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

1 Purpose of Application

1.1 The minor resubmission sought to address the outstanding clinical, economic and financial areas of concern relating to the previous submissions of nivolumab as an adjuvant treatment for patients with resected Stage III and Stage IV melanoma at the July 2018 and March 2019 PBAC meetings.

2 Background

2.1 Nivolumab was registered by the TGA in April 2018 for adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.

2.2 Nivolumab was previously considered for this indication by the PBAC at its July 2018 and March 2019 meetings. At these meetings the PBAC decided not to recommend nivolumab. The PBAC acknowledged that there was a high unmet clinical need; however, considered that there was uncertainty in the magnitude of the clinical benefit and in the incremental cost-effectiveness ratio (ICER) due to the immaturity of the clinical data, and that the estimated financial impact remained high and uncertain (paragraph 7.1, Nivolumab minutes, March 2019).

2.3 Table 1 provides a summary of the key issues identified by the PBAC at the March 2019 meeting and the manner in which the minor resubmission has addressed them.

Table 1: Key issues identified by the PBAC in March 2019 and how they were addressed in the minor resubmission

Issue identified by PBAC in March 2019 minutes	How issue was addressed in July 2019 resubmission
[paragraph 7.4] The PBAC noted that limited data were presented for patients with Stage IIIA disease in the CA238 trial and that patients with Stage IIIA disease have a relatively low risk of recurrence and a five year melanoma-specific survival rate of 93%. The PBAC therefore foreshadowed that PBS-subsidised treatment in the adjuvant setting should be restricted to patients with completely resected Stage IIIB, IIIC, IIID and Stage IV disease (staged using the 8th edition of the AJCC melanoma staging system).	Agreed; however, no updated restrictions were provided in the minor resubmission.
[paragraph 7.7] The PBAC noted that resubmission again presented an indirect comparison between nivolumab and placebo, with ipilimumab as the common comparator, and used the same clinical trials (CA238: nivolumab versus ipilimumab; and CA029: ipilimumab versus placebo). ….the PBAC agreed with ESC in considering that a number of issues remained, including the differing durations of ipilimumab treatment and the differing treatment periods.	Not addressed.
[paragraph 7.9] The PBAC considered….. due to the immaturity of the data and the use of an indirect comparison, the magnitude of the treatment effect was highly uncertain.	The minor resubmission provided data updates for the two key trials CA238 and CA029. RFS data at a minimum of 36 months follow-up was provided for CA238 (compared to 24 months in March 2019) and a 7-year update for CA029 was provided (5-year data was provided in March 2019).

Issue identified by PBAC in March 2019 minutes	How issue was addressed in July 2019 resubmission

[paragraph 7.11] The PBAC considered that the resultant ICER, \$45,000-\$75,000, was high and uncertain. The PBAC:
• considered that, although the revised base case model in the pre-PBAC response converged the RFS, DMFS and OS curves from year 5 to year 30, the period for convergence was too long. The PBAC considered that, as there was a lack of data to determine whether nivolumab delayed or prevented recurrence as well as the overall impact on OS, the model should be conservative and that convergence should occur at 15 years;
• noted that the OS curve in the observation arm, which was a key driver of the economic model:
  ○ was informed by Australian data from Haydu (2017). ….the PBAC considered that the use of this non-trial population introduced a number of additional applicability uncertainties including a different patient population to that identified by the proposed PBS restriction (Stage III patients only with resected and unresectable disease) and, as it included patients diagnosed between 1970 and 2013, a population that most likely did not reflect current SOC;
  ○ was considered pessimistic by the ESC, particularly when the three year OS (67%) was compared to the observation arm of the COMBI-AD dabrafenib plus trametinib study, Long (2017) (77%). The PBAC noted that in the base case model presented in the resubmission, the OS HR was adjusted by a factor of 0.91 (which resulted in an additional 1.47 life years) to account for improved survival due to current unresectable or metastatic treatments. In response to concerns noted by ESC, the adjustment factor was altered to 0.89 (which resulted in an additional 1.80 life years) in the pre-PBAC response. The PBAC considered that the observation OS curve remained underestimated.
	The minor resubmission:
	• did not consider that the application of convergence at 15 years was appropriate given i) the clinical plausibility of treatment effect based on the nivolumab mode of action; ii) OS trial evidence for ipilimumab versus placebo; and iii) the implausible resulting hazard ratios for OS in the nivolumab arm that the convergence assumption produces;
	• provided an updated model in which the arms converged from Year 5 to Year 25;
	• provided a comparison of OS outcomes by treatment group in the CA238, CA029 and COMBI-AD trials to illustrate that the economic model based on CA029 remained the most reliable estimate of the comparative effectiveness and cost-effectiveness of nivolumab relative to standard of care

[paragraph 7.12] The PBAC…considered that a reasonable ICER for adjuvant melanoma therapy would be less than \$30,000 per QALY.	The minor resubmission provided a [redacted]% price reduction for nivolumab which reduced the ICER to less than \$30,000 if convergence was applied from Year 5 to Year 25.
[paragraph 7.13] The PBAC noted that a price reduction, in combination with the exclusion of Stage IIIA patients and adjustments to the grandfathered patients in the pre-PBAC response resulted in lower estimated costs per year than proposed in July 2018. The PBAC still considered that the estimated financial implications were uncertain, particularly with regards to the cost-offsets, which were not well justified, and the proportion of patients initially diagnosed with Stage I or II disease that experience a disease recurrence with resectable Stage III or Stage IV disease.	The minor resubmission provided revised utilisation and financial estimates which excluded Stage IIIA patients, revised assumptions regarding flow-on cost offsets in the unresectable or metastatic setting and incorporated new assumptions regard the proportion of patients progressing from Stage I and II disease to resectable Stage III and IV disease.

Issue identified by PBAC in March 2019 minutes	How issue was addressed in July 2019 resubmission
[paragraph 7.14] The PBAC considered that any proposed RSA must consider the implications on the current RSA for the use of PD-1 inhibitors in the unresectable or metastatic setting. The PBAC considered that a hard cap that encompassed adjuvant and unresectable use of BRAF/MEK, PD-1 and PDL-1 inhibitors would be appropriate.	The minor resubmission requested a SPA for nivolumab based on the weighted effective price across the adjuvant and unresectable or metastatic settings. In addition, the minor resubmission proposed a RSA, which would have hard caps beyond which [redacted]% rebates would be applied which encompassed adjuvant and unresectable or metastatic use of BRAF/MEK, PD-1 and PDL-1 inhibitors.

AJCC = American Joint Committee on Cancer; DMFS = distant metastases free survival; ESC = Economics Sub-Committee; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RFS = recurrence free survival; RSA = Risk Sharing Arrangement; SPA = Special Pricing Arrangement

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

3 Requested listing

3.1 The minor resubmission did not provide updated proposed restrictions for nivolumab in the adjuvant setting or for retreatment in the unresectable or metastatic setting. The minor resubmission did agree with the recommendations made by the PBAC in March 2019, stating that:

- The patient population would be restricted to patients with a completely resected Stage IIIB, IIIC, IIID and Stage IV disease stage using the 8th edition of the American Joint Committee on Cancer (AJCC) melanoma staging system i.e. patients with Stage IIIA disease would be excluded (paragraph 7.4, Nivolumab minutes, March 2018);
- Retreatment of patients in the unresectable or metastatic setting was clinically appropriate if a patient had responded well to adjuvant therapy (paragraph 7.3, Nivolumab minutes, March 2019).

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 as it was a minor submission.

Consumer comments

4.2 The PBAC noted and welcomed the input from individuals (18), health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The consumer and health professional comments described a range of benefits of treatment with adjuvant nivolumab for the treatment of completely resected Stage IIIB, IIIC, IIID or Stage IV melanoma including a reduced risk of recurrence, prolonged life, improved quality of life and few side effects.

4.3 The PBAC noted the correspondence received from i) Melanoma Patients Australia, and ii) Australian Melanoma Consumer Alliance and Melanoma Research Victoria

Consumer Reference Group. These organisations reiterated their previous support for nivolumab, citing the high clinical need.

4.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for adjuvant nivolumab treatment for completely resected Stage IIIB, IIIC, IIID or Stage IV melanoma, categorising it as one of the therapies of 'highest priority for PBS listing' on the basis of the CA238 Phase III 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, which was the highest grade (out of C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy of new potentially curative therapies), based on a comparison with ipilimumab in the CA238 trial.[1]

Clinical trials

4.5 The minor resubmission provided updated data from both of the key clinical trials, CA238 (nivolumab versus ipilimumab) and CA029 (ipilimumab versus placebo). Specifically, a data update for CA238 provided RFS and DMFS data at a minimum of 36 months follow-up, and a 7-year update is available for CA029.

4.6 The minor resubmission stated that the updated results provide confidence that treatment effect is maintained with additional follow-up, and addresses any remaining uncertainty regarding the immaturity of the data.

4.7 The updated results from CA238 are provided below. No OS data were provided for CA238. The Secretariat noted that the pre-PBAC response from the March 2019 consideration provided a descriptive analysis of OS at the 24 month data lock. At 24 months, [redacted] deaths had occurred; approximately [redacted]% of the protocol-expected number. Of the [redacted] deaths, [redacted] were in the ipilimumab arm (n = 453) and [redacted] were in the nivolumab arm (n = 453).

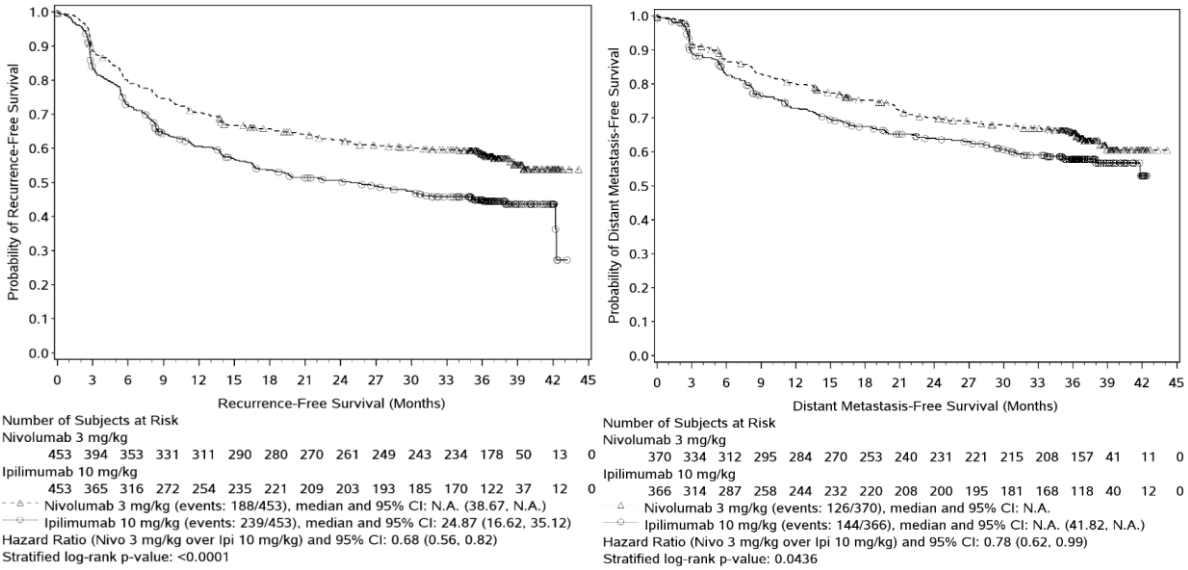
Table 2: RFS and DMFS results from CA238 (nivolumab versus ipilimumab) at a minimum of 24 and 36 months follow-up

	HR (95% CI); p-value	Proportion recurrence free, %	
		Nivolumab	Ipilimumab
RFS			
24 months[a]	0.66 (0.54, 0.81); p < 0.0001	62.5%	20.7%
36 months	0.68 (0.56, 0.82); p < 0.0001	58.4%	44.9%
DMFS			
24 months[a]	0.76 (0.59, 0.98); p = 0.0340	70.1%	64.0%
36 months	0.78 (0.62, 0.99); p = 0.0436	65.6%	57.8%

DMFS = distant metastases-free survival; CI = confidence interval; HR = hazard ratio; RFS = recurrence-free survival
Source: Tables 1 and 2, p3 of the minor submission
a A minimum of 24 months follow-up data were presented in the March 2019 resubmission

[1] Cherny N, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefits scale, version 1.1. *Annals of Oncology*. 2017; 28: 2340-2366.

Figure 1: Kaplan-Meier plots of RFS (LEFT) and DMFS (RIGHT) from CA238



CI = confidence interval; DMFS = distant metastases-free survival; Ipi = ipilimumab; NA = not available; Nivo = nivolumab; RFS = recurrence-free survival
Source: Figures 1 and 2, pp3-4 of the minor resubmission

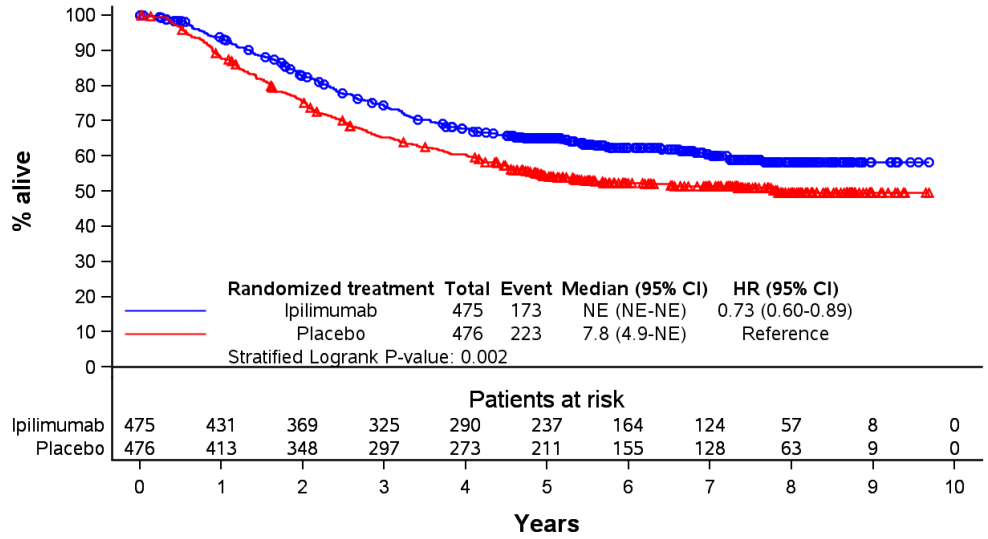
4.8 Updated results from CA029 are provided below.

Table 3: Efficacy outcomes from CA029 (ipilimumab versus placebo) at a minimum of 5 and 7 years follow-up

Minimum follow-up	Median follow-up	HR (95% CI), p-value		
		RFS	DMFS	OS
5 years	5.3 years	0.76 (0.64, 0.89); p < 0.001	0.76 (0.64, 0.92); p = 0.002	0.72 (0.58, 0.88); p = 0.001
7 years	6.9 years	0.75 (0.63, 0.88); p < 0.001	0.76 (0.64, 0.90); p = 0.002	0.73 (0.60, 0.89); p = 0.002

CI = confidence interval; DMFS = distant metastases-free survival; HR = hazard ratio; OS = overall survival; RFS = recurrence-free survival
Source: Table 3, p4 of the minor resubmission

Figure 2: Kaplan-Meier plot of OS from CA029



CI = confidence interval; HR = hazard ratio; NE = not estimable; OS = overall survival
Source: Figure 3, p5 of the minor resubmission

Indirect comparisons

Nivolumab versus dabrafenib+trametinib

4.9 A submission for dabrafenib+trametinib for the adjuvant treatment of melanoma was also considered at the July 2019 PBAC meeting. An indirect comparison of RFS between nivolumab and dabrafenib+trametinib, using ipilimumab and placebo as the common comparators, was presented as an Appendix to the March 2019 nivolumab resubmission.

4.10 The results of the indirect comparison are presented below. The data informing the efficacy of nivolumab included BRAF mutant and BRAF wildtype patients; however, based on the pre-specified subgroup analyses of the CA238 trial, patients had similar RFS rates regardless of BRAF mutational status.

Table 4: Results of the 2 step indirect comparison between nivolumab and dabrafenib+trametinib

	BRAF status	HR_{RFS} (95% CI)	Trials involved [Common reference]
Indirect: NIVO vs. PBO	BRAF MT and WT	0.50 (0.38, 0.65)	CA238 vs. CA029 [IPI]
Direct: DAB+TRAM vs. PBO	BRAF MT	0.47 (0.39, 0.57)	COMBI-AD [none - direct]
2 Step indirect: NIVO vs. DAB+TRAM	-	**1.06 (0.77, 1.48); p=0.71**	**(CA238 vs. CA029) vs. COMBI-AD [Placebo]**

CI = confidence interval; DAB+TRAM = dabrafenib+trametinib; HR = hazard ratio; IPI = ipilimumab; MT = mutant; NIVO = nivolumab; PBO = placebo; RFS = recurrence-free survival; WT = wildtype
Source: Modified from Table 5 from Attachment 8a and Table 3 from Attachment 7a to the March 2019 resubmission.

4.11 The March 2019 resubmission concluded that there was no statistically significant difference between nivolumab and dabrafenib+trametinib in terms of the primary endpoint, RFS.

4.12 Based on the results of a naïve comparison, the March 2019 resubmission stated that nivolumab was likely to be associated with less toxicity than dabrafenib+trametinib.

Nivolumab versus pembrolizumab

4.13 A submission for pembrolizumab for the adjuvant treatment of melanoma was also considered at the July 2019 PBAC meeting. An indirect comparison of RFS between nivolumab and pembrolizumab, using ipilimumab and placebo as the common comparators, was presented as an Appendix to the March 2019 nivolumab resubmission.

4.14 The results of the indirect comparison are presented below.

Table 5: Results of the 2 step indirect comparison between nivolumab and pembrolizumab

	BRAF status	HR_{RFS} (95% CI)	Trials involved [Common reference]
Indirect: NIVO vs. PBO	BRAF MT and WT	0.50 (0.38, 0.65)	CA238 vs. CA029 [IPI]
Direct: PEMBRO vs. PBO	BRAF MT and WT	0.57 (98.4% CI: 0.43, 0.74)	KN054 [none - direct]
2 Step indirect: NIVO vs. PEMBRO	-	**0.88 (0.60, 1.28); p=0.50**	**(CA238 vs. CA029) vs. KN054 [Placebo]**

CI = confidence interval; HR = hazard ratio; IPI = ipilimumab; MT = mutant; NIVO = nivolumab; PBO = placebo; PEMBRO = pembrolizumab; RFS = recurrence-free survival; WT = wildtype
Source: Modified from Table 5 from Attachment 8a and Table 3 from Attachment 7a to the March 2019 resubmission.

4.15 The March 2019 resubmission concluded that there was no statistically significant difference between nivolumab and pembrolizumab in terms of the primary endpoint, RFS.

4.16 Based on the results of a naïve comparison, the March 2019 resubmission stated that nivolumab and pembrolizumab were likely to be associated with similar toxicity.

Economic analysis

4.17 The pre-PBAC response to the March 2019 resubmission proposed an ICER of $45,000-$75,000 per QALY.

Validity of the OS curve in the observation arm

4.18 The PBAC noted that in the March 2019 resubmission the OS curve in the observation arm, which was a key driver of the model, was informed by data from Haydu (2017) rather than CA029, as per the July 2018 submission. The PBAC previously considered that the use of a non-trial population introduced a number of applicability uncertainties. In addition, the PBAC considered that the OS curve was pessimistic,

particularly when compared to the observation arm of the COMBI-AD trial, which was presented in the dabrafenib+trametinib submission (paragraph 7.11, Nivolumab minutes, March 2019).

4.19 The minor resubmission presented a comparison of the OS curves, noting that the observation arm in the COMBI-AD trial also outperformed the ipilimumab arm of the CA029 trial, suggesting that the trial populations differed. In addition, the minor resubmission identified that the nivolumab arm of the model, which was based on the CA029 trial, was also potentially underestimated when compared to the observed survival data from the CA238 trial (CA238 survival at 2 years = [redacted]%; model survival at 2 years = 80.0%).

Figure 3: Comparison of OS outcomes by treatment group from the CA238, CA029 and COMBI-AD trials

[redacted]

DAB = dabrafenib+trametinib; IPI = ipilimumab; ITT = intention to treat; NIVO = nivolumab; OS = overall survival; PBO = placebo; SoC = standard of care
Source: Figure 6, p8 of the minor submission

4.20 The minor resubmission claimed that as the survival outcomes for both the observation arm and the nivolumab arm were underestimated, the use of the CA029 trial was appropriate to estimate the comparative effectiveness and cost-effectiveness of nivolumab relative to standard of care.

Application of convergence

4.21 The PBAC previously considered that the period of convergence from 5 to 30 years for the RFS, DMFS and OS curves presented in the pre-PBAC response to the March 2019 submission was too long, and that the model should be conservative and convergence should occur at 15 years (paragraph 7.11, Nivolumab minutes, March 2019).

4.22 The minor resubmission considered the application of convergence at 15 years to be inappropriate given (i) the clinical plausibility of the treatment effect based on the mode of action of nivolumab; (ii) the lack of convergence in RFS, DMFS and OS in CA029 (ipilimumab versus placebo) at a minimum follow-up of seven years; and (iii) the implausible resulting OS hazard ratio's (HR) in the nivolumab arm that this convergence assumption produces.

4.23 The minor resubmission stated that when convergence from 5 to 15 years was applied, this implied HRs for the convergence period of 1.69, 1.53 and 1.20 for RFS, DMFS and OS respectively for nivolumab relative to standard of care. The minor resubmission claimed that this was implausible. The minor resubmission presented a revised base case which applied convergence from years 5 to 25 which it stated resulted in more realistic HRs (RFS = 1.45; DMFS = 1.33; and OS = 1.10).

ICER of less than $30,000 per QALY

4.24 The PBAC, noting that it had previously accepted more conservative ICERs for adjuvant treatment of early breast cancer, considered that a reasonable ICER for adjuvant melanoma therapy would be less than $30,000 per QALY (paragraph 7.12, Nivolumab minutes, March 2019).

4.25 The minor resubmission presented a comparison of the economic model presented for nivolumab for adjuvant melanoma with that presented for trastuzumab for early breast cancer in November 2006. Although acknowledging that the comparison was somewhat superficial, the minor resubmission concluded that the nivolumab model was more conservative.

4.26 The minor resubmission provided a revised price ($[redacted]/100 mg vial, which was a [redacted]% reduction from the March 2019 resubmission price of $[redacted]/100 mg vial and a [redacted]% reduction from the March 2019 pre-PBAC response price of $[redacted]/100 mg vial) which reduced the ICER to less than $30,000 when using a 3 mg/kg every two weeks dosing regimen for nivolumab and applying convergence at 25 years.

Table 6: Results of the economic model by point of convergence and dosing regimen, ICER per QALY

Point of convergence (HR after 5 years)	Nivolumab dosing regimen		
	3 mg/kg Q2W	240 mg Q2W	480 mg Q4W
15 years – PBAC proposed base case	$[redacted]	$[redacted]	$[redacted]
25 years – sponsor proposed base case	**$[redacted]**	**$[redacted]**	**$[redacted]**
30 years	$[redacted]	$[redacted]	$[redacted]
No convergence	$[redacted]	$[redacted]	$[redacted]

ICER = incremental cost-effectiveness ratio; NA = not applicable; QALY = quality-adjusted life year; Q2W = every 2 weeks; Q4W = every 4 weeks

Source: Table 6, p15 of the minor submission

4.27 The minor resubmission stated that the flat dosing regimen of 480 mg every four weeks is likely to be utilised by the majority of patients following its recommendation by the PBAC in March 2019. In the pre-PBAC response, data from the patient access program (PAP) indicated that 48% of patients are receiving 480 mg at 4 weekly

intervals, 47% are receiving 240 mg at two weekly intervals and 5% remain on weight based dosing.

Drug cost/patient/course: $[redacted]

4.28 The drug cost per patient was calculated using a recommended dose of 240 mg every two weeks, and assuming 70% will be dispensed for use in a private hospital (based on PBS statistics for ipilimumab, nivolumab and pembrolizumab in the unresectable melanoma setting), resulting in a total cost per infusion of $[redacted]. The expected average number of doses of nivolumab, 19.6 doses, was observed in CA238 (i.e. 39.2 weeks' total duration).

4.29 The drug cost per patient per 12 months treatment (26 doses) was calculated to be $[redacted].

4.30 Using the 480 mg every four weeks recommended dose, the total cost per infusion was $[redacted] (70% dispensed in a private hospital) and the expected average number of doses was 9.8. This resulted in an average cost per patient per 39.2 weeks treatment of $[redacted] and a drug cost per 12 months treatment (13 doses) of $[redacted].

Estimated PBS usage & financial implications

4.31 The proportion of patients initially diagnosed with Stage I or II disease that experience a disease recurrence with resectable Stage III or IV disease has been reduced from 23% in the March 2019 resubmission to 17%. This was validated using two different methods.

4.32 The minor resubmission also assumed that 22% of patients would be excluded due to being Stage IIIA, that [redacted] grandfathered patients would be treated in Year 1 (reduced from 720 in March 2019) and that the uptake rate would be 90% (increased from 70% in Year 1 and 80% in Year 6 in the March 2019 submission). Overall, these changes resulted in approximately [redacted]% less patients treated with nivolumab compared to the March 2019 submission.

4.33 In addition, the minor resubmission assumed that patients would receive 240 mg of nivolumab every two weeks. As the minor resubmission stated that 480 mg every four weeks would be the most utilised regimen, the Secretariat presented revised use and financial implication estimates. The March 2019 submission utilised a 3 mg/kg every two weeks dosing regimen that resulted in patients receiving on average 254 mg of nivolumab.

4.34 The updated utilisation and financial impact estimations are presented below.

Table 7: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patients						
Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate	90%	90%	90%	90%	90%	90%
Total patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
240 mg every two weeks						
Infusions						
Infusions per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to the PBS/RPBS						
Net effective cost	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
480 mg every four weeks						
Infusions						
Infusions per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to the PBS/RPBS						
Net effective cost	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
Pre-PBAC response to March 2019 resubmission						
Total patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net effective cost	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Source: Table 17, p26 of the minor submission, Attachment 5_Minor resubmission proposed RSA – Excel file and Table 14, p38 of the Nivolumab minutes, March 2019

[a] Grandfathered patients

The redacted table shows that at year 6, the estimated number of patients treated was less than 10,000 and the net cost to PBS would be $30-$60 million.

4.35 The eligible patient population was calculated assuming 86% of Stage III and 13% of Stage IV patients had completely resectable disease. The PBAC noted these percentages were based on a survey and hence, were uncertain. The PBAC considered that the proportion of patients with Stage III disease which was completely resectable was overestimated.

Risk-sharing arrangement

4.36 The minor resubmission proposed a RSA which included a [redacted]% cap covering adjuvant and unresectable or metastatic use of BRAF/MEK, PD-1 and PDL-1 inhibitors for melanoma, which was in-line with that proposed by the PBAC at the March 2019 meeting. The PBAC recalled that it had recommended a RSA which encompassed adjuvant and unresectable or metastatic use of BRAF/MEK, PD-1 and PDL-1 inhibitors; however, on reconsideration, the PBAC determined that this would be difficult to implement and advised that any RSA should encompass adjuvant and unresectable or metastatic use of the PD-1 inhibitors only. The PBAC considered that any other PD-1s recommended for the treatment of adjuvant melanoma in the future should be included within the same financial caps.

4.37 The minor resubmission also proposed a weighted effective price for nivolumab across the adjuvant and unresectable or metastatic settings.

4.38 The proposed combined cap was derived from:

- Extrapolation of current expenditure in the unresectable or metastatic setting, less the flow on reductions associated with the introduction of adjuvant treatment; and
- Financial estimates for the net cost to the PBS/RPBS for adjuvant treatment, as presented above in Table 7.

4.39 The March 2019 resubmission calculated that 58% of patients receiving treatment for unresectable or metastatic melanoma could have been eligible to receive adjuvant treatment. In the March 2019 economic evaluation, the number needed to treat with adjuvant therapy to prevent a distant metastatic recurrence was nine patients (11%). Therefore, a 6.4% reduction (58% x 11%) in unresectable or metastatic expenditure was applied to the estimated financial implications of listing adjuvant nivolumab.

4.40 The minor resubmission used data from New South Wales Cancer Statistics to estimate that approximately [redacted]% of patients who died from melanoma had an initial diagnosis of local or regional disease. Therefore, the updated estimates applied a reduction of [redacted]% ([redacted]% x [redacted]%) to unresectable or metastatic expenditure in Years 2 to 6. The PBAC considered that the inclusion of a reduction to the existing caps in the unresectable or metastatic setting to account for patients who no longer required treatment was appropriate. The PBAC considered that any reduction in use in the unresectable or metastatic setting was unlikely to be observed in the first year of the adjuvant listing.

4.41 The key assumptions utilised in deriving the unresectable or metastatic component of the proposed caps are outlined below.

Table 8: Key assumptions of the unresectable or metastatic component of the proposed RSA caps

Description	Assumption	Source
Future PD-1 Commonwealth expenditure on unresectable or metastatic melanoma	- Current caps plus [redacted]% annual growth	- Annual growth trend of current caps
Future BRAF/MEK Commonwealth expenditure on unresectable or metastatic melanoma	- Current Commonwealth expenditure; - Plus [redacted]% annual growth; - Less [redacted]% SPA rebate	- Historical PBS item statistics (July 2018 to June 2018) for Commonwealth expenditure; - Growth rate based on the growth in incident unresectable or metastatic incident patients treated from January to June 2018; - Assumption
Reduction in unresectable or metastatic use following adjuvant listing	- Year 1 = [redacted]% - Years 2-5 = 7.3%	- Estimated % of unresectable or metastatic melanoma patients eligible to receive adjuvant treatment ([redacted]%) - CA238: 9 patients NNT to prevent [redacted] distant metastatic recurrence at 10 years ([redacted]%)

NNT = number needed to treat; RSA = risk-sharing arrangement
Source: Table 14, p24 of the minor resubmission

4.42 The proposed combined caps, as presented in the minor resubmission, are reproduced below.

Table 9: Proposed melanoma caps

		2020	2021	2022	2023	2024	2025
Unresectable or metastatic setting							
A	PD-1 expenditure	$	$	$	$	$	$
B	BRAF/MEK expenditure	$	$	$	$	$	$
C (A + B)	Cost	$	$	$	$	$	$
D	Expected reduction in use	%	%	%	%	%	%
E (C x D)	Expected savings	$0	$	$	$	$	$
F (C - E)	Total cost	$	$	$	$	$	$
Adjuvant setting							
G	Total cost	$	$	$	$	$	$
Combined cap							
H (F + G)	**Proposed cap**	**$**	**$**	**$**	**$**	**$**	**$**

Source: Tables 15 and 18, pp25-26 of the minor submission

4.43 Regarding the proposed caps, the PBAC noted the usage estimates informing these would need to be revised to consider:

- Removal of BRAF/MEK expenditure in the unresectable setting (paragraph 4.36);
- The use in the adjuvant setting which was likely to be overestimated due to the overestimation of the proportion of Stage III patients with completely resectable disease (paragraph 4.35);
- The use in the adjuvant setting would need to be revised based on the proportion of patients receiving each of the nivolumab dosing regimens (paragraph 4.27); and
- The use in the adjuvant setting would need to be revised to account for use of BRAF/MEK drugs if also listed for use in the adjuvant setting.

4.44 In addition, the minor resubmission proposed a weighted effective price for nivolumab across the adjuvant and unresectable or metastatic settings.

4.45 In the unresectable or metastatic setting, nivolumab has an agreed effective price of $2,076.75 per 100 mg vial. As outlined below, the net price for nivolumab in the unresectable or metastatic setting post reimbursement for the current subsidisation caps is lower. Omitting the Year 1 effective price, during which the initial uptake was not representative of stabilised utilisation, resulted in an average net effective price of nivolumab in the unresectable or metastatic setting of $.

Table 10: Effective price of nivolumab in the unresectable or metastatic setting

	Year 1: Sep 15 – Aug 16	Year 2: Sep 16 – Aug 17	Year 3: Sep 17 – Aug 18	Year 4: Sep 18 – Aug 19*
PD-1 expenditure	$	$	$	$
PD-1 cap	$	$	$	$
Rebate	$	$	$	$
Rebate % of PD-1 expenditure	%	%	%	%
Agreed effective price	$	$	$	$
Net effective price	$	$	$	$
Average net effective price, Years 2 to 4		**$**		

* Sep 18 – Aug 19 calculated by doubling the actual expenditure from Sep 18 – Feb 19
Source: Table 20, p27 of the minor submission

4.46 The Secretariat advised that it may have been more appropriate to use a net effective price from the most recent year that has completed (i.e. Year 3: $).

4.47 The weighted nivolumab melanoma price of $ was based on the estimated expenditure split within the proposed combined caps. When the net effective price in the unresectable or metastatic setting from Year 3 was used, the weighted nivolumab price was $.

Table 11: Weighted nivolumab melanoma price

	Adjuvant setting	Unresectable or metastatic setting
Effective price per 100 mg vial	$	$ Year 3 price: $
Weighting	%	%
Weighted melanoma price	$ Using Year 3 price: $	

Source: Table 21, p28 of the minor submission

4.48 The PBAC considered that the use of a weighted average effective AEMP for nivolumab across the adjuvant and unresectable or metastatic settings was reasonable. The PBAC considered that should the effective price be weighted across the two populations, the weighting applied should be consistent with the agreed final financial estimates and joint RSA across the two settings.

4.49 The minor resubmission requested a Special Pricing Arrangement (SPA) rebate be included in any new combined Deed, as outlined below.

Table 12: Special pricing arrangement rebate calculations

	Published price	Published price – average co-payment	Effective price	Effective price – average co-payment	Rebate
Dispensed price per administration (240 mg)	$	$	$	$	%
Average co-payment	$				

Source: Table 22, p28 of the minor submission

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

5 PBAC Outcome

5.1 The PBAC deferred making a decision regarding the listing of nivolumab as adjuvant treatment for patients with completely resected Stage IIIB, IIIC, IIID or Stage IV melanoma to allow for further discussions regarding an acceptable price and risk sharing arrangement.

5.2 The PBAC acknowledged that there was a high unmet clinical need for effective therapies to reduce the risk of recurrence for patients with resected Stage IIIB, IIIC, IIID or Stage IV melanoma. The PBAC acknowledged the consumer comments, which were supportive of the PBS listing. In particular, the PBAC noted comments that there are currently no PBS-listed treatment options for adjuvant melanoma, and those that described a range of benefits of nivolumab treatment, including improved survival and quality of life.

5.3 In terms of the clinical place in therapy, the PBAC noted that this was amended to align with recommendations made in the March 2019 minutes and that the resubmission proposed that nivolumab would supplement routine care in completely resected Stage IIIB, IIIC, IIID or Stage IV melanoma.

5.4 The PBAC advised that an Authority Required (telephone) listing would be appropriate for both the initial and continuing treatment phases to prevent leakage to patients with Stage IIIA disease and to ensure treatment was capped at 12 months.

5.5 The PBAC considered that there would be flow-on restriction changes to the current PBS listing for nivolumab (and the other PD-1 inhibitor, pembrolizumab) to allow retreatment in the unresectable or metastatic setting for those patients who experience disease recurrence at least six months after completion of treatment in the adjuvant setting.

5.6 The PBAC reaffirmed that standard of care (routine follow-up) was the appropriate main comparator for nivolumab as adjuvant treatment for melanoma. Pembrolizumab was also considered for the same indication at the July 2019 meeting and was a near market comparator. Dabrafenib+trametinib was also considered for adjuvant treatment of patients with BRAF mutant melanoma at the July 2019 meeting and was a near market comparator for the BRAF mutant subgroup of patients.

5.7 The PBAC recalled that it had previously considered it likely that adjuvant nivolumab provides, for some patients, a significant improvement in efficacy over routine follow-up, in terms of recurrence free survival (RFS). The PBAC noted that although the indirect comparison between nivolumab and placebo, with ipilimumab as the common comparator, was not updated, the resubmission did present updated data from the two key clinical trials. A data update from CA238, nivolumab versus ipilimumab, provided RFS and distant metastases free survival (DMFS) data at a minimum of 36 months follow-up (compared to 24 months in the March 2019 submission), and a 7-year update was available for CA029 (ipilimumab versus placebo,

compared to 5-years in the March 2019 submission). The PBAC noted that treatment effect for nivolumab versus ipilimumab was maintained in terms of RFS and DMFS at 36 months follow-up. The PBAC noted that no updated OS data was provided for CA238. The PBC noted that the treatment effect for ipilimumab versus placebo was maintained in terms of OS at 7 years of follow-up.

5.8 The PBAC noted the indirect comparisons between nivolumab and dabrafenib+trametinib and nivolumab and pembrolizumab. Acknowledging the indirect nature of the comparisons and the likely transitivity issues between the trials, the PBAC noted that in terms of RFS, there were no statistically significant differences between nivolumab and dabrafenib+trametinib (HR = 1.06; 95% CI: 0.77, 1.48) or nivolumab and pembrolizumab (HR = 0.88; 95% CI: 0.60, 1.28), and that the upper 95% confidence limits supported a claim of non-inferior efficacy.

5.9 As for use in the unresectable setting, the PBAC considered that nivolumab has a non-inferior safety profile to pembrolizumab in the adjuvant setting. The PBAC considered that nivolumab may be better tolerated than dabrafenib+trametinib in the adjuvant setting, noting that dabrafenib+trametinib is associated with more Grade 3 and 4 adverse events and more patients discontinuing treatment due to adverse events.

5.10 In considering the economic model for nivolumab versus routine follow-up, the PBAC noted that the minor resubmission partially addressed the issue of convergence of the RFS, DMFS and OS curves. The PBAC noted that the period of convergence for the curves was reduced from Year 5 to Year 30 in the March 2019 pre-PBAC response to convergence from Year 5 to Year 25 in the July 2019 minor resubmission. The PBAC noted that the minor resubmission provided a revised effective approved ex-manufacturer price (AEMP) which resulted in ICERs ranging from $15,000/QALY - $45,000/QALY depending on the nivolumab dosing regimen applied, when convergence was applied from Year 5 to Year 25. The PBAC noted that the ICER ranged from $45,000/QALY - $75,000/QALY when convergence was applied from Year 5 to Year 15.

5.11 The PBAC noted the challenges of making comparisons across the nivolumab, pembrolizumab and dabrafenib+trametinib submissions, given the distinct economic modelling approaches adopted. However, in a comparative assessment of the outcomes across the models, the PBAC considered that the nivolumab model may have resulted in an underestimate of the incremental benefits when applying convergence from Year 5 to Year 15 (0.4158 QALYs), and thus an overestimate of the ICER per QALY. The PBAC considered, given the model structure and inputs, that applying convergence from Year 5 to Year 25 was acceptable. The PBAC noted for this scenario the ICERs were less than $30,000 per QALY, the threshold the PBAC considered at the March 2019 meeting to be reasonable.

5.12 The PBAC considered if pembrolizumab was listed on the PBS for the adjuvant treatment of melanoma, it would be appropriate for nivolumab to be cost minimised

to pembrolizumab. The PBAC considered if dabrafenib+trametinib was listed on the PBS for the adjuvant treatment of BRAF mutant melanoma, it would be appropriate for nivolumab to be cost minimised to dabrafenib+trametinib for the proportion of the population that is BRAF mutant positive.

5.13 The PBAC noted that the estimated financial implications of listing nivolumab on the PBS for use in adjuvant melanoma had been updated from the March 2019 submission and appeared more reasonable, although noted that the proportion of Stage III patients with completely resectable disease (86%) may have been overestimated (paragraph 4.35). The PBAC considered that the net effective cost of adjuvant nivolumab should be recalculated based on the dosing regimen ratios provided in the pre-PBAC response (i.e. 47% of patients receiving 240 mg at two weekly intervals, 48% are receiving 480 mg at four weekly intervals and 5% are receiving weight-based dosing).

5.14 The PBAC recalled that it previously advised that any proposed RSA should encompass adjuvant and unresectable use of BRAF/MEK, PD-1 and PDL-1 inhibitors. However, the PBAC now considered that this would be difficult to implement, and advised that the RSA should encompass adjuvant and unresectable use of the PD-1 inhibitors only.

5.15 The PBAC considered that, in the context of the uncertain use across the adjuvant and unresectable or metastatic settings, the proposal of a RSA consisting of subsidisation caps across both the adjuvant and unresectable or metastatic settings, beyond which [redacted]% rebates would apply, was appropriate. The PBAC also considered that the use of a weighted average effective AEMP for nivolumab across the adjuvant and unresectable or metastatic settings was reasonable. The PBAC considered that should the effective price be weighted across the two populations, the weighting applied should be consistent with the agreed final financial estimates and joint RSA across the two settings.

5.16 The PBAC noted that the expenditure caps proposed in the minor resubmission would need to be revised as outlined in paragraph 4.43.

Outcome:

Deferred

6 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.

7 Sponsor's Comment

The sponsor had no comment.