

11.05 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 of Submission

- 1.1 The Category 3 submission requested an increase to the expenditure caps for the current Risk Sharing Arrangement (RSA) to reflect the inclusion of the first line oesophageal squamous cell carcinoma (1L OSCC) indication to the existing PBS listings of nivolumab for advanced or metastatic gastro-oesophageal cancers.
- 1.2 The submission requested the PBAC to consider changes to the estimated patient numbers and financial implications that inform the RSA. The submission presented revised financial estimates that were specific to the OSCC population, including:
 - estimated patient numbers for 1L OSCC, whose tumour cell programmed death-ligand 1 (PD-L1) expression is $\geq 1\%$
 - grandfathered patients who had accessed nivolumab as first line therapy through the sponsor's compassionate supply program
 - revised patient numbers for second line (2L) OSCC

2 Background

- 2.1 Nivolumab has been PBS-listed for advanced or metastatic gastro-oesophageal cancers as defined by the specific tumour types included in the approved Australian Product Information (PI) since 1 October 2022.

Registration status

- 2.2 Nivolumab was registered on the Australian Register for Therapeutic Goods (ARTG) on 22 February 2021 and 31 January 2022, respectively, for:
 - Second line treatment as monotherapy for patients with unresectable advanced, recurrent or metastatic OSCC after prior fluoropyrimidine and platinum (FP) based chemotherapy
 - First line treatment, in combination with FP based combination chemotherapy, for patients with human epidermal growth factor receptor 2 (HER-2) negative advanced or metastatic gastric cancer (GC) or gastro-oesophageal junction cancer (GOJC), or oesophageal adenocarcinoma (OAC)

- 2.3 At the time of PBAC consideration, nivolumab was not TGA registered for 1L OSCC but the TGA Delegate's Overview was available. The TGA Delegate was supportive of registration for the following indication: (i) in combination with FP based combination chemotherapy for the first line treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC with tumour cell PD-L1 expression $\geq 1\%$ and (ii) in combination with ipilimumab for the first line treatment of adult patients with unresectable advanced, recurrent or metastatic OSCC with tumour cell PD-L1 expression $\geq 1\%$. The sponsor advised it agreed with the TGA's proposed indication for 1L OSCC that is restricted to a subgroup of patients with tumour cell PD-L1 expression $\geq 1\%$ (as determined by a validated test).

Previous PBAC consideration

- 2.4 Nivolumab was considered by the PBAC for 2L OSCC in July 2021 and March 2022, and for 1L HER-2 negative advanced or metastatic GC, GOJC, or OAC in November 2021 and March 2022.
- 2.5 A summary of previous PBAC considerations is provided in Table 1.

Table 1: Previous relevant PBAC considerations

Meeting date	Request	Outcome	Detail
July 2021	An Authority Required (STREAMLINED) listing of nivolumab for the treatment of advanced or metastatic OSCC in patients who have failed one fluoropyrimidine and platinum (FP)-based chemotherapy treatment regimen, with a WHO performance status (PS) of 0 or 1.	Recommended	The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required (STREAMLINED) listing of nivolumab for the treatment of patients with advanced or metastatic OSCC who have disease progression following treatment with a FP-based chemotherapy regimen. The PBAC considered that the ICER was high at the proposed price and a price reduction would be required to ensure nivolumab is cost-effective in this population.
November 2021	An Authority Required listing of nivolumab in combination with platinum-containing plus fluoropyrimidine-containing chemotherapy for the treatment of non-HER-2 positive advanced or metastatic gastric cancer (GC), gastro-oesophageal junction cancer, (GOJC) or oesophageal adenocarcinoma (OAC).	Not recommended	The PBAC did not recommend the listing of nivolumab in combination with chemotherapy for the treatment of non-HER-2 positive advanced or metastatic GC, GOJC or OAC. The PBAC considered the ICER in this setting at the proposed price was high and moderately uncertain.
March 2022 (out of session)	An early resolution resubmission was sought to address the PBAC's concerns from its November 2021 meeting, for the treatment of non-HER-2 positive advanced or metastatic GC, GOJC or OAC.	Recommended	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.
March 2022	A request for the PBAC to reconsider its July 2021 recommendation for a Section 100 (Efficient Funding of Chemotherapy), Authority Required (STREAMLINED) listing for the second line treatment of OSCC after prior FP based chemotherapy.	Recommended	The PBAC considered it would be cost-effective at the same price per 100 mg vial recommended for the first line treatment of gastro-oesophageal cancers. The PBAC considered it would be appropriate to implement a single listing for gastro-oesophageal cancers with the financial estimates for the second line population added to the expenditure caps for the first line population.

Source: nivolumab Public Summary Documents (PSDs), July 2021, November 2021, March 2022 (HER-2 negative GC, GOJC, or OAC), and March 2022 (2L OSCC) PBAC meetings

Abbreviation: WHO: World Health Organization, ICER: incremental cost effectiveness ratio, HER-2: human epidermal growth factor receptor 2

2.6 Between the November 2021 and March 2022 PBAC meetings, as part of its recommendation for 1L HER-2 negative advanced or metastatic GC, GOJC, or OAC, the PBAC considered it would be appropriate for nivolumab 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 PI, and the expenditure caps for the RSA should be based on the financial estimates of listing for the specific tumour types that are TGA approved. Further, the PBAC advised that, if nivolumab was recommended for 2L OSCC, it would 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 (nivolumab (HER-2 negative GC, GOJC, or OAC) Public Summary Document (PSD), March 2022).

- 2.7 At its March 2022 meeting, the PBAC recommended the listing of nivolumab for 2L OSCC and reiterated that it would be appropriate to implement a single listing for gastro-oesophageal cancers with the financial estimates for the 2L OSCC population added to the expenditure caps for the 1L gastro-oesophageal cancer population (nivolumab (2L OSCC) PSD, March 2022).

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

3 Requested listing

- 3.1 The submission requested no changes to the existing listings of nivolumab for advanced or metastatic gastro-oesophageal cancers.

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item.

Consumer comments

- 4.2 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the nivolumab submission, categorising it as one of the therapies of ‘high priority for PBS listing’ on the basis of the Checkmate 648 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for nivolumab in 1L OSCC, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement).

Current RSA and expenditure

- 4.3 There is an RSA for advanced or metastatic gastro-oesophageal cancers to manage the risk of nivolumab use outside the intended population. Details of patient numbers and expenditure for the current agreed caps from October 2022 to September 2027 are provided in Table 2.

Table 2: Details of patient numbers and financial estimates agreed in the Deed

	Year 1	Year 2	Year 3	Year 4	Year 5
Agreed patient estimates					
Patients treated for 2L OSCC	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Patients treated for 1L gastro-oesophageal cancer	█ ²	█ ²	█ ²	█ ²	█ ²
Agreed financial implications for the PBS/RPBS					
Financial estimates for 2L OSCC (\$)	█ ³	█ ³	█ ³	█ ³	█ ³
Financial estimates for 1L gastro-oesophageal cancer (\$)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Subsidisation Cap 1 (\$)	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Subsidisation Cap 2 (\$)	█ ⁵	█ ⁵	█ ⁵	█ ⁵	█ ⁵

Source: Attachment 5 - Deed of Agreement for the supply of nivolumab for the treatment of advanced or metastatic gastro-oesophageal cancers, Attachment 6 - financial model workbook for 2L OSCC, and Attachment 7 - financial model workbook for 1L HER-2 negative advanced or metastatic GC, GOJC, or OAC,

Abbreviations: Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks

Note: effective approved ex-manufacturer price (AMEP): 40 mg in 4 mL = \$█, 100 mg in 10 mL = \$█; Year 1 patients treated for 2L OSCC included < 500 grandfathered patients, dosing regimens: 240 mg Q2W or 480 mg Q4W; Year 1 patients treated for 1L gastro-oesophageal cancer included < 500 grandfathered patients, dosing regimens: 240 mg Q2W or 360 mg Q3W

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ \$30 million to < \$40 million

⁵ \$40 million to < \$50 million

4.4 The PBAC noted that the 1L OSCC population had not been accounted for in the expenditure caps.

Estimated PBS usage and financial implications

4.5 The sponsor provided an updated estimate of the patient numbers and financial implications to align with the TGA proposed population for 1L OSCC (patients with PD-L1 ≥1%).

4.6 Table 3 outlines key inputs and assumptions applied in the utilisation and financial estimates.

Table 3: Key inputs and assumptions applied in the utilisation and financial estimates

Data	Value and Source	Note
Patients with OSCC eligible for nivolumab treatment		
Estimated incident patients with OC	Calculated based on estimated number of patients (1,587) diagnosed with OC in 2020 (AIHW, 2020), applying a population growth rate of 1.3% per annum (ABS, 2020)	Consistent with parameter values and data source to estimate patient numbers diagnosed with OC in previous submission (July 2021 PBAC meeting) for 2L OSCC
Proportion of patients with OSCC	35.3% Source: AIHW 2021 report - Oesophageal and stomach cancers.	Consistent with parameter values and data source for the proportion of OC with SCC histology in previous submission for 2L OSCC

Public Summary Document – March 2023 PBAC Meeting

Data	Value and Source	Note
Disease stage at diagnosis	Stage I: 10.4% Stage II/III: 56.8% Stage IV: 27.2% Source: Nguyen, T. M., et al. (2019). Pattern of care for cancer of the oesophagus in a western population.	Consistent with parameter values and data source for the proportion of disease stages in previous submission for 2L OSCC
Proportion of patients treated immediately with palliative therapy	Stage I: 10.3% Stage II/III: 36.2% Stage IV: 99.0% Source: Nguyen, T. M., et al. (2019). Pattern of care for cancer of the oesophagus in a western population.	These parameters were applied to estimate the proportion of patients eligible for 1L chemotherapy at diagnosis in previous submission. This submission applied the same parameters to estimate an incident population eligible for treatment.
Patient estimates for 1L OSCC		
Proportion of patients with WHO performance status of 0 or 1	74.4% Source: Jaffe, D. H., (2019), A global perspective in second line treatment patterns for patients with advanced esophageal squamous cell carcinoma.	This submission assumed that patients with WHO performance status score of 0 or 1 to be eligible for treatment.
Proportion of patients with PD-L1 ≥ 1%	75% Source: Checkmate 648 (CA209648): a randomized multicentre phase 3 study of nivolumab plus ipilimumab or nivolumab combined with fluorouracil plus cisplatin versus fluorouracil plus cisplatin in subjects with unresectable advanced, recurrent or metastatic previously untreated OSCC.	This submission noted that less than half of the trial population (Checkmate 648) who received nivolumab plus chemotherapy had tumour cell PD-L1 expression ≥ 1%. Given that PD-L1 testing is not routinely used in Australia, 75% was applied to estimate a patient population whose tumour cell PD-L1 expression level is ≥ 1%.
Proportion of patients electing 1L nivolumab therapy	██████% Source: Advisory board	This submission assumed that ██████% of the eligible patients would elect 1L nivolumab therapy.
Patient estimates for 2L OSCC		
Proportion of patients with WHO performance status of 0 or 1	74.4% Source: Jaffe, D. H., (2019), A global perspective in second line treatment patterns for patients with advanced esophageal squamous cell carcinoma.	This submission assumed that patients with WHO performance status score of 0 or 1 to be eligible for treatment.
Proportion of patients electing 1L chemotherapy	70% Source: DUSC advice July 2021	This submission assumed that 70% of the eligible patients would receive 1L chemotherapy, which was an increase from 61% to account for DUSC commentary in previous submission.
Proportion of patients electing 2L therapy	80% Source: Advisory board	This submission assumed that 80% of patients would receive 2L systemic therapy following 1L FP based chemotherapy.
Proportion of patients eligible for 2L nivolumab therapy	90% - 10% Assumption only	A declining number of patients with OSCC eligible for 2L nivolumab therapy is expected as a number of patients who received 1L nivolumab therapy would increase over time.
Proportion of patients electing 2L nivolumab therapy	██████% Source: Advisory board	This submission assumed that ██████% of the eligible patient population would elect 2L nivolumab therapy.

Source: Table 16 of nivolumab PSD, July 2021, Attachment 4 - financial model workbook for 1L OSCC updated

Abbreviations: ABS = Australian Bureau of Statistics; AIHW = Australian Institute of Health and Welfare; OC = oesophageal cancer; OSCC = oesophageal squamous cell carcinoma; FP = fluoropyrimidine and platinum

4.7 Table 4 presents revised financial estimates and the proposed increase to the current expenditure caps due to the inclusion of 1L OSCC patients.

Table 4: Estimated usage and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients treated						
- First line OSCC	1	1	1	1	1	1
- First line OSCC (GF)	1	-	-	-	-	-
- Second line OSCC	1	1	1	1	1	1
Total patients treated	1	1	1	1	1	1
Estimated financial implications of nivolumab						
Cost to PBS/RPBS less co-payments						
- First line OSCC (\$)	2	2	2	2	2	2
- First line OSCC (GF) (\$)	2	-	-	-	-	-
- Second line OSCC (\$)	2	2	2	2	2	2
Total expenditure (\$)	2	2	2	2	2	2
Estimated increase to expenditure caps due to the inclusion of 1L OSCC						
Cost to PBS/RPBS for 1L and 2L OSCC (\$)	2	2	2	2	2	-
Expenditure caps agreed for 2L OSCC (\$)	3	3	3	3	3	-
Net increase to expenditure caps (\$)	2	2	2	2	2	-

Source: Tables 1, 2, 4, 5 of the main submission updated

Abbreviations: MBS = Medical Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme. GF = grandfathered; Q2W = every 2 weeks; Q4W = every 4 weeks

Note: dosing regimens: 2L OSCC: 240 mg Q2W or 480 mg Q4W; 1L OSCC: 240 mg Q2W; effective approved ex-manufacturer price (AMEP): 40 mg in 4 mL = \$█, 100 mg in 10 mL = \$█

The redacted values correspond to the following ranges:

¹ < 500

² \$0 to < \$10 million

³ net cost saving

4.8 The submission stated that, although the TGA proposed indication allows patients to access nivolumab through the PBS and ipilimumab privately, the sponsor had only accounted for an increase in patient numbers, when nivolumab is used in combination with fluorouracil plus cisplatin in the first line setting. As of the March 2023 PBAC meeting, ipilimumab had not been listed on the PBS for this indication.

4.9 The submission included < 500 patients receiving nivolumab for 1L OSCC via compassionate access who may require transitioning to PBS subsidised treatment. The submission anticipated a declining number of 2L OSCC patients over time as patients are expected to be treated with nivolumab earlier in the treatment pathway upon TGA registration for 1L OSCC and patients who are treated with nivolumab as first line therapy will not be eligible for nivolumab in the second line setting.

4.10 While less than half of the trial population (Checkmate 648) who received nivolumab plus chemotherapy were those with tumour cell PD-L1 expression $\geq 1\%$, the updated submission assumed that a higher proportion of patients (75%) would access nivolumab as first line therapy under the restricted indication, on the basis that PD-L1 immunohistochemistry (IHC) testing is not routinely used in practice and therefore it is likely that clinicians will still use nivolumab for a range of patient characteristics.

- 4.11 The updated submission also assumed that 100% of 1L OSCC patients would elect nivolumab over pembrolizumab. However, the PBAC previously considered that, while the indications for nivolumab and pembrolizumab are not fully aligned, there would be an impact on nivolumab utilisation as there is likely to be significant overlap in patients who are treated with nivolumab or pembrolizumab in clinical practice, if pembrolizumab was recommended for PBS listing in a similar population (nivolumab (HER-2 negative GC, GOJC, or OAC) PSD, March 2022). In May 2022, the PBAC recommended the listing of pembrolizumab 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.
- 4.12 The sponsor requested that the current RSA be revised to reflect the updated financial estimates. The net financial impact to the PBS/RPBS for the inclusion of the 1L OSCC indication was estimated to be \$10 million to < \$20 million over the first 5 years of listing and \$10 million to < \$20 million over 6 years, excluding the incremental net cost of chemotherapy agents (i.e., fluorouracil and cisplatin) being used in combination with nivolumab for the first line treatment of OSCC.

Committee-In-Confidence information

- 4.13 [Redacted]
- 4.14 [Redacted]
- [Redacted]
- 4.15 [Redacted]
- [Redacted]
- 4.16 [Redacted]

End Committee-In-Confidence information

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

5 PBAC Outcome

- 5.1 The PBAC recommended amending the current risk sharing arrangement (RSA) expenditure caps for nivolumab for the treatment of advanced or metastatic gastro-oesophageal cancers. The PBAC advised that it was supportive of the requested increase to the expenditure caps to account for the expected additional use of nivolumab should the first line treatment of advanced or metastatic oesophageal squamous cell carcinoma (OSCC) in patients with tumour cell programmed death-ligand 1 (PD-L1) expression $\geq 1\%$, either in combination with fluoropyrimidine and platinum (FP) based chemotherapy or in combination with ipilimumab, be included in the approved Australian Product Information (PI) for nivolumab.
- 5.2 The PBAC recalled its previous consideration that the expenditure caps for the RSA should be based on the financial estimates of listing for the specific tumour types included in the approved TGA indications. As such, the PBAC considered that, given the restriction criteria that allow OSCC patients access nivolumab as first line therapy upon TGA registration for 1L OSCC, it would be appropriate to include the expenditure for this population in the RSA caps.
- 5.3 The PBAC noted the revised financial estimates incorporated the additional patient estimates for 1L OSCC. The PBAC advised that the estimated number of patients expected to be treated with nivolumab for 1L OSCC were reasonable and consistent with those considered by the PBAC in May 2022 for pembrolizumab (see Table 6), noting that a lower incidence of oesophageal cancer (1,587) and annual growth rate (1.3% per annum) based on more recent data applied in the estimates for nivolumab. The PBAC considered that, overall, the assumptions applied in the revised financial estimates were reasonable, although it was unlikely that 100% of OSCC patients would elect nivolumab over pembrolizumab as first line treatment should the listing for pembrolizumab for the first line treatment of advanced or metastatic gastro-oesophageal cancers proceed.
- 5.4 The PBAC noted that the submission assumed that OSCC patients would likely be treated with nivolumab earlier in the treatment pathway due to the inclusion of the 1L OSCC indication and therefore the decrease in patient numbers for 2L OSCC is expected over time. The PBAC considered this assumption was reasonable.
- 5.5 The PBAC also noted that the submission included < 500 patients receiving nivolumab for 1L OSCC via compassionate access who may require transitioning to PBS subsidised treatment in Year 1 of the patient estimates.
- 5.6 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:

Recommended

6 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.

7 Sponsor's Comment

The Sponsor welcomes the PBAC's recommendation to increase to the expenditure caps for the current Risk Sharing Arrangement to reflect the inclusion of the first line oesophageal squamous cell carcinoma (1L OSCC) indication to the existing PBS listings of nivolumab for advanced or metastatic gastro-oesophageal cancers.