

7.17 NIVOLUMAB

**Concentrate solution for infusion of 10 mg/mL, 1 x 4 mL vial,
1 x 10 mL vial,
Opdivo[®],
Bristol Myers Squibb Australia Pty Ltd.**

1 Purpose of Application

1.1 The minor resubmission requested that the PBAC reconsider PBS Authority Required (Streamlined) listing of nivolumab for the second-line treatment of renal cell carcinoma (RCC).

1.2 The minor resubmission provided a re-specified economic model as well as revised financial estimates to support the request for listing.

2 Requested listing

2.1 The minor resubmission stated that the PBAC and the sponsor are aligned on the proposed restriction and did not provide any further statements relevant to the restriction. The PBAC PSD (paragraph 7.3) stated that the PBAC agreed with ESC that any PBS listing of nivolumab for RCC be restricted to Stage IV disease; and also that any PBS restriction would be limited to patients with a WHO performance score of 0 to 2; and any PBS restriction for continuation would be modelled on the existing restriction for nivolumab in melanoma to account for the rare circumstance of pseudo-progression. The original requested restriction is provided below, with the PBAC-recommended changes from the July 2016 PBAC PSD included.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
NIVOLUMAB				
40 mg/4 mL injection 1 x 4 mL vial	360 mg	5	\$830.70 (Published price) \$█ (Effective price)	Opdivo [®] BQ
100 mg/10 mL injection 1 x 10 mL vial	360 mg	5	\$2,076.75 (Published price) \$█ (Effective price)	

Category / program	Section 100 - Efficient Funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Initial treatment
Restriction level / method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined

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Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have a WHO performance status of 2 or less AND Patient must have progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST) following first line treatment with a tyrosine kinase inhibitor OR Patient must have developed intolerance to a tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal
Definitions	Response Evaluation Criteria in Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions. Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) is small changes that do not meet above criteria.
Prescriber instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	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. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
NIVOLUMAB				
40 mg/4 mL injection 1 × 4 mL vial	360 mg	5	\$830.70 (Published price) \$ [REDACTED] (Effective price)	Opdivo® BQ
100 mg/10 mL injection 1 × 10 mL vial	360 mg	5	\$2,076.75 (Published price) \$ [REDACTED] (Effective price)	

Category / program	Section 100 - Efficient Funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Continuing treatment
Restriction level / method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition, AND Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST), AND The treatment must be the sole PBS-subsidised therapy for this condition.
Definitions	Response Evaluation Criteria in Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions. Partial response (PR) is a 30% decrease in the sum of the longest diameter of target

	<p>lesions. Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) is small changes that do not meet above criteria.</p>
Prescriber instructions	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.
Administrative Advice	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.

3 Background

- 3.1 An application to the TGA for nivolumab for the treatment of RCC was lodged on 1 December 2015. The Delegate's Overview was received on 17 October 2016 and the ARTG outcome on 26 October 2016. At the time of the PBAC consideration ARTG registration was not approved.
- 3.2 There had been one previous consideration by the PBAC of nivolumab for the treatment of RCC at its July 2016 meeting. The decision was not to recommend, based primarily on an unacceptably high and uncertain ICER at the requested effective price (paragraph 7.1 of the July 2016 PBAC PSD).
- 3.3 The recommendations made by the PBAC following consideration of the July 2016 nivolumab RCC submission, including recommendations for re-specification of the economic model, as well as the responses provided in the minor resubmission are listed in the table below.

Table 1: Summary of PBAC recommendations for the July 2016 submission and minor resubmission response

PBAC recommendation July 2016 PBAC PSD	Response - minor resubmission
<ul style="list-style-type: none"> The PBAC agreed with the ESC that any PBS-listing of nivolumab be restricted to Stage IV disease, consistent with the first- and second-line agents currently listed for the treatment of RCC. Consistent with the recruited population in the key trial, the PBAC also foreshadowed that any PBS restriction would be limited to patients with a WHO performance score of 0 to 2. Further, any PBS restriction for continuation would be modelled on the existing restriction for nivolumab in melanoma to account for the rare circumstance of pseudo-progression (paragraph 7.3). 	<ul style="list-style-type: none"> The minor resubmission stated (p1) that the PBAC and the sponsor are aligned on the proposed PBS restriction. No details of the restriction or discussion of the points raised by the PBAC in paragraph 7.3 of the PSD were provided in the minor resubmission.
<ul style="list-style-type: none"> The more standard PFS (allowing the RECIST criteria to be modified to avoid stopping the medicine in the context of early pseudo-progression as determined for nivolumab in melanoma) be used in any future PBS restriction and in the economic modelling (paragraph 7.5). 	<ul style="list-style-type: none"> With the exception of the statement made on page 1 of the minor resubmission that the PBAC and the sponsor are aligned on the proposed PBS restriction, the minor resubmission did not provide any discussion of the proposed restriction (which already cited RECIST criteria). PFS-based on RECIST criteria were used to determine duration of therapy and drug costs for the

PBAC recommendation July 2016 PBAC PSD	Response - minor resubmission
<ul style="list-style-type: none"> • The PSD proposed the following respecified base case for the economic model (paragraph 7.10): <ul style="list-style-type: none"> ○ █ infusions of nivolumab reflecting time to progression in CA209-025 and costed according to the per cycle approach. ○ The mean duration of use of everolimus and subsequent TKIs as observed in the PBS costed according to the per cycle approach. ○ 5-year time horizon. ○ No other changes to the method of generating the QALY estimates. ○ Effective prices of everolimus, axitinib and sorafenib. ○ Back-calculated effective price of nivolumab to provide a base case ICER/QALY of no greater than \$45,000/QALY - \$75,000/QALY. 	<p>everolimus arm of the economic model while all other PFS-relevant variables in the economic model were based on clinical PFS.</p> <ul style="list-style-type: none"> • The revised model used █ infusions of nivolumab, which was costed according to the per cycle approach. • The mean duration of everolimus use was based on RECIST PFS from CA209-025. Everolimus use was costed according to the per cycle approach. • The revised model used a 5-year time horizon. • The minor resubmission noted effective prices for everolimus, axitinib and sorafenib could not be applied as they are unknown to the sponsor. • The minor resubmission did not back-calculate the effective price of nivolumab as it stated that the sponsor's global partner has indicated no further reduction from \$█/100 mg vial is possible. Instead, the minor resubmission limited duration of costed treatment with nivolumab to █ months (█ infusions) to arrive at an ICER/QALY of \$45,000/QALY-\$75,000/QALY.
<ul style="list-style-type: none"> • The PBAC advised that the assumed uptake rate of 90% for nivolumab was implausibly high compared to the existing uptake rate of 16% to 25% for any second-line treatment following a TKI. However, the PBAC also noted that the submission possibly underestimated the number of patients receiving first-line TKIs. The PBAC recommended that a reduced uptake rate of nivolumab should be identified (and justified) in order to support a risk share arrangement (paragraph 7.12). 	<ul style="list-style-type: none"> • The minor resubmission stated (p8) "...the sponsor is willing to accept a 10% reduction to the assumption of the proportion of patients initiated on second-line therapy with an associated reduction to the assumption of the nivolumab uptake rate to maintain the 10% increment". • The secretariat noted that while the proportion of patients initiated on second-line treatment was reduced by 10%, the uptake rate of nivolumab has remained the same as in the July 2016 submission (90% in Year 1 increasing to 95% in Years 2 to 5).

Source: compiled during the preparation of the overview; PSD – Public Summary Document

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

4 Clinical place for the proposed therapy

- 4.1 The original July 2016 submission and the minor resubmission requested that nivolumab be used as second-line treatment of RCC as an alternative to everolimus, axitinib and sorafenib.

5 Comparator

- 5.1 The main comparator remained everolimus, which the PBAC considered reasonable (paragraph 5.1, July 2016 PBAC PSD) in its consideration of the July 2016 submission.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (7), health care professionals (9) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with nivolumab including the excellent response in those that do respond, few side effects, the ability of some patients to return to the work force and the addition of a new subsidised drug for treatment to those currently reimbursed on the PBS. The PBAC particularly noted that MOGA provided its support to the submission for nivolumab in RCC, and noted that its ESMO-MCBS evaluation score for non-curative therapies is 5 out of a maximum of 5 (where 5 and 4 represent the grades with substantial improvement)^[1] for the comparison of nivolumab with everolimus.

Clinical trials

- 6.3 The minor resubmission focused solely on the economic model and financial estimates with no clinical evidence presented. The clinical evidence presented in the July 2016 submission was based on one head-to-head trial comparing nivolumab to everolimus (CA209-025; N=821). The sponsor agreed with the position of the PBAC as outlined in the July 2016 PSD.
- 6.4 To support the requested PBS listing for nivolumab, the minor resubmission provided a revised economic model (see 'Economic analysis' below) and revised financial implications (see 'Estimated PBS usage and financial implications' below).
- 6.5 The PBAC noted that the Pre-PBAC response included 2-year follow-up OS data from CA209-025 including cross-over data.

Comparative effectiveness

- 6.6 No new clinical evidence was presented in the minor resubmission; the 2-year follow-up OS data received in the Pre-PBAC response is included in the following table and Figure 2 for completeness. For reference, a summary of the key results presented in

^[1] Chemy NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 26:1547-73, 2015

the July 2016 submission are provided in the table below, followed by the Kaplan-Meier plot for overall survival.

Table 2: Results of overall survival and progression-free survival in trial CA209-025

	Nivolumab (N=410)	Everolimus (N=411)	Absolute difference	HR (95% CI)
Overall survival (18 June 2015 database lock, 14-month minimum follow up, no cross-over)				
OS median months (98.52% CI) ^a	25.00 (21.75, NR)	19.55 (17.64, 23.06)	5.45	0.73 (0.57, 0.93) ^a
Extended overall survival (Pre-PBAC response, 24-month minimum follow up, % cross-over)^b				
OS median months (95% CI)				
RECIST v1.1-defined progression-free survival				
PFS median months (95% CI)	4.60 (3.71, 5.39)	4.44 (3.71, 5.52)	0.16	0.88 (0.75, 1.03)
Clinical progression-free survival				
PFS median months (95% CI)				

Source: Table 26, p65 and Table 28, p68-69 of the July 2016 submission and Pre-PBAC response November 2016.

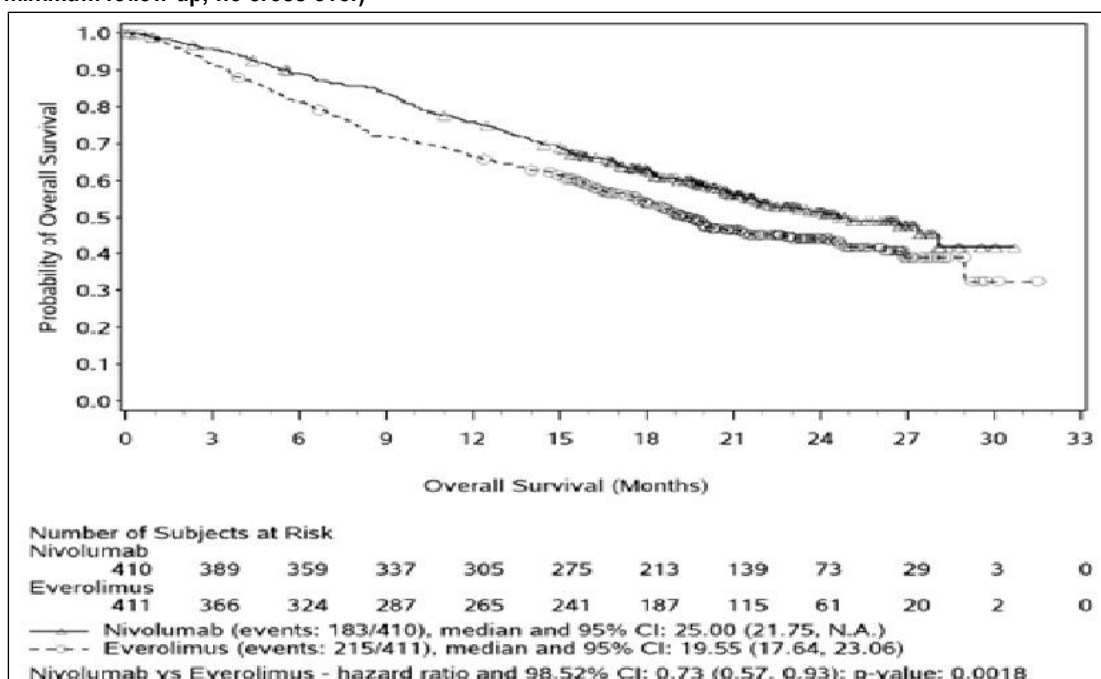
HR=hazard ratio; NR=not reported; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours.

^a 98.52% CI. The 98.52% CI was used for the OS results as the trial outcomes were based on the interim analysis, where the pre-determined boundary for significance was at p-value of 0.0148 (100%-1.48%=98.52%).

^b Data provided in summary form only in the Pre-PBAC response were not evaluated.

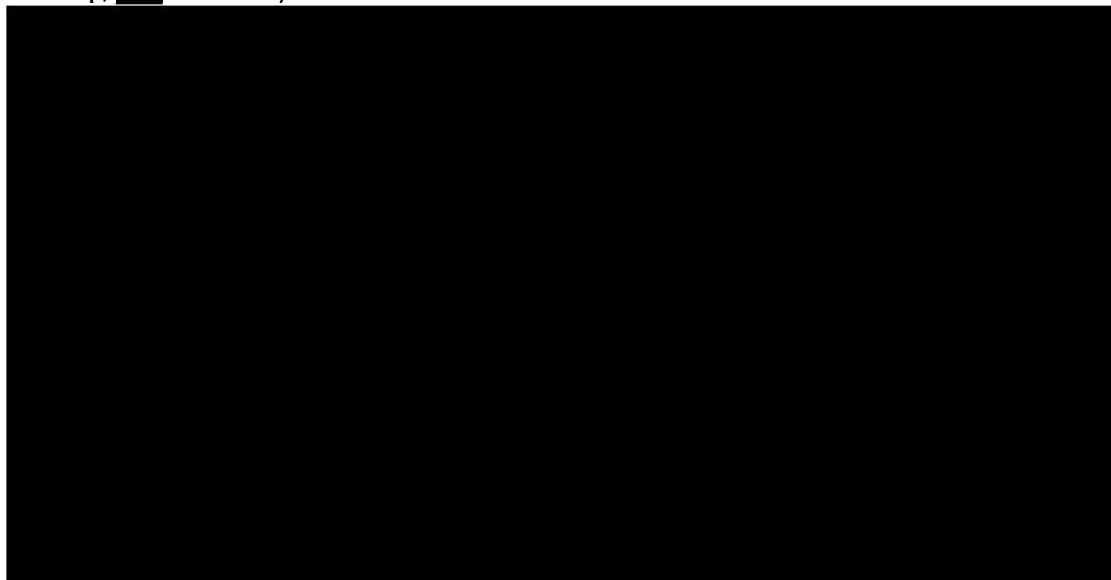
^c CI. The CI was used for the HR OS results, where the pre-determined boundary for significance was at p-value of

Figure 1: Kaplan-Meier overall survival plot from trial CA209-025 (18 June 2015 database lock, 14-month minimum follow up, no cross-over)



Source: Figure 6, p66 of the July 2016 submission.

Figure 2: Kaplan-Meier overall survival plot from trial CA209-025 (Pre-PBAC response, 24-month minimum follow up, [REDACTED] cross-over)



Source: Pre-PBAC response (p2).

- 6.7 While the PBAC previously accepted that nivolumab was associated with a statistically significant improvement in overall survival compared to everolimus (paragraph 7.6, July 2016 PBAC PSD), the PBAC also noted that as the trial was stopped early, the degree of overall survival gain may have been overestimated as the general bias in stopping trials early has been demonstrated in meta-analyses and because hazard ratios tend to become less favourable over time (paragraph 7.7, July 2016 PBAC PSD). The PBAC noted this overall survival benefit [REDACTED], as presented in the Pre-PBAC response.
- 6.8 The PBAC also previously noted that there was no significant difference between everolimus and nivolumab for PFS as defined by RECIST v1.1; and that the post-hoc use of a 'clinical PFS' outcome for economic modelling was not validated, nor necessarily representative of use in Australian practice (paragraph 7.5, July 2016 PBAC PSD). The minor resubmission did not address this issue regarding the use of 'clinical PFS' raised by the PBAC.

Comparative harms

- 6.9 The July 2016 submission claimed that nivolumab had a favourable safety profile compared to everolimus, with a statistically significantly reduced incidence of drug-related AEs (eg anaemia). The PBAC indicated that the claim of favourable safety for nivolumab over everolimus was not adequately supported by the data supplied (paragraph 7.8, July 2016 PBAC PSD). The revised economic model presented in the minor resubmission included four grade 3-4 immune-mediated adverse events (colitis, hepatitis, pneumonitis, and nephritis and renal dysfunction) and drug-related grade 3-4 anaemia.

Economic analysis

- 6.10 The minor resubmission provided a re-specification of the base case of the economic model, reflecting the recommended parameters contained in paragraph 7.10 of the July 2016 PBAC PSD. The model re-specification as proposed by the PBAC was as follows:
- [REDACTED] infusions of nivolumab reflecting time to progression in the key trial and costed according to the per cycle approach in the model.
 - The mean duration of use of everolimus and subsequent TKIs as observed in the PBS costed according to the per cycle approach in the model.
 - 5-year time horizon for the model.
 - No other changes to the method of generating the QALY estimates by the model.
 - Effective prices of everolimus, axitinib and sorafenib.
 - Back-calculated effective price of nivolumab to give the submission's base case ICER/QALY of no greater than \$45,000 - \$75,000/QALY.
- 6.11 While not listed as one of the parameters for re-specification of the model in paragraph 7.10, the PBAC also stated in paragraph 7.5 of the July 2016 PBAC PSD that the post-hoc use of a clinical PFS outcome for economic modelling was not validated, nor necessarily representative of use in Australian practice. The PBAC then recommended that the more standard PFS (allowing the RECIST criteria to be modified to avoid stopping the medicine in the context of early pseudo-progression as determined for nivolumab in melanoma) be used in the economic modelling (paragraph 7.5 of the July 2016 PBAC PSD).
- 6.12 The corresponding changes in the minor resubmission's revised model to the PBAC recommendations were:
- [REDACTED] infusions of nivolumab, costed according to the per cycle approach. The minor resubmission pointed out that the [REDACTED] infusions cited by the PBAC were based on the summation of life-year gains over a 10-year time horizon, and for a 5-year time horizon, [REDACTED] infusions would be required. The revised model did not apply the [REDACTED] infusions because the sponsor limited the number of nivolumab infusions in order to meet the required ICER (see below for further detail).
 - The mean duration of everolimus use was calculated using a separate tunnel state based on RECIST PFS, and was costed according to the per cycle approach. The minor resubmission did not base everolimus use on that observed in the PBS as recommended by the PBAC in paragraph 7.10 of the July 2016 PSD as it was claimed there was unlikely to be any credible means by which the clinical trial data could be adjusted to account for usage consistent with circumstances of use on the PBS. The minor resubmission stated that there was likely to be discordance between the trial-based setting and clinical practice, given that in the trial environment RECIST scanning was conducted every 4 weeks which differs from clinical practice, where symptomatic progression would more likely act as a trigger for further investigation; and it would be inappropriate for a clinical trial to be conducted via a protocol that allows each investigator to independently determine the frequency of scanning. The minor resubmission also cited paragraph 6.8 of the July PBAC PSD, where the ESC had noted that continuing treatment in the absence of evidence regarding a progression event is not the equivalent of actively continuing treatment in the presence of a known progression event as

occurred in the trial. The PBAC PSD continued in paragraph 6.8 to state that the ESC had agreed with the July 2016 commentary that the circumstances of use for everolimus in the trial differed from the Australian clinical setting and that the trial results presented in the submission, including the outcomes relating to 'clinical PFS', would be unlikely to be representative of the intended PBS setting. The minor resubmission concluded that, given the factors cited above, it was unlikely there would be any credible means by which the clinical trial data could be adjusted to account for usage consistent with the circumstances of use on the PBS. Consequently, the minor resubmission based the duration of everolimus use on RECIST PFS in CA209-025. The application of RECIST-based PFS to determine treatment duration and drug cost for everolimus created an inconsistency in the model, with 'clinical PFS' used for determining QALYs and also for all nivolumab variables (see below for further discussion).

- A 5-year time horizon was used for the revised model.
- No other changes were made to the method of generating the QALY estimates. The minor resubmission stated since the PBAC did not request any changes to the method of generating QALY estimates, that indicated acceptance of the following elements of the model: the health states and their definition (clinical PFS and clinical disease progression) were appropriate; log-logistic extrapolation of clinical PFS and OS were appropriate; and EQ-5D utilities calculated on the basis of clinical PFS were appropriate. The above claims by the minor resubmission were not in concordance with statements made in the July 2016 PBAC PSD, such as paragraph 7.5 where it was stated "The PBAC indicated that the post hoc use of a "clinical PFS" outcome for economic modelling was not validated, nor necessarily representative of use in Australian practice. Consequently, the PBAC recommended that the more standard PFS (allowing the RECIST criteria to be modified to avoid stopping the medicine in the context of early pseudo-progression as determined for nivolumab in melanoma) be used in any future PBS restriction and in the economic modelling". Therefore the continued use of clinical PFS in the economic model would not be appropriate. The revisions to the model, where RECIST-based PFS was applied for determining the duration of everolimus use, but clinical PFS was used for determining QALYs and for all relevant nivolumab variables resulted in a situation where two different definitions or types of PFS were used for everolimus while only clinical PFS was applied to nivolumab, which did not allow for an accurate determination of incremental differences.
- The minor resubmission stated that the sponsor was awaiting disclosure of the effective prices of everolimus, axitinib and sorafenib following a positive PBAC recommendation.
- The minor resubmission did not back-calculate the effective price of nivolumab to arrive at a base case ICER/QALY for the revised model of no greater than \$45,000/QALY-\$75,000/QALY. The minor resubmission stated that the sponsor's global partner had indicated that no further reduction from the \$██████████ per 100 mg vial was possible for use of nivolumab in RCC. To arrive at the specified ICER, the minor resubmission proposed an arrangement where the maximum duration of use of costed treatment with nivolumab would be █████ months, or an average of █████ infusions. This duration of nivolumab usage resulted in a base case ICER/QALY of \$45,000 - \$75,000/QALY. The minor resubmission also stated that, since pricing could not be adjusted, the most practical means by which to limit the duration of nivolumab costs would be through an appropriately

constructed financial arrangement; however, given other requirements of the PBAC, such as incorporation of the unknown effective price for everolimus, it was not possible to provide more specificity around the implementation or acceptability of such arrangements. While the ICER/QALY based on effective prices for everolimus and subsequent TKIs could not yet be known by the sponsor, it was likely that the maximum duration of treatment with nivolumab would need to be altered further than the [REDACTED] cycles used in the minor resubmission's revised model.

- The minor resubmission stated that “In adopting the PBAC’s recommendation, the economic model utilises an unlikely assumption that reduced exposure to everolimus would not impact treatment effect, when an associated reduction in LYs and QALYs is probable” and the minor resubmission added that “The sponsor wishes to note that components of the PBAC’s respecified base case model specific to i) the use of RECIST PFS to determine everolimus arm drug costs without a corresponding LY/QALY adjustment, and ii) a 5-year time horizon, are not within a realistic application of health economic or HTA principles” (minor resubmission p3. It was noted that the PBAC did not request that RECIST-based PFS be applied only to determine treatment duration and drug cost with everolimus without a corresponding LY/QALY adjustment.

6.13 The results of the revised economic model (5-year time horizon, per cycle costs, RECIST-based PFS used for everolimus and [REDACTED] cycles of nivolumab treatment) are provided in the table below. The redacted table below shows that the incremental cost of nivolumab vs everolimus was \$45,000 - \$75,000 per LY gained, and \$45,000 - \$75,000 per QALY gained.

Table 3: Results of the revised economic model

Component	Nivolumab	Everolimus	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	1.86	1.51	0.35
Incremental cost/ LY gained			\$ [REDACTED]
Incremental cost/ QALY gained			\$ [REDACTED]

Source: Table 1, p3 of the minor resubmission and the supplied Excel file 'Appendix 1_CEA_NIVO RCC August 2016'.
LY=life year; QALY=quality adjusted life year.

6.14 For reference, the following table provides a summary of the key components of the economic model and resultant ICERs across the July 2016 PBAC submission, the pre-PBAC response and the revised model provided in the minor resubmission. For the minor resubmission, this includes results based on nivolumab costs for the estimated treatment duration under a 5-year time horizon (ICER of \$75,000 - \$105,000/QALY) as well as the ICER when nivolumab treatment duration was limited to [REDACTED] infusions, to meet the specified ICER of less than \$45,000 - \$75,000/QALY.

Table 4: Summary of key model components across submissions

	Nivo price 100 mg vial	Time horizon	Costing approach	Treatment duration			Δ QALY	Δ cost	ICER
				Nivo	Evero	Subseq't therapy			
July 2016 submission	\$██████	10 years	Front- loaded	19.2 infusions	██████ months	██████ months	0.43	\$██████	\$██████ ^a
PSCR	\$██████	10 years	Per cycle	██████ infusions	██████ months	██████ months	0.43	\$██████	\$██████
Pre-PBAC response	\$██████	5 years	Per cycle	██████ infusions	██████ months	██████ months	0.35	\$██████	\$██████
Minor resubmission	\$██████	5 years	Per cycle	██████ infusions	██████ months	██████ months	0.35	\$██████	\$██████
	\$██████	5 years	Per cycle	██████ infusions	██████ months	██████ months	0.35	\$██████	\$██████

Source: Compiled during the preparation of the overview.

Evero=everolimus; Nivo=nivolumab; Subseq't=subsequent

^a The base case ICER for the July 2016 submission presented here used the updated preparation fee of \$102.67 and the updated DPMQ for everolimus of \$5,276.87.

6.15 Application of the parameters proposed by the PBAC for re-specification of the model (5-year time horizon, per cycle costing) resulted in a base case ICER of \$75,000/QALY-\$105,000/QALY. The resubmission did not back-calculate the required effective price of nivolumab to arrive at an ICER/QALY less than \$45,000/QALY-\$75,000/QALY, the minor resubmission proposed to limit treatment duration with nivolumab to ██████ infusions. While this resulted in an ICER of the required value (\$45,000/QALY-\$75,000/QALY), there remained concerns with the modelled evaluation. In particular:

- The revised model employed RECIST-based PFS to determine duration of therapy for everolimus only, and otherwise maintained the use of clinical PFS. The PBAC had recommended (paragraph 7.5, July 2016 PSD) that the more standard RECIST-based PFS be used in the economic modelling and it would be appropriate to apply this to all aspects of the model, not just everolimus treatment duration. The continued use of the post-hoc clinical PFS for everolimus treatment effect, and all nivolumab PFS outcomes meant that the model was still dependent on an outcome that was not validated.
- The revised version of the economic model provided with the minor resubmission used both RECIST-based PFS and clinical PFS for the everolimus arm, which created an inconsistency in the application of PFS to determine outcomes within the everolimus arm, and also created an inconsistency with determination of PFS-relevant nivolumab outcomes, which were based solely on clinical PFS. This did not allow for accurate estimation of incremental differences between the two therapies. Since there was no statistically significant difference between nivolumab and everolimus treatment for RECIST-based PFS in CA209-025, this discordant application of PFS outcomes was likely to favour nivolumab.
- The PBAC had previously indicated (paragraphs 6.26 and 7.7, July 2016 PBAC PSD) that the overall survival gain in CA209-025 may have been overestimated. The July 2016 model was sensitive to overall survival, with the use of the upper 98.25% CI of the overall survival hazard ratio more than doubling the ICER. A similar result occurred with the revised model, as when the upper CI level of the HR was applied, the ICER increased to \$105,000 - \$200,000/QALY for the minor

resubmission's base case using [REDACTED] nivolumab infusions and to \$105,000 - \$200,000/QALY for [REDACTED] nivolumab infusions.

- Although the recommendations made by the PBAC for re-specification of the model did not detail extrapolation methods, the PBAC had previously noted that the ICER was highly sensitive to variations in incremental OS arising from the extrapolation assumptions including the biological plausibility of the extrapolation methods examined (paragraph 6.26, July 2016 PSD). The log-logistic methods applied in the July 2016 submission and the minor resubmission resulted in curves that did not asymptote and instead suggested a prolonged effect in a proportion of patients, which was not consistent with the trial evidence. The minor resubmission did not provide any sensitivity analyses assessing extrapolation methods.
- 6.16 It was likely that the revisions made to the model did not provide an accurate estimate of the cost-effectiveness of nivolumab for the treatment of RCC. It would have been informative for the model to include, or at least for sensitivity analysis to be provided, using RECIST-based PFS for all everolimus components and also for nivolumab, as recommended by the PBAC (paragraph 7.5 July 2016 PSD). It would also have been informative for sensitivity analyses using alternate extrapolation methods to have been applied.
- 6.17 The PBAC noted that the Pre-PBAC response included sensitivity analyses, which reduced the ICER from its base case of \$45,000 - \$75,000/QALY, by applying costs and outcomes to everolimus and nivolumab based on either clinical PFS (to \$45,000 - \$75,000/QALY) or RECIST PFS (to less than \$15,000 per QALY).

Drug cost/patient/course: \$ [REDACTED]

- 6.18 The following table provides a summary of estimated drug cost based on the minor resubmission and the July 2016 submission. The cost per course of treatment in the minor resubmission increased slightly from that in the July 2016 submission, due to the increase in treatment duration (from [REDACTED] infusions ([REDACTED] months) to [REDACTED] infusions ([REDACTED] months)), countered by the decrease in requested effective price. In its proposed risk share arrangement, the sponsor proposed to cap the costs of the number of nivolumab infusions at [REDACTED], in order to meet the required ICER target.

Table 5: Summary of drug cost/patient/course for nivolumab in the minor resubmission and the July 2016 submission

Parameter	Minor resubmission	July 2016 submission
Nivolumab infusions	[REDACTED]	19.2
100 mg vial requested price	\$ [REDACTED]	\$ [REDACTED]
Drug cost/infusion ^a	\$ [REDACTED]	\$ [REDACTED]
Drug cost/patient/course	\$ [REDACTED]	\$ [REDACTED]
Drug cost/patient/course plus administration cost ^b	\$ [REDACTED]	\$ [REDACTED]

Source: Compiled during the preparation of the overview.

^a The cost included ex-manufacturer price for the required vials (one 40 mg; two 100 mg) and applicable fees. The total drug cost per infusion was calculated based on an assumption that the public vs. private weighting would be 70% vs. 30%. The July 2016 submission used \$82.67 for the preparation fee as part of the applicable fees, which was updated to \$102.67 during the preparation of the overview. The minor resubmission preparation fee was updated from \$83.22 to \$103.22.

^b Administration cost was based on MBS item 13915: \$55.30 per infusion (85% MBS benefit).

Estimated PBS usage & financial implications

- 6.19 In regard to the usage and financial estimates made in the July 2016 submission, the PBAC advised that the assumed uptake rate of 90% for nivolumab was implausibly high, given the existing uptake rate of 16% to 25% for any second-line treatment following a TKI. The PBAC also noted that the submission had possibly underestimated the number of patients receiving first-line TKIs. PBAC recommended that a reduced uptake rate of nivolumab should be identified, and justified, in order to support a risk share arrangement (paragraph 7.12, July 2016 PSD).
- 6.20 The minor resubmission argued that the cited PBS data provided a flawed estimate of future nivolumab utilisation (24.8%) in a second-line setting, and again proposed 80% or greater with arguments based on immaturity of RCC second-line PBS data, expert advice, published data and nivolumab uptake rate in the second-line RCC named patient program. Details of the arguments provided by the minor resubmission for each of these factors are provided below.
- 6.21 Second-line PBS data: The minor resubmission stated that the second-line treatment setting for RCC in Australia is immature, as everolimus was PBS-listed in September 2014, sorafenib in April 2015 and axitinib in December 2015. Therefore, PBS-subsidised therapies were not available for all patients who received a first-line TKI during the 2013 to 2014 period, and the 2015 data was too immature to capture all patients who have progressed following treatment with a TKI. In addition, the PBS statistics did not take into account patients treated in clinical trials or via patient access programs. Consequently the sponsor believed the estimate of 24.8% of patients initiating on a TKI going onto second-line therapy was a significant underestimate.
- 6.22 Expert advice: On the basis of expert advice (N=8 advisors), the July 2016 submission claimed that, of the patients who have progressed on TKIs, about 80% would go on to second-line therapy. While it was likely that patients commencing TKI treatment in 2013 may not have had PBS-listed second-line drugs available, without an estimate of the proportion of patients who progress on TKIs, it was difficult to determine the impact of this identified data immaturity on the number of patients using second-line therapy on the PBS. The minor resubmission appeared to suggest that second-line use would increase from 16%-25% to 70%-80%. The cited immaturity of the PBS data was unlikely to account for this large of an increase in the usage estimate, and it seemed that the proportion of patients using second-line treatment as estimated by the July 2016 submission and the minor resubmission was an overestimate. The minor resubmission commented on this expert advice, suggesting that it was robust because it came from clinicians who were involved in the clinical research for nivolumab and related agents, and were also involved in the compassionate access program for nivolumab.
- 6.23 Published data: The minor resubmission cited Day (2015), a retrospective review of patterns of care for RCC in Australia, based on 173 patients receiving treatment between 2006 and 2012, which reported that 45% of patients receiving first-line treatment went on to receive second-line treatment. The minor resubmission stated that this was a likely underestimate, as it pre-dated the PBS listing of everolimus, sorafenib and axitinib.

- 6.24 Marketing report: To support the claim of high uptake of second line agents, the submission provided a marketing report which stated that 80% of patients who received drug therapy would be alive and eligible to receive second-line therapy, and that overall, 75% of patients would receive second-line drug treatment. The marketing report estimates were based on the opinions of 20 'thought leaders', 212 physician surveys (USA, France, Germany, Spain, Italy, UK, Japan), the market model of Decision Resources and country-specific treatment rates.
- 6.25 Uptake of nivolumab in the RCC named patient program: The minor resubmission provided a description of the named patient program run by the sponsor, which enrolled ■■■ patients from the end of May 2015 to the end of February 2016. Analysis of a 10% PBS sample provided to the sponsor by a consultant estimated that, between July 2015 and February 2016, a total of ■■■ patients were initiated on treatment, and of these ■■■, or ■■■ were second-line patients. The minor resubmission concluded that patients who progress following treatment with a TKI would cycle through more than one second-line therapy, that the majority of patients who progress following treatment with a TKI would receive second-line therapy, and therefore the 80% estimated by the expert advisors was reasonable. The numbers provided by the minor resubmission based on the 10% PBS sample in the additional Excel spreadsheet could not be verified, and in particular the numbers for 'total market' were greater in most months than the number of patients using each drug, and no explanation for this anomaly was provided. Also, the minor resubmission appeared to be calculating proportions of patients using second-line treatment by determining the number of patients using first-line treatment and second-line treatment over the same time period. However, this could not provide an accurate estimate of the proportion of patients who, after receiving first-line treatment, would move on to second-line treatment - such would need to be assessed longitudinally.
- 6.26 The minor resubmission also stated that it would be reasonable to assume that nivolumab would lead to a 10% increase in the uptake rate of second-line therapies, but the sponsor was willing to accept a 10% reduction to the assumption of the proportion of patients initiated on second-line therapy with an associated reduction to the assumption of nivolumab uptake rate to maintain the 10% increment. Consequently, the minor-resubmission provided revised patient numbers, using an 80% usage rate for second-line therapies (assuming nivolumab is PBS-listed) instead of the 90% used in the July 2016 submission. The uptake rate, or market share, of nivolumab remained the same, 90% in Year 1 increasing to 95% in Years 2 to 5. The table below provides the revised financial estimates, along with the estimates from the July 2016 submission for reference.

Table 6: Revised estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
New patients initiating a TKI (July 2016 and minor resub)	█	█	█	█	█
% receiving second-line treatment (minor resubmission)	80%	80%	80%	80%	80%
% receiving second-line treatment (July 2016)	90%	90%	90%	90%	90%
Number receiving second-line treatment (minor resubmission)	█	█	█	█	█
Number receiving second-line treatment (July 2016)	█	█	█	█	█
Market share nivolumab (July 2016 and minor resub)	90%	95%	95%	95%	95%
Number of treated patients (minor resubmission)					
Number of treated patients (July 2016)	█	█	█	█	█
Estimated net cost to PBS/MBS					
Net cost to PBS/RPBS (minor resubmission)	\$█	\$█	\$█	\$█	\$█
Net cost to PBS/RPBS (July 2016)	\$█	\$█	\$█	\$█	\$2█
Net cost to MBS (minor resub)	\$█	\$█	\$█	\$█	\$█
Net cost to MBS (July 2016)	\$█	\$█	\$█	\$█	\$█
Net cost to state/territory gov'ts (minor resubmission)	\$█	\$█	\$█	\$█	\$█
Net cost to state/territory gov'ts (July 2016)	\$█	\$9█	\$█	\$█	\$█
Estimated total net cost					
Net costs to Government (minor resubmission)	\$█	\$█	\$█	\$█	\$█
Net costs to Government (July 2016)	\$1█	\$█	\$█	\$█	\$█

Source: Compiled during the preparation of the overview.

Note: For the July 2016 submission costs were updated to apply the 85% benefit to MBS item 13309 (from \$284.85 to \$242.15); to adjust the preparation fee (from \$82.67 to \$102.67) and the DPMQ for everolimus (from \$5,241.90 to \$5,276.87). For the minor resubmission the 85% benefit for MBS item 13309 was applied (\$242.15); the preparation fee was increased from \$83.22 to \$103.22; and to correct the error in the minor resubmission's Excel workbook for calculation of transfusion administration costs for anaemia, these costs were subtracted.

- 6.27 The redacted table above shows that at year 5 the estimated number of patients was less than 10,000 per year. With a 10% drop in proportion of patients receiving second-line treatment for RCC, the estimated number of patients treated with nivolumab decreased by approximately █ patients per year. Overall estimated net costs were \$10 - \$20 million in Year 1, increasing to \$10 - \$20 million in Year 5, for a total of \$60 - \$100 million over the first 5 years of listing. While this was a decrease in total estimated net cost compared to the July 2016 submission (more than \$100 million), there remained uncertainties around the estimate. While there was a small decrease in the proportion of patients receiving second-line treatment and this would impact uptake rate, the minor resubmission did not decrease the uptake rate, or market share, of nivolumab, as recommended by the PBAC (paragraph 7.12, July 2016 PBAC PSD); and the proportion of patients receiving

second-line treatment remained high, at 80%. In addition, the estimated costs assumed that patients receive [REDACTED] nivolumab infusions, which was an economic-model derived value. Given that the economic model did not provide an accurate estimate of the cost-effectiveness of nivolumab, relying on an economic model-determined value to estimate costs may not provide an accurate estimate of cost.

- 6.28 There was a minor error noted in the calculation of MBS costs in the minor resubmission's financial estimates; and this error was also in the July 2016 estimates. While the minor resubmission appropriately subtracted MBS costs for anaemia treatment, costs for transfusion administration for anaemia were added, when these costs should have been subtracted. This error, which had a very small impact of around \$[REDACTED] per year, was corrected during the preparation of the overview, and the values reported in the table above represent the corrected numbers.
- 6.29 The cost offsets for adverse events that occurred less frequently in nivolumab-treated patients (anaemia and pneumonitis) were calculated in both the minor resubmission and the July 2016 submission in a manner that overstated the cost offset. The standard methodology to determine the difference in adverse events would be to calculate the number of patients with the adverse event or frequency of occurrence for the adverse event in each group and subtract one from the other to determine the difference. The minor resubmission instead calculated the difference in event rate (eg for anaemia 1.7% for nivolumab; 7.8% for everolimus) and multiplied this by the number of patients no longer receiving treatment with the substituted therapies (everolimus, sorafenib, axitinib). For pneumonitis, the minor resubmission and the July 2016 submission multiplied by the number of patients treated with nivolumab, which was inconsistent with the methodology used for the anaemia calculation. The methodology favoured nivolumab, and also applied an adverse event rate based on everolimus data from CA209-025 to patients assumed to be taking sorafenib or axitinib.
- 6.30 The minor resubmission and July 2016 submission were also inconsistent in their calculation of number of patients with events - for anaemia the number of patients who would no longer be treated with everolimus, sorafenib or axitinib (n=[REDACTED]) were used as the multiplier, while for pneumonitis the number of patients treated with nivolumab (n=[REDACTED]) were used as the multiplier (which also favours nivolumab).
- 6.31 Neither the minor resubmission nor the July 2016 submission provided a detailed rationale for the methodology employed to calculate patient numbers used to determine adverse event costs. Given the cost impact was minimal (less than \$10 million per year), the methodology used in the minor resubmission's Excel workbook was not altered. However it was noted that the patient number estimates and associated MBS cost estimates for treatment of adverse events provided by the minor resubmission and July 2016 submission were not accurate. The sponsor should provide a rationale for the methodology used to calculate these patient numbers in any resubmission.
- 6.32 Given the continued use of a high nivolumab uptake rate, dependence on an economic-model determined duration of treatment for nivolumab (further impacted by the sponsor's decision to limit therapy to reach the required ICER value), along with the minor error in the calculation of MBS costs, as well as the calculation of adverse

events costs favouring nivolumab, it was likely that the revised financial estimates provided were not accurate.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of nivolumab for the treatment of advanced or metastatic clear cell variant renal cell carcinoma (RCC) on grounds of unfavourable and uncertain cost-effectiveness. The PBAC considered that the benefit of treatment with nivolumab was uncertain and likely overestimated and that the proposed risk sharing arrangement would not address this uncertainty.
- 7.2 The PBAC recalled its previous consideration of nivolumab in July 2016 where it recognised the clinical need for more effective therapies in patients with clear cell renal carcinoma who had failed first-line treatments.
- 7.3 The PBAC also recalled that, although there was no significant difference between everolimus and nivolumab treatment in progression-free survival (PFS), nivolumab statistically significantly increased overall survival (OS) compared to everolimus. The PBAC noted the updated 2-year follow-up data on OS which [REDACTED] however considered that the degree of benefit in a PBS population was still uncertain as the trial contained patients whose nivolumab treatment continued after disease progression.
- 7.4 The PBAC was satisfied that nivolumab provides, for some patients no increase in toxicity and an improvement in overall survival over everolimus however, the size of this improvement was uncertain.
- 7.5 The PBAC recalled its July 2016 concerns with the economic modelling and that they had proposed the following respecification of the base case for the model for any resubmission:
- [REDACTED] infusions of nivolumab reflecting time to progression in the key trial and costed according to the per cycle approach in the model
 - the mean duration of use of everolimus and subsequent TKIs as observed in the PBS costed according to the per cycle approach in the model
 - 5-year time horizon for the model
 - no other changes to the method of generating the QALY estimates by the model
 - effective prices of everolimus, axitinib and sorafenib
 - back-calculated effective price of nivolumab to give the submission's base case ICER/QALY of no greater than \$45,000 - \$75,000/QALY.
- 7.6 The PBAC noted that the sponsor had complied with some, but not all, of the respecified base case as proposed by the PBAC. The resubmission's model complied with the respecified time horizon of 5 years. However the duration of treatment with everolimus (based on extrapolated RECIST-defined PFS) in the model was longer would have been the case than using the basis nominated by the PBAC. In addition, the resubmission proposed to use a risk share arrangement to cap the cost of nivolumab to [REDACTED] infusions, reduced from the extrapolated [REDACTED] infusions

from the 5-year model (based on post-hoc assessment of “clinical PFS”, compared to the extrapolated █████ infusions from the 10-year model using “clinical PFS”) in order to achieve the target ICER of \$45,000 - \$75,000/QALY. The model also did not use the effective prices of everolimus, axitinib and sorafenib.

- 7.7 The PBAC noted that RECIST PFS and “clinical PFS” were inconsistently used by the model in the resubmission across everolimus and nivolumab creating further uncertainty in the resultant ICER. The PBAC therefore decided that the RECIST-PFS criteria, rather than the “clinical PFS” criteria, should be used for all treatment arms in generating the QALY estimates for the base case in the economic evaluation of any resubmission, noting that this also differed from its July 2016 specification.
- 7.8 The PBAC acknowledged that the sponsor was unaware of the effective prices of everolimus, axitinib and sorafenib, but reiterated that the use of the published prices in the model underestimated the ICER. The PBAC did not support the minor resubmission’s proposal to use risk share expenditure caps based on a limited duration of nivolumab treatment to achieve a lower effective nivolumab price and thus an acceptable ICER in the model. This was because the capping approach would be subject to too many other uncertainties to be considered a reliable method to reduce and maintain an acceptable ICER. The PBAC also noted that the use of effective prices for everolimus, axitinib and sorafenib would require a further reduction in the estimated duration of treatment with nivolumab to derive an effective nivolumab price sufficient to maintain an acceptable ICER.
- 7.9 The PBAC thus summarised its respecification of the base case for the model for any resubmission as follows:
- 5-year time horizon for the model
 - use of the RECIST-PFS criteria, rather than the “clinical PFS” criteria for all treatment arms reflecting time to progression in the key trial in generating the QALY estimates
 - use of the RECIST-PFS criteria, rather than the “clinical PFS” criteria reflecting time to progression in the key trial and costed according to the per cycle approach in the model in generating the number of infusions of nivolumab (with any further modification to reduce the effective price of nivolumab)
 - use of the RECIST-PFS criteria, rather than the “clinical PFS” criteria reflecting time to progression in the key trial and costed according to the per cycle approach in the model generating the mean duration of use of everolimus and subsequent TKIs (to reflect the same basis as the estimate of infusions of nivolumab)
 - effective prices of everolimus, axitinib and sorafenib
 - back-calculated effective price of nivolumab to give the submission’s base case ICER/QALY of no greater than \$45,000 - \$75,000/QALY.
- 7.10 The PBAC noted that the resubmission reduced the estimated uptake of second-line therapy in RCC from 90% to 80% if nivolumab was listed with 90% to 95% market share for nivolumab. The PBAC considered that this was still an overestimation of the expected uptake of nivolumab based on current PBS data on uptake of second-line therapy after progression from a TKI.

- 7.11 The PBAC noted that the revised uptake figures used in the financial estimates resulted in a 5-year net cost to the Commonwealth of \$60 - \$100 million. The PBAC indicated that the financial estimates remained unreliably high due to overestimation of the duration of therapy for replacement therapies acting as cost off-sets, the use of duration of therapy for nivolumab from the unreliable economic model, overestimated uptake of nivolumab in second-line therapy, and reliance on published rather than effective prices of everolimus, axitinib and sorafenib.
- 7.12 The PBAC noted that the sponsor was open to a risk share arrangement however, the specific details of such an arrangement were not included in the resubmission. However, although an RSA would be an appropriate method to manage total financial impact, the likely impact of the proposed Cap was subject to too many uncertainties and, as noted above, the PBAC did not consider that an RSA was a suitable approach to address the outstanding concerns of an uncertain level of benefit from treatment and unfavourable and uncertain cost-effectiveness.
- 7.13 The PBAC indicated that any resubmission should address the above issues in the form of a major resubmission.
- 7.14 The PBAC noted that this submission is eligible for an Independent Review as the requested listing is for an entirely different disease (RCC) to that which nivolumab is currently subsidised (melanoma).

Outcome:

Rejected

8 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.

9 Sponsor's Comment

The sponsor had no comment.