7.07 PEMBROLIZUMAB, Solution concentrate for I.V. infusion 100 mg in 4 mL, Keytruda®, Merck Sharp & Dohme (Australia) Pty Ltd

1 Purpose of Application

1.1 The resubmission requested a Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital), Authority Required listing for pembrolizumab for the treatment of locally advanced (LA) or metastatic urothelial cancer (mUC) patients after failure of a platinum-based therapy. An application seeking listing in the same indication was considered and rejected at the November 2017 PBAC meeting.

1.2 The resubmission presented one head-to-head clinical trial (KEY-NOTE 045, KN045) which formed the basis of a cost-effectiveness/utility analysis against standard of care (SOC). The key components of the resubmission are summarised in Table 1.

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

Component	Description
Population	Patients with locally advanced or metastatic urothelial cancer after failure of a platinum-containing regimen.
Intervention	Pembrolizumab fixed dose 200 mg IV, once every 3 weeks.
Comparator	SOC; paclitaxel 175 mg/m^2 IV, once every 3 weeks, or docetaxel 75 mg/m^2, IV once every 3 weeks.
Outcomes	Primary: Progression free survival (PFS); overall survival (OS) Secondary: ORR, duration of response, HRQoL, safety.
Clinical claim	Pembrolizumab is superior to SOC in efficacy, providing statistically significant and clinically significant increase in OS (the primary outcome), increasing response rates, providing more durable responses and improved HRQoL. Pembrolizumab was non-inferior to SOC with respect to PFS but was associated with superior safety. These claims were supported by the data presented. At its November 2017 meeting, the PBAC noted that the claim of superior effectiveness was adequately supported by the OS data which showed a modest but statistically significant OS gain. It also noted that the claim of superior safety was reasonable (pembrolizumab Public Summary Document, November 2017, point 7.4 and 7.7).

Abbreviations: IV= intravenous; HRQoL= health related quality of life; ITT= Intention to treat; mg/m^2 = milligram per square metre; Nov = November; ORR= objective response rate; OS= overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PFS= progression free survival; SOC= standard of care.
Source: Table 1-2, p. 5 of resubmission.

2 Requested listing

2.1 The requested listing is summarised in Table 2 and is largely consistent with KN045 (see point 2.4 below). Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Table 2: Summary of the proposed PBS listing

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer	
PEMBROLIZUMAB 100mg vial for infusion; 1 x 100mg vial	200 mg	6	Published Public: $9,023.22 Private: $9,187.35 Effective Public: $[redacted] Private: $[redacted]	Keytruda®	Merck Sharp & Dohme (Australia) Pty Ltd

Episodicity:	N/A
Category/program:	Section 100 (Public/Private), Efficient Funding of Chemotherapy
Severity:	Locally advanced (Stage III) or metastatic (Stage IV)
Condition:	Urothelial cancer
PBS Indication:	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
Treatment phase:	Initial
Restriction:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ✓ Streamlined
Clinical criteria:	Treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have failed a platinum-containing regimen for this condition in the metastatic setting or for inoperable locally advanced disease OR Patient must have received adjuvant platinum-containing therapy following cystectomy for localised muscle-invasive urothelial cancer, with recurrence or progression ≤12 months following completion of therapy OR Patient must have received neoadjuvant platinum-containing therapy prior to cystectomy for localised muscle-invasive urothelial cancer, with recurrence ≤12 months following completion of therapy; AND Patient must have *WHO* performance status ~~score~~ of 2 or less
Administrative Advice	No increase in the maximum quantity or number of units or number of repeats will be authorised. 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. *Special Pricing Arrangements apply.*

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer	
PEMBROLIZUMAB 100mg vial for infusion; 1 x 100mg vial	200 mg	6	Published Public: $9,023.22 Private: $9,187.35 Effective Public: $[redacted] Private: $[redacted]	Keytruda®	Merck Sharp & Dohme (Australia) Pty Ltd

Episodicity:	N/A
Category/program:	Section 100 (Public/Private), Efficient Funding of Chemotherapy
Severity:	Advanced (Stage III) or metastatic (Stage IV)
Condition:	Urothelial cancer
PBS Indication:	Advanced (Stage III) or metastatic (Stage IV) urothelial cancer
Treatment phase:	Continuing
Restriction:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ✓ Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition, AND Treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have stable or responding disease, AND The total treatment received, inclusive of initial treatment, must not exceed 35 cycles at a dose of 200 mg every 3 weeks
Administrative Advice	No increase in the maximum quantity or number of units or number of repeats will be authorised. *Special Pricing Arrangements apply.*

Name, Restriction, Manner of administration and form	**Max. Amount**	**№.of Rpts**	**Dispensed Price for Max. Amount**	**Proprietary Name and Manufacturer**	
PEMBROLIZUMAB 100mg vial for infusion; 1 x 100mg vial	200 mg	5	Published Public: $9,023.22 Private: $9,187.35 Effective Public: $[redacted] Private: $[redacted]	Keytruda®	Merck Sharp & Dohme (Australia) Pty Ltd

Episodicity:	N/A
Category/program:	Section 100 (Public/Private), Efficient Funding of Chemotherapy
Severity:	Advanced (unresectable Stage III) or metastatic (Stage IV)
Condition:	Urothelial cancer
PBS Indication:	Advanced (unresectable Stage III) or metastatic (Stage IV) urothelial cancer
Treatment phase:	Grandfathering treatment
Restriction:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ✓ Streamlined

Clinical criteria:	Patient must have received non-PBS treatment with this drug for this condition prior to [date of PBS listing], AND Treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have failed a platinum-containing regimen for this condition in the metastatic setting or for inoperable locally advanced disease OR Patient must have received adjuvant platinum-containing therapy following cystectomy for localised muscle-invasive urothelial cancer, with recurrence/progression ≤12 months following completion of therapy OR Patient must have received neoadjuvant platinum-containing therapy prior to cystectomy for localised muscle-invasive urothelial cancer, with recurrence ≤12 months following completion of therapy; AND Patient must have stable or responding disease, AND The total treatment received must not exceed 35 cycles at a dose of 200 mg every 3 weeks
Administrative Advice	No increase in the maximum quantity or number of units or number of repeats will be authorised. *Special Pricing Arrangements apply.*

2.2 The resubmission proposed a special pricing arrangement (SPA). The price was reduced from $[redacted] in the November 2017 submission to $[redacted], with a proposed [redacted]% rebate for treatment beyond [redacted]. Due to changes to the sponsor's proposed base case, the Pre-Sub-Committee Response (PSCR) presented a further reduced price of pembrolizumab of $[redacted] per vial.

2.3 The restriction proposed in the resubmission does not reflect the eligible population as stated in the TGA approved Product Information (PI); the approved TGA restriction is broader than the proposed PBS restriction as it also includes treatment for cisplatin ineligible patients first line. Therefore, there is the potential for use of pembrolizumab beyond the requested PBS indication (and outside of the clinical and cost-effectiveness evidence presented in the resubmission). The ESC noted that pembrolizumab use outside of the restriction would likely be by patients who were ineligible for chemotherapy, rather than specifically patients who were ineligible for first line cisplatin. The ESC noted that if a patient was not able to use cisplatin, then carboplatin would be the alternative therapy, and it was therefore likely that the risk of use outside the requested indication was mostly in patients who were ineligible for any chemotherapy. The PBAC noted there was emerging data suggesting that there was decreased survival when PD-1 inhibitors are used first line in PD-L1-low expressing urothelial cancer[1,2,3]. Therefore, the PBAC considered it was less likely that there would be use outside the proposed restriction into the first line setting.

[1] US Food and Drug Administration (2018). Keytruda (pembrolizumab) or Tecentriq (atezolizumab): FDA Alerts Health Care Professionals and Investigators: FDA Statement - Decreased Survival in Some Patients in Clinical Trials Associated with Monotherapy.
https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm608253.htm

2.4 The proposed restriction also stated that patients must have stable or responding disease in order to be eligible for access to continuing treatment with pembrolizumab. The pre-PBAC response disagreed with the need to stipulate treatment response according to RECIST v1.1 stating that given other indications for anti-PD1 therapies do not include detailed assessment response criteria (melanoma, classic Hodgkin's lymphoma, 2L NSCLC), there would be inequity across indications by including this for LA or mUC. It would also lead to confusion with clinicians who treat across multiple indications if some indications have response criteria and others do not. The PBAC considered this was acceptable and noted that the RECIST criteria should not be included in the restrictions.

2.5 The proposed restriction also included a grandfather restriction for patients with LA or mUC who are currently receiving pembrolizumab outside the PBS and met the initiation criteria. However, it remained unclear what mechanisms would ensure that the combined (pre and post PBS listing) use in such patients would not exceed 35 treatment cycles. The PSCR proposed a clarification to the restriction wording for grandfathering and continuation to be, "The total treatment received must not exceed a total of 35 cycles (pre and post PBS listing) at a dose of 200 mg every 3 weeks". The PBAC considered that this amendment would be appropriate to include in the restriction. The PBAC considered the request for a grandfather restriction was acceptable. The PBAC considered it would be appropriate to include the following clinical criterion "Patient must have WHO performance status of 2 or less prior to initiating treatment with this drug for this condition" to be aligned with the Committee's consideration of the grandfather restriction for pembrolizumab for non-small cell lung cancer at its March 2018 meeting. The PBAC also considered that it would be appropriate for the grandfather restriction to have 6 repeats so that it is aligned with the continuing restriction.

2.6 The PBAC noted that the wording of the clinical criteria and administrative advice would need to be updated to conform to the electronic requirements for listings.

2.7 The PBAC noted that the resubmission only requested to list the 100 mg vial presentation. In the November 2017 major submission, the 100 mg and 50 mg vial presentations were requested. The resubmission stated that the [redacted]

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

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[2] Gourd E (2018). EMA restricts use of anti-PD-1 drugs for bladder cancer. *Lancet Oncology 19, 7:e341, DOI:* https://doi.org/10.1016/S1470-2045(18)30433-9

[3] European Medicines Agency (2018). EMA restricts use of Keytruda and Tecentriq in bladder cancer. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2018/05/WC500249798.pdf

3 Background

Registration status

3.1 Pembrolizumab was TGA registered on January 2018 for patients with LA or mUC in patients: (1) who are not eligible for cisplatin containing therapy, and (2) who have received platinum-containing chemotherapy.

3.2 Overall, the TGA Delegate reported a positive risk-benefit assessment for pembrolizumab. However, the Delegate's report noted that a warning be included for a higher risk of death in the pembrolizumab arm than the chemotherapy arm; this warning has been included in the pembrolizumab PI.

Previous PBAC considerations

3.3 At the November 2017 meeting, the PBAC did not recommend the PBS listing for pembrolizumab for the treatment of LA or mUC based on a highly uncertain and likely underestimated incremental cost-effectiveness ratio (ICER) and financial estimates (pembrolizumab PSD, November 2017, point 7.1).

3.4 The summary of the main issues of concern to the PBAC in November 2017 and how the resubmission addressed those issues is presented in Table 3.

Table 3: Summary of outstanding matter of concern

Component	Matter of concern November 2017	Approach in the July 2018 Resubmission
Clinical Issues		
PBS listed restriction	The PBAC considered that there was a risk that pembrolizumab would be used outside the requested restriction (into first-line treatment for cisplatin-ineligible patients) (pembrolizumab PSD, Nov 2017 point 7.11)	The resubmission proposed that the risk of use outside the requested restriction will be addressed through the RSA. The RSA proposed does not fully address these issues, as the budget impact estimates utilise time on treatment (TOT) to estimate the average number of administrations per person, and do not account directly for potential uncertainty in the number of eligible patients. The PSCR proposed a rebate rate of [redacted]% of treatment costs exceeding the agreed cap in each year.
Fixed dosing regimen vs weight-based dosing regimen	The PBAC noted that the November 2017 submission proposed pembrolizumab as a fixed dosing regimen for locally advanced or metastatic urothelial cancer, whereas pembrolizumab treatment for other PBS-listed indications has used a weight-based dosing regimen. The PBAC suggested that the price be reduced to account for what could effectively be wastage from the fixed dose regimen. (pembrolizumab PSD, Nov 2017 point 7.12)	While the resubmission included a price reduction this was not specifically to account for the fixed dose regimen used in the model. The resubmission justified that there is no evidence supporting weight-based dosing in this patient population and the approved TGA indication is based on a fixed dosing regimen.
Economic Issues		

Component	Matter of concern November 2017	Approach in the July 2018 Resubmission
Treatment duration	PFS was used to estimate the duration of treatment. However, patients in the trial received treatment beyond progression. The PBAC requested the use of TOT rather than PFS to estimate cost of treatment. (pembrolizumab PSD, Nov 2017 point 7.10 and 7.11).	Addressed by using TOT to estimate cost of treatment in the resubmission. The mean number of cycles of pembrolizumab estimated in the base-case in the resubmission increased to [redacted] from [redacted] in the November 2017 submission.
Use of KM data in the model	The start point for using data from extrapolation for both OS and PFS in the model was very early. The PBAC requested the use of observed Kaplan-Meier data in the model up to the median duration of follow-up. (pembrolizumab PSD, Nov 2017 point 7.10)	Addressed by using the observed Kaplan-Meier results in the model up to the median duration of follow-up (27.7 months) for both OS and PFS.
Use of KM data for extrapolation	The approach of excluding early Kaplan-Meier data from the estimation of the extrapolation functions from the assessment of the goodness of fit was inappropriate. The PBAC requested that the model development use all the Kaplan-Meier data at least up to the median follow-up to inform the extrapolation functions. (pembrolizumab PSD, Nov 2017 point 7.10)	Partially addressed. While the resubmission used all the Kaplan-Meier data to inform the extrapolation function for OS, it excluded the first 9 weeks of data from the development of the extrapolation curves for PFS. The resubmission does not justify its approach. The resulting ICER was not sensitive to variations in PFS.
Different extrapolation distribution, and conservative extrapolation	The model applied different parametric distributions between arms to the same outcomes. The PBAC requested that the same extrapolation distribution be applied across treatment arms for both PFS and OS. The PBAC also requested that a conservative set of extrapolation curves be applied due to modest follow-up post median duration of follow-up (that take into account the remaining uncertainty in the magnitude of PFS and OS benefit) (pembrolizumab PSD, Nov 2017 point 7.10).	Not addressed. The resubmission applied different extrapolation distributions across outcomes on the basis of information criteria (AIC/BIC) and face validity. The resubmission included a sensitivity analysis that showed the result was robust to this approach: applying the same distribution resulted in the ICER increasing by 0.3%.
Converging the extrapolation curves	The PBAC requested that survival curves be converged at a base case time horizon of 5 years (pembrolizumab PSD, Nov 2017 point 7.10).	Partially addressed. The resubmission increased the time horizon from 5 years to 7.5 years, applying convergence at that latter time point. Increasing the time horizon to 7.5 years was not well justified and is subject to heavy censoring and few patients at risk in the latter stages of follow-up. The PSCR stated that the sponsor would be willing to accept a 6.5-year time horizon with convergence from 5 years as the base-case.
Maintaining the ICER	The PBAC advised that the requested price of pembrolizumab should be adjusted to maintain the ICER at or below the ICER presented at the November 2017 submission (pembrolizumab PSD, Nov 2017 point 7.10). (The list price of pembrolizumab in the November 2017 submission was $[redacted] (DPMA) for 100 mg vial.)	Addressed. The list price of pembrolizumab was reduced to $[redacted] (DPMA) for 100 mg vial (plus a [redacted]% rebate from week 79). The resubmission maintained the ICER at $[redacted]/QALY. The PSCR proposed changes to the base case to 6.5-year time horizon with convergence from 5 years and reduced the effective price of pembrolizumab to $[redacted] per vial to maintain a similar ICER.

Component	Matter of concern November 2017	Approach in the July 2018 Resubmission
Financial Issues		
Number of patients estimated	The PBAC considered that the numbers of patients were likely underestimated. (pembrolizumab PSD, Nov 2017 point 7.11)	The resubmission maintained the same number of patients estimated in the November 2017 submission. The resubmission argued that there was no recent epidemiological data to support a change in the approached used to determine the patient population or to update the patient numbers.
Risk-sharing arrangements	The PBAC was unclear as to how the RSA would fully address the uncertainties related to treatment duration, particularly given that the magnitude of the proposed rebate was not specified for expenditure over the caps (pembrolizumab PSD, Nov 2017, point 7.13).	Not addressed. While the resubmission reiterated the proposed RSA it did not clarify the proposed rebate proportions, noting only that the rebate proportion would be considerable. The PSCR proposed a rebate rate of [redacted]% above agreed caps. The pre-PBAC response clarified that this was in addition to the rebate of [redacted]% after week 79.

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; DPMA = Dispensed price for maximum amount; ICER = Incremental cost effectiveness ratio; KM = Kaplan-Meier curve; Nov = November; PBAC = Pharmaceutical Benefits Advisory Committee; PFS = Progression free survival; PSD = Public summary document; OS = Overall survival; RSA = Risk-Sharing Arrangement; SOC = Standard of care; TGA = Therapeutics Goods Administration; TOT = Time on treatment
Source: Developed as part of the evaluation.

3.5 SOC in KN045 included vinflunine. At its July 2017 meeting, the PBAC did not recommend the PBS listing for vinflunine for the treatment of LA or metastatic transitional cell carcinoma of the urothelial tract (TCCU), on the basis of a lack of evidence of an incremental gain in OS versus currently available alternative active chemotherapy (vinflunine PSD, July 2017, p17). Vinflunine was rejected for the third time by the PBAC in July 2017.

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

4 Population and disease

4.1 The vast majority of urothelial carcinomas originate in the bladder and the vast majority of bladder cancers (BC) are of urothelial (transitional cell) histology. BC is the 10th most commonly diagnosed cancer in Australia. The majority of patients are male (77%) and the average age at diagnosis is 74.7 years. OS from BC has declined over the last 30 years (around 1,196 Australians will die of BC in 2018). The resubmission noted that the reason for this decline is unclear.

4.2 Pembrolizumab is proposed as a second line treatment in patients who progress following treatment with platinum-based therapy.

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

5 Comparator

5.1 The resubmission nominated SOC (as in the November 2017 submission) as the main comparator (paclitaxel, docetaxel). The PBAC considered this was appropriate (pembrolizumab PSD, November 2017, point 7.3).

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 sponsor's medical director of oncology presented a patient's experience of treatment with pembrolizumab, it's efficacy in treating the patient's urothelial cancer and noted the current inequitable access to this medicine. The clinician also presented on the effectiveness and tolerability of pembrolizumab using the pivotal trial data provided in the submission. The PBAC considered that the hearing was not informative as it did not add substantively to the evidence presented in the submission and the consumer information was already provided through the Consumer Comments facility.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (10) and health care professionals (9) via the Consumer Comments facility on the PBS website. Similar to the comments received for the previous submission, the comments described that pembrolizumab was effective in treating urothelial cancer where symptoms were improved and the medicine was well tolerated compared to chemotherapy. The benefits of using pembrolizumab over chemotherapy included having more energy and improved quality of life because it was painless and allowed patients to resume their normal lives. The comments also emphasized that there were limited treatment options for this type of cancer.

6.3 The Medical Oncology Group of Australia (MOGA) maintained its strong support for the pembrolizumab submission for urothelial cancer. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab, which was 5 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[4], based on a comparison with chemotherapy. In the PBAC's November 2017 consideration of pembrolizumab, MOGA presented an ESMO-MCBS score of 4 out of 5 and noted that the score would increase to 5 when the overall survival data matured for

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

pembrolizumab.

Clinical trials

6.4 The resubmission was based on one head-to-head trial comparing pembrolizumab with SOC, KN045 (n=542). Details of the trial presented in the submission are provided in Table 4.

Table 4: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
KN045		
CSR	A Phase III Randomized Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel, Docetaxel or Vinflunine in Patients with Recurrent or Progressive Metastatic Urothelial Cancer	Dec 2016.
Extended follow-up report 1	Extended follow-up data for KN045, data cut-off 18 Jan 2017	18 Jan 2017
Extended follow-up report 2	Extended follow-up data for KN045, data cut-off 26 Oct 2017	26 Oct 2017
Key Publication	Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma.	N Engl J Med. 2017 Feb 17. doi: 10.1056/NEJMoa1613683. [Epub ahead of print]
	De Wit R., Vaughn D.J., Fradet Y., et al, Pembrolizumab (pembro) versus paclitaxel, docetaxel, or vinflunine for recurrent, advanced urothelial cancer (UC): Mature results from the phase 3 KEYNOTE-045 trial.	Annals of Oncology (2017) 28 Supplement 5 (v623). Date of Publication: 1 Sep 2017, conf. date 2017-09-08 to 2017-09-12
	Petrylak D., Vogelzang N.J., Fradet Y., et al, Subgroup analyses from KEYNOTE-045: Pembrolizumab (pembro) versus individual investigator's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer (uc).	Annals of Oncology (2017) 28 Supplement 5 (v298). Date of Publication: 1 Sep 2017, conf. date 2017-09-08 to 2017-09-12
	Quinn D., Vaughn D.J., Bellmunt J., et al, Health-related quality of life (HRQOL) of pembrolizumab vs chemotherapy for previously treated advanced urothelial cancer (UC) in keynote-045.	Asia-Pacific Journal of Clinical Oncology (2017) 13 Supplement 1 (56). Date of Publication: 1 Jul 2017, conf. date 2017-07-16 to 2017-07-18
	Quinn D., Bellmunt J., De Wit R., et al, Keynote-045: Open-label, phase 3 study of pembrolizumab versus investigator's choice of paclitaxel, docetaxel, or vinflunine for previously treated advanced urothelial cancer.	Asia-Pacific Journal of Clinical Oncology (2017) 13 Supplement 1 (35). Date of Publication: 1 Jul 2017, conf. date 2017-07-16 to 2017-07-18
	De Wit R., Bajorin D.F., Bellmunt J., et al, Health-related quality of life (HRQoL) of pembrolizumab (pembro) vs chemotherapy (chemo) for previously treated advanced urothelial cancer (UC) in KEYNOTE-045.	Journal of Clinical Oncology (2017) 35:15 Supplement 1. Date of Publication: 20 Jun 2017, conf. date 2017-06-02 to 2017-06-06
	Bajorin D.F., De Wit R., Vaughn D.J., et al, Planned survival analysis from KEYNOTE-045: Phase 3, open-label study of pembrolizumab (pembro) versus paclitaxel, docetaxel, or vinflunine in recurrent, advanced urothelial cancer (UC).	Journal of Clinical Oncology (2017) 35:15 Supplement 1. Date of Publication: 20 Jun 2017, conf. date 2017-06-02 to 2017-06-06
	Bellmunt J., Vaughn D.J., De Wit R., et al, Two-year follow-up from the phase 3 KEYNOTE-045 trial of pembrolizumab (pembro) vs investigator's choice (paclitaxel, docetaxel, or vinflunine) in recurrent, advanced urothelial cancer (UC).	J Clin Oncol 36, 2018 (suppl 6S; abstr 410), conf. date 2018-10-02

Trial ID	Protocol title/ Publication title	Publication citation
	Vaughn D.J., Bellmunt J., Fradet Y., et al, Quality-of-Life Analysis from Keynote-045: A Phase 3 Study of Pembrolizumab Versus Chemotherapy for Previously Treated Advanced Urothelial Cancer.	Accepted by J Clin Oncol, but not yet published-Confidential
Abstracts	Vaughn DJ; Bellmunt J; de Wit R; et al. Health-Related Quality of Life of Pembrolizumab vs Chemotherapy for Previously Treated Advanced Urothelial Cancer in KEYNOTE-045 2017	Genitourinary Cancers Symposium Orlando, FL February 16-18, 2017
	Bajorin DF; de Wit R; et al. Planned survival analysis from KEYNOTE-045: Phase 3, Open-Label Study of Pembrolizumab versus Paclitaxel, Docetexel, or Vinflunine in Recurrent, Advanced Urothelial Cancer. 2017	American Society for Clinical Oncology (ASCO) Annual Meeting Chicago, IL (oral presentation)
	de Wit R; Bajorin, D; Bellmunt, J. Health-Related Quality of Life of Pembrolizumab vs Chemotherapy for Previously Treated Advanced Urothelial Cancer in KEYNOTE-045. 2017	ASCO Annual Meeting Chicago, IL (poster)

Source: Table 2-2, p. 28 of the resubmission.

6.5 The key features of the direct randomised trial are summarised in Table 5.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Pembrolizumab vs. SOC						
KN045	542	R, OL, MC Interim analysis: 1. September 2016: Median OS 14.1 months 2. January 2017 Median OS 18.5 months 3. 26th October 2017 Median OS 27.7 months	Moderate	Failed platinum-based chemotherapy.	OS, PFS, ORR	Survival and progression free gain.

Abbreviations: MC=multi-centre; N = total participants in group; OL=open label; ORR = objective response rate; OS=overall survival; PFS=progression-free survival; R=randomised, SOC= standard of care.
Source: compiled during the evaluation

6.6 KN045 had high performance bias and low/unclear selection, detection, attrition, reporting and misclassification bias. The main source of bias was due to the trial being 'open label', whereby participants and personnel were not blinded to treatment allocation.

6.7 Patients in KN045 could continue treatment beyond progression, provided there was clinical benefit, or up to 24 months of treatment (35 cycles). Continuing treatment was available to patients who had achieved a CR (complete response) prior to the end of 24 months, or who at reaching 24 months, had at least stable disease, and subsequently experienced disease progression (Clinical trial protocol, p 111).

Comparative effectiveness

6.8 The resubmission presented an extended follow-up analysis that provided an additional 13.6 months of follow-up compared with that in the November 2017 submission. These data showed a higher rate of crossover in the SOC arm ([redacted]% receiving immunotherapies post-progression vs. 12.9% in the November 2017 submission).

6.9 The updated overall survival (OS) and progression free survival (PFS) results showed a continued survival benefit for pembrolizumab compared to SOC (OS HR= 0.70 (95% CI; 0.57, 0.85), but no difference in PFS (see Table 6 and Figure 2). Figure 1 presents the updated Kaplan-Meier (KM) analysis of OS.

Figure 1: Kaplan-Meier estimate of Overall Survival (ITT population)

Abbreviations: ITT = intention to treat.
Source: Figure 2.2, p. 56 of the resubmission.

6.10 The KM analysis for PFS is presented in Figure 2. A total of 486 PFS events were reported at the time of the updated analysis. The median PFS was 2.1 months (95% CI: 2.0, 2.2) in the pembrolizumab arm compared with 3.3 months (95% CI: 2.4, 3.5) in the SOC arm with an estimated HR=0.96 (95% CI; 0.79-1.16). This did not differ from the outcome for PFS reported in the November 2017 submission. At the November 2017 PBAC meeting, the PBAC considered that PFS may not be a meaningful surrogate for clinical benefit in this indication (pembrolizumab PSD,

November 2017, point 7.6). The PBAC considered that having a difference in OS but no difference in PFS suggested that pembrolizumab may be effective in some patients and not others, indicating that better targeting of this treatment may be useful. The PBAC noted that a stratified analysis did not identify any clinically significant interactions within the subgroups identified but considered that a positive interaction may become more apparent with more data.

Figure 2: Kaplan-Meier estimate of PFS (ITT population)

Abbreviations: ITT = intention to treat; PFS = progression free survival.
Source: Figure 2.3, p. 58 of the resubmission.

6.11 A summary of the clinical outcomes is presented in Table 6.

Table 6: Summary of survival outcomes (PFS and OS) in KN045 (all three interim analyses)

	Pembrolizumab n/N (%)	SOC n/N (%)	Absolute difference	HR (95% CI)
PFS				
Database cut-off: 18th January 2017				
Patients with event	[redacted]	[redacted]	-	-
Median PFS months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)	-1.2 months	0.96 (0.79, 1.16)
Database cut-off: 26th October 2017				
Patients with event	[redacted]	[redacted]	-	-
Median PFS months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.4, 3.5)	-1.2 months	0.96 (0.79, 1.16)
OS				
Clinical study report (included in the November 2017 submission)				
Patients with event	155/270 (57.4)	179/272 (52)		
Median months OS (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)	**+2.9 months**	**0.73 (0.59, 0.91) p=0.00224**
Database cut-off: 18th January 2017				
Patients with event	[redacted]	[redacted]	-	-
Median months OS (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)	**+2.9 months**	**0.70 (0.57, 0.86) p-value = 0.0004**
Database cut-off: 26th October 2017				
Patients with event	[redacted]	[redacted]		
Median months OS (95% CI)	10.3 (8.0, 12.3)	7.3 (6.1, 8.1)	**+3.0 months**	**0.70 (0.57, 0.85) p-value = 0.00017**

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT, intention to treat; n = number of participants with event; N = total participants in group; NR = not reported; PFS = progression free survival; OS = overall survival; SOC= active chemotherapy.
Source: Table 2-14, p. 46 of resubmission. Table 2-15, p. 51 of resubmission.

6.12 The resubmission showed that treatment with pembrolizumab was associated with a higher response rate when compared with SOC (the absolute difference in response rate was 10.0 percentage points 95% CI: 3.9, 16.2 p=0.00068). Pembrolizumab-treated patients also exhibited more durable responses; approximately twice as many pembrolizumab patients had responses ≥ 6 months (84% vs 47%) and ≥12 months (68% vs 35%) compared with SOC.

6.13 Two subgroup analyses were presented in the resubmission containing updated results from KN045 (using the database cut-off 26th October 2017):

- An analysis excluding vinflunine as a possible comparator: The updated data showed no significant differences in PFS with vinflunine vs PFS without vinflunine or OS with vinflunine vs OS without vinflunine. At the November 2017 meeting, the PBAC noted that excluding vinflunine as a comparator was unlikely to affect the overall results (pembrolizumab PSD, November 2017, point 7.3).
- An analysis presenting results stratified by PD-L1 status. In November 2017, the PBAC concluded that, based on results stratified by PD-L1 status, there

was no strong signal to consider selecting patients based on PD-1 expression (pembrolizumab PSD, November 2017, point 6.20).

6.14 The resubmission included additional results for change in health related quality of life (HRQoL) as assessed using the EORTC QLQ-C30 (database cut-off of 18th January 2017 not included in the November 2017 submission). The results of the change from baseline to Week 15 in the EORTC QLQ-C30 are presented in Table 7.

Table 7: Results from the EORTC QLQ-C30

Trial ID	Pembrolizumab (200 mg) Baseline mean score	Pembrolizumab (200 mg) Week 15 score	Change from baseline to Week 15, LS Mean (95% CI)	SOC Baseline mean score	SOC Week 15 score	Change from baseline to Week 15, LS Mean (95% CI)	P-value	Difference in LS means (95% CI)
Clinical study report (November 2017 submission)	61.1 (23.1) N=260	67.6 (22.6) N=157	+0.75 (-2.34 to +3.83)	59.1 (22.1) N=243	57.9 (19.5) N=118	-8.30 (-11.76 to -4.83)	**<0.001**	**9.05 (4.61 to 13.48)**
Database cut-off: 18th January 2017	N=266		+0.69 (-2.40, 3.77)	N=253		-8.36 (-11.84, -4.89)	**<0.001**	**9.05 (4.61 to 13.50)**

Abbreviations: CI=confidence interval; EORTC QLQ-C30 = Electronic European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; LS=least squares; mg = milligram; N = total number of participants in group; SOC = standard of care.
Source: Table 2-18, p. 64 of the resubmission.
Note: Bold text indicates statistically significant results.

6.15 Mean EQ-5D index values (utilities) for the combined patient groups and according to disease progression, are presented in Table 8. The resubmission reported utility values calculated using the EQ-5D scores, for each of the health states utilised in the economic evaluation. The values were transformed appropriately using the Australian algorithm.

Table 8: Results of EQ-5D

	Control + Pembrolizumab				
	n†	n‡	Mean	SE	95% CI
Progression-Free	462	1621	[redacted]	[redacted]	([redacted], [redacted])
On treatment	441	1503	[redacted]	[redacted]	([redacted], [redacted])
Off treatment	82	118	[redacted]	[redacted]	([redacted], [redacted])
Progressive	320	742	[redacted]	[redacted]	([redacted], [redacted])

Abbreviations: CI = confidence interval; EQ-5D = EuroQol five-dimensions; SE = standard error.
Source: Table 5, Att 10 of the resubmission. † n=Number of patients with non-missing EQ-5D score ‡ n=Number of records with non-missing EQ-5D score. EQ-5D score during baseline is not included
Note: bold text indicates statistical significant differences.

6.16 The resubmission included an adjustment for crossover, but lacked important supportive information pertaining to the crossover method, namely: (1) the baseline characteristics of switchers and non-switchers; (2) the reasons for switching and the number of patients switching for each category; (3) the extent and timing of

switching; and (4) a KM curve reflecting the adjusted OS for SOC compared to ITT with the corresponding risk table with information regarding censored patients. Thus, while the selected method for crossover adjustment (the two-stage approach) was likely to be appropriate, this was not well justified and could not be verified. Moreover, the two-stage adjustment yielded the best result for effectiveness for pembrolizumab and produced the most favourable ICER relative to the other approaches.

Comparative harms

6.17 The extended assessment of comparative harms (data cut-off 4th March 2017 to 3rd September 2017) did not identify any new safety signals and the overall conclusion of superior safety for pembrolizumab remains unchanged as per the November 2017 submission. The total number of adverse events (AEs), treatment related AEs, and AEs leading to discontinuation were all higher in the SOC group than the pembrolizumab group (see Table 9). The TGA Clinical Evaluation Report noted this favourable safety profile of pembrolizumab, the consumer comments submitted to the PBAC and by the PBAC at the November 2017 meeting (pembrolizumab PSD, November 2017, points 7.2 and 7.7).

Table 9: Summary of key adverse events in the trials

Trial ID	Pembrolizumab n/N with event (%)	SOC n/N with event (%)	Risk difference % (95% CI)	Relative risk (95% CI)
Database cut-off: March 2017 (November 2017 submission)				
Any AE	248/266 (93.2)	250/255 (98.0)	**-4.8% (-8.3, -1.3)**	**0.95 (0.92, 0.99)**
Any SAE (≥ Grade 3)	139/266 (52.3)	160/255 (62.7)	**-10.5%(-18.9,-2.0)**	**0.83 (0.72, 0.97)**
AE leading to discontinuation of treatment (any grade)	22/266 (8.3)	32/255 (12.5)	-4.3% (-9.5, 1.0)	0.66 (0.39, 1.10)
AE resulting in death	13/266 (4.9)	8/255 (3.1)	1.7% (-1.6, 5.1)	1.56 (0.66, 3.70)
Database cut-off: 26th October 2017				
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE (≥ Grade 3)	[redacted]	[redacted]	[redacted]	[redacted]
AE leading to discontinuation of treatment (any grade)	[redacted]	[redacted]	[redacted]	[redacted]
AE resulting in death	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE = adverse events; APaT = all patients as treated; CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; SAE = serious adverse events; SOC = standard of care.
Source: Adapted from Table 2-20, p.69 of the resubmission.
Note: bold text indicates statistically significant results.

Benefits/harms

6.18 A summary of the comparative benefits and harms for pembrolizumab versus SOC is presented in the Table 10.

Table 10: Summary of comparative benefits and harms for pembrolizumab and SOC

Benefits					
Event: Deaths	**Pembrolizumab, N=270**		**SOC, N=272**	**Absolute difference**	**HR (95% CI)**
Number of events	[redacted]		[redacted]		**0.70 (0.57, 0.85)**
Median months	10.3 (8.0, 12.3)		7.3 (6.1, 8.1)	3.0 months	
Alive at 12 months, %	[redacted]		[redacted]	[redacted]	
Alive at 18 months, %	[redacted]		[redacted]	[redacted]	
Harms					
KN045	**Pembrolizumab N=266**	**SOC N=255**	**Risk ratio (95% CI)**	**Events/100 patients***	**Risk difference**
				Pembrolizumab / **SOC**	
With toxicity grade 3-5 treatment adverse event	44	128	**0.68 (0.62, 0.76)**	16.5 / 50.2	-28.6% (-35.4, -21.7)
Discontinued due to serious drug related adverse event	[redacted]	[redacted]	[redacted]	[redacted] / [redacted]	[redacted]
Died due to treatment related adverse even	[redacted]	[redacted]	[redacted]	[redacted] / [redacted]	[redacted]

Abbreviations: CI = confidence interval; HR = hazard ratio; n= number of participants with event; N = total participants in group; SOC = standard of care.
Source: Table 2-14 p54, Table 2-20 p.69-70 of the resubmission; compiled during the evaluation
Notes: *Median duration of follow-up: 27.7 months; bold text indicates statistically significant results.

6.19 On the basis of the direct comparison presented by the resubmission, for every 100 patients treated with pembrolizumab rather than SOC, there would be:

- approximately [redacted] additional patients alive 18 months after the start of treatment;
- approximately [redacted] fewer treatment related grade 3-5 adverse events over 27.7 months follow up.

Clinical claim

6.20 Pembrolizumab is superior to SOC in terms of effectiveness, given the demonstration of better OS, higher and more durable response rates and improved HRQoL. Pembrolizumab was non-inferior to SOC with respect to PFS, and was associated with superior safety. These claims were supported by the data presented in the resubmission and consistent with the data presented in the November 2017 submission.

6.21 The PBAC considered that the claims of superior comparative effectiveness and safety were reasonable and adequately supported by the data.

Economic analysis

6.22 The resubmission presented a cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). Health benefits were reported as life years gained (LYGs) and quality adjusted life years (QALYs) gained, respectively.

6.23 Several changes were implemented in the economic evaluation that are summarised in Table 11.

Table 11: Summary of model structure, rationale and differences between the November 2017 submission and March 2018 resubmission.

Component	November 2017 submission	Base Case of resubmission
Type of analysis	CEA and CUA	No change
Outcomes	LYGs and QALYs	No change
Time horizon	14.1 months median follow-up in KN045 vs 5 years in the model base case. Sensitivity analyses: 7 and 10 years	27.7 months median follow-up in KN045 vs 7.5 years in the model base case. Sensitivity analyses: 5 and 10 years PSCR willing to accept time horizon of 6.5 years.
Methods used to generate results	Partitioned survival model	No change
Health states	Progression free (PFS), progressive disease (PD) and dead.	No change
Cycle length	1 week	No change
Area under the curve	The KM estimates for PFS and OS were derived directly from KN045.	No change, except for updated data used to build the curves.
Perspective	Health care perspective	No change
Discount rate	5% per year for costs and benefits	No change
Software package	Excel 2010	No change
Health resources costs and utilization.	Derived from PFS	Derived from TOT
Point from which extrapolation functions were applied	Cut-points applied at 27 weeks for PFS and 40 weeks for OS	27.7 months (median duration of follow-up) for both PFS and OS
Data for extrapolation	Informed by data after the cut-points applied (27 weeks for PFS and 40 weeks for OS)	OS: full data set to inform goodness of fit PFS: cut-off point from week 9
Parametric curves: PFS	Log-normal for both pembrolizumab and SOC	Pembrolizumab: log-normal SOC: Weibull
Parametric curves: OS	Pembrolizumab: log-normal SOC: exponential	Pembrolizumab: log-normal SOC: log-logistic
PFS and OS convergence	Not implemented	Converged from year 5 to year 7.5 PSCR willing to accept convergence from year 5 to year 6.5.
Treatment effect adjustment	No adjustment	Adjustment for crossover using the two-stage approach.
Pembrolizumab price	$[redacted] AUD per 100 mg vial	$[redacted] AUD per 100 mg vial

Abbreviations: AUC= area under the curve; AUD = Australian dollar; BSC= best supportive care; CEA= cost-effectiveness analysis; CUA = cost-utility analysis; KM= Kaplan-Meier; LYG= life years gained; N/A= not applicable; OS= overall survival; PD= progressive disease; PFS= progression free survival; QALYs= quality adjusted life years, SOC= standard of care; TOT= time on treatment.
Source: Table 3-1, p. 105 of the resubmission.

6.24 The ESC noted that the 'off treatment' utility values may reflect two different groups – those stopping treatment due to adverse events and those coming off treatment after completing the maximum number of treatment cycles. The latter group may be

underrepresented in the utility data relative to their representation in the model. The ESC considered that lower utility values should not be applied to patients completing treatment. The pre-PBAC response argued that aggregating the utility scores for these patients as presented in the economic model was highly conservative and favoured SOC. There were more patients in the control arm that discontinued due to adverse events ([redacted]%) than in the pembrolizumab arm ([redacted]%). In addition, there were [redacted]% of patients in the pembrolizumab arm that completed the full duration of treatment or stopped due to having a complete response compared to only 0.4% of patients in the SoC arm. The pre-PBAC response further stated that when treatment specific utility scores were used for both the pre-progression and post-progression health states, the base case ICER reduced by less than $15,000/QALY (to $45,000/QALY – $75,000/QALY). Using this approach for estimating utilities and not adjusting for the treatment effect of cross-over resulted in an ICER of $45,000/QALY – $75,000/QALY.

6.25 A summary of the key drivers of the economic model is shown in Table 12. The key drivers in the model assessed in November 2017 included the points from which data were extrapolated, the application of different functional forms in extrapolating the data, and the use of PFS as the basis to assess drug exposure. These are no longer key drivers of the economic model.

Table 12: Key drivers of the model in the resubmission

Description	**Method/Value**	**Impact on ICER** (Base: $[redacted])
Time horizon plus adjustment for crossover	Reduce time horizon to 5 years and do not adjust OS treatment effect for crossover.	High, favours pembrolizumab (SA: $[redacted], +29.7%)
Time horizon and convergence	5 year-time horizon assuming PFS and OS curves converge from year 4 to year 5.	High, favours pembrolizumab (SA: $[redacted], +15.7%)
Adjustment for crossover	No adjustment	High, favours pembrolizumab (SA: $[redacted], +15.2%)
No convergence	7.5-year time horizon assuming curves do not converge.	High, favours SOC (SA: $[redacted], -14.6%)
Pembrolizumab price	No [redacted]% rebate and no price cap (pembrolizumab price equals to AUD $[redacted])	Moderate, favours pembrolizumab (SA: $[redacted], +9.8%)

Abbreviations: AUD = Australian dollar; ICER= incremental cost effectiveness ratio; PFS = progression free survival; OS = overall survival; SA, sensitivity analysis; SOC = standard of care.
Source: Table 3-18, p. 144 of the resubmission, compiled during the evaluation

6.26 A stepped economic evaluation was presented (see Table 13): Step 1 was a trial-based economic evaluation; Step 2 extrapolated results to a 7.5-year time horizon; and Step 3 transformed the outcomes, LYG, to QALYs.

Table 13: Results of the stepped economic evaluation

Steps undertaken	Proposed PEM costs	SOC costs	Inc. costs	PEM outcomes	Comparator outcomes	Inc. outcomes	ICER
Step 1. Comparative study data (27.7 months follow-up)	$[redacted]	$[redacted]	$[redacted]	[redacted] LYs	[redacted] LYs	[redacted] LYs	$[redacted] / LY
Step 2. Extrapolated to the 7.5-year time horizon	$[redacted]	$[redacted]	$[redacted]	[redacted] LYs	[redacted] LYs	[redacted] LYs	$[redacted] / LY
Step 3. Extrapolated to the 7.5-year and transformed into QALYs	$[redacted]	$[redacted]	$[redacted]	[redacted] QALYs	[redacted] QALYs	[redacted] QALYs	$[redacted] / QALY

Abbreviations: ICER= incremental cost effectiveness ratio; Inc= incremental; LYs = life years; PEM= pembrolizumab, QALYs= quality adjusted life years, SOC= standard of care
Source: Table 3-13, p 139 of the resubmission.

6.27 The results from the economic evaluation show that the time horizon had an important impact on the ICER. All steps presented included the impact of the adjustment for crossover. It would have been valuable to have an additional step presenting the trial duration ICER without crossover adjustment. The transformation of the outcome from LYG to QALYs also had an important impact on the cost-effectiveness results. The differences between the results reported in the November 2017 submission and the resubmission are mainly explained by the extension of the time horizon and the adjustment for crossover.

6.28 The submission applied appropriate methodology to estimate the total expected costs based on TOT. The sources for valuing health resources were appropriate.

6.29 Selected univariate sensitivity analyses specified by the resubmission and additional analyses (univariate and multivariate) conducted during the evaluation are presented in Table 14 and Figure 3.

Table 14: Results of the sensitivity and scenario analyses characterising the uncertainty around the ICER

Variable or assumption	Base-case value	Plausible alternative(s) or range of values	Incremental QALYs	Incremental costs	ICER ($/ QALY)	% change
Base case			[redacted]	$[redacted]	$[redacted]	
Discounting	Outcomes and costs = 5%	Outcomes and costs = 3.5%	[redacted]	$[redacted]	$[redacted]	-2.7%
	Outcomes and costs = 5%	Outcomes and costs = 0%	[redacted]	$[redacted]	$[redacted]	-9.5%
Extrapolation of OS data beyond trial period	KM to 107 weeks	No KM	[redacted]	$[redacted]	$[redacted]	-0.7%
	Log-Normal distribution for Pembro	Gen Gamma distribution	[redacted]	$[redacted]	$[redacted]	-2.2%
	Log-Normal distribution for Pembro	Log-Logistic distribution	[redacted]	$[redacted]	$[redacted]	+0.8%
	Log-Logistic for SoC	Log-Normal distribution	[redacted]	$[redacted]	$[redacted]	0%
Crossover adjustment method	2-stage adjustment	IPCW	[redacted]	$[redacted]	$[redacted]	+3.3%
	2-stage adjustment	RPSFT	[redacted]	$[redacted]	$[redacted]	+13.0%
	2-stage adjustment	No adjustment	[redacted]	$[redacted]	$[redacted]	+15.2%
Time horizon	7.5 years	5 years	[redacted]	$[redacted]	$[redacted]	+6.1%
	7.5 years	7.5 years (no convergence)	[redacted]	$[redacted]	$[redacted]	-14.6%
Additional analyses						
Converge extrapolation curves	Converge extrapolation curves to 7.5 years from a starting point of 5 years.	Converge extrapolation curves to 5 years (from a starting point of 4 years)	[redacted]	$[redacted]	$[redacted]	+15.7%
Pembrolizumab price	Pembrolizumab price equals to $[redacted] and [redacted]% rebate from [redacted].	No [redacted]% rebate and no price cap (pembro price equals to AUD [redacted])	[redacted]	$[redacted]	$[redacted]	+9.8%
Converge extrapolation curves plus adjustment for crossover	Time horizon equals to 7.5 years and adjusted for cross over	Converge extrapolation curves to 5 years (from a starting point of 4 years)and no adjustment for cross over	[redacted]	$[redacted]	$[redacted]	+29.7%

Abbreviations: ICER= incremental cost effectiveness ratio, IPCW= inverse probability of censoring weighted, KM=Kaplan-Meier, OS= overall survival, Pembro= pembrolizumab, QALY= quality adjusted life years, RPSFT= rank-preserving structural failure time, SOC= standard of care

Source: Table 3-18, p. 144 of the resubmission, with additional analyses conducted during the evaluation.

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

Figure 3: Tornado graph of sensitivity analyses

Abbreviation: AUD= Australian dollar, ICER= incremental cost effectiveness ratio, IPCW= inverse probability of censoring weighted, KM= Kaplan Meier, OS= overall survival, PFS= progression free survival, RPSFT= rank-preserving structural failure time, SOC= standard of care
Source: Figure 3-12, p145 of the resubmission, plus additional analysis conducted during evaluation.
Note: highlighted in yellow are additional scenarios conducted as part of the evaluation.

6.30 The results from the sensitivity analyses provided in the resubmission showed that the ICER estimates were most sensitive to variations in the time horizon, convergence of PFS and OS curves, and adjustment for crossover.

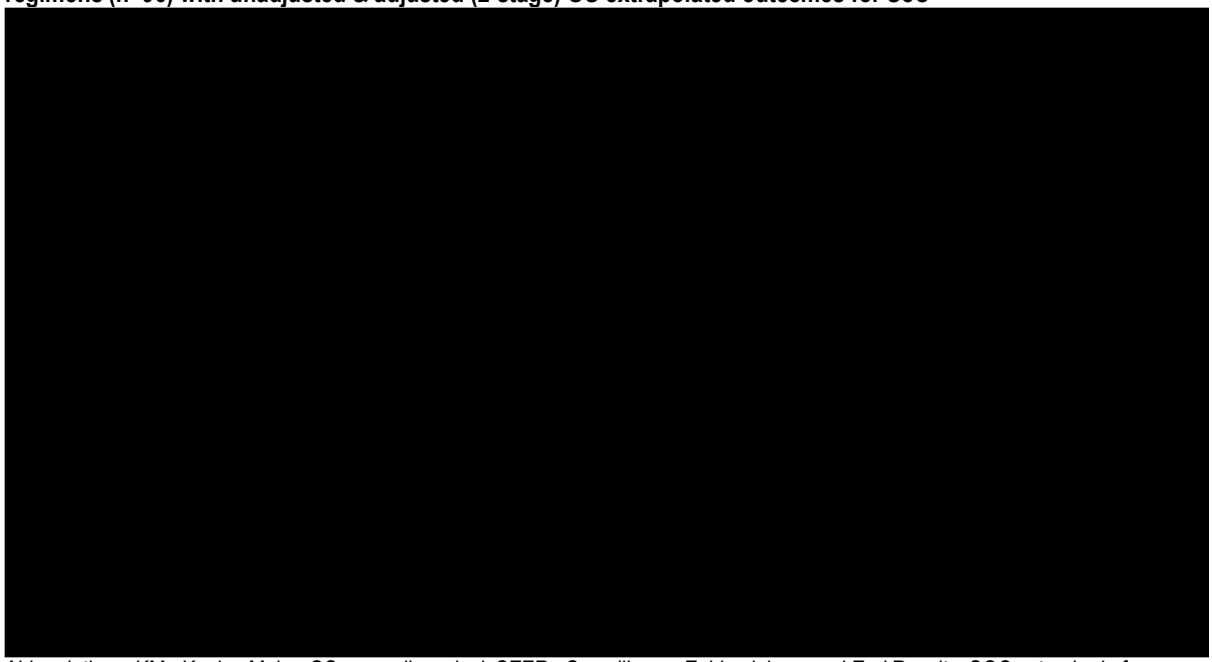
6.31 In terms of the adjustment for crossover, the ESC noted that relatively few patients crossed-over and hence adjustment for this should only have a small impact on the point-estimate of the difference in OS. The ESC also noted that there were limitations with all three methods of adjustment for treatment switching.

6.32 The PSCR stated the two-stage method was the most appropriate of the presented methods as patients were allowed to switch to the new treatment after progression of disease, but patients switched treatment at varying lengths of time after disease progression (PSCR, "Adjusting for treatment switchover" report, p2). The ESC noted that the two-stage method assumes that all patients would switch on progression, but this was not the case in the trial. The ESC considered that the number of patients switching impacted on the validity of the two-stage adjustment method. The PSCR also stated that "the estimated post-progression treatment estimate suggests that switching to anti-PDL1 treatment increases survival time by a large factor of 4.09…, [which is] not very precise due in particular to the limited number of patients who were eligible to switch and switched (PSCR, "Adjusting for treatment switchover" report, p2). The ESC considered that this likely indicated a moderate influence of unmeasured confounders unable to be controlled for in the analysis. The ESC noted that for two-stage cross-over adjustment, re-censoring should occur once the revised survival times have been estimated but this was not performed. In this case, re-censoring in this fashion imparts a potential bias secondary to informative censoring, where the loss of events to study disproportionately effects one

comparison arm greater than the other. The pre-PBAC response maintained the view that the two-stage method was the most appropriate method and that re-censoring data as suggested by the ESC introduces a risk of bias due to non-proportionality of hazards and the time-dependent treatment effect observed in this study, which is characteristic of immunotherapy.

6.33 Figure 4 compares the extrapolated OS with and without adjustment for treatment switching to Surveillance, Epidemiology, and End Results (SEER) registry data. The ESC was of the view that the two-stage crossover adjustment may underestimate the OS for standard of care, and the unadjusted data may be more representative of OS, particularly in later time periods. The PBAC agreed with the ESC and considered that the crossover adjustment presented was unreliable and it was the Committee's preference to not apply crossover adjustments in the model.

Figure 4: Comparison of SEER-Medicare Registry data for bladder cancer patients receiving 2L non-platinum regimens (n=96) with unadjusted & adjusted (2-stage) OS extrapolated outcomes for SoC



Abbreviations: KM= Kaplan Meier, OS= overall survival, SEER= Surveillance, Epidemiology, and End Results, SOC= standard of care
Source: Figure 3-11, p 137 of the submission; adjusted as part of ESC evaluation.

6.34 In terms of extrapolation of the pembrolizumab arm, six alternative extrapolation models were presented for the two-stage adjustment analysis (Figure 5). The ESC considered that the selected curves appeared reasonable; however no extrapolation figures were presented for the unadjusted analysis, nor the alternative adjustment methods, so it was not possible to assess the reasonableness of the extrapolation for these analyses.

Figure 5: OS parametric functions fitted in the pembrolizumab arm

Abbreviations: GenGamma= generalized gamma; KM= Kaplan Meier; Lnormal= log-normal; Llogistic= log-logistic; OS= overall survival
Source: Figure 3-7, p 121 of the resubmission.

6.35 The ESC noted that the SEER registry data suggests 5% OS at 5 years. The extrapolations suggest 5-year survival for pembrolizumab treated patients is between 5% and 15% and hence convergence of the pembrolizumab and SOC curves at 5 years or soon after would be appropriate. The PSCR maintained that the time horizon of 7.5 years without convergence of the extrapolation curves used in the economic evaluation model was appropriate. The PSCR referred to a recent decision by the PBAC (March 2018) for nivolumab in second line non-small cell lung cancer in which a 7.5-year time horizon was applied. The PSCR also argued that converging the curves from 5 years in the base-case represents a conservative approach to extrapolating as it assumes patients in the pembrolizumab arm progress and die more rapidly than the SOC arm from year 5 onwards. Although the submission originally proposed convergence at 7.5 years, the PSCR was willing to accept a revised time horizon of 6.5 years. The PBAC considered a 5-year time horizon was appropriate. The PBAC noted a Norwegian study of life expectancy for patients diagnosed with urothelial cancer[5], where half the study population within the 75 year age bracket died within 2 years. The PBAC noted that the mean age in the Australian setting is 75 years (higher than the trial setting) therefore the Norwegian data supported the Committee's preference for a 5 year time horizon given the relatively low 5 year survival for these patients.

[5] Andreassen BK, Myklebust TA, Haug ES, Crude mortality and loss of life expectancy of patients diagnosed with urothelial carcinoma of the urinary bladder in Norway. Scand J Urol. 2017 Feb;51(1):38-43.

6.36 The ESC considered that given the uncertainties regarding adjustment for treatment switching and the time horizon, additional sensitivity analyses would be informative. Table 15 presents the resulting ICERs from additional sensitivity analyses that were carried out with and without adjustments for crossover, different time horizons and convergence assumptions, and with the revised price from the PSCR .

Table 15: Additional sensitivity analyses

	Adjustment	Horizon	Convergence	Original price ($[redacted]/vial) ICER	PSCR revised price ($[redacted]/vial) ICER#
1	None	5 years	From 4 years	$[redacted]*	$[redacted]
2	None	5 years	None	$[redacted]*	$[redacted]
3	2-stage adjustment	5 years	From 4 years	$[redacted]*	$[redacted]
4	2-stage adjustment	5 years	None	$[redacted]**	$[redacted]
5	None	6.5 years	From 5 years	$[redacted]#	$[redacted]
6	2-stage adjustment	6.5 years	From 5 years	$[redacted]#	$[redacted]***

Notes: *Provided as additional multivariate sensitivity analyses in commentary Table 3.9.2.
**Provided in submission
***PSCR reported this ICER as $[redacted], recalculated by evaluators
#ICER recalculated by evaluators for the ESC consideration

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

6.37 The PSCR stated that the sponsor would be willing to accept a 6.5-year time horizon with convergence from 5 years as the base-case and maintaining the ICER at $45,000/QALY – $75,000/QALY per QALY, resulting in a reduced effective price of $[redacted]/vial. This ICER could not be reproduced. Application of the revised cost per vial for the scenario proposed in the PSCR resulted in an ICER of $45,000/QALY – $75,000/QALY per QALY. The PBAC considered that the most appropriate model inputs would be a 5-year time horizon with convergence at year 5 and no crossover (scenario 1 in Table 15 and within the tornado plot in Figure 3). However, recognising the high clinical need in this patient population and that there was uncertainty in all scenarios, the PBAC considered that based on the additional sensitivity analyses provided in Table 15, scenario 2 (5-year time horizon, two-stage adjustment for cross-over and convergence) and scenario 3 (5-year time horizon, no crossover and no convergence) may also be acceptable as the basis for assessing the cost-effectiveness of pembrolizumab. The PBAC noted that a further price reduction of 12-20% from the revised price of $[redacted] would be required for pembrolizumab to achieve an ICER of <$60,000 per QALY under any of these modelled scenarios.

Drug cost/patient/treatment course: $[redacted] ($[redacted] per vial)

6.38 Based on a fixed dose of 200 mg per person, the average cost per patient per treatment cycle of pembrolizumab was $[redacted](2 X 100 mg vials, at $[redacted] per vial),

every 3 weeks. Due to changes to the base case presented in the PSCR , the price of pembrolizumab was further reduced to $[redacted] per vial. Therefore, the average cost per patient per treatment cycle of pembrolizumab was $[redacted].

6.39 The average number of administrations was based on the TOT curve adapted from the economic evaluation. This is appropriate. The mean average number of administrations was [redacted] per patient. The average (undiscounted) cost per treatment course per patient was determined to be $[redacted] for pembrolizumab patients (inclusive of a [redacted]% discount from [redacted] ($[redacted] x [redacted])). Using the reduced price of $[redacted] proposed in the PSCR , the average (undiscounted) cost per treatment course per patient was determined to be $[redacted] for pembrolizumab patients.

Estimated PBS usage & financial implications

6.40 This resubmission was not considered by DUSC. The resubmission maintained the epidemiological approach used in the November 2017 submission to estimate the eligible population each year. Specifically, it used projected BC mortality data as a proxy to identify patients with LA or mUC (AIHW), and then expert opinion (Tracey et al 2014) to estimate the proportion of those patients likely to be treated with first and second line agents in the Australian population.

6.41 The resubmission's estimates of the number of patients to be treated, use of pembrolizumab, substitution of SOC and resulting cost to Government are presented in Table 16. The estimated number of patients at year 6 was less than 10,000. The estimated total cost to the PBS/RPBS over the first six years of listing, taking account of co-payments and substitution for SOC, was $60 - $100 million. The PSCR updated the financial estimates to include the reduced effective price of $[redacted]/vial. Therefore, the updated estimated total cost to the PBS/RPBS over the first six years of listing, taking account of co-payments and substitution for SOC, was $60 - $100 million. The PSCR also proposed a rebate rate of [redacted]% of treatment costs if subsidisation caps are exceeded that year. The proposed caps are shown in Table 16.

Table 16: Estimated use and financial implications

	2018	2019	2020	2021	2022	2023
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of pembrolizumab						
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]
Cost to PBS/RPBS (updated in PSCR)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for standard of care						
Cost to PBS/RPBS						
Paclitaxel 100mg vial	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Docetaxel 160mg vial	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments						
Paclitaxel 100mg vial	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Docetaxel 160mg vial	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments						
Paclitaxel 100mg vial	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Docetaxel 160mg vial	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS (updated in PSCR)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Proposed expenditure caps (provided in PSCR)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Abbreviations: mg = milligram; PBAC = Pharmaceutical Benefits Advisory Committee; PBS= Pharmaceutical Benefits Scheme; PSCR = Pre-Sub-Committee Response; RPBS = Repatriation Pharmaceutical Benefits Scheme

Note: [a] Assuming [redacted] scripts in Year 1 and [redacted] in Year 2 (average [redacted] per year) as estimated by the resubmission.

Source: Table 4.5 p.155; Table 4.7 p.156; Table 4.26-4.28 p.166-157; Table 4.30 p.167; revised as a part of the evaluation (Att. 15 financial impact.xlsx).

6.42 At the November 2017 meeting the PBAC noted:

- that the number of eligible patients was likely underestimated, in part due to a risk of use outside the requested restriction (patients who are ineligible to receive platinum-based chemotherapy). The ESC noted that pembrolizumab use outside of the restriction would likely be by patients who were ineligible for chemotherapy, rather than patients who were ineligible specifically for first line cisplatin. The ESC

noted that if a patient was not able to use cisplatin, then carboplatin would be the alternative therapy. The PBAC considered that use in the first line setting may be reduced given there was emerging data suggesting that there was decreased survival when PD-1 inhibitors are used first line in PD-L1-low expressing urothelial cancer[6,7,8].

- there was uncertainty regarding pembrolizumab treatment duration (in the trial, patients were allowed to receive treatment beyond progression and access an additional 12 months of treatment if certain conditions were met). The resubmission proposed a RSA to address these two issues by defining expenditure caps reflecting the number of patients receiving pembrolizumab and the number of cycles per patient based on the TOT curve. The PSCR proposed a rebate rate of [redacted]% of treatment costs if subsidisation caps are exceeded. The pre-PBAC response confirmed that this was in addition to the [redacted]% rebate for use beyond [redacted]. Further discussion around the rebate rate proposed is discussed in the 'Financial Management' section.
- pembrolizumab was administered as a fixed dosing regimen which results in [redacted]% more pembrolizumab being used per patient. The PBAC stated that urothelial cancer patients were given a greater dose, at a greater cost with no evidence of additional benefit (pembrolizumab PSD, November 2017, point 7.12), hence it "may be reasonable for the price paid for pembrolizumab in urothelial cancer to reflect the cost if weight-based 2 mg/kg dosing was used rather than fixed 200 mg dosing" (pembrolizumab PSD, November 2017, point 7.12). This issue was not addressed by the resubmission.

Financial Management – Risk Sharing Arrangements

6.43 A RSA was proposed in the form of expenditure caps "calculated to reflect the number of patients receiving pembrolizumab and the number of pembrolizumab cycles per patient as included in the base case economic model and budget impact using TOT duration of treatment". The PSCR proposed a rebate rate of [redacted]% of treatment costs above the annual caps, which is aligned with an RSA for pembrolizumab for treatment of classic Hodgkin's lymphoma. The pre-PBAC response confirmed that this was in addition to the [redacted]% rebate for use beyond [redacted]. The PSCR reiterated that the price and rebate proposed are conditional on receipt of [redacted]. The PBAC considered the RSA was required

[6] US Food and Drug Administration (2018). Keytruda (pembrolizumab) or Tecentriq (atezolizumab): FDA Alerts Health Care Professionals and Investigators: FDA Statement - Decreased Survival in Some Patients in Clinical Trials Associated with Monotherapy.
https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm608253.htm
[7] Gourd E (2018). EMA restricts use of anti-PD-1 drugs for bladder cancer. *Lancet Oncology 19, 7:e341, DOI:* https://doi.org/10.1016/S1470-2045(18)30433-9
[8] European Medicines Agency (2018). EMA restricts use of Keytruda and Tecentriq in bladder cancer.
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2018/05/WC500249798.pdf

to address potential use outside the proposed restriction and the uncertain treatment duration.

Quality Use of Medicines

6.44 The PBAC noted in its previous consideration of pembrolizumab for urothelial cancer that the fixed dosing regimen proposed results in a considerable proportion of patients with urothelial cancer being given a greater dose, at a greater cost, with no evidence of additional benefit and advised that it would be appropriate for the price of pembrolizumab in urothelial cancer to be reduced by a further proportion to account for what could effectively be considered wastage (Paragraph 7.12, 6.11 pembrolizumab PSD, November 2017). At the March 2018 meeting, the PBAC considered a minor submission for pembrolizumab requesting a change to the pembrolizumab dosing for malignant melanoma from 2 mg/kg to a fixed dose of 200mg per infusion. The PBAC recommended an amendment to the existing PBS restrictions to allow either a weight-based dose of 2 mg/kg or a fixed dose of 200 mg every three weeks. However, because the submission argued that there was a flat relationship between pembrolizumab exposure and efficacy or safety within the dose range of 2 to 10mg/kg, the PBAC concluded that, for patients who are currently on a weight-based dose of less than 200mg, there is no extra clinical benefit achieved by increasing to the fixed 200mg dose, but there could potentially be more toxicity (Paragraph 5.2, 6.13 pembrolizumab (melanoma) PSD, March 2018 meeting). The PBAC noted that the dose proposed is consistent with the trial but that using the fixed dose results in more drug being used, on average, per patient.

6.45 The resubmission acknowledged that whilst the tolerability profile of pembrolizumab is superior to that observed with other new agents listed on the PBS, being a new medicine, it is important that resources are devoted to ensuring its appropriate use in clinical practice.

6.46 The sponsor proposed developing materials and holding professional development programs (face-to-face workshops) with health professionals to assist in the identification and management of potential treatment-related adverse events with pembrolizumab. No materials or example content of these workshops were presented.

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

7 PBAC Outcome

7.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required (STREAMLINED) listing of pembrolizumab for the treatment of locally advanced (LA) or metastatic urothelial cancer (mUC) patients after failure of a platinum-based therapy. The PBAC acknowledged the high clinical need for new treatments for urothelial cancer. The PBAC is satisfied that pembrolizumab provides for some patients, a significant

improvement in OS over standard of care (SOC). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of pembrolizumab could be brought into an acceptable range with a reduced effective price.

7.2 The PBAC acknowledged the high clinical need for new treatments in urothelial cancer. The PBAC considered it was appropriate for pembrolizumab to be listed as second line treatment in patients who progress following treatment with platinum-based therapy.

7.3 The PBAC acknowledged the sponsor hearing and the consumer comments noting the limited treatment options available for this type of cancer. The PBAC noted that the consumer comments were similar to those provided for the November 2017 submission, where pembrolizumab was described as more effective and tolerable than chemotherapy.

7.4 The PBAC recommended listing pembrolizumab as an Authority Required (STREAMLINED) listing under the Section 100 Efficient Funding of Chemotherapy program.

7.5 The PBAC considered that use outside the proposed restriction into the first line setting may be less likely as there was emerging data suggesting decreased survival when PD-1 inhibitors are used first line in PD-L1-low expressing urothelial cancer [9,10,11]. The PBAC noted that the risk sharing arrangement (RSA) would assist in addressing the financial implications of treatment beyond 35 cycles.

7.6 The PBAC considered that it was appropriate to have a grandfather restriction to allow continued treatment for patients who are currently accessing non-PBS subsidised pembrolizumab. The PBAC recommended the grandfathering restriction have six repeats and include the following clinical criterion "Patient must have WHO performance status of 2 or less prior to initiating treatment with this drug for this condition".

7.7 The PBAC maintained its view from the November 2017 consideration that SOC, which included paclitaxel or docetaxel, as the main comparator was appropriate.

7.8 The November 2017 submission and the resubmission were based on one head-to-head randomised trial comparing pembrolizumab to SOC (KN045). The PBAC noted that the resubmission presented an extended follow-up analysis that provided an

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[9] US Food and Drug Administration (2018). Keytruda (pembrolizumab) or Tecentriq (atezolizumab): FDA Alerts Health Care Professionals and Investigators: FDA Statement - Decreased Survival in Some Patients in Clinical Trials Associated with Monotherapy.
https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm608253.htm

[10] Gourd E (2018). EMA restricts use of anti-PD-1 drugs for bladder cancer. *Lancet Oncology 19, 7:e341, DOI:* https://doi.org/10.1016/S1470-2045(18)30433-9

[11] European Medicines Agency (2018). EMA restricts use of Keytruda and Tecentriq in bladder cancer.
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2018/05/WC500249798.pdf

additional 13.6 months of data compared to the November 2017 submission. The PBAC noted that these data showed a higher rate of crossover in the SOC arm ([redacted]% receiving immunotherapies post-progression vs. 12.9% in the November 2017 submission). The PBAC noted that, consistent with the November 2017 submission, the updated overall survival (OS) and progression free survival (PFS) results showed a continued survival benefit for pembrolizumab compared to SOC (OS HR= 0.70 (95% CI; 0.57, 0.85), but no difference in PFS. The PBAC maintained that PFS may not be a meaningful surrogate for clinical benefit in this indication.

7.9 The PBAC considered that the claim of superior effectiveness was adequately supported by the OS data, where the evidence from KN045 demonstrated better OS, higher and more durable response rates and improved health related quality of life (HRQoL) for the pembrolizumab arm compared with the SOC arm.

7.10 The PBAC considered that the claim of superior comparative safety was reasonable and adequately supported by the data. The PBAC noted that the extended assessment of comparative harms (data cut-off 4th March 2017 to 3rd September 2017) did not identify any new safety signals and the overall conclusion of superior safety for pembrolizumab remains unchanged as per the November 2017 submission.

7.11 The PBAC maintained its view that there was insufficient evidence of clinically important treatment effect modification by either PD-L1 expression or age to justify restricting pembrolizumab to a specific subgroup defined using either variable.

7.12 The PBAC noted the additional data provided showed no significant differences in PFS with vinflunine vs PFS without vinflunine or OS with vinflunine vs OS without vinflunine. The PBAC maintained its view from the November 2017 meeting that excluding vinflunine as a comparator was unlikely to affect the overall results (pembrolizumab PSD, November 2017, point 7.3).

7.13 The resubmission presented a cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). Health benefits were reported as life years gained (LYGs) and quality adjusted life years (QALYs) gained, respectively. The PBAC considered that the resubmission addressed the key concerns affecting the cost-effectiveness of pembrolizumab as raised by the PBAC in November 2017, although issues regarding the extrapolation of the trial data were only partially addressed. The analysis presented in the resubmission also included additional follow-up data, an extended time horizon (from 5 to 7.5 years) and an adjustment for crossover.

7.14 The PBAC was of the view that the two-stage crossover adjustment may underestimate the OS for SOC, and the unadjusted data may be more representative of OS, particularly in later periods. The PBAC considered that the crossover adjustment presented was unreliable and as it introduced additional uncertainty to the incremental benefit, it was the Committee's preference to not apply crossover adjustments in the model.

7.15 The resubmission applied a 7.5-year time horizon, which was revised to a 6.5-year time horizon, with convergence from 5 years. The PBAC did not accept these proposed time horizons and considered that a 5-year time horizon was appropriate given the short life-expectancy in the relevant population and that benefits in urothelial cancer are derived within the first 5 years of treatment.

7.16 The PBAC considered that the most appropriate model inputs would be a 5-year time horizon with convergence at year 5 and no adjustment for crossover. However, recognising the high clinical need in this patient population and that there was uncertainty in all scenarios, the PBAC considered that scenarios from the additional sensitivity analyses provided in Table 15 with a 5 year time horizon and either two-stage adjustment for cross-over or without convergence may also be acceptable as the basis for assessing the cost-effectiveness of pembrolizumab. The PBAC noted that a further price reduction of [redacted]-[redacted]% from the revised price of $[redacted] would be required for pembrolizumab to achieve an ICER of <$60,000 per QALY that would be considered cost-effective under any of these modelled scenarios.

7.17 The PBAC noted that a [redacted]% rebate for use beyond [redacted] was included in the calculation of the cost per patient for both the economic and financial analyses, thus contributing to both the ICER/QALY and budget estimates. The PBAC also noted the sponsor's proposed RSA included a [redacted]% rebate of any treatment costs above the annual caps, which is aligned with an RSA for pembrolizumab for treatment of classic Hodgkin's lymphoma. The PBAC recommended that, consistent with its recommendation for pembrolizumab for the treatment of non-small cell lung cancer, the rebate for treatment costs above the annual caps be 100% in order to retain the ICER/QALY estimates. The calculation of the cost per patient in the RSA for pembrolizumab for treatment of classic Hodgkin's lymphoma is less relevant because it [redacted].

7.18 Under section 101(3BA) of the *National Health Act 1953*, the PBAC recommended that pembrolizumab should not be treated as interchangeable on an individual patient basis with any other drugs.

7.19 The PBAC advised that pembrolizumab is not suitable for prescribing by nurse practitioners as antineoplastic agents are currently considered to be out of scope for prescribing by nurse practitioners.

7.20 The PBAC recommended that the Early Supply Rule should not apply as it currently does not apply to Section 100 Efficient Funding of Chemotherapy listings.

7.21 The PBAC noted that this submission is not eligible for an Independent Review because it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Proprietary Name and Manufacturer
PEMBROLIZUMAB 100 mg/4 mL injection, 4 mL vial	200 mg	6	Keytruda® Merck Sharp & Dohme (Australia) Pty Ltd

Episodicity:	N/A
Category/program:	Section 100 (Public/Private), Efficient Funding of Chemotherapy
Severity:	Locally advanced (Stage III) or metastatic (Stage IV)
Condition:	Urothelial cancer
PBS Indication:	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
Treatment phase:	Initial treatment
Restriction:	✓ Streamlined
Clinical criteria:	The treatment must be the sole PBS-subsidised treatment for this condition, AND The condition must have progressed on or after prior platinum based chemotherapy. OR The condition must have progressed on or within 12 months of completion of adjuvant platinum-containing chemotherapy following cystectomy for localised muscle-invasive urothelial cancer OR The condition must have progressed on or within 12 months of completion of neoadjuvant platinum-containing chemotherapy prior to cystectomy for localised muscle-invasive urothelial cancer AND Patient must have WHO performance status of 2 or less
Administrative Advice	No increase in the maximum quantity or number of units will be authorised. No increase in the maximum number of repeats may be authorised. 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. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	Proprietary Name and Manufacturer
PEMBROLIZUMAB 100 mg/4 mL injection, 4 mL vial	200 mg	6	Keytruda® Merck Sharp & Dohme (Australia) Pty Ltd

Episodicity:	N/A
Category/program:	Section 100 (Public/Private), Efficient Funding of Chemotherapy
Severity:	Advanced (Stage III) or metastatic (Stage IV)
Condition:	Urothelial cancer
PBS Indication:	Advanced (Stage III) or metastatic (Stage IV) urothelial cancer

Treatment phase:	Continuing treatment
Restriction:	✓ Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Treatment must be the sole PBS-subsidised treatment for this condition, AND Patient must have stable or responding disease, AND The treatment must not exceed 35 cycles in total at a dose of 200 mg every 3 weeks with this drug for this condition
Administrative Advice	No increase in the maximum quantity or number of units will be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	**Max. Amount**	**№.of Rpts**	**Proprietary Name and Manufacturer**
PEMBROLIZUMAB 100 mg/4 mL injection, 4 mL vial	200 mg	6	Keytruda® Merck Sharp & Dohme (Australia) Pty Ltd

Episodicity:	N/A
Category/program:	Section 100 (Public/Private), Efficient Funding of Chemotherapy
Severity:	Advanced (unresectable Stage III) or metastatic (Stage IV)
Condition:	Urothelial cancer
PBS Indication:	Advanced (unresectable Stage III) or metastatic (Stage IV) urothelial cancer
Treatment phase:	Grandfathering treatment
Restriction:	✓ Streamlined

Clinical criteria:	Patient must have received non-PBS treatment with this drug for this condition prior to [date of PBS listing], AND Treatment must be the sole PBS-subsidised treatment for this condition, AND The condition must have progressed on or after prior platinum based chemotherapy prior to initiating treatment with this drug for this condition OR The condition must have progressed on or within 12 months of completion of adjuvant platinum-containing chemotherapy following cystectomy for localised muscle-invasive urothelial cancer prior to initiating treatment with this drug for this condition OR The condition must have progressed on or within 12 months of completion of neoadjuvant platinum-containing chemotherapy prior to cystectomy for localised muscle-invasive urothelial cancer prior to initiating treatment with this drug for this condition AND Patient must have WHO performance status of 2 or less prior to initiating treatment with this drug for this condition; AND Patient must have stable or responding disease, AND The treatment must not exceed 35 cycles in total at a dose of 200 mg every 3 weeks with this drug for this condition
Administrative Advice	No increase in the maximum quantity or number of units will be authorised. No increase in the maximum number of repeats may be authorised. A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria. Special Pricing Arrangements apply.

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.