7.14 NIVOLUMAB, concentrate solution for infusion, 10 mg/mL, 1 x 4 mL vial, 1 x 10 mL vial, Opdivo®, Bristol Myers Squibb

1 Purpose of Application

1.1 The minor re-submission requested a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for the treatment of unresectable Stage III or Stage IV malignant melanoma.

2 Requested listing

2.1 The re-submission requested the same restriction as per the previous July 2015 submission. Secretariat suggested wording as per the July 2015 submission is reproduced below with suggestions and additions in *italics* and deletions in ~~strikethrough~~:

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer	
NIVOLUMAB nivolumab 40 mg/4 mL injection, 1 x 4 mL vial nivolumab 100 mg/10 mL injection, 1 x 10 mL vial	*360 mg*	5	-	Opdivo	Bristol-Myers Squibb Australia

Initial treatment - BRAF V600 mutation negative

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined

Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition AND The condition must not have been treated previously with *a PD-1 inhibitor* ~~nivolumab~~; *OR* *Patient must have developed intolerance to another PD-1 inhibitor of a severity necessitating permanent treatment withdrawal* *AND* *The condition must be negative for a BRAF V600 mutation*
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	~~The recommended dose of nivolumab is 3 mg/kg administered intravenously over 60 minutes every 2 weeks.~~ *No increase in the maximum number of repeats may be authorised.* *Special Pricing Arrangements apply.*

Initial treatment - BRAF V600 mutation positive

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined

Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition AND The condition must not have been treated previously with *a PD-1 inhibitor* ~~nivolumab~~; *OR* *Patient must have developed intolerance to another PD-1 inhibitor of a severity necessitating permanent treatment withdrawal* *AND* *The condition must be positive for a BRAF V600 mutation* *AND* *The condition must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor) unless contraindicated or not tolerated according to the TGA approved Product Information.*
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	~~The recommended dose of nivolumab is 3 mg/kg administered intravenously over 60 minutes every 2 weeks.~~ *No increase in the maximum number of repeats may be authorised.* *Special Pricing Arrangements apply.*

Continuing treatment

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Continuing
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined

Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug AND The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have stable or responding disease.
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	~~The recommended dose of nivolumab is 3 mg/kg administered intravenously over 60 minutes every 2 weeks.~~ *No increase in the maximum number of repeats may be authorised.* *Special Pricing Arrangements apply.*

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

3 Background

3.1 TGA status at time of PBAC consideration: at the time of PBAC consideration, the TGA Delegate's Overview was available. Nivolumab was expected to be considered at the December 2015 meeting of the Advisory Committee on Prescription Medicines.

3.2 This is the second consideration of nivolumab by the PBAC. A submission for nivolumab (as monotherapy) for the treatment unresectable Stage III or Stage IV malignant melanoma was rejected by the PBAC in July 2015. In reaching this conclusion, the PBAC did not accept that ipilimumab, as presented in the submission, was the appropriate comparator.

3.3 Another PD-1 inhibitor, pembrolizumab, was considered by the PBAC in March 2015, and since the PBAC considered ipilimumab for the treatment of unresectable Stage III or Stage IV metastatic melanoma in November 2012, it has considered vemurafenib (March 2013), dabrafenib (July 2014) and trametinib (November 2014).

4 Clinical place for the proposed therapy

4.1 The requested listing specified monotherapy treatment of unresectable Stage III or Stage IV malignant melanoma in previously untreated patients (BRAF wild-type) as well as monotherapy treatment in patients who have progressed on or after a BRAF inhibitor regimen or after ipilimumab therapy (BRAF mutant).

5 Comparator

5.1 The minor re-submission nominated pembrolizumab as the main comparator.

6 PBAC consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item as it was a minor submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from organisations (2) via the Consumer Comments facility on the PBS website. The comments described the importance of immunotherapy treatment options for melanoma patients in Australia.

Clinical trials

6.3 As a minor submission, no new clinical trials were presented in the re-submission.

Comparative effectiveness

6.4 An indirect comparison against pembrolizumab was presented in the May 2015 PSCR (comparing CA209-067 and KN-006). The table below presents the results of the indirect comparison.

6.5 Beside the concerns raised previously by the PBAC (see below), the most apparent concern regarding the indirect comparison was the width of the confidence intervals for overall and progression-free survival. An interval of 0.70 to 1.54 indicates that a patient treated with nivolumab could be 70% to 154% as likely at any given time to die than a patient treated with pembrolizumab. With such a high upper limit of the confidence interval of the hazard ratio, the submission has not presented any evidence regarding a minimum clinically important difference (MCID). In order for there to be a statistically reliable claim of non-inferiority in this case, the MCID would have to be a 54% increase in overall survival hazard ratio, which is highly unlikely. Consequently, the submission's claim of non-inferior efficacy was not strongly supported.

Table 1: Indirect comparison of nivolumab versus pembrolizumab via ipilimumab as common comparator

	KN-006	CA-209-067	Indirect
	Pembro vs. Ipi (95% CI)	Nivo vs Ipi (95% CI)	(95% CI)
Overall survival (HR)	0.69 (0.52, 0.90)	0.72 (0.54, 0.95)	1.04 (0.70, 1.54)
Progression-free survival (HR)	0.58 (0.47, 0.72)	0.57 (0.47, 0.70)	0.99 (0.74, 1.32)
Adverse events (RR)			
Total (drug-related)	1.00 (0.90, 1.11)	0.95 (0.89, 1.02)	0.95 (0.84, 1.08)
Diarrhoea	0.64 (0.44, 0.92)	0.58 (0.44, 0.76)	0.91 (0.57, 1.44)
Colitis	0.44 (0.21, 0.92)	0.11 (0.04, 0.31)	0.25 (0.07, 0.88)

Source: Table 2, p3 of nivolumab monotherapy PSCR.
CI= confidence interval; HR = hazard ratio; Ipi = ipilimumab; Nivo = nivolumab; Pembro = pembrolizumab; RR = relative risk

Comparative harms

6.6 Regarding the indirect safety comparison, the lack of data prevents a robust analysis of comparative safety, but the statistical comparison of total drug-related adverse events and diarrhoea suggest non-inferiority.

Clinical claim

6.7 The updated therapeutic claim for nivolumab monotherapy was:

- in metastatic melanoma patients, nivolumab is non-inferior to pembrolizumab in efficacy and safety.

6.8 The claim is based on the indirect comparison against pembrolizumab presented in the May 2015 PSCR (comparing CA209-067 and KN-006). The minor submission noted the July 2015 PBAC comments regarding the indirect comparison, specifically pertaining to:

- the limited evidence to assess exchangeability between the trials (specifically duration of follow-up) (paragraph 7.6 of the July 2015 PBAC minutes)
- trial CA209-067 was designed to compare nivolumab plus ipilimumab combination therapy to ipilimumab monotherapy and was not designed to compare monotherapy arms (paragraph 7.7)
- CA209-067 was still collecting overall survival data, while KN-006 was not (paragraph 7.7).

6.9 The minor re-submission considered that these concerns will not be addressed over time with future reporting of nivolumab data, largely because the KN-006 trial has ceased. Although KN-006 has ceased, exchangeability between the trials remains relevant.

Economic analysis

6.10 The minor re-submission proposed that:

- nivolumab be listed on the PBS on a cost-minimisation basis to pembrolizumab
- the PBS restriction for nivolumab be aligned with the original PBAC submission - the patients with unresectable Stage III or Stage IV malignant melanoma
- the pricing of nivolumab be derived to ensure the same cost per patient as pembrolizumab, minus the additional infusion costs associated with nivolumab treatment
- the pricing of nivolumab upon PBS listing be set such that it is not linked to the pricing of the pembrolizumab MES.

6.11 The minor re-submission proposed relying on existing PBAC processes rather than applying pembrolizumab MES conditions to nivolumab. The submission considered that this negates the ability to use the pembrolizumab MES construct to seek an increased price for nivolumab in the future. The sponsor considered this provides the Commonwealth with greater certainty regarding the future pricing for nivolumab. While the submission's description of its proposal's effect on price was accurate, it was not complete. The pembrolizumab MES includes mechanisms that ensure that over time ipilimumab and pembrolizumab have the same cost per patient to the PBS. However, at the end of the pembrolizumab MES, the main question would be

whether the later evidence justifies an increased price per patient than ipilimumab and thus a variation to these mechanisms. In this context, the proposal to list nivolumab monotherapy on a non-inferiority and thus cost-minimisation basis against pembrolizumab while its MES is operating and including the request that the price of nivolumab not be linked to "the pricing of the pembrolizumab MES" would keep pembrolizumab and nivolumab monotherapy at the same cost per patient to the PBS as ipilimumab. In the unlikely event that the pembrolizumab MES reveals pembrolizumab to be clinically inferior to ipilimumab, the cost per patient for both pembrolizumab and nivolumab monotherapy would need to be reconsidered.

6.12 The minor re-submission has included a formula to derive the equivalent net cost per patient for nivolumab:

[redacted]

6.13 The minor re-submission also stated that data from existing trials (included in the original nivolumab PBAC submission) would be used to derive the number of infusions and infusion costs, with existing supply mechanisms used to determine the number of patients treated with nivolumab, if required. The sponsor also expressed its willingness to work proactively with the Department on agreeing and finalising specifics of the arrangement to ensure patient cost parity.

6.14 Acknowledging the sponsor's 'willingness to work proactively' the following concerns remained with the minor submission's approach:

- The minor re-submission's claim of non-inferiority is not strong as the confidence interval for the indirect comparison is very wide.
- Relying on nivolumab trial data to inform the number of infusions: as the restriction for nivolumab does not limit nivolumab use after progression, it is likely that in the Australian setting patients could continue to receive nivolumab indefinitely. Using nivolumab trial data would necessarily underestimate the number of infusions and overall per patient cost of nivolumab.
- Without consideration of the basis of the cost per patient to the PBS of pembrolizumab at the start of the MES, the net cost per person to the PBS of nivolumab cannot be correctly determined and an accurate cost-minimisation cannot be calculated.
- It is necessary to consider the principle of the request, without being able to accurately calculate the consequence for the cost per patient to the PBS of nivolumab.

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

7 PBAC Outcome

7.1 The PBAC recommended listing nivolumab as monotherapy treatment for patients with unresectable stage III or stage IV malignant melanoma, noting the revised main comparator in the re-submission, pembrolizumab, and a pricing proposal that provided the Commonwealth with greater certainty of the nivolumab pricing.

7.2 The recommendation was made on a cost-minimisation basis with pembrolizumab, where the price of nivolumab is derived to ensure the same cost per patient to the PBS as has been agreed for pembrolizumab, minus the additional infusion costs associated with more frequent nivolumab infusions.

7.3 The PBAC considered that the restriction for nivolumab should be aligned with the restriction for pembrolizumab, i.e. that PBS listing should be limited to patients who have not been exposed to ipilimumab. Both the nivolumab and pembrolizumab restrictions should also reflect that a patient who has progressive disease when treated with one PD-1 inhibitor, is subsequently not eligible to receive the alternate PD-1 inhibitor. These changes are to minimise PBS subsidy of the sequential use of these immunotherapies, for which evidence of effectiveness and cost-effectiveness has not been provided.

7.4 The revised nominated comparator in the re-submission, pembrolizumab, was considered to be appropriate.

7.5 The PBAC considered that the indirect comparison of nivolumab and pembrolizumab, based on CA209-067 and KN-006 with ipilimumab as the common reference, suggested that they may be similar in terms of effectiveness. The PBAC recalled that in July 2015, it had reached the same conclusion, noting that limited information was available to assess the exchangeability of the two trials. The resubmission argued, and the PBAC agreed, that differences in trial design, patient populations and study follow-up, make additional comparative assessments challenging. Given the limited available data, the PBAC considered that a clinical claim of non-inferior comparative effectiveness to pembrolizumab was reasonable. Noting the paucity of comparative safety data, the PBAC considered that the indirect comparison provided suggested that nivolumab has a non-inferior safety profile to pembrolizumab overall.

7.6 The PBAC recommended that the pricing of nivolumab upon PBS listing be determined only with reference to the initial pricing conditions of the pembrolizumab MES. Any future pricing adjustment that may be sought for pembrolizumab as part of the conditions of the pembrolizumab MES would not apply to nivolumab, thus providing the Commonwealth certainty of the nivolumab pricing. Future applications to prove cost effectiveness of nivolumab over pembrolizumab may be made at any time by the sponsor, if warranted by future clinical trial data. In the unlikely event that the pembrolizumab MES reveals pembrolizumab to be clinically inferior to ipilimumab, then the cost per patient to the PBS for both pembrolizumab and nivolumab monotherapy would need to be reconsidered. The PBAC noted that a rebating arrangement would be needed to achieve the intended pricing outcome. The Committee recommended that the Department negotiate a rebating arrangement with the sponsor in a manner that can be implemented and managed by the Department.

7.7 The PBAC noted that the re-submission did not provide revised estimates of utilisation. The PBAC agreed with the ESC's view of the July 2015 submission, that the patient numbers were overestimated and should be based on a market share.

7.8 The PBAC recommended that nivolumab should not be treated as interchangeable on an individual patient basis with any other drugs.

7.9 The PBAC advised that nivolumab is not suitable for prescribing by nurse practitioners.

7.10 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

7.11 The PBAC noted that this submission is not eligible for an Independent Review.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Proprietary Name and Manufacturer	
NIVOLUMAB nivolumab 40 mg/4 mL injection, 1 x 4 mL vial nivolumab 100 mg/10 mL injection, 1 x 10 mL vial	360 mg	8	Opdivo	Bristol-Myers Squibb Australia

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined

Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition, AND The condition must be negative for a BRAF V600 mutation, AND Patient must not have received prior treatment with ipilimumab or a PD-1 inhibitor, AND The treatment must not exceed a total of 9 doses at a maximum dose of 3 mg per kg every 2 weeks.
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	No increase in the maximum number of repeats may be authorised. 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.

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined

Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition, AND The condition must be positive for a BRAF V600 mutation, AND The condition must have progressed following treatment with a BRAF inhibitor (with or without a MEK inhibitor) unless contraindicated or not tolerated according to the TGA approved Product Information, AND Patient must not have received prior treatment with ipilimumab or a PD-1 inhibitor AND The treatment must not exceed a total of 9 doses at a maximum dose of 3 mg per kg every 2 weeks.
Prescriber Instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	No increase in the maximum number of repeats may be authorised. 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.

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Proprietary Name and Manufacturer	
NIVOLUMAB nivolumab 40 mg/4 mL injection, 1 x 4 mL vial nivolumab 100 mg/10 mL injection, 1 x 10 mL vial	360 mg	11	Opdivo	Bristol-Myers Squibb Australia

Category / Program	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Unresectable Stage III or Stage IV
Condition:	Malignant melanoma
PBS Indication:	Unresectable Stage III or Stage IV malignant melanoma
Treatment phase:	Continuing

Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ Streamlined
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have previously been issued with an authority prescription for this drug for this condition AND Patient must have stable or responding disease AND The treatment must not exceed a maximum dose of 3 mg per kg every 2 weeks.
Administrative Advice	No increase in the maximum number of repeats may be authorised.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor acknowledges the collaborative work of all stakeholders pre and post the positive PBAC recommendation and looks forward to Australian patients being able to access nivolumab via the PBS in the near future.