

6.02 AVELUMAB, Solution concentrate for I.V. infusion 200 mg in 10 mL, Bavencio[®], Merck Healthcare Pty Ltd.

1 Purpose of submission

- 1.1 The submission requested an Authority Required listing for avelumab in combination with axitinib (AVE + AXI) for first-line treatment of advanced (stage IV) clear cell variant renal cell carcinoma (RCC).
- 1.2 The submission also requested that the PBAC consider a broad listing, agnostic to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk criteria based on ‘unmet clinical need’ for more effective treatments for the first-line treatment of advanced RCC patients classified as favourable according to IMDC risk criteria and that there is currently no immunotherapy regimen listed on the PBS for this population. The Pre-Sub-Committee Response (PSCR) clarified that the submission did not ‘formally request’ listing in the favourable risk patient group and stated that ‘the Committee may wish to consider a listing which is agnostic to prognostic risk classification in view of the high clinical need for this patient group’.
- 1.3 Listing was requested on the basis of a cost-minimisation analysis (CMA) against nivolumab in combination with ipilimumab (NIVO + IPI), with sunitinib as a common reference. The key components addressed by the submission are shown in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as presented in the submission)

Component	Description
Population	Patients with stage IV clear cell variant renal cell carcinoma classified as intermediate to poor prognostic risk according to the IMDC prognostic risk criteria
Intervention	Avelumab 800 mg IV every 2 weeks + axitinib 5 mg orally twice daily
Comparator ^a	Nivolumab + ipilimumab
Outcomes	PFS, OS and ORR
Clinical claim	Avelumab + axitinib has non-inferior efficacy versus nivolumab + ipilimumab, with a different but non-inferior safety profile compared with nivolumab + ipilimumab.

Source: Table 1.1-2, p17 of the Submission.

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IV = intravenous; ORR = objective response rate; OS = overall survival; PFS = progression free survival

^a The submission also presented pembrolizumab + axitinib as a potential near market comparator.

2 Background

Registration status

- 2.1 **TGA status:** The submission was made under the TGA/PBAC Parallel Process. At the time of evaluation of the submission, the TGA Clinical Evaluation Report was available. At the time of PBAC consideration, the TGA Delegate’s Overview was available.
- 2.2 The requested TGA indication was: ‘Avelumab in combination with axitinib is indicated for the treatment of patients with advanced RCC’. The Delegate recommended that the proposed indication be approved, providing the indication is amended to be used in patients ‘in the first-line setting’ (and subject to the concerns identified regarding product information documents for avelumab being addressed satisfactorily and completion of recommendations of the Risk Management Plan report).
- 2.3 The Delegate’s Overview raised the following issues:
- The ‘failure to demonstrate a statistically significant improvement in overall survival (versus sunitinib) at present may be of some concern’ ;
 - ‘Patient reported outcomes suggests a poorer quality of life for the patients receiving AVE + AXI (versus sunitinib), despite improved disease control rates, with higher discontinuation rates due to adverse events in this group’ ;
 - Serious adverse events were more common in the AVE + AXI arm (than the sunitinib arm) with an increased risk of cardiac events, gastrointestinal toxicity, hepatotoxicity and infusion-related reactions ;
 - ‘the current recommended standard first line treatment for this patient population is pembrolizumab plus axitinib (or, alternatively NIVO + IPI in patients with intermediate or poor risk disease). This change in algorithm raises uncertainty of the role of first line AVE + AXI in view of the new standard of care; longer follow up for mature overall survival data will be informative’ .
- 2.4 Avelumab is currently TGA registered for the treatment of adults and paediatric patients 12 years and older with metastatic Merkel Cell Carcinoma.
- 2.5 Axitinib, which is sponsored by Pfizer, is TGA registered for the treatment of advanced RCC after failure of one prior systemic therapy. There is no TGA application for axitinib in the first-line setting, the indication sought for AVE + AXI. The submission for AVE + AXI relies solely on the TGA indication and Product Information (PI) for avelumab, which includes the axitinib data in this setting.
- 2.6 The evaluation raised two issues regarding the PIs for avelumab and axitinib. Firstly, the clinical information for AVE + AXI would not be reflected in the axitinib PI, which could increase safety risks for patients and clinicians. This concern was also raised in the TGA Clinical Evaluation Report. Secondly, the dose escalation/reduction recommendations for axitinib were not reflected in the proposed draft avelumab PI. The dose escalations/reduction recommendations are based on individual tolerability, and are consistent between the currently published axitinib PI and the clinical trial

from which the submission drew its key evidence (JAVELIN Renal 101, hereafter referred to as JAVELIN).

- 2.7 The PSCR stated that the draft PI for avelumab includes axitinib data in this setting. However, the ESC considered that the lack of relevant dosing and clinical information in the axitinib PI raised quality use of medicines issues.

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

3 Requested listing

- 3.1 The target population for the submission is patients with stage IV clear cell variant RCC who are treatment-naïve and have a WHO performance status of two or less. The submission formally requested listing for patients meeting intermediate or poor IMDC prognostic risk, however, requested that the PBAC also consider a listing agnostic to prognostic risk classification.
- 3.2 The restrictions requested in the submission are presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough. The submission requested listing in grandfathered patients, however the requested grandfathered restrictions are not included below for brevity.

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Avelumab

Name, Restriction, Manner of administration and form	Max Amt (mg)	No. of Rpts	Dispensed Price Max Amt	Proprietary Name and Manufacturer
Avelumab, infusion, 200 mg/10 mL vial	800	5 (initial) 11 (continuing) 5 (grandfathering)	Public: \$ [REDACTED] Private: \$ [REDACTED]	BAVENCIO®, Merck Healthcare Pty Ltd

Avelumab (Initial treatment)

Category/Program:	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
PBS indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Initial treatment
Restriction:	Authority Streamlined
Clinical criteria:	<i>The condition must be classified as intermediate to poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)</i> <i>AND</i> <i>The condition must not have previously been treated</i> <i>AND</i> <i>Patient must have a WHO performance status of 2 or less</i> <i>AND</i> <i>The treatment must be in combination with PBS-subsidised treatment with axitinib for this condition</i>
Caution	<i>Treatment with avelumab and axitinib is associated with immune-related adverse reactions. Monitoring at least prior to each dose is recommended.</i>
Administrative advice:	<i>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.</i> <i>No increase in the maximum quantity or number of units may be authorised</i> <i>No increase in the maximum number of repeats may be authorised</i>

Avelumab (Continuing treatment)

Category/Program:	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
PBS indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Continuation
Restriction:	Authority Streamlined
Clinical criteria:	<i>Patient must have previously received PBS-subsidised treatment with this drug for this condition,</i> <i>AND</i> <i>Patient must not have developed disease progression while being treated with this drug for this condition</i> <i>AND</i> <i>The treatment must be in combination with PBS-subsidised treatment with axitinib for this condition.</i>
Caution	<i>Treatment with avelumab and axitinib is associated with immune-related adverse reactions. Monitoring at least prior to each dose is recommended.</i>
Administrative advice:	<i>No increase in the maximum quantity or number of units may be authorised</i> <i>No increase in the maximum number of repeats may be authorised</i>

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Axitinib

Name, Restriction, Manner of administration and form	Max Qty (pack)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
Axitinib 1 mg tablet, 28	4 2 ^a	2 (initial) 2 5 ^b (continuing) 2 5 ^b (grandfathering)	\$ [REDACTED]	INLYTA®, Pfizer Australia Pty Ltd
Axitinib 5 mg tablet, 28	2	2 (initial) 5 (continuing) 2 5 ^b (grandfathering)	\$ [REDACTED]	INLYTA®, Pfizer Australia Pty Ltd

Axitinib (Initial treatment)

Category/Program:	GENERAL – General Schedule (Code GE)
PBS indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Initial treatment
Restriction:	Authority Streamlined
Clinical criteria:	The condition must not have previously been treated AND Patient must have a WHO performance status of 2 or less, AND The treatment must be in combination with PBS-subsidised treatment with avelumab for this condition.
Prescriber Instructions:	<u>1 mg strength only</u> <i>Prescribers may request an increased maximum quantity sufficient to provide up to one month's supply for patients who require dose adjustment</i> <u>5 mg strength only</u> <i>No increase in the maximum quantity or number of units may be authorised.</i> <i>No increase in the maximum number of repeats may be authorised.</i>
Caution	<i>Combination treatment with avelumab and axitinib is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.</i>

^a The maximum quantity (in all settings) for axitinib 1 mg was updated in the PSCR to be consistent with the current listing of axitinib (in the later-line setting)

^b The maximum number of repeats (in the continuing setting) was updated to provide sufficient supply for six months of treatment.

Axitinib (Continuing treatment)

Category/Program:	GENERAL – General Schedule (Code GE)
PBS indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment phase:	Continuation
Restriction:	Authority Streamlined
Clinical criteria:	Patient must have received an initial authority prescription for this drug for this condition <i>Patient must have previously received PBS-subsidised treatment with this drug for this condition</i> AND Patient must not have developed disease progression while being treated with this drug for this condition AND The treatment must be in combination with PBS-subsidised treatment with avelumab for this condition.
Administrative advice:	<u>1 mg strength only</u> <i>Prescribers may request an increased maximum quantity sufficient to provide up to one month's supply for patients who require dose adjustment</i> <u>5 mg strength only</u> <i>No increase in the maximum quantity or number of units may be authorised.</i>

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	<i>No increase in the maximum number of repeats may be authorised.</i>
Caution	<i>Combination treatment with avelumab and axitinib is associated with an increase incidence and severity of immune-related adverse reactions compared with monotherapy with these agents. Monitoring at least prior to each dose is recommended.</i>

- 3.3 The submission noted that special pricing arrangements (SPAs) apply to nivolumab and ipilimumab. Avelumab and axitinib are currently PBS listed with SPAs, and the PSCR stated that the sponsor will seek a SPA for avelumab in this indication. The price of avelumab used in the submission was [REDACTED].
- 3.4 The proposed restriction for AVE + AXI specifies that avelumab must be used in combination with axitinib, and does not allow for monotherapy with either drug, while patients in the JAVELIN trial were allowed to discontinue avelumab or axitinib independently from each other. The PBAC considered that the requirement for concomitant use was appropriate, consistent with the proposed TGA indication.
- 3.5 The current PBS listing for axitinib (in progressive disease following prior TKI treatment) is an Authority Required listing for initiation of treatment. However, the proposed initiation restriction is for a Streamlined Authority listing, consistent with the listing of NIVO + IPI. Different Authority approval methods for axitinib in different lines of therapy in RCC could lead to confusion for prescribers and impracticalities. The authority approval methods for continuation therapy are consistent between the current and proposed PBS listings (both are Streamlined Authorities).
- 3.6 The requested listing for avelumab correlates with a flat dose of 800 mg every two weeks, which aligns with the draft PI. While the key trial (JAVELIN) used weight-based dosing of 10 mg/kg every two weeks, the TGA Delegate’s Overview stated that the recommended dose of avelumab in combination with axitinib is 800 mg every two weeks.
- 3.7 The requested restriction would allow use of avelumab irrespective of PD-L1 expression, which was consistent with the TGA indication recommended by the Delegate.
- 3.8 The PSCR accepted the Secretariat’s changes to the proposed restrictions:
- The addition of IMDC risk criterion if the PBAC recommend listing in the intermediate or poor IMDC prognostic risk population;
 - Inclusion of requirements for monitoring of immune-related adverse events for consistency with the NIVO + IPI listing. However, the PSCR noted that the criterion in the NIVO + IPI restriction states ‘Combination treatment with ipilimumab and nivolumab is associated with an increased incidence and severity of immune-related adverse reactions compared with monotherapy with these agents’. The PSCR argued that the wording would need to be amended given that AVE + AXI is

unlikely to increase the incidence and severity of immune-related adverse events versus avelumab monotherapy (since this regimen is not combination immunotherapy). Further, the PSCR stated this should only be included in the restriction for avelumab (i.e. not in the axitinib restriction) as it is not an immunotherapy. The Delegate's Overview stated that 'there was a higher than would be expected rate of adverse events than for either agent as monotherapy, as consistent with a combination treatment'.

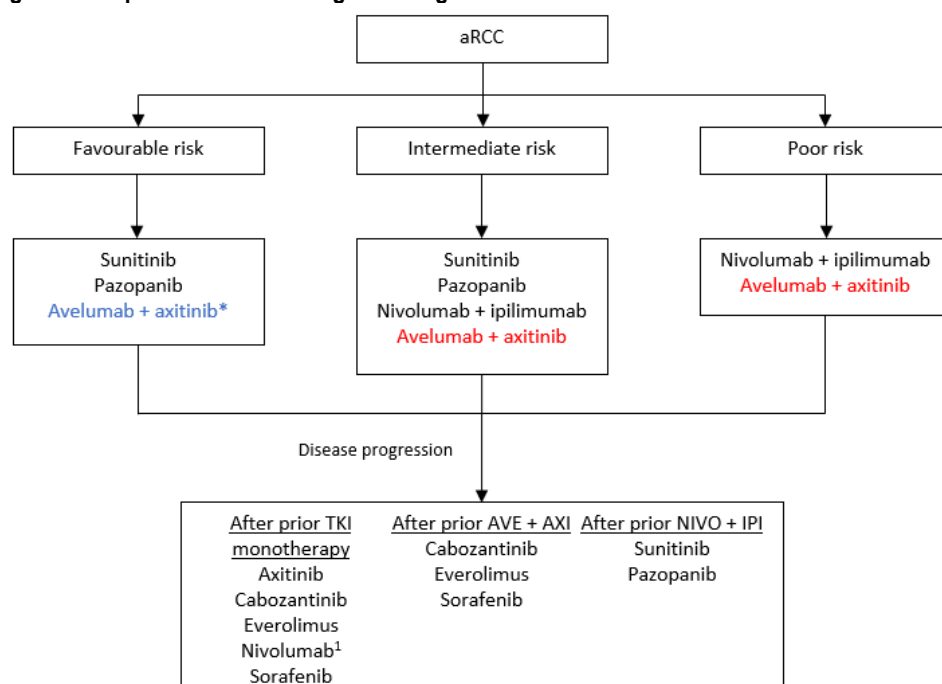
- Inclusion of wording regarding pseudo-progression to be consistent with NIVO + IPI listing.
- 3.9 The proposed restriction is considered to be complex as it will have restriction flow-on effects to other listings. The existing axitinib restriction would require amendment to clarify that patients cannot be re-treated with axitinib following progression on AVE + AXI. Further, the restrictions for cabozantinib, everolimus and sorafenib (which are currently listed for use in patients who have progressive disease following prior treatment with a tyrosine kinase inhibitor) may require amendment to ensure that PBS usage is consistent with the intended place in therapy.

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

4 Population and disease

- 4.1 RCC is the most common form of kidney cancer and arises from the cells of the renal tubules, accounting for up to 90% of primary renal neoplasms. Clear cell variant RCC is the most common subtype and accounts for 70-80% of all RCC cases (paragraph 4.1, NIVO + IPI, Public Summary Document (PSD), July 2018 PBAC meeting). As more than 50% of patients with RCC are asymptomatic, diagnosis occurs incidentally and approximately 25-30% of newly diagnosed RCC are advanced or have metastasised. An additional 30% of patients who had been treated with curative intent will develop metastases that are detected during follow-up.
- 4.2 Avelumab is a programmed death ligand-1 (PD-L1) inhibitor and axitinib is an oral, second-generation TKI that is selective for vascular epidermal growth factor (VEGFR). The submission's proposed place in therapy for the combined use of AVE + AXI for advanced RCC is presented in Figure 1.

Figure 1: Proposed clinical management algorithm



Source: Figure 1.2-2, p29 of the Submission

Abbreviations: aRCC = advanced clear cell renal cell carcinoma; TKI = tyrosine kinase inhibitor

Avelumab + axitinib denoted in red indicates first-line treatment of advanced (stage IV) clear cell variant RCC in patients classified as having intermediate to poor prognostic risk according to the IMDC prognostic risk criteria.

* The submission also requested the PBAC consider a listing agnostic to prognostic risk classification, though the PSCR stated this was not a formal request

¹ For patients who have progressive disease with a prior TKI or intolerance to a TKI necessitating permanent treatment withdrawal and patient must not have received treatment with a PD-1 or PD-L1 inhibitor for this condition

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

5 Comparator

- 5.1 The submission nominated combination therapy with NIVO + IPI as the main comparator, and combination treatment with pembrolizumab and axitinib (PEM + AXI) as a near market comparator. The justification and choice of NIVO + IPI as the comparator for patients with intermediate to poor risk disease was appropriate.
- 5.2 With regard to the request for consideration of listing in favourable risk disease, NIVO + IPI is not TGA approved/PBS listed for this indication. The submission did not nominate any comparators for use in favourable risk disease. Both sunitinib and pazopanib may be considered alternative therapies to AVE + AXI for patients with favourable risk disease.
- 5.3 PEM + AXI is not currently TGA approved or PBS listed for use in the first-line treatment of patients with stage IV RCC. The submission provided a clinical comparison of these treatments.

- 5.4 The PBAC noted that, while PEM + AXI was not an appropriate comparator in this submission, the National Comprehensive Cancer Network (NCCN) Guidelines version 2.2020 list NIVO + IPI or PEM + AXI as preferred immunotherapy regimens in intermediate to poor risk patients, while AVE + AXI is listed as an ‘other recommended regimen’.¹

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item

Consumer comments

- 6.2 The PBAC noted and welcomed the input from organisations (2) via the Consumer Comments facility on the PBS website. The PBAC noted the advice received from Rare Cancers Australia outlining that AVE + AXI would provide an alternative treatment option for patients with advanced disease, and that AVE + AXI is expected to provide synergistic benefits greater than either agent alone. The PBAC noted that this advice was supportive of the evidence provided in the submission.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the AVE + AXI submission, categorising it as a “supported application” on the basis of the JAVELIN trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for AVE + AXI, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)², based on a comparison with sunitinib. MOGA noted that the OS data were immature.

Clinical trials

- 6.4 The submission stated that there were no direct head-to-head trials of AVE + AXI compared to NIVO + IPI or the near market comparator PEM + AXI for the first-line treatment of advanced RCC. Accordingly, the submission presented an indirect treatment comparison (ITC) based on two phase 3, open label, randomised control trials: JAVELIN (N=886) which compared AVE + AXI with sunitinib in previously untreated patients with advanced RCC; and CheckMate 214 (N=1,096) which compared NIVO + IPI with sunitinib in previously untreated advanced RCC. An ITC with

¹ NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Kidney Cancer, NCCN Evidence Blocks, Version 2.2020, August 2019, Principles of systemic therapy for relapse or Stage IV disease. Table titled ‘First-line therapy for clear cell histology’.

² Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017]

PEM + AXI was also presented and was based on JAVELIN and Keynote-426 (N=861) which compared PEM + AXI with sunitinib in previously untreated advanced RCC.

6.5 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
JAVELIN	A phase 3, multinational, randomized, open-label, parallel arm study of avelumab (MSB0010718C) in combination with axitinib (Inlyta®) versus sunitinib (Sutent®) monotherapy in the first-line treatment of patients with advanced renal cell carcinoma	June 2015
	Motzer et al (2019). Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.	New Engl J Med 2019; 380:1103-1115
CheckMate 214	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	July 2014
	Motzer et al (2019). Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma	New Engl J Med 2018; 378 (14): 1277-1290.
	Cella et al. (2019). Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): a randomised, phase 3 trial	Lancet Oncol 2019; 20: 297-310.
	Tannir et al. (2019). Thirty-month follow-up of the phase III CheckMate 214 trial of first-line nivolumab + ipilimumab (N+I) or sunitinib (S) in patients (pts) with advanced renal cell carcinoma (advanced RCC).	J Clin Oncol 2019; 37: 547
	Motzer et al. (2019) Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial	Lancet Oncol 2019; 20: 1370-85.
Keynote-426	Rini et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma.	NEJM 2019; 380 (12): 1116-1127.

Source: Table 2.2-2 p48, Table 2(a).2-1 p8 in Appendix 2 of the Submission; CheckMate 214, Motzer 2019.

6.6 The key features of the JAVELIN, CheckMate 214 and Keynote-426 are summarised in Table 3.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
AVE + AXI vs sunitinib						
JAVELIN	886	MC, R, OL Minimum: 13 months ^a Median: 19 months	Low	Previously untreated patients with advanced clear cell RCC. Any risk group. Primary endpoint: PD-L1(+)	PFS, OS ^b	PFS
NIVO + IPI vs sunitinib						
CheckMate 214	1,096	MC, R, OL Minimum: 17.5 months ^c . Extended analyses conducted at 30 and 42 months.	Moderate to high ^e	Previously untreated patients with advanced clear cell RCC Primary endpoint: intermediate and poor risk	PFS, OS, ORR ^d	Not used in base case (PFS used in sensitivity analysis)
Near market comparator: PEM + AXI vs sunitinib						
Keynote-426	861	MC, R, OL Median: 12.8 months	Low	Previously untreated patients with advanced clear cell RCC	OS, PFS	Not used

Source: Table 2.3-1 p55 of the submission; Table 2(a).3-1 p12 of Appendix 2. Developed during the evaluation
Abbreviations: MC = multi-centre; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R = randomised; RCC = renal cell carcinoma;

^a JAVELIN Second Interim Analysis data cut-off 28 January 2019, minimum duration follow-up was 13 months

^b Primary outcomes were measured in PD-L1 positive tumours

^c CheckMate 214 primary analysis data cut off was 7 August 2017, minimum duration of follow-up was 17.5 months

^d Primary outcomes were measured in the intermediate or poor prognostic risk population

^e The PBAC have previously considered that the overall risk of bias in CheckMate 214 was high for outcomes PFS and EQ-5D; and moderate to unclear for OS (Table 3, NIVO + IPI, PSD, July 2018 PBAC meeting)

- 6.7 The primary endpoints for JAVELIN were PFS and OS among patients with PD-L1 positive tumours, irrespective of IMDC risk. The primary endpoints for CheckMate 214 were OS, ORR and PFS among patients with intermediate to poor prognostic risk. The secondary endpoints in both studies included the measurement of the primary outcomes in the intent to treat (ITT) population, which included patients irrespective of IMDC risk and PD-L1 status. The submission appropriately presented a post-hoc analysis for JAVELIN by IMDC prognostic risk to conduct the ITC.
- 6.8 The original primary objective for JAVELIN was to show superiority of AVE + AXI over sunitinib in advanced RCC irrespective of PD-L1 expression. However, a protocol amendment was made based on clinical data showing overall benefits among patients with RCC using immune checkpoint inhibitors. This amendment changed the primary objective of the trial to show the superiority of AVE + AXI over sunitinib with respect to either PFS or OS among patients with PD-L1–positive tumors.
- 6.9 Baseline patient demographics were similar between the ITT populations of the studies with respect to age (median range: 61.0-62.0 years across the arms of both studies) and gender (74.5% male in JAVELIN vs. 73.7% male in CheckMate 214). Furthermore, the distribution of patients across the favourable and intermediate or poor prognostic risk categories was similar between the two trials. However, the proportion of patients who had PD-L1 positive tumours was substantially higher in

JAVELIN compared with CheckMate 214 in the ITT population. The predictive and prognostic value of PD-L1 expression levels in patients with RCC is unclear.

- 6.10 The duration of follow-up for JAVELIN was shorter than for CheckMate 214. At the first interim analysis for JAVELIN the minimum follow-up was 6 months and the second interim analysis occurred at minimum follow-up of 13 months. Whereas, for CheckMate 214, the minimum follow-up for the primary analysis was 17.5 months. A 30 month (and 42 month) an extended follow-up phase analysis was also undertaken for CheckMate 214, however the efficacy results were not directly comparable with those for JAVELIN due to protocol amendments.
- 6.11 The PSCR included information (in a sponsor response to the TGA Clinical Evaluator’s comments) outlining that next planned analysis of the JAVELIN trial [REDACTED]

Comparative effectiveness

PFS (ITT and PD-L1 positive patients)

- 6.12 A summary of the PFS results are provided in Table 4. The difference in PFS between the two arms of JAVELIN (ITT) is greater compared to the two arms of CheckMate 214 (ITT). The median PFS in the sunitinib arm of CheckMate 214 is higher (12.3 months) than in JAVELIN (ITT, 8.0 months) which may suggest patients in CheckMate 214 had a better underlying prognosis for a response to sunitinib.

Table 4: Results of progression free survival: JAVELIN and CheckMate 214 (favourable, intermediate, poor risk patients)

PFS	JAVELIN IA2 ^a				CheckMate 214 ^{b,c}	
	PD-L1 positive		ITT		ITT	
	AVE + AXI N = 270	SUN N = 290	AVE + AXI N = 442	SUN N = 444	NIVO + IPI N = 550	SUN N = 546
Events, n (%)	138 (51.1)	171 (59.0)	229 (51.8)	258 (58.1)	296 (53.8)	271 (49.6)
Median (95% CI), months	13.8 (10.1, 20.7)	7.0 (5.7, 9.6)	13.3 (11.1, 15.3)	8.0 (6.7, 9.8)	12.4 (9.9, 16.5)	12.3 (9.8, 15.2)
Difference in median PFS, months	6.8		5.3		0.1	
HR (95% CI)	0.62 (0.490, 0.777)		0.69 (0.574, 0.825)		0.98 (0.79, 1.23) ^d	
p-value	< 0.0001		< 0.0001		0.85	

Source: Compiled during evaluation; Table 2.5-1 p68 and Table 2.5-6 p79 of the Submission; p1376, CheckMate 214 Motzer 2019, Table 5 NIVO + IPI, PSD, July 2018 PBAC meeting.

Abbreviations: AVE + AXI = avelumab + axitinib; CI = confidence interval; HR = hazard ratio; IA2 = second interim analysis; ITT = intention-to-treat; NIVO + IPI = nivolumab + ipilimumab; PD-L1 = programmed death ligand 1; PFS = progression free survival; SUN = sunitinib

^a Data cut off for IA2 was 28 January 2019, minimum duration of follow-up was 13 months, PFS was assessed by blinded independent central review (BICR).

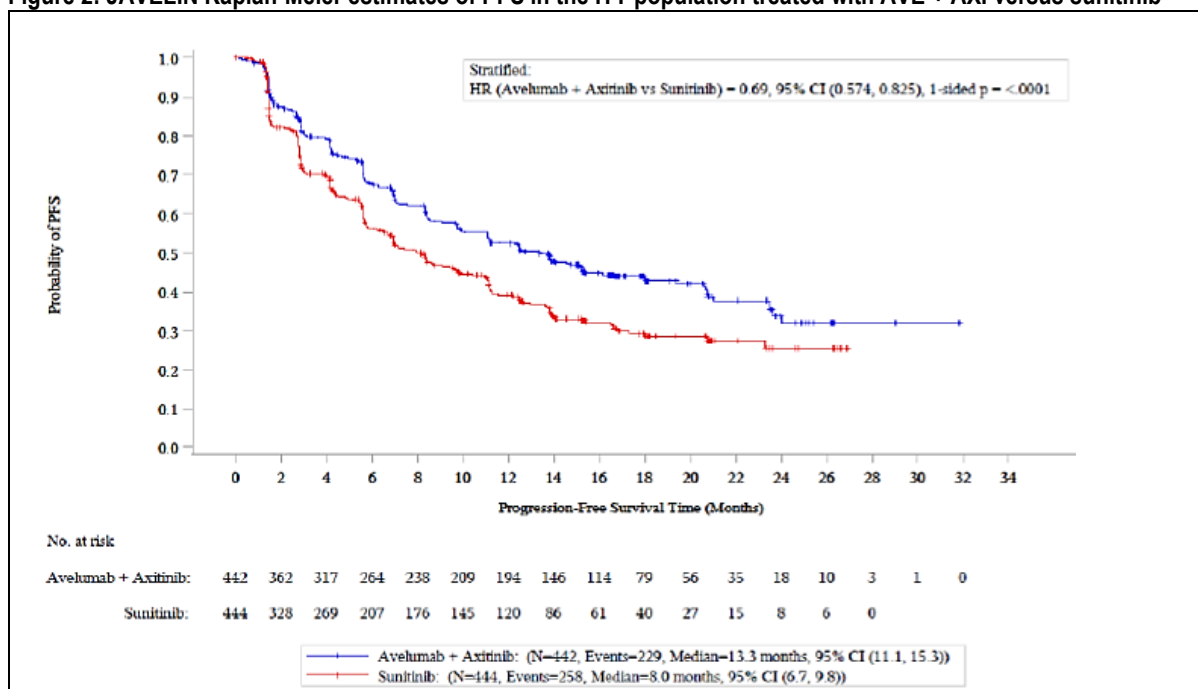
^b Data cut off was 7 August 2017, minimum duration of follow-up was 17.5 months. PFS was assessed by independent radiology review committee (IRRC).

^c PD-L1 stratified PFS outcomes were not reported in CheckMate 214

^d CheckMate 214 presented the HR 99.1%CI at primary analysis.
 Bold indicates statistical significance.

6.13 The Kaplan-Meier estimates for PFS in the ITT population of JAVELIN is presented in Figure 2. Early separation of the Kaplan-Meier curves was observed between the AVE + AXI and sunitinib treatment arms for both patient populations. Kaplan Meier estimates for the ITT population of CheckMate 214 were not reported in the publication.

Figure 2: JAVELIN Kaplan-Meier estimates of PFS in the ITT population treated with AVE + AXI versus sunitinib



Source: Figure 2.5-1 p69 of the Submission

Abbreviations: AVE + AXI = avelumab + axitinib; CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; NE = not estimable; PD-L1 = programmed death ligand 1; PFS = progression free survival.

OS (ITT and PD-L1 positive patients)

6.14 A summary of the OS results are provided in Table 5. At the time of the JAVELIN second interim analysis data cut-off (minimum follow up 13 months), the median follow-up for OS in the ITT population was 19.3 months (IQR: 18.6, 20.0) for patients in the AVE + AXI arm and 19.2 months (IQR: 18.3, 19.8) in the sunitinib arm. The Kaplan-Meier estimates for OS in the ITT population for JAVELIN are presented in Figure 3 (Kaplan-Meier estimates were not available for the ITT population of CheckMate 214). The OS data for both studies were relatively immature in that neither had achieved the point of median OS for their respective intervention groups and OS was subjective to heavy censoring.

Table 5: Results of overall survival; JAVELIN and CheckMate 214 (favourable, intermediate, poor risk)

OS	JAVELIN IA2 ^a				CheckMate 214 ^{b,c}	
	PD-L1 positive patients		ITT		ITT	
	AVE + AXI N = 270	SUN N = 290	AVE + AXI N = 442	SUN N = 444	NIVO + IPI N = 550	SUN N = 546
Events, n (%)	66 (24.4)	79 (27.2)	109 (24.7)	129 (29.1)	161 ^d (29.3)	204 ^d (37.4)
Median (95% CI), months	NE (NE, NE)	28.6 (27.4, NE)	NE (30.0, NE)	NE (27.4, NE)	NE	32.9
HR ^e	0.83 (95% CI: 0.596, 1.151)		0.80 (95% CI: 0.616, 1.027)		0.68 (99.8% CI: 0.49, 0.95) ^e	
p-value ^f	0.1301		0.0392		< 0.001	

Source: Compiled during the evaluation; Table 2.5-2 p71 and Table 2.5-7 p81 of the Submission.

Abbreviations: AVE + AXI = avelumab + axitinib; CI = confidence interval; HR = hazard ratio; IA2 = second interim analysis; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intention-to-treat; NE = not established; NIVO + IPI = nivolumab + ipilimumab; OS = overall survival; PD-L1 = programmed death ligand 1; SUN = sunitinib

^a Data cut off for IA2 was 28 January 2019, minimum duration of follow-up was 13 months.

^b Data cut off was 7 August 2017, minimum duration of follow-up was 17.5 months.

^c OS by PD-L1 subgroup were not reported in CheckMate 214

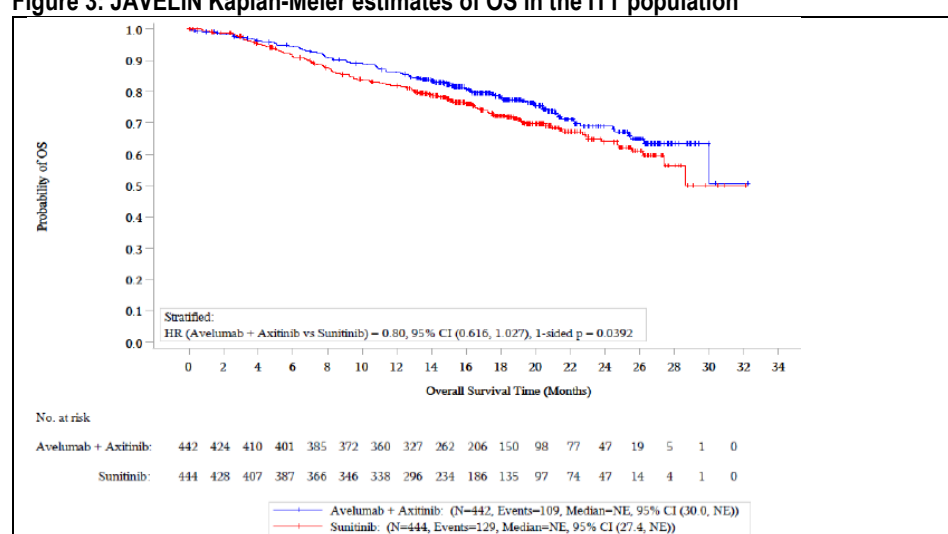
^d Submission calculation: obtained by adding the number of patient deaths in the favourable and the intermediate to poor IMDC risk groups.

^e CheckMate 214 presented the HR 99.8% CI

^f The p-value is based on a one-sided test

Bold indicates statistical significance.

Figure 3: JAVELIN Kaplan-Meier estimates of OS in the ITT population



Source: Figure 2.5-3 p72 of the Submission.

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; NE = not estimable; OS = overall survival; PD-L1 = programmed death ligand 1.

Patient-reported outcomes

6.15 Both studies used the Functional Assessment of Cancer Therapy-Kidney Symptom Index-19 (FKSI-19) and EuroQol five dimensions (EQ-5D) to estimate patient reported outcomes for quality of life. In addition to these, CheckMate 214 included the Functional Assessment of Cancer Therapy General (FACT-G) instrument.

6.16 The estimated mean changes in JAVELIN over 18 cycles were not statistically different between the two arms with an estimated mean difference in FKSI-19 of [REDACTED]

[REDACTED] and mean difference in EQ-5D-5L of [REDACTED].

- 6.17 In CheckMate 214, the improvement in FKSI-19 from baseline to week 103 was significantly greater with NIVO + IPI compared with sunitinib. In patients with intermediate or poor IMDC risk, the change from baseline to Week 103 in FACT-G total score was 4.77 (95% CI: 1.73, 7.82) for NIVO + IPI and 4.32 (95% CI: 8.54, 0.11) for SUNI ($p = 0.0005$). However, the difference in mean EQ-5D-3L visual analogue rating scale scores was not statistically significant between treatment arms. The overall completion rates were higher in JAVELIN than in CheckMate 214; the effects and reasons for non-compliance are unclear.

PFS results by IMDC prognostic risk group

- 6.18 Subgroup analyses for PFS, OS and ORR for the JAVELIN ITT population by IMDC prognostic risk criteria and PD-L1 expression status were presented in the submission to determine if differences in these parameters were likely to affect the efficacy estimates. The submission claimed no treatment effect modification by either risk criteria or PD-L1 status for PFS [REDACTED]

Although not statistically significant, the study was not powered to test for treatment effect variation across subgroups.

- 6.19 The JAVELIN post-hoc Kaplan-Meier estimates are presented in Figures 4 (PFS) and 6 (OS) respectively for patients with intermediate or poor, and favourable IMDC prognostic risk.
- 6.20 Comparison of PFS by risk subgroup shows a consistency across the studies in terms of the absolute and relative treatment effect observed in intermediate/poor risk patients. However, there is a clear difference in effect with respect to favourable risk patients; AVE + AXI demonstrates a gain in PFS relative to sunitinib, while sunitinib demonstrates a gain in PFS relative to NIVO + IPI (see Table 6).

Table 6: Results of progression free survival across JAVELIN and CheckMate 214 by IMDC prognostic risk

PFS	JAVELIN IA2 ^a						CheckMate 214 ^b					
	ITT		Intermed/poor		Favourable		ITT		Intermed/poor		Favourable	
	AVE+AXI N = 442	SUN N = 444	AVE+AXI N = [REDACTED]	SUN N = [REDACTED]	AVE+AXI N = 94	SUN N = 96	NIVO+IPI N = 550	SUN N = 546	NIVO+IPI N = 425	SUN N = 422	NIVO+IPI N = 125	SUN N = 124
Events, n (%)	229 (51.8)	258 (58.1)	[REDACTED]	[REDACTED]	34 (36.2)	43 (44.8)	296 (53.8)	271 (49.6)	NR	NR	NR	NR
Median (95% CI), months	13.3 (11.1, 15.3)	8.0 (6.7, 9.8)	[REDACTED]	[REDACTED]	24.0 (20.7, NE)	16.7 (12.6, NE)	12.4 (9.9, 16.5)	12.3 (9.8, 15.2)	11.6 (8.7, 15.5)	8.4 (7.0, 10.8)	15.3 (9.7, 20.3)	25.1 (20.9, NE)
Median diff PFS, months	5.3		[REDACTED]		7.3		0.1		3.2		-9.8	
HR (95% CI)	0.69 (0.574, 0.825)		[REDACTED]		0.626 (0.397, 0.986)		0.98 ^c (0.79, 1.23)		0.82 ^c (0.64, 1.05)		2.18 ^c (1.29, 3.68)	
p-value	< 0.0001		[REDACTED]		0.043		0.85		0.03		< 0.001	

Source: Compiled during the evaluation; Table 2.5-1 p68 of the Submission, Table 2.5-6 p79 of the Submission, Table 2.6-1 p101 of the Submission; pp1280,1283 Motzer 2018; p1376 CheckMate 214, Motzer 2019; Table 5 NIVO + IPI, PSD, July 2018 PBAC meeting.

Abbreviations: AVE + AXI = avelumab + axitinib; BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; IA2 = second interim analysis; IRRC = independent radiology review committee; ITT = intention-to-treat; NE = not estimable; NIVO + IPI = nivolumab + ipilimumab; NR = not reported; PD-L1 = programmed death ligand 1; PFS = progression free survival; SUN = sunitinib

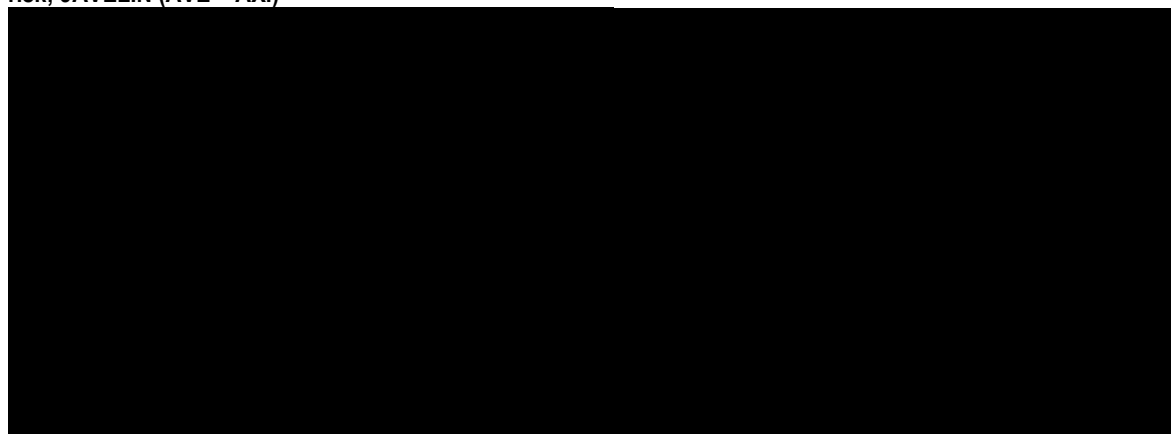
^a Data cut off for IA2 was 28 January 2019, minimum duration of follow-up was 13 months, PFS was assessed by BICR.

^b Data cut off was 7 August 2017, minimum duration of follow-up was 17.5 months. PFS was assessed by IRRC.

^c CheckMate 214 presented the HR 99.1%CI at primary analysis

Bold indicates statistical significance.

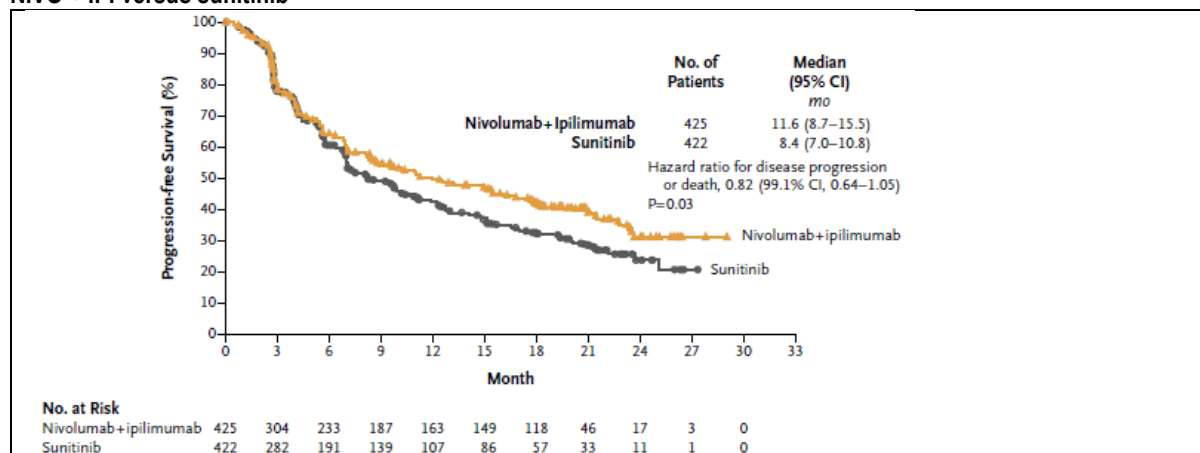
Figure 4: Kaplan-Meier estimates for PFS in patients with intermediate or poor (A) or favourable (B) IMDC prognostic risk; JAVELIN (AVE + AXI)



Source: Figure 2.6-1 p102 of the Submission.

Abbreviations: AVE + AXI = avelumab + axitinib; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; PFS = progression free survival; SUNI = sunitinib.

Figure 5: CheckMate 214 Kaplan-Meier curves for PFS in patients with intermediate or poor IMDC risk treated with NIVO + IPI versus sunitinib



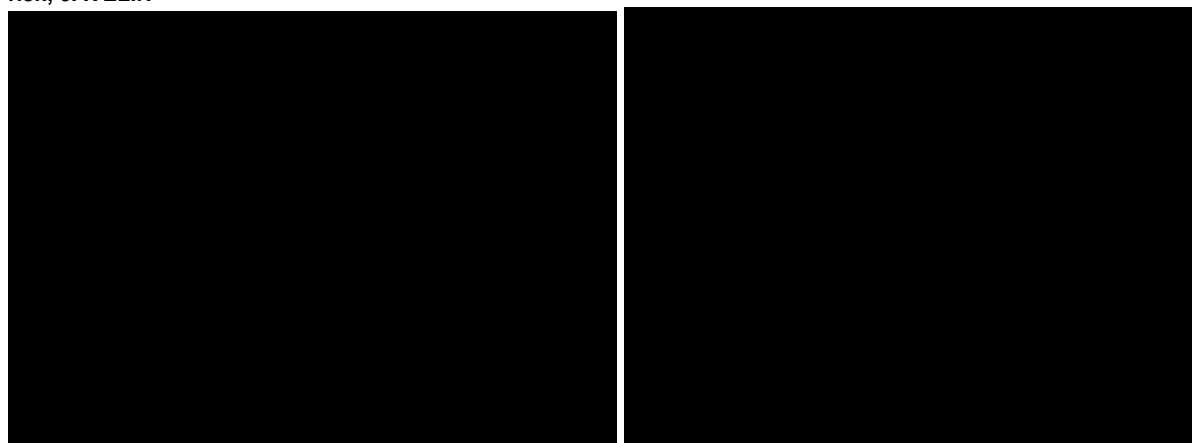
Source: Figure 2.5-6 p80 of the Submission

Abbreviations: CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; NIVO + IPI = nivolumab + ipilimumab; PFS = progression free survival; SUNI = sunitinib

OS results by IMDC prognostic risk group

6.21 In the favourable risk group, the HR for OS for AVE + AXI was 0.812 (95% CI 0.336, 1.96; $p = 0.643$). The results were immature as ████% in the AVE + AXI arm and ████% of patients in the sunitinib arm had died at second interim analysis for JAVELIN.

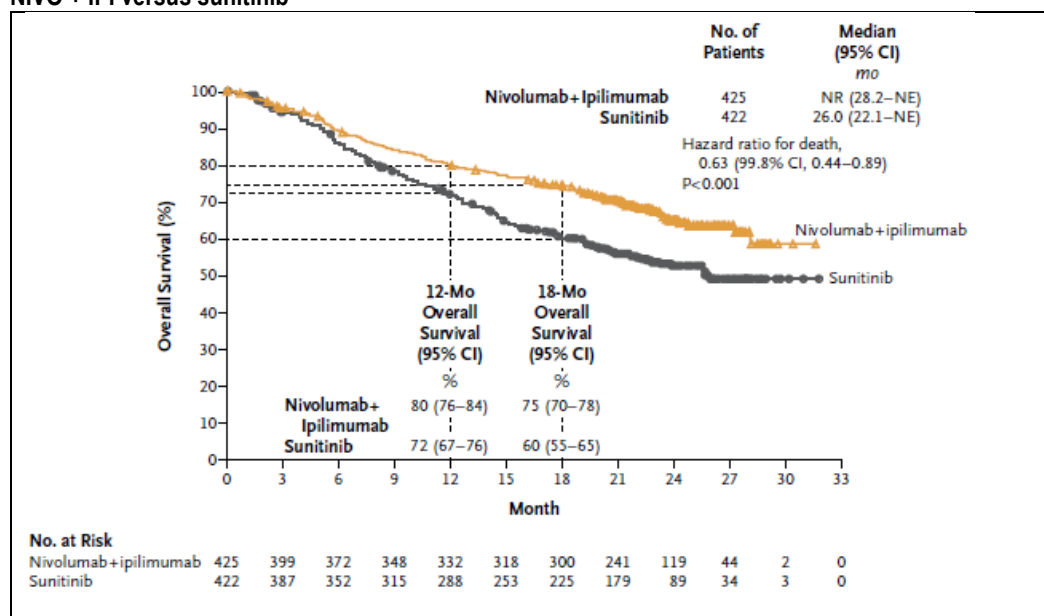
Figure 6: Kaplan-Meier estimates for OS in patients with intermediate or poor (A) or favourable (B) IMDC prognostic risk; JAVELIN



Source: Figure 2.6-2 p104 of the Submission.

Abbreviations: AVE + AXI = avelumab + axitinib; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; PFS = progression free survival; SUNI = sunitinib.

Figure 7: CheckMate 214 Kaplan-Meier curves for OS in patients with intermediate or poor IMDC risk treated with NIVO + IPI versus sunitinib



Source: Figure 2.5-7 p82 of the Submission.

Abbreviations: CI = confidence interval; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; NE = not estimable; NIVO + IPI = nivolumab + ipilimumab; NR = not reached; OS = overall survival; SUNI = sunitinib

Indirect trial comparison (ITC) outcomes

6.22 The submission presented an indirect comparison of JAVELIN and CheckMate 214, using sunitinib as the common comparator. The key outcomes presented in the ITC were PFS, OS and ORR. The results from the ITC for PFS are presented in Table 7.

6.23 The main differences between the trials that may impact on the transitivity of the trials included:

- post-progression treatment whereby patients in CheckMate 214 were allowed to receive subsequent anticancer therapy before progression; the proportion of patients this affected was not reported in the submission or publications for CheckMate 214.
- minimum duration of follow-up for JAVELIN was 13 months compared to 17.4 months in CheckMate 214 at the primary analysis, thus the JAVELIN results were less mature than those from CheckMate 214.
- substantially more patients with positive PD-L1 expression were enrolled in JAVELIN (ITT: 65.3% sunitinib) than in CheckMate 214 (ITT: 25% sunitinib). However, the predictive value of PD-L1 expression with respect to the prognosis and treatment response of patients with RCC remains unclear.
- results in the common comparator arm (sunitinib): the median PFS in the sunitinib arm of JAVELIN was shorter than the sunitinib arm of CheckMate 214 (6.7 vs 8.4

months), which may indicate that patients in CheckMate 214 had a better prognosis for a response to sunitinib than those in JAVELIN.

- 6.24 The differences pertaining to study design impacting on transitivity, as reflected by the differences in sunitinib outcomes across the trials, were not addressed by the submission, nor were the results of the ITC adjusted for the differences in outcomes.
- 6.25 The submission compared the ITT population for AVE + AXI (consistent with its view that the treatment effect is agnostic of risk) with the intermediate or poor IMDC risk subgroup from the CheckMate 214 study for NIVO + IPI (refer to Table 7). It justified this approach on the basis that there was no treatment modification of AVE + AXI versus sunitinib by risk criteria for PFS, OS and ORR and hence the hazard ratios of the ITT population of JAVELIN was representative of the subgroups (i.e. the intermediate or poor IMDC risk subgroup).
- 6.26 The submission used the intermediate or poor prognostic risk subgroup of JAVELIN to calculate the absolute treatment benefit (e.g. difference in median survival) as it was considered the relevant population for the comparison with NIVO + IPI.
- 6.27 The indirect comparison of the ITT populations found a statistically significant difference in PFS favouring AVE + AXI (HR 0.70 (95% CI: 0.55, 0.90)). Given the ITT population in JAVELIN included ~21% of patients with a favourable IMDC prognostic risk, comparison of the two ITT populations was biased against NIVO + IPI as NIVO + IPI has a negative PFS outcome in that risk group (and is not indicated for use in those patients).

Table 7: ITC – Progression free survival

Trial ID		Event n/N (%)	Median PFS (months)	HR (95% CI)	Indirect comparison HR (95% CI)
ITT (JAVELIN) versus intermediate or poor IMDC risk (CheckMate 214)					
JAVELIN ^c	AVE + AXI		13.3 (11.1, 15.3)		
	SUN	258/444 (58.1)	8.0 (6.7, 9.8)		
CheckMate 214 ^d	NIVO + IPI	NR/425	11.6 (8.7, 15.5)		
	SUN	NR/422	8.4 (7.0, 10.8)		
Intermediate or poor IMDC risk versus intermediate or poor IMDC risk					
JAVELIN ^c	AVE + AXI				
	SUN				
CheckMate 214 ^d	NIVO + IPI				
	SUN				
ITT population versus ITT population^b					
JAVELIN ^c	AVE + AXI	229/442 (51.8)	13.3 (11.1, 15.3)		
	SUN	258/444 (58.1)	8.0 (6.7, 9.8)		
CheckMate 214 ^d	NIVO + IPI	296/550 (53.8)	12.4 (9.9, 16.5)		
	SUN	271/546 (49.6)	12.3 (9.8, 15.2)		

Source: Table 2.6-5 p109 of the Submission, Table 5 NIVO + IPI, PSD, July 2018 PBAC meeting.

Abbreviations: AVE + AXI = avelumab + axitinib; CI = confidence interval; HR = hazard ratio; IA2 = second interim analysis; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITC = indirect treatment comparison; ITT = intention-to-treat; NIVO + IPI = nivolumab + ipilimumab; NR = not reported; PFS = progression free survival; SUN = sunitinib

^a The submission calculated the 95% confidence intervals using 99.1% confidence intervals from publication

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^b The comparison of the ITT populations is provided in the Submission for completeness but is not further discussed (p108 of the Submission).

^c JAVELIN, data-cut off: IA2, 28 January 2019, minimum duration of follow-up was 13 months.

^d CheckMate 214 data-cut off: was 7 August 2017, minimum duration of follow-up was 17.5 months.

Bold indicates statistical significance.

6.28 The results for the ITC for OS outcome are provided in Table 8. No statistically significant difference in the risk of death was observed between AVE + AXI and NIVO + IPI, regardless of the basis of comparison. The submission claimed the indirect comparison of OS was biased against AVE + AXI due to: higher subsequent use of nivolumab in the sunitinib arm of JAVELIN compared with CheckMate 214; the shorter median duration of treatment with NIVO + IPI compared with AVE + AXI; and the higher proportion of patients receiving subsequent treatment in the NIVO + IPI arm compared with AVE + AXI. There was no statistically significant difference in OS between the two arms of JAVELIN (ITT; HR: 0.8; 95% CI 0.616, 1.027, $p = 0.0392$) whereas in CheckMate 214 a statistically significant improvement in OS was observed (HR: 0.68; 99.8% CI 0.49, 0.95, $p < 0.001$).

Table 8: ITC – Overall survival

Trial ID		Event n/N (%)	Median OS (months)	HR (95% CI)	Indirect comparison HR (95% CI)
JAVELIN ITT versus CheckMate 214, intermediate or poor IMDC risk					
JAVELIN ^a	AVE + AXI	109/442 (24.7)	NE (30.0, NE)	0.8	0.616, 1.027
	SUN	129/444 (29.1)	NE (27.4, NE)		
CheckMate 214 ^b	NIVO + IPI	140/425 (32.9)	NE (28.2, NE)	0.68	0.49, 0.95
	SUN	188/422 (44.5)	26.0 (22.1, NE)		
JAVELIN Intermediate or poor IMDC risk versus CheckMate 214 intermediate or poor IMDC risk					
JAVELIN ^a	AVE + AXI	0.8	0.616, 1.027	0.8	0.616, 1.027
	SUN	0.8	0.616, 1.027		
CheckMate 214 ^b	NIVO + IPI	0.68	0.49, 0.95	0.68	0.49, 0.95
	SUN	0.68	0.49, 0.95		
JAVELIN ITT population versus CheckMate 214 ITT population ^e					
JAVELIN ^a	AVE + AXI	109/442 (24.7)	NE (30.0, NE)	0.8	0.616, 1.027
	SUN	129/444 (29.1)	NE (27.4, NE)		
CheckMate 214 ^b	NIVO + IPI	161/550 (29.3) ^d	NE	0.68	0.49, 0.95
	SUN	204/546 (37.4) ^d	32.9		

Source: Table 2.5-6 p112 of the Submission

Abbreviations: AVE + AXI = avelumab + axitinib; CI = confidence interval; HR = hazard ratio; IA2 = second interim analysis; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITC = indirect treatment comparison; ITT = intention-to-treat; NE = not estimable; NIVO + IPI = nivolumab + ipilimumab; OS = overall survival; SUN = sunitinib

^a JAVELIN, data-cut off: IA2, 28 January 2019, minimum duration of follow-up was 13 months;

^b CheckMate 214 data-cut off: Data cut off was 7 August 2017, minimum duration of follow-up was 17.5 months.

^c The submission calculated the 95% confidence intervals using 99.1% confidence intervals from publication. The calculation was not verified during the evaluation.

^d The submission obtained the calculation by adding the number of patient deaths in the favourable and the intermediate to poor IMDC risk groups

^e The comparison of the ITT populations is provided in the Submission for completeness but is not further discussed (p108 of the Submission).

Bold indicates statistical significance.

- 6.29 The pre-PBAC response stated that the OS data were confounded by subsequent treatments, with a higher proportion of patients in the sunitinib arm of JAVELIN receiving subsequent anti-PD-L1 therapy (35.9%) than in the corresponding arm of CheckMate 214 (26.9%). The pre-PBAC response stated that after adjusting for subsequent anti-PD-L1 therapy in the sunitinib arm, the results of a rank-preserving structural failure time analysis found a statistically significant difference between AVE + AXI and sunitinib (HR 0.66; 95% CI: 0.41, 0.94). This new analysis was provided in the pre-PBAC response, and thus could not be evaluated.

Comparative harms

- 6.30 Safety outcomes for both JAVELIN and CheckMate 214 were reported in all patients who received at least one dose of study treatment. The submission presented an ITC of the safety outcomes from the first interim analysis of JAVELIN (minimum follow-up of 6 months) instead of using data from the second interim analysis (minimum follow-up of 13 months), to compare safety with CheckMate 214; see Table 9. The submission stated that the safety data for the second interim analysis were limited and could not be used to conduct the ITC and that the median duration of treatment for the sunitinib treatment group in JAVELIN at the first interim analysis was similar to the sunitinib treatment group in CheckMate 214.
- 6.31 In JAVELIN, treatment related AEs (TRAEs) of any grade occurred in similar proportions of patients in the AVE + AXI arm (95.4%) and the sunitinib arm (96.4%). More serious TRAEs occurred in patients treated with AVE + AXI (17.1%) compared to sunitinib (13.0%). A higher proportion of patients treated with AVE + AXI experienced hypertension (AVE + AXI, 47.9% vs sunitinib, 32.3% all grades; 24.4% and 15.3% grade ≥ 3), dysphonia (26.7% vs 2.7%), hypothyroidism (24.2% vs 13.4%), dyspnoea (12.2% vs 5.5%), pruritus (12.2% vs 4.3%) and arthralgia (12.0% vs 5.5%) of any grade.
- 6.32 The TGA Delegate's Overview noted that there was an increased risk of treatment-related deaths with AVE + AXI compared with sunitinib, which appear to have occurred in at least 7 patients, compared to 1 patient in the sunitinib arm. At least 3 deaths were from immune-mediated AEs including 2 patients with pancreatitis and one death from myocarditis. The TGA Delegate's Overview also noted an increased risk of cardiac and cardiovascular toxicities was clearly evident in patients on AVE + AXI than sunitinib, with fatal events observed.

Table 9: ITC - Treatment related adverse effects

AEs, n (%)	Intervention n (%)	SUN n (%)	Relative risk ^a (95% CI)	Risk difference ^a (95% CI)	Odds ratio ^a (95% CI)
Treatment related adverse event of any grade					
Any AEs					
JAVELIN ^b	414 (95.4)	423 (96.4)			
CheckMate 214 ^c	509 (93.1)	521 (97.4)			
Indirect comparison: AVE + AXI vs NIVO + IPI					
AEs Grade ≥ 3					
JAVELIN ^b	246 (56.7)	243 (55.4)			
CheckMate 214 ^c	250 (45.7)	335 (62.6)			
Indirect comparison: AVE + AXI vs NIVO + IPI					
SAEs					
JAVELIN ^b	74 (17.1)	57 (13.0)			
CheckMate 214 ^c	162 (29.6)	81 (15.1)			
Indirect comparison: AVE + AXI vs NIVO + IPI					
Discontinuation of any drug due to AEs					
JAVELIN ^b	80 (18.4)	35 (8.0)			
CheckMate 214 ^c	118 (21.6)	63 (11.8)			
Indirect comparison: AVE + AXI vs NIVO + IPI					
Death					
JAVELIN ^b	5 (1.2)	1 (0.2)			
CheckMate 214 ^c	8 (1.5)	4 (0.7)			
Indirect comparison: AVE + AXI vs NIVO + IPI					

Source: Compiled during the evaluation; Table 2.5-9 p85 of the Submission, Table 2.5-10 p88 of the Submission, Table 2.5-12 p91 of the Submission, Table 2.5-13 p93 of the Submission; Table 2.6-10 pp120-122 of the Submission, Table 2.6-11 pp124-125 of the Submission. Abbreviations: AE = adverse event; AVE + AXI = avelumab + axitinib; CI = confidence interval; IA1 = first interim analysis; NIVO + IPI = nivolumab + ipilimumab; SUN = sunitinib; SAEs = serious adverse event

^a Submission used RevMan v5.3 to calculate RR, RD and OR.

^b JAVELIN, data-cut off: IA1, 20 June 2018, minimum duration of follow-up was 6 months (median duration of treatment 8.6 months for avelumab, 9.0 months for axitinib and 8.3 months for sunitinib)

^c CheckMate 214 data-cut off: Data cut off was 7 August 2017, minimum duration of follow-up was 17.5 months.

Bold indicates statistical significance.

6.33 The proportion of patients reporting immune-related adverse events (irAEs) was numerically lower in the AVE + AXI arm compared to the NIVO + IPI arm. The comparison of irAEs was based on a naïve comparison and the validity of the ITC in terms of clinical implications and statistical significance was inconclusive. Infusion reactions for avelumab were higher than NIVO + IPI (all grades) despite JAVELIN specifying premedication with an antihistamine and paracetamol, whilst no routine premeditation was administered prior to NIVO + IPI.

Benefits/harms

6.34 A summary of the benefits and harms was not presented given the non-inferiority nature of the claim.

Clinical claim

- 6.35 On the basis of the ITC, the submission claimed that AVE + AXI was non-inferior in terms of efficacy and had a different but non-inferior safety profile compared to NIVO + IPI.
- 6.36 The overall survival (OS) data for AVE + AXI were immature (28.6% of patients in the AVE + AXI arm and 34.0% in the sunitinib arm had died at the second interim analysis of JAVELIN) and no statistically significant difference in OS was observed versus sunitinib (in the JAVELIN trial). This was in contrast to the statistically significant OS gains reported for NIVO + IPI versus sunitinib (in the CheckMate 214 trial). The PBAC previously accepted the claim of clinical superiority of NIVO + IPI versus sunitinib on the basis of the statistically significant improvement in OS observed in CheckMate 214 (para 6.8, nivolumab and ipilimumab, November 2018 PBAC meeting). Further, the ITC was limited by transitivity issues between JAVELIN and CheckMate 214 notably due to differences in study follow-up, post-progression treatment, and baseline disease characteristics with respect to CNS penetration of disease and PD-L1 expression.
- 6.37 While the PFS HR for the indirect comparison (in the intermediate to poor risk subgroups) was [REDACTED], a non-inferiority margin was not proposed, and PFS may not be a reliable measure of the clinical effectiveness of immunotherapies as tumour responses can occur after conventional RECIST-defined progressive disease (i.e. the tumour flare effect).
- 6.38 The submission included an ‘informal’ request for the PBAC to also consider listing AVE + AXI in favourable risk patients (who are estimated to represent 24% of the population). Although monotherapy with sunitinib and pazopanib are used in first line treatment for patients with a favourable IMDC risk profile, the submission did not nominate sunitinib or pazopanib as comparators and did not make a clinical claim for comparative efficacy or safety for either of these treatments. The results from JAVELIN would support the superiority of AVE + AXI over sunitinib in that subgroup of patients, however as shown in Figure 6(B), the OS results are immature in the favourable risk group (with [REDACTED] % of patients in the sunitinib arm having died at the data-cut presented).
- 6.39 The PBAC considered that the claim of non-inferior comparative effectiveness of AVE + AXI versus NIVO + IPI was not adequately supported by the data, given the difference in OS for AVE + AXI versus sunitinib was not statistically significant (in the JAVELIN trial), while NIVO + IPI had demonstrated a statistically significant improvement in OS versus sunitinib (in the CheckMate 214 trial).
- 6.40 The PBAC considered that the claim of different but non-inferior safety was reasonable.

Economic analysis

- 6.41 A cost-minimisation analysis (CMA) comparing AVE + AXI with NIVO + IPI was presented by the submission. NIVO + IPI is only PBS listed for patients with an IMDC

prognostic risk of intermediate to poor. Other treatments that are PBS listed and more suitable as comparators for patients with a favourable risk profile are the TKIs, sunitinib and pazopanib, each as monotherapy. As such the CMA is only informative for patients with intermediate to poor risk disease.

6.42 The submission estimated the equi-effective doses as:

- avelumab 800 mg Q2W plus axitinib 5 mg BID; and
- nivolumab 3 mg/kg plus ipilimumab 1 mg/kg for four treatments, followed by nivolumab monotherapy (3 mg/kg Q2W or 240 mg Q2W or 480 mg Q4W).

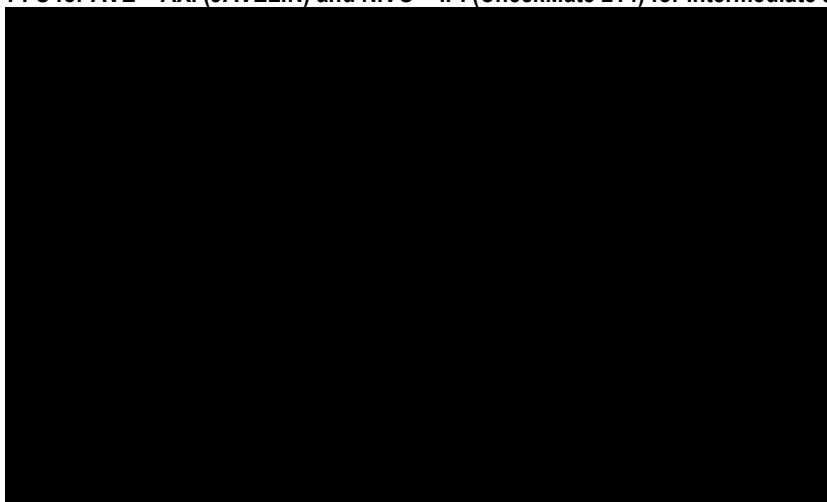
The dosage regimens for each treatment were based on the recommended dosage in the draft PI of avelumab, and the PIs of nivolumab and ipilimumab.

6.43 The submission assumed that both regimens would have the same average duration of treatment (■ months), which was based on extrapolated PFS for AVE + AXI from the JAVELIN trial. PFS is a surrogate outcome and extrapolation of PFS may not be a reliable basis upon which to estimate treatment exposure. The evaluation considered that the main issue with this assumption is that this approach is confounded by differences in the duration of follow-up and study design where treatment switching was permitted in CheckMate 214 prior to disease progression³. The ESC and PBAC have previously stated that cost-minimisation on the basis of the total drug cost that achieves the same OS outcomes may be a more reasonable approach (paragraph 7.9, Alectinib, PSD, July 2017 PBAC meeting). However, both studies permitted patients to continue treatment beyond disease progression, and thus time to treatment discontinuation may not reflect utilisation under the PBS.

6.44 The ESC considered that it may be reasonable, in this case, to assume that both regimens have the same average duration of treatment given (a) the heterogeneity between the trials; and (b) that the assumption is likely to be conservative, in this case. Sensitivity analyses indicated that a scenario using PFS data from CheckMate 214 for the NIVO + IPI arm and PFS data from JAVELIN for the AVE + AXI arm was not conservative (i.e. would result in a higher price per dose of avelumab). This was because NIVO + IPI had longer PFS as shown in Figure 8 (and thus was assumed to be used for a longer duration, particularly during the extrapolated period).

³ In CheckMate 214, 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.

Figure 8: PFS for AVE + AXI (JAVELIN) and NIVO + IPI (CheckMate 214) for intermediate and poor risk patients



Source: Figure 3.4-1, p 151 of the submission

PFS data for NIVO + IPI was estimated by digitising the PFS Kaplan-Meier curve from CheckMate 214 (for intermediate and poor risk patients).

- 6.45 Rather than truncating the data at ■ months when ■% of patients remained progression free, the submission extrapolated the AVE + AXI PFS data by fitting parametric survival functions to the observed data. For the base case, the submission extrapolated PFS (from the AVE + AXI arm) based on the exponential function stating that this had the best fit based on visual inspection, and because it resulted in a similar mean number of nivolumab doses per treatment course (■■■■■■) to that stated in the NIVO + IPI Public Summary Document (32.8 doses, based on Table 5, NIVO + IPI PSD, November 2018 PBAC meeting). The ESC noted that the gamma function had the best fit based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), followed by the log-normal function. However, the ESC noted these two functions resulted in ■% and ■% of patients remaining on treatment at 10 years, respectively (versus ■% with the base case exponential function) which the ESC considered was unlikely to be clinically plausible.
- 6.46 PFS was extrapolated to ten years. This was conservative relative to a shorter time horizon because it attenuates the high initial cost of NIVO + IPI, with the ipilimumab component administered for the induction period only (first 4 doses).
- 6.47 The dosage of axitinib applied (5 mg twice daily) was based on the recommended dosage stated in the avelumab draft PI. The ESC noted that, in the JAVELIN trial and axitinib PI, the recommended starting dosage is 5 mg twice daily and patients who tolerate this may have their dosage increased to a maximum of 10 mg twice daily. Management of some adverse drug reactions may require temporary or permanent discontinuation and/or dose reduction of axitinib (to 2 mg to 3 mg twice daily). The mean dose in JAVELIN was ■ mg twice daily. While a ■ mg dose would cost less than a 5 mg dose (as axitinib is priced on a per mg basis), it is unclear whether the majority of dose reductions would be temporary which may result in wastage of the 1 mg tablets (which may increase the cost of axitinib). The ESC considered that the mean

dose of axitinib that will be used in clinical practice is unclear, and noted that higher doses of axitinib (above 5 mg twice daily) or wastage of the 1 mg tablets would increase the vial price of avelumab (if the axitinib price remains constant). The ESC considered that the cost of AVE + AXI in the model was thus potentially underestimated. The pre-PBAC response (p3) noted that axitinib dose reductions and escalations were permitted in JAVELIN and occurred in 42.2% and 10.8% of patients, respectively. It remained unclear whether the dose reductions were temporary (which may result in wastage of the 1 mg tablets). The TGA Delegate's Overview (p33) stated that dose escalation of axitinib was associated with a broad range of toxicities and treatment delays with no evidence to support the benefit of dose escalation, and that the Prescribing Information should reflect this.

6.48 Other issues with the estimated equi-effective doses include:

- Dosing of NIVO + IPI in the induction phase (the first four doses) is weight-based. The submission assumed an average patient weight of 83 kg based on the average weight of patients in JAVELIN. The commentary noted that assuming a higher average weight is not conservative, and conducted a sensitivity analysis based on an average weight of 80kg (which would require one less nivolumab 40 mg vial per induction dose). The PSCR argued that the average weight of Australian patients (based on the Kidney Cancer Australian Registry and Biobank) is higher (mean weight of 86 kg) than that reported in JAVELIN. The ESC noted that the number of NIVO + IPI vials required for treatment of a person weighing 83 kg or 86 kg is the same.
- The nivolumab PI specifies three possible dosing regimens for maintenance treatment (i.e. after the first four doses), whereas the submission assumed only one dose regimen is administered as maintenance treatment (nivolumab 240 mg Q2W). The assumed dosing regimen affects other costs associated with specialist visits and scripts. The PBAC previously considered that whilst the estimated utilisation between the different nivolumab dosing regimens was uncertain, it was reasonable to assume that the majority of patients would be prescribed the nivolumab 480 mg Q4W dosing regimen if available. As such, there would be cost savings associated with a reduction in infusion administrations (paragraph 5.4, Nivolumab, PSD, March 2019 PBAC meeting).

6.49 The submission assumed that there would be additional costs for the intravenous (IV) administration of avelumab, nivolumab and ipilimumab, and for initiation and supervision by a specialist prior to the administration of the IV infusion. This is reasonable. This assumption is applied to both AVE + AXI and NIVO + IPI.

6.50 The submission stated that there are no differences in monitoring requirements or the safety profiles between treatment with AVE + AXI and NIVO + IPI that are expected to result in differences in costs. The assumption that there are no differences in cost due to differences in safety may not be reasonable; difference in the safety profiles may influence the results of the CMA but the impact is likely to be negligible.

- 6.51 The CMA was conducted using dispensed prices, however CMAs are usually conducted using ex-manufacturer prices.
- 6.52 The results of the CMA are presented in Table 10. The submission noted that NIVO + IPI have SPAs with effective prices that are unknown to the sponsor, and thus the CMA uses published prices. The submission stated that ‘while the result of the CMA is therefore necessarily uninformative, the methods used provide a framework for an analysis based on the effective prices that ensures that the total cost of treatment with AVE + AXI is no more than that with NIVO + IPI’. While the ‘framework’ provided in the submission resulted in AVE + AXI being more expensive than NIVO + IPI (incremental total cost: \$45,000 - \$75,000), the pre-PBAC response clarified that the intent of the framework is for the incremental cost to be nil when the effective prices of NIVO + IPI are applied.

Table 10: Results of the cost-minimisation analysis (based on published DPMQ/DPMA)

	AVE + AXI	NIVO ^a + IPI	Incremental
Base case			
Medicines			
Administration			
Specialist visit			
Total cost of treatment			

Source: Table 3.4-9 p160 of the submission; CMA Avelumab Axitinib vs Nivolumab Ipilimumab.xlsx, worksheet 'Results'.

- 6.53 The results of sensitivity analyses are provided in Table 11. The sensitivity analyses were based on a scenario in which the incremental cost of treatment with AVE + AXI is set to \$0. The table includes a column outlining the DPMA per 800 mg dose of avelumab required to achieve an incremental cost of \$0 in each analysis. This was conducted by adjusting the avelumab price only (i.e. the axitinib price was assumed to remain the same).

Table 13: Key inputs for financial estimates

Parameter	Value applied	Source	Comment
Eligible population			
Incident (total) patients (with aRCC).	█ in year 1 increasing to █ in year 6.	10% PBS sample data (November 2009 to June 2019).	This is reasonable.
IMDC intermediate or poor risk criteria (%)	█%	Distribution of patients enrolled in clinical trials:	Tested in sensitivity analysis during the evaluation. Patients with favourable IMDC prognostic risk were excluded from the financial estimates.
Treatment utilisation			
Uptake rate	█% in Year 1 increasing to █% in Year 6.	Submission assumption.	Tested in sensitivity analysis during evaluation.
Average duration of treatment	█ months	Assumed to be the same for AVE + AXI and NIVO + IPI.	Mean PFS in JAVELIN IA2 was 13.3 months (95% CI, 11.1, 15.3 months).
Costs			
MBS costs	\$99.50	IV administration MBS Item 13918: duration ≥ 1 hour and < 6 hours. MBS Item 13915: duration < 1-hour	This is reasonable.
	\$66.10		
	\$77.90	MBS Item 116: Specialist visit	This is reasonable.

Source: Compiled during the evaluation using Table 4.1.1 p163, Table 4.1.3 p166, Table 4.1.7 p170, Table 4.1.8 p170, Table 4.1.9 p171, Table 4.1.10 p171, Table 4.1.11 p172 of the submission.

6.58 A summary of the estimated use and financial implications for listing AVE + AXI on the PBS is presented in Table 14.

Table 14: Estimated use and financial implications (based on published prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated						
Number of scripts dispensed ^a						
Estimated financial implications of AVE + AXI						
Cost to PBS/RPBS less copayments	\$	\$	\$	\$	\$	\$
Estimated financial implications for NIVO + IPI						
Reduction in cost to PBS/RPBS (less copayments)	-\$	-\$	-\$	-\$	-\$	-\$
Net financial implications						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Net cost to MBS	\$	\$	\$	\$	\$	\$
Net cost to Health Budget	\$	\$	\$	\$	\$	\$

Source Table 4.1.4 p167, Table 4.1.5 p169, Table 4.2.2 p174, Table 4.2.4 p177, Table 4.2.5 p179 and Table 4.2.6 p181, Table 4.5.3 p192 of the submission.

Abbreviations: PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme, MBS = Medicare benefits schedule, DHS = Department of Human Services; Q4W = every four weeks.

^a Assuming [redacted] scripts per year of avelumab and [redacted] scripts per patient of axitinib as estimated by the submission.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be \$10 - \$20 million.

- 6.59 The total cost to the PBS/RPBS of listing AVE + AXI for intermediate to poor risk patients was estimated to be \$10 - \$20 million in Year 6, and a total of \$60 - \$100 million in the first 6 years of listing (based on published prices). The submission stated that AVE + AXI is proposed to be listed on a cost-minimisation basis to NIVO + IPI, and that the net financial implications for the health budget after accounting for effective prices is intended to be nil for each cohort of patients that newly commence treatment over a two-year period.
- 6.60 The submission included less than 10,000 grandfathered patients in the financial estimates. The submission did not adjust the estimates to account for the duration of prior therapy of grandfathered patients (a potential source of overestimating AVE + AXI use in the submission).

Quality Use of Medicines

- 6.61 The submission stated that educational materials targeted for clinicians, healthcare providers and patients will be developed. The submission also stated that sponsors for avelumab and axitinib will support Kidney Cancer Australia Registry and Biobank database through the Walter & Eliza Hall Medical Research Institute so that data about patients' experiences are measured.
- 6.62 There is a potential for confusion regarding dosing of axitinib given the recommended doses in the avelumab draft PI and axitinib PI differ. Further, the lack of clinical information in the axitinib PI regarding this indication raises quality use of medicines issues.

Financial Management – Risk Sharing Arrangements

- 6.63 No risk sharing arrangements were proposed for the listing of AVE + AXI. The PBAC previously considered that an RSA would be required for the first-line listing of NIVO + IPI (paragraph 6.16, NIVO + IPI PSD, November 2018).
- 6.64 There is a risk of leakage in patients with a favourable IMDC risk profile.
For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of avelumab in combination with axitinib (AVE + AXI) for the first-line treatment of advanced (stage VI) clear cell variant RCC. The PBAC noted that AVE + AXI did not demonstrate a statistically significant difference in OS versus sunitinib, which was in contrast to the statistically significant OS gains reported for NIVO + IPI versus sunitinib. Further, the PBAC considered that PFS may not be a reliable measure of the clinical effectiveness of immunotherapies in this setting, and noted that AVE + AXI was not associated with an improvement in quality of life versus sunitinib. Overall, the PBAC considered that the submission had not adequately demonstrated non-inferiority versus NIVO + IPI.
- 7.2 The PBAC noted that the submission also included an 'informal' request for listing in favourable risk patients (who are estimated to represent 24% of patients with previously untreated advanced clear cell variant RCC). The PBAC considered that monotherapy with sunitinib or pazopanib would be the appropriate comparators in this setting, and noted that the submission did not make a clinical claim regarding comparative efficacy or safety or present an economic analysis against sunitinib or pazopanib. The PBAC noted that the OS results from JAVELIN are very immature in the favourable risk group (with █% of patients in the sunitinib arm having died at the data-cut presented), with updated OS data likely to be available in the near future.
- 7.3 The PBAC noted that patients with intermediate and poor risk advanced RCC have access to effective immunotherapy in the first-line setting, NIVO+IPI, and thus the clinical need for an alternative immunotherapy combination was modest.
- 7.4 The PBAC considered that NIVO + IPI was the appropriate comparator for RCC patients with an intermediate to poor risk.
- 7.5 The PBAC noted that, while PEM + AXI was not an appropriate comparator in this submission as it is not TGA-registered or PBS-listed, the NCCN Guidelines (version 2.2020) list NIVO + IPI or PEM + AXI as preferred immunotherapy regimens in intermediate to poor risk patients, while AVE + AXI is listed as an 'other recommended regimen'. Similarly, the TGA Delegate's Overview stated that 'the current recommended standard first line treatment for this patient population is PEM + AXI (or, alternatively NIVO + IPI in patients with intermediate or poor risk disease). This change in algorithm raises uncertainty of the role of first line AVE + AXI in view of the

new standard of care; longer follow up for mature overall survival data will be informative’.

- 7.6 AVE + AXI did not demonstrate a statistically significant difference in OS versus sunitinib in the JAVELIN trial (based on the second interim analysis presented in the submission) with a HR of 0.80 (95% CI: 0.62, 1.03) in the ITT population. This was in contrast to the statistically significant OS gains reported for NIVO + IPI versus sunitinib in the CheckMate 214 trial ITT population (HR: 0.68; 99.8% CI 0.49, 0.95). The PBAC recalled that it had previously accepted the claim of clinical superiority of NIVO + IPI versus sunitinib on the basis of the statistically significant improvement in OS observed in CheckMate 214 (para 6.8, nivolumab and ipilimumab, November 2018 PBAC meeting). The PBAC considered that, in the absence of a statistically significant improvement in OS for AVE + AXI versus the common comparator (sunitinib), the submission had not adequately demonstrated that AVE + AXI was non-inferior to NIVO + IPI.
- 7.7 The indirect comparison of AVE + AXI versus NIVO + IPI (using sunitinib as the common comparator) found a HR for OS of [REDACTED] for the comparison based on the intermediate or poor risk subgroups. The PBAC noted the transitivity issues between JAVELIN and CheckMate 214 (notably due to differences in study follow-up, differences in post-progression treatment and baseline disease characteristics) and the pre-PBAC response’s argument that JAVELIN was not powered to detect a difference in the intermediate or poor risk subgroups. The PBAC noted that the upper 95% confidence limit was [REDACTED], which it considered was too high to support a conclusion of non-inferiority, especially in the context of a significant difference in OS for AVE + AXI versus sunitinib not having been demonstrated.
- 7.8 The PBAC considered that the OS results from JAVELIN were immature with 24.7% of participants in the AVE + AXI arm (and 29.1% in the sunitinib arm) having died at the data-cut presented in the submission. The PBAC agreed with the Delegate’s Overview that ‘longer follow up is required to assess for any OS benefit’. The PBAC noted that updated OS data may be available in the near future, [REDACTED].
- 7.9 The PBAC noted there was a statistically significant difference in PFS for AVE + AXI versus sunitinib in the JAVELIN trial, with a HR of 0.69 (95% CI: 0.57, 0.83) in the ITT population. In the indirect comparison versus NIVO + IPI, the HR was 0.86 (95% CI: 0.65, 1.13) for the comparison based on the intermediate and poor risk patients. However, the PBAC considered that PFS may not be a reliable measure of the clinical effectiveness of immunotherapies in this setting as tumour responses can occur after conventional RECIST-defined progressive disease (i.e. the tumour flare effect). The PBAC also noted that AVE + AXI was not associated with an improvement in quality of life versus sunitinib in the JAVELIN trial.
- 7.10 The PBAC considered that the claim of different but non-inferior safety for AVE + AXI versus NIVO + IPI was reasonable.

- 7.11 The PBAC considered that the equi-effective doses estimated in the submission may not be reliable, as (a) it was unclear whether the equi-effective dose of axitinib adequately accounted for wastage of the 1 mg tablets in temporary dose reductions and (b) the majority of patients would be prescribed the nivolumab 480 mg Q4W dosing regimen (as outlined in Paragraph 6.48 and 6.49).
- 7.12 The PBAC noted that a CMA should result in the cost of AVE + AXI being no more than the cost of NIVO + IPI based on effective prices, and, noting axitinib is supplied by a different sponsor, that it was not specified in the submission how the total cost should be apportioned across avelumab and axitinib.
- 7.13 The PBAC considered there should be no financial implications to the Commonwealth associated with the listing of AVE + AXI in the intermediate and poor risk population, as it would substitute for NIVO + IPI. The PBAC advised that, if recommended in the future, AVE + AXI should join the RSA for NIVO + IPI for the same indication with no changes to the cap.
- 7.14 The PBAC considered that any resubmission would need to be a major submission and would need to provide updated OS data. The PBAC foreshadowed that acceptance of non-inferior efficacy versus NIVO + IPI in patients with intermediate or poor-risk disease would require more compelling evidence of superior overall survival versus sunitinib.
- 7.15 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 through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Merck Healthcare is disappointed with the PBAC decision and will continue to work with the PBAC and the Department of Health to pursue reimbursement for Bavencio in combination with axitinib for the first line treatment of patients with advanced renal cell carcinoma in line with the TGA registration (effective 6 May 2020).