

### **6.03 NIVOLUMAB, CONCENTRATE SOLUTION FOR INFUSION OF 10 MG/ML, 1 X 4 ML VIAL, 1 X 10 ML VIAL, OPDIVO®, BRISTOL MYERS SQUIBB**

#### **1 Purpose of Application**

- 1.1 Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required listing for the treatment of advanced or metastatic clear cell variant renal cell carcinoma (RCC) in patients who have progressed according to Response Evaluation Criteria in Solid Tumours (RECIST) following first-line treatment with a tyrosine-kinase inhibitor (TKI).

#### **2 Requested listing**

- 2.1 The submission requested the restriction provided below at a published price consistent with that of the current melanoma PBS listing and the requested non-small cell lung cancer (NSCLC) listings, with an effective price [REDACTED] that of the melanoma listing. The submission did not request separate listings by initial or continuing treatment. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

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Name, Restriction, Manner of administration and form	Max. Qty	Nº. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
NIVOLUMAB 40 mg/4 mL injection 1 x 4 mL vial	360 mg	44-5	\$830.70 (Published price) \$ [REDACTED] (Effective price)	Opdivo	Bristol-Myers Squibb Australia Pty Ltd
100 mg/10 mL injection 1 x 4 mL vial	360 mg	44-5	\$2,076.75 (Published price) \$ [REDACTED] (Effective price)		

<b>Category / Program</b>	Section 100 – Efficient funding of Chemotherapy.
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	<del>Advanced or metastatic</del> Stage III or Stage IV
<b>Condition:</b>	Clear cell variant renal cell carcinoma (RCC)
<b>PBS Indication:</b>	<del>Advanced or metastatic</del> Stage III or Stage IV clear cell variant renal cell carcinoma (RCC)
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<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
<b>Treatment criteria:</b>	<del>The treatment must be the sole PBS-subsidised therapy for this condition</del>
<b>Clinical criteria:</b>	<i>The treatment must be the sole PBS-subsidised therapy for this condition</i>  AND  <i>Patient must have a WHO performance status of 2 or less</i>  AND  Patient must have progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) following first-line treatment with a tyrosine kinase inhibitor  OR  Patients <del>who</del> must have developed intolerance to a tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal.
<b>Definitions</b>	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.
<b>Prescriber Instructions</b>	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
NIVOLUMAB					
40 mg/4 mL injection 1 x 4 mL vial	360 mg	11	\$830.70 (Published price) \$ [REDACTED] (Effective price)	Opdivo	Bristol-Myers Squibb Australia Pty Ltd
100 mg/10 mL injection 1 x 4 mL vial	360 mg	11	\$2,076.75 (Published price) \$ [REDACTED] (Effective price)		

<b>Category / Program</b>	Section 100 – Efficient funding of Chemotherapy.
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	<del>Advanced or metastatic</del> Stage III or Stage IV
<b>Condition:</b>	Clear cell variant renal cell carcinoma (RCC)
<b>PBS Indication:</b>	<del>Advanced or metastatic</del> Stage III or Stage IV clear cell variant renal cell carcinoma (RCC)
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<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
<b>Treatment criteria:</b>	The treatment must be the sole PBS-subsidised therapy for this condition
<b>Clinical criteria:</b>	<i>Patient must have previously been issued with an authority prescription for this drug for this condition,</i>  <i>AND</i>  <i>Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST),</i>  <i>AND</i>  <i>The treatment must be the sole PBS-subsidised therapy for this condition.</i>
<b>Definitions</b>	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.
<b>Prescriber Instructions</b>	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.

2.2 The ESC noted that the requested restriction includes locally advanced (Stage III) as well as metastatic (Stage IV) disease. This differs from those of currently-funded PBS

therapies for renal cell carcinoma including sunitinib, pazopanib, everolimus, axitinib or sorafenib (all Stage IV only), and would potentially increase the eligible population for PBS subsidised treatment of renal cell carcinoma. The ESC noted that the PBAC has not previously assessed the cost-effectiveness of everolimus in locally advanced (Stage III) RCC, despite patients with this stage of RCC being included in the key trial and the requested PBS restriction of nivolumab. The ESC suggested 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.

- 2.3 No stopping rule was requested for nivolumab in contrast to the existing listings of everolimus, axitinib and sorafenib, where patients who have progressive disease are no longer eligible for PBS-subsidised drug. The ESC advised that a stopping rule on progression of disease should be included in the restriction, consistent with other PBS-listed drugs for metastatic RCC.
- 2.4 The submission requested that grandfathering of patients from the sponsor's named patient program (approximately 54 patients) be permitted upon implementation of the PBS listing of nivolumab.
- 2.5 The submission sought listing on the basis of a cost utility analysis compared to everolimus, via a head-to-head comparison.

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

### **3 Background**

- 3.1 TGA Status at time of PBAC: Nivolumab was submitted to the TGA on 1 December 2015, but the TGA Delegate's Overview was not available before the July 2016 PBAC deliberations.
- 3.2 This was the first consideration of nivolumab by the PBAC for the treatment of RCC. A submission to list nivolumab for Stage III/IV melanoma was rejected in July 2015 but recommended by the PBAC in November 2015. Earlier submissions to list nivolumab for squamous and non-squamous NSCLC were both rejected in March 2016 by the PBAC. The PBAC recommended listing of everolimus at the March 2014 PBAC meeting, and both axitinib and sorafenib at the November 2014 PBAC meeting for the treatment of Stage IV clear cell variant RCC in patients who have failed prior therapy with a TKI.

### **4 Clinical place for the proposed therapy**

- 4.1 RCC is a type of kidney cancer that arises from the lining of renal tubules. Its incidence has been increasing, and despite the improved management of the disease, most patients are diagnosed with advanced RCC, which is often resistant to systemic therapy and difficult to treat. The submission requested nivolumab to be used as second-line treatment of advanced or metastatic clear cell variant RCC as an alternative to everolimus, axitinib and sorafenib. The ESC noted that this would be consistent with current treatment recommendations and guidelines.

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

## **5 Comparator**

- 5.1 The submission nominated everolimus as the main comparator, and axitinib and sorafenib as secondary comparators. The PBAC considered this was reasonable.

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

## **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 (1), health care professionals (7) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with nivolumab including an overall survival benefit in some patients, a reduction in disease burden, and quality of life improvements, all with relatively low toxicity.

### ***Clinical trials***

- 6.3 The submission was based on one head-to-head trial comparing nivolumab to everolimus (CA209-025; N=821). The secondary comparisons to axitinib and sorafenib were indirect comparisons using CA209-025 as well as RECORD-1 (everolimus vs. placebo), TARGET (sorafenib vs. placebo) and AXIS (axitinib vs. sorafenib). Details of the trials presented in the submission are provided in the table below.

**Table 1: Trials presented in the submission**

Trial	Description	Protocol title/Publication title	Publication citation
<b>Direct randomised trial</b>			
CA209-025 (nivolumab vs. everolimus)	R, OL, MC	A randomised, open-label, phase 3 study of nivolumab (BMS-936558) versus everolimus in subjects with advanced or metastatic clear-cell renal cell carcinoma who have received prior anti-angiogenic therapy (CheckMate 025, CHECKpoint pathway and nivolumab clinical Trial Evaluation)	21 August 2015  NEJM. 2015; 373 (191): 1803-1813.
<b>Supplementary analysis – trials included in the indirect comparisons</b>			<b>Comparable?</b>
RECORD-1 (everolimus vs. placebo)	R, DB, MC	Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. <i>Cancer</i> . 2010; 116 (18): 4256-4265.  Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. <i>Lancet</i> . 2008; 372 (9637): 449-456.	No
TARGET (sorafenib vs. placebo)	R, DB, MC	Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. <i>Journal of Clinical Oncology</i> . 2009; 27 (20): 3312-3318.  Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. <i>The New England Journal of Medicine</i> . 2007; 356 (2): 125-134.	No
AXIS (axitinib vs. sorafenib)	R, OL, MC	Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. <i>The Lancet Oncology</i> . 2013; 14 (6): 552-562.  Rin BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. <i>Lancet</i> . 2011; 378 (9807):1931-1939.	No

Source: Table 10, p39 of the submission.

Abbreviations: DB=double blind; MC=multicentre; OL=open-label; R=randomised.

- 6.4 The submission claimed that the results of the indirect comparisons were considered uninformative because of (i) poor exchangeability of the trials, (ii) extensive cross-over in the placebo controlled trials (RECORD-1 and TARGET), and (iii) uncertainty associated with the nature of the indirect comparison. This was reasonable. The results of the indirect comparisons were not used to make any key clinical or economic claims in the submission.
- 6.5 The key features of the randomised trial used in the head-to-head comparison of nivolumab and everolimus are summarised in the table below.

**Table 2: Key features of the included evidence**

Trial ID	N	Comparison	Trial design	Primary outcome	Use in the economic evaluation
CA209-025	821	Nivolumab 3mg/kg Q2W n=410 Everolimus 10mg po n=411	Phase III R, OL, MC	Overall survival	Extrapolated survival data

Source: Table 11, p42 of the submission.

Abbreviations: MC=multicentre; po=oral administration; OL=open-label; Q2W=every two weeks; R=randomised.

6.6 As the pre-specified boundary for significance was crossed at the first interim analysis of overall survival (OS), CA209-025 was terminated early to allow the everolimus treated patients to receive nivolumab. The outcomes presented in the submission were based on the 18 June 2015 database lock and were not confounded by cross-over.

6.7 There were two key consequences of the early termination of the trial:

- The mean duration of therapy was likely to have been underestimated. Patients in both treatment arms (16.3% for nivolumab; 6.8% for everolimus) were continuing therapy at time of the database lock.
- The treatment effect on OS at the time of trial cessation may have been overestimated in favour of nivolumab, as comparative treatment effects tend to become less favourable over time (paragraph 6.8, July 2015 nivolumab PSD).

Therefore, the treatment duration and treatment effect of OS estimated in the trial would be unlikely to be observed in the intended PBS setting. The ESC noted that the trial included patients with locally advanced disease (Stage III) for whom the prognosis for survival is better than those with Stage IV disease. Results were not stratified by disease stage, so it is not possible to discern the impact this had on (i) the overall estimate of OS, or (ii) the incremental OS for nivolumab, given that currently only Stage IV patients can access treatment on the PBS with TKIs or mTORs in the first and second-line setting.

6.8 In both arms of trial CA209-025, patients were able to continue receiving treatment beyond progression if they were assessed as still deriving clinical benefit and tolerating treatment. The submission claimed that progression based on discontinuation of treatment would be more clinically representative for the patients continuing treatment beyond progression. The submission therefore conducted a post-hoc analysis of trial CA209-025 where the definition of progression was defined as follows:

- For patients who discontinued therapy prior to or at progression: same as RECIST v1.1-defined progression-free survival (PFS).
- For patients who discontinued therapy after progression (44.1% for nivolumab; 46.1% for everolimus): the time of discontinuing therapy.

The submission referred to this definition of PFS as “clinical PFS”. The use of the “treatment beyond progression” approach and “clinical PFS” was consistent with the requested listing of nivolumab. The use of the novel endpoint of “clinical PFS” was consistent with the treatment beyond progression approach however, it is a novel endpoint which has not been validated. Furthermore, this approach was not appropriate for everolimus given its PBS restriction for RCC, which would require patients to stop the treatment upon progression. In the Pre-Sub-Committee Response (PSCR), the sponsor claimed that this appropriately reflects current practice according to the PBS stopping criteria for everolimus due to patients

potentially progressing between scans in the clinical setting, and the advent of clinical symptoms precipitating the need for scans. However, ESC noted that continuing treatment in the absence of evidence regarding a progression event as described above is not the equivalent of actively continuing treatment in the presence of a known progression event as occurred in the trial. The ESC therefore agreed with the 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 ESC considered that treatment beyond clinical progression should be handled consistently in the economic evaluation unless there is good evidence to justify prescribers using these medicines differently in Australian practice.

### Comparative effectiveness

6.9 Table 3 provides the OS and PFS results from CA209-025 while Figures 1 to 3 provide the corresponding Kaplan-Meier curves.

**Table 3: Results of overall survival and progression-free survival in trial CA209-025**

	Nivolumab (N=410)	Everolimus (N=411)	Absolute difference	HR (95% CI)
<b>Overall survival</b>				
Death, n (%)	183 (44.6)	215 (52.3)	-	-
OS median months (95% CI)	25.00 (21.75, NR)	19.55 (17.64, 23.06)	5.45	0.73 (0.57, 0.93) <sup>a</sup>
<b>RECIST v1.1-defined progression-free survival</b>				
Progressed, n (%)	311 (75.9)	312 (75.9)	-	-
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)
<b>Clinical progression-free survival</b>				
PFS median months (95% CI)	■ (■, ■)	■ (■, ■)	■	■ (■, ■) <sup>b</sup>

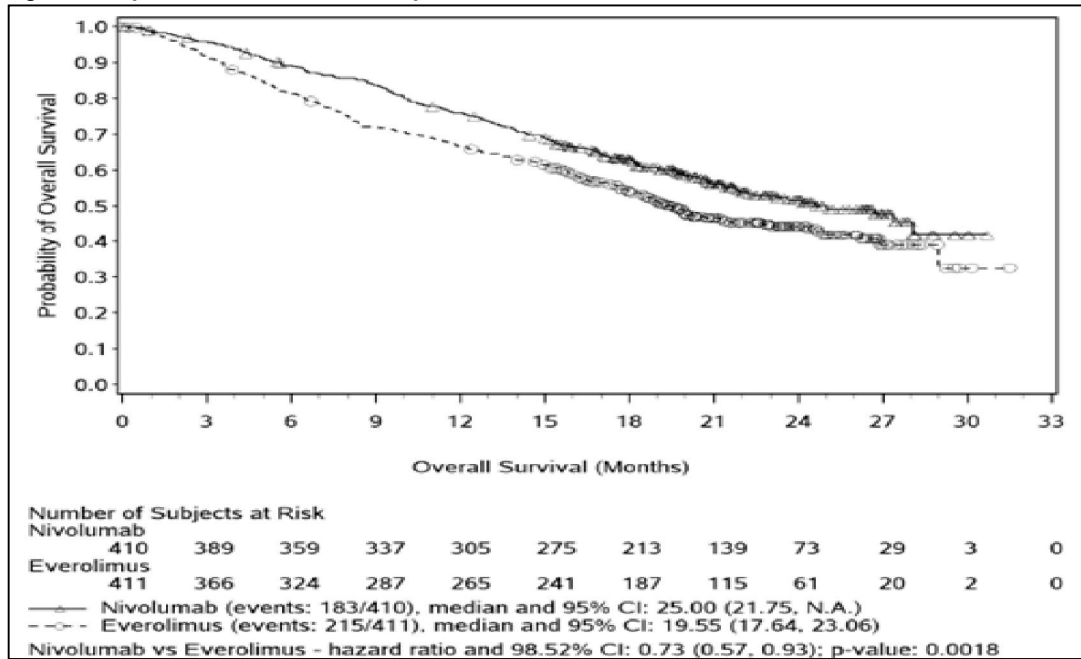
Sources: Table 26, p65 of the submission; Table 28, p68-69 of the submission.

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

<sup>a</sup> 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%).

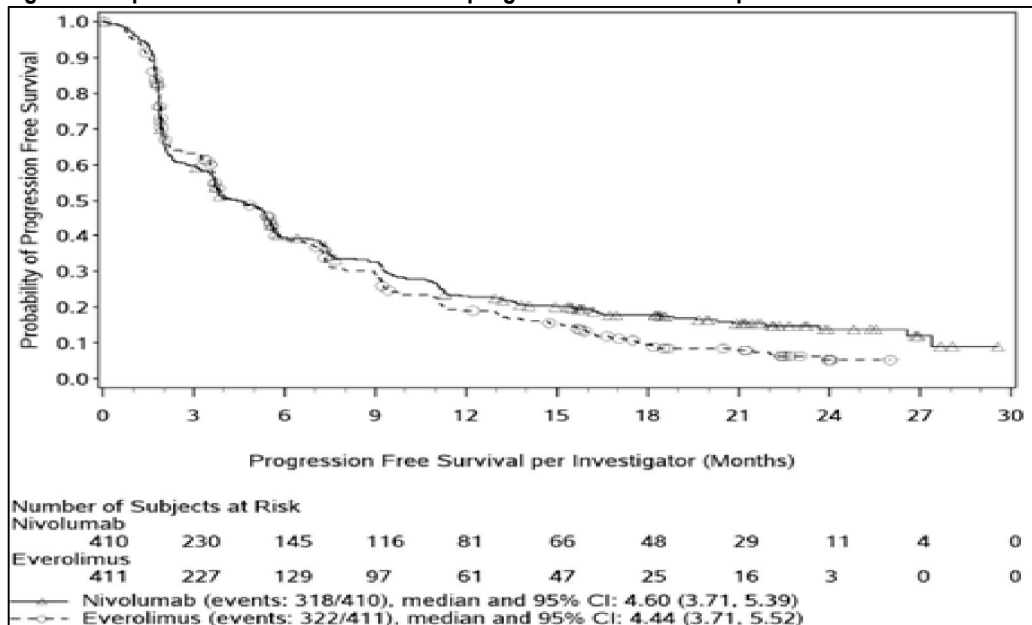
<sup>b</sup> Rounded off to the second decimal digits during the evaluation.

Figure 1: Kaplan-Meier overall survival plot from trial CA209-025



Source: Figure 6, p66 of the submission.

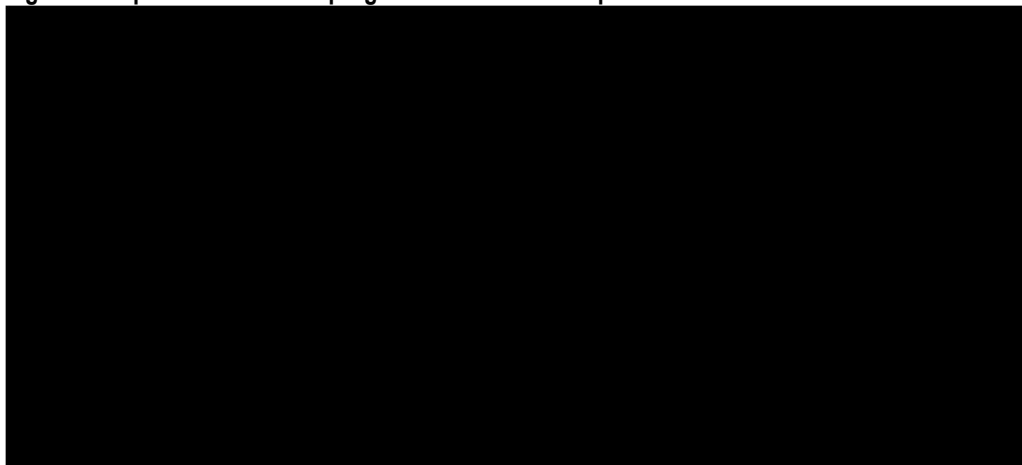
Figure 2: Kaplan-Meier RECIST v1.1-defined progression-free survival plot from trial CA209-025



Source: Figure 8, p70 of the submission.

Abbreviation: RECIST=Response Evaluation Criteria in Solid Tumours.

Figure 3: Kaplan-Meier clinical progression-free survival plot from trial CA209-025



Source: Figure 9, p70 of the submission.

- 6.10 Nivolumab treated patients had statistically significantly longer OS compared to everolimus treated patients ( $p=0.002$ ). At the database lock (18 June 2015), the median survival was prolonged by 5.45 months, and the estimated proportion of patients alive after 2 years of follow-up was improved from approximately 45% to 50%. The ESC considered that there is a clear OS benefit demonstrated in the trial at the time of trial termination. Given the early termination of the trial and variation of circumstances of everolimus use between the trial and the clinical practice (whereas patients in the trial were allowed to continue everolimus therapy beyond progression, the PBS restriction does not permit therapy beyond progression), the extent of overall survival benefit observed in the trial would be unlikely to be observed in the proposed PBS setting. The PSCR commented that the Kaplan-Meier curves remain parallel and that hence proportional hazards assumption holds true.
- 6.11 There was no statistically significant difference in RECIST v1.1-defined PFS for patients treated with nivolumab compared to everolimus. Post-hoc “clinical PFS” demonstrated a statistically significantly longer median “clinical PFS” for nivolumab-treated patients with a gain of [REDACTED] months in comparison to everolimus “clinical PFS”. In the everolimus arm, the median “clinical PFS” was greater than the median RECIST v1.1-defined PFS by [REDACTED]% ([REDACTED] months), although the confidence intervals on these estimates overlap. This difference would be unlikely to be observed in the actual clinical setting since patients would discontinue everolimus upon progression in practice and thus progression would refer to treatment discontinuation. This indicated that the “clinical PFS” hazard ratio of [REDACTED] was likely to be a conservative estimate favouring everolimus, and unlikely to be reproduced in the intended PBS setting. The ESC noted that the PFS curves demonstrated ongoing accumulation of progression events to 100%, which did not support any claim for a prolonged effect in a proportion of treated patients.

### **Comparative harms**

- 6.12 Table 4 provides a summary of key adverse events (AEs) in CA209-025.

**Table 4: Summary of key adverse events in trial CA209-025**

	<b>Nivolumab (N=406)</b>	<b>Everolimus (N=397)</b>	<b>RD% (95% CI)</b>
<b>All causality AE (any grade), n (%)</b>	397 (97.8)	386 (97.2)	0.6 (-1.6, 2.7)
<b>All causality SAE, n (%)</b>			
Any grade	194 (47.8)	173 (43.6)	4.2 (-2.7, 11.1)
Grade 3 or 4	148 (36.5)	116 (29.2)	7.2 (0.8, 13.7)
<b>Drug-related AEs, n (%)</b>			
Any grade	319 (78.6)	349 (87.9)	-9.3 (-14.5, -4.2)
Grade 3 or 4 AE	76 (18.7)	145 (36.5)	-17.8 (-23.9, -11.7)
Grade 3 or 4 anaemia	7 (1.7)	31 (7.8)	-6.1 (-9.0, -3.2)
<b>AE leading to discontinuation, n (%)</b>			
Any grade	72 (17.7)	82 (20.7)	-2.9 (-8.4, 2.5)
Grade 3 or 4 AE	45 (11.1)	45 (11.3)	-0.3 (-4.6, 4.1)
<b>Grade 3 or 4 IMAE, n (%)</b>			
Diarrhoea/Colitis	( )	( )	-
Hepatitis	( )	( )	-
Pneumonitis	( )	( )	-
Nephritis and renal dysfunction	( )	( )	-

Sources: Table 35, p84; Table 36, p85-86; Table 37, p86 of the submission; Table 8.5.2-1, p160 of the CA209-025 CSR.

Abbreviations: AE=adverse event; IMAE=immune mediated adverse event; RD=risk difference; SAE=serious adverse event.

- 6.13 The submission claimed that nivolumab had a favourable safety profile compared to everolimus, with a statistically significantly reduced incidence of drug-related AEs. Table 4 above indicates statistically significantly reduced frequency of some drug-related AEs (eg anaemia, and stomatitis) for nivolumab however, no significant difference in all causality adverse events between groups, and a higher proportion of all causality grade 3 or 4 serious adverse events for nivolumab. Given the small patient numbers, no comparisons could be made for immune-related events such as diarrhoea/colitis and pneumonitis. While the submission did not claim superior safety, four grade 3-4 IMAEs (colitis, hepatitis, pneumonitis, and nephritis and renal dysfunction) and drug-related grade 3-4 anaemia were included in the economic model.
- 6.14 Given the PBS restriction of everolimus, patients would not be permitted to continue everolimus therapy beyond progression in clinical practice. However, in CA209-025, almost half of patients in the everolimus arm (46.1%) were treated beyond progression and thus exposed to the drug longer in the trial than they would have been in clinical practice. Therefore, the comparative safety of nivolumab to everolimus observed in CA209-025 was unlikely to represent the intended PBS setting.

**Benefits/harms**

- 6.15 A summary of the comparative benefits and harms for nivolumab versus everolimus is presented in Table 5.

**Table 5: Summary of comparative benefits and harms for nivolumab and everolimus from CA209-025**

<b>Benefits</b>					
	<b>Nivolumab</b>	<b>Everolimus</b>	<b>Absolute difference</b>		<b>HR (95% CI)</b>
<b>Overall survival</b>					
Death, n (%)	183/410 (44.6)	215/411 (52.3)			-
OS median months (95% CI)	25.00 (21.75, NR)	19.55 (17.64, 23.06)	5.45		0.73 (0.57, 0.93) <sup>a</sup>
<b>RECIST v1.1-defined progression-free survival</b>					
Progressed, n (%)	311/410 (75.9)	312/411 (75.9)			-
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)
<b>Harms<sup>c</sup></b>					
	<b>Nivolumab</b>	<b>Everolimus</b>	<b>Event rate/100 patients</b>		<b>RD% (95% CI)</b>
			<b>Nivolumab</b>	<b>Everolimus</b>	
Any drug-related AE (graded ≥3)	76/406	145/397	18.7	36.5	-17.8 (-23.9, -11.7)
Drug-related anaemia (graded ≥3)	7/406	31/397	1.7	7.8	-6.1 (-9.0, -3.2)

Source: compiled during the evaluation.

Abbreviations: AE=adverse event; HR=hazard ratio; NR=not reported; OS=overall survival; PFS=progression-free survival; RD=risk difference.

<sup>a</sup> 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%).

<sup>b</sup> Rounded off to the second decimal digits during the evaluation.

<sup>c</sup> Statistical comparisons were not undertaken for Grade 3 or 4 IMAE during the evaluation due to the small patient numbers reported. Thus, no comparative conclusion could be made.

6.16 On the basis of the direct evidence presented by the submission, for every 100 patients treated with nivolumab in comparison to everolimus:

- Approximately 18 fewer patients would have grade 3 or 4 drug-related AEs over a mean duration of follow up of 22 months.
- Approximately 6 fewer patients would have grade 3 or 4 drug-related anaemia over a mean duration of follow up of 22 months.

The evidence also reported there would be a difference in median overall survival of approximately 5 months in a group of patients treated with nivolumab compared to everolimus, however there would be no difference in median progression-free survival between these two groups.

### **Clinical claim**

6.17 The submission described nivolumab as superior in terms of comparative efficacy and favourable in terms of comparative safety to everolimus.

6.18 The claim was adequately supported in relation to superior comparative efficacy as a statistically significant advantage in OS in the nivolumab group was demonstrated, there was no statistically significant advantage for nivolumab for RECIST v1.1-defined PFS, there was a statistically significant advantage for nivolumab for the post-hoc assessment of 'clinical PFS' (ie based on treatment discontinuation), with this latter outcome used in the economic evaluation. The ESC questioned whether the PBAC should accept 'clinical PFS', defined for the purposes of this submission, as the basis for estimating the proportions of time in the various health states defined for the economic evaluation; noting that other measures have been proposed to modify response criteria for immunotherapy (eg WHO irRC and irRECIST). The PBAC did not support the use of 'clinical PFS' as an endpoint as this analysis was conducted post-hoc and not validated.

- 6.19 The safety claim was supported by a statistically significantly reduced frequency of some drug-related AEs (eg anaemia and stomatitis) for nivolumab. However, as noted above, given that almost half of patients in the everolimus arm (46.1%) were treated beyond progression and thus exposed to the drug longer in the trial than they would have been in clinical practice, the comparative safety of nivolumab to everolimus observed in CA209-025 was unlikely to represent the intended PBS setting. The PBAC considered that the difficulty in attributing causality with a novel immunotherapy did not support the claim of less drug related AE's.
- 6.20 Importantly, the trial outcomes presented in the submission were unlikely to be representative of the Australian clinical setting for the following reasons:
- The early termination of the trial: As the pre-specified boundary for significance was crossed at the interim analysis of OS (the 18 June 2015 database lock), the trial was stopped early to allow everolimus treated patients to receive nivolumab (that is, prior to allowing for cross-over). The early termination was likely to have underestimated the duration of therapy, and overestimated the treatment effect of OS in favour of nivolumab.
  - Variation of circumstances of use for everolimus: Patients in the everolimus group of the trial were allowed to continue treatment beyond progression. However, this is not permitted in clinical practice in Australia, as the PBS restriction for everolimus does not allow continuation of therapy beyond progression. The ESC noted that this was conservative against nivolumab. However, the trial also included patients with advanced disease who would not be able to receive everolimus on the PBS. Such patients have an improved prognosis for survival, resulting in a bias towards nivolumab.
- 6.21 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.22 The PBAC considered that the claim of favourable comparative safety was not adequately supported by the data.

### ***Economic analysis***

- 6.23 The submission presented a modelled cost utility analysis of nivolumab compared to everolimus.

**Table 6: Summary of model structure and rationale**

<b>Component</b>	<b>Summary</b>
Time horizon	10 years in the model base case versus 25 months (median KM data available) in trial CA209-025.
Outcomes	LYs and QALYs
Methods used to generate results	Markov model. 'Clinical PFS' and OS were extrapolated using parametric functions.
Health states	Three mutually exclusive states of clinical PF, clinical DP and death (absorbing)
Cycle length	Two weeks. Half cycle correction applied (but not to second- or third-line costs with 'upfront loading').
Transition probabilities	Economic model based on log-logistic extrapolations of "clinical PFS" and OS

Source: compiled during the evaluation.

Abbreviations: DP=disease progression; KM=Kaplan-Meier; LYs=life years; OS=overall survival; PF=progression free; PFS=progression-free survival; QALYs=quality-adjusted life years.

6.24 Key drivers of the model are identified in the table below.

**Table 7: Key drivers of the model**

Description	Method/Value	Impact
Hazard ratio for OS	0.73	High, unclear. The modelled incremental OS was potentially biased. The early termination of the trial was likely to have overestimated the treatment effect of OS favouring nivolumab, while allowing treatment beyond progression in the everolimus arm could have biased the survival benefit against nivolumab. The ESC noted that inclusion of Stage III patients in the trial would also have affected the resulting HR to an unknown extent. The direction and magnitude of the overall bias on the OS results could not be determined.
Duration of therapy with nivolumab	19.2 infusions	High, favours nivolumab. For nivolumab, the duration of therapy and consequently its cost were likely underestimated given the early termination of the trial. Nivolumab costs were only applied for 19.2 infusions (dosed every 2 weeks), while the model had a 10-year duration. The ESC noted that nivolumab costs would be more appropriately modelled on a per-cycle basis.
Mean patient weight	█ kg	Moderate, favours nivolumab. While the base case █ kg was derived from the sponsor's NPP, the greater weight of 82.4 kg was observed in the trial and this resulted in greater vial use. Consideration for patient weight distribution and associated vial wastage would have been more informative.
Time horizon	10 years	Moderate, favours nivolumab. Given the immaturity of the trial data and the poor prognosis of patients with advanced/metastatic RCC, a 10-year time horizon was considered optimistic. The ESC noted that the PBAC has previously accepted 5-year time horizons with second-line treatment of metastatic RCC, with 10-year time horizons only associated with first-line treatment of metastatic RCC. The ESC noted that, if appropriate, the inclusion of advanced (stage III) patients might warrant increasing the acceptable time horizon beyond 5 years.
Extrapolation method	Log-logistic survival curves	Likely high, unclear. Log-logistic extrapolation was employed in the base case analysis of the economic evaluation, which is inconsistent with the trial evidence, which does not support any claim for a prolonged effect in a proportion of treated patients. Only the log-normal ('clinical PFS'), and the Weibull (OS and 'clinical PFS') extrapolation methods were tested in sensitivity analyses. One of the better fits based on the goodness of fit statistics, the gamma distribution should also have been considered.
Utility values	Trial based difference for Clinical PF	Moderate, favours nivolumab. The ESC noted that the observed difference between treatment groups in utility values for clinical progression free was █, which is at the margins of what is considered meaningful, and produced an ICER/QALY of \$75,000 - \$105,000.

Source: compiled during the evaluation.

Abbreviations: NPP=named patient program; OS=overall survival; PFS=progression-free survival; RCC=renal cell carcinoma.

6.25 The table below provides the results of the modelled evaluation. The model presented by the submission used \$82.67 for the preparation fee, and \$5,241.90 for the dispensed price per maximum quantity (DPMQ) for everolimus. Updating of these during the evaluation (\$102.67 preparation fee; \$5,276.87 DPMQ for everolimus) changed the incremental cost per QALY gained from \$45,000 - \$75,000/QALY to \$45,000 - \$75,000/QALY.

**Table 8: Results of the economic evaluation**

Component	Nivolumab	Everolimus	Increment
Costs <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
<b>Incremental cost/ LY gained</b>			\$ [REDACTED]
<b>Incremental cost/ QALY gained</b>			\$ [REDACTED]

Sources: Table 77, p163-164 of the submission.

Abbreviations: LY=life year; QALY=quality-adjusted life year.

<sup>a</sup> Costs have been updated during the evaluation for the preparation fee (from \$82.67 to \$102.67) and the DPMQ for everolimus (from \$5,241.90 to \$5,276.87).

Note: The submission reported the results of its economic evaluation for a cohort of 1,000 patients. These values were divided by 1,000 (individual patient average values) during the evaluation for clarity.

6.26 The submission’s base case incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) was considered unreliable for the following reasons:

- The extrapolation of OS from relatively immature trial data was likely to have overestimated the incremental benefit in favour of nivolumab. The ICER was highly sensitive to variations in incremental OS arising from the extrapolation assumptions including the biological plausibility of the extrapolation methods examined and the choice of time horizon.
- The submission’s economic model was an incomplete cost-effectiveness analysis as it did not endeavour to incorporate the full cost of nivolumab therapy. The submission used the cost of nivolumab over 19.2 infusions (dosed every 2 weeks) to represent the total cost of patient treatment with nivolumab over the 10-year time horizon. The submission stated this was done as the duration of therapy is uncertain and the intention is to negotiate with the Government to manage the risk to cost-effectiveness (and overall cost to the PBS/RPBS). This justification was not reasonable. Any negotiations with the Government about the financial risk would only concern the distribution of costs between Government and the sponsor. The ESC noted that the model results were highly sensitive to how the duration of therapy was included (see Table 9). The ESC advised that early termination of the trial was also likely to have underestimated the duration of therapy. Patients in both treatment arms (16.3% for nivolumab; 6.8% for everolimus) were continuing therapy at time of trial termination. The ESC noted that this posed a financial risk known to the sponsor.
- The ESC advised that circumstances of use for everolimus in the trial differed from the PBS setting. Everolimus therapy was allowed to continue beyond progression in the trial, whereas its PBS restriction would require patients to discontinue everolimus therapy upon progression. The ESC was aware that, despite the PBS listing for continuing treatment of everolimus stating “must have stable or responding disease according to the RECIST criteria”, there is no mandate to perform scans (necessary for assessment of response by RECIST) and judgment of progressive disease is a clinical decision based on symptomatic disease in practice. Hence, the submitted trial may reflect current clinical practice if not the PBS restriction.
- Given that both nivolumab and everolimus are ongoing therapy, allocating treatment on a per-cycle basis to both groups would be more appropriate. In the PSCR, this resulted in an ICER/QALY of \$75,000 - \$105,000 (with treatment costs for both nivolumab and everolimus applied over the model’s 10-year time horizon instead of the ‘front-loading’ approach used in the submission’s base case where drug costs were applied in the first cycle of the model based on a

treatment duration of 19.2 infusions for nivolumab and █████ months of therapy with everolimus). The commentary had presented a sensitivity analysis extending only nivolumab costs throughout the 10-year model duration, but applying the everolimus costs in the ‘front-loading’ approach used by the submission, which resulted in an ICER/QALY of \$105,000 - \$200,000. The ESC noted that the ICER based on per-cycle costs with treatment costs for both drugs over 10 years instead of the submission’s ‘front-loading’ approach would be much higher if restricted to a more appropriate 5-year time horizon. The PBAC noted that assuming on-going therapy with both nivolumab and everolimus resulted in an ICER/QALY of \$105,000 - \$200,000 using a time horizon of 5 years compared to \$75,000 - \$105,000 presented in the PSCR using a time horizon of 10 years.

- However, the ESC noted that the use of everolimus in the trial and used in the analysis differed from the likely Australian clinical setting as the PBS listing for everolimus would require therapy to be discontinued upon progression. The ESC disagreed with the sponsor’s claim in the PSCR that current clinical practice is consistent with treatment beyond progression. The ESC advised that modelling of treatment duration (on a per-cycle basis) would be best applied to both treatment arms, and that the model should be based on similar assumptions across the two arms in terms of duration of nivolumab and everolimus therapy after progression reflecting their PBS restrictions unless there is good evidence to justify prescribers using these medicines differently in Australian practice.
- The ESC agreed with the PSCR that it would be standard for economic models to contain the same health states in both treatment groups. Incorporating treatment cessation at RECIST-defined progression might be accomplished either through the use of a tunnel state or fourth health state in the model. The ESC observed that such a structure could have been informed by the data from the trial for which patients’ RECIST progression status or “clinical PFS” status were known, e.g. for nivolumab there were 311 patients with a RECIST-defined progression event (excluding death), of whom 179 continued treatment beyond progression. However, the ESC also advised that basing the economic model on the health state “clinical PFS” and assuming that treatment continues in this health state beyond RECIST-defined progression introduces uncertainty because the prognostic value of this health state is unknown.
- The Commentary-updated base case ICER/QALY (\$45,000 - \$75,000) was sensitive to incremental OS (98.52% CI; varying the ICER/QALY from \$45,000 - \$75,000 to \$105,000 - \$200,000), duration of therapy with nivolumab (20% increase; \$75,000 - \$105,000), time horizon (truncating at year five; \$75,000 - \$105,000) and patient weight (82.4 kg derived from the trial CA209-025; \$75,000 - \$105,000).
- The ESC noted that the submission excluded radiotherapy from the cost of subsequent treatment, yet nearly a third of patients in each group received such care. This should have been addressed given the potential impact on cost-effectiveness, and to be consistent with the inclusion of patients who received immunotherapy in the estimates of subsequent therapy, even though the use of such therapies did not differ between groups. The submission also excluded the cost of pazopanib use as subsequent therapy; although this was used in the trial, the PBAC noted that pazopanib is only PBS-listed for first-line treatment in this indication, and so considered that its exclusion was acceptable.

- The ESC also noted that the population included in the trial, and in the proposed PBS population of advanced or metastatic RCC (Stage III or Stage IV RCC), includes patients for whom the efficacy and cost-effectiveness of everolimus have not been previously assessed. This further complicated the consideration of the incremental effectiveness and cost-effectiveness. The ESC suggested 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. The sponsor is requested to address whether this would also likely improve the estimates of incremental effectiveness and cost-effectiveness of nivolumab.

**Table 9: Comparison of modelled ICER results**

Source	Time horizon	Treatment cost calculations	Ongoing everolimus	Ongoing nivolumab	ICER/QALY
Submission	10 years	Per course	No	No	\$ [redacted]
Commentary	10 years	Per cycle	Yes	No	\$ [redacted]
PSCR	10 years	Per cycle	Yes	Yes	\$ [redacted]
PBAC	5 years	Per cycle	Yes	Yes	\$ [redacted] <sup>1</sup>

Abbreviations: ICER=incremental cost-effectiveness ratio; QALY= quality-adjusted life year

<sup>1</sup> Calculated and presented at PBAC meeting

The redacted table shows ICERs in the range of \$45,000 - \$75,000, \$75,000 - \$105,000/QALY and \$105,000 - \$200,000/QALY.

- 6.27 The PBAC also considered the following matters in assessing the economic evaluation of nivolumab. Table 10 below provides a summary of the costing methodology used in the submission’s model base case, where initial drug costs were applied in the first cycle of the model only (‘front-loaded’) as well as the methodology that was used for the ‘per-cycle’ approach applied in a commentary sensitivity analysis and in the PSCR.

**Table 10: Treatment cost calculations per course and per cycle**

Method	Costing
Per course - submission base case	<ul style="list-style-type: none"> <li>For the ‘per course’ method of treatment costing, the cost of treatment was applied in the first cycle of the model. Cost was based on requested price plus infusion cost multiplied by the number of infusions (19.2).</li> <li>The number of nivolumab infusions was sourced from trial CA209-025 and was the mean number of infusions received in the trial up to the end of follow-up. 19.2 infusions represents 8.8 months of treatment.</li> <li>For everolimus a treatment duration of [redacted] months, requiring [redacted] scripts, was applied. This treatment duration was sourced from the follow-up of CA209-025.</li> <li>The same duration of [redacted] months was assumed to apply to the subsequent use of sorafenib and axitinib in those patients who were modelled to receive it (and also to the subsequent use of everolimus in those patients treated with nivolumab who were modelled to receive it).</li> <li>The model used these durations separately, eg a patient would receive everolimus for [redacted] months, and then would receive sorafenib or axitinib for [redacted] months.</li> </ul>
Per cycle - sensitivity analysis and PSCR	<ul style="list-style-type: none"> <li>For the ‘per-cycle’ method of costing, treatment costs were applied in each cycle of the model over its 10-year duration.</li> <li>Treatment costs were based on the proportion of patients in the progression-free state, ie these patients were assumed to be receiving on-going treatment, in each cycle multiplied by the requested price and administration cost.</li> </ul>

- 6.28 Treatment duration based on the per-cycle approach (■■■■ infusions of nivolumab or ■■■■ months of treatment, and ■■■■ months of everolimus) was greater than that used in the submission base case. These treatment durations represent the mean time on treatment predicted by the model assuming that treatment continues to disease progression and then stops.
- 6.29 The per-cycle approach provided a calculation of treatment cost based on the proportion of patients in each cycle of the model who had not progressed, ie were assumed to be receiving on-going treatment. The model thus predicted that the average treatment duration with nivolumab was ■■■■ months, a likely better estimate than the ■■■■ months used in the submission’s base case model, which reflected the truncated treatment duration reported in the trial.
- 6.30 Everolimus, axitinib and sorafenib each have a special pricing arrangement for the second-line treatment of RCC, with effective prices for everolimus (10 mg; Max Qty 30), axitinib (5 mg; Max Qty 56) and sorafenib (200 mg; Max Qty 120). The ICERs (without adjusting to calculate treatment costs on a per cycle basis) for the requested listing of nivolumab using the effective prices of everolimus, axitinib and sorafenib are presented in Table 11 below.

**Table 11: Results of the economic evaluation using effective prices of everolimus, axitinib and sorafenib**

Component	Nivolumab	Everolimus	Increment
Costs <sup>a</sup>	\$■■■■	\$■■■■	\$■■■■
LY	■■■■	■■■■	■■■■
Incremental cost/LY gained (submission base case = \$■■■■)			\$■■■■
QALY	■■■■	■■■■	■■■■
Incremental cost/QALY gained (submission base case = \$■■■■)			\$■■■■ (10 years) \$■■■■ (5 years)

Source: Section D workbook.

Abbreviations: LY=life year; QALY=quality-adjusted life year.

<sup>a</sup> Costs have been updated during the evaluation for the preparation fee (from \$82.67 to \$102.67).

Note: The submission reported the results of its economic evaluation for a cohort of 1,000 patients. These values were divided by 1,000 (individual patient average values) during the evaluation for clarity.

**Drug cost/patient/course: \$■■■■■**

- 6.31 A summary of the estimated drug cost/patient/course for nivolumab is presented in the table below.

**Table 12: Summary of drug cost/patient/course for nivolumab**

Parameter	Source	Number of vials and doses	Drug cost/infusion	Drug cost/patient/course
Doses per patient	CA209-025: 3mg/kg; mean number of infusions = 19.2	Average dose of [redacted] mg per infusion (dosing every 2 weeks)	\$ [redacted] <sup>a</sup>	\$ [redacted] <sup>b</sup>
Vials per infusion	NPP: mean weight of [redacted] kg for nivolumab patients	40mg: [redacted] 100mg: [redacted]		

Sources: Table 60, p130; Table 61, p131 of the submission.

Abbreviation: NPP=named patient program.

<sup>a</sup> The cost included (i) ex-manufacturer price (\$ [redacted]) for the required vials (one 40mg; two 100mg), mark-up fee of \$ [redacted] for private setting, and applicable fees of \$102.67 and \$140.26 in public and private settings respectively. The total drug cost per infusion was calculated based on an assumption that the public vs. private weighting would be [redacted]% vs. [redacted]%. The submission used \$82.67 for the preparation fee as part of the applicable fee, which was updated to \$102.67 during the evaluation.

<sup>b</sup> Including administration cost (MBS item 13915: \$55.30 per infusion (85% MBS benefit)), the total drug and administration cost per patient per course would be \$ [redacted].

- 6.32 The submission acknowledged that the full cost of nivolumab per course of treatment is unknown due to the unknown duration of use and indicated the sponsor was willing to negotiate to manage the risk to cost-effectiveness and overall cost to the PBS via a Risk Share Arrangement.

**Estimated PBS usage & financial implications**

- 6.33 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the number of patients who would be eligible for nivolumab, and a market share approach to estimate the proportion of patients likely to be displaced from everolimus, axitinib and sorafenib.
- 6.34 Estimated use and financial implications are presented in the table below. During the evaluation, the preparation fee and the DPMQ for everolimus were updated to match the current price. Furthermore, the 85% benefit was applied to MBS item 13309 (blood transfusion). These corrections changed the overall cost to Government from more than \$100 million over the first five years of listing estimated in the submission to more than \$100 million.

**Table 13: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
Nivolumab treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab cost	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Substituted therapies	\$ [redacted]	-\$ [redacted]	-\$ [redacted]	-\$ [redacted]	-\$ [redacted]
Net cost to the PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost to the MBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost to State and territory governments	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
<b>Net cost to health budget</b>	<b>\$ [redacted]</b>	<b>\$ [redacted]</b>	<b>\$ [redacted]</b>	<b>\$ [redacted]</b>	<b>\$ [redacted]</b>

Sources: Table 85, p181; Table 86, p182; Table 89, p186; Table 93, p190 of the submission.

Abbreviation: MBS=Medicare Benefits Schedule.

Note: Costs have been updated for the MBS item fee (applying the 85% MBS benefit for the MBS item 13309; from \$284.85 to \$242.15), the preparation fee (from \$82.67 to \$102.67) and the DPMQ for everolimus (from \$5,241.90 to \$5,276.87).

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year, and the net cost to the PBS/RPBS would be \$20 million - \$30 million per year.

- 6.35 The ESC advised that the overall net costs to the health budget were highly unreliable mainly due to the underestimation of duration of nivolumab treatment, overestimation of the duration of therapy for replacement therapies, and the potential for more patients with RCC to receive a first-line TKI in order to become eligible for nivolumab. The ESC noted that the same issues that were highlighted in paragraph 6.26 in regards to duration of post-progression therapy also applied to estimating the magnitude of these net costs.
- 6.36 The overall net costs were most sensitive to following three assumptions:
- The duration of nivolumab treatment: Increasing the duration of treatment with nivolumab by 20% increased the overall net costs to more than \$100 million.
  - The rate of initiation of second-line therapy: It was assumed that 80% of current patients initiate second-line therapy and that this would increase to 90% of patients following listing of second-line nivolumab. The submission based these estimates on advice from the sponsor's Advisory Board (N=8), although the Minutes of the Advisory Board showed the panel failed to reach agreement on this issue. If no increase in the proportion of patients from current therapy to nivolumab was assumed, the overall costs would be \$60 - \$100 million rather than \$60 - \$100 million.
  - The number of patients treated with a first-line TKI: Using the June 2014 DUSC report, the submission tested the sensitivity of the number of patients treated with a first-line TKI to the overall costs. When it was assumed that less than 10,000 patients were treated over the five years following the listing of nivolumab, the overall costs decreased to \$60 - \$100 million. The Minutes of the Advisory Board showed that some members of the panel also considered that the use of TKIs in the first-line setting might increase (amongst patients with low-volume disease) by a small amount, presumably to afford them subsequent access to nivolumab. This was not modelled in the financial implications. Assuming a 5% increase in the number of patients receiving a TKI, the overall cost to Government increased from \$60 - \$100 million to more than \$100 million.
- 6.37 The ESC advised that the number of patients accessing first-line treatment with a TKI would be expected to increase in order to become eligible for subsequent treatment with nivolumab, especially if Stage III RCC was included in the restriction. The PBAC agreed that the indication should be restricted to Stage IV clear cell variant of RCC consistent with other second-line therapies including everolimus.
- 6.38 Everolimus, axitinib and sorafenib each have a Special Pricing Arrangement for the second-line treatment of RCC. The actual costs to Government for the requested listing of nivolumab using the approach in the submission and the effective prices of everolimus, axitinib and sorafenib are presented in Table 14 below.

**Table 14: Cost to Government health budgets for the requested listing of nivolumab using effective prices of everolimus, axitinib and sorafenib**

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net impact on other budgets	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Net cost to health budget</b>	<b>\$ [REDACTED]</b>	<b>\$ [REDACTED]</b>	<b>\$ [REDACTED]</b>	<b>\$ [REDACTED]</b>	<b>\$ [REDACTED]</b>

Source: Section E workbook.

Note: Costs have been updated for the MBS item fee (applying the 85% MBS benefit for the MBS item 13309; from \$284.85 to \$242.15), the preparation fee (from \$82.67 to \$102.67).

### Quality Use of Medicines

- 6.39 The submission provided a summary of the sponsor’s current practice and plans regarding the quality use of medicines. Details were provided on:
- Education initiatives supporting nivolumab use:
    - Physician education;
    - Immuno-oncology preceptorship and peer-to-peer mentorship;
    - Nursing and pharmacy in-services;
    - Educational materials and tools for awareness and management of immune-related adverse reactions (irAR).
  - Guidance on monitoring and treating irARs.

### Financial Management – Risk Sharing Arrangements

- 6.40 The submission requested a Special Pricing Arrangement (SPA) with a rebate proposed to accommodate the difference between a published price and an effective price.
- 6.41 The submission stated that the existing cap arrangements that would apply to everolimus, axitinib and sorafenib would be inappropriate for nivolumab given the cost-effectiveness claim made, the future treatment algorithm, the likelihood nivolumab would displace current second-line RCC treatments to third-line, and that nivolumab treatment may continue beyond RECIST defined progression. The submission acknowledged that the duration of therapy for nivolumab is uncertain and given the sensitivity of the ICER and financial estimates to the duration of therapy, the sponsor would be committed to negotiations to manage the risk to cost-effectiveness and overall cost to the PBS. The submission did not propose any further details for a Risk Sharing Arrangement.
- 6.42 The ESC suggested that the proposed details of any such Risk Sharing Arrangement would be informative for PBAC consideration. The ESC also noted that, given concerns on potential differences in trial-based efficacy and clinical effectiveness, the local clinical community is proposing a study to monitor the effectiveness of nivolumab in local practice. The PBAC noted the sponsor’s willingness to enter into a Risk Sharing Arrangement and agreed that one would be necessary to mitigate the financial risk from the uncertain duration of treatment with nivolumab.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”.*

## 7 PBAC Outcome

- 7.1 The PBAC decided not to recommend that nivolumab be listed in the PBS for the treatment of advanced or metastatic clear cell variant renal cell carcinoma (RCC) based on an unacceptably high and uncertain incremental cost-effectiveness ratio (ICER) at the requested effective price. The PBAC also noted that the relevant TGA delegate's overview was not yet available for its consideration.
- 7.2 The PBAC recognised the clinical need for nivolumab in patients with clear cell renal carcinoma who had failed first-line treatments.
- 7.3 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.
- 7.4 The PBAC considered that everolimus was an appropriate comparator and that axitinib and sorafenib were secondary comparators.
- 7.5 The PBAC noted that there was no significant difference between everolimus and nivolumab treatment in progression-free survival (PFS) as defined by RECIST v1.1 for the pre-specified analysis of the trial. 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.
- 7.6 The PBAC accepted that, according to the primary analysis of the key trial, nivolumab statistically significantly increased overall survival compared to everolimus. The PBAC noted that there was no clear relationship between the relative survival benefit for nivolumab according to expression of PDL-1 at a 1% or 5% cut-off. Therefore it was agreed that PDL-1 status should not be a consideration in any PBS restriction for nivolumab in renal cell carcinoma at this time.
- 7.7 The PBAC considered that the early stopping of the key trial after the planned interim analysis met the pre-specified early stopping rule but may have over-estimated the degree of overall survival gain because this general bias in stopping trials early has been demonstrated in meta-analyses and because hazard ratios tend to become less favourable over time. The early stopping of this trial underestimated the average treatment duration of nivolumab because some trial participants were still receiving nivolumab when the trial was stopped. The PBAC considered that the uncertainty around the duration of treatment of a PBS listing could be addressed through an RSA, where the expenditure caps would be

calculated to reflect the duration of nivolumab treatment reported by the interim analysis of the key trial.

- 7.8 The PBAC considered that the difficulty in determining causality of AEs in the nivolumab arm of the key trial did not support the claim of less drug-related AEs. The PBAC indicated that the clinical claim of 'favourable' safety for nivolumab over everolimus was not adequately supported by the data supplied.
- 7.9 The PBAC advised that the model should be restricted to a 5-year time horizon not the 10-year time horizon as proposed in the submission, in the PSCR, and in the Pre-PBAC response, consistent with the Committee's previous preference for a 5-year time horizon with second-line treatment of metastatic RCC. The PBAC also advised that treatment costs should be applied in each cycle of the model whilst in the progression-free health state because this would more likely reflect the duration of use of nivolumab and everolimus. The PBAC noted that, when the model was specified according to this advice, the ICER/QALY using published prices was unacceptably high at \$105,000 - \$200,000 and would be even higher using the effective prices of everolimus, axitinib and sorafenib. The PBAC noted that the sponsor could not be aware of these effective prices, but noted that these could be appropriately revealed following a positive PBAC recommendation. The PBAC also noted that the sponsor had indicated in its pre-PBAC response that it was prepared to compromise on price, but considered that the suggestion of 'designating expenditure tiers rather than a full adjustment in price' did not provide sufficient basis for any recommendation to list.
- 7.10 The PBAC proposed the following respecified base case for the model:
- ■■■■ 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.
- 7.11 The PBAC noted that recent PBS data indicated that approximately 16.0% (in 2013) to 24.8% (in 2014) of patients initiating on a TKI for RCC went on to be prescribed a second-line therapy, which suggested that the submission's assumed uptakes (of 80% for current second-line therapy and 90% for nivolumab once listed) were substantial overestimates.
- 7.12 The PBAC indicated that, despite the underestimation of the duration of nivolumab treatment, the resultant financial estimates were unreliably high due to overestimation of the duration of therapy for replacement therapies acting as cost off-sets, overestimated uptake of nivolumab in second-line therapy, and reliance on published rather than effective prices of everolimus, axitinib and sorafenib. In particular, 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. Accordingly, the PBAC recommended that a reduced uptake rate of nivolumab should be identified (and justified) in order to support a Risk Sharing Arrangement.

- 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 is disappointed with the outcome, however is committed to working with the PBAC to ensure nivolumab is available to Australian patients for the treatment of RCC via the PBS in the earliest possible timeframe.