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

NIVOLUMAB (OPDIVO®) concentrate solution for intravenous infusion, 40 mg/4 mL, 1 x 4 mL vial, concentrate solution for intravenous infusion, 100 mg/10 mL, 1 x 10 mL vial, Bristol-Myers Squibb, plus

IPILIMUMAB (YERVOY®) concentrate solution for intravenous infusion 50 mg/10 mL, 1 x 10 mL, Bristol-Myers Squibb

1 Purpose of Application

1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy) listing for nivolumab in combination with ipilimumab (NIVO+IPI) as the first line treatment of Stage IV clear cell variant renal cell carcinoma (RCC) in patients meeting the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate to poor risk group criteria.

1.2 The requested listing was based on a cost-utility analysis of NIVO+IPI compared with sunitinib. The key components of the clinical issue addressed by the submission are summarised below.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Intermediate or poor risk (per IMDC scoring system) stage IV* clear cell variant RCC with a WHO performance status ≤ 2
Intervention	Initial combination phase: Nivolumab 3mg/kg IV combined with ipilimumab 1mg/kg IV every 3 weeks for 4 doses. Single agent maintenance phase: Nivolumab 3mg/kg IV every 2 weeks, until RECIST v 1.1 defined progression or unacceptable toxicity The doses in the initial combination phase differed to those proposed in the malignant melanoma setting, which were: nivolumab 1 mg/kg + ipilimumab 3mg/kg for up to 4 doses.
Comparator	Sunitinib 50mg po once daily for 4 weeks followed by 2 weeks off, every cycle. Treatment was continued until RECIST v 1.1 defined progression or unacceptable toxicity
Primary Outcomes	OS, PFS, ORR
Clinical claim	Nivolumab in combination with ipilimumab is superior in terms of efficacy (on the basis of OS), when compared to sunitinib and has a clinically acceptable safety profile for patients with treatment naive advanced/metastatic clear cell variant RCC of intermediate/poor risk according to the IMDC scoring system

Abbreviations: IMDC = International Metastatic RCC Database Consortium; IV = intravenously; ORR = objective response rate; OS = overall survival; PFS = progression free survival; po = per oral administration; RCC = renal cell carcinoma; RECIST v 1.1 = Response Evaluation Criteria In Solid Tumours version 1.1; WHO = World Health Organisation

* Stage IV was staged according to the American Joint Committee on Cancer.

Source: Table 1, p 17 and Table 31, p 57 of the submission.

2 Requested listing

Name, restriction, manner of administration, form	Maximum qty	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Induction phase				
NIVOLUMAB Injection 40 mg/4 mL 1 x 4 mL vial Injection 100 mg/10 mL 1 x 10 mL vial	360 mg	3	$7,560.13 published price $[redacted] effective price	OPDIVO Bristol-Myers Squibb Australia Pty Ltd
IPILIMUMAB Injection 50 mg/10 mL 1 x 10 mL vial	120 mg	3	$17,849.89 published price $[redacted] effective price	YERVOY Bristol-Myers Squibb Australia Pty Ltd
Continuing phase				
NIVOLUMAB Injection 40 mg/4 mL 1 x 4 mL vial Injection 100 mg/10 mL 1 x 10 mL vial	360 mg	11	$7,560.13 published price $[redacted] effective price	OPDIVO Bristol-Myers Squibb Australia Pty Ltd

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

Name, restriction, manner of administration, form	Maximum qty	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Restriction:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined			
Treatment criteria:	Patient must meet the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate to poor risk group criteria AND Patient must have WHO performance status of 2 or less AND Patient must receive this PBS subsidised nivolumab and ipilimumab concomitantly as the first line of treatment for this condition AND The treatment with nivolumab must not exceed a total of 4 doses at a maximum dose of 3 mg per kg every 3 weeks AND The treatment with ipilimumab must not exceed a total of 4 doses at a maximum dose of 1 mg per kg every 3 weeks			
Prescriber Instructions:	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated			
Administrative Advice:	In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.			
Treatment phase:	Continuing treatment (nivolumab maintenance)			
Restriction:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined			
Treatment criteria:	Patient must have previously been issued with authority prescriptions for induction phase nivolumab and ipilimumab combination therapy for this condition AND This drug must be the sole PBS-subsided treatment for this condition AND Patient must have stable or responding disease AND The treatment with nivolumab must not exceed a maximum dose of 3 mg per kg every 2 weeks.			
Prescriber Instructions:	The patient's body weight must be documented in the patient's medical records at the time treatment is initiated			
Administrative Advice:	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.			

Abbreviations: WHO = World Health Organisation; Source: pp 49 &50 of the submission.

2.1 The submission proposed a Special Pricing Arrangement (SPA) for both nivolumab and ipilimumab, which was consistent with the current monotherapy PBS listing of each drug (nivolumab for metastatic melanoma, second-line non-small cell lung cancer and second-line RCC; ipilimumab for metastatic melanoma).

2.2 Compared with the submission, the pre-PBAC response proposed a [redacted]% lower effective price for nivolumab, by reducing the 100 mg vial price from $[redacted] to $[redacted] (with a corresponding reduction to the 40 mg nivolumab vial price). The proposed price for ipilimumab remained unchanged.

2.3 The requested restriction included patients with a World Health Organisation (WHO) performance status of ≤ 2. The submission stated this was included to align with the clinical criteria for other PBS listed medicines for RCC. However, the key clinical evidence only included patients with a Karnofsky Performance Status (KPS) ≥ 70, with 90% of patients having a KPS ≥ 80. Although the literature is inconsistent regarding the translation of KPS to WHO/Eastern Cooperative Oncology Group (ECOG) performance status, literature by West et al[a] (2015) suggested that KPS ≥ 70 corresponds to WHO/ECOG ≤1. Therefore, the requested restriction would allow patients with worse performance status and more limited functional capacity to be treated than those patients who were included in the key clinical evidence (CA209214).

2.4 The ESC acknowledged that including WHO performance status ≤ 2 in the restriction (rather than KPS ≥ 70) may enable use in a broader patient group than included in the key trial. However, the ESC considered that WHO performance status is more commonly used in Australian clinical practice, and noted that use of WHO performance status ≤ 2 (rather than KPS) would align with the restrictions for other PBS-listed medicines for RCC including sunitinib (the comparator) and nivolumab in later-line RCC. Therefore, the ESC and the PBAC considered that it would be appropriate for the restriction to include WHO performance status ≤ 2, as requested by the submission.

2.5 The sponsor is seeking PBS listing for combined NIVO+IPI as a first line treatment of RCC before either nivolumab or ipilimumab monotherapy have been determined as being acceptable first line treatments for RCC. Nivolumab monotherapy is not currently PBS listed for first line treatment of RCC, and ipilimumab is not currently listed on the PBS for RCC. Therefore, the evaluation and the PBAC considered that the contribution of each medicine to the combined treatment effect was unclear, as was the benefit and harm balance of combination therapy over each of the individual medicines.

2.6 The Pre-Sub-Committee Response (PSCR) provided information regarding the objective response rates observed in exploratory and phase II studies of nivolumab or ipilimumab monotherapy, or as combination therapy at different doses. The objective response rates

[a] West, H and Jin JO. Performance status in patients with cancer. JAMA Oncol, 2015; 1 (7): 998.

for nivolumab monotherapy (CA209009, n = 24) and ipilimumab monotherapy (MDX010-11, n = 12) were 13% and 25%, respectively which the PSCR described as "suboptimal", versus 42% for NIVO+IPI in the pivotal trial, CA209214. The ESC considered that there was a biological rationale for the combination and that it was clinically appropriate to combine the two agents.

2.7 The proposed listing allowed patients to be continued on treatment after suspected progression and requested a confirmatory scan to be taken at least four weeks later. This was consistent with the key clinical evidence CA209214, where patients in both arms were permitted to continue treatment beyond initial investigator assessed progression where clinical benefit and toleration of study drug was being observed. The incidence of pseudo-progression events needs to be weighed against the harms of overtreatment with immunotherapy and delayed or missed opportunities for alternate therapeutic options for genuine progression.

2.8 The submission requested a flow-on change to the current restriction for nivolumab in the second-line RCC setting: removal of the requirement for patients to have received prior tyrosine kinase inhibitor (TKI) therapy. The submission stated this was because of "inequitable access issues for patients who received NIVO+IPI as a first line therapy". The submission similarly requested removal of the requirement for patients to have received prior TKI therapy before commencing everolimus, axitinib, sorafenib or cabozantinib. The PBS requirement for prior TKI use in the current nivolumab listing reflects the patient population enrolled in the key nivolumab trial CA025 (July 2016 PBAC Meeting) and is consistent with the TGA approved indication for use of nivolumab monotherapy in RCC which specifies that patients should have had prior anti-angiogenic therapy (e.g. sunitinib and pazopanib). Additionally, no evidence was provided in the submission to support the use of nivolumab monotherapy following progression after first line treatment with NIVO+IPI.

2.9 The ESC considered that it may not be clinically appropriate for patients who progress on NIVO+IPI to then be treated with second-line nivolumab monotherapy (noting that the requested NIVO+IPI regimen involves four doses of NIVO+IPI induction, followed by nivolumab monotherapy until progression; and the requested restriction did not require patients to have completed the full four doses of ipilimumab prior to commencing nivolumab monotherapy). The ESC noted that the submission similarly requested removal of the requirement for patients to have received prior TKI therapy before commencing everolimus, axitinib, sorafenib or cabozantinib. The ESC and PBAC noted that no evidence was presented to support this request, and considered that the current requirement for patients to trial TKI therapy prior to these therapies (i.e. everolimus, axitinib, sorafenib and cabozantinib) remained clinically appropriate.

2.10 The proposed restriction for NIVO+IPI was based on the IMDC system, rather than the Memorial Sloan-Kettering Cancer Center (MSKCC) system that is used in the sunitinib restriction. The submission stated that the two systems have a high level of concordance,

but that MSKCC has been superseded by IMDC. The PBAC agreed that the IMDC system (rather than MSKCC) is currently used in clinical practice and thus would be more appropriate for inclusion in the PBS restriction for NIVO + IPI.

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

3 Background

Registration status

3.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the TGA approval letter was available which stated that the Delegate has decided to approve the registration of nivolumab for: "nivolumab, in combination with ipilimumab, is indicated for the treatment of patients with intermediate/poor-risk, previously untreated advanced renal cell carcinoma. Nivolumab, as monotherapy, is indicated for the treatment of patients with advanced clear cell renal cell carcinoma after prior anti-angiogenic therapy."

3.2 The PBAC also noted that there were ongoing trials for a range of other regimens for the first-line treatment of RCC, including single-agent pembrolizumab, pembrolizumab in combination with other therapies, avelumab + axitinib, and nivolumab + cabozantinib.

Previous PBAC consideration

3.3 This was the first submission to the PBAC for NIVO+IPI for the treatment of Stage IV clear cell variant RCC.

3.4 There was a concurrent submission for consideration at the July 2018 PBAC meeting for NIVO+IPI for the treatment of metastatic melanoma.

4 Population and disease

4.1 Renal cell carcinoma (RCC) is a form of kidney cancer that arises from the cells of the renal tubule, and accounts for up to 90% of primary renal neoplasms[b]. Clear cell variants accounts for 70-80% of all RCC cases[c]. For patients with treatment naïve metastatic RCC, their prognosis can be categorised as favourable, intermediate or poor based on the IMDC or MSKCC systems.

4.2 The life expectancy for intermediate and poor risk patients is generally short (22.5 months and 7.8 months respectively)[d]. NIVO+IPI was proposed as a first line treatment

[b] Mohammadian M, Pakzad R, Towhidi F, Makhsosi BR, Ahmadi A, Salehiniya H. Incidence and mortality of kidney cancer and its relationship with HDI (Human Development Index) in the world in 2012. Clujul Medical. 2017;90(3):286-93.
[c] Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. Lancet. 2009;373:1119-32.
[d] Heng DYC, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. The Lancet Oncology.

for patients with clear cell variant RCC whose prognosis was categorised as intermediate to poor based on IMDC.

5 Comparator

5.1 The submission nominated sunitinib as the main comparator. The submission argued that sunitinib was the standard of care for patients with Stage IV RCC who are capable of receiving systemic first-line treatment. The submission further argued that sunitinib was the first PBS-listed targeted therapy for the treatment of Stage IV, clear cell variant RCC, with pazopanib listed on a cost-minimisation basis to sunitinib in the first-line setting.

5.2 Sunitinib is currently listed on the PBS as a first line treatment for RCC patients whose prognosis was categorised as favourable to intermediate. However, the proposed restriction for NIVO+IPI is for patients at intermediate to poor risk (that is, sunitinib is not PBS-listed for patients at poor prognostic risk).

5.3 The submission and the PSCR argued that, in clinical practice, the majority of patients at poor risk who are capable of receiving systemic treatment currently receive sunitinib (or pazopanib), despite such use being outside the PBS restriction. The PSCR stated that a patterns of care analysis of patients with RCC in Australia (Day 2015) indicated that the majority of poor risk patients (18/28, 64.3%) received sunitinib. Further, the PSCR stated that an advisory panel of local oncologists (n = 12) indicated that sunitinib was used irrespective of prognostic risk in clinical practice.

5.4 The submission stated that patients at poor risk were likely to have been excluded from the sunitinib PBS restriction due to a lack of evidence to demonstrate a superior treatment effect versus interferon-α in this population at the time of the PBAC consideration for sunitinib.

5.5 Overall, the evaluation considered that sunitinib may not be an appropriate comparator for the patients with poor prognostic risk, and that best supportive care may have been a more appropriate comparator in this population in the absence of any PBS-listed medicines. The evaluation considered that the effectiveness and cost-effectiveness of NIVO+IPI compared with a potentially cost-ineffective treatment (sunitinib) in patients with a poor prognosis was likely to favour NIVO+IPI.

5.6 The PSCR argued that the clinical effectiveness and cost-effectiveness of sunitinib were "unclear" in patients with a poor prognosis as the PBAC has not made any conclusion regarding sunitinib in this setting.

5.7 The ESC and the PBAC considered that in clinical practice, many patients with a poor prognostic risk who are capable of receiving systemic treatment will currently receive

2013;14(2):141-8.

sunitinib, despite such use being outside the PBS restriction. However, the ESC considered that the clinical effectiveness and cost-effectiveness of sunitinib is unknown in this setting.

5.8 The PBAC considered that in clinical practice, many patients with a poor prognostic risk who are capable of receiving systemic treatment will currently receive sunitinib, despite such use being outside the PBS restriction. The PBAC considered that sunitinib (and pazopanib) was likely to be of limited efficacy in the poor prognostic risk population, but may be associated with significant toxicity.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician outlined the importance of effective therapies in the first-line RCC treatment setting, and the clinical importance of trial data showing that 9% of patients achieved a complete response with NIVO+IPI versus 1% with sunitinib.

6.2 The clinician outlined the difference in adverse event profiles between NIVO+IPI and sunitinib, stating that sunitinib was associated with a higher rate of long-term adverse events that impact patient quality of life, such as prolonged fatigue, taste changes (dysgeusia), nausea, and painful hands and feet (palmar–plantar erythrodysesthesia). The clinician considered that these adverse events, particularly fatigue, may impact a patient's ability to work while on sunitinib. The clinician stated that, on the other hand, nivolumab was associated with adverse events that were short-term and that often resolved with treatment (e.g. rash that responds to steroid treatment). The clinician considered that the high discontinuation rate observed in the NIVO+IPI arm of the trial was due to the trial protocol e.g. patients who experienced any Grade 3 toxicities were required to withdraw from the trial, while in clinical practice many patients would recommence nivolumab once an adverse event resolves.

6.3 The clinician considered that most of the toxicity of NIVO+IPI was associated with the ipilimumab component, which is only given for the first three months. The clinician stated that, in practice, adverse events likely associated with ipilimumab would be managed by ceasing NIVO+IPI and re-challenging with nivolumab monotherapy. The clinician also highlighted that ipilimumab dosing is lower in RCC than in melanoma (e.g. 1 mg/kg in RCC, rather than 3 mg/kg in melanoma) which may lead to a milder adverse event profile in RCC.

6.4 The clinician acknowledged that sunitinib is unlikely to be effective in patients with a poor prognosis, but that these patients are still treated with sunitinib as no other options are

available. The clinician also acknowledged that the incremental benefit of adding ipilimumab to nivolumab was unknown.

Consumer comments

6.5 The PBAC noted and welcomed the input from individuals (7), health care professionals (3) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with NIVO+IPI including increased quality of life in some patients and reductions in adverse events compared with some other chemotherapies, a potential for increased overall survival, and the lack of alternative treatments for poor risk patients. The comments also noted the lack of affordability of NIVO+IPI in the absence of a PBS subsidy.

6.6 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the NIVO+IPI for RCC submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the CA209214 trial. The PBAC noted that the MOGA was unable to calculate the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) score for NIVO+IPI for RCC, as the data were immature and the median survival time for the NIVO+IPI arm had not been reached.[e]

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

Clinical trials

6.7 The submission was based on a Phase III, head-to-head, randomised, open-label trial (CA209214) of NIVO+IPI compared with sunitinib monotherapy in previously untreated patients with Stage IV clear cell variant RCC (n=1,096).

6.8 Patients were randomised 1:1 to either NIVO+IPI or sunitinib and stratified by IMDC prognostic risk scores (0 (favourable) versus 1-2 (intermediate) versus 3-6 (poor)) and region. Patients were subsequently characterised into two groups at registration; favourable or intermediate/poor risk. Both patient subgroups received treatment with NIVO+IPI or sunitinib but the intermediate/poor risk subgroup was the primary focus of the trial (the "primary efficacy population"). For this subgroup (NIVO+IPI n = 425; sunitinib n = 422) the co-primary endpoints were overall survival (OS), progression-free survival (PFS) and objective response rate (ORR), where PFS and ORR were based on interpretation by an independent radiology review committee (IRRC) using Response Evaluation Criteria in Solid Tumours (RECIST) v 1.1 and investigator assessment.

6.9 Details of the trial presented in the submission are provided in the table below.

Table 2: Trial and associated report presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Study CA209214	Clinical Study Report. A Phase 3, Randomized, Open-Label Study of Nivolumab Combined with Ipilimumab versus Sunitinib Monotherapy in Subjects with Previously Untreated, Advanced or Metastatic Renal Cell Carcinoma	September 2017
	Escudier B, Tannir NM, McDermott DF, et al. Checkmate 214: Efficacy and safety of nivolumab 1 ipilimumab (N1I) v sunitinib (S) for treatment-naïve advanced or metastatic renal cell carcinoma (mRCC), including IMDC risk and PD-L1 expression subgroups.	Annals of Oncology. 2017; 28(Suppl5): LBA5
	Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab + Ipilimumab (N+I) vs Sunitinib (S) for treatment-naïve advanced or metastatic renal cell carcinoma (aRCC): results from CheckMate 214, including overall survival by subgroups.	Journal of Immuno Therapy of Cancer. 2017; 5(Suppl 3): 89, O38:p2.
	Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma.	The New England Journal of Medicine. 2018; 378(14):1277-1290.

Source: Table 30, p 55 of the submission.

6.10 The key features of the direct randomised trial are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
NIVO+IPI compared with sunitinib						
Patients with intermediate/poor prognosis included in Study CA209214	[redacted]	R, OL [redacted] mths[a]	High for PFS and EQ-5D; moderate to unclear for OS [b]	Previously untreated Stage IV clear cell variant RCC who have intermediate to poor prognostic risk	ORR[c], PFS[c], OS, EQ-5D	PFS, OS, EQ-5D used

Abbreviations: R=randomised; OL=open label; RCC = renal cell carcinoma; ORR = objective response rate; PFS=progression-free survival; OS=overall survival.

[a] derived from Individual Patient Data for Study CA209214.

[b] The commentary assigned a high risk of bias for PFS due to patients being allowed to receive subsequent therapy prior to disease progression. The ESC agreed that this led to a high risk of bias for the PFS outcome. Given additional information provided in the PSCR regarding use of subsequent therapies (discussed below), the ESC considered that the risk of bias for OS was moderate to unclear. The ESC considered that there was a high risk of bias for patient reported outcomes (some adverse events, and quality of life data) due to the open-label design.

[c] PFS and ORR were based on interpretation by an independent radiology review committee (IRRC) using Response Evaluation Criteria in Solid Tumours (RECIST) v 1.1 and investigator's assessment.

Source: compiled during the evaluation based on Sections 2.3 and 2.4 of the submission.

6.11 The clinical database was locked in August 2017 for the planned interim analysis for OS and planned final analysis of PFS and ORR in patients with intermediate/poor risk. An independent data monitoring committee confirmed one month after the database lock, that the interim OS data had crossed the pre-specified boundary for gains in OS (nominal significance level $p < 0.002$) and recommended that the study results be made available.

6.12 Patients were allowed to receive subsequent systemic anticancer therapies before disease progression. For PFS analyses, patients were censored at the date of the last tumour assessment, conducted prior to the initiation of new therapies. However the evaluation, ESC and PBAC considered that PFS analyses may still be biased if patients who were censored due to receiving subsequent therapies were systematically different from those who remain in the allocated treatment, in terms of both prognosis and responses to the allocated treatment. Thus the ESC and the PBAC considered that there was a high risk of bias for the PFS results.

6.13 The PSCR provided additional information regarding patients who received subsequent therapies, which is shown in the table below. This was provided to address concerns raised in the evaluation that there was potential for extensive and early use of subsequent therapies in the NIVO+IPI arm, in patients who discontinue in the induction phase due to adverse events.

Table 4: Post-hoc analyses for patients who received subsequent therapies prior to progression

Study CA209214, n(%); Intermediate/poor risk	NIVO + IPI (N=425)	Sunitinib (N=422)
Patients with any subsequent therapy (before or after progression) - Patients with any subsequent systemic therapy - Time to first subsequent systemic therapy, median months (range)	[redacted]	[redacted]
Patients with any subsequent therapy who were censored for PFS due to subsequent therapies [a] - Censored patients who received subsequent systemic therapy	[redacted]	[redacted]
Patients not continuing due to study drug toxicity [b] - Patients discontinuing during induction - Patients who received subsequent systemic therapy	[redacted]	[redacted]

Source: Table 2, page 2 of the PSCR,

[a] In Study CA209214 the primary definition for PFS, patients who received subsequent therapy prior to documented progression were censored at the date of the last tumour assessment prior to the initiation of the new therapy

[b] These figures differ to Table 6 which are based on all treated patients, while Table 4 above is specific to patients at intermediate/poor risk.

6.14 The PSCR argued that the trial results may be biased in favour of sunitinib as more patients received subsequent systemic therapies in the sunitinib arm than the NIVO+IPI arm ([redacted]% versus [redacted]%), and more patients received subsequent systemic therapies prior to documented progression in the sunitinib arm ([redacted]% for sunitinib versus [redacted]% for NIVO+IPI). The ESC considered that a rationale for this difference may be that, when a patient experiences adverse events necessitating cessation of NIVO+IPI, clinicians may persist with a period of observation off all treatment to determine if a patient responds or continues to respond to NIVO+IPI. If sunitinib is ceased due to adverse events then clinicians are more likely to start a new treatment straight away given the different mechanisms of actions of these types of therapies and the potentially lower likelihood of an ongoing response after cessation of sunitinib.

6.15 Data from the *post hoc* analyses showed that [redacted]% of patients in the NIVO+IPI arm received subsequent systemic therapies after discontinuing due to adverse events during the induction phase, versus [redacted]% in the sunitinib arm. The PSCR stated that, given these proportions were low, this mitigated the evaluation's concerns that there was potential for the OS results to have been biased by earlier and higher use of subsequent therapies in the NIVO + IPI arm. The ESC agreed that this reduced the risk of bias in the OS results. However, the ESC also noted that these data were based on *post hoc* analyses and it was unclear how data relating to subsequent use of therapies were collected once patients were no longer actively participating in the trial. More patients discontinued NIVO+IPI due to drug toxicity, particularly during the induction phase ([redacted]% versus [redacted]%). It was not clear what treatments (if any) the remaining patients who discontinued during induction received (i.e. it appeared that [redacted]% of patients in the NIVO+IPI arm discontinued during induction but did not go on to receive subsequent systemic therapies).

6.16 The submission argued that results presented in the clinical evaluation were not confounded by the crossover of sunitinib-treated patients to NIVO+IPI. As reported in the CSR, while 20% of patients in the NIVO+IPI group received subsequent treatment with

sunitinib, [redacted]% of patients in the sunitinib group received subsequent therapy with nivolumab or pembrolizumab (but not NIVO+IPI). The impact of this on overall survival is uncertain.

6.17 Given the open label design of the study, the assessment of patient reported outcomes, such as quality of life (QoL) data and subjective reporting of adverse events (AEs) may be biased.

6.18 The PBAC considered that the trial population may not be representative of the Australian population, noting that in the NIVO+IPI arm (of the intermediate-poor risk group): 62% of patients were less than 65 years of age, while only 8% of patients were 75 years or older; 69.5% were KPS 90-100; and the trial excluded patients with pre-existing autoimmune disease, or those with a history of, or current, central nervous system (CNS) metastases. While the PBAC noted that the submission had compared the characteristics of patients enrolled in the trial to a retrospective study of Australian patients with RCC (Day et al, 2015), the PBAC noted that only limited and summarised patient characteristic data were available in the publication by Day et al, 2015. Overall, the PBAC considered that the patients included in the trial may represent a fitter group with better performance status than the likely PBS population.

6.19 An exploratory objective of Study CA209214 was to evaluate generic health related quality of life based on the EuroQol-5 dimension (EQ-5D) index score. However, the evaluation considered that insufficient detail was provided in the submission to draw any firm conclusions on the impact of NIVO+IPI on health-related quality of life based on the EQ-5D. Tables referenced in the CSR pertaining to this exploratory endpoint were not attached to the CSR provided in the submission. The PSCR provided further information regarding completion rates of the EQ-5D questionnaire, which is discussed in the 'Economic analysis' section.

Comparative effectiveness

6.20 The PFS and OS results for the intermediate/poor risk patients are summarised in the table below.

Table 5: Results of subgroup analysis in RCC patients with intermediate/poor and favourable prognosis as defined by IMDC and the all randomised (any-risk) subjects.

Outcomes	CA209214	Requested population		Not requested for PBS listing			
		Intermediate to poor risk patients		Favourable risk patients		All randomised (any-risk) patients	
		NIVO+IPI N = 425	Sunitinib N = 422	NIVO+IPI N = 125	Sunitinib N = 124	NIVO+IPI N = 550	Sunitinib N = 546
Overall Survival (OS)	n events (%)	140 (32.9)	188 (44.5)	[redacted]	[redacted]	[redacted]	[redacted]
	Median OS (months)[a]	NA	25.95	[redacted]	[redacted]	NA	32.92
	Exact 95% CI	(28.16, NA)	(22.08, NA)	[redacted]	[redacted]	-	(NA, NA)
	HR (99.8% CI)[b]	**0.63 (0.44, 0.89)**		[redacted]		**0.68 (0.49, 0.95)**	
	p-value[c]	<0.0001		[redacted]		0.0003	
Progressive Free Survival (PFS) assessed by IRRC	n events (%)	[redacted]	[redacted]	[redacted]	[redacted]	296 (53.8)	271 (49.6)
	Median (months)[d]	11.56	8.38	[redacted]	[redacted]	12.42	12.32
	Exact 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	(9.89, 16.53)	(9.79, 15.24)
	HR (99.1% CI)[e]	0.82 (0.64, 1.05)		[redacted]		0.98 (0.79, 1.23)	
	p-value[f]	0.0331		[redacted]		0.8498	
Objective Response Rate (ORR) assessed by IRRC	n responders (%)	177 (41.6)	112 (26.5)	[redacted]	[redacted]	213 (38.7)	176 (32.2)
	Exact 95% CI[g]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in ORR (95% CI)[h,i]	**16.0 (9.8, 22.2)**		[redacted]		**7.2 (1.8, 12.7)**	
	p-value[j]	[redacted]		[redacted]		[redacted]	
Complete Response	n responders (%)	[redacted]	[redacted]	-		[redacted]	[redacted]

Abbreviations: CI = confidence interval; DNP = Data not provided; HR = Hazard Ratio; IMDC = International Metastatic RCC Database Consortium; IRRC = Independent Radiology Review Committee; n = number of events or responders; N = total participants in group; NA = not applicable; NIVO+IPI = nivolumab = ipilimumab; RCC = renal cell carcinoma.

a = Median computed using Kaplan-Meier method; b = stratified Cox proportional hazard model. Hazard Ratio is NIVO+IPI over sunitinib; c = Log-rank Test stratified by IMDC prognostic risk score (0,1-2,3-6) and region (United States of America, Canada/Western Europe/Northern Europe, Rest of World) as entered into the interactive voice response system; d = Median computed using Kaplan-Meier method; e = stratified HR; f = 2-sided p value - not statistically significant according to 2-sided α of 0.009 adapted for PFS; g = CI based on the Clopper and Pearson method; h = Strata adjusted difference in ORR (NIVO+IPI) – sunitinib) based on DerSimonian and Laird method; i = Stratified by IMDC prognostic risk score (0,1-2,3-6) and region (United States of America, Canada/Western Europe/Northern Europe, Rest of World) as entered into the interactive voice response system; j = Two-sided p-value from DerSimonian and Laird Test

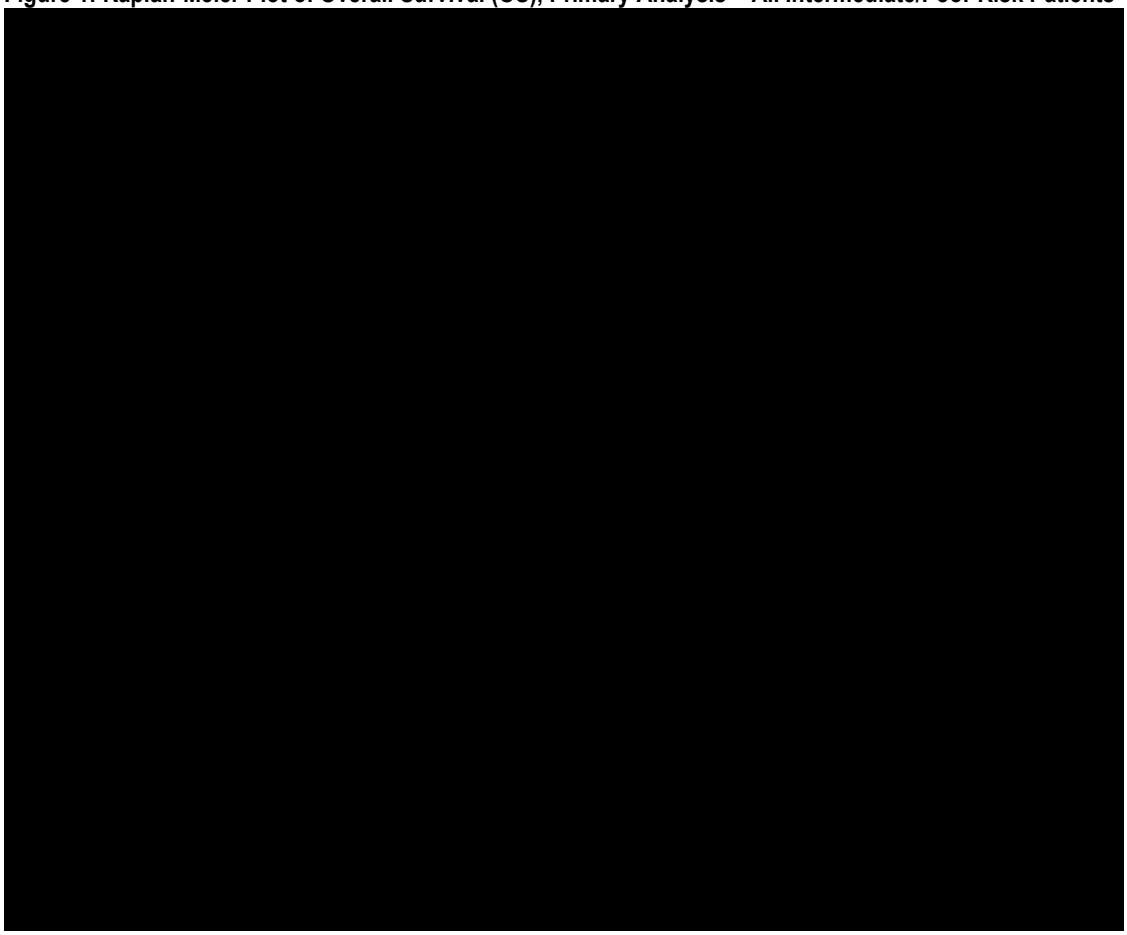
Source: Table 7.1-1, p 96-99 of CA209214 Clinical Study Report; Table S.5.21E of CA209214 Clinical Study Report; p 126 &141 of CA209214 Clinical Study Report.

6.21 In intermediate/poor risk patients, NIVO+IPI demonstrated statistically significant and superior OS compared with sunitinib at the planned interim OS analysis. Median OS in the NIVO+IPI group was not reached at the time of database lock for the interim report, but was [redacted] months in the sunitinib group. Figure 1 shows the Kaplan-Meier plot for OS in intermediate/poor risk patients. The PBAC noted that the OS data were immature, with a median follow-up of 25 months and [redacted]% of patients still alive (across both arms of the intermediate to poor risk group). Thus, the absolute magnitude of the treatment effect, in terms of the difference in median OS between the treatment groups, could not be determined.

6.22 Exploratory analyses in the favourable risk group (IMDC = 0) showed a statistically significant treatment effect favouring sunitinib over NIVO+IPI for PFS and ORR. This group

was not included in the proposed PBS restriction or the proposed TGA indication. The TGA Delegate's Overview stated that advice from impartial Australian clinicians included that a biological basis for such a discrepancy was not obvious, but it was hypothesised that sunitinib may work to a degree in most people for some duration, and that non-responders to immunotherapy may be more likely to be found in the favourable risk group.

Figure 1: Kaplan-Meier Plot of Overall Survival (OS), Primary Analysis – All Intermediate/Poor Risk Patients



Source: Figure 15, p 79 of submission

6.23 The analysis of IRRC-assessed PFS using RECIST v1.1 and censoring for subsequent therapy, favoured NIVO+IPI versus sunitinib (HR = 0.82; 99.1% CI 0.64 to 1.05), but the difference did not reach the pre-specified statistical significance.

6.24 The effectiveness of NIVO+IPI combination therapy compared to monotherapy with either agent is unknown.

Comparative harms

6.25 The key adverse event data are summarised below for the all treated population. Serious adverse events (SAEs) and AEs leading to drug discontinuation were more frequent in the NIVO+IPI arm than in the sunitinib arm.

Table 6: Summary of key adverse events in the trial

n (%)		All Treated Population			
		NIVO+IPI N= 547	Sunitinib N= 535	RR (95% CI)	RD (95% CI)
All causality – any grade					
AEs	Any grade	544 (99.5)	532 (99.4)	1.0 (0.99, 1.01)	0.00 (-0.01, 0.01)
	Grade 3-4	357 (65.3)	407 (76.1)	**0.86 (0.79, 0.93)**	**-0.11 (-0.16, -0.05)**
SAEs	Any grade	305 (55.8)	213 (39.8)	**1.4 (1.23, 1.59)**	**0.16 (0.10, 0.22)**
	Grade 3-4	227 (41.5)	161 (30.1)	**1.38 (1.17, 1.62)**	**0.11 (0.06, 0.17)**
AEs leading to discontinuation	Any grade	168 (30.7)	114 (21.3)	**1.44 (1.17, 1.77)**	**0.09 (0.05, 0.15)**
	Grade 3-4	118 (21.6)	74 (13.8)	**1.56 (1.20, 2.03)**	**0.08 (0.03, 0.12)**
Drug related					
AEs	Any grade	509 (93.1)	521 (97.4)	**0.96 (0.93, 0.98)**	**-0.04 (-0.07, -0.02)**
	Grade 3-4	250 (45.7)	335 (62.6)	**0.73 (0.65, 0.82)**	**-0.17 (-0.23, -0.11)**
SAEs	Any grade	162 (29.6)	81 (15.1)	**1.96 (1.54, 2.48)**	**0.15 (0.10, 0.19)**
	Grade 3-4	121 (22.1)	64 (12.0)	**1.85 (1.40, 2.44)**	**0.10 (0.06, 0.15)**
AEs leading to discontinuation	Any grade	118 (21.6)	63 (11.8)	**1.83 (1.38, 2.43)**	**0.10 (0.05, 0.14)**
	Grade 3-4	84 (15.4)	37 (6.9)	**2.22 (1.54, 3.21)**	**0.08 (0.05, 0.12)**
Immune-mediated adverse events					
Pneumonitis, n (%)		[redacted]	[redacted]	[redacted]	[redacted]
Hepatitis, n (%)		[redacted]	[redacted]	[redacted]	[redacted]
Nephritis or renal dysfunction, n (%)		[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea/Colitis, n (%)		[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 or 4 diarrhoea/Colitis, n (%)		[redacted]	[redacted]	[redacted]	[redacted]
Endocrine disorders					
Hypophysitis n (%)		[redacted]	[redacted]	[redacted]	[redacted]
Adrenal insufficiency n (%)		[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse event; SAE = serious adverse event; CI = confidence interval; n = number of participants reporting data; N = total participants in group; NA = not applicable; RD = risk difference; RR = relative risk.

Source: Table 51, p 92 of the submission; Table 54, p 101 of the submission; Clinical Study Report of CA209214, Table 8.1-1, Table 8.8.2-1 – 8.8.2-5, pp 216, 219, 222, 225.

6.26 Adverse events (AEs) leading to discontinuation in the NIVO+IPI group included increased alanine transaminase and diarrhoea ([redacted]% each), malignant neoplasm progression ([redacted]%), increased aspartate aminotransferase ([redacted]%), pneumonitis (2.0%) and colitis and hypophysitis ([redacted]% each), while for the sunitinib group, AEs leading to discontinuation were malignant neoplasm progression ([redacted]%) and fatigue ([redacted]%). Drug related discontinuations were at least twice as high with NIVO+IPI as sunitinib, with nearly a quarter of patients discontinuing NIVO+IPI due to any grade adverse events.

6.27 There was a significant increase in the risk of immune related AEs in the NIVO+IPI treatment arm compared to the sunitinib treatment arm in terms of pneumonitis ([redacted]% versus [redacted]%; RR=[redacted]; 95%CI: [redacted], [redacted]), hepatitis ([redacted]% versus 0.4%; RR=[redacted];

95%CI: [redacted], [redacted]), nephritis ([redacted]% versus 0.6%; RR=[redacted]; 95%CI: [redacted], [redacted]) and colitis ([redacted]% versus [redacted]%; RR not calculable).

6.28 The comparative safety of NIVO+IPI versus sunitinib in intermediate/poor prognostic patients was similar to that in the all treated population. No safety data were reported in Study CA209214 for patients with favourable prognosis.

6.29 Patients with active or recent history of auto immune disease were excluded from the trial. Therefore, the PBAC considered that the risk of immune-related adverse events in clinical practice is likely to be higher than observed in the clinical trial.

6.30 The PBAC acknowledged that clinicians were becoming better versed in treating the adverse events associated with NIVO+IPI, particularly in the urban setting, but noted that safety in the more rural and remote settings and private hospitals remained a concern. The PBAC noted that there was a need for improved access to high-cost rescue therapies in these settings, for example infliximab for treatment-induced colitis which is not currently PBS-funded for this indication nor routinely available on hospital formularies.

6.31 The PBAC also noted that the trial used the 4:2 sunitinib dosing schedule (4 weeks on sunitinib, followed by 2 weeks off every cycle) that may be associated with a higher rate of adverse events than the 2:1 schedule. Thus the trial may have underestimated the comparative toxicity of NIVO+IPI versus sunitinib that would occur in the PBS population (where some clinicians may use the 2:1 schedule).

6.32 The ESC noted that the incidence of drug-related adverse events (any grade, and Grade 3-4) was higher in the sunitinib arm (e.g. any grade drug-related adverse events were 97% in the sunitinib arm versus 93% in the NIVO+IPI arm). The ESC considered that almost all patients treated with sunitinib would be likely to experience adverse events, while some patients treated with NIVO+IPI would not experience any clinically significant drug-related adverse events.

Benefits/harms

6.33 A summary of the comparative benefits and harms for NIVO+IPI versus sunitinib is presented in the table below.

Table 7: Summary of comparative benefits (intermediate/poor risk group) and harms (all treated population)

Benefits (intermediate/poor risk group)					
	NIVO+IPI N = 425	**Sunitinib N = 422**	**Absolute difference**		**HR (95% CI)**
OS data (immature, data cut off August 2017, median follow up of 25 months)					
Deaths, n (%)	140 (32.9)	188 (44.5)			**0.63 (0.44, 0.89)** p-value < 0.0001
% surviving at 12 months (95% CI)	80.1 (75.9, 83.6)	72.1 (67.4, 76.2)	8		
% surviving at 18 months (95% CI)	75 (70, 78)	60 (55, 65)	15		
Harms (All treated population)*					
	NIVO+IPI N=547	**Sunitinib N=535**	**Event rate/100 patients**		**RD% (95% CI)**
			NIVO+IPI	**Sunitinib**	
Drug-related AEs (any grade) leading to drug discontinuation	118 (21.6)	63 (11.8)	21.6	11.8	10 (5, 14)
Drug related SAEs Grade 3-4	121 (22.1)	64 (12.0)	22.1	12.0	10 (6, 15)

* Reported from the first dose and up to and including 100 days following the last dose of study

Abbreviations: AE = adverse event; SAE = serious adverse event; NIVO+IPI = nivolumab in combination with ipilimumab; OS = overall survival; HR = hazard ratio; CI = confidence interval; RD = risk difference.

Source: compiled during the evaluation based on Table 44, p 78, and Table 51, p 92 of the submission and protocol Study CA209214 p 10, Figure 1, p. 1282 Motzer et al, New England Journal of Medicine, 2018.

6.34 On the basis of the direct evidence (CA209214) presented in the submission, for every 100 patients with intermediate/poor risk treated with NIVO+IPI in comparison to sunitinib,

- Approximately 8 additional patients will be alive at 12 months,
- Approximately 10 additional patients[f] will experience a drug-related AE that leads to drug discontinuation over the median duration of follow-up of [redacted] months,
- Approximately 10 additional patients[f] will experience a drug-related Grade 3-4 SAE over the median duration of follow-up of [redacted] months.

Clinical claim

6.35 The submission described NIVO+IPI as superior to sunitinib in terms of OS with a clinically acceptable safety profile for patients with advanced/metastatic clear cell variant RCC who have an intermediate to poor prognostic risk.

6.36 Given that the OS data were immature, and the median OS had not been reached for the patients treated with NIVO+IPI, the magnitude of the treatment effect, in terms of the differences in median OS between the treatment groups, could not be determined.

6.37 The ESC and the PBAC considered that the claim of clinical superiority of NIVO+IPI versus sunitinib was adequately supported given the statistically significant improvement in OS observed in the pivotal trial, but considered that the magnitude of the benefit was difficult to quantify given the immaturity of the data. The PBAC also considered that the trial population may be healthier than the likely PBS population, and thus the trial may

[f] Data is from all treated patients

have overestimated the incremental effectiveness of NIVO+IPI versus sunitinib. The proportion of patients experiencing SAEs and AEs leading to drug discontinuation was significantly higher in the NIVO+IPI treatment arm compared to the sunitinib arm. Specifically, the incidence of immune related AEs (pneumonitis, nephritis, hepatitis and colitis) was significantly higher in the NIVO+IPI treatment arm compared to that in the sunitinib treatment arm.

6.38 The PBAC[g] previously considered that combination treatment of NIVO+IPI, at the doses used to treat malignant melanoma, has a significantly inferior safety profile and higher rates of SAEs compared to the respective immune monotherapies for the treatment of malignant melanoma. The PBAC was also concerned by early reports of endocrine toxicity with possibility of irreversible diabetes with NIVO+IPI. The ESC noted that the dose of ipilimumab used in the RCC trial CA209214 (1mg/kg every 3 weeks for 4 doses) was lower than that used in the malignant melanoma trial CA209067 (3mg/kg) and considered this may result in a lower rate of adverse events in the RCC setting.

6.39 The ESC acknowledged that NIVO+IPI and sunitinib have different safety profiles, but considered that NIVO+IPI was associated with inferior comparative safety versus sunitinib.

6.40 The PBAC considered that the claim of superior comparative effectiveness was reasonable, though the magnitude of the incremental gain was uncertain and likely overestimated.

6.41 The PBAC considered that NIVO+IPI was associated with inferior comparative safety versus sunitinib, given NIVO+IPI was associated with a higher rate of serious adverse events and adverse events requiring treatment discontinuation.

Economic analysis

6.42 The submission presented a stepped economic evaluation based on the direct randomised trial CA209214 and implemented a modelled cost-utility analysis.

6.43 A Markov model was presented with three health states: Progression free (PF), progressive disease (PD) and dead. A separate tunnel state informed by the time to treatment discontinuation curves (TTD) was used to determine per-cycle drug costs for NIVO+IPI and sunitinib.

[g] Public Summary Document March 2017, PBAC Meeting 7.06 Nivolumab plus Ipilimumab, paragraph 6.23, p 15

Table 8: Summary of model structure and rationale

Component	Description
Type of analysis	Cost utility-analysis, cost effectiveness analysis
Outcomes	Life years gained, quality-adjusted life years gained
Time horizon	[redacted] years in the model base case ([redacted] years in pre-PBAC response revised base case) vs. mean duration of follow up of ~23 months in the trial
Methods used to generate results	Markov expected-value analysis
Health states	Progression-free, progressive-disease, and dead (time until treatment discontinuation as a tunnel state).
Cycle length	[redacted]
Transition probabilities	CA209214: primary population (intermediate/poor risk per IMDC system) KM PFS, OS and TTD curves until mean duration of follow-up; From mean duration of follow-up, parametric functions were used to extrapolate the curves: PFS & OS: [redacted]; TTD: [redacted] Convergence of the NIVO+IPI curve (commencement from [redacted] years in the submission; [redacted] years in the pre-PBAC response revised base case) to sunitinib at the end of modelled time horizon ([redacted] years in submission; [redacted] years in pre-PBAC response revised base case)
Software package	Excel 2010

PFS = progression free survival, OS = overall survival; KM = Kaplan Meier; AIC = Akaike information criterion; BIC = Bayesian information criterion; TTD = time to treatment discontinuation; NIVO = nivolumab; IPI = ipilimumab
Source: Table 73, p129 Section 3 of the submission

6.44 In the base case of the economic evaluation:

- KM estimates from CA209214 were used until the mean duration of follow-up for the PFS (NIVO+IPI [redacted] months; sunitinib [redacted] months), OS (NIVO+IPI [redacted] months; sunitinib [redacted] months) and TTD curves (NIVO+IPI [redacted] months; sunitinib [redacted] months);
- The PFS, OS and TTD curves were extrapolated from the mean duration of follow up until [redacted] months ([redacted] years);
- Beyond 6 years, the PFS, OS and TTD curves were assumed to converge between the beginning of year [redacted] and the end of year [redacted].

6.45 For the extrapolation of overall survival to [redacted] years, the submission assumed that the proportional hazards assumption held on the basis of a visual inspection of the log cumulative hazard plot beyond [redacted] months. The ESC and the PBAC considered that the measure of relative treatment effect beyond the trial duration was highly uncertain given that median OS had not yet been reached in the NIVO+IPI arm.

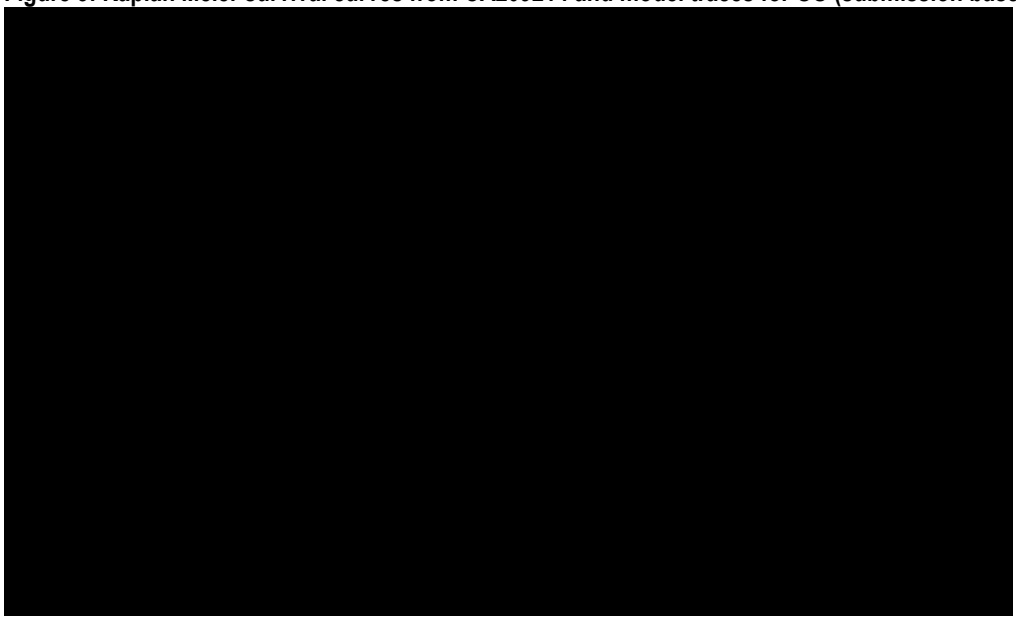
6.46 The PSCR argued that the assumption of proportional hazards was justified on the basis of parallel characteristics in the log cumulative hazard plot for OS beyond [redacted] months, refer to Figure 2(b). However, the ESC considered that proportional hazards observed in the early stages of follow-up are frequently not maintained. The ESC considered that the OS curves appear to start to converge from around [redacted] months follow-up, although acknowledged there may be limited numbers of patients at risk at this time. Given the immaturity of the trial data, the ESC considered that it was not reasonable to assume proportional hazards for [redacted] months.

Figure 2: (a) Kaplan Meier plot for Overall Survival – intermediate and poor risk, CA209214 (b) Log cumulative hazard plot for OS – intermediate/poor risk, CA209214

Source: Figures 30 and 31, p150 Section 3 of the submission

6.47 The figure below shows the extrapolated OS curves from the base case of the submission's economic model and the Kaplan Meier OS curve observed in the clinical trial. The figure shows the period in which proportional hazards were assumed [redacted] to [redacted] years), followed by the period of convergence ([redacted] to [redacted] years). The ESC and the PBAC considered that the overall extrapolation method resulted in a prolonged duration in which a survival benefit was assumed, which was not adequately supported by the clinical data (which had a mean duration of follow-up of [redacted] months for OS).

Figure 3: Kaplan Meier survival curves from CA209214 and model traces for OS (submission base case)



Source: 'Active traces' tab of the economic model 'Att_12_CEA_NIVO+IPI_1LRCC'

6.48 While the Pre-PBAC response acknowledged that the assumptions relating to extrapolation and convergence were subjective, it stated that commencing convergence immediately following the trial-based period would "misrepresent the survival characteristics of immunotherapies observed in the pivotal trial, early phase studies and

the ongoing benefit" that it stated was observed across solid tumors treated with nivolumab.

6.49 The pre-PBAC response proposed a revised base case with proportional hazards applied from [redacted] months to [redacted] years (rather than [redacted] years), followed by the period of convergence to [redacted] years (rather than [redacted] years) and a time horizon of [redacted] years (rather than [redacted] years). The pre-PBAC response argued that these parameters represented "a plausible lower limit of efficacy".

6.50 For the extrapolation of PFS, the submission identified that the best fitting independent parametric functions for NIVO+IPI and sunitinib was the [redacted] followed by the [redacted] distribution ([redacted]). The submission also noted that none of the parametric functions fit the KM curve particularly well. The evaluation considered that alternative more flexible extrapolation approaches with multiple points of inflexion (i.e. piecewise spline models) could have been explored to better facilitate extrapolation based on the section of the KM curve that is most representative of long-term survival. However, the evaluation also noted that the structure of the model was such that the results were not sensitive to changes in the measure of PFS.

6.51 The figure below provides the Kaplan Meier survival curves from CA209214 and the modelled OS, PFS and TTD curves used in the economic evaluation (submission base case).

Figure 4: Kaplan Meier survival curves from CA209214 and model traces for the OS, PFS and TTD curves.

[redacted]

Source: 'Active Traces', Att_12_CEA_NIVO+IPI_1LRCC.xlsx.

6.52 The ESC considered that the extrapolated Time to Treatment Discontinuation curve (green dotted curve in Figure 4) would likely be expected to trend toward the PFS curve (purple dotted curve) over time. This is because higher discontinuation rates are expected in the initial period when patients discontinue treatment due to adverse events. The observed discontinuation rate reduces at around [redacted] months and so the ESC considered that extrapolating TTD to the full data may overestimate discontinuation and underestimate treatment costs. The ESC considered that the large difference between the extrapolated Time to Treatment Discontinuation and PFS curves resulted in under-estimated treatment costs.

6.53 The pre-PBAC response stated that PFS may not be a reliable proxy for treatment exposure and considered that any adjustment of Time to Treatment Discontinuation towards PFS would be arbitrary. The PBAC considered that, in this case, extrapolation of Time to Treatment Discontinuation was likely more appropriate than extrapolation of PFS for determining treatment exposure.

6.54 Health state utilities applied in the model were based on the EQ-5D individual patient data from Study CA209214, converted using the Australian-specific scoring algorithm published by Viney 2011. The submission stated that disutilities associated with adverse events were assumed to be captured in the treatment based health state utilities in the economic model. The evaluation considered that it was difficult to assess whether disutilities associated with treatment were accurately reflected in the utility values as no information was provided in the submission regarding those patients lost to follow up, nor changes in utility values over patient follow up.

6.55 Health state utilities applied in the economic model are summarised in the table below.

Table 9: Utility values used in the economic evaluation

Health state	Utility	Nature of estimate/translations	Source of estimate	Average application in the model (undiscounted)	
				NIVO+IPI	sunitinib
PF NIVO+IPI arm	[redacted]	EQ-5D with Australian preference weights	CA209214[a]	[redacted] years	
PF sunitinib arm	[redacted]	EQ-5D with Australian preference weights	CA209214[a]		[redacted] years
PD NIVO+IPI arm	[redacted]	EQ-5D with Australian preference weights	CA209214[a]	[redacted] years	
PD sunitinib arm	[redacted]	EQ-5D with Australian preference weights	CA209214[a]		[redacted] years

PD = progressed disease; PF = progression free; NIVO = nivolumab; IPI = ipilimumab; EQ-5D
[a] intermediate/poor risk subpopulation
Source: Table 89, p160 Section 3 of the submission, Average application in the model taken from 'Att_12_CEA_NIVO+IPI_1LRCC.xlsx',

6.56 The evaluation considered that it was unclear why the health state utility was higher in the NIVO+IPI arm compared to the sunitinib arm in both the progression-free and progressive health states. Since patients in the NIVO+IPI arm reported a higher frequency

of drug-related serious adverse events than patients in the sunitinib arm ([redacted]% vs [redacted]% for any grade; and [redacted]% vs [redacted]% for grade 3-4 SAEs for the intermediate/poor risk subgroup), the evaluation considered that a higher utility for NIVO+IPI than for sunitinib may not be reasonable. One possible explanation may be the higher rates of AEs lead to discontinuations in the NIVO+IPI arm. It is unclear whether EQ-5D questionnaires were administered to patients following discontinuation of treatment or the timing of the EQ-5D data collection.

6.57 Due to the lack of detail in the submission regarding the EQ-5D completion rates in the trial, characteristics of non-completers, whether the EQ-5D was administered to those experiencing adverse events and the time points of the EQ-5D data collection following radiological progression, the evaluation considered that the estimates from the trial were highly uncertain.

6.58 The PSCR provided further information regarding the EQ-5D completion rates in the trial, which are provided in the table below. The PSCR also outlined that patients were scheduled for regular follow-up assessments for EQ-5D after their last dose of study drug. However, the PSCR did not indicate the proportion of patients who completed the survey post-progression nor the duration since progression of any of the results, which would impact the reliability of the utility values applied in the PD health states (especially given that a constant utility value was applied in the PD health state over the [redacted] year time horizon).

Table 10: EQ-5D completion rates in CA209214, n (%)

Weeks	0	12	24	36	48	60	72	84	96
NIVO+IPI	([redacted]%)	([redacted]%)	([redacted]%)	([redacted]%)	[redacted] ([redacted]%)	([redacted]%)	([redacted]%)	([redacted]%)	([redacted]%)
Sunitinib	([redacted]%)	([redacted]%)	([redacted]%)	([redacted]%)	([redacted]%)	([redacted]%)	([redacted]%)	([redacted]%)	([redacted]%)

NIVO = nivolumab; IPI = ipilimumab
Source: Page 5 of the PSCR

6.59 The PSCR stated that in intermediate/poor risk patients, EQ-5D completion rates were maintained at approximately [redacted]% or higher over the first [redacted] weeks of the trial. The ESC considered that the data showed reasonably high completion rates, though these were consistently lower in the NIVO+IPI arm. The ESC considered that this may have been because patients who experienced severe adverse events may have been less likely to complete the survey (as outlined earlier).

6.60 The ESC considered that it may have been clinically plausible for patients (in the progression-free health state) to experience better quality of life in the NIVO+IPI arm because there may be a proportion of patients who experience no clinically significant adverse events with NIVO+IPI, however almost all patients are likely to experience some adverse events that affect quality of life with sunitinib. However, the ESC acknowledged that this was not able to be verified based on the data available.

6.61 The evaluation, ESC and the PBAC considered that the utility estimates appeared high in relation to other economic evaluations, and utility values identified in the literature. Further, the ESC and PBAC noted that the utility estimates were similar to population norms (e.g. the mean EQ-5D-3L score in Australians aged: 55-64 years is 0.85; and 65-74 years is 0.82, as reported in Clemens et al, 2014). It is unlikely that patients will experience such a high utility consistently over the time horizon of the model, particularly given an ageing population and subsequent disease progressions.

6.62 In its consideration of sunitinib for first-line treatment of mRCC, NICE considered that a difference of 0.08 between the utility assigned to a progression-free health state [redacted]) and progressed health state ([redacted]) was too small[h]. The difference between the progression-free and progressed health states applied in the submission's economic model was [redacted] for the NIVO+IPI arm and [redacted] for the sunitinib arm. The economic model was sensitive to the utility values applied.

6.63 The pre-PBAC response stated that there were applicability issues associated with the utility values sourced from the literature, e.g. utilities from the NICE submission for sunitinib were based on a clinical setting of >10 years ago and may not represent current management of first-line RCC.

6.64 The key drivers of the model are provided in the table below.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	Extrapolation of overall survival from immature data in the trial assuming proportional hazards to [redacted] years ([redacted] years in the pre-PBAC response), then convergence from [redacted] to [redacted] years (from [redacted] to [redacted] years in the pre-PBAC response).	High, favours NIVO+IPI
Utilities	• High values from EQ-5D data in CA209214 with Australian preference weights (mean utility scores). Utility values used in the economic evaluation are higher than those identified in the literature. • Utility values for the NIVO+IPI arm are higher than the sunitinib arm despite a higher incidence of Grade 3-4 serious adverse events.	High, favours NIVO+IPI
Intervention costs	• The extrapolated TTD curve does not converge with the PFS curve. • Assumes mean weight and dose intensity (+ wastage) from CA209214.	Moderate to high favours NIVO+IPI

NIVO = nivolumab; IPI = ipilimumab; TTD = time to treatment discontinuation.
Source: compiled during the evaluation based on Section 3.9 of the submission

6.65 Results of the stepped economic evaluation provided in the submission are provided in the table below. The pre-PBAC response provided a revised base case, also outlined in the table below, based on convergence commencing at [redacted] years and ending at 10 years,

[h] Paragraph 4.3.10, National Institute for Health and Clinical Excellence, final appraisal determination, sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma, 2009; url https://www.nice.org.uk/guidance/ta169/documents/sunitinib-for-the-firstline-treatment-of-advanced-andor-metastatic-renal-cell-carcinoma-final-appraisal-determination3, Accessed 14 May 2018.

with a [redacted] year time horizon. The pre-PBAC response also applied a [redacted]% reduction to the nivolumab price to maintain the ICER at $45,000/QALY - $75,000/QALY.

Table 12: Results of the stepped economic evaluation

Steps	Outcomes and Extrapolation	Costs			Outcomes			ICER
		NIVO+IPI	SUNI	Δ	NIVO+IPI	SUNI	Δ	
Step 1	Trial based evaluation: OS, TTD and PFS per KM estimates over the median duration of follow-up ([redacted] months)	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	$[redacted]/LYG
Step 2	KM estimates applied to mean follow-up for OS, PFS and TTD; parametric extrapolation over [redacted] year time horizon	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	$[redacted]/LYG
Step 3	Treatment outcomes and TTD for NIVO+IPI converged to SUNI (from[redacted] months) over the [redacted] year time horizon	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	$[redacted]/LYG
Step 4	Attachment of treatment arm, trial based utilities (CA209214)				[redacted]	[redacted]	[redacted]	$[redacted]/QALY
Revised base case in pre-PBAC response								
Step 5	Commencement of convergence at Year [redacted] and ending at [redacted] years, with a [redacted] year time horizon	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	$[redacted]/QALY
Step 6	With reduced price in pre-PBAC response ([redacted]% reduction in nivolumab price) [a]	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	$[redacted]/QALY

IPI = ipilimumab; KM = Kaplan-Meier; NIVO = nivolumab; OS = overall survival; PFS = progression free survival; TTD = time to treatment discontinuation; QALY = quality-adjusted life year; LYG = life year gained; SUNI = sunitinib.

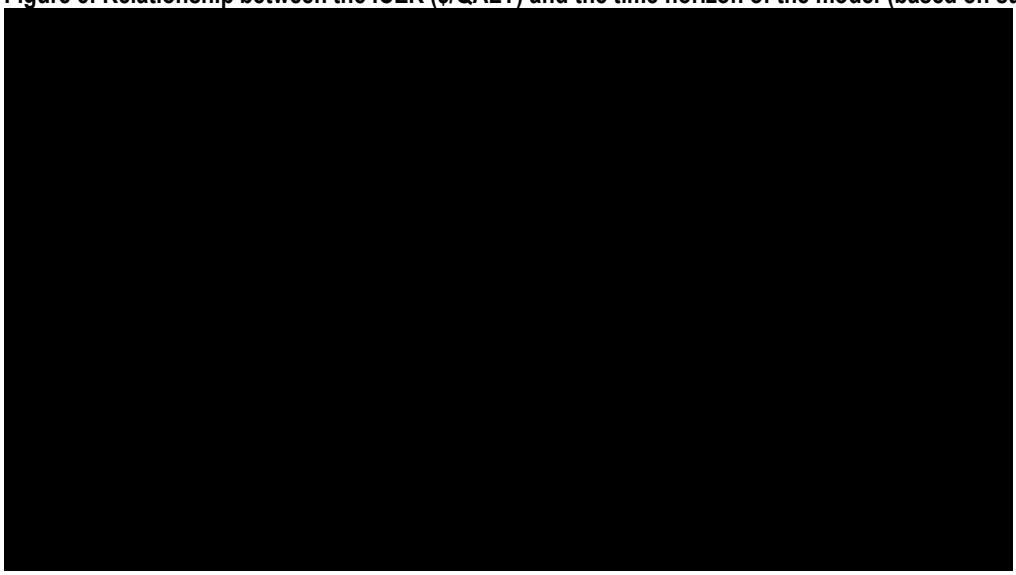
Source: Table 96, p171 Section 3 of the submission; Tables 2-3 (pp. 2-3) pre-PBAC response

[a] From $[redacted] to $[redacted] for the 100 mg vial, with corresponding reductions also applied to the 40 mg vial price.

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

6.66 The relationship between the ICER ($/QALY) and the time horizon of the model is provided in the figure below. After year [redacted], the ICER remained stable until the end of year [redacted].

Figure 5: Relationship between the ICER ($/QALY) and the time horizon of the model (based on submission base case)



Source: Compiled during the evaluation based on Att_12_CEA_NIVO+IPI_1LRCC.xlsx

6.67 Although the submission's model applied convergence of survival curves from Year [redacted] to Year [redacted], this did not have a major impact on the results of the model, which indicated that the modelled health benefit is mostly accumulated within the first [redacted] years (see above figure). During the evaluation, sensitivity analyses were conducted to explore the impact of assumptions used in the extrapolation of the OS and PFS curves (including assumptions about the convergence of these curves). See below.

6.68 Results of selected sensitivity analyses are provided in the table below, based on the submission's base case.

Table 13: Results of key sensitivity analyses for the economic evaluation (based on submission base case)

Variable	ΔCost	ΔLYG	ΔQALY	Cost/ LYG	Cost/ QALY	% change
Base case (from submission)	$			$	$	-
Univariate analyses						
Extrapolation. Base case: Convergence of OS and PFS begins at years, end at years						
Convergence begin at months for PFS and OS, end at years^	$			$	$	%
Convergence begin at months for PFS and OS, end at years^	$			$	$	%
TTD and PFS extrapolated separately in both arms						
TTD curve adjusted so that proportion on treatment at month was: for NIVO+IPI; and for sunitinib [a]	$			$	$	%
Health state utilities. Base case: NIVO+IPI: PF: , PD: ; SUNI: PF: , PD						
PF and PD health state utilities set to PF: , PD (utilities based on sunitinib arm from CA209214)^	$			$	$	%
PF and PD health state utilities set as average of PF and PD health state utilities from the literature, as calculated by the submission (PF = , PD =)^	$			$	$	%
Multivariate analyses						
Extrapolation of PFS and OS; & health state utilities ^ Base case: Convergence of OS and PFS begins at years and ends at years; Utilities treatment arm specific NIVO+IPI: PF: , PD: ; SUNI: PF: , PD						
Convergence begins at months and ends at years for PFS and OS; Utilities in NIVO+IPI arm set equal to those in the sunitinib arm^	$			$	$	%
Convergence begins at months and ends at years for PFS and OS; Utilities in NIVO+IPI and sunitinib arms equal to the average utilities from the literature (see Section 3.5; PF = , PD =)^	$			$	$	%
Extrapolation of PFS and OS; TTD curves & health state utilities						
• Convergence begins at months and ends at years for PFS &OS. • TTD curves adjusted so that proportion on treatment at month was: for NIVO+IPI; and for sunitinib [a] • Utilities in NIVO+IPI and sunitinib arms equal to the average utilities from the literature (see Section 3.5; PF = , PD =)^	$			$	$	%

^Conducted during the evaluation

[a] Conducted as part of the ESC advice. The TTD curve for NIVO+IPI was re-aligned, starting at mean duration of follow up (months) such that the proportion on treatment at month is . The TTD curve for sunitinib was re-aligned, starting at mean duration of follow up (months), such that the proportion on treatment at month is .

DoT = duration of therapy; IPI = ipilimumab; LYG = life year gained; NIVO = nivolumab; OS = overall survival; PD = progressive disease; PFS = progression free survival; QALY = quality adjusted life year; TTD = Time to Treatment Discontinuation

Source: Table 101, p 177 Section 3 of the submission

This redacted table shows ICERs in the range of $45,000/LYG - $200,000/LYG; and $45,000/QALY - $200,000/QALY.

6.69 The sensitivity analyses indicated that the model was sensitive to the utilities applied and the extrapolation of OS (particularly as part of multivariate analyses where utilities were also changed). The ESC noted that the model was also sensitive to the extrapolation of the Time to Treatment Discontinuation curve (though acknowledged the analysis relied on the base case PFS extrapolation which may not have been reliable).

6.70 The ESC considered that a more realistic scenario would need to address: the assumption of proportional hazards to years and convergence at years; the large difference

between the extrapolated TTD and PFS curves; and the high utility values applied (i.e. the utilities were similar to population norms and were considerably higher than those sourced from the literature).

Drug cost/patient/course: $[redacted] (based on price proposed in submission)

6.71 This consists of a cost per patient per course of $[redacted] for ipilimumab and $[redacted] for nivolumab.

6.72 In the base case, the cost associated with NIVO+IPI was calculated on the basis of:

- A dose of 3mg/kg for nivolumab every 3 weeks for the first four doses, then every 2 weeks thereafter until disease progression or unacceptable toxicity was assumed, consistent with the doses in CA209214, and the proposed TGA PI.
- A dose of 1mg/kg for ipilimumab every three weeks, for an average of [redacted] infusions (CA209214)
- Using a mean patient weight of [redacted]kg, based on CA209214 and distribution of dose intensity from CA209214. This resulted in an average dose of [redacted]mg per dose per patient for nivolumab, and [redacted]mg for ipilimumab.
- A most efficient vial combination of 2x100mg and 1x40mg vials of nivolumab (240mg), and 2x 50mg ipilimumab vials (100mg) would be dispensed per dose;
- The submission proposed an effective ex-manufacturer price for nivolumab of: 40mg vial $[redacted]; 100mg vial $[redacted]; and the proposed effective ex-manufacturer price of $[redacted] per 50mg vial of ipilimumab. The pre-PBAC response proposed a [redacted]% lower price of nivolumab (no change was proposed to the ipilimumab price).
- Assuming a public/private split of [redacted]:[redacted].
- The duration of treatment for nivolumab was based the extrapolation of the TTD curve, which estimated an average of [redacted] doses ([redacted] months of treatment, including [redacted] doses in the induction phase). The changes to the OS extrapolation and time horizon proposed in the pre-PBAC response would reduce the estimated average number of nivolumab doses to 33.6 per patient.

6.73 The cost per patient per course for the main comparator, sunitinib, was $[redacted] per patient per course. This was calculated on the following basis:

- The dosing of sunitinib in CA209214 and the TGA approved PI for sunitinib is 50mg for 4 weeks, followed by 2 weeks off, allowing for dose adjustments.
- The average daily dose (mg/day) of sunitinib in CA209214 ([redacted]mg/day, multiplied by [redacted]/[redacted] to get [redacted]mg average dose per day of sunitinib in the four treatment weeks).
- Given that multiple strengths were available (12.5mg, 25mg, 37.5mg, 50mg) a weighted cost/mg was applied ($[redacted]/mg) based on prescriptions dispensed since listing (May 2009 - November 2017);
- This resulted in a cost of sunitinib per 6-week treatment cycle (4 weeks on treatment, followed by two weeks off treatment) of $[redacted].
- The duration of sunitinib treatment was based on the extrapolated TTD curve, which

estimated an average of [redacted] packs per treatment course ([redacted] months of treatment or [redacted] treatment cycles).

Estimated PBS usage & financial implications

6.74 This submission was not considered by DUSC.

6.75 The submission used a mixed market- and epidemiological-based method to estimate the extent of use and financial implications of listing NIVO+IPI on the PBS.

6.76 The size of the eligible patient population was based on:

- The historical number of patients to be treated with PBS-subsidised therapies for RCC (100% PBS sample from the Department of Human Services). The submission used the number of patients initiating RCC therapy in the 12 months prior to 30 June 2016 to estimate the number of patients initiating therapy for first-line (1L) RCC in 2016 ([redacted] patients). The submission referenced the total number of patients initiating therapy with PBS items used to treat RCC, in any line of therapy, rather than those initiating first-line therapy only. The evaluation considered that this would likely overestimate the number of patients currently seeking PBS-subsidised therapy for RCC in the first-line setting. The PSCR stated that the estimate was based on the number of patients who received a PBS script for RCC therapy after having had no PBS scripts for RCC therapies in the previous 12 months, and that the numbers were similar when a 24 month look-back period was used. The PSCR stated that this only captured patients commencing treatment in the first-line setting. The ESC considered that the submission's assumption, that most patients with no scripts for RCC therapies in the previous 12 or 24 months would be in the first-line setting, was generally reasonable but may have slightly underestimated the eligible patient population as it may exclude some patient with intervening surgery or on clinical trials (acknowledging the latter was accounted for in a subsequent step).
- The estimated increase in the size of the incident population with RCC was based on a linear extrapolation of Australian Cancer Incidence and Mortality (ACIM) books kidney cancer rates from 2001 to 2014[i]. This equated to an increase of approximately 2-3% per year.
- Increasing the size of the PBS-treated population by [redacted]%, to account for a high level of clinical trial activity occurring in Australia for first-line RCC, which the submission argued had led to a decrease in the PBS treated population. The figure of [redacted]% due to increased clinical trial activity, was based on Bristol-Myers Squibb 1L RCC trial participation. A total of four Australian Bristol-Myers Squibb 1L RCC clinical trials were referenced from 2014 to 2018 (CA209-9ER, CA209-800, CA209-214 and CA018-

[i] Australian Institute of Health and Welfare (AHIW). Figures by cancer type (kidney-cancer). 2017 [updated April 2018]; Available from: https://www.aihw.gov.au/reports/cancer/acim-books/contents/acim-books.

005) and included a total of [redacted] patients. The submission also referenced 1L RCC ongoing trials by pharmaceutical companies Roche and Pfizer, but participant numbers were not provided.

- The submission estimated that [redacted]% of the 1L treated advanced/metastatic RCC patients had intermediate or poor risk prognostic scores based on IMDC. This was based on a weighted average from a number of international trials[j] as well as an Australian retrospective study[k] and phase III comparative studies (COMPARZ[l] and Study CA209214). This appeared reasonable.

6.77 The submission estimated the uptake of NIVO+IPI combination in future Australian practice is [redacted]% in patients with intermediate/poor risk, with a potential lower limit of [redacted]% (meeting minutes of Bristol Myers Squibb 1L Renal cell carcinoma advisory board- Appendix 3 of submission).

6.78 The submission reported that the most likely PBS medicines affected by the listing of NIVO+IPI for 1L RCC therapy were the currently listed therapies in the 1L, 2L and 3L setting. The submission stated that the utilisation of sunitinib and pazopanib in the 1L setting and nivolumab in the 2L setting were anticipated to be reduced, and therefore represented the majority of PBS/RPBS cost offsets over the six year forecast period.

6.79 The proportion of patients requiring subsequent 2L therapy ([redacted]%) and 3L therapy ([redacted]%) were consistent with figures previously accepted by PBAC for the listing of nivolumab for use in the 2L treatment for RCC. As reported by PBAC, an increased [redacted]% initiation of 2L therapy was considered to be a likely overestimation, although this figure represented a reasonable upper limit for the purposes of calculating risk sharing arrangement caps (Paragraph 6.46, Nivolumab Public Summary Document, March 2017). The PBAC therefore considered it was likely that cost offsets associated substituted 2L and 3L therapies may be overestimated.

6.80 The relative market share of subsequent therapies in second- and third-line settings were informed by the virtual advisory board. These values were based on a small number of oncologists (n=9/12), and their opinions may not be representative of the Australian clinical practice.

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[j] Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. Br J Cancer. 2015;113(1):12-9.
Heng DYC, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. The Lancet Oncology. 2013;14(2):141-8.
Ruiz-Morales JM, Swierkowski M, Wells JC, Fraccon AP, Pasini F, Donskov F, et al. First-line sunitinib versus pazopanib in metastatic renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur J Cancer. 2016;65:102-8.
[k] Day D, Kanjanapan Y, Kwan E, Yip D, Lawrentschuk N, Andrews M, et al. Patterns of care for metastatic renal cell carcinoma in Australia. BJU Int. 2015;116 Suppl 3:36-41.
[l] Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013;369(8):722-31.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of NIVO+IPI						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Induction infusions/year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance infusions/year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of NIVO+IPI						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for other PBS medicines						
Cost to PBS/RPBS Revised^	-$[redacted] -$[redacted]	-$[redacted] -$[redacted]	-$[redacted] -$[redacted]	-$[redacted] -$[redacted]	-$[redacted] -$[redacted]	-$[redacted] -$[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Cost to PBS/RPBS less copayments Revised^	-$[redacted] -$[redacted]	-$[redacted] -$[redacted]	-$[redacted] -$[redacted]	-$[redacted] -$[redacted]	-$[redacted] -$[redacted]	-$[redacted] -$[redacted]
Net financial implications						
Net cost to PBS/RPBS Revised^	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]
Net cost to MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS/MBS Revised^	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]	$[redacted] $[redacted]

^Revised during the evaluation to apply the published ex-manufacturer price for these medicines. It was unclear where the effective prices for these medicines used in the financial estimates were sourced from.

Source: compiled during the evaluation based on information presented in 'Att_13_BIM_NIVO+IPI_1LRCC.xlsx'

6.81 The submission estimated a cost to the PBS/RPBS of $30 - $60 million in Year 5 and more than $100 million over the first six years of listing, and a net cost to the PBS/RPBS (including offsets) of more than $100 million over the first six years. The reduced nivolumab vial price proposed in the pre-PBAC response and lower estimated number of vials per patient (due to changed economic model parameters in the pre-PBAC response) would result in a lower estimated cost to the PBS/RPBS.

6.82 The PBAC considered that the estimated financial implications for other PBS medicines (cost offsets), particularly those relating to second- or later-line settings, is likely to be overestimated due to the high proportion of patients assumed to seek treatment in these settings.

6.83 Further, similar to an issue raised in the DUSC Advice for Item 7.05 (NIVO+IPI in malignant melanoma), in the pivotal RCC trial patients had to receive the full four doses of ipilimumab induction therapy before they could proceed to the nivolumab monotherapy continuation phase. A substantial proportion of patients discontinued NIVO+IPI during the induction phase due to drug toxicity ([redacted]%) in the trial. The ESC considered that, in

clinical practice, patients who experience adverse events during NIVO+IPI induction may go on to receive nivolumab monotherapy (rather than discontinue). This may have further underestimated the number of nivolumab prescriptions per patient that would be used in clinical practice.

6.84 The pre-PBAC response stated that use of nivolumab monotherapy in patients who had discontinued NIVO+IPI induction was likely to be minimal as only [redacted]% of patients ([redacted]/425) received an anti-PD-1 treatment following NIVO+IPI therapy. However, the clinician at the sponsor hearing indicated that, in most cases, ipilimumab was responsible for toxicities that occur during the induction phase, and in such cases it is generally appropriate to cease all treatment and rechallenge with nivolumab monotherapy once the toxicity resolves.

Quality Use of Medicines

6.85 The submissions reported sponsor activities to support the safe and effective use of NIVO+IPI in Australia, included physician education and nursing and pharmacy in-services. The submission reported that following TGA approval of NIVO+IPI for RCC, educational resources would be available for health care professionals and patients including immune related Adverse Reactions (irAR) management guide, irAR symptom checklist and wallet alert card. The submission explained that patients would access educational material from the oncologist only, and not via the sponsor.

6.86 The sponsor is seeking PBS listing for combined NIVO+IPI as a first line treatment of RCC before either nivolumab or ipilimumab monotherapy have been determined as being acceptable first line treatments for RCC. Neither nivolumab monotherapy nor ipilimumab monotherapy are currently listed on the PBS or TGA-approved for RCC in the first-line setting. It is, therefore, unclear as to the contribution of each medicine to the combined treatment effect, and whether patients would be unnecessarily exposed to additional toxicities associated with combined treatment.

6.87 The sponsor recognised, there was potential for leakage of NIVO+IPI in patients with favourable risk. Efficacy results indicate that NIVO+IPI may be inferior to sunitinib in favourable risk patients, in terms of OS, PFS and ORR, and thus there is potential for harm in this subset of patients. The PBAC considered that categorisation of patients into level of risk was reasonably straightforward in clinical practice (using IMDC), minimising the risk of using NIVO+IPI in favourable risk patients.

Financial Management – Risk Sharing Arrangements

6.88 The sponsor recognised there was potential for leakage of NIVO+IPI and were willing to enter a risk share arrangement with a [redacted]% rebate beyond the agreed subsidisation caps to mitigate any financial uncertainty.

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

7 PBAC Outcome

7.1 The PBAC decided not to recommend nivolumab in combination with ipilimumab (NIVO+IPI) for the first-line treatment of Stage IV clear cell variant renal cell carcinoma (RCC) in patients at intermediate to poor prognostic risk. The PBAC acknowledged the high clinical need for effective first-line therapies, especially in patients who are categorised as being at poor prognostic risk. However, the PBAC considered that the incremental survival and quality of life benefits were overestimated in the economic model presented, and that the incremental cost-effectiveness ratio (ICER) was uncertain and unacceptably high. The PBAC considered that a price reduction would be required to bring the estimated ICER into an acceptable range.

7.2 The PBAC considered that there is a high clinical need for effective first-line therapies for RCC, especially in the poor-risk patient population for whom no PBS-subsidised therapies are available.

7.3 The PBAC considered that the restriction criteria for NIVO+IPI should be based on International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), rather than the Memorial Sloan Kettering Cancer Center (MSKCC) criteria, to reflect current clinical practice where IMDC has superseded MSKCC. The PBAC further noted that the current restrictions for sunitinib and pazopanib in RCC are based on the MSKCC criteria, and considered that, should NIVO+IPI be listed for RCC in the future, then the restrictions for sunitinib and pazopanib could similarly be changed to IMDC for consistency.

7.4 The PBAC noted that the requested restriction included patients with a WHO performance status of ≤ 2, rather than the trial inclusion of Karnofsky Performance Status (KPS) ≥ 70, in order to align with the restrictions for other PBS-listed medicines for RCC. The PBAC considered that WHO performance status is more commonly used in Australian clinical practice, and as such, it would be appropriate for the restriction to include WHO performance status ≤ 2, as requested by the submission

7.5 The PBAC noted that the submission requested a flow-on change to the existing restrictions for second- and later-line RCC therapies: removal of the requirement for patients to have received prior TKI therapy before commencing second-line nivolumab, everolimus, axitinib, sorafenib or cabozantinib. The PBAC considered that this was not appropriate given that no evidence had been provided to support this change.

7.6 The PBAC noted that the submission proposed sunitinib as the comparator in the proposed population (i.e. in both intermediate and poor risk patients), despite sunitinib not being PBS-listed for use in poor risk patients. The PBAC acknowledged that sunitinib (and pazopanib) are used in clinical practice in patients who are at poor prognostic risk. While accepting sunitinib as the appropriate comparator, the PBAC expressed concern that patients at poor prognostic risk are currently being treated with sunitinib and pazopanib, which are likely to have limited efficacy in this population, but may be associated with significant toxicity.

7.7 The PBAC noted that NIVO+IPI was associated with a [redacted]% improvement in OS at 18 months versus sunitinib, with a hazard ratio for death of 0.63 (95% CI: 0.44, 0.89), which the PBAC considered was indicative of an important improvement in OS. However, the PBAC considered that the absolute magnitude of the treatment effect could not be reliably estimated because the OS data from the pivotal trial were immature, with 61% of patients still alive at the data-cut reported in the submission (across both arms of the intermediate to poor risk group). However, the PBAC acknowledged that any longer term data (subsequent data-cuts) would be further confounded by subsequent therapies.

7.8 The PBAC considered that the trial may have overestimated the incremental effectiveness, and underestimated the incremental toxicity, of NIVO+IPI versus sunitinib that would be observed in the PBS population as the trial population may have been healthier than the likely PBS population. For example: [redacted]% of patients in the NIVO+IPI arm of the trial were < 65 years of age, while only [redacted]% of patients were ≥ 75 years; [redacted]% were KPS 90-100; and the trial excluded patients with CNS and used the less tolerable sunitinib 4:2 dosing regimen.

7.9 The PBAC acknowledged that NIVO+IPI is associated with a different adverse event profile than sunitinib. The PBAC considered that with immunotherapies such as NIVO+IPI there is likely to be a group of patient who experience severe toxicity and other patients who experience no adverse events. On the other hand, with sunitinib most patients will experience some low-grade adverse events. However, overall the PBAC considered that NIVO+IPI was associated with inferior comparative safety versus sunitinib, given NIVO+IPI was associated with a higher rate of serious adverse events and adverse events requiring treatment discontinuation than sunitinib.

7.10 Further, the PBAC considered that the adverse events associated with NIVO+IPI may be challenging to manage outside major tertiary centres (e.g. in the more rural and remote settings and private hospitals). The PBAC considered that there was a need for improved access to immune-modulating rescue therapies in these settings, for example infliximab for treatment-induced colitis which are not currently PBS-funded for this indication nor routinely available on hospital formularies.

7.11 The PBAC noted that NIVO+IPI was associated with potentially worse outcomes than sunitinib in the group of patients with a favourable prognosis (a statistically significant decrease in PFS and ORR was observed in the trial), and considered that the reasons for this were unclear. However, the PBAC considered that determination of a patient's prognostic risk was reasonably clear, which would minimise the risk of use of NIVO+IPI in patients with a favourable prognosis.

7.12 The PBAC acknowledged that the pre-PBAC response had made modest changes to the economic model survival extrapolations, but considered that the ICER/QALY remained uncertain and overly optimistic due to:

- the assumption of proportional hazards from the mean duration of follow-up to five

years, which the PBAC considered was highly uncertain given that median OS had not yet been reached in the NIVO+IPI arm. The PBAC considered it would be more reasonable to assume that convergence of the OS (and PFS) curves begins at [redacted] months);

- the utility estimates were similar to population norms and were considerably higher than those sourced from the literature. The PBAC noted that the utility value applied in the progressed disease health state was [redacted] in the NIVO+IPI arm ([redacted] in the sunitinib arm), and considered it was unlikely that patients would experience such a high utility consistently over the time horizon of the model. The PBAC considered that it would be more reasonable to assume that the utilities would be consistent with the average utilities from the literature (progression free health state utility = [redacted], progressed disease health state utility = [redacted]).
- the PBAC considered that the time horizon ([redacted] years in the pre-PBAC response) was not reasonable given the short duration of follow-up in the trial and the uncertainties with the extrapolation. Further, the Committee noted that the model estimated that [redacted]% of patients in the sunitinib arm would be alive at [redacted] years, which the PBAC considered was not realistic for a population of patients with poor/intermediate risk Stage IV RCC. While the PBAC noted that economic model was relatively insensitive to the time horizon, the PBAC considered that a time horizon of [redacted] years would be more realistic in this population group.

7.13 The PBAC considered that NIVO+IPI would be cost-effective at an ICER of less than $45,000/QALY - $75,000/QALY, using the updated model parameters outlined above.

7.14 The PBAC considered that the estimated net cost to the PBS/RPBS was high and potentially underestimated given:

- There is potential for a higher rate and duration of use of nivolumab maintenance therapy in clinical practice than was observed in the trial. In clinical practice, patients who experience adverse events during NIVO+IPI induction may go on to receive nivolumab monotherapy, rather than discontinue as was required by the trial protocol.
- The estimated financial implications for other PBS medicines (cost offsets), particularly those relating to second- or later-line settings, was likely to have been overestimated due to the high proportion of patients assumed to seek treatment in these settings.

7.15 The PBAC considered that any resubmission would need to be a major resubmission and would need to:

- provide a revised economic model based on the parameters outlined above;
- update the financial estimates as outlined above;
- include an RSA with a [redacted]% rebate beyond estimated utilisation. The PBAC considered that listing NIVO+IPI in the first-line setting would reduce second-line use of nivolumab, and so flow-on changes would be required to the existing RSA for

second-line nivolumab.

7.16 The PBAC noted that this submission is eligible for an Independent Review

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.