

7.09 NIVOLUMAB (OPDIVO®) plus IPILIMUMAB (YERVOY®)

NIVOLUMAB

Concentrate solution for intravenous infusion, 40 mg/4 mL, 1 x 4 mL vial, concentrate solution for intravenous infusion, 100 mg/10 mL, 1 x 10 mL vial Opdivo®; plus

IPILIMUMAB

Concentrate solution for intravenous infusion 50 mg/10 mL, 1 x 10 mL, Yervoy®, Bristol-Myers Squibb

1 Purpose of Application

- 1.1 The minor resubmission requested Section 100 (Efficient Funding of Chemotherapy) listing for nivolumab in combination with ipilimumab (NIVO+IPI) as the first line treatment of Stage IV clear cell variant renal cell carcinoma (RCC) in patients meeting the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate to poor risk group criteria.
- 1.2 NIVO+IPI was rejected by the PBAC for this indication in July 2018. The minor resubmission attempted to address concerns raised in that consideration.
- 1.3 The basis for the requested listing was unchanged from the previous submission and was a cost-utility analysis of NIVO+IPI compared with sunitinib.

2 Requested listing

- 2.1 Compared with the previous submission, the only change to the requested restriction was that a grandfathering restriction was proposed.
- 2.2 The requested restriction is outlined below with the PBAC's additions in italics and deletions in strikethrough.

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Nivolumab induction

Name, restriction, manner of administration, form	Maximum qty	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Induction phase				
NIVOLUMAB Injection 40 mg/4 mL 1 x 4 mL vial Injection 100 mg/10 mL 1 x 10 mL vial	360 mg	3	\$7,560.13 published price Effective prices: Public: \$ [REDACTED] Private: \$ [REDACTED]	OPDIVO Bristol-Myers Squibb Australia Pty Ltd

Category/Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Induction (combination) treatment
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must meet the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate to poor risk group criteria AND Patient must have a WHO performance status of 2 or less AND Patient must receive this PBS subsidised nivolumab and ipilimumab concomitantly as the first line of treatment for this condition <i>The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction for this condition</i> AND <i>The treatment must be for first-line therapy for this condition</i> AND The treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks</p>
Prescriber Instructions:	<p>The Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks</p> <p>The patient's body weight must be documented in the patient's medical records at the time treatment is initiated</p>
Administrative Advice:	<p>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.</p> <p><i>No increase in the maximum quantity or number of units may be authorised.</i> No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
Caution	<i>Combination treatment with ipilimumab and nivolumab is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.</i>

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Ipilimumab induction

Name, restriction, manner of administration, form	Maximum qty	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
IPILIMUMAB Injection 50 mg/10 mL 1 x 10 mL vial	120 mg	3	\$17,849.89 published price Effective prices: Public: \$ [REDACTED] Private: \$ [REDACTED]	YERVOY Bristol-Myers Squibb Australia Pty Ltd

Category/Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Induction (combination) treatment
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must meet the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor risk group criteria AND Patient must have a WHO performance status of 2 or less AND Patient must receive this PBS subsidised nivolumab and ipilimumab concomitantly as the first line of treatment for this condition The treatment must be in combination with PBS-subsidised treatment with nivolumab as induction therapy for this condition AND The treatment must be for first-line therapy for this condition AND The treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks</p>
Prescriber Instructions:	<p>The Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks</p> <p>The patient's body weight must be documented in the patient's medical records at the time treatment is initiated</p>
Administrative Advice:	<p>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.</p> <p><i>No increase in the maximum quantity or number of units may be authorised.</i> No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
Caution	<i>Combination treatment with ipilimumab and nivolumab is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.</i>

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Continuing treatment with nivolumab

Continuing phase				
NIVOLUMAB Injection 40 mg/4 mL 1 x 4 mL vial Injection 100 mg/10 mL 1 x 10 mL vial	360 mg	11	\$7,560.13 published price Effective prices: Public: \$ [REDACTED] Private: \$ [REDACTED]	OPDIVO Bristol-Myers Squibb Australia Pty Ltd
Category/ Program	Section 100 - Efficient funding of Chemotherapy			
Prescriber type	Medical Practitioners			
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 with nivolumab monotherapy following first line nivolumab plus ipilimumab induction			
Restriction:	<input checked="" type="checkbox"/> Streamlined			
Clinical criteria:	Patient must have previously received up to a maximum of 4 doses of PBS-subsidised combined treatment with been issued with an authority prescriptions for induction phase nivolumab and ipilimumab as induction combination therapy for this condition AND This drug The treatment must be as monotherapy the sole PBS-subsidised treatment for this condition AND Patient must have stable or responding disease			
Prescriber Instructions:	The Maintenance treatment with nivolumab must not exceed a maximum dose of 3 mg per kg every 2 weeks. The patient's body weight must be documented in the patient's medical records at the time treatment is initiated			
Administrative Advice:	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. <input type="checkbox"/> Special Pricing Arrangements apply.			

Grandfathering restriction – nivolumab induction and continuing

NIVOLUMAB Injection 40 mg/4 mL 1 x 4 mL vial Injection 100 mg/10 mL 1 x 10 mL vial	360 mg	2	\$7,560.13 published price Effective prices: Public: \$ [REDACTED] Private: \$ [REDACTED]	OPDIVO Bristol-Myers Squibb Australia Pty Ltd
Category / Program	Section 100 - Efficient funding of Chemotherapy			
Prescriber type	Medical Practitioners			
Severity:	Stage IV			
Condition:	Clear cell variant renal cell carcinoma (RCC)			
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)			
Treatment phase:	Grandfather treatment patients – Induction OR Grandfather patients - Continuing treatment with nivolumab monotherapy following first line nivolumab plus ipilimumab induction			
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined			
Clinical criteria:	Patient must have received non-PBS-subsidised treatment combined therapy with ipilimumab and nivolumab concomitantly as first line therapy as induction for this condition prior to <PBS listing date> OR Patient must have received monotherapy with nivolumab as maintenance for this condition prior to <PBS listing date>			

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	<p>AND Patient must have met meet the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate to poor risk group criteria prior to initiating non-PBS subsidised treatment with nivolumab and ipilimumab</p> <p>AND Patient must have had a WHO performance status of 2 or less <i>prior to initiating non-PBS-subsidised treatment with nivolumab and ipilimumab</i></p> <p>AND <i>The treatment must be for first-line therapy for this condition</i></p> <p>AND <i>The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction for this condition OR</i> <i>The treatment must be the sole PBS-subsidised therapy for this condition</i></p> <p>AND <i>Patient must have stable or responding disease</i></p>
Prescriber Instructions	<p><i>Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks</i></p> <p><i>Maintenance treatment with nivolumab must not exceed a maximum dose of 3 mg per kg every 2 weeks.</i></p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</p> <p><i>The patient's body weight must be documented in the patient's medical records at the time treatment is initiated</i></p>
Administrative Advice	<p>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.</p> <p>No increase in the maximum number of repeats may be authorised. <i>No increase in the maximum quantity or number of units may be authorised.</i></p> <p>Special Pricing Arrangements apply.</p>
Caution	<p><i>Combination treatment with ipilimumab and nivolumab is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.</i></p>

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Grandfathering restriction – ipilimumab induction

Name, restriction, manner of administration, form	Maximum qty	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
IPILIMUMAB Injection 50 mg/10 mL 1 x 10 mL vial	120 mg	2	\$17,849.89 published price Effective prices: Public: \$ [REDACTED] Private: \$ [REDACTED]	YERVOY Bristol-Myers Squibb Australia Pty Ltd

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Grandfather treatment patients – Induction
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have received non-PBS subsidised treatment <i>combined therapy</i> with ipilimumab and nivolumab concomitantly as first line therapy <i>as induction</i> for this condition prior to <PBS listing date> AND Patient must have met <i>meet</i> the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate to poor risk group criteria prior to initiating non-PBS subsidised treatment with nivolumab and ipilimumab AND Patient must have had a WHO performance status of 2 or less <i>prior to initiating non-PBS-subsidised treatment with nivolumab and ipilimumab</i> AND <i>The treatment must be for first-line therapy for this condition</i> AND <i>The treatment must be in combination with PBS-subsidised treatment with nivolumab as induction for this condition</i> AND <i>Patient must have stable or responding disease</i></p>
Prescriber Instructions	<p>A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</p> <p><i>Induction</i> treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks</p> <p><i>The patient's body weight must be documented in the patient's medical records at the time treatment is initiated</i></p>
Administrative Advice	<p>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.</p> <p>No increase in the maximum number of repeats may be authorised. <i>No increase in the maximum quantity or number of units may be authorised.</i></p> <p>Special Pricing Arrangements apply.</p>

2.3 The PBAC previously considered that the restriction should be based on WHO performance status and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic criteria, as these both reflect current Australian clinical practice (Paragraphs 7.3 and 7.4, PBAC Public Summary Document (PSD) July 2018). The PBAC noted this was appropriately reflected in the proposed restriction.

- 2.4 The resubmission proposed that the continuing restriction should state: “Patient must have stable or responding disease”. While the restriction for the comparator (sunitinib) includes a requirement that this must be according to the Response Evaluation Criteria In Solid Tumours (RECIST) criteria, the pre-PBAC response stated that the RECIST criteria should not be included in the nivolumab restriction because patients in the key trial (CA209-214) could receive nivolumab beyond progression. The PBAC also noted that the RECIST criteria are not included in the nivolumab restrictions in other settings. The PBAC agreed that the RECIST criteria should not be included in the continuation restriction, consistent with other nivolumab restrictions.
- 2.5 The PBAC noted that the proposed initial nivolumab restriction allows continuation in patients who have a tumour flare in the first few months after starting immunotherapy, stating that “when progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later”. The PBAC considered this was appropriate as it was consistent with the key trial (CA209-214).
- 2.6 The PBAC considered that separate restrictions would be required for nivolumab and ipilimumab (in both the induction and grandfathering settings).
- 2.7 The resubmission stated that it intends to open a Patient Access Program six months prior to PBS listing, and estimated that █████ patients will be grandfathered to PBS reimbursement (discussed further in ‘Estimated PBS usage and financial implications’). The resubmission further stated that it intended that all patients enrolled in the Patient Access Program would meet the PBS eligibility criteria. The PBAC considered that grandfathering restrictions would be required to allow patients already commenced on NIVO+IPI to continue therapy under the PBS, for patients who are otherwise eligible under the PBS criteria. The PBAC considered that it would be appropriate to have grandfathering restrictions for both the induction and continuation phases.

Flow-on change – removal of requirement for prior treatment with TKIs to be in first-line

- 2.8 The minor resubmission requested a flow-on change to the restrictions for drugs that are currently listed in the second- and later- line settings (i.e. axitinib, cabozantinib, sorafenib, everolimus, and NIVO monotherapy). The PBS restrictions for these drugs currently include the following clinical criteria (underlining for emphasis):
- Patient must have progressive disease according to the Response Evaluation Criteria In Solid Tumours (RECIST) following first-line treatment with a tyrosine kinase inhibitor.
- 2.9 With NIVO+IPI listed first-line, the treatment algorithm would change and many patients would receive TKI therapy second-line (rather than first-line). The resubmission stated this would mean that the existing second- and later- line therapies would not be PBS-subsidised for patients who receive first-line NIVO+IPI. This would reduce the third- and later-line therapies available for patients and would

have flow-on implications for the cost of subsequent therapies. The PBAC noted that the resubmission had conducted analyses to demonstrate the potential impact to the economic evaluation and financial estimates.

- 2.10 To address this, the PBAC considered that the PBS restrictions for axitinib, cabozantinib, sorafenib and everolimus should be amended as follows:

Patient must have progressive disease according to the Response Evaluation Criteria In Solid Tumours (RECIST) following ~~first-line~~ prior treatment with a tyrosine kinase inhibitor.

- 2.11 The PBAC noted that patients would still be required to have received prior TKI therapy before commencing axitinib, cabozantinib, sorafenib and everolimus (i.e. the amendment just removes the requirement that the prior TKI therapy be in first-line). This is consistent with the PBAC's previous consideration that removal of the requirement for patients to have received prior TKI therapy was not appropriate given that no evidence had been provided to support this change (Paragraph 7.5, PBAC PSD July 2018).
- 2.12 The PBAC considered that patients who receive first-line NIVO+IPI should not subsequently receive nivolumab monotherapy in a later line of therapy, as no evidence has been provided regarding the efficacy of multiple lines of nivolumab. As such, the PBAC considered that the PBS restriction for nivolumab monotherapy should be amended to include the following criterion: "Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition". The pre-PBAC response and the PBAC noted this would align with PBS restrictions for nivolumab in other settings. With this amendment incorporated, the PBAC considered it would also be appropriate to include the following amendment for consistency: "Patient must have progressive disease according to the Response Evaluation Criteria In Solid Tumours (RECIST) following ~~first-line~~ prior treatment with a tyrosine kinase inhibitor".

Flow-on change – IMDC prognostic scoring system for sunitinib and pazopanib

- 2.13 NIVO+IPI is proposed for listing in patients categorised as having intermediate/poor prognosis based on the IMDC prognostic scoring system, which was consistent with the key clinical evidence. On the other hand, the Memorial Sloan Kettering Cancer Center (MSKCC) criteria is the basis for determining risk stratification in the PBS clinical criteria for pazopanib and sunitinib (these are PBS-listed for patients who meet the MSKCC low to intermediate risk group criteria). The PBAC re-iterated its previous consideration that the restriction for NIVO+IPI should be based on IMDC "to reflect current clinical practice where IMDC has superseded MSKCC" and "should NIVO+IPI be listed for RCC in the future, then the restrictions for sunitinib and pazopanib could similarly be changed to IMDC for consistency" (Paragraph 7.3, PBAC PSD July 2018).

- 2.14 As such, the PBAC considered that the restrictions for sunitinib and pazopanib for RCC (for the listings for treatment phase: initial treatment) should be amended as follows:

Patient must meet the ~~Memorial Sloan-Kettering Cancer Centre (MSKCC) low to intermediate risk group criteria~~ International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) favourable to intermediate risk group criteria.

For more detail on PBAC’s view, see section 6 PBAC outcome.

3 Background

- 3.1 Nivolumab is TGA registered for: “nivolumab, in combination with ipilimumab, is indicated for the treatment of patients with intermediate/poor-risk, previously untreated advanced renal cell carcinoma. Nivolumab, as monotherapy, is indicated for the treatment of patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy”. Ipilimumab is TGA registered for: “in combination with OPDIVO (nivolumab), is indicated for the treatment of patients with intermediate/poor-risk, previously untreated advanced renal cell carcinoma”.
- 3.2 The PBAC noted there are ongoing studies of other regimens for the first-line treatment of RCC including single-agent pembrolizumab, pembrolizumab in combination with other therapies, avelumab + axitinib, nivolumab + cabozantinib, cabozantinib, and atezolizumab + bevacizumab.
- 3.3 The PBAC previously considered NIVO+IPI for this indication in July 2018. The key outstanding matters of concern were that the incremental survival and quality of life benefits were overestimated in the economic model presented, and that the incremental cost-effectiveness ratio (ICER) was uncertain and unacceptably high. The July 2018 PBAC considered that a price reduction would be required to bring the estimated ICER into an acceptable range (Paragraph 7.1, PBAC PSD July 2018).
- 3.4 Relevant details compared with the previous consideration are provided in the table below.

Table 1: Summary of previous submission and the current resubmission

	Previous submission (July 2018)	Current resubmission
Requested PBS listing	Para 7.3 and 7.4 July 2018 PSD: Restriction should be based on IMDC criteria and WHO performance status (as requested in submission).	Restriction continues to be based on IMDC criteria and WHO performance status (per PBAC advice).
Flow-on changes	Requested a flow-on change to the existing restrictions for second- and later-line RCC therapies: removal of the requirement for patients to have received prior TKI therapy before commencing second-line nivolumab, everolimus, axitinib, sorafenib or cabozantinib. Para 7.5 July 2018 PSD: The PBAC considered that this was not appropriate given that no evidence had been provided to support this change	Requested a flow-on change to the restrictions for current 2nd- and later-line RCC therapies: removal of the requirement for patients to have received prior <u>first-line</u> TKI therapy (as TKIs may be used 2nd-line if NIVO+IPI is listed 1st-line).
Requested effective DPMA	DPMA per average infusion NIVO: \$ [REDACTED] IPI: \$ [REDACTED]	DPMA per average infusion NIVO: \$ [REDACTED] ([REDACTED] % reduction) IPI: \$ [REDACTED] ([REDACTED] % reduction)

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	Previous submission (July 2018)	Current resubmission
Comparator	Sunitinib Para 7.6 July 2018 PSD: Accepted sunitinib as appropriate main comparator	Unchanged
Key effectiveness data	CA209-214 trial (NIVO+IPI vs sunitinib) HR for OS: 0.63 (95% CI: 0.44, 0.89) Median OS: Not reached for NIVO+IPI, 26 months for sunitinib 18 month survival: 75% (95% CI: 70, 78) for NIVO+IPI; 60% (95% CI: 55, 65%) for sunitinib Para 7.7 and 7.8 July 2018 PSD: Data are indicative of an important improvement in OS. However, the absolute magnitude of the treatment effect could not be reliably estimated because the OS were immature. Trial may have overestimated effectiveness, and underestimated toxicity as the trial population may have been healthier than the likely PBS population.	Unchanged
Clinical claim	NIVO+IPI is superior to sunitinib in terms of OS with a clinically acceptable safety profile Para 6.37 July 2018 PSD: claim of clinical superiority of NIVO+IPI versus sunitinib was adequately supported. Paras 7.39, 7.10 July 2018 PSD: Inferior comparative safety versus sunitinib. Adverse events may be challenging to manage outside major tertiary centres, where there a need for improved access to immune-modulating rescue therapies.	Unchanged
Economic evaluation	- Extrapolation: assumed proportional hazards from mean follow-up to 5 years; - Utilities: based on key trial. PFS: ■■■ for NIVO+IPI, ■■■ for sunitinib. Progressed: ■■■ for NIVO+IPI, ■■■ for sunitinib; - Time horizon: ■■■ years. Paras 7.12 and 7.13 July 2018 PBAC minutes: ICER/QALY was uncertain and overly optimistic due to: - Extrapolation: highly uncertain. More reasonable to assume convergence begins at ■■■ months; - Utilities: higher than those in literature and similar to population norms. - Time horizon: not reasonable. ■■■ years would be more realistic; - Cost-effective at an ICER less than \$45,000/QALY – \$75,000/QALY.	- Extrapolation: assumed convergence begins at ■■■ month, as requested; - Utilities: PFS: unchanged; progressed disease: ■■■ in both arms. - Time horizon: ■■■ years, as requested - ICER: \$45,000/QALY – \$75,000/QALY (if restrictions for current 2 nd - and later-line therapies are changed to allow prior TKIs to be in 2 nd -line).
Number of initiating patients	Less than 10,000 in Year 1, increasing to less than 10,000 in Year 6.	Less than 10,000 in Year 1, less than 10,000 in Year 6. Higher in Year 1 due to the inclusion of less than 10,000 grandfathered patients.
Estimated net cost to PBS	Cost of NIVO+IPI: \$30 – \$60 million in Year 5 and more than \$100 million over the first 6 years. Including offsets for later-line therapies: more than \$100 million over 6 years (based on price proposed in submission, not the lower price proposed in the pre-PBAC response). Para 7.14 July 2018 PSD: Estimated net cost to the PBS/RPBS was high and potentially underestimated given: potential for a higher rate and duration of use of nivolumab maintenance therapy in clinical practice; estimated financial implications for other PBS medicines (cost offsets), particularly those relating to second- or later-line settings, was likely to have been overestimated due to the high proportion of patients assumed to seek treatment in these settings.	Cost of NIVO+IPI: \$30 – \$60 million in Year 5 and more than \$100 million over the first 6 years. Including offsets for later-line therapies: more than \$100 million over 6 years (if prior TKI therapy can be in the 2 nd -line setting). Key changes included: - inclusion of grandfathered patients; - reductions to the proposed AEMP; - increase to the average number of NIVO infusions per patient; - cost-offsets were phased rather than front-loaded.

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	Previous submission (July 2018)	Current resubmission
Risk sharing arrangement	100% rebate beyond estimated utilisation Did not take into account reductions in second-line use of nivolumab in proposed RSA. Para 7.15 July 2018 PBAC minutes: a 100% rebate beyond estimated utilisation. Listing in first-line setting would reduce second-line use of nivolumab, and so flow-on changes would be required to the existing RSA for second-line nivolumab.	Proposed RSA with 100% rebate beyond estimated utilisation; sponsor stated it is willing to work with the Department to incorporate flow-on changes to the existing RSA for second-line NIVO
PBAC decision	Reject.	-

Source: Compiled during the preparation of the Minor Overview.
ICER = incremental cost effectiveness ratio

For more detail on PBAC’s view, see section 6 PBAC outcome.

4 Comparator

- 4.1 The nominated comparator, sunitinib, was unchanged from the previous submission.
- 4.2 The PBAC previously accepted sunitinib as the appropriate main comparator, but expressed concern that patients at poor prognostic risk are currently being treated with sunitinib and pazopanib, which are likely to have limited efficacy in this population, but may be associated with significant toxicity (Paragraph 7.6, PBAC PSD July 2018).

For more detail on PBAC’s view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

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

Consumer comments

- 5.2 The PBAC noted and welcomed the input from individuals (two) and health professionals (four) via the Consumer Comments facility on the PBS website. The comments described the rates of complete remission achieved with NIVO+IPI, the potential for more durable responses and the potential for cure. The comments also noted the positive impact of NIVO+IPI on quality of life, and that the adverse events with immunotherapies are manageable.
- 5.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the NIVO+IPI for RCC submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the CA209214 trial. The PBAC noted that the MOGA was unable to calculate the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) score for NIVO+IPI for RCC, as the

data were immature and the median survival time for the NIVO+IPI arm had not been reached.¹

Clinical trials

5.4 No clinical trials were presented in the minor resubmission.

Clinical claim

5.5 The minor resubmission did not present any new information regarding the clinical claim.

5.6 In its previous consideration, the PBAC considered that the claim of clinical superiority of NIVO+IPI versus sunitinib was adequately supported given the statistically significant improvement in OS observed in the pivotal trial, but considered that the magnitude of the benefit was difficult to quantify given the immaturity of the data. The PBAC also considered that the trial population may be healthier than the likely PBS population, and thus the trial may have overestimated the incremental effectiveness of NIVO+IPI versus sunitinib (Paragraph 6.37, PBAC PSD July 2018).

5.7 The PBAC previously considered that NIVO+IPI was associated with inferior comparative safety versus sunitinib, given NIVO+IPI was associated with a higher rate of serious adverse events and adverse events requiring treatment discontinuation (Paragraph 7.9, PBAC PSD July 2018).

Economic analysis

5.8 The PBAC previously considered that the ICER/QALY was uncertain and overly optimistic due to the extrapolation method, time horizon and utility values applied. These issues and how they were addressed in the resubmission are outlined in the table below.

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

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Table 2: Changes to the economic evaluation

Previous submission (July 2018 Pre-PBAC response)	PBAC Minutes July 2018, Paragraphs 7.12 and 7.13	November 2018 resubmission
Assumed proportional hazards from the mean duration of follow-up (■ months) to ■ years.	More reasonable to assume that convergence of OS (and PFS) curves begins at ■ months	Appropriately addressed as requested by PBAC.
Utilities were based on the EQ-5D data from Study CA209-214. Progression free: ■ for NIVO+IPI; ■ for SUNI; Progressed disease: ■ for NIVO+IPI; ■ for SUNI	Utilities were similar to population norms and considerably higher than those sourced from the literature. Utility value of ■ in the progressed disease health state: unlikely that patients would experience such a high utility consistently over the time horizon of the model. More reasonable to assume that utilities would be consistent with the average utilities from the literature (Progression free = ■, Progressed disease = ■)	Progression free: ■ for NIVO+IPI; ■ for SUNI. Unchanged, based on CA209-214. Progressed disease: ■ for both arms. Reduced by ■ (or ■), based on study of RCC in a later-line setting.
Time horizon of ■ years	A time horizon of ■ years would be more realistic given the population group, the short duration of follow-up in the trial, and the uncertainties with the extrapolation.	Appropriately addressed as requested by PBAC.
Drug cost: DPMA per average infusion Nivo: \$■ Ipi: \$■		DPMA per average infusion Nivo: \$■ (■% lower) Ipi: \$■ (■% lower)
Base case ICER of \$45,000/QALY – \$75,000/QALY	NIVO+IPI would be cost-effective at an ICER of less than \$45,000/QALY – \$75,000/QALY, using the updated model parameters outlined above	\$45,000/QALY – \$75,000/QALY if restrictions for current 2 nd line drugs are amended (or \$45,000/QALY – \$75,000/QALY if restrictions are not amended)

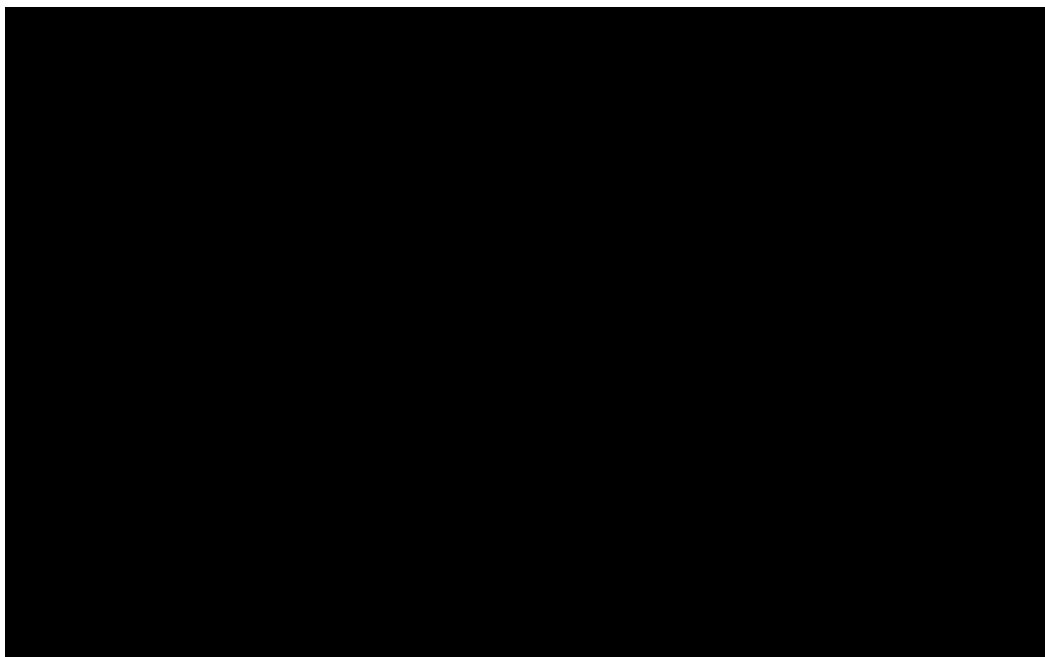
Source: Table 1, p 1 of the minor resubmission; PBAC Minutes July 2018.

IPI = ipilimumab; NIVO = nivolumab; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life year; SUNI = sunitinib. OS = overall survival; PD = progressive disease; PF = progression free; PFS = progression free survival

5.9 The resubmission appropriately addressed two of the issues raised by the PBAC in its previous consideration:

- The assumption of proportional hazards from the mean duration of follow-up to five years, which the PBAC previously considered was highly uncertain given that median OS had not yet been reached in the NIVO+IPI arm. As requested by the July 2018 PBAC, the resubmission assumed that convergence of the OS (and PFS) curves begins at ■ months, as shown in the figure below;
- The time horizon of ■ years, which the PBAC previously considered was not reasonable given the population group, the short duration of follow-up in the trial and the uncertainties with the extrapolation. As requested by the July 2018 PBAC, the resubmission assumed a time horizon of ■ years (Paragraph 7.12, PBAC Minutes July 2018).

Figure 1: Model traces for the OS, PFS and TTD curves: current resubmission (solid lines) versus previous model (dotted lines, July 2018 Pre-PBAC Response)



Source: 'Active traces' of App_CEA_NIVO+IPI1LRCC_Aug18.xlsx

Figure 1 is based on the "leakage scenario", wherein PBS usage of current second- and later-line therapies for RCC is assumed to occur in the third- and later-line settings, which would require the restriction to be updated to remove the requirement for TKIs to be used in the first-line setting.

- 5.10 Figure 1 also shows that the Time to Treatment Discontinuation curve for NIVO+IPI begins to converge at ■ months (solid green line), but converges at a faster rate than in the previous submission (dotted green line) as it is now assumed to converge within the shorter modelled time horizon. Thus, drug costs were reduced in the NIVO+IPI arm (this change alone reduced the average number of nivolumab doses per patient from ■ to ■). The change to the extrapolation of the Time to Treatment Discontinuation curve was tested in sensitivity analyses conducted during preparation of the Minor Overview.

Utilities

- 5.11 In its July 2018 consideration, the PBAC considered that the utility estimates were similar to population norms and were considerably higher than those sourced from the literature. The PBAC had noted that the utility value applied in the progressed disease health state was [REDACTED] in the NIVO+IPI arm ([REDACTED] in the sunitinib arm), and considered it was unlikely that patients would experience such a high utility consistently over the time horizon of the model. The PBAC considered that it may be more reasonable to assume that the utilities would be consistent with the average utilities from the literature, which were noted to be: progression free health state utility = [REDACTED], progressed disease health state utility = [REDACTED] (Paragraph 7.12, PBAC Minutes July 2018).
- 5.12 The resubmission claimed that there were applicability issues with the utility values sourced from the literature because they were from studies conducted over 10 years ago (early TKI studies), with management of the condition having changed in this timeframe. Further, the resubmission claimed that some of the studies may have been confounded by cross-over or may have used treatment sequences that do not reflect current clinical practice (e.g. one of the trials investigated switching between pazopanib and sunitinib).
- 5.13 For the progressed disease health state, the resubmission applied the utility values that were used in the March 2017 submission for NIVO in the second-line RCC setting, which were NIVO = [REDACTED], everolimus = [REDACTED]. These were trial based utilities from CA209-025 (a randomised, open label study of NIVO versus everolimus, in patients who had progressed following prior treatment with a TKI) derived based on EQ-5D and adjusted using Australian preference weights. The minor resubmission appeared to apply the mid-point between the utility for NIVO and everolimus (rounded to [REDACTED]) in the progressed disease health state.
- 5.14 The health state utilities from the relevant studies, and those applied in the economic model are summarised in the table below. The only change from the previous submission was that the utility value was reduced by [REDACTED] ([REDACTED] lower for the sunitinib arm) in the progressed disease health state.

Table 3: Utility values from studies of NIVO and those applied in the model

Health state	Previous submission CA209-214 ^a		Average values from literature	March 2017 NIVO monotherapy CA209-025		Used in model	
	Utility NIVO+IPI	Utility SUNI	Both arms	Utility NIVO	Utility of comparator (everolimus)	Utility NIVO+IPI	Utility SUNI
Progression free	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
						Source: CA209-214	
Progressed disease	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
						Source: average of CA209-025.	

Source: Table 89, p160 Section 3 of the submission, Average application in the model taken from 'Att_12_CEA_NIVO+IPI_1LRCC.xlsx'. PD = progressed disease; PF = progression free; NIVO = nivolumab; IPI = ipilimumab;
^a intermediate/poor risk subpopulation

Results of economic evaluation

5.15 The results of the economic evaluation are summarised in the table below, with each change presented as a separate step. This is based on the scenario in which the restrictions for drugs that are currently listed in the second- and later- line settings (i.e. axitinib, cabozantinib, sorafenib, everolimus and nivolumab monotherapy) are changed to enable use following prior TKI therapy, irrespective of the line of treatment in which the TKI was used.

Table 4: Results of the economic evaluation (if restrictions are changed for existing second-line therapies)

	Costs			Outcomes			ICER/QALY
	NIVO+IPI	SUNI	Δ	NIVO+IPI	SUNI	Δ	
Previous submission (pre-PBAC response)	\$ [redacted]	\$ [redacted]	\$ [redacted]	[redacted]	[redacted]	[redacted]	\$ [redacted]
Step 1: Convergence commencing at [redacted] months, per PBAC request ^a	\$ [redacted]	\$ [redacted]	\$ [redacted]	[redacted]	[redacted]	[redacted]	\$ [redacted]
Step 2: Utilities (outlined in table above)	\$ [redacted]	\$ [redacted]	\$ [redacted]	[redacted]	[redacted]	[redacted]	\$ [redacted]
Step 3: Time horizon reduced to [redacted] years	\$ [redacted]	\$ [redacted]	\$ [redacted]	[redacted]	[redacted]	[redacted]	\$ [redacted]
Step 4: Drug cost for NIVO and IPI reduced	\$ [redacted]	\$ [redacted]	\$ [redacted]	[redacted]	[redacted]	[redacted]	\$ [redacted] ^b

Source: Table 12, PBAC Minutes July 2018; Table 5, p 7 Minor Resubmission; “App_CEA_NIVO+IPI_RCC_Aug18.xlsx” spreadsheet.

IPI = ipilimumab; NIVO = nivolumab; OS = overall survival; PFS = progression free survival; QALY = quality-adjusted life year; SUNI = sunitinib.

^a Convergence of OS, PFS began at [redacted] months, rather than [redacted] months. Convergence of Duration of Therapy began at [redacted] months, rather than [redacted] months.

^b Note that the ICER is \$45,000/QALY – \$75,000/QALY in the scenario in which the restrictions are not amended, which was also presented as part of the base case in the resubmission

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

5.16 The resubmission estimated an ICER of \$45,000/QALY – \$75,000/QALY if the restrictions for drugs that are currently listed in the second- and later- line settings are changed. The resubmission presented an alternative scenario wherein the restriction for current second-line therapies remains unchanged (which would significantly limit the use of axitinib, cabozantinib, sorafenib, everolimus), which resulted in an ICER of \$45,000/QALY – \$75,000/QALY.

5.17 The resubmission stated that these ICERs were below the “indicative thresholds most recently considered by the PBAC for RCC (2L: \$ [redacted]; 1L: [redacted])”. However, it is noted that the ICER for second-line treatment reflects a reduced cost per patient and different level of incremental benefit. A comparison of the requested/accepted price per dose in the two settings is presented in the table below.

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Table 5: Comparison of price in the first- versus second (and later) line RCC setting for nivolumab

	Effective AEMP		Estimated avg. dose (PI dose)	DPMA for avg dose	Avg number of doses per course ^c	Frequency of administration ^d
	100mg vial	40 mg vial				
Nivolumab first-line: requested	\$ [REDACTED]	\$ [REDACTED]	240 mg (3mg/kg)	\$ [REDACTED]	32.8	Q3w for 4 doses, q2w thereafter
Nivolumab second-line: effective	\$ [REDACTED] ^a	\$ [REDACTED] ^a	240 mg (3mg/kg)	\$ [REDACTED] ^a	20.7 ^b	Q2w

Source: Constructed during preparation of the Minor Overview based on "App_BIM_NIVO+IPI_1LRCC_Minor resubmission.xlsx" spreadsheet.

Avg = average; IPI = ipilimumab; NIVO = nivolumab; PI = Product Information; q2w = every 2 weeks

^a Source: '4c. Displaced – EFF' Rows 100 to 118

^b Source: '4a. Volumes – displaced' Cell D163 and G163

^c As estimated in each submission

^d Source: Nivolumab Product Information

5.18 The pre-PBAC response stated “The Sponsor notes that the confidential Special Pricing Arrangement for first-line comparator therapies has not yet been included in the economic model and that once this is accounted for, net pricing for the NIVO+IPI combination will be adjusted accordingly.”

5.19 The results of sensitivity analyses are presented in the table below.

Table 6: Sensitivity and scenario analyses

	Δ Costs	Δ Outcomes	ICER/QALY
Base case (if restrictions are changed for existing second-line therapies)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Resubmission alternative scenario: No change to restriction for current 2 nd -line therapies (i.e. can only use current 2 nd -line therapies if TKIs were used 1st-line) ^a	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Use of later-line NIVO monotherapy: (base case: permitted post NIVO+IPI)			
- Not permitted following prior NIVO+IPI therapy ^b			
- Assume patients receive no therapy (rather than NIVO monotherapy)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
- Assume patients receive pazopanib (rather than NIVO monotherapy) ^c	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Utilities: Base case Progression free: NIVO+IPI: [REDACTED], SUNI: [REDACTED]. Progressed: [REDACTED]			
- Average from literature PF: [REDACTED]; Progressed: [REDACTED] (per Table 13, July 2018 PBAC Minutes)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Time horizon: [REDACTED] years in base case			
- [REDACTED] years	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Convergence of Duration of Therapy: converges within modelled time horizon ([REDACTED] years) in the base case			
- Does not converge within [REDACTED] years (using same extrapolation assumptions as previous model, refer to green dotted line in Figure 1) ^d	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Nivolumab drug cost: Base case \$ [REDACTED] for 100 mg vial (DPMA: \$ [REDACTED])			
- \$ [REDACTED] for 100 mg vial (DPMA: \$ [REDACTED]), i.e. a [REDACTED] % reduction in DMPA	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

Source: Table 5, minor resubmission; "App_CEA_NIVO+IPI_RCC_Aug18.xlsx" spreadsheet. Ital = figures in italics were calculated during preparation of the Minor Overview.

^a Not evaluated during preparation of the minor overview. This was presented as part of the base case in the minor resubmission.

^b The model assumed that [REDACTED] of patients in the NIVO+IPI arm would receive subsequent nivolumab monotherapy. This was based on the subsequent therapies used in the pivotal trial (CA209214). This differed to the assumptions used in the financial estimates, which were based on an advisory board. In this sensitivity analysis, only the costs of subsequent therapy are changed (and not the efficacy, which is based on survival curves from CA209214). In the first sensitivity analysis, cell

^c Pazopanib was selected as this was the most commonly used subsequent therapy in CA209214.

^d This would increase the average number of nivolumab doses per patient from [REDACTED] to [REDACTED], which would impact the financial estimates.

- 5.20 The PBAC noted that the ICER would be around \$45,000/QALY – \$75,000/QALY if the restrictions for axitinib, cabozantinib, sorafenib and everolimus are changed, and nivolumab monotherapy is not subsidised following prior NIVO+IPI. The PBAC noted that this scenario aligned with the restriction changes that it considered would be appropriate.

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

- 5.21 This consists of a cost per patient per course of \$ [REDACTED] for NIVO and \$ [REDACTED] for IPI.
- 5.22 For NIVO, this cost was based on: an average of [REDACTED] infusions per patient (from the economic model), and the effective DPMA of \$ [REDACTED]. This cost (\$ [REDACTED]) was lower than estimated in the previous submission (\$ [REDACTED] per patient) because the estimated number of doses was lower ([REDACTED] versus [REDACTED]) due to the changes to the time horizon and extrapolation of treatment duration, and the lower proposed price of NIVO.
- 5.23 For IPI, this cost was based on: an average of [REDACTED] infusions per patient (from the economic model), and the effective DPMA of \$ [REDACTED]. This cost (\$ [REDACTED]) was lower than the estimated cost of IPI in the previous submission (\$ [REDACTED]) due to the lower proposed price.

Estimated PBS usage & financial implications

- 5.24 Compared with the previous submission, four key changes were made to the financial estimates, and these are outlined below.
- 5.25 Firstly, the resubmission assumed a higher number of NIVO maintenance scripts per patient. This was to address the PBAC's previous concerns that, in clinical practice, patients who experience adverse events during NIVO+IPI induction may go on to receive nivolumab monotherapy, rather than discontinue as was required by the trial protocol (Paragraph 7.14, PBAC PSD July 2018). The July 2018 PBAC Minutes noted that [REDACTED]% of patients discontinued NIVO+IPI during the induction phase in Study CA209-214 due to drug toxicity. To account for this, the resubmission assumed that each patient would require [REDACTED]% more maintenance infusions than observed in the clinical trial (i.e. this increased the average number of infusions per patient from [REDACTED] to [REDACTED] infusions).
- 5.26 Secondly, grandfathering provisions were requested in the resubmission. The sponsor proposed that a Patient Access Program would be commenced [REDACTED] months prior to PBS listing. Patient numbers for the grandfathering provisions were calculated using the same methodology as was used to estimate the PBS population (e.g. a [REDACTED] market share was assumed even in the first month of the Patient Access Program, which significantly overestimated the number of grandfathered patients). The resubmission estimated that less than 10,000 patients would be grandfathered to PBS reimbursement at time of listing.
- 5.27 As part of its pre-PBAC response, the sponsor was requested to identify the number

of patients enrolled in the Patient Access Program at the time of the PBAC meeting. The PBAC noted that this information was not provided in the pre-PBAC response. The pre-PBAC response reiterated that the sponsor intends to open a Patient Access Program ■ months prior to PBS listing and requested the PBAC consider including less than 10,000 grandfathered patients in the subsidisation caps.

- 5.28 Thirdly, the resubmission added assumptions regarding the timing of offsets for reduced use of subsequent therapies. In the previous submission, the costs of subsequent therapy were ‘front-loaded’ (all subsequent therapy costs were applied in the same year the patient initiated first-line therapy). This overestimated subsequent therapy costs (cost-offsets) on an annual basis. To address this, the resubmission’s financial estimates ‘phased’ the application of subsequent therapy costs based on the PFS curve for NIVO+IPI from CA209-214 (it estimated that ■% of first-line patients progress within 12 months, with the remaining ■% of second-line therapy costs incurred in Year 2), and the PFS curve for NIVO from the second-line NIVO monotherapy study, CA209-025 (it estimated that ■% second-line therapy costs are incurred in Year 2, with the remaining ■% incurred in Year 3).
- 5.29 Fourthly, flow-on changes from the economic model were incorporated, including changes to the mean number of NIVO infusions per patient (due to changes to the extrapolation and time horizon) and the requested price of NIVO + IPI was reduced.
- 5.30 The resubmission assumed there would be PBS cost-offsets primarily from reduced use of sunitinib and pazopanib in the first-line setting and NIVO monotherapy (and other subsequent therapies) in the second-line and third-line settings. The resubmission continued to assume that ■% of patients receive subsequent second-line therapy, and ■% receive subsequent third-line therapy (in the scenario in which the restrictions for current second-line therapies are amended to allow prior TKI therapy in second-line settings). This was unchanged from the previous submission and did not address the PBAC’s previous concerns that “it was likely that cost offsets associated with substituted 2L and 3L therapies may be overestimated” (Paragraph 6.79, July 2018 PBAC PSD). The resubmission’s rationale for not addressing this comment was that the RCC market is evolving with new agents becoming available (e.g. nivolumab PBS listed 1 August 2017, and cabozantinib PBS listed 1 June 2018), which may increase the number of options available. The PBAC noted that the proportion of patients receiving second- and third-line therapies were consistent with figures previously accepted by PBAC for the listing of NIVO in second- and later-lines of RCC. In this context, the March 2017 PBAC had considered these were likely overestimated, but represented a reasonable upper limit for the purposes of calculating risk sharing arrangement caps (Paragraph 6.46, Nivolumab Public Summary Document, March 2017). The PBAC again considered these were likely reasonable upper limits of likely use in the context of estimating flow-on changes to the existing NIVO market in RCC.
- 5.31 The method for calculating the eligible population was unchanged from the previous submission, and included a step in which the eligible population was increased by

█% to account for a high level of clinical trial activity occurring in Australia for first-line RCC.

5.32 The estimated utilisation and financial impacts are shown in the table below. For the cost-offsets (financial implications for other PBS-listed medicines), the numbers presented assume that the PBS restriction for the current second- and later-line therapies will be amended to remove the requirement for prior TKI use to have been in the first-line setting. The PBAC noted the estimates would also need to be updated to take into account the restriction amendment where patients who receive first-line NIVO+IPI should not subsequently receive nivolumab monotherapy in a later line of therapy.

Table 7: Estimated use and financial implications: as presented in the pre-PBAC response

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of NIVO+IPI						
Total number of patients treated with 1L RCC therapy ^a	█	█	█	█	█	█
Number of initiating patients treated with NIVO+IPI (inc. █ GF)	█	█	█	█	█	█
Previous sub: No. of initiating patients treated with NIVO+IPI	█	█	█	█	█	█
Induction infusions/year	█	█	█	█	█	█
Maintenance infusions/year	█	█	█	█	█	█
Estimated financial implications of NIVO+IPI						
Cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Copayments	\$█	\$█	\$█	\$█	\$█	\$█
Cost to PBS/RPBS less copayments	\$█	\$█	\$█	\$█	\$█	\$█
Previous sub: PBS/RPBS less copayments	\$█	\$█	\$█	\$█	\$█	\$█
Estimated financial implications for other PBS medicines (per Sensitivity Analysis 5: subsequent therapies based on original submission, and corrected during preparation of the Minor Overview ^b)						
Cost to PBS/RPBS less copayments	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Of above, cost for NIVO 2 nd -line	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Previous sub: PBS/RPBS less copayments	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Net financial implications						
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to MBS	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to PBS/RPBS/MBS	\$█	\$█	\$█	\$█	\$█	\$█
Previous submission	\$█	\$█	\$█	\$█	\$█	\$█

Source: compiled based on information presented in 'Item 7.09 Pre-PBAC Response for nivolumab + ipilimumab ATTACHMENT 1.xlsx'

GF = grandfathered; 1L = first line

^a Includes: patients with a favourable prognosis, and patients who are assumed to be treated with sunitinib or pazopanib rather than NIVO+IPI. Also includes patients who are assumed to be treated in a clinical trial setting.

5.33 The resubmission (pre-PBAC response) estimated a net cost to the PBS/RPBS of \$20 – \$30 million in Year 6 of listing, with a total net cost to the PBS/RPBS of more than \$100 million over the first six years of listing (if the restrictions for all current second-

and later-line therapies are amended).

- 5.34 The PBAC noted that the total number of patients estimated to be treated with first-line RCC therapy was significantly higher than was accepted in the financial estimates for NIVO monotherapy.
- 5.35 Offsets from reduced use of NIVO monotherapy in the second- and third-line settings are also shown in the table above, and total \$60 – \$100 million over six years.
- 5.36 Over time, usage of NIVO monotherapy would significantly reduce if NIVO+IPI were listed first-line, with use of NIVO monotherapy likely limited to those patients who either received first-line treatment prior to NIVO+IPI being listed, those who are contraindicated to IPI, and patients with a favourable prognosis (who would not be eligible for first-line NIVO+IPI).

Financial Management – Risk Sharing Arrangements

- 5.37 The resubmission proposed a RSA with █████% rebate beyond estimated utilisation and stated that it is willing to work with the Department to incorporate flow-on changes to the existing RSA for second-line NIVO, which was in line with PBAC's previous advice (Paragraph 7.15, PBAC Minutes July 2018).
- 5.38 The resubmission stated that it is willing to consider a deed covering nivolumab in first- and second-line RCC (and an ipilimumab deed covering first-line RCC). The resubmission stated that adjustment to the existing RSA for second-line RCC should include consideration of “near term future agents and associated market share implications”. The PBAC noted that this would likely create a high level of uncertainty and may not be appropriate in managing risk around the proposed listing.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC recommended extending the Section 100 (Efficient funding of chemotherapy) Authority Required (STREAMLINED) listing of NIVO+IPI to include the first-line treatment of Stage IV clear cell variant RCC in patients at intermediate to poor prognostic risk. The PBAC considered that the resubmission's revised economic model parameters, utilisation estimates and risk-sharing arrangement helped to address many of its previous concerns. However, the PBAC advised that a price reduction would be required to bring the estimated ICER into an acceptable range.
- 6.2 The PBAC is satisfied that NIVO+IPI provides, for some patients, a significant improvement in efficacy over sunitinib. However, the PBAC considered that the magnitude of benefit obtained from the addition of ipilimumab to the combination with nivolumab remains uncertain.
- 6.3 The PBAC reiterated its previous consideration that there is a high clinical need for effective first-line therapies for RCC, especially in the poor prognostic risk patient population for whom no PBS-subsidised therapies are available.

- 6.4 The PBAC considered that the continuing restriction should state: “Patient must not have developed disease progression while being treated with this drug for this condition”. The criterion should not reference the RECIST criteria, consistent with the pivotal trial (CA209-214) and the nivolumab restrictions in other settings. The PBAC also recommended that flow-on changes be made to other restrictions for nivolumab in different lines of therapy and other indications as well as other PD-1 and PD-L1 inhibitors with similar indications to change the criterion “Patient must have stable or responding disease” to “Patient must not have developed disease progression while being treated with this drug for this condition”.
- 6.5 The PBAC noted that, with NIVO+IPI available in the first-line setting, the treatment algorithm would change and many patients would receive TKI therapy second-line (rather than first-line). Thus, the PBAC considered that the PBS restrictions for axitinib, cabozantinib, sorafenib and everolimus (which are used subsequent to TKIs) should be amended to remove the requirement for the prior TKI therapy to have been in the first-line setting. The PBAC considered that this amendment should also be made to the existing restriction for nivolumab monotherapy for consistency. The PBAC considered that patients should still be required to have received prior TKI therapy before commencing axitinib, cabozantinib, sorafenib, everolimus and nivolumab monotherapy (i.e. the amendment just removes the requirement that the prior TKI therapy be in first-line).
- 6.6 Further, the PBAC considered that patients who receive first-line NIVO+IPI (or other PD-1 or PD-L1 inhibitors) should not subsequently receive nivolumab monotherapy in a later line of therapy, as no evidence has been provided regarding the efficacy of such use. The PBAC noted that this would require an amendment to the existing later-line nivolumab monotherapy restriction.
- 6.7 The PBAC noted that, consistent with its previous advice, the proposed restriction was based on IMDC criteria, which reflects current clinical practice where IMDC has superseded the MSKCC criteria. The PBAC re-iterated its previous consideration that the current restrictions for sunitinib and pazopanib should similarly be changed from MSKCC to IMDC for consistency.
- 6.8 The PBAC recalled that it had previously considered that the claim of clinical superiority of NIVO+IPI versus sunitinib was adequately supported given the statistically significant improvement in OS observed in the pivotal trial, but considered that the magnitude of the benefit was difficult to quantify given the immaturity of the data. Further, the PBAC previously considered that NIVO+IPI was associated with inferior comparative safety versus sunitinib.
- 6.9 The PBAC recalled its previous consideration that the adverse events associated with NIVO+IPI may be challenging to manage outside major tertiary centres (e.g. in more rural and remote settings and private hospitals). The PBAC reiterated its previous view that there was a need for access to immune-modulating rescue therapies in these settings, for example infliximab for treatment-induced colitis, which are not currently PBS-funded for this indication nor routinely available on hospital

formularies.

- 6.10 The PBAC recalled that it previously considered that the ICER/QALY was uncertain and overly optimistic due to:
- The assumption of proportional hazards from the mean duration of follow-up to five years. As requested by the PBAC in July 2018, the resubmission assumed that convergence of the OS (and PFS) curves begins at █ months.
 - The use of a █ year time horizon. As requested by the PBAC in July 2018, the resubmission applied a time horizon of █ years.
 - The utility estimates were similar to population norms and the PBAC (in July 2018) had considered it was unlikely that patients in the progressed disease health state would experience a utility of █ consistently over the model time horizon (or █ in the sunitinib arm). The PBAC noted that the resubmission had reduced the utility value applied in the progressed disease health state to █ based on the utility value from the March 2017 submission for NIVO in the second-line RCC setting. The PBAC considered the utility values applied in the resubmission remained high.
- 6.11 The PBAC noted that the ICER would be \$45,000/QALY – \$75,000/QALY with the restriction changes it had recommended for subsequent therapies. As such, the PBAC considered this would be the most appropriate base case.
- 6.12 The PBAC re-iterated its previous consideration that NIVO+IPI would be cost-effective at an ICER of less than \$45,000 – \$75,000 per QALY, using the base case outlined in the paragraph above with the effective sunitinib price applied. The PBAC noted that a price reduction would be required to bring the estimated ICER into an acceptable range. The PBAC considered that a price reduction to the NIVO component in preference to the IPI component would provide greater certainty that this ICER would be achieved in practice, given there is potential for NIVO to be used for longer in clinical practice than occurred in the trial (patients who experience adverse events during NIVO+IPI induction may go on to receive nivolumab monotherapy, rather than discontinue as was required by the trial protocol).
- 6.13 The PBAC noted that the NIVO+IPI submission increased the size of the PBS-treated population by █% to account for clinical trials occurring in Australia for first-line RCC. The PBAC considered that this assumption was not reasonable, and had overestimated the eligible population, because clinical trial activity was likely to continue and would not change the likely pool of patients available for first-line treatment on the PBS.
- 6.14 The PBAC noted that the number of patients estimated to be treated with first-line therapy for RCC did not align with the previously agreed financial estimates for NIVO monotherapy and considered that this created a level of uncertainty around the likely total use of NIVO in both settings. The total number of patients treated in first-line RCC that was agreed for the NIVO monotherapy financial estimates allowed for additional patients taking up therapy due to the availability of NIVO. Thus, the PBAC considered that the total first-line RCC market should not be any higher than that

agreed for NIVO monotherapy. These numbers allowed for a maximum of less than 10,000 patients treated in 2020 regardless of line of therapy, increasing by less than 10,000 patients per year.

- 6.15 The PBAC noted that the resubmission had estimated that less than 10,000 patients would be grandfathered to PBS reimbursement at time of listing (less than 10,000 patients were requested in the pre-PBAC response). The PBAC noted that the usual practice adopted by the Department has been to subsidise the costs for all eligible patients who commenced treatment through a Patient Access Program (or similar) prior to the date of the PBAC meeting at which the submission received a positive recommendation. However, the PBAC noted that no estimates had been provided as to the number of patients enrolled in the Patient Access Program at the time of the PBAC meeting. The PBAC noted that patients enrolled thereafter who are eligible for PBS-subsidised access to therapy should already be accounted for in the financial modelling and hence would be included in any subsidisation caps. The PBAC was therefore of the view that no additional inclusion of grandfathered patients should need to be accounted for.
- 6.16 The PBAC reiterated its previous advice that an RSA with a [REDACTED] % rebate beyond estimated utilisation would be required, and flow-on changes would be required to the existing RSA for second-line nivolumab in light of the significantly reduced use of later-line NIVO once NIVO+IPI is listed first-line. The PBAC also considered it may be appropriate to implement a single financial RSA cap across both settings for NIVO as these are likely to be based on the same treated population.
- 6.17 The PBAC noted that flow-on restriction changes would be required to later-line drugs for RCC as outlined in Paragraphs 6.5 to 6.7. As such, the restriction is considered to be complex.
- 6.18 The PBAC advised that NIVO+IPI is not suitable for prescribing by nurse practitioners.
- 6.19 The PBAC recommended that the Early Supply Rule should not apply.
- 6.20 The PBAC noted that this submission is not eligible for an Independent Review as it was a positive recommendation.

Outcome:

Recommended

7 Recommended listing

Restrictions to be finalised:

7.1 Add new items:

Nivolumab induction

Name, restriction, manner of administration, form	Maximum Amount	No. of repeats	Proprietary name and manufacturer
Induction phase			
NIVOLUMAB Injection 40 mg/4 mL 1 x 4 mL vial Injection 100 mg/10 mL 1 x 10 mL vial	360 mg	3	OPDIVO Bristol-Myers Squibb Australia Pty Ltd

Category/Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Induction (combination) treatment
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must meet the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate to poor risk group criteria AND Patient must have a WHO performance status of 2 or less AND The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction for this condition AND The treatment must be for first-line therapy for this condition
Prescriber Instructions:	Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks 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. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
Caution	Combination treatment with ipilimumab and nivolumab is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.

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Ipilimumab induction

Name, restriction, manner of administration, form	Maximum Amount	No. of repeats	Proprietary name and manufacturer
IPILIMUMAB Injection 50 mg/10 mL 1 x 10 mL vial	120 mg	3	YERVOY Bristol-Myers Squibb Australia Pty Ltd

Category/Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Induction (combination) treatment
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must meet the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor risk group criteria AND Patient must have a WHO performance status of 2 or less AND The treatment must be in combination with PBS-subsidised treatment with nivolumab as induction therapy for this condition AND The treatment must be for first-line therapy for this condition
Prescriber Instructions:	Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks 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. No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
Caution	Combination treatment with ipilimumab and nivolumab is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.

Continuing treatment with nivolumab

Name, restriction, manner of administration, form	Maximum Amount	No. of repeats	Proprietary name and manufacturer
Continuing phase NIVOLUMAB Injection 40 mg/4 mL 1 x 4 mL vial Injection 100 mg/10 mL 1 x 10 mL vial	360 mg	11	OPDIVO Bristol-Myers Squibb Australia Pty Ltd

Category/ Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)

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Treatment phase:	Continuing treatment with nivolumab monotherapy following first line nivolumab plus ipilimumab induction
Restriction:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received up to a maximum of 4 doses of PBS-subsidised combined treatment with nivolumab and ipilimumab as induction therapy for this condition AND The treatment must be as monotherapy for this condition AND Patient must not have developed disease progression while being treated with this drug for this condition
Prescriber Instructions:	Maintenance treatment with nivolumab must not exceed a maximum dose of 3 mg per kg every 2 weeks. The patient's body weight must be documented in the patient's medical records at the time treatment is initiated
Administrative Advice:	No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply.

Grandfathering restriction – nivolumab induction and continuing

Name, restriction, manner of administration, form	Maximum Amount	No. of repeats	Proprietary name and manufacturer
NIVOLUMAB Injection 40 mg/4 mL 1 x 4 mL vial Injection 100 mg/10 mL 1 x 10 mL vial	360 mg	2	OPDIVO Bristol-Myers Squibb Australia Pty Ltd

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Grandfather patients – Induction OR Grandfather patients - Continuing treatment with nivolumab monotherapy following first line nivolumab plus ipilimumab induction
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have received combined therapy with ipilimumab and nivolumab as induction for this condition prior to <PBS listing date> OR Patient must have received monotherapy with nivolumab as maintenance for this condition prior to <PBS listing date> AND Patient must have met the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate to poor risk group criteria prior to initiating non-PBS subsidised treatment with nivolumab and ipilimumab AND Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment with nivolumab and ipilimumab AND The treatment must be for first-line therapy for this condition AND Patient must not have developed disease progression while being treated with this drug for this condition AND

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	The treatment must be in combination with PBS-subsidised treatment with ipilimumab as induction for this condition OR The treatment must be the sole PBS-subsidised therapy for this condition
Prescriber Instructions	Induction treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks Maintenance treatment with nivolumab must not exceed a maximum dose of 3 mg per kg every 2 weeks. A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria. 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. No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply.
Caution	Combination treatment with ipilimumab and nivolumab is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.

Grandfathering restriction – ipilimumab induction

Name, restriction, manner of administration, form	Maximum Amount	No. of repeats	Proprietary name and manufacturer
IPILIMUMAB Injection 50 mg/10 mL 1 x 10 mL vial	120 mg	2	YERVOY Bristol-Myers Squibb Australia Pty Ltd

Category / Program	Section 100 - Efficient funding of Chemotherapy
Prescriber type	Medical Practitioners
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
PBS Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Grandfather patients – Induction
Restriction Level / Method:	<input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have received combined therapy with ipilimumab and nivolumab as induction for this condition prior to <PBS listing date> AND Patient must have met the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate to poor risk group criteria prior to initiating non-PBS subsidised treatment with nivolumab and ipilimumab AND Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment with nivolumab and ipilimumab AND The treatment must be for first-line therapy for this condition AND The treatment must be in combination with PBS-subsidised treatment with nivolumab as induction

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	for this condition AND Patient must not have developed disease progression while being treated with this drug for this condition
Prescriber Instructions	A patient may qualify for PBS-subsidised treatment under this restriction once only. Induction treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks 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. No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply.

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 thanks the PBAC for its consideration of this item and looks forward to eligible Australian patients being able to access nivolumab and ipilimumab for the treatment of first line RCC via the PBS in the near future.