14.04 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 To consider whether nivolumab for advanced or metastatic oesophageal squamous cell carcinoma (OSCC) should be agnostic to PD-L1 status.

1.2 This consideration was initiated by the Department of Health and Aged Care to address a gap in access to PD-L1 treatment for patients with OSCC and PD-L1 < 1%.

2 Background

2.1 Nivolumab has the following TGA marketing approvals in advanced unresectable, recurrent, metastatic gastro-oesophageal cancers:

Oesophageal Squamous Cell Carcinoma (OSCC)

OPDIVO in combination with ipilimumab is indicated for the first-line treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1% as determined by a validated test.

OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1% as determined by a validated test.

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.

Gastric Cancer (GC), Gastro-oesophageal Junction Cancer (GOJC), or Oesophageal Adenocarcinoma (OAC)

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.

2.2 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, March 2022 and March 2023.

2.3 PBAC has previously noted a high clinical need for effective treatments for OSCC, oesophageal adenocarcinoma (OAC), human epidermal growth factor receptor 2 (HER2)-negative adenocarcinoma (AC) of the gastro-oesophageal junction (GOJ), and HER2-negative gastric AC, given the poor prognosis for patients and the poor efficacy and high toxicity of current treatments (see paragraph 7.1, November 2021 Public Summary Document (PSD), pembrolizumab for advanced or metastatic gastro-oesophageal cancer).

2.4 The PBAC has previously noted differences in design and patient populations across the pembrolizumab and nivolumab trials, but considered that, overall, there was unlikely to be any difference between pembrolizumab and nivolumab in clinical practice for the first line treatment of gastro-oesophageal cancers in terms of clinical benefit, tolerability and treatment duration (see paragraph 13.6, March 2022 Addendum to November 2021 PSD, pembrolizumab for advanced or metastatic gastro-oesophageal cancer).

2.5 More generally, the PBAC's previous recommendations on listing medicines in the intention-to-treat (ITT) population versus a biomarker-defined subgroup are made on a case-by-case basis and have depended on a variety of real-world clinical factors including efficacy and toxicity of available treatments, severity of disease, ability of the biomarker to predict treatment effect, turn-around time for the test, and size of the subgroup.

2.6 Pembrolizumab was recommended by the PBAC at the May 2022 intra-cycle meeting for advanced/ or metastatic oesophageal/gastro-oesophageal junction cancers. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of pembrolizumab (as a first-line treatment) would be acceptable at the same or lower cost per 3 weekly treatment cycle as for nivolumab (as a first line treatment) for gastro-oesophageal cancers. The PBAC considered it was appropriate for pembrolizumab to be included in the risk share arrangement recommended for nivolumab, with the expenditure caps increased to account for the expected additional use in the first line treatment of OSCC (see Committee in Confidence – Table 1).

Committee-in-Confidence

[redacted]

End Committee-in-Confidence

3 Requested listing

3.1 The nivolumab advanced/metastatic gastro-oesophageal cancers PBS listing as on 1 June 2023 is reproduced below.

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
MEDICINAL PRODUCT Form	**PBS item code**	**Maximum amount**	**No. of Repeats**
NIVOLUMAB Injection	13121N (Public Hospital) 13117J (Private Hospital) MP	480 mg	13
Available brands			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)			
Authority Required (STREAMLINED)			
Indication: Advanced or metastatic gastro-oesophageal cancers			
Clinical criteria:			
The condition must be a gastro-oesophageal cancer type as specified in the drug's 'Indications' section of the approved Australian Product Information			
AND			
Clinical criteria:			
The treatment must be prescribed in accordance with the drug's 'Indications' section of the approved Australian Production Information with respect to each of: (i) concomitant drugs/therapies, (ii) line of therapy (i.e. prior treatments, if any)			
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:			
Patient must be untreated with programmed cell death-1/ligand-1 (PD-1/PD-L1) inhibitor therapy for gastro-oesophageal cancer			
Treatment 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 from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs			
Caution: 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.			

Administrative Advice: The stated maximum amount in this listing is based on this drug's approved Product Information recommended dosing in 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 (Dose and Method of Administration or Clinical Trials sections) for the recommended dosing in the specific cancer type.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

3.2 The PBAC was asked to consider two options for amending the restriction. The first would see the restriction amended to be silent on PDL1 status, line of therapy and concomitant therapy. The second would amend the restriction to be silent on PDL1 status but specify line of therapy and concomitant therapy. Bristol Myers Squibb Australia (BMSA) the responsible person (RP) for nivolumab on the PBS, indicated it would not be able to proceed with the first option without first undertaking an assessment of its impact on utilisation which would necessitate a delay in PBAC consideration.

4 Estimated PBS usage, financial implications, and risk sharing arrangements

4.1 In March 2023, via a Category 3 submission from BMSA, the PBAC recommended 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, PD-L1>1%) listing to the existing PBS listings of nivolumab for advanced or metastatic gastro-oesophageal cancers.

4.2 BMSA requested a further increase to the RSA expenditure caps to accommodate uptake in patients with PDL1 <1% (Table 3).

Table 3: Financial estimates and proposed increase to existing caps requested by BMSA alongside PBS restriction change detailed in Option 1

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients treated						
Additional 1L OSCC patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of nivolumab						
Cost to PBS/RPBS less co-payments						
Additional total expenditure due to 1L OSCC restriction change ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated increase to expenditure caps due to the inclusion of 1L OSCC						
Net increase to expenditure caps ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	-

The redacted values correspond to the following ranges:
[1] < 500
[2] $0 to < $10 million

4.3 Table 4 provides revised financial estimates calculated to reflect the patient number estimates previously considered by the PBAC for the extended population. (These estimates have been calculated on a pro-rata basis compared with the requested

increases in Table 3. These revised estimates are subject to agreement with the Department of Finance).

Table 4: Secretariat revised net financial impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost to PBS/RPBS ($)	[1]	[1]	[1]	[1]	[1]

The redacted values correspond to the following ranges:
[1] $0 to < $10 million

5 PBAC Outcome

5.1 The PBAC recommended the current PBS listing for nivolumab for OSCC within the broader indication of 'advanced or metastatic gastro-oesophageal cancers' be amended so that it is silent on PD-L1 status, but specifies concomitant/backbone therapy, line-of-therapy and HER-2 status.

5.2 The PBAC reiterated its view that there is a high clinical need for effective treatments for oesophageal squamous cell carcinoma (OSCC), oesophageal adenocarcinoma (OAC), human epidermal growth factor receptor 2 (HER2)-negative adenocarcinoma (AC) of the gastro-oesophageal junction (GOJ), and HER2-negative gastric AC, given the poor prognosis for patients and the poor efficacy and high toxicity of current treatments. The PBAC noted that the recommended expanded listing will enable access to a PD-L1 inhibitor for a subset of patients with OSCC that do not currently have access to PBS-subsidised immunotherapy.

5.3 In making this recommendation, the PBAC recalled it had previously noted differences in design and patient populations across the pembrolizumab and nivolumab trials in gastro-oesophageal cancers, but considered that, overall, there was unlikely to be any difference between pembrolizumab and nivolumab in clinical practice for the first line treatment of gastro-oesophageal cancers in terms of clinical benefit, tolerability and treatment duration. Thus, the PBAC was satisfied the extended PBS listing of nivolumab will provide, for some patients, a significant improvement in efficacy over the comparator, chemotherapy alone.

5.4 The PBAC recommended the current nivolumab restriction for advanced or metastatic gastro-oesophageal cancers be amended to:

i. Remove the criterion "The treatment must be prescribed in accordance with the drug's 'Indications' section of the approved Australian Production Information with respect to each of: (i) concomitant drugs/therapies, (ii) line of therapy (i.e. prior treatments, if any)"

ii. Describe three patient population subsets with the following findings:

Population 1

Conditions: gastric cancer, gastro-oesophageal junction cancer, oesophageal adenocarcinoma

Concomitant therapies: chemotherapy containing at least a fluoropyrimidine drug plus a platinum drug

Line of treatment: first-line drug treatment

Additional clinical finding: HER2 negative

Population 2

Condition: oesophageal squamous cell carcinoma (can be recurrent)

Concomitant therapies: chemotherapy containing at least a fluoropyrimidine drug plus a platinum drug

Line of treatment: first-line drug treatment

Additional clinical finding: unresectable

Population 3

Condition: oesophageal squamous cell carcinoma (can be recurrent)

Line of treatment: second-line drug treatment after chemotherapy containing at least a fluoropyrimidine drug plus a platinum drug

Additional clinical finding: unresectable

5.5 The PBAC recommended the RSA caps for nivolumab for gastro-oesophageal cancers could be increased in line with the estimates presented in Table 3 above, reflecting the lower patient number estimates previously considered by the PBAC for the extended patient population.

The PBAC stated a future application for HER2-positive patients would be welcomed. This would provide the Committee with an opportunity to consider the strengths and weaknesses of available data for HER2-positive patients and the likely utilisation in Australia.

Outcome:
Recommended

6 Recommended listing

6.1 Amend the existing restriction as follows:

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
MEDICINAL PRODUCT Form	**PBS item code**	**Maximum amount**	**No. of Repeats**
NIVOLUMAB Injection	13121N (Public Hospital) 13117J (Private Hospital) MP	480 mg	13
Available brands			
Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)			

Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)	
Edit Restriction Summary 13881 / ToC: 13888: Authority Required: Streamlined	
	Indication: Advanced or metastatic gastro-oesophageal cancers
	~~**Clinical criteria:**~~
	~~The condition must be a gastro-oesophageal cancer type as specified in the drug's 'Indications' section of the approved Australian Product Information~~
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~The treatment must be prescribed in accordance with the drug's 'Indications' section of the approved Australian Production Information with respect to each of: (i) concomitant drugs/therapies, (ii) line of therapy (i.e. prior treatments, if any)~~
	~~**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:
	~~Patient must be untreated with programmed cell death 1/ligand 1 (PD 1/PD L1) inhibitor therapy for gastro-oesophageal cancer~~ *Patient must be untreated (up until initiating this drug) with programmed cell death-1/ligand-1 (PD-1/PD-L1) inhibitor therapy for gastro-oesophageal cancer*
	Treatment criteria:
	Patient must not be undergoing treatment with this drug as a PBS benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 months from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs
	Population criteria:
	Patient must be in one of the three population subsets described below
	Prescribing Instructions: *Population 1* *Conditions: gastric cancer, gastro-oesophageal junction cancer, oesophageal adenocarcinoma* *Concomitant therapies: chemotherapy containing at least a fluoropyrimidine drug plus a platinum drug* *Line of treatment: first-line drug treatment* *Additional clinical finding: HER2 negative* *Population 2* *Condition: oesophageal squamous cell carcinoma (can be recurrent)* *Concomitant therapies: chemotherapy containing at least a fluoropyrimidine drug plus a platinum drug* *Line of treatment: first-line drug treatment* *Additional clinical finding: unresectable* *Population 3* *Condition: oesophageal squamous cell carcinoma (can be recurrent)* *Line of treatment: second-line drug treatment after chemotherapy containing at least a fluoropyrimidine drug plus a platinum drug* *Additional clinical finding: unresectable*
	Caution: 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.
	Administrative Advice: The stated maximum amount in this listing is based on this drug's approved Product Information recommended dosing in 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 (Dose and Method of Administration or Clinical Trials sections) for the recommended dosing in the specific cancer type.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: 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.

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 had no comment.