

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

1 Purpose of Application

1.1 To request a Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required listing for the treatment of Stage IV 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 proposed PBS listings for nivolumab (initial and continuing treatments) are presented below.

Proposed PBS listing for initial treatment

| Name, Restriction, Manner of administration and form | Max. Qty | №.of Rpts | Proposed AEMP (resubmission addendum – “PBAC amended base case”) | Proprietary Name and Manufacturer |
|---------------------------------------------------------|-------------|--------------|---------------------------------------------------------------------------|-------------------------------------------|
| Nivolumab 40 mg/4 mL injection 1 x 4 mL vial | 360 mg | 8 | \$830.70 (published) \$██████ (effective) | OPDIVO® |
| 100 mg/10 mL injection 1 x 10 mL vial | | | \$2076.50 (published) \$██████ (effective) | Bristol-Myers Squibb Australia Pty Ltd |

| | |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Category / Program | Section 100 - Efficient funding of Chemotherapy |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| 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: | Initial treatment |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |

Public Summary Document – March 2017 PBAC Meeting

| | |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical criteria: | <p>The treatment must be the sole PBS-subsidised therapy for this condition</p> <p>AND</p> <p>Patient must have a WHO performance status of 2 or less</p> <p>AND</p> <p>Patient must have progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) following first-line treatment with a tyrosine kinase inhibitor</p> <p>OR</p> <p>Patient must have developed intolerance to a tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal</p> |
| Definitions | <p>Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows:</p> <p>Complete response (CR) is disappearance of all target lesions.</p> <p>Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.</p> <p>Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.</p> <p>Stable disease (SD) is small changes that do not meet above criteria.</p> |
| Prescriber Instructions | <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> |

Proposed PBS listing for continuing treatment

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Proposed AEMP (resubmission addendum – "PBAC amended base case") | Proprietary Name and Manufacturer |
|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------------------------------------------------------|-------------------------------------------|
| Nivolumab 40 mg/4 mL injection 1 x 4 mL vial | 360 mg | 11 | \$830.70 (published) \$ (effective) | OPDIVO® |
| 100 mg/10 mL injection 1 x 10 mL vial | | | \$2076.50 (published) \$ (effective) | Bristol-Myers Squibb Australia Pty Ltd |
| Category / Program | Section 100 - Efficient funding of Chemotherapy | | | |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives | | | |
| 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 | | | |

Public Summary Document – March 2017 PBAC Meeting

| | |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined |
| Clinical criteria: | <p>Patient must have previously been issued with an authority prescription for this drug for this condition,</p> <p>AND</p> <p>Patient must have stable or responding disease,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p> |
| Prescriber Instructions | <p>The patient's body weight must be documented in the patient's medical records at the time treatment is initiated.</p> |

- 2.2 In the resubmission-addendum, the proposed AEMP for the product was increased to either \$ [REDACTED] or \$ [REDACTED] per 100 mg vial, with a corresponding increase envisaged for the 40 mg vial. The difference in price was due to the resubmission-addendum presenting two analyses using different time horizons, with the drug cost adjusted to meet a target ICER of \$45,000/QALY - \$75,000/QALY (see detail below).
- 2.3 The application for listing of nivolumab presented a cost-utility analysis against everolimus, a drug currently listed on the PBS for this indication.
- 2.4 The requested listing in the resubmission adopted key changes recommended by the Secretariat and supported by the Economics Sub-Committee (ESC) in their respective reviews of the original submission. Changes included separate listings for initial and continuing treatment and a restriction that patients must have Stage IV clear cell variant RCC and a World Health Organisation (WHO) performance status of 2 or less. The ratified minutes of the July 2016 PBAC meeting note that the PBAC had a preference that any future restriction on continuation should be based on standard RECIST-defined progression-free survival (PFS) criteria, allowing the RECIST criteria to be modified to avoid stopping the medicine in the context of early pseudo-progression as is currently the case in current PBS listings of nivolumab for melanoma (7.5 of ratified minutes). The resubmission and Pre-Sub-Committee-Response (PSCR) strongly emphasised that the implementation of a RECIST-based stopping rule for nivolumab would “not be appropriate under any circumstance”, given that this would represent a significant departure from the accepted approach to the utilisation of nivolumab. The ESC noted that the intent of the November 2016 PBAC in recommending that the continuation criteria should exclude pseudo-progression as per nivolumab melanoma restriction, but that this restriction does not specifically define any criteria for determining “stable and responding disease”. The ESC indicated if that the PBAC also wanted to specify RECIST criteria to define stable or responding disease in a continuing restriction for RCC to ensure that clinicians monitor for progression on these grounds rather than clinical observation,

then consideration should be given to the consistency of approach with this continuing criterion for melanoma.

- 2.5 The PBAC's preference was that restrictions on treatment should be based on standard PFS criteria (but allowing the RECIST criteria to be modified to avoid stopping the medicine in the context of early pseudo-progression) and so the PBAC recommended that the Administrative Advice in the initial treatment restriction for renal cell carcinoma should be based on that for nivolumab in melanoma to allow for a repeat scan to confirm progression.

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

3 Background

- 3.1 Nivolumab was approved by the Therapeutic Goods Administration (TGA) on 16 November 2016 for "the treatment of adult patients with advanced clear cell renal cell carcinoma (RCC) who had received prior antiangiogenic therapy". This is in addition to other approved indications (unresectable or metastatic melanoma, locally advanced or metastatic squamous or non-squamous non-small cell lung cancer) for the product.
- 3.2 The PBAC originally considered an application to list nivolumab on the PBS for the treatment of RCC at its July 2016 meeting. The PBAC decided not to recommend that nivolumab be listed on the PBS for this indication based on an unacceptably high and uncertain incremental cost-effectiveness ratio (ICER) at the requested effective price. Other issues arising from that submission are summarised in Table 1 below.
- 3.3 Subsequent to the sponsor's review of the ratified minutes of the July 2016 meeting and discussions with the PBAC Chair and Secretariat, a minor resubmission was lodged for consideration at the November 2016 meeting. This minor resubmission addressed some issues of uncertainty in the clinical evidence by providing additional Kaplan-Meier (KM) supporting evidence for OS. Re-specification parameters for the economic model set out in section 7.10 of the ratified minutes were addressed. These included reducing the modelled time horizon to 5 years and applying treatment costs for nivolumab and everolimus on a per-cycle basis reflecting time to progression in the key trial, rather than the front-loading approach used previously. The effective price of nivolumab was reduced (together with a proposal for a cap on the number of nivolumab infusions to be paid for by the Government and an accompanying risk sharing arrangement) to ensure that the ICER was not greater than the value presented (\$45,000/QALY - \$75,000/QALY) in the original submission's base case. Proposed uptake rates of second line treatments in RCC that had been considered over-estimated by the PBAC were also reduced in deriving the financial estimates.
- 3.4 At its November 2016 meeting, the PBAC decided not to recommend the listing of nivolumab for the treatment of RCC on the grounds of unfavourable and uncertain cost-effectiveness. The PBAC considered that the benefit of treatment with nivolumab was uncertain, and likely overestimated, and that the proposed risk sharing arrangement would not address this uncertainty. The PBAC further updated

Public Summary Document – March 2017 PBAC Meeting

the respecified parameters to confirm the requirement that RECIST-defined PFS be used to inform both arms of the economic model.

- 3.5 Concurrent with the minor resubmission presented for consideration at the November 2016 meeting, the sponsor had also prepared a major resubmission for consideration by the PBAC at its March 2017 meeting. The resubmission included a full analysis of the clinical evidence from the pivotal trial based on a second database cut-off (minimum follow up 26 months), as well as evidence and arguments to justify a revised economic model and financial estimates.
- 3.6 On review of the ratified minutes of the PBAC November 2016 meeting and following discussion with the Secretariat, the sponsor then submitted an addendum to its major resubmission in December 2016. It was intended that this addendum be linked to the resubmission and be considered in parallel at the March 2017 PBAC meeting. This addendum primarily addressed a requested re-specified base case economic model, as confirmed by the PBAC minutes of November 2016, including prices for nivolumab that were higher than those proposed in the resubmission. The sponsor subsequently submitted updated financial estimates in January 2017. The PBAC considered all three sources of information at its March 2017 meeting.
- 3.7 The key features of the submissions for nivolumab in RCC considered at the July 2016 (original submission) and November 2016 (minor resubmission) PBAC meeting and the current major resubmission and resubmission-addendum are presented in Table 1 below.

Table 1: Summary of the previous submissions and current re-submission

| | July 2016 major submission | November 2016 minor resubmission | March 2017 major resubmission | March 2017 resubmission-addendum |
|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Requested PBS listing | Nivolumab for advanced or metastatic clear cell variant RCC in patients with RECIST-defined progressed disease. PBAC Comment: Should be restricted to Stage IV disease and patients with WHO performance status 2 or less. Standard PFS to be used in a future restriction as eligibility criterion (July 2016 minutes 7.5). | Resubmission stated (p1) that the sponsor and PBAC are aligned with the proposed restriction recommended by ESC. PBAC Comment: none | Requested restriction did not include a criterion that eligibility for continuation would be based on RECIST-defined PFS. | Addendum re-emphasised that it would be clinically inappropriate to include RECIST-defined PFS in the proposed continuing restriction. |
| Requested price | \$ [REDACTED] (100 mg vial) | \$ [REDACTED] (100 mg vial) with maximum costed nivolumab infusions capped at [REDACTED]. | \$ [REDACTED] (100 mg vial) with maximum costed nivolumab infusions capped at [REDACTED]. | \$ [REDACTED] (100 mg vial) based on sponsor proposed 8-year time horizon. \$ [REDACTED] (100 mg vial) based on PBAC proposed 5-year time horizon. No cap proposed on the number of nivolumab infusions. |

Public Summary Document – March 2017 PBAC Meeting

| | July 2016 major submission | November 2016 minor resubmission | March 2017 major resubmission | March 2017 resubmission-addendum |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| Main comparator | Everolimus 10 mg p.o. daily. PBAC Comment: Appropriate comparator (7.3) | Everolimus 10 mg p.o. daily. | Everolimus 10 mg p.o. daily. | Everolimus 10 mg p.o. daily. |
| Clinical evidence | CA209025 study (Nivolumab 3 mg/kg every 2 weeks n=410 vs everolimus 10 mg po daily n= 411, phase III, R, OL, MC) 18 June 2015 cut-off (14 months minimum follow up). PBAC Comment: Early stopping of the key trial may have over-estimated the degree of overall survival gain (July 2016 minutes 7.7). The post-hoc use of a “clinical PFS” outcome for economic modelling was not validated, nor necessarily representative of use in Australian practice (July 2016 minutes 7.5). | Additional supporting KM estimates for OS comparing the original database lock (14 month minimum follow up) versus the latest database lock (26.1 months minimum follow up). PBAC comment: “The PBAC noted the updated 2-year follow-up data on OS which [REDACTED], however considered that the degree of benefit in a PBS population was still uncertain” (November 2016 minutes 7.3). | The updated results from the May 2016 database lock (26.1 months minimum follow-up) were provided. In order to support a time horizon beyond 5 years, the sponsor presented evidence relating to the survival of patients treated second line in RCC. | No new clinical evidence presented. |
| Key effectiveness data | First database lock (14 months minimum follow-up). OS median months 25.00 (21.75, NR) for nivolumab and 19.55 (17.64, 23.06) for everolimus. 5.45 months absolute difference; HR= 0.73 (0.57, 0.93). <u>RECIST-defined PFS median months</u> 4.60 (3.71, 5.39) for nivolumab and 4.44 (3.71, 5.52) for everolimus. 0.16 months absolute difference; HR = 0.88 (0.75, 1.03). <u>Clinical PFS median months</u> [REDACTED] PBAC Comment: The PBAC accepted that nivolumab statistically significantly increased overall survival compared to everolimus (July 2016 minutes 7.6). | Second database lock (26.1 months minimum follow-up). OS median months [REDACTED] PBAC comment: “the degree of benefit in a PBS population was still uncertain as the trial contained patients whose nivolumab treatment continued after disease progression” (July 2016 minutes 7.3). | Second database lock (26.1 months minimum follow-up). OS median months [REDACTED] <u>RECIST-defined PFS median months</u> [REDACTED] <u>Clinical PFS median months (second database lock)</u> [REDACTED] | No effectiveness data were presented in the resubmission addendum. |

Public Summary Document – March 2017 PBAC Meeting

| | July 2016 major submission | November 2016 minor resubmission | March 2017 major resubmission | March 2017 resubmission-addendum |
|---------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Key safety data | <p>Submission claimed an acceptable safety profile for the treatment of RCC that compared favourably with everolimus, given the significantly reduced frequency of drug related AEs (any grade, grade 3-4) and deaths.</p> <p>PBAC Comment: The PBAC concluded that the clinical claim of 'favourable' safety for nivolumab over everolimus was not adequately supported by the data supplied (7.8).</p> | No additional safety data presented. | Maintained the view that nivolumab provides favourable safety over everolimus and therefore disagreed with PBAC view. The resubmission considered that this disagreement is inconsequential to the cost effectiveness assessment given that the costs of adverse events that occur more frequently in the nivolumab group are included in the economic analysis. | No additional safety data presented. |
| Clinical claim | <p>The submission described nivolumab as superior in terms of comparative efficacy and as favourable in terms of comparative safety to everolimus.</p> <p>PBAC Comment: The PBAC accepted that, nivolumab statistically significantly increased overall survival compared to everolimus although the early stopping of the trial may have over-estimated the extent of benefit. The claim of favourable safety was not adequately supported by the data provided (7.6, 7.7, 7.8).</p> | No new clinical claim. | <p>Nivolumab demonstrated a clear OS benefit over everolimus. RECIST-defined PFS data suggest a benefit for nivolumab over everolimus, although this was not statistically significant. The post-hoc analysis of clinical PFS</p> <p>[REDACTED]</p> <p>The resubmission maintained the view that the clinical trial data supported a claim of favourable safety for nivolumab over everolimus.</p> | No new clinical claim. |
| Economic evaluation | <p>Cost-utility model with cost/QALY \$45,000/QALY - \$75,000/QALY.</p> <p>PBAC Comment: Unacceptably high and uncertain ICER at the requested effective price (7.1). The PBAC proposed a respecified base case to be adopted in a resubmission with a back calculated effective price of nivolumab to achieve an ICER not greater than \$45,000/QALY gained -</p> | <p>Cost-utility model with cost/QALY \$45,000/QALY - \$75,000/QALY.</p> <p>Re-specification of the base case undertaken to reduce the modelled time horizon to 5 years, treatment costs to the per cycle approach, and reduced cost of nivolumab which was capped at [REDACTED] costed infusions.</p> <p>PBAC comment: Unfavourable and uncertain</p> | <p>Cost-utility model with cost/QALY \$45,000/QALY - \$75,000/QALY.</p> <p>Further re-specification of the base case undertaken with changes including a modelled time horizon of 8 years, costs of nivolumab capped at [REDACTED] infusions and treatment costs for everolimus based on</p> | <p>Cost-utility model with cost/QALY \$45,000/QALY - \$75,000/QALY.</p> <p>Two amended scenarios were presented based on an 8-year time horizon (sponsor preferred) and 5-year horizon (PBAC preferred). Progression states for all arms defined by RECIST-defined PFS rather than</p> |

Public Summary Document – March 2017 PBAC Meeting

| | July 2016 major submission | November 2016 minor resubmission | March 2017 major resubmission | March 2017 resubmission-addendum |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | \$75,000/QALY gained(7.10). | cost-effectiveness (7.1). The sponsor had complied with some, but not all, of the respecified base case as proposed by the PBAC (7.6). | RECIST-defined PFS rather than clinical PFS. | clinical PFS, and QALY estimates and costs adjusted accordingly. Prices of nivolumab vials were increased (from November resubmission) with no proposed cap on treatment duration. |
| Number of patients | Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5. PBAC Comment: “The PBAC advised that the assumed uptake rate ...for nivolumab was implausibly high 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 ... in order to support a Risk Sharing Arrangement (7.12).” | Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5. PBAC Comment: “The PBAC noted that the resubmission reduced the estimated uptake of second-line therapy in RCC The PBAC considered that this was still an overestimation of the expected uptake of nivolumab based on current PBS data on uptake of second-line therapy after progression from a TKI” (7.10). | Less than 10,000 in Year 1 increasing to less than 10,000in Year 5. | Unchanged March 2017 financial addendum Unchanged |
| Estimated net cost to PBS | \$10 - \$20 million in Year 1 increasing to \$20 - \$30 million in Year 5 for a total of \$60 - \$100 million over the first 5 years of listing. PBAC Comment: “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” (7.12). | \$10 - \$20 million in Year 1 increasing to \$10 - \$20 million in Year 5 for a total of \$60 - \$100 million over the first 5 years of listing. PBAC Comment: “The PBAC indicated that the financial estimates remained unreliably high due to overestimation of the duration of therapy for replacement therapies acting as cost off-sets, the use of duration of therapy for nivolumab from the unreliable economic model, overestimated uptake of nivolumab in second-line therapy, and reliance on published rather than effective prices of everolimus, axitinib and sorafenib” (7.11). | \$20 - \$30 million in Year 1 increasing to \$20 - \$30 million in Year 5 for a total of more than \$100 million over the first 5 years of listing. | Unchanged March 2017 financial addendum \$20 - \$30 million in Year 1 increasing to \$20 - \$30 million in Year 5 for a total of more than \$100 million over the first 5 years of listing. (5 year, “PBAC amended base case”), and \$20 - \$30 million in Year 1 increasing to \$20 - \$30 million in Year 5 for a total of more than \$100 million over the first 5 years of listing (8 year “sponsor amended, base case”). |
| PBAC decision | Reject. “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) | Reject. “The PBAC did not recommend the listing of nivolumab for the treatment of advanced or metastatic clear cell variant renal cell carcinoma (RCC) on grounds of unfavourable and | | |

Public Summary Document – March 2017 PBAC Meeting

| | July 2016 major submission | November 2016 minor resubmission | March 2017 major resubmission | March 2017 resubmission-addendum |
|--|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|----------------------------------|
| | based on an unacceptably high and uncertain incremental cost-effectiveness ratio (ICER) at the requested effective price" (7.1). | uncertain cost-effectiveness. The PBAC considered that the benefit of treatment with nivolumab was uncertain and likely overestimated and that the proposed risk sharing arrangement would not address this uncertainty" (7.1). | | |

Source: Compiled during the evaluation

Abbreviations: PBS, Pharmaceutical Benefits Scheme; RCC, Renal Cell Carcinoma; ESC, Economics Sub-Committee; PFS, Progression-Free Survival; WHO, World Health Organisation; PO, oral; R, Randomised; OL, Open Label; MC, Multi-Center; KM, Kaplan-Meier; OS, Overall Survival; NR, Not Reported; HR, Hazard Ratio; AE, Adverse Event; QALY, Quality Adjusted Life Year; ICER, Incremental Cost Effectiveness Ratio.

3.8 Outstanding matters of concern to the PBAC, and how they are addressed by the resubmission and resubmission-addendum, are summarised in Table 2 below.

Table 2: Outstanding matters of concern to the PBAC

| Matters of concern | How the re-submission addresses it |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Requested PBS listing | |
| PBS-listing of nivolumab should be restricted to Stage IV disease, consistent with the first- and second-line agents currently listed for the treatment of RCC. PBS restriction would be limited to patients with a WHO performance score of 0 to 2. 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. [7.2 and 7.5, July 2016 ratified minutes] | Initiation and continuation criteria were proposed, including restricting access to patients with Stage IV disease and with a WHO performance status of 0 to 2. The requested restriction did not include a criterion that eligibility for treatment would be based on standard PFS. The continuation criteria proposed included a requirement that patients must have stable or responding disease, and the resubmission strongly emphasised that the implementation of a RECIST-based stopping rule for nivolumab would "not be appropriate under any circumstance", given this would represent a significant departure from the accepted approach to the utilisation of nivolumab. |
| Clinical effectiveness | |
| The post-hoc use of a "clinical PFS" outcome for economic modelling was not validated, nor necessarily representative of use in Australian practice. | In the key trial supporting the submission, 46% of nivolumab and 48% of everolimus patients had continued therapy beyond RECIST-defined progression. The resubmission used RECIST-defined progression to model treatment duration for everolimus, but outcomes for both arms and costs for nivolumab were based on clinical PFS. In the resubmission-addendum, progression health states were modelled on RECIST-defined PFS as were costs for both arms. |
| According to the primary analysis of the key trial, nivolumab statistically significantly increased overall survival compared to everolimus [7.6, July 2016 ratified minutes]. The early stopping of the key trial after the planned interim analysis met the pre-specified early stopping rule 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. [7.7, July 2016 ratified minutes] | Presentation of updated results from the 11 May 2016 database lock showing ██████████% of participants randomised to everolimus crossing over to nivolumab therapy. |

Public Summary Document – March 2017 PBAC Meeting

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>The PBAC noted the updated data on OS [REDACTED] [REDACTED], however considered that the degree of benefit in a PBS population was still uncertain as the trial contained patients whose nivolumab treatment continued after disease progression. [7.3, November 2016 ratified minutes]</p> | |
| <p>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 fewer 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. [7.8, July 2016 ratified minutes]</p> | <p>The resubmission maintained the view that the clinical trial data supported a claim of favourable safety for nivolumab over everolimus, and recognised that the PBAC had not agreed with this claim at the July 2016 meeting based on the evidence presented. It was stated that such disagreement was inconsequential as the economic model had not valued a safety advantage.</p> |
| <p>Economic evaluation</p> | |
| <p>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 economic modelling. [7.5, July 2016 ratified minutes]</p> | <p>The resubmission used RECIST-defined progression to model treatment duration for everolimus, but outcomes for both arms and costs for nivolumab were based on clinical PFS. In the resubmission-addendum progression health states were modelled on RECIST-defined PFS as were costs for both arms.</p> |
| <p>The July 2016 PBAC meeting proposed the following respecified base case for the model:</p> <ul style="list-style-type: none"> • [REDACTED] infusions of nivolumab reflecting time to progression in the key trial and costed according to the per cycle approach in the model. • The mean duration of use of everolimus and subsequent TKIs as observed in the PBS costed according to the per cycle approach in the model. • 5-year time horizon for the model. • No other changes to the method of generating the QALY estimates by the model. • Use of 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/QALY - \$75,000/QALY. <p>[7.10, July 2016 ratified minutes]</p> | <p>The March 2017 resubmission applied the following respecified base case:</p> <ul style="list-style-type: none"> • [REDACTED] infusions (capped after 5 years), costed according to the per cycle approach. • Mean duration of everolimus use ([REDACTED] months) was calculated using a separate tunnel state based on RECIST-defined PFS, and was costed according to the per cycle approach. Costs of subsequent TKIs were front-loaded. • An 8 year time horizon (with convergence of treatment benefit between 5 and 8 years) was proposed, with clinical evidence supporting long-term survivorship in RCC presented. • No changes were included to the method of generating QALY estimates. • As effective prices of other drugs are not known to the sponsor, they were not included in the resubmission. • At a cost of \$[REDACTED] per 100 mg vial and maximum duration of costed infusions applied at 60 months, an ICER/QALY of \$45,000/QALY - \$75,000/QALY was derived. |
| <p>The PBAC summarised further its respecification of the base case for the model for any resubmission as follows:</p> <ul style="list-style-type: none"> • 5-year time horizon for the model. • Use of the RECIST-defined PFS criteria, rather than the "clinical PFS" criteria for all treatment arms reflecting time to progression in the key trial in generating the QALY estimates. • Use of the RECIST-defined PFS criteria, rather than the "clinical PFS" criteria reflecting time to progression in the key trial and costed according to the per cycle approach in the model in generating the number of infusions of nivolumab (with any further modification | <p>In the resubmission-addendum the sponsor has further respecified the model as follows:</p> <ul style="list-style-type: none"> • Two scenarios are presented for consideration by the PBAC. These include an 8-year time horizon (sponsor preferred) and a 5-year time horizon (PBAC preferred). Two different (higher) prices were submitted for consideration. • RECIST-defined PFS criteria were used for all treatment arms in defining progression. • Number of infusions of nivolumab costed as per RECIST-defined PFS time to progression and adopting the per-cycle approach. |

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>to reduce the effective price of nivolumab).</p> <ul style="list-style-type: none"> • Use of the RECIST-defined PFS criteria, rather than the “clinical PFS” criteria reflecting time to progression in the key trial and costed according to the per cycle approach in the model generating the mean duration of use of everolimus and subsequent TKIs (to reflect the same basis as the estimate of infusions of nivolumab). • Use of 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/QALY - \$75,000/QALY. <p>[7.9, November 2016 ratified minutes]</p> | <ul style="list-style-type: none"> • Mean duration of everolimus use was calculated based on RECIST-defined PFS, and was costed according to the per cycle approach. Costs of subsequent TKIs front loaded. • As effective prices of other drugs are not known to the sponsor, they are not included in the resubmission-addendum. • At a cost of \$ [REDACTED] per 100 mg vial over an 8-year time horizon or \$ [REDACTED] per 100 mg vial over a 5-year horizon (without a maximum duration) an ICER/QALY of \$45,000/QALY - \$75,000/QALY was maintained. |
| <p>Financial estimates</p> | |
| <p>The PBAC considered the submission’s assumed uptakes of 80% for current second-line therapy and 90% for nivolumab (once listed) to be substantial overestimates given that current PBS data indicated an uptake rate of 16 to 25% for any second line treatment following a TKI. Accordingly, the PBAC recommended that a reduced uptake rate for nivolumab should be identified (and justified) in order to support a risk sharing arrangement.</p> <p>[7.11 and 7.12, July 2016 ratified minutes]</p> | <p>The resubmission and financial addendum reduced the estimated uptake rates of second line treatments following a TKI as follows:</p> <ul style="list-style-type: none"> • 70% (where nivolumab is not PBS listed) • 85% (where nivolumab is listed, and with a market share of 95% for nivolumab). |

Source: Compiled during the evaluation

Abbreviations: PBS, Pharmaceutical Benefits Scheme; RCC, Renal Cell Carcinoma; WHO, World Health Organisation; PFS, Progression-Free Survival; OS, Overall Survival; AE, Adverse Event; TKI, Tyrosine Kinase Inhibitor; QALY, Quality Adjusted Life Year; ICER, Incremental Cost Effectiveness Ratio.

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

4 Clinical place for the proposed therapy

4.1 Renal cell carcinoma (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 resubmission requested that nivolumab be used as second-line treatment for advanced or metastatic clear cell variant RCC following first line treatment with a tyrosine kinase inhibitor (TKI). Nivolumab would be an alternative to everolimus, axitinib and sorafenib. The proposed place in therapy is unchanged from the July 2016 submission. The ratified minutes of the July 2016 PBAC meeting record that the Committee “recognised the clinical need for nivolumab in patients with clear cell renal carcinoma who had failed first-line treatments”. The PBAC reiterated that there remained a clinical need for treatments in patients with clear cell renal carcinoma who had failed first-line treatments.

5 Comparator

- 5.1 As with the July 2016 submission, the resubmission nominated everolimus as the main comparator. This was appropriate.
- 5.2 In the July 2016 submission, axitinib and sorafenib had been nominated as secondary comparators, and indirect comparisons had been presented as secondary evidence. Given that the primary purpose of the March 2017 resubmission was to update the clinical evidence and respecify the economic and financial estimates, no restatements of these indirect comparisons were provided in the resubmission. This was appropriate.

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 (4), health care professionals (4) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with nivolumab including an improvement in disease state, a reduction in tumour bulk and an improvement in quality of life, and supported the inclusion of nivolumab on the PBS as an alternative to other second-line therapies due to perceived increased efficacy and lower toxicity.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the nivolumab submission, on the basis of increased survival benefit and decreased toxicity. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) in this context as being 5 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on a comparison of nivolumab with everolimus.

Clinical trials

- 6.4 The resubmission was based on one head-to-head trial comparing nivolumab to everolimus (n=821). This is the same trial that was presented in the July 2016 submission, but the evidence presented was updated based on the second database lock (11 May 2016), for which there is a minimum follow up of 26.1 months (range 26.1 to 42.6).
- 6.5 Details of the trials presented in the re-submission are provided in Table 3 below.

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

Table 3: Details of trial publications presented in the resubmission

| | Protocol title/ Publication title | Publication citation |
|-----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| CA209025 | | |
| Clinical Study Report | A Randomized, 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). CSR 21 August 2015 | The clinical study report (CSR) was not provided for the updated database cut-off. A full CSR was provided with the July 2016 submission. |
| | Motzer R. et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. | New England Journal of Medicine. 2015; 373 (191): 1803-1813. |
| | Cella, D., et al. "Quality of life in patients with advanced renal cell carcinoma given nivolumab versus everolimus in CheckMate 025: A randomised, open-label, phase 3 trial." | The Lancet Oncology.2016 (17): 994–1003 |
| | Escudier, B. J., et al. "Treatment beyond progression with nivolumab (nivo) in patients (pts) with advanced renal cell carcinoma (aRCC) in the phase III CheckMate 025 study." | Journal of Clinical Oncology 34, 2016 (suppl, abstr 4509) |
| | Motzer, R. J., et al. "Correlation of response with overall survival (OS) for nivolumab vs everolimus in advanced renal cell carcinoma (aRCC): Results from the phase III CheckMate 025 study." | Journal of Clinical Oncology 34, 2016 (suppl, abstr 4552) |
| | Motzer, R. J., et al. "CheckMate 025 phase III trial: Outcomes by key baseline factors and prior therapy for nivolumab (NIVO) versus everolimus (EVE) in advanced renal cell carcinoma (RCC)." | Journal of Clinical Oncology 34, 2016 (suppl, abstr 498) |

Source: Table 6, page 24 of the resubmission.

6.6 The key features of the trial used in the head-to-head comparison of nivolumab and everolimus are summarised in Table 4 below.

Table 4: Key features of the included evidence

| Trial | N | Design | Risk of bias | Patient population | Outcome(s) | Use in modelled evaluation |
|------------------------------------|-----|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Nivolumab versus everolimus | | | | | | |
| CA209025 | 821 | Phase II, R, OL, MC Nivolumab 3 mg/kg Q2W n=410 Everolimus 10 mg po n=411 | Moderate (due to open-label design, and potential for early termination to influence magnitude of treatment effect). | RCC progressed following first line treatment. | OS, PFS (RECIST-defined), EQ-5D, Safety and tolerability | Extrapolated OS data. RECIST-defined PFS in the estimation of everolimus costs*. EQ-5D to estimate utility values. Modelled adverse events. |

Source: Table 7, p27 of the submission.

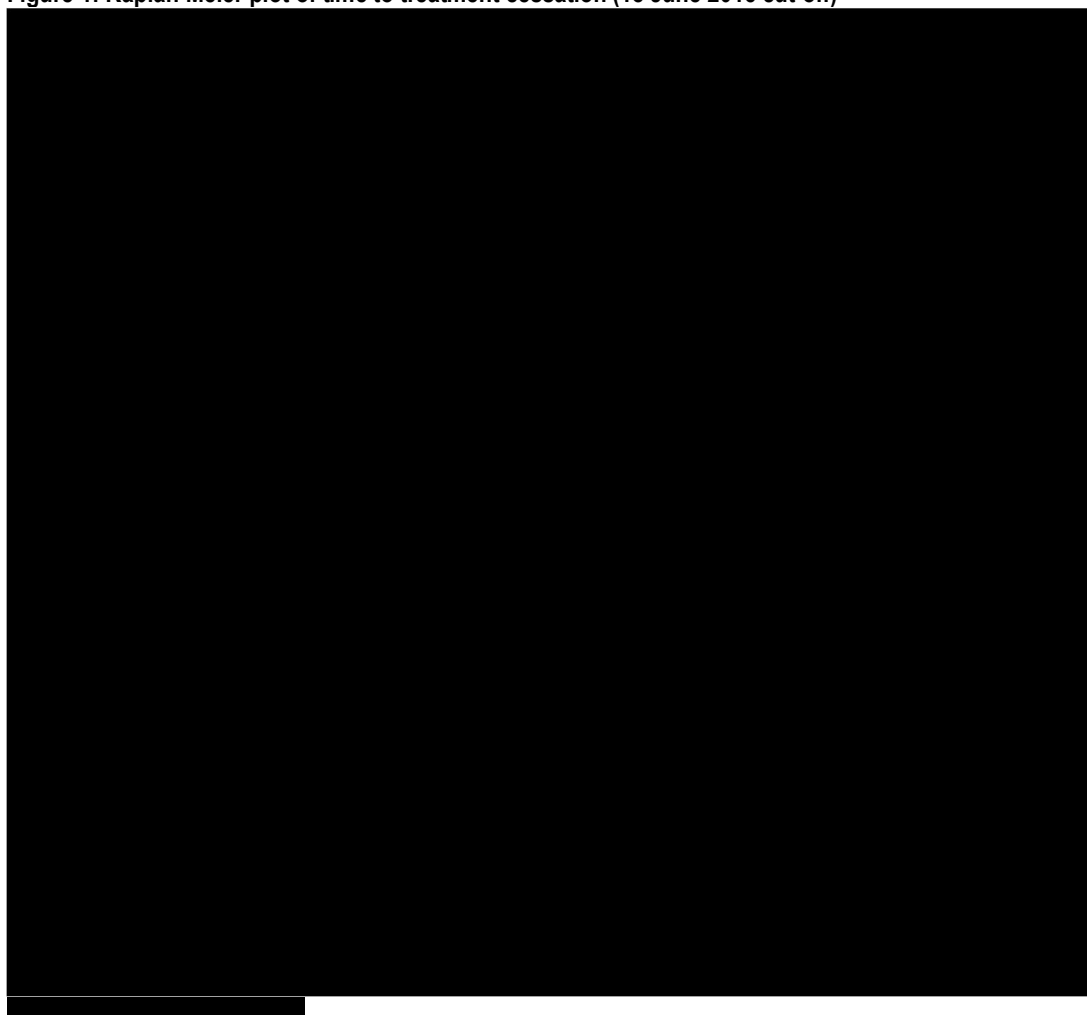
* In the addendum to the resubmission, RECIST-defined PFS was used to model costs and benefits of both treatment arms. Abbreviations: MC, multicentre; po, oral administration; OL, open-label; Q2W, every two weeks; R, randomised.

6.7 An outcome referred to as clinical PFS was defined in the July 2016 submission, developed post-hoc for the submission to the PBAC, and was included in the resubmission. In defining this outcome, the (re)submissions had argued that it would not be unreasonable to assume that the treatment discontinuation time-point in the trial would be representative of when the investigators concluded no further clinical benefit could be derived from either treatment. Therefore, it would be more clinically representative if recorded progression events for these patients were informed by the time from randomisation to discontinuation of treatment, rather than RECIST-defined PFS. This post-hoc outcome was used in the economic model to define the health state of PFS. The PBAC noted that the resubmission addendum used RECIST-defined PFS in the economic model and confirmed that it remained concerned that

clinical-PFS as defined for the purposes of the trial was neither validated nor necessarily reflective of Australian clinical practice.

- 6.8 Section 7.5 of the ratified minutes of the July 2016 PBAC meeting records that the Committee indicated that the post-hoc use of clinical PFS for economic modelling was not validated, nor was its interpretation necessarily representative of use in Australian practice. 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. This was reaffirmed in the November 2016 meeting minutes where the PBAC determined that the use of the RECIST-defined PFS criteria, rather than the “clinical PFS” criteria, should be used for all treatment arms reflecting time to progression in the key trial in generating the QALY estimates and in generating the costs of nivolumab and everolimus. Within study CA209025, patients with RECIST-defined progression events were permitted to continue therapy with either nivolumab or everolimus if there was investigator-defined clinical benefit. This resulted in 46% of nivolumab patients and 48% of everolimus patients continuing therapy beyond RECIST-defined progression. The mean number of nivolumab infusions received was [REDACTED] (a mean dose was not reported for everolimus). The mean duration of everolimus treatment was [REDACTED] months. The mean duration of nivolumab treatment was not reported (median 5.54 months; see the KM data for time on treatment in Figure 1).

Figure 1: Kaplan-Meier plot of time to treatment cessation (18 June 2015 cut-off)



Comparative effectiveness

- 6.9 The key results from the clinical trial are summarised in Tables 5 to 7 and in Figures 2 to 4 below; the results presented in the July 2016 submission for the original database cut-off of 18 June 2015 are compared alongside the updated analysis from the 11 May 2016 cut-off in each of the tables.
- 6.10 A summary of OS is provided in Table 5, and the KM plot for OS based on the May 2016 cut-off is at Figure 2. At 26.1 months follow-up (second database cut-off), treatment for OS [REDACTED]. The degree of benefit for OS may be overstated relative to what might occur with treatment via the PBS given that a significant proportion of patients in both treatment groups continued treatment beyond progression. At the May 2016 cut-off, [REDACTED]% of patients in the nivolumab arm and [REDACTED]% of patients in the everolimus arm continued to be treated beyond progression. An estimate of OS benefit in this subgroup (n = 459) was not presented in the resubmission or resubmission-addendum. In the July 2016 submission, an exploratory subgroup analyses for patients that had been treated beyond RECIST-defined progression was presented and demonstrated [REDACTED].

Table 5: Study CA209025 summary of results for overall survival

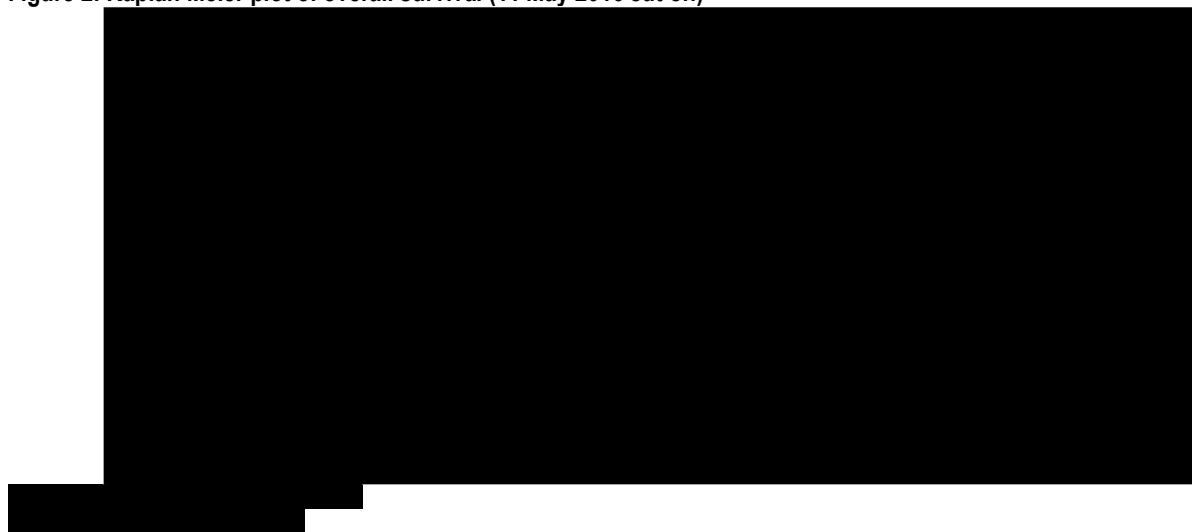
| | | 18 June 2015 cut-off | | 11 May 2016 cut-off | |
|------------------------------|----------|-------------------------------------|----------------------|---------------------|---------------------|
| | | Nivolumab N=410 | Everolimus N=411 | Nivolumab N=410 | Everolimus N=411 |
| Events (deaths), n (%) | | 183 (44.6) | 215 (52.3) | | |
| Median months (95% CI) | | 25.00 (21.75, NR) | 19.55 (17.64, 23.06) | | |
| Survival rate, % (95% CI) | 6 month | 89.2 (85.7, 91.8) | 81.2 (77.0, 84.7) | | |
| | 12 month | 76.0 (71.5, 79.9) | 66.7 (61.8, 71.0) | | |
| | 18 month | NR | NR | | |
| | 24 month | NR | NR | | |
| HR (^CI) | | 0.73 (0.57, 0.93), p-value = 0.0018 | | | |

Source: Table 9, p 34 of resubmission.

^aHR calculated with 98.52% CI for 18 June 2015 cut-off and % CI for 11 May 2016 cut-off.

Abbreviations: CI, Confidence Intervals; NR, Not Reported; HR, Hazard Ratio.

Figure 2: Kaplan-Meier plot of overall survival (11 May 2016 cut-off)



6.11 A summary of results for RECIST-defined PFS in study CA09025 for both database locks is provided in Table 6. The plot of the KM estimate of PFS from the second database lock is provided in Figure 4.

Table 6: Study CA209025 summary of results for RECIST-defined progression-free survival

| | | 18 June 2015 cut-off | | 11 May 2016 cut-off | |
|-------------------------|-----------|-------------------------------------|---------------------|---------------------|---------------------|
| | | Nivolumab N=410 | Everolimus N=411 | Nivolumab N=410 | Everolimus N=411 |
| Median months (95% CI) | | 4.60 (3.71, 5.39) | 4.44 (3.71, 5.52) | | |
| PFS rate, % (95% CI) | 6 month* | 39 (35, 44) | 39 (33, 44) | | |
| | 12 month* | 23 (19, 27) | 19 (15, 23) | | |
| | 18 month | NR | NR | | |
| | 24 month | NR | NR | | |
| HR (95% CI) | | 0.88 (0.75, 1.03); p-value = 0.1135 | | | |

Source: Table 10, p 36 of resubmission.

* PFS rates at 6 and 12 months in the 18 June 2015 data have been converted in the commentary to percentage figures for comparability with the 11 May 2016 data. These rates are incorrectly referred to as "survival rates" in the resubmission.

Abbreviations: CI, confidence interval. HR: Hazard ratio. NR, Not Reported.

6.12



6.13 A summary of results for clinical PFS in study CA09025 for both database locks is provided in Table 7, with the plot of the KM estimates from the second database lock in Figure 3.

Table 7: Study CA209025 summary of results for clinical PFS

| | 18 June 2015 cut-off | | 11 May 2016 cut-off | |
|------------------------|----------------------|---------------------|---------------------|---------------------|
| | Nivolumab N=410 | Everolimus N=411 | Nivolumab N=410 | Everolimus N=411 |
| Median months (95% CI) | | | | |
| HR (95% CI) | | | | |

Source: Table 11, p 38 of resubmission.
Abbreviations: CI, confidence interval. HR: Hazard ratio.

6.14 The post-hoc analysis indicated



Figure 3: Kaplan-Meier clinical PFS plot (11 May 2016 cut-off)



Comparative harms

6.15 The resubmission indicated that the safety profile of nivolumab with longer follow-up remained consistent with the results from the initial analysis. A summary of overall safety from the 11 May 2016 cut-off is presented in Table 8 below.

Table 8: Summary of overall clinical safety (11 May 2016 cut-off)

| n (%) | | Nivolumab (n=406) | Everolimus (n=397) | RR (95% CI) | RD (95% CI) |
|----------------|-----------|----------------------|-----------------------|-------------|-------------|
| All cause AEs | Any grade | | | | |
| | Grade 3-4 | | | | |
| All cause SAEs | Any grade | | | | |

Public Summary Document – March 2017 PBAC Meeting

| | | | | | | | | | |
|---------------------------------------------|-----------|--|--|--|--|--|--|--|--|
| | Grade 3-4 | | | | | | | | |
| All cause AEs leading to DC | Any grade | | | | | | | | |
| | Grade 3-4 | | | | | | | | |
| All cause death due to AE | Grade 5 | | | | | | | | |
| Drug related AEs | Any grade | | | | | | | | |
| | Grade 3-4 | | | | | | | | |
| Drug-related SAEs | Any grade | | | | | | | | |
| | Grade 3-4 | | | | | | | | |
| Drug related AEs leading to discontinuation | Any grade | | | | | | | | |
| | Grade 3-4 | | | | | | | | |
| Drug-related death due to AE | Grade 5 | | | | | | | | |

Source: Table 13, p 41 of resubmission.

Abbreviations: AE, adverse event; DC, discontinuation; RR, relative risk; RD, risk difference; SAE, serious adverse event.

6.16 These data indicated [redacted] between nivolumab and everolimus across all cause adverse events (AEs), all cause serious adverse events (SAEs) or all cause AEs leading to treatment discontinuation. Drug-related AEs were reported [redacted] in the nivolumab group compared to the everolimus group, with a [redacted] nivolumab observed for any grade drug-related AEs [redacted] and Grade 3-4 drug-related AEs [redacted].

6.17 [redacted].

6.18 Immune-related adverse events (IMAE) Grade 3 or 4 occurred [redacted]. Costs for the treatment of these events (colitis, hepatitis, pneumonitis and nephritis) were included in the economic model.

Benefits/harms

6.19 A summary of the comparative benefits and harms for nivolumab versus everolimus is presented in Table 9 below.

Table 9: Summary of comparative benefits and harms for nivolumab and everolimus from CA209025 (data from the 11 May 2016 database cut-off)

| Benefits | | | | | |
|---------------------------------|-----------|------------|-------------------------|------------|--------------|
| | Nivolumab | Everolimus | Absolute difference | | HR (95% CI) |
| Overall survival | | | | | |
| Deaths, n (%) | | | | | |
| OS median months (95% CI) | | | | | |
| RECIST-defined PFS | | | | | |
| Progressed, n (%) | | | | | |
| PFS median months (95% CI) | | | | | |
| Harms | | | | | |
| | Nivolumab | Everolimus | Event rate/100 patients | | RD% (95% CI) |
| | | | Nivolumab | Everolimus | |
| Any drug-related AE (graded ≥3) | | | | | |
| Drug-related SAE (graded ≥3) | | | | | |

Source: compiled during the evaluation.

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

6.20 On the basis of the updated evidence presented in the resubmission, for every 100 patients treated with nivolumab in comparison to everolimus:

- Approximately [redacted] patients would have Grade 3 or 4 drug-related AEs over a mean duration of follow-up of [redacted] months.
- Approximately [redacted] patient would have Grade 3 or 4 drug-related serious adverse event over a mean duration of follow-up of [redacted] months.

From the evidence it was also estimated that there would be a difference in median OS of approximately [redacted] months in a group of patients treated with nivolumab compared to everolimus. [redacted] median RECIST-defined PFS [redacted].

Clinical claim

6.21 The resubmission made the claim that nivolumab demonstrated a clear OS benefit over everolimus. The existence of a benefit is adequately supported by the evidence presented; the extent of that benefit is uncertain due to early termination of the randomised comparison within the trial and patients continuing treatment beyond progression.

6.22 The resubmission claimed that RECIST-defined PFS data suggest a benefit for nivolumab over everolimus, although this was not statistically significant. The post-hoc analysis of clinical PFS indicated [redacted]. Previously the PBAC has considered that the RECIST-defined PFS was a more reliable indicator of the actual PFS for nivolumab.

6.23 The resubmission maintained the view that the clinical trial data supported a claim of favourable safety for nivolumab over everolimus, and recognised that the PBAC had

not agreed with this claim at the July 2016 meeting based on the evidence presented. The ratified minutes of the July 2016 PBAC meeting record that the Committee considered that the difficulty in determining causality of AEs in the nivolumab arm of the key trial did not support the claim of fewer drug-related AEs; the clinical claim of ‘favourable’ safety for nivolumab over everolimus was not adequately supported by the data supplied. The minutes of the November 2016 meeting record that the PBAC “was satisfied that nivolumab provides, for some patients no increase in toxicity”. In the resubmission, it was stated that disagreement over the safety claim was inconsequential as the economic model had not valued a safety advantage. Given differences in the occurrence of immune related events and SAEs, on balance the evidence suggests that safety for nivolumab is no worse than that with everolimus.

- 6.24 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.25 The PBAC restated that it was satisfied that nivolumab provides, for some patients no increase in toxicity.

Economic analysis

- 6.26 The resubmission presented a modelled cost-utility analysis using direct evidence from study CA209025. The model structure and rationale are summarised in Table 10 below. The July 2016 submission and the November 2016 minor resubmission also performed a modelled cost-utility analysis.

Table 10: Summary of model structure and rationale

| Component | Summary |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Time horizon | 8 years in the model base case (clinical data are available for a median follow-up of 2.8 years from the latest database cut-off). 5 years in the “PBAC amended base case” in the resubmission addendum. |
| Outcomes | LYs and QALYs |
| Methods used to generate results | Markov model with three mutually exclusive health states of clinical progression-free, clinical disease progression and death (absorbing) and one RECIST-defined progression-free tunnel state. Clinical PFS, RECIST-defined PFS and OS were extrapolated using log-logistic functions. |
| Cycle length | Two weeks. Half cycle correction applied. |
| Transition probabilities | Transition probabilities for the first 14 (for clinical PFS and OS) and 26 (for RECIST-defined PFS) months were derived from the KM curves from Study CA209025, using the first database cut-off for clinical PFS and OS and the second database cut-off for RECIST-defined PFS. Transition probabilities beyond this period were obtained from log-logistic extrapolations. |

Source: compiled during the evaluation

Abbreviations: LYs, life years; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life years.

- 6.27 The resubmission-addendum provided a re-specified base case economic model. This was following review of the minutes of the November 2016 PBAC meeting in which the Committee had explicitly specified that RECIST-defined PFS rather than clinical PFS be used in all treatment arms to reflect the time to progression in generating QALY estimates, and that RECIST-defined PFS criteria rather than clinical PFS be used per cycle in generating the number of nivolumab infusions and their costs, and the mean duration of use of everolimus and subsequent TKIs. Although the overall economic model structure was not changed in the addendum, it contained three scenarios with varying input parameters:

- March 2017 major resubmission base case – parameters originally included in the resubmission.
- Resubmission-addendum (“sponsor amended base case”) – utilised an 8-year time horizon for the economic model, with log-logistic extrapolation of treatment effects from the trial to a 5-year time horizon and subsequent linear convergence to 8-years. It removed caps previously applied to the number of nivolumab treatments, assumed treatment duration for nivolumab and everolimus is based on RECIST-defined PFS, and proposed a higher price for the 100 mg vial.
- Resubmission-addendum (“PBAC amended base case”) – utilised a 5-year time horizon. It removed caps previously applied to the number of nivolumab treatments, assumed treatment duration for nivolumab and everolimus is based on RECIST-defined PFS, and proposed a higher price (but lower than in the “sponsor amended base case”) for the 100 mg vial.

6.28 The input parameters of each of the three scenarios are shown in Table 11 below.

Table 11: Key variables applied in economic model scenarios

| | Key variables | | | | |
|-----------------------------|---------------|-----------------------|---------------------|-------------------------------------------------|-------------------------------------------------|
| | Time horizon | Duration of therapy | | | Nivolumab vial price (100 mg) |
| | | Nivolumab (infusions) | Everolimus (months) | Subsequent therapies | |
| March 2017 resubmission | 8 years | █ (PC – cPF) | █ (PC – rPF) | Linked to everolimus mean DoT estimated from PC | \$█ + Max duration of NIVO (█ costed infusions) |
| “Sponsor amended base case” | 8 years | █ (PC – rPF) | █ (PC – rPF) | Linked to everolimus mean DoT estimated from PC | \$█ |
| “PBAC amended base case” | 5 years | █ (PC – rPF) | █ (PC – rPF) | Linked to everolimus mean DoT estimated from PC | \$█ |

Source: Page 5 of resubmission addendum.

Abbreviations: cPF, clinical progression-free; DoT, duration of therapy; FL, front loaded model; ICER, incremental cost effectiveness ratio; LY, life year; PC, per cycle model; QALY, quality adjusted life year; rPF, RECIST-defined progression-free.

6.29 In extrapolating the observed KM data for PFS to estimate treatment duration, the model had appended the extrapolated log-logistic data from month 26 onwards directly onto the KM data at the end of month 25. This resulted in a sharp drop in the proportion of nivolumab patients assumed to be progression-free, and thus who remained on nivolumab. This favoured nivolumab in the assessment of costs. An adjustment was made that applied the extrapolated proportions of individuals who were progression-free at month 26 to the observed proportions progression-free at month 25, and the extrapolated data thereafter. The impact on the resulting Markov traces is shown in Figure 5 compared with the observed KM at the late data cut from the clinical trial in Figure 4.

Figure 4: Kaplan-Meier plot of RECIST-defined progression-free survival plot (11 May 2016 cut-off)



Figure 5: Kaplan-Meier curves and Markov survival traces for overall survival and RECIST-defined progression-free survival – adjusted for extrapolation



6.30 The ESC considered that the extrapolation method used by the sponsor in applying the overall extrapolation PFS curve to the end of the observed Kaplan-Meier curve was problematic. This resulted in a sharp drop in the curve at the point where the two

curves join which is not biologically plausible and had a major impact on the resultant modelled results with the greatest effect being to reduce the estimated nivolumab costs. The ESC noted that this sharp drop was apparent in both data cut-off curves. The ESC noted that the PSCR claimed that the extrapolation is a summary of the entire curve, and hence the drop is reasonable.

6.31 The ESC noted the amended extrapolation compiled during the evaluation of the resubmission-addendum where the observed Kaplan-Meier curve was used up to the end of the observed data and the best fit extrapolation was used to continue the Kaplan-Meier curve to inform the Markov model. The ICER was sensitive to this method of extrapolation as can be seen in Table 13.

6.32 The PBAC accepted that the “PBAC amended base case” adopted its respecifications from its November 2016 meeting. The PBAC noted that the Pre-PBAC response considered that the adjusted extrapolation method considered by ESC was not appropriate and considered that the method used to extrapolate costs and outcomes past the data cut-off in the resubmission addendum was the most appropriate. Overall, although the PBAC considered that the method of extrapolation as used by the sponsor in the resubmission did introduce some uncertainties, these were insufficient to require a further respecification.

6.33 The key drivers of the economic model are provided in Table 12 below.

Table 12: Key drivers of the model

| Description | Method/Value | Use | Impact on ICER |
|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| Hazard ratio for overall survival | 0.73 in all base cases, based on CA209025. | March 2017 resubmission. Resubmission-addendum. | High, lower hazard ratio favours nivolumab. |
| Time horizon | 8 years; trial follow-up was median 2.8 years. | March 2017 resubmission. Resubmission-addendum; “sponsor amended base case”. | High, longer time horizon favours nivolumab. |
| PFS assumptions | Clinical PFS instead of RECIST-defined PFS for nivolumab treatment duration in the resubmission. | March 2017 resubmission. | High, increased nivolumab costs favours everolimus. |
| Patient weight | Based on named patient program instead of trial CA209025. | March 2017 resubmission. Resubmission-addendum; “sponsor amended base case”. Resubmission-addendum; “PBAC amended base case”. | High, reduced patient weight favours nivolumab. |
| Prices for the comparator drug and third-line therapies | Published prices instead of effective prices. | March 2017 resubmission. Resubmission-addendum; “sponsor amended base case”. Resubmission-addendum; “PBAC amended base case”. | High, favours nivolumab. |
| Nivolumab price | Increased from \$ [redacted] in the resubmission to \$ [redacted] (“sponsor amended base case”) and \$ [redacted] (“PBAC amended base case”) in the resubmission-addendum. | March 2017 resubmission-addendum; “sponsor amended base case”. Resubmission-addendum; “PBAC amended base case”. | High, favours everolimus. |

Source: compiled during the evaluation

Abbreviations: PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours.

6.34 The results of the economic evaluations in the resubmission and resubmission-addendum are provided in Table 13.

Table 13: Results of the economic evaluation

| July 2016 submission | | | |
|-------------------------------------------------------------------------------------------------------------|---------------|---------------|----------------------------|
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |
| November 2016 minor resubmission | | | |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |
| March 2017 major resubmission (cost per 100mg vial = \$ [REDACTED]) | | | |
| Component | Nivolumab | Everolimus | Increment |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs | 2.12 | 1.72 | 0.41 |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |
| March 2017 resubmission-addendum (“sponsor amended base case”) (cost per 100mg vial = \$ [REDACTED]) | | | |
| Component | Nivolumab | Everolimus | Increment |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs | 2.10 | 1.71 | 0.39 |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] |
| Adjusted for extrapolation | | | \$ [REDACTED] |
| March 2017 resubmission-addendum (“PBAC amended base case”) (cost per 100mg vial = \$ [REDACTED]) | | | |
| Component | Nivolumab | Everolimus | Increment |
| Costs | \$ [REDACTED] | \$ [REDACTED] | \$ [REDACTED] |
| QALYs | 1.84 | 1.50 | 0.33 |
| Incremental cost/extra QALY gained | | | \$ [REDACTED] ² |
| Adjusted for extrapolation | | | \$ [REDACTED] |

Source: Table 39, p 93 of the March 2017 resubmission.

Abbreviations: QALYs, quality-adjusted life years.

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

- 6.35 Sensitivity analyses in the resubmission showed that the ICER was most sensitive to reducing the time horizon from 8 to 6 years, increasing the ICER from the resubmission’s base case of \$45,000/QALY gained - \$75,000/QALY gained to \$45,000/QALY gained - \$75,000/QALY gained. Further reducing the time horizon to 5 years, consistent with the PBAC request, further increased the ICER to \$75,000/QALY - \$105,000/QALY. In the resubmission-addendum, a reduced time horizon (“PBAC amended base case”) was combined with a reduced nivolumab price (relative to the “sponsor amended base case”, but higher than that in the resubmission) to maintain the ICER. The ESC noted that the issue of selection of an appropriate time horizon was addressed in the resubmission-addendum by supplying economic analyses using both an 8 year (“sponsor amended base case”) and 5 year (“PBAC amended base case”) time horizon and considered that the 5 year time horizon as specified previously by the PBAC was the most appropriate for consideration. The PBAC reaffirmed that the 5 year time horizon in the “PBAC amended base case” in the resubmission addendum was appropriate.
- 6.36 Sensitivity analyses conducted during the evaluation show that the model results are highly sensitive to variations in the extent of clinical benefit as captured by the HR. Use of the upper and lower bounds of the 95% CI resulted in ICERs for the resubmission’s base case of \$45,000/QALY - \$75,000/QALY varying to \$100,000/QALY - \$200,000/QALY and \$45,000/QALY - \$75,000/QALY, respectively. The same sensitivity analyses in the resubmission-addendum resulted in increased ICERs at both the upper and lower bounds, over the resubmission base case in both the “PBAC amended base case” and the “sponsor amended base case”.

- 6.37 Nivolumab treatment costs were estimated using patient weight, which was based on mean patient weight in the named patient program (NPP). If the higher mean weight observed in the clinical study was adopted in the adjusted resubmission-addendum's base cases, the ICER would increase from \$45,000/QALY - \$75,000/QALY to approximately \$75,000/QALY - \$105,000/QALY in the "PBAC amended base case" and higher in the "sponsor amended base case".
- 6.38 Prices for the comparator drug and third line treatments (everolimus, axitinib and sorafenib) were based on published PBS list prices. Due to special pricing arrangements, the effective prices for these drugs are substantially lower. The impact of using the effective prices instead of the PBS list prices was presented as Committee-in-Confidence. The sponsor noted that ultimately the nivolumab price "will need to be adjusted post PBAC approval taking into account the effective prices of everolimus, axitinib and sorafenib". The ESC noted that the PSCR stated that price negotiation would occur after a positive PBAC recommendation. The PBAC noted the sponsors' preparedness to adjust the nivolumab prices following a PBAC recommendation to take into account the effective prices of everolimus, axitinib and sorafenib and agreed that this reduction would need to be reflected in the final pricing agreement between the Department and the sponsor.
- 6.39 Using RECIST-defined PFS instead of clinical PFS to determine the outcomes and costs in both arms substantially reduced the ICER in the resubmission from \$45,000/QALY - \$75,000/QALY (base case from the March 2017 resubmission) to \$45,000/QALY - \$75,000/QALY. This decrease in the ICER reflected a decrease in costs and an earlier progression to the DP health state, reducing the modelled QALY gains. The corresponding reduction in nivolumab drug costs was proportionally greater than the reduction in QALYs gained. OS was not adjusted even though a large number of patients in both arms continued with treatment beyond RECIST-defined progression. The effect of assuming shorter treatment duration on OS was unknown. If the nivolumab price from the resubmission was maintained in the resubmission-addendum (not adjusted for extrapolation issues), the resulting ICER would have been \$45,000/QALY gained - \$75,000/QALY gained in the "sponsor amended base case". This was more than the \$15,000/QALY gained - \$45,000/QALY gained in the RECIST-defined PFS sensitivity analysis in the resubmission. The difference was due to removing the treatment cap in the resubmission-addendum. The ESC observed that modelling using RECIST-defined PFS reduced the ICER in part due to the assumption that the incremental benefits can be based on what was observed in the clinical trial whilst reducing the incremental costs by reducing the duration of treatment from what was observed in the clinical trial. The PBAC acknowledged that using RECIST-defined PFS to limit costs without adjusting the survival outcome introduced some uncertainty into the validity of the ICER however, the committee reiterated that the use of RECIST-defined PFS be used to inform the costs of the model was appropriate.
- 6.40 In the resubmission economic model, the average number of nivolumab infusions per patient was modelled at [REDACTED] (capped at [REDACTED] in the resubmission's proposed risk sharing arrangement) when using an 8-year time horizon and patients being treated until clinical PFS. Based on the use of RECIST-defined PFS as the basis for treatment duration, the average number of nivolumab infusions per patient was modelled at [REDACTED] when using an 8-year time horizon ("sponsor amended base

case”) and [REDACTED] when using a 5-year time horizon (“PBAC amended base case”). At the time of database lock on 11 May 2016, [REDACTED]% of patients in the nivolumab treatment arm had discontinued therapy in the treatment period, and the mean number of nivolumab doses received was [REDACTED] (lower than the average number of infusions assumed in the economic analysis). Based on the adjusted PFS curve, [REDACTED]% of patients were progression-free - and thus remained on treatment with nivolumab – in the model at 30 months. This was consistent with the data on treatment duration presented in Figure 1.

- 6.41 A sensitivity analysis was performed using the resubmission-addendum model to determine what the ICER would be in case patients were treated up to clinical PFS consistent with study CA209025 (instead of RECIST-defined PFS consistent with the PBAC respecifications) while maintaining the resubmission-addendum drug prices. This increased the ICER from \$75,000/QALY - \$105,000/QALY to \$105,000/QALY - \$200,000/QALY in the “PBAC amended base case” and from \$75,000/QALY - \$105,000/QALY to \$105,000/QALY - \$200,000/QALY in the “sponsor amended base case”. Using treatment cessation (from digitised CSR data) duration instead of RECIST-defined PFS to determine drug use increased the ICER (using the adjusted extrapolations) from \$75,000/QALY - \$105,000/QALY to \$105,000/QALY to \$200,000/QALY for the “PBAC amended base case” and from \$75,000/QALY - \$105,000/QALY to \$105,000/QALY - \$200,000/QALY for the “sponsor amended base case”. The PBAC considered that patients should not be treated beyond progression except in cases where pseudo-progression was suspected and recommended that the calculation of the proposed risk sharing arrangement caps reflect the [REDACTED] nivolumab infusions per patient as per the “PBAC amended base case”.
- 6.42 The nivolumab 100 mg vial price in the resubmission was a minimum of \$ [REDACTED]. The nivolumab 100 mg vial price in the resubmission-addendum was \$ [REDACTED] in the “sponsor amended base case” and \$ [REDACTED] in the “PBAC amended base case”, “to achieve the target ICER” of \$45,000/QALY gained - \$75,000/QALY gained. This assumed that the PBAC had intended that ICER as a target rather than as a maximum, while the July 2016 PBAC meeting minutes specify the use of a “back-calculated effective price of nivolumab to give the submission’s base case ICER/QALY of no greater than \$45,000/QALY - \$75,000/QALY”. If the nivolumab price from the resubmission were maintained in the resubmission-addendum, the resulting ICER would have been lower than \$45,000/QALY - \$75,000/QALY in both the “PBAC amended base case” and the “sponsor amended base case”. The PBAC advised that the price per vial of nivolumab would need to be back calculated to achieve an ICER of ≤ \$45,000/QALY - \$75,000/QALY, using the effective prices of everolimus, axitinib and sorafenib.

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

- 6.43 Table 14 below provides a summary of the estimated drug cost per patient per course based on the March 2017 resubmission and resubmission-addendum. The cost per course of treatment in the resubmission increased from that in the July 2016 submission (\$ [REDACTED]) due to the increase in the number of infusions patients were assumed to receive. In the proposed risk sharing arrangement detailed in the resubmission, the sponsor had proposed to cap the costs of the number of nivolumab infusions at [REDACTED] in order to meet the required ICER target. Within the

resubmission-addendum this cap was removed, and RECIST-defined PFS used as the basis to determine treatment duration. While this resulted in fewer infusions per patient, the resulting cost per course remained higher than in the July 2016 submission due to the higher prices proposed in the resubmission-addendum. The PBAC noted that the cost per patient would reduce upon back calculation of the vial price of nivolumab using the effective prices of everolimus, axitinib and sorafenib.

Table 14: Summary of drug cost/patient/course for nivolumab in the resubmission and in the alternative scenarios proposed in the addendum

| Parameter | March 2017 resubmission | March 2017 resubmission addendum (sponsor preferred scenario) | March 2017 resubmission addendum (PBAC preferred scenario) |
|----------------------------------------------------------------|-------------------------|---------------------------------------------------------------|------------------------------------------------------------|
| Nivolumab infusions | ██████████ | ██████████ | ██████████ |
| 100 mg vial requested price | \$ ██████████ | \$ ██████████ | \$ ██████████ |
| Drug cost/infusion ¹ | \$ ██████████ | \$ ██████████ | \$ ██████████ |
| Drug cost/patient/course | \$ ██████████ | \$ ██████████ | \$ ██████████ |
| Drug cost/patient/course plus administration cost ² | \$ ██████████ | \$ ██████████ | \$ ██████████ |

Source: compiled during the evaluation.

¹ The cost included ex-manufacturer price for the required vials (one 40 mg; two 100 mg) and applicable fees. The total drug cost per infusion was calculated based on an assumption that the public vs. private weighting would be 70% vs. 30%. The preparation fee was \$103.22.

² Administration cost was based on MBS item 13915: \$55.30 per infusion (85% MBS benefit).

³ These numbers were higher (██████ in the "sponsor amended base case" and ██████ in the "PBAC amended base case") after an adjustment in the application of transition probabilities for RECIST-defined PFS.

Estimated PBS usage & financial implications

- 6.44 The re-submission was not considered by DUSC. The financial estimates arising from the resubmission-addendum were provided shortly before consideration by the ESC.
- 6.45 The total number of patients likely to be treated with nivolumab over the 5-year forecast period was derived by applying second-line treatment rates to the forecast for the number of patients initiated on TKI therapy each year and factoring in the estimated market share of nivolumab and additional patients to be treated with a first-line TKI in order to be eligible to receive nivolumab in the second-line setting. Estimated utilisation and subsequent costs to the PBS, including from the financial-addendum, are presented in Table 15, including a comparison with the estimates presented in the July 2016 submission.

Table 15: Estimated use and financial implications

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Years 1-5 |
|--------------------------------------------------------------------------------------------------|--------|--------|--------|--------|--------|-----------|
| Estimated extent of use | | | | | | |
| Nivolumab treated patients March 2017 resubmission and addendums | ■ | ■ | ■ | ■ | ■ | ■ |
| Nivolumab treated patients July 2016 submission | ■ | ■ | ■ | ■ | ■ | ■ |
| Nivolumab infusions ¹ | ■ | ■ | ■ | ■ | ■ | ■ |
| Nivolumab infusions ² July 2016 submission | ■ | ■ | ■ | ■ | ■ | ■ |
| Nivolumab infusions March 2017 financial-addendum "PBAC amended base case" ³ | ■ | ■ | ■ | ■ | ■ | ■ |
| Nivolumab infusions March 2017 financial-addendum "sponsor amended base case" ⁴ | ■ | ■ | ■ | ■ | ■ | ■ |
| Estimated net cost to government, \$ | | | | | | |
| Net cost to PBS/RPBS | ■ | ■ | ■ | ■ | ■ | ■ |
| Net cost to PBS/RPBS July 2016 submission | ■ | ■ | ■ | ■ | ■ | ■ |
| Net cost to MBS ⁵ | ■ | ■ | ■ | ■ | ■ | ■ |
| Net cost to MBS July 2016 submission | ■ | ■ | ■ | ■ | ■ | ■ |
| Net cost to State and Territory governments | ■ | ■ | ■ | ■ | ■ | ■ |
| Net cost to State and Territory governments | ■ | ■ | ■ | ■ | ■ | ■ |
| Estimated total net cost | | | | | | |
| Net cost government⁵ March 2017 resubmission | ■ | ■ | ■ | ■ | ■ | ■ |
| Net cost government July 2016 submission | ■ | ■ | ■ | ■ | ■ | ■ |
| Financial-addendum estimated costs.⁶ | | | | | | |
| Net cost to the PBS/RPBS "PBAC amended base case". | ■ | ■ | ■ | ■ | ■ | ■ |
| Net cost to the PBS/RPBS "sponsor amended base case". | ■ | ■ | ■ | ■ | ■ | ■ |

Source: Compiled during the evaluation

Abbreviations: MBS, Medicare Benefit Schedule; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

¹ Mean ■ infusions per treatment course.

² Mean 19.2 infusions per treatment course.

³ Mean ■ infusions per treatment course.

⁴ Mean ■ infusions per treatment course.

⁵ These numbers from the resubmission were corrected during the evaluation.

⁶ As provided in the financial-addendum.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 and the estimated net cost to the PBS is more than \$100 million ("PBAC amended base case") and more than \$100 million ("sponsor amended base case").

6.46 The number of nivolumab treated patients assumed in the resubmission was lower than in the July 2016 submission. This is due to the assumed lower number of first-line TKI users (based on a forecasted trend using 100% PBS data 2014-2016 instead of the previously used 10% PBS sample 2009-2015) and lower uptake of second-line

treatments, both of which are highly uncertain. Use of the revised forecast trend growth of first-line TKI users in the resubmission resulted in a lower estimate for the number of eligible patients than in the July 2016 submission, despite an assumed increase in the number of patients treated first-line with TKIs when nivolumab is listed. The PBAC noted the Pre-PBAC response which defended the patient number estimates however, it considered that there remained uncertainty over the number of patients because the assumption of an increased 85% initiation of second line therapy upon a successful PBS listing of nivolumab was considered to be a likely overestimation. However, the PBAC confirmed that the patient numbers as provided in the resubmission represented reasonable upper limits for the purposes of calculating risk sharing arrangement caps.

6.47 The net cost/year for the PBS may be higher or lower than estimated in the resubmission due to potential variations in both the estimated number of patients and the extent of use of nivolumab and its substituted therapies. The following sensitivity analyses were prepared in the evaluation of the financial-addendum and are summarised in Table 16:

- The forecasted trend of first-line TKI users is uncertain. The impact on the resulting financial estimates is uncertain. The number of first-line TKI users is an important driver of the financial forecasts.
- The potential increase in the number of first-line TKI-users when nivolumab is listed is uncertain. Higher first-line TKI use would result in higher costs to the PBS.
- The uptake rate of patients initiating second-line treatment (with or without nivolumab) following progression with a TKI may have been overestimated. During the evaluation, uptake rates of second line treatment were reduced from 70% (without nivolumab) and 85% (with nivolumab) in the base case to 51% (without nivolumab) and 67% (with nivolumab) in a sensitivity analysis. This decreased the overall net cost from more than \$100 million to more than \$100 million ("PBAC amended base case") and from more than \$100 million to more than \$100 million ("sponsor amended base case").
- The duration of therapy for treatments acting as cost-offsets may have been overestimated. Shorter duration of treatment for substituted therapies (e.g. 4.1 [mean duration of PBS therapy with everolimus is 4.1 scripts] instead of [redacted] ("PBAC amended base case", adjusted) and [redacted] ("sponsor amended base case", adjusted)) would increase the estimated net costs to the PBS from more than \$100 million to more than \$100 million ("PBAC amended base case") and from more than \$100 million to more than \$100 million ("sponsor amended base case").
- Published rather than effective prices were used for everolimus, axitinib and sorafenib. Use of effective prices would increase the estimated net-PBS costs.
- Grandfathering has not been taken into account. This would be anticipated to increase the cost to the PBS from more than \$100 million to more than \$100 million ("PBAC amended base case") and from more than \$100 million to more than \$100 million ("sponsor amended base case").
- The assumed market share of 90% (year 1) and 95% (later years) for nivolumab may be too high. A lower market share would reduce the estimated cost to the PBS.
- In the resubmission, the number of nivolumab infusions per year was based on treatment up to clinical progression instead of RECIST-defined progression. As specified in the Ratified Minutes from the November 2016 PBAC meeting (not

- available when the resubmission was drafted), RECIST-defined PFS was to be used to determine treatment duration and costs for nivolumab as well as everolimus. Doing this without making any other adjustments (such as an increase in nivolumab price) would decrease the overall net cost to the PBS.
- The resubmission-addendum assumed that patients are not treated beyond RECIST-defined PFS and the price of nivolumab was increased compared to the price proposed in the March 2017 resubmission. The treatment cap was removed, but the number of nivolumab infusions was based on the economic model using an 8-year (for the “sponsor amended base case”) and a 5-year (for the “PBAC amended base case”) time horizon. These parameters in the financial-addendum resulted in total 5-year costs of more than \$100 million and more than \$100 million using the “sponsor amended base case” and “PBAC amended base case” prices respectively, instead of more than \$100 million in the resubmission base case.
 - Adverse event-related PBS costs associated with the use of nivolumab, everolimus or third-line systemic treatments were not taken into account. The impact of AE treatments on the PBS is uncertain as it is likely to affect nivolumab and its substituted therapies.
 - Body weight was based on the Australian NPP (■■■ kg) instead of the pivotal trial (82.4 kg) and has a substantial impact on the financial forecasts (increasing from more than \$100 million to more than \$100 million (“PBAC amended base case”) and from more than \$100 million to more than \$100 million (“sponsor amended base case”)).
 - The PBAC considered that, given these uncertainties in the financial estimates, a rebate of 100% should apply for any expenditure over its recommended basis for calculating risk sharing arrangement expenditure caps.

Table 16: Sensitivity analyses from the financial-addendum results

| | Assumption | Overall net cost to PBS/RPBS over the first 5 years | |
|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------|
| | | “PBAC amended base case” | “Sponsor amended base case” |
| | Base case | More than \$100 million | More than \$100 million |
| | Base case adjusted for change in application of transition probabilities “PBAC amended base case”: ██████ nivolumab infusions per treatment course, mean ██████ months everolimus. “Sponsor amended base case”: mean ██████ nivolumab infusions per treatment course, mean ██████ months everolimus. | More than \$100 million | More than \$100 million |
| AddSA1 | Increase in number of new patients initiated on TKI from ██████-█████ per year to ██████ per year | More than \$100 million | More than \$100 million |
| AddSA2 | No increase (instead of 10% increase) in patients receiving a 1L TKI to become eligible for nivolumab | More than \$100 million | More than \$100 million |
| AddSA3 | Increase in mean number of 1L TKI scripts per additional patient treated with 1L TKI, from 3 to 6 | More than \$100 million | More than \$100 million |
| AddSA4 | Increase in mean body weight (kg) for nivolumab patients from ██████ to 82.4 kg | More than \$100 million | More than \$100 million |
| AddSA5 | Decrease in mean body weight (kg) for nivolumab patients from ██████ to 74.6 kg | More than \$100 million | More than \$100 million |
| AddSA6 | Decrease in % of patients initiated on 2L therapy from 70% to 60% - world without nivolumab | More than \$100 million | More than \$100 million |
| AddSA7 | Increase in % of patients initiated on 2L therapy from 85% to 90% - world with nivolumab | More than \$100 million | More than \$100 million |
| AddSA8 | Decrease in mean duration of 2L treatment with substituted therapies from ██████ (“PBAC amended base case”, adjusted) and ██████ (“sponsor amended base case”, adjusted) to 4.1 months | More than \$100 million | More than \$100 million |
| AddSA10 | Increase in the number of nivolumab patients by less than 10,000 in year 1, to account for grandfathering. | More than \$100 million | More than \$100 million |
| AddSA11 | Uptake rates of 2L treatment decreased from 70% (without nivolumab) and 85% (with nivolumab) to 51% (without nivolumab) and 67% (with nivolumab), based on the clinician survey. | More than \$100 million | More than \$100 million |
| AddSA12 | Drug use based on treatment cessation curve, clinical benefit based on RECIST-defined PFS. “PBAC amended base case”: ██████ nivolumab infusions per treatment course, mean ██████ months everolimus. “Sponsor amended base case”: mean ██████ nivolumab infusions per treatment course, mean ██████ months everolimus. | More than \$100 million | More than \$100 million |

Source: compiled during evaluation.

Abbreviations: 1L, first line; 2L, second line; AddSA, additional sensitivity analysis; PBS, Pharmaceutical Benefits Scheme; RPBS, repatriation pharmaceutical benefits scheme; SA, sensitivity analysis.

Quality Use of Medicines

6.48 The resubmission did not report any change from the July 2016 submission with respect to the quality use of medicines. The July 2016 submission provided a summary of the sponsor’s current practice and plans regarding the quality use of medicines, including (1) education initiatives supporting nivolumab use and (2) guidance on monitoring and treating immune-related adverse reactions.

Financial Management – Risk Sharing Arrangements

- 6.49 The resubmission emphasised that any potential Risk Sharing Arrangement would need to reflect the “PBAC’s pre-specified level of cost-effectiveness” (ICER/QALY \$45,000 - \$75,000). The sponsor proposed alternative effective prices, conditional on previously proposed expenditure caps: \$ [REDACTED] with a cap of [REDACTED] costed infusions (= [REDACTED] months), \$ [REDACTED] with a cap of [REDACTED] costed infusions (= [REDACTED] months) and \$ [REDACTED] with a cap of [REDACTED] costed infusions (= [REDACTED] months). The PBAC confirmed that it had not pre-specified a target ICER/QALY of \$45,000 - \$75,000, but rather considered this to represent an upper limit to the cost-effectiveness of nivolumab in RCC.
- 6.50 The resubmission-addendum proposed increased nivolumab 100 mg vial prices of \$ [REDACTED] (“sponsor amended base case”) and \$ [REDACTED] (“PBAC amended base case”) and removed the offer of an expenditure cap, assuming patients cease treatment at RECIST-defined progression. The suggested price increases were not supported by improved data regarding the incremental effectiveness of nivolumab. Since the proposed restriction did not have a RECIST-based stopping rule and no expenditure cap was offered, it is unlikely that the treatment duration costed on the PBS would match the scenario in the resubmission-addendum (i.e. treatment costed up to RECIST-defined progression). The PBAC recommended that the calculation of the proposed Risk Sharing Arrangement caps reflect the RECIST-defined PFS duration of treatment, of [REDACTED] nivolumab infusions, to mitigate the risk of treatment beyond progression.
- 6.51 The sponsor recognised that prices would need to be adjusted following a PBAC recommendation, taking into account the effective prices of everolimus, axitinib and sorafenib. The PBAC noted this and agreed that this adjustment, using the “PBAC amended base case” economic evaluation for all other inputs to the calculations, would be required prior to any listing.
- 6.52 The sponsor indicated that it remained committed to working with the PBAC to address any residual financial uncertainties.
- 6.53 The PBAC recommended that a Risk Sharing Arrangement be finalised with the sponsor to reduce the level of uncertainty in the overall cost to the Commonwealth due to unresolved issues with the modelling, uncertain patient numbers, and the possibility of treatment beyond progression.
- 6.54 The PBAC recommended that the Risk Sharing Arrangement caps reflect the back-calculated vial prices of nivolumab, to achieve an ICER/QALY of \leq \$45,000 - \$75,000, using the effective prices of everolimus, axitinib and sorafenib, with the number of patients per year included as per the resubmission, and the duration of treatment capped with reference to RECIST-defined PFS basis of [REDACTED] nivolumab infusions. The PBAC further recommended that any expenditure over the Risk Sharing Arrangement caps should be 100% rebated to the Government.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of nivolumab, on the basis that it be available only under special arrangements under Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) for the treatment of Stage IV 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). The PBAC was satisfied that nivolumab provides, for some patients, a significant improvement in efficacy and reduction in toxicity over everolimus.
- 7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of nivolumab would be acceptable at the price calculated using the effective prices of everolimus, axitinib and sorafenib in the "PBAC amended base case" evaluation, and a Risk Sharing Arrangement with expenditure caps calculated reflecting the number of patients receiving nivolumab and the number of nivolumab infusions per patient capped as specified above.
- 7.3 The PBAC confirmed that there was a continued clinical need for further treatment options in metastatic renal cell carcinoma after progression on a TKI and that nivolumab provided an improvement in overall survival with no increase in overall toxicity over the comparator, everolimus.
- 7.4 The PBAC considered that there continued to be uncertainty in the extent of benefit in overall survival in relation to the PBS population due to 46% of nivolumab patients in the clinical trial continuing treatment beyond progression.
- 7.5 The PBAC re-stipulated that the use of RECIST-defined progression free survival extrapolated from the clinical trial, along with a 5-year time horizon, were appropriate for use in the economic evaluation and financial estimates. The PBAC considered that the risk of treatment beyond progression needed to be addressed in the calculation of the proposed Risk Sharing Arrangement by limiting treatment duration to the RECIST-defined PFS duration of ████████ nivolumab infusions.
- 7.6 The PBAC considered that there remained some uncertainty with regards to patient numbers as these were highly dependent on the uptake of second-line treatment following progression on a TKI, however the PBAC considered that patient numbers as provided in the resubmission were a reasonable upper limit for the purposes of finalising a Risk Sharing Arrangement. The PBAC further advised that any expenditure over the proposed Risk Sharing Arrangement caps should be 100% rebated to the Government.
- 7.7 The PBAC recommended that the Administrative Advice in the initial treatment restriction should be based on that for nivolumab in melanoma to recommend a repeat scan at least 4 weeks after suspected pseudo-progression. The PBAC recommended that patients should only continue on PBS subsidised treatment if they have stable or responding disease.
- 7.8 The PBAC advised that nivolumab is not suitable for prescribing by nurse practitioners.

- 7.9 The PBAC recommended that nivolumab should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.10 The PBAC recommended that the Early Supply Rule should apply.
- 7.11 The PBAC noted that this submission was not eligible for an Independent Review as it was a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Proprietary Name and Manufacturer |
|----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|----------------------------------------------------------|
| Nivolumab 40 mg/4 mL injection 1 x 4 mL vial 100 mg/10 mL injection 1 x 10 mL vial | 360 mg | 8 | OPDIVO® Bristol-Myers Squibb Australia Pty Ltd |
| Category / Program | Section 100 - Efficient funding of Chemotherapy | | |
| Prescriber type: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives | | |
| 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: | Initial treatment | | |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined | | |
| Clinical criteria: | The treatment must be the sole PBS-subsidised treatment for this condition AND Patient must have a WHO performance status of 2 or less 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 | | |

Public Summary Document – March 2017 PBAC Meeting

| | |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | Patient must have developed intolerance to a tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal |
| Prescriber Instructions | The patient's body weight must be documented in the patient's medical records at the time treatment is initiated. |
| Administrative Advice | <p>Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows:</p> <p>Complete response (CR) is disappearance of all target lesions.</p> <p>Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.</p> <p>Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.</p> <p>Stable disease (SD) is small changes that do not meet above criteria.</p> <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.</p> <p>Special Pricing Arrangements apply.</p> |

PBS listing for continuing treatment

| Name, Restriction, Manner of administration and form | Max. Qty | No. of Rpts | Proprietary Name and Manufacturer |
|----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|----------------------------------------------------------|
| Nivolumab 40 mg/4 mL injection 1 x 4 mL vial 100 mg/10 mL injection 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: | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives | | |
| 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 | | |
| Restriction Level / Method: | <input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined | | |
| Clinical criteria: | Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must have stable or responding disease, AND The treatment must be the sole PBS-subsidised therapy for this condition. | | |
| Prescriber Instructions | The patient's body weight must be documented in the patient's medical records at the time treatment is initiated. | | |
| Administration Advice | No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply. | | |

9 Context for Decision

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

10 Sponsor's Comment

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