting. The PBAC considered it would be appropriate for the financial estimates to assume 49% of patients who receive nivolumab in the adjuvant setting would have received treatment with immunotherapy in the advanced / metastatic setting if nivolumab was not available in Year 1, 21% in Year 2, 7% in Year 3, 4% in Year 4 and 3% in Year 5, consistent with the economic model (as outlined in paragraph 4.20). Additionally, the PBAC considered it would be appropriate for the financial estimates to assume reduced use of immunotherapy in the advanced / metastatic setting for approximately 80% of patients.
- 5.10 The PBAC considered the additional expenditure associated with nivolumab in the adjuvant treatment setting, taking into account the reduced effective price (as outlined in paragraph 5.8) and offsets for reduced use of subsequent immunotherapy (as outlined in paragraph 5.9), could be added to the expenditure caps in the current risk sharing arrangement in place for gastro-oesophageal cancers.
- 5.11 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for nivolumab:

- a) The treatment is expected to provide a moderate improvement in efficacy over standard of care ('watch and wait' surveillance) on the basis of the clinical evidence considered at the July 2022 meeting;
- b) The treatment is not expected to address a high and urgent unmet clinical need;
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

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

Outcome:

Recommended

6 Recommended listing

6.1 Add new indication as follows:

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
NIVOLUMAB Injection	NEW (Public) NEW (Private)	480	5
Available brands			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)			
Restriction Summary [new] / Treatment of Concept: [new]			
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners		
	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)		
	Episodicity: Adjuvant treatment of		
	Severity: stage II or III		
	Condition: oesophageal cancer or gastro-oesophageal cancer		
	Indication: Adjuvant treatment of stage II or III oesophageal cancer or gastro-oesophageal cancer		
	Treatment Phase: [blank]		
	Clinical criteria:		
	The condition must have histological evidence confirming a diagnosis of a least one of: (i) adenocarcinoma, (ii) squamous cell cancer; document this evidence in the patient's medical records		
	AND		
	Clinical criteria:		
	The condition must have been treated with neoadjuvant platinum-based chemoradiotherapy		
	AND		

Public Summary Document – November 2022 PBAC Meeting

	Clinical criteria:
	The treatment must be for the purposes of adjuvant use following complete surgical resection that occurred within 16 weeks prior to initiating this drug
	AND
	Clinical criteria:
	The condition must have evidence, through resected specimen, that residual disease meets the Tumour Nodes Metastases (TNM) staging system (as published by the Union for International Cancer Control) of either: (i) at least ypT1, (ii) at least ypN1; document this evidence in the patient's medical records
	AND
	Clinical criteria:
	Patient must have/have had, at the time of initiating treatment with this drug, a WHO performance status no higher than 1
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	Treatment criteria:
	Patient must be undergoing treatment with a dosing regimen as set out in the drug's approved Australian Product Information
	AND
	Treatment criteria:
	Patient must not be undergoing PBS subsidised treatment with this drug where this prescription extends treatment beyond whichever comes first: (i) 12 months from treatment initiation, irrespective of whether initial treatment was PBS-subsidised/non-PBS subsidised, (ii) disease recurrence despite treatment with this drug; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: Up to an additional 2 repeat prescriptions (7 in total) may be sought only where dosing is on a 2-weekly schedule in the first 16 weeks of treatment. This listing's stated number of repeat prescriptions is based on 4-weekly dosing.
	Administrative Advice: No increase in the maximum amount or number of units may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.

6.2 Flow on changes:

Add the following Clinical criteria to the Initial treatment phase restriction of the following drug listings:

	Clinical criteria
	Patient must be untreated with programmed cell death-1/ligand-1 (PD-1/PD-L1) inhibitor therapy for gastro-oesophageal cancer

PBS item code	Restriction Summary (as at 1/11/22; for internal Dept. use)	Drug	Indication
	13280	Nivolumab	Advanced or metastatic gastro-oesophageal cancers

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

7 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.

8 Sponsor's Comment

The Sponsor welcomes the PBAC's decision to recommend nivolumab for the adjuvant treatment of patients with oesophageal cancer (OC) or gastroesophageal junction cancer (GOJC) who have received platinum-based chemoradiotherapy and surgery. We look forward to working with the Department of Health to bring this important treatment to patients in a timely manner.