

## 6.11 PEMBROLIZUMAB, Powder for injection 50 mg, Solution concentrate for I.V. infusion 100 mg in 4 mL, Keytruda<sup>®</sup>, Merck Sharp & Dohme (Australia) Pty Ltd

### 1 Purpose of application

- 1.1 The submission requested a Section 100, Streamlined Authority Required listing for pembrolizumab for treatment of patients with locally advanced (LA) or metastatic urothelial cancer (mUC) after failure of a platinum-containing regimen. Pembrolizumab has not been considered previously by the PBAC for this indication. The key components of the clinical issues presented in the submission are summarised in Table 1.
- 1.2 The proposed basis for listing was a cost-effectiveness analysis comparing pembrolizumab with standard of care (SOC), which included the use of docetaxel and paclitaxel in the PBS setting.

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

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 <sup>2</sup> IV, once every 3 weeks, and docetaxel 75 mg/m <sup>2</sup> IV once every 3 weeks were nominated as the primary comparators upon which the clinical and cost-effectiveness data presented were based. While vinflunine was not a proposed main comparator in this submission, the trial included vinflunine as part of the SOC arm. Vinflunine was rejected for the third time by the PBAC in July 2017. The submission appropriately presented pre-specified subgroup analyses, with and without vinflunine, which demonstrated that vinflunine provided similar overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) to current SOC. On this basis, the intention to treat (ITT) data with regards to PFS and OS were used throughout the submission.
Outcomes	PFS and OS.
Clinical claim	In the primary comparison of OS, pembrolizumab was superior to SOC in terms of effectiveness, non-inferior in the primary comparison of PFS, and superior in terms of safety. The overall safety profile is acceptable in consideration of the improvements in OS. These claims are supported by the data presented.

Source: Table 1.1, p.2 of the submission.

Abbreviations: ITT = Intention to treat; IV = intravenous; OS = overall survival; PFS = progression-free survival; SOC = standard of care.

### 2 Requested listing

- 2.1 The requested restriction was for three separate settings: i) initial treatment, ii) continuing treatment, and iii) grandfathering provisions. 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: Proposed PBS restriction wording for pembrolizumab: Initial treatment**

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
PEMBOLIZUMAB 100 mg vial for infusion; 1 x 100 mg vial	200 mg	56	Published Public: \$9,023.22 Private: \$9,186.18 Effective Public: \$ [REDACTED] Private: \$ [REDACTED]	Keytruda® Merck Sharp & Dohme (Australia) Pty Ltd
50 mg vial for infusion; 1 x 50 mg vial	200 mg	56	Published Public: \$9,023.22 Private: \$9,186.18 Effective Public: \$ [REDACTED] Private: \$ [REDACTED]	

<b>Category / Program</b>	Section 100 – Efficient funding of Chemotherapy
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	NA
<b>Severity:</b>	Locally advanced (Stage III) or metastatic (Stage IV)
<b>Condition:</b>	Urothelial cancer
<b>PBS Indication:</b>	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	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 a World Health Organisation (WHO) Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less; AND <del>Treatment must be discontinued in patients who experience disease progression;</del> AND <del>The treatment must not exceed a total of 6 cycles at a maximum dose of 200 mg every 3 weeks.</del>
<b>Administrative Advice</b>	No increase in the maximum <i>quantity or number of units</i> or 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

**Table 3: Proposed PBS restriction wording for pembrolizumab: Continuing treatment**

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for Max. Amount	Proprietary Name and Manufacturer
PEMBOLIZUMAB 100 mg vial for infusion; 1 x 100 mg vial	200 mg	76	Published Public: \$9,023.22 Private: \$9,186.18	Keytruda® Merck Sharp & Dohme (Australia) Pty Ltd
			Effective Public: \$ [REDACTED] Private: \$ [REDACTED]	
50 mg vial for infusion; 1 x 50 mg vial	200 mg	76	Published Public: \$9,023.22 Private: \$9,186.18	
			Effective Public: \$ [REDACTED] Private: \$ [REDACTED]	

<b>Category / Program</b>	Section 100 – Efficient funding of Chemotherapy
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	NA
<b>Severity:</b>	Locally advanced (Stage III) or metastatic (Stage IV)
<b>Condition:</b>	Urothelial cancer
<b>PBS Indication:</b>	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
<b>Treatment phase:</b>	Continuing
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	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
<b>Administrative Advice</b>	No increase in the maximum <i>quantity or number of units</i> or number of repeats will be authorised.

**Table 4: Proposed PBS restriction wording for pembrolizumab: Continuing treatment (grandfathering provision)**

Name, Restriction, Manner of administration and form	Max. Amount	No. of Rpts	Dispensed Price for	Proprietary Name and Manufacturer
PEMBOLIZUMAB 100 mg vial for infusion; 1 x 100 mg vial	200 mg	5	Published Public: \$9,023.22 Private: \$9,186.18	Keytruda® Merck Sharp & Dohme (Australia) Pty Ltd
			Effective Public: \$ [REDACTED] Private: \$ [REDACTED]	
50 mg vial for infusion; 1 x 50 mg vial	200 mg	5	Published Public: \$9,023.22 Private: \$9,186.18	
			Effective Public: \$ [REDACTED] Private: \$ [REDACTED]	

<b>Category / Program</b>	Section 100 – Efficient funding of Chemotherapy
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	
<b>Severity:</b>	Locally advanced (Stage III) or metastatic (Stage IV)
<b>Condition:</b>	Urothelial cancer
<b>PBS Indication:</b>	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
<b>Treatment phase:</b>	Grandfathering treatment
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	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
<b>Administrative Advice</b>	No increase in the maximum quantity or number of units or number of repeats will be authorised.

2.2 The submission proposed that patients would be able to access a maximum of 35 cycles of pembrolizumab on the PBS, on the basis that this was consistent with the design of the trial of pembrolizumab in LA or mUC (KN045; submission p17) which discontinued treatment after 24 months (35 cycles) of pembrolizumab. The KN045 Clinical Study Report (CSR Att 12, p70) noted that patients may be eligible for an additional 12 months of treatment, a “second course”, if they progressed after

24 months of pembrolizumab. The submission incorporated the proposed maximum number of cycles in both the economic evaluation and estimates of the financial implications of listing pembrolizumab. The ESC noted that a two year treatment course may be too short for a selected minority of patients and that the inclusion of a limit on the number of cycles in the restriction may therefore be inappropriate.

- 2.3 The Pre-Sub-Committee Response PSCR (p4) agreed to the Secretariat-proposed changes to the restriction so that the proposed maximum number of cycles, i.e. seven (1+6) cycles through the initial prescription followed by a maximum of 4 continuing prescriptions of seven (1+6) cycles each, would total a maximum of 35 cycles.

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

### **3 Background**

#### ***Registration status***

- 3.1 TGA status at the time of PBAC consideration: The submission was lodged under the TGA/PBAC parallel process as pembrolizumab had not yet been approved as a treatment option in LA or mUC. The TGA clinical evaluation report and the TGA Delegate's Overview were available at the time of PBAC consideration. The TGA delegate indicated that there was no reason why the proposed extension to the indication should not be approved, and did not have any specific questions for ACM. The proposed indication for pembrolizumab was for:

“Patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing therapy, and for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy.”

- 3.2 The proposed TGA indication was broader than the proposed PBS restriction because it also included first-line treatment for patients who are not eligible for cisplatin-containing therapy. This may present potential for use beyond the requested restriction.

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

### **4 Population and disease**

- 4.1 Urothelial cancer refers to carcinomas that arise from urothelial endothelial cells (transitional cells) which line the renal pelvis, ureter, urinary bladder, and urethra; the vast majority of urothelial carcinomas originate in the bladder and the vast majority of bladder cancers are of urothelial (transitional cell) histology. Bladder cancer is the 10<sup>th</sup> most commonly diagnosed cancer in Australia, with 3,084 Australians estimated to be diagnosed with bladder cancer in 2018.
- 4.2 The overall survival from bladder cancer has declined over the last 30 years; it was projected that 1,196 Australians would die of bladder cancer in 2018. The relevant population for this submission is patients with LA or mUC whose disease has progressed after failure of a platinum-containing regimen. The PBAC considered that

there is currently a high unmet need for a relatively large group of patients, where the disease is highly aggressive and the prognosis is poor.

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

## **5 Comparator**

- 5.1 The proposed clinical management algorithms for managing patients with LA or mUC after failure of a platinum-containing regimen were based on the principle that patients for whom second-line therapy is indicated will be offered pembrolizumab. The PBAC noted that the clinical management algorithms were based on international guidelines, trial data and current experts, and considered that they were appropriate.
- 5.2 The submission nominated SOC, which included paclitaxel or docetaxel, as the main comparator. Paclitaxel and docetaxel are the PBS listed treatments that are most likely to be replaced in the event of a positive listing for pembrolizumab therapy. The PBAC considered this was appropriate.
- 5.3 The submission acknowledged vinflunine as a possible alternative treatment to pembrolizumab in the clinical algorithm. Vinflunine is not currently PBS listed and was not considered as an appropriate comparator in the submission. The PBAC considered that this was appropriate. The algorithm is consistent with previous PBAC decisions not to recommend vinflunine in this patient population (vinflunine Public Summary Document (PSD), July 2017).
- 5.4 Nivolumab, durvalumab and avelumab were approved by the FDA for use in urothelial cancer post platinum-based chemotherapy in January 2017 (nivolumab) and May 2017 (durvalumab and avelumab). The submission acknowledged that, if any of these three immunotherapies were to become available on the PBS for LA or mUC in patients who had failed prior platinum-based chemotherapy, they would be relevant comparators for pembrolizumab. The submission presented supplementary naïve indirect comparisons of pembrolizumab with these agents. However, to date no submissions have been made to the PBAC relating to the use of these medicines in urothelial cancer.

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

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and indicated that there is a high clinical need for this treatment as the available second-line chemotherapy options are poorly tolerated, have a poor response and higher rates of progression and death. The clinician noted that pembrolizumab reduced the impact of pain, had manageable side effects and allowed some patients to return to an active lifestyle. The clinician advised that a patient who had clinical and radiological progression would stop pembrolizumab treatment immediately and that patients who don't respond to pembrolizumab are usually detected early. However, if a patient had radiological progression and

appeared to present with clinical benefits, another 2 cycles would be administered before reassessment. The PBAC considered that the hearing was informative as it provided a clinical perspective on treatment with pembrolizumab for this disease.

### Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (9), health care professionals (3) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of perceived benefits of treatment with pembrolizumab including the ability to return to work, fewer side effects and improvements to quality of life compared to chemotherapy. The comments acknowledged that not all patients would respond to treatment with pembrolizumab, but ongoing benefits are seen in those who do respond. The comments also indicated that there is a clinical need for new treatments, that pembrolizumab had fewer side effects, and that cost is currently a barrier to accessing treatment for some patients. The PBAC noted the advice received from Rare Cancer Australia supporting the listing of pembrolizumab for urothelial cancer and presenting a case study. The PBAC noted that this advice was supportive of the evidence provided in the submission.
- 6.3 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the pembrolizumab submission for urothelial carcinoma. The PBAC noted that the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for pembrolizumab was 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>1</sup>, based on a comparison with chemotherapy. The MOGA noted that when overall survival data matures for pembrolizumab, the ESMO-MCBS score may increase to 5.

### Clinical trials

- 6.4 The submission was based on one head-to-head randomised trial comparing pembrolizumab to SOC (KN045). Publication details are provided in the table below.

**Table 5: Trials and associated reports presented in the submission**

Trial ID/First Author	Protocol title/ Publication title	Publication citation
KN045	A Phase III Randomized Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel, Docetaxel or Vinflunine in Patients with Recurrent or Progressive Metastatic Urothelial Cancer. Clinical Study Report.	Dec 2016.
KN045	Extended follow-up data for KN045, data cut off 18 Jan 2017	18 Jan 2017
Bellmunt	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]

Source: Table 2.2, pp24-25 of the submission.

- 6.5 The key features of KN045 are summarised in Table 6.

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

**Table 6: Key features of the included evidence, pembrolizumab vs SOC**

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
KN045	542	R, OL First data cut off (September 2016) median OS 14.1 months Second interim analysis (January 2017) median OS 18.5 months	Moderate	Patients with LA or mUC who have failed a platinum-based regimen.	OS, PFS, ORR	Used

Abbreviations: DB=double blind; LA=locally advanced; MC=multi-centre; mUC=metastatic urothelial cancer; OL=open label; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; R=randomised.

Source: compiled during the evaluation.

6.6 KN045 was subject to a moderate degree of bias. It was a Phase III trial of 542 patients, with co-primary outcome measures of OS and PFS.

6.7 The main source of bias was due to the inadequate concealment of randomisation (participants and personnel were not blinded to treatment allocation). The key areas of uncertainty as a result of this bias were:

- There was a higher rate of withdrawal prior to treatment if patients were allocated to the chemotherapy arm (17/272) compared with the pembrolizumab arm (4/270). This may represent a selection bias, which may favour pembrolizumab in the efficacy analysis using the ITT population.
- Higher numbers of patients also withdrew consent during the course of the trial from the SOC arm when compared to the pembrolizumab arm (29 patients vs. 3), which may reflect the unacceptability of chemotherapy and/or occurrence of unacceptable toxicities. The TGA clinical evaluator noted that “these two rates of withdrawal confirm the high unmet need for a more effective, less toxic alternative to chemotherapy” (TGA clinical evaluation report, p 74).
- A number of data recording errors occurred at randomisation. The majority of these errors related to time since chemotherapy, which was associated with patients being classified as being ‘more-healthy’ than they actually were. These errors were not addressed in the submission, and therefore their distribution between the treatment groups is unknown. Regardless, all patients randomised to each arm of KN045 were included in the analysis set for efficacy and safety. The TGA clinical evaluator has requested a sensitivity analysis which corrects for data recording errors that occurred at randomisation (identified 6.4; TGA clinical evaluation report). The direction of bias was unknown.

6.8 There was also the potential for observer bias evidenced by the higher rate of discontinuations due to ‘physician decision’ (10.6% for chemotherapy vs. 2.3% for pembrolizumab) in KN045, which fall outside clinical reasons for stopping (‘adverse event’ or ‘clinical progression’). The submission does not provide adequate details on treatment exposure to determine the impact of these discontinuations. However, they are likely to impact on the representativeness of any subgroup analyses where the sample sizes are already small, notably PD-L1 expression (for which there are compounding issues of bias).

- 6.9 The PBAC noted the TGA clinical evaluator reported that the use of a fixed 200 mg dose resulted in a significantly higher treatment dose for a significant number of patients in KN045, when compared to the dose they would have received if the dosing strategy was consistent with the mg per kg patient weight dose employed in pembrolizumab trials for other indications (melanoma and non-small cell lung carcinoma). This was due to patients in KN045 having a lower mean weight than patients in studies in which pembrolizumab is dosed on a mg per kg basis. The PBAC noted that the fixed-dosing approach was different to the dosing regimens for other approved indications for pembrolizumab which applied weight-based dosing, and that this resulted in a significantly higher treatment dose for a number of patients in the trial. The PBAC also noted that there is evidence to suggest that the higher dose did not increase the effectiveness of pembrolizumab.<sup>2</sup>
- 6.10 The TGA clinical evaluation report highlighted a number of uncertainties with regards to KN045. The key areas of concern included:
- Issues in patient randomisation, treatment and discontinuations due to physician's decisions (for which the direction of bias is unknown).
  - The representativeness of KN045 for patients with ECOG status = 2 and patients with a creatinine clearance <30 ml.
  - The relatively short trial follow-up and the resulting uncertainty with regards to the number of long-term survivors.
  - The importance and clinical utility of PD-L1 expression being unclear, with little evidence supporting PD-L1 as a predictive biomarker. The PBS listing proposed in the submission does not specify a level of PD-L1 expression, adopting an all-comers approach that does not rely on PD-L1 as a predictive biomarker. This is consistent with the approach applied to the current listings for pembrolizumab (melanoma) and nivolumab (melanoma, non-small cell lung carcinoma, renal cell carcinoma).
  - A lack of detailed analysis with regards to early progression and death in the pembrolizumab arm. This combined with treatment effect differences in subgroup analyses led the TGA clinical evaluator to recommend a precautionary statement in the PI that warns of the possible risk of early progression and death. A similar issue has been addressed in the TGA listing of nivolumab, for non-small cell lung carcinoma (point 12, p201 TGA clinical evaluation report).

### **Comparative effectiveness**

- 6.11 Overall survival (OS) and progression-free survival (PFS) from the second interim analysis (database cut-off September 7, 2016) and extended follow-up (database cut off January 17, 2017) are shown in Table 7. The Kaplan-Meier analysis of OS for the extended follow-up analysis is presented in Figure 1.

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<sup>2</sup> Goldstein *et al.* 2017. "A Pharmacoeconomic analysis of personalized dosing vs. fixed dosing of pembrolizumab in firstline PD-L1-positive non-small cell lung cancer" *J Nat Can Inst.* 109 (11).

**Table 7: Results of overall survival and progression-free survival in the direct randomised trial: KN045**

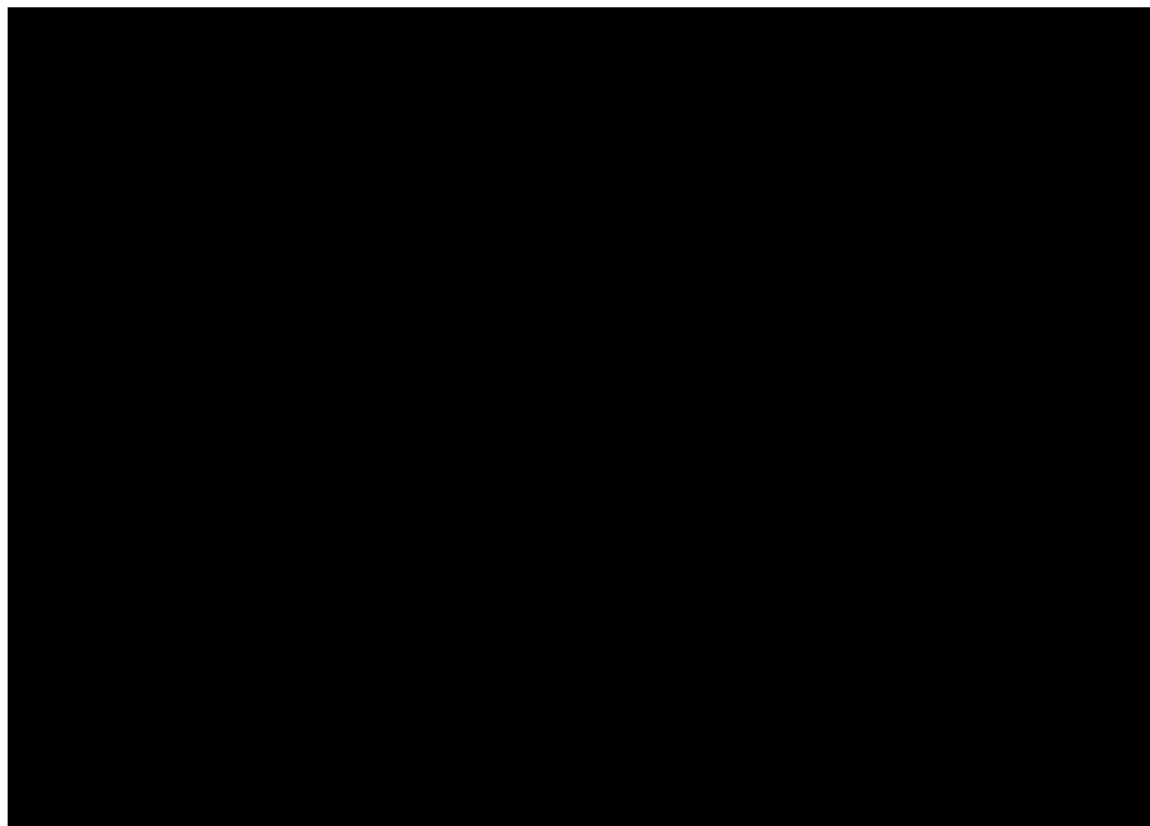
Trial ID	Pembrolizumab (200 mg) n/N with event (%)	Pembrolizumab (200 mg) Median time to event, months (95% CI)	SOC n/N with event (%)	SOC Median time to event, months (95% CI)	Difference in medians, months	P-value	Hazard ratio (95% CI)
<b>Overall survival</b>							
Second interim analysis	155/270 (57.4)	10.3 (8.0, 11.8)	179/272 (52.0)	7.4 (6.1, 8.3)	+2.9	0.00224	0.73 (0.59, 0.91)
Extended follow-up							
<b>Progression-free survival</b>							
Second interim analysis	218/270 (80.7)	2.1 (2.0, 2.2)	219/272 (80.5)	3.3 (2.3, 3.5)	-1.2	NS	0.98 (0.81, 1.19)
Extended follow-up							

Source: Table 2.14, p 46 and Table 2.15, p 51 of the submission.

Notes: KN045 Second interim data cut= September 7, 2016, Length of follow-up=14.5 months (median); Extended follow-up data cut January 18, 2017 = Length of follow-up=18.5 months (median).

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; OS = overall survival; SOC= active chemotherapy

**Figure 1: Kaplan-Meier plot of overall survival**



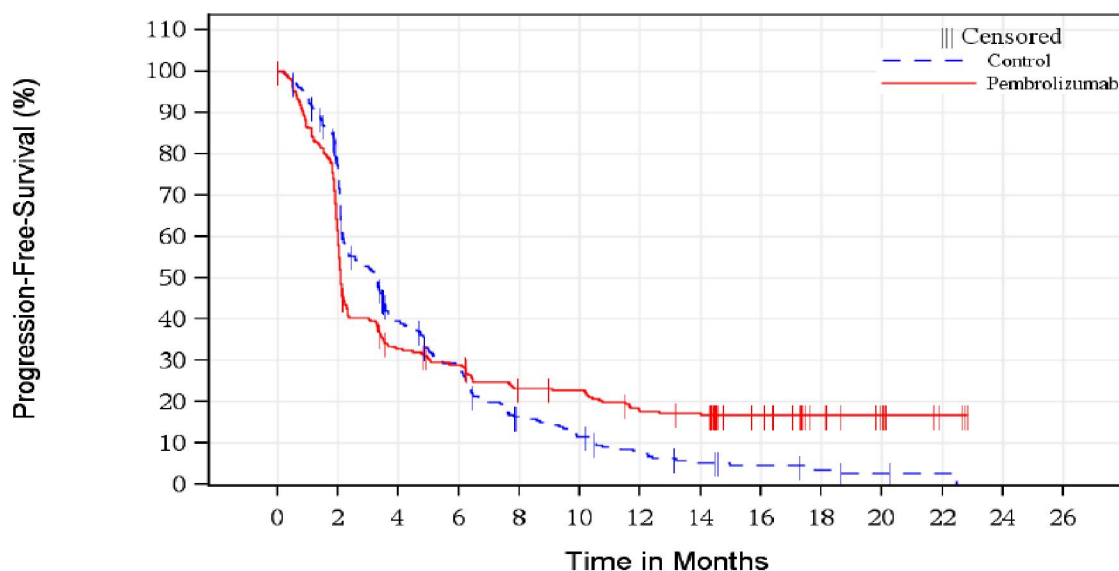
Source: p4 Att 11 of the submission.

6.12 The OS data indicated that more patients died in the pembrolizumab arm in the first 3 months of the trial when compared to SOC. The submission did not present any detailed analysis of this subgroup (patients who died within the first three months) or time-period. The PSCR (p4) provided the additional data requested by the TGA, which showed no significant differences across treatment arms in baseline

characteristics for patients who died in the first three months. The PBAC agreed with the ESC that, while this was a rare, but serious, adverse event, these results should be considered with caution due to the low numbers of deaths in this time period.

- 6.13 The secondary endpoints (overall response rate and duration of response) showed no significant difference between pembrolizumab and SOC, although the TGA clinical evaluator noted that the range of median time to response was greater in the pembrolizumab arm, indicating a greater time taken to achieve maximal effect. The TGA clinical evaluator stated that “this delayed effect may explain the poorer outcomes identified in those with more aggressive disease and inclusion of a PI statement to reflect this has been recommended” (TGA clinical evaluation report p104).
- 6.14 To justify its use of OS, PFS and quality of life (QOL) estimates from the ITT population, the submission presented the whole population and a subgroup analysis to demonstrate non-inferiority of vinflunine compared with docetaxel and paclitaxel. This is appropriate; no claims in the submission relied on the outcomes of those subgroup analyses.
- 6.15 A total of 366 (67.5%) deaths were observed among all patients in the ITT population as of the data cut-off date of January 18, 2017. The median OS was 10.3 months (95% CI: 8.0, 12.3) in the pembrolizumab arm compared to 7.4 months (95% CI: 6.3, 8.1) in the SOC arm. The HR for OS was 0.70 (95% CI: 0.57, 0.86), with a one-sided p-value of 0.0004 in favour of pembrolizumab. The median (range) follow-up duration for all patients in the ITT population was 18.5 months (range: 14.2 to 26.5).
- 6.16 The Kaplan-Meier analysis for PFS is presented in Figure 2. A total of 437 PFS events were reported at the time of the second interim data cut-off. The median PFS was 2.1 months (95% CI: 2.0, 2.2) in the pembrolizumab arm compared with 3.3 months (95% CI: 2.3, 3.5) in the SOC arm (HR = 0.98 [95% CI: 0.81, 1.19]; p=0.416). These data indicated that pembrolizumab may be numerically inferior to SOC with respect to PFS. While the hazard ratio was not statistically significant, the 95% confidence intervals on median PFS did not overlap. In the pembrolizumab arm, a proportion of patients who progressed earlier, also died earlier, as indicated by the OS curve above.

Figure 2: Kaplan Meier plot of progression-free survival

**Number of subject at risk**

Control	272	190	91	64	34	24	15	9	6	4	2	1	0	0
Pembrolizumab	270	165	85	73	56	54	41	39	24	13	8	3	0	0

- 6.17 The results from KN045 show a statistically significant difference in OS in favour of pembrolizumab, but no statistically significant difference in PFS. This apparent disparity in efficacy may be due to the manner in which PFS has been assessed in this study; there is some discussion in the literature on the appropriateness of RECIST 1.1 criteria to accurately measure progression in patients receiving immunotherapy. The PSCR (p2) referred to a secondary analysis that was performed in the trial based on modified RECIST criteria (CSR p 312), which included a confirmatory assessment of progression. Compared with the primary analysis, the hazard ratio for PFS improved only slightly from 0.98 (95% CI: 0.81, 1.19) to [REDACTED] (95% CI: [REDACTED]) which suggested that pseudoprogression did not have a significant impact on PFS. The PBAC noted the difficulty in using the RECIST criteria for this class of agents and considered that PFS based on usual criteria appeared a less useful endpoint in this setting.
- 6.18 The TGA clinical evaluator noted that the PI for pembrolizumab contains advice regarding continuing treatment beyond progression based on ‘pseudoprogression’. The TGA clinical evaluator has requested that the sponsor “provide any data from this trial that clearly supports demonstration of any such benefit and in particular any PRs [partial responses] or CRs [complete responses]. In the absence of evidence, the PI should not recommend continuation beyond progression in this population and a specific statement should be included in the Clinical Trials and Dosage and Administration section advising no CRs or PRs have been observed to balance the decision” (TGA clinical evaluator report, p91).
- 6.19 The key efficacy results for KN045 were also tested for potential treatment effect modification arising due to a number of factors, including (but not limited to) PD-L1 expression and age. As an inhibitor of PD-1, there is biological plausibility to test for

the potential treatment effect modification for pembrolizumab arising from PD-L1 expression. This was tested using pre-specified cut-offs for stratifications for PD-L1 expression (1% and 10%). The analyses were adjusted for multiplicity, but were not included within strata tests for interaction or comparisons of effect.

- 6.20 The results suggested a numerically lower, and non-significant, OS benefit in patients with PD-L1 expression below each cut-point (see Table 8). A similar outcome was observed for PFS. No statistics were provided reporting on differences within strata for either outcome, although it is noted that the 95% CI overlap within strata. While analyses by PD-L1 were pre-specified in the trial, a protocol modification occurred after recruitment of patients based on external data. This resulted in new objective hypotheses and efficacy endpoints and meant that there was an imbalance in the stratification based on PD-L1 expression. On this basis, any conclusions based on PD-L1 status should be considered with caution, and the PBAC agreed with the ESC that the results suggest that there was no strong signal to consider selecting patients for treatment with pembrolizumab on the basis of PD-L1 expression.

**Table 8: Summary results of progression-free survival and overall survival, by PD-L1 expression**

Study drug	N	n with event/N (%)	N	n with event/N (%)	HR (95% CI)
	Pembrolizumab		SOC		
<b>Progression-free survival</b>					
Total population	270	218 (80.7)	272	219 (80.5)	0.98 (0.81, 1.19)
PD-L1 <1%					
PD-L1 ≥1%					
PD-L1 <10%					
PD-L1 ≥10%					
<b>Overall survival</b>					
Total population	270	155 (57.4)	272	179 (65.8)	0.73 (0.59, 0.91)
PD-L1 <1%	151	89 (58.9)	147	95 (64.6)	0.89 (0.66, 1.20)
PD-L1 ≥1%	110	61 (55.5)	120	81 (67.5)	0.61 (0.43, 0.86)
PD-L1 <10%	186	106 (57.0)	176	116 (65.9)	0.80 (0.61, 1.05)
PD-L1 ≥10%	74	44 (59.5)	90	60 (66.7)	0.57 (0.37, 0.88)

Source: Table 2.25, Table 2.26 pp 68-69 of the submission and Table 11-4 p 127; Table 14.2-6 p 314; Table 14.2-11 p 324; Table 14.2-23 p 355; Table 14.2-16 p 337; Table 11-5 p134 of the Clinical Study Report.

Notes: a Median OS or PFS was not pre-specified or reported for the PD-L1 <1% subgroup

Abbreviations: CI = confidence interval; HR = hazard ratio; n = number of participants with event; N = total participants in group; NR = not reported; SOC=standard of care.

- 6.21 The PBAC has previously considered that it was plausible that immunotherapies relying on stimulating an immune response may prove to be less effective in older patients whose immune systems may no longer be able to respond to such a stimulus (PSD for nivolumab in non-small cell lung cancer, November 2016). In this case, subgroup analyses by age showed a smaller treatment effect for pembrolizumab among those aged 75-85 years, that favoured pembrolizumab with the median OS of [REDACTED] (91% CI: [REDACTED]), when compared with [REDACTED] for the SOC arm (95% CI: [REDACTED]), but not with the HR of [REDACTED] (95% CI: [REDACTED]). No comparison was possible for patients >85 years, but [REDACTED] patients in that age bracket treated with pembrolizumab had a progression event during the analysis period (1 patient randomised to the pembrolizumab arm was not treated). The submission also claimed that there was no biologically plausible reason for an immunosenescence effect associated with age (p98 of the submission).

- 6.22 The ESC advised that the comparison of efficacy by age should be interpreted with caution given that this was an underpowered, *post-hoc* subgroup analysis, but also noted that efficacy is often lower in non-trial populations. The PSCR (p1) provided additional subgroup analyses which suggested a statistically significant OS benefit for patients in the subgroup aged up to 80 years ( [95% CI: ]), consistent with the survival benefit observed in the total population and the pre-PBAC response (p1) also provided an analysis demonstrating no significant difference between OS for patients aged <65 vs ≥65 years. The PBAC considered that there was insufficient evidence to justify restricting treatment by patient age, but remained concerned that there was also insufficient evidence to rule out immunosenescence as a source of reduced effectiveness, particularly in patients >75 years of age.
- 6.23 Other notable differences were in the lower treatment effect (OS) observed in patients with more heavily pre-treated disease (third line of treatment in the trial), those with less than 3 months since their previous chemotherapy regimen and those with greater than median tumour volume (see Table 9). While these were pre-specified subgroups, these analyses were not adjusted for multiplicity, and there were no tests for differences between groups in each of the subgroups investigated.

**Table 9: Overall survival – selected subgroup analyses from KN045**

Subgroup	Pembrolizumab (200 mg) n/N with event (%)	SOC n/N with event (%)	P-value	Hazard ratio (95% CI)
<b>Most recent prior therapy</b>				
Neo adjuvant	9/19 (47.4)	13/22 (59.1)	NR	0.53 (0.20, 1.41)
Adjuvant	5/12 (41.7)	22/31 (71.0)	NR	0.53 (0.18, 1.57)
First line metastatic	104/183 (56.8)	99/157 (63.1)	NR	0.72 (0.54, 0.95)
Second line metastatic	36/55 (65.5)	44/60 (73.3)	NR	0.83 (0.52, 1.33)
<b>Time from chemotherapy</b>				
≥3 months	88/166 (53.0)	105/167 (62.9)	NR	0.66 (0.49, 0.89)
<3 months	66/103 (64.1)	74/104 (71.2)	NR	0.82 (0.58, 1.15)
<b>Baseline tumour volume</b>				
< median	63/132 (47.7)	68/117 (58.1)	NR	0.54 (0.38, 0.78)
≥ median	81/115 (70.4)	102/135 (75.6)	NR	0.91 (0.68, 1.23)

Source: Table 14.2-11 p324 CSR Att 11 of the submission.

Notes: KN045 Second interim data cut= September 7, 2016, Length of follow-up=14.5 months (median). Hazard ratios based on Cox regression model with treatment as covariates and stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0/1 vs. 2), presence or absence of liver metastases, hemoglobin (≥10 g/dL vs. <10 g/dL), and time from completion of most recent chemotherapy (<3 months or ≥3 months).

Abbreviations: CI = confidence interval; n = number of participants with event; N = total participants in group; NR = not reported; SOC= active chemotherapy

### Comparative harms

- 6.24 The Kaplan-Meier average duration of treatment exposure for participants was 5.6 months (SD=5.37) in the pembrolizumab arm, compared to 2.74 months (SD=2.71) in the SOC arm. Pembrolizumab appears to have a more favourable safety profile compared with SOC. The total number of events, treatment-related adverse events, and adverse events leading to discontinuation were all higher in the SOC group than the pembrolizumab group (see Table 10). There was a higher rate of adverse events resulting in death in the pembrolizumab arm, although not statistically significant. Data on the underlying cause of death showed that [redacted] patients in the pembrolizumab arm died of pneumonia, compared with only [redacted] in the SOC arm. The

ESC considered this to be consistent with use in clinical practice. The ESC also advised that these complications were serious but rare.

**Table 10: Treatment-related adverse events by category in KN045 (APaT population)**

KN045	Pembrolizumab, N=266 n (%)	SOC, N=255 n (%)	Relative risk (95% CI)
Any AE	162 (60.9)	230 (90.2)	0.68 (0.61, 0.75)
Any SAE (≥ Grade 3)	40 (15.0)	126 (49.4)	0.30 (0.22, 0.42)
AE leading to discontinuation of treatment	15 (5.6)	28 (11.0)	0.51 (0.28, 0.94)
AE resulting in death	9(3.3)	4 (1.6)	0.72 (0.35, 1.49)

Source: Attachment 2.5, p96 of the commentary.

Abbreviations: APaT, all patients as treated, SOC = Standard of care, AE = Adverse event, SAE = serious adverse event.

- 6.25 The extended assessment of comparative harms showed a higher rate of adverse events of significant interest in the pembrolizumab arm compared to the SOC arm (16.9% vs. 7.5%). These included colitis (2.3% vs. 0.4%), hypothyroidism (6.4% vs. 1.2%), hyperthyroidism (3.8% vs. 0.4%) and pneumonitis (3.8% vs. 0.4%) for pembrolizumab compared with SOC respectively. The TGA clinical evaluation report noted that the length of data follow-up was relatively short, but concluded that the safety of pembrolizumab was superior to cytotoxic options and appeared broadly similar to other PD-L1 therapies.
- 6.26 The ESC noted that only a small number of patients enrolled in the trial had an ECOG performance status of 2. The ESC also noted that additional data provided in the PSCR (pp1-2) from trial KN-52, in which pembrolizumab was used as first-line therapy in cisplatin ineligible patients, showed equivalent responses between subjects with ECOG = 0-1 and ECOG = 2. The PBAC agreed with the ESC that given the low toxicity of pembrolizumab compared to chemotherapy, it would be unlikely that there would be significant safety issues if patients with ECOG = 2 were able to access treatment with pembrolizumab.

### ***Benefits and harms***

- 6.27 A summary of the comparative benefits and harms for pembrolizumab versus SOC is presented in the table below.

Table 11: Summary of comparative benefits and harms for pembrolizumab and SOC

<b>Benefits</b>						
Event	Pembrolizumab, N= 270	SOC, N=272	Absolute difference	HR (95% CI)		
Progressed at 18.5 months, n (%)	██████	██████	██████	██████		
Alive at 18.5 months, n (%)	██████	██████	██████	██████		
<b>Harms</b>						
	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	█	█	██████	█	█	█
With serious treatment-related adverse event	█	█	██████	█	█	█
Discontinued due to serious drug related adverse event	█	█	██████	█	█	█
Died due to treatment-related adverse even	█	█	██████	█	█	█

Notes: \* Maximum duration of exposure: Trial I = 22 months; <sup>a</sup> Extended follow-up.

Source: Compiled during the evaluation/Attachment 2.5 of the submission.

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

- approximately █ more patients alive over a duration of exposure of 18.5 months;
- approximately █ fewer treatment-related grade 3-5 adverse events over a duration of exposure of 18.5 months; and
- approximately █ fewer treatment-related serious adverse events over a duration of exposure of 18.5 months.

### ***Interpretation of the clinical evidence***

6.29 The submission claimed that pembrolizumab is superior in terms of effectiveness compared with SOC and superior in terms of safety compared with SOC.

6.30 The PBAC considered that the claim of superior effectiveness appeared reasonable. The evidence from KN045 indicated a modest but statistically significant OS gain for the pembrolizumab arm compared with the SOC arm. The PBAC noted there was no significant difference in PFS but considered that PFS may not be a meaningful surrogate for clinical benefit for this class of drug in this disease. However, the PBAC noted that the TGA clinical evaluator reported that considering the earlier progression and mortality in the pembrolizumab arm in the first 3 months of the trial, there appears to be a subgroup of patients with rapidly progressing disease and/or higher tumour burden, for whom pembrolizumab may not be superior to SOC.

6.31 The PBAC considered that the claim of superior safety to be reasonable. The evidence from KN045 indicated a statistically significant lower rate of  $\geq$  Grade 3 adverse events for the pembrolizumab arm compared with SOC arm. The TGA clinical evaluation report also supported this claim.

### Economic analysis

- 6.32 The submission presented a cost-utility analysis (CUA) to estimate the cost-effectiveness of pembrolizumab, with the incremental cost per quality adjusted life year (QALY) gained as the main outcome of the evaluation.
- 6.33 The CUA used observed data from KN045 and extrapolation beyond the submission defined cut-off points to estimate the costs and benefits of treatment in either arm of the model.
- 6.34 A summary of the model, key drivers and results of the stepped evaluation is provided in Table 12 to Table 14 below.

**Table 12: Summary of model structure and rationale**

Component	Description
Type(s) of analysis	Cost-utility analysis, Cost-effectiveness analysis
Outcomes	Quality-adjusted life years, Life-years gained
Time horizon	5 years in the model base case (vs 14.1 months median follow-up in the key trial with 19 months follow-up data provided in the validation section). Sensitivity analyses included time horizons of 7 and 10 years
Method(s) used to generate results	Cohort analysis of partitioned survival (i.e. area under the curve analysis).
Health states	Three health states: Progression-free disease, Progressive disease and Death.
Cycle length	1 week
Transition probabilities	No specific transition probabilities were modelled. Health state allocation over time was determined by progression-free and overall survival curves from KN045 (using a partitioned survival analysis).

Source: Table 3.1, p86 of the submission.

**Table 13: Key drivers of the model**

Description	Method/Value	Impact
Extrapolation	Use of different distributions to extrapolate the intervention and comparator arm.	Moderate to high, favours pembrolizumab
Treatment	Use of PFS rather than ToT to measure treatment duration	Moderate to high, favours pembrolizumab
PFS	Using 3 weeks (rather than 1 week) to measure health state allocation.	Unclear
PFS	Extrapolation of a non-significant difference in PFS. The ESC noted that the Kaplan-Meier curve indicated a separation between the arms and therefore a difference beyond the follow-up may be reasonable.	Minor

Source: compiled during the evaluation using Section 3.4, pp 98-100 of the submission, Submission\Att14.xls.  
Abbreviations: PFS = progression-free survival; ToT = time on treatment.

**Table 14: Results of the stepped economic evaluation**

Step and component	Pembrolizumab	SOC	Increment
<b>Step 1: Comparative study data (as presented in the clinical evaluation based on 14.1 months follow-up)</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LY gained			\$ [REDACTED]
<b>Step 2: Study evidence extrapolated to the 5-year time horizon (life years)</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LY	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra LY gained			\$ [REDACTED]
<b>Step 3: Study evidence extrapolated to the time horizon and transformed into a relevant health outcome (QALYs)</b>			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]

Abbreviations: ICER=Incremental cost-effectiveness ratio; LY=life year; QALY = quality-adjusted life year.

Source: Submission files/attn14.xls.

6.35 The base case ICER of \$45,000/QALY - \$75,000/QALY was produced using a public/private weighted price of \$ [REDACTED] per fixed dose of 200 mg of pembrolizumab.

**Table 15: Results of key sensitivity analyses**

Sensitivity analyses	Incremental costs (\$)	Incremental effectiveness	Incremental cost-effectiveness (\$/QALY)
Base case	[REDACTED]	[REDACTED]	[REDACTED]
Revised base case (price disclosure Oct 2017)	[REDACTED]	[REDACTED]	[REDACTED]
Time horizon – 7 years (from 5 years)	[REDACTED]	[REDACTED]	[REDACTED]
Time horizon – 10 years (from 5 years)	[REDACTED]	[REDACTED]	[REDACTED]
Utility values – use of pooled values across treatment groups for Progression-free disease and Progressive disease states.	[REDACTED]	[REDACTED]	[REDACTED]
Utility values – use of alternative health state values defined by time to death.	[REDACTED]	[REDACTED]	[REDACTED]
Alternative point of extrapolation for PFS and OS using full KM data to extended follow-up and allowing for censoring (87 weeks).	[REDACTED]	[REDACTED]	[REDACTED]
Alternative point of extrapolation for PFS and OS using full KM data to extended follow-up and allowing for censoring (87 weeks), and use of log-normal distributions for extrapolation.	[REDACTED]	[REDACTED]	[REDACTED]
Alternative approach to extrapolation using log-logistic distributions for PFS and OS for both pembrolizumab and SOC.	[REDACTED]	[REDACTED]	[REDACTED]
Use of ToT rather than PFS to measure treatment duration.	[REDACTED]	[REDACTED]	[REDACTED]
Use of treatment group specific utility values from KN045.	[REDACTED]	[REDACTED]	[REDACTED]
Use of log-logistic distributions for extrapolation, and use of ToT.	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: KM=Kaplan-Meier; OS=overall survival; PFS=progression-free survival; QALY = quality-adjusted life year; SOC=standard of care; ToT=time on treatment.

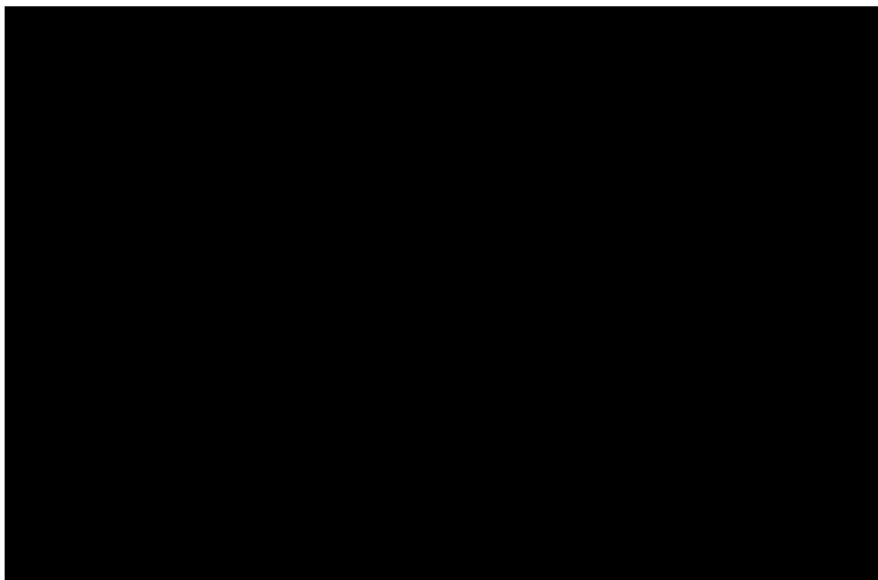
Source: Submission files/attn14.xls.

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

- 6.36 The univariate sensitivity analyses conducted by the submission showed that the ICER was most sensitive to variations in the time horizon. The PBAC considered that the base case time horizon of 5 years was more appropriate than the time horizons included in the sensitivity analyses of 7 and 10 years. The ESC considered that the assumptions regarding the utility values were appropriate (see Table 15 for key changes and their impact).
- 6.37 The start point of extrapolation used in the submission was defined as 27 weeks for PFS and 40 weeks for OS, whereas the Kaplan-Meier data reflects median follow-up of 18.5 months (80 weeks) at the extended analysis. The PSCR (p2) stated that the extrapolation time points were selected based on the results of Chow tests. The PBAC recalled that the ESC and PBAC has previously advised that this *post-hoc* use of the Chow test is inappropriate for this purpose with respect to another model from this sponsor (see Table 9, pembrolizumab Public Summary Document, March 2017). The pre-PBAC response (p3) acknowledged the limitations of using the Chow tests in the *post-hoc* setting, but argued that there is no consensus on the method for detecting structural change in this setting and that one piece parametric models did not appear to have a good fit to the observed data. The PBAC considered that this was insufficient justification and instead advised that the extrapolation of both PFS and OS should start from the time point defined by the median duration of follow-up across the trial (which appeared to be approximately 18 months from Figure 1).
- 6.38 The PBAC also noted that the submission stated that the model base case used a two-phase approach to model PFS and OS for each arm of the model, in which the initial part of the survival curve before a cut-off point was based on the actual clinical trial Kaplan-Meier results, and the latter part was based on parametric functions developed to fit the PFS and OS data after the cut-off point. The cut-off point in each case was determined with reference to the results of Chow tests and corresponded with the time at which extrapolation started for that case in the model. Whilst the PBAC considered that the specific approach used in the submission was unclear, the approach of excluding early Kaplan-Meier to inform the extrapolation functions from the assessment of the goodness of fit was inappropriate. The PBAC considered that the model should use all the Kaplan-Meier results at least up to the median follow-up to inform the extrapolation functions.
- 6.39 The submission also used different parametric distributions within PFS (Weibull for pembrolizumab and exponential for SOC) and OS (log-normal for pembrolizumab and exponential for SOC) within the one condition (LA or mUC). The ESC considered that applying different parametric distributions did not seem to be biologically plausible when comparing treatments for the same condition, and noted that applying a consistent distribution increased the ICER. The PBAC considered that it would be more appropriate to apply the same parametric distribution across arms for the same outcome.
- 6.40 The assumption in the submission that PFS also defined the treatment duration was uncertain. The PBAC noted that patients in KN045 were permitted to continue treatment beyond radiographic disease progression if there was evidence of a reduction, or no increase, in overall tumour burden (CSR p76). As shown in Figure 3, this resulted in time on treatment (ToT) exceeding PFS for pembrolizumab treated patients for the majority of the trial; median ToT was [REDACTED] months compared with

2.2 months for PFS. The key exception was during the first three months when ToT was lower, potentially due to the deaths which occurred during that period.

Figure 3: Kaplan Meier plot for pembrolizumab comparing progression-free survival with time on treatment



Source: prepared during the evaluation using data from KN045\_1, Attachment 14 of the submission.  
Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival; ToT, time on treatment.

- 6.41 Using the alternative assumption of ToT (which reflects the potential for patients to continue treatment beyond progression) instead of PFS for the pembrolizumab arm, and extrapolated in the same manner as PFS, increased the ICER from \$45,000/QALY - \$75,000/QALY to \$45,000/QALY - \$75,000/QALY. The PBAC agreed with the ESC and considered that it was not appropriate to assume that pembrolizumab would be ceased on progression reported in the trial. Furthermore, the PBAC considered that evidence of progression is less likely to be monitored for as intensively in regular clinical practice compared with the trial, suggesting that this aspect of the trial reflects pembrolizumab use beyond progression. The PBAC also recalled that the trial showed that progression events were not convincing surrogate outcomes. Therefore, the PBAC considered that using ToT was a more reasonable approach to estimating utilisation and would have better internal validity with the model's basis for estimating effectiveness from the trial. For consistency and the internal validity of the model, the PBAC preferred that ToT be extrapolated in the same way as for the health outcome variables in the model, but could not judge what extra effect this would have on the ICER.
- 6.42 The ESC noted that using the submission's points of extrapolation, but assuming the log-logistic parametric curves for all outcomes, and applying treatment costs according to ToT, which the ESC considered more reasonable, the ICER increased to \$75,000 - \$105,000 per QALY.

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

- 6.43 Based on a fixed dose of 200 mg per person, the average cost per patient per treatment cycle of pembrolizumab is \$ [REDACTED] (2 X 100 mg vials, at \$ [REDACTED] per vial), every 3 weeks.

- 6.44 The expected number of treatment cycles per patient was based on time in the progression-free health states, estimated from the extrapolated PFS curves, up to a maximum treatment duration of 35 cycles for pembrolizumab. The average (undiscounted) cost per treatment per patient was determined to be \$ [REDACTED] (\$ [REDACTED] x [REDACTED] cycles) for pembrolizumab patients.

***Estimated PBS usage & financial implications***

- 6.45 This submission was not considered by DUSC. The submission used an epidemiological approach for the estimation of the total number of patients likely to be diagnosed with LA or mUC each year. Specifically, it used projected bladder cancer 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.
- 6.46 The submission commissioned a study (ONCOSight) to provide epidemiological data and treatment patterns on patients with urothelial cancer in Australia, on the basis that, whilst the AIHW reports the number of incident and prevalent patients with bladder cancer, it is difficult to accurately determine the sub-classifications specific to urothelial disease and the subsequent patterns of treatment. The ONCOSight model tracked cancer patients throughout the duration of their cancer, from initial diagnosis to cure or death. The submission did not sufficiently justify why it did not use the ONCOSight report to estimate the number of eligible patients.
- 6.47 The submission'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 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.

**Table 16: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	■	■	■	■	■	■
Number of scripts dispensed <sup>a</sup>	■	■	■	■	■	■
<b>Estimated financial implications of pembrolizumab</b>						
Cost to PBS/RPBS	■	■	■	■	■	■
Copayments	■	■	■	■	■	■
Cost to PBS/RPBS less copayments	■	■	■	■	■	■
<b>Estimated financial implications for standard of care</b>						
Cost offsets to PBS/RPBS						
Paclitaxel 100 mg vial	■	■	■	■	■	■
Docetaxel 160 mg vial	■	■	■	■	■	■
Copayments						
Paclitaxel 100 mg vial	■	■	■	■	■	■
Docetaxel 160 mg vial	■	■	■	■	■	■
Cost offsets to PBS/RPBS less copayments						
Paclitaxel 100 mg vial	■	■	■	■	■	■
Docetaxel 160 mg vial	■	■	■	■	■	■
<b>Net financial implications</b>						
Net cost to PBS/RPBS	■	■	■	■	■	■

Note: <sup>a</sup> Assuming ■ scripts in Year 1 and ■ in Year 2 (average ■ per year) as estimated by the submission.  
 Source: Table 4.1.1 to Table 4.5.1, pp 66-76 of the submission/Excel workbook.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$10 - \$20 million per year.

6.48 The main sources of uncertainty are related to the submission’s approach to estimating eligible patients and the estimated treatment exposure:

- The ONCOSight model estimated that 50% of LA or mUC patients were being treated with second-line therapies. The submission proposed that once more tolerable therapies, such as pembrolizumab, become available this would increase the treatment rate to ■%. The pre-PBAC response (p3) stated this is justified given the magnitude of benefit pembrolizumab offers versus current chemotherapy treatments in terms of superior efficacy, superior safety and improved quality of life.
- The submission did not consider that a proportion of patients would receive an additional line of treatment after failure of pembrolizumab (displacement of SOC therapies), which would increase the net costs to government. Based on the ONCOSight model, 35% of metastatic patients received further lines of treatment beyond failure (i.e. displacement of SOC after failure of pembrolizumab). The PBAC considered that the number of patients would be small, and noted that

allowing for the impact of displacement had a modest financial impact due to the low cost of SOC relative to pembrolizumab.

- The submission used a mortality approach to estimate the proportion of eligible patients, rather than the ONCOSight model. Measuring the impact of this second source of patient estimates on the financial estimates would have been informative, and the impact on the financial estimates is unknown.
- The expected number of treatment cycles per patient was based on time in the progression-free health states, estimated from the extrapolated PFS curves (every 3 weeks), up to a maximum treatment duration of 35 cycles for pembrolizumab, and ten treatment cycles for the comparator arm (30 weeks). The model estimated that, on average, [REDACTED] cycles are administered to pembrolizumab patients based on the extrapolated PFS. These estimates are thus subject to the same uncertainties identified in relation to the economic analysis regarding the point from which the data were extrapolated and the parametric form assumed.
- The estimates used PFS to measure treatment exposure, which is consistent with the proposed PBS restriction. However, patients in KN045 were permitted to continue treatment beyond progression resulting in ToT that exceeded PFS (see Figure 3). Use of ToT instead of PFS to estimate treatment exposure resulted in a revised cost to the PBS/RPBS of \$60- \$100 million over the first six years. The PBAC considered that for the same reasons as outlined in paragraph 6.41, ToT would be a more appropriate measure.
- KN045 permitted patients to undergo a “second course” of treatment if they experience progression after an initial CR, or after having a minimum of SD at the end of the 35 cycles. There is the potential for such use to enter clinical practice, representing a risk for use beyond the proposed PBS restriction.

6.49 The PBAC considered that as a result of these factors, the estimates provided by the submission were highly uncertain.

### ***Quality use of medicines***

6.50 Pembrolizumab belongs to a new immunotherapy class, so the submission proposed the provision of professional development and resources to ensure appropriate use in clinical practice. These were not provided with the submission.

### ***Financial management – risk sharing arrangements***

6.51 The PSCR (p4) proposed a risk sharing arrangement (RSA), consistent with the approach recommended by PBAC for PBS-listing of nivolumab in RCC (nivolumab RCC PSD November 2016), to address the potential for use beyond the proposed maximum of 35 cycles. It was proposed that the expenditure caps would be based on the estimated use of [REDACTED] pembrolizumab cycles per patient. The PBAC agreed with the ESC that the RSA may not fully address the uncertainties such as treatment duration or the risk of use beyond 35 cycles, particularly for grandfathered patients. Additionally, the proposed rebate was not specified for expenditure over the caps.

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

## **7 PBAC outcome**

- 7.1 The PBAC decided not to recommend pembrolizumab for the treatment of patients with locally advanced (LA) or metastatic urothelial cancer (mUC) after failure of a platinum-containing regimen on the basis that the incremental cost-effectiveness ratio compared to standard of care (SOC) was highly uncertain and likely an underestimate, and the financial implications were considerable and uncertain. However, the PBAC acknowledged the high clinical need and the evidence of positive overall survival benefit and reduced toxicity in this population.
- 7.2 The PBAC acknowledged the sponsor hearing and the consumer comments noting a high unmet need for a relatively large group of patients with a poor prognosis. The PBAC also noted that the consumer comments included they perceived that pembrolizumab was associated with fewer side effects and improved quality of life compared to chemotherapy.
- 7.3 The PBAC considered that SOC, which included paclitaxel or docetaxel, as the main comparator was appropriate. However, the PBAC also considered that pembrolizumab may displace rather than replace some paclitaxel and docetaxel use. The PBAC noted the submission acknowledged that three immunotherapies nivolumab, durvalumab and avelumab were possible alternative comparators. However, the PBAC considered it was reasonable to exclude these drugs because a submission to the PBAC to consider listing in urothelial cancer has not been received as yet. The PBAC also agreed with the submission's view that, on the basis of the PBAC's recent rejection of vinflunine for urothelial cancer, it was reasonable to exclude vinflunine as a comparator. The PBAC noted that excluding vinflunine as a comparator would be unlikely to materially affect its overall conclusions as the subgroup analysis in the key trial suggested vinflunine has similar progression-free survival (PFS) and overall survival (OS) to other current SOC options.
- 7.4 The submission was based on one head-to-head randomised trial comparing pembrolizumab to SOC (KN045). The PBAC considered that the claim of superior effectiveness was adequately supported by the OS data, where the evidence from KN045 indicated a modest but statistically significant OS gain for the pembrolizumab arm compared with the SOC arm.
- 7.5 The PBAC noted that more patients died in the pembrolizumab arm in the first three months of the trial, and that there were no significant differences across treatment arms in baseline characteristics for patients who died in the first three months. The PBAC considered that for some patients pembrolizumab does not provide a survival advantage, however these results should be considered with caution due to the low numbers of events.
- 7.6 The PBAC noted that there was no significant difference in PFS between pembrolizumab and SOC, but considered that PFS may not be a meaningful surrogate for clinical benefit in this indication.
- 7.7 The PBAC considered the claim of superior safety to be reasonable. The evidence from KN045 indicated a statistically significantly lower rate of  $\geq$  Grade 3 adverse events

with pembrolizumab compared with SOC. The TGA clinical evaluation report and consumer comments also supported this claim. The PBAC also considered that given pembrolizumab had a better safety profile, there were unlikely to be unreasonable safety issues for patients with a performance status score of ECOG = 2 receiving pembrolizumab treatment.

7.8 The PBAC considered 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.

7.9 The PBAC noted the submission presented a cost-utility analysis (CUA) to estimate the cost-effectiveness of pembrolizumab with a base case ICER of \$45,000/QALY - \$75,000/QALY. The PBAC considered the cost-effectiveness of pembrolizumab was overly optimistic and highly uncertain for the following reasons.

- PFS was used to estimate the costs of pembrolizumab rather than time on treatment, with patients in the trial accessing treatment beyond progression. Further, evidence of progression is less likely to be monitored as intensively in regular clinical practice compared with the trial.
- The start point of extrapolation was very early in the data (27 weeks for PFS and 40 weeks for OS), and the associated truncated overlap of the goodness of fit assessment of the parametric functions forming these extrapolations with the observed Kaplan-Meier results, were insufficiently justified because they were based on inappropriate *post-hoc* applications of the Chow test.
- Applying different parametric distributions between arms was not justified as being biologically plausible when comparing treatments for the same condition.
- There was limited long-term follow-up (extended interim analysis 18.5 months), which increased uncertainty in the magnitude of clinical benefit.

7.10 The PBAC advised that any future resubmission should respecify the base case of the economic model to:

- extrapolate the observed ToT to estimate treatment duration for estimating the costs of treatment;
- use the observed Kaplan-Meier results in the model up to the median duration of follow-up;
- extrapolate the PFS and OS curves in the model beyond this time point with reference to parametric functions generated by appropriately using the observed Kaplan-Meier results for each treatment arm to inform their goodness of fit assessment (i.e. not excluding any Kaplan-Meier results by relying on the Chow test);
- apply the same extrapolation function between treatment arms for both PFS and OS;
- apply a conservative set of extrapolation curves after the median duration of follow-up that take into account the remaining uncertainty in the magnitude of PFS and OS benefit due to the modest follow-up data available; and

- converge the extrapolation curves to a base case time horizon of 5 years.

The PBAC also advised that the requested price for pembrolizumab should then be adjusted to maintain the ICER at or below the ICER presented for this submission's base case. The PBAC considered that an acceptable ICER/QALY was critical to ensuring the cost effective listing of pembrolizumab and expected that the requested effective price of pembrolizumab would need to be reduced to achieve this target.

7.11 The PBAC considered the financial impact of pembrolizumab was highly uncertain because:

- the patient numbers were likely underestimated;
- there was a risk of use outside the requested restriction into first-line treatment for cisplatin-ineligible patients; and
- the duration of pembrolizumab use may be longer than estimated. Some patients in KN045 were treated beyond progression, and some were allowed to access an additional 12 months of treatment if they progressed after 24 months of pembrolizumab. Further, evidence of progression is less likely to be monitored as intensively in regular clinical practice compared with the trial.

7.12 The PBAC also noted that this submission presented pembrolizumab as a fixed dosing regimen, whereas pembrolizumab treatment for other PBS-listed indications has used a weight-based dosing regimen. This 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. The PBAC therefore considered that 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. The PBAC therefore 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.

7.13 The PBAC noted that a RSA was proposed in the PSCR (p4) to address the potential for use beyond the proposed maximum of 35 administrations, but that it was unclear if 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. The PBAC also noted that approximately [REDACTED] patients may be eligible for grandfathering to treatment with pembrolizumab on the PBS, and that it remained unclear what mechanisms are in place to ensure that the combined total use (pre and post PBS listing) would not exceed 35 administrations.

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

**Outcome:**

Rejected

## **8 Context for Decision**

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

## **9 Sponsor's Comment**

MSD is disappointed that access to Keytruda has not yet been achieved for 2L mUC patients in Australia. However, MSD is pleased that the PBAC is supportive of the clinical benefit that pembrolizumab offers over current standard of care for these patients and that there is an unmet clinical need for new therapies. The company is committed to working with the government to make pembrolizumab available to these patients as soon as possible.