5.02 DURVALUMAB, Solution concentrate for I.V. infusion 120 mg in 2.4 mL; Solution concentrate for I.V. infusion 500 mg in 10 mL, Imfinzi™, AstraZeneca Pty Ltd

1 Purpose of Application

1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) listing of durvalumab for the treatment of patients with locally advanced or metastatic urothelial cancer who have disease progression during or following platinum-based chemotherapy. The PBAC has not previously considered durvalumab for the treatment of urothelial cancer.

1.2 The listing was requested on a cost-minimisation basis compared to pembrolizumab (Table 1).

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

Component	Description
Population	Patients with locally advanced or metastatic urothelial cancer who have disease progression during or following platinum-based chemotherapy.
Intervention	Durvalumab 10 mg/kg administered every two weeks by IV infusion.
Comparator	Pembrolizumab 200 mg administered every three weeks by IV infusion.
Outcomes	Overall survival, progression-free survival, objective response rate, duration of response, health-related quality of life, safety/tolerability.
Clinical claim	In patients with locally advanced or metastatic urothelial cancer whose disease has progressed during or following platinum-based chemotherapy, durvalumab 10 mg/kg every two weeks is non-inferior to pembrolizumab 200 mg every three weeks, in terms of clinical effectiveness and safety/tolerability.

Source: Table 1.1.1, p.13 of the submission.
Abbreviations: IV, intravenous.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Max. Qty	No. of repeats	DPMA Public	DPMA Private	Proprietary name and manufacturer
Durvalumab 500 mg/10 mL, concentrated solution for IV infusion; 120 mg/2.4 mL, concentrated solution for IV infusion	1240 mg	8	$[redacted][1]	$[redacted][1]	Imfinzi™ AstraZeneca Pty Ltd

Category / Program:	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists

	☐Midwives
Severity:	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
Condition:	Urothelial cancer
PBS Indication:	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒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 *for this condition in the metastatic setting or for inoperable locally advanced disease* 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 AND The treatment must not exceed a total of 9 doses at 10 mg/kg/dose every 2 weeks for this condition under this restriction.
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.

Category / Program:	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
Condition:	Urothelial cancer
PBS Indication:	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒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 Treatment must not exceed 54 weeks in total, at 10 mg/kg/dose every 2 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.

Category / Program:	Section 100 – Efficient Funding of Chemotherapy
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
Condition:	Urothelial cancer
PBS Indication:	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
Treatment phase:	Grandfathering treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒Streamlined

Clinical criteria:	Patient must have received non-PBS treatment with this drug for this condition prior to [date of PBS listing] AND 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 *for this condition in the metastatic setting or for inoperable locally advanced disease* 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 prior to initiating treatment with this drug for this condition AND Patient must have stable or responding disease AND Treatment must not exceed 54 weeks in total, at 10 mg/kg/dose every 2 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.

2.2 The requested published price is the same as the price requested for the Stage III non-small cell lung cancer (NSCLC) indication. The pre-sub-committee response (PSCR) reiterated the requirement for the same published vial price as the NSCLC indication for international reference pricing purposes. The submission noted that the comparator, pembrolizumab, is subject to a special pricing arrangement. The submission requested a special pricing arrangement for durvalumab with an effective price that is cost-minimised to the pembrolizumab effective price.

2.3 The submission requested eight repeats under the proposed restriction, which would provide up to 18 weeks of treatment per prescription (compared to 21 weeks for each pembrolizumab prescription).

2.4 The submission noted that the PBS listing of pembrolizumab for urothelial cancer does not include criteria relating to PD-L1 status, and claimed that PD-L1 testing would not be required to determine access to treatment with durvalumab. However, PD-L1 expression appeared to be a strong predictor of overall survival for patients treated

with durvalumab in Study 1108.

2.5 The proposed restriction includes patients with an ECOG score of ≤2. However, no clinical data was presented for patients with an ECOG score of 2. The inclusion criteria for Study 1108 required patients to have an ECOG score of ≤1.

2.6 The proposed initial treatment restriction is identical to the pembrolizumab urothelial cancer restriction, apart from a difference in the maximum duration of therapy under the initial treatment restriction (18 weeks for durvalumab versus 21 weeks for pembrolizumab).

2.7 The proposed continuing treatment restriction is identical to the pembrolizumab urothelial cancer restriction, apart from the maximum duration of therapy (54 weeks for durvalumab versus 2 years for pembrolizumab). The 54-week maximum treatment duration for durvalumab is consistent with the maximum planned treatment duration in Study 1108. The proposed restriction is narrower than the TGA restriction, which states that treatment may be continued for as long as clinical benefit is observed or until unacceptable toxicity develops. The ESC noted the sponsor's argument in the TGA Clinical Evaluation Report (CER) that PD-L1 antibodies don't alter the expression of PD-L1 on tumour cells, so continuous blockade is probably needed to maintain response. The PBAC noted that the submission provided no rationale for limiting the duration of treatment other than the trial design. The PBAC were uncertain regarding the optimal duration of treatment for patients who are responding to treatment, given the lack of available data on clinical outcomes following durvalumab cessation.

2.8 In Study 1108, patients with confirmed disease progression could continue to receive durvalumab in the absence of clinical deterioration if the investigator considered that the patients were continuing to receive benefit from the treatment. Patients experiencing disease recurrence after the protocol-based cessation of treatment at 12 months were eligible to receive another 12 months of treatment. However, no data are currently available regarding treatment outcomes among retreated patients.

2.9 There is the potential for growth of the PD-1/PD-L1 inhibitor market due to the sequential use of pembrolizumab and durvalumab. The current pembrolizumab restriction and the proposed durvalumab restriction do not preclude prior use of other PD-L1/PD-1 inhibitors. The PSCR stated the sponsor would be accepting of an amendment to the proposed restrictions for both pembrolizumab and durvalumab to prevent sequential use of PD-L1/PD-1 inhibitors if the PBAC considered this necessary. The PBAC considered the restriction should not allow sequential use of PD-L1/PD-1 inhibitors if durvalumab were to be listed.

2.10 The submission also requested grandfathering provisions for patients currently participating in a Patient Access Program for locally advanced or metastatic urothelial cancer post platinum-based chemotherapy.

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

3 Background

Registration status

3.1 Durvalumab was registered on the Australian Register of Therapeutic Goods (ARTG) on 2 October 2018 for:

"Treatment of patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy.
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

This indication is approved based on the objective response rate and duration of response in a single arm study (Study 1108). An improvement in survival or disease-related symptoms has not been established."

3.2 The ESC noted that the clinical evaluator recommended rejection because of a lack of phase 3 randomised controlled trials (RCT) comparing durvalumab with an established treatment. A note on the limitations of the clinical data was included in the indication (as above). The ESC also noted that the clinical evaluator advised that approval should be restricted to those with PD-L1 high disease as defined in study 1108. The delegate's file note noted that there was a >10% higher incidence of grade 3 or 4 AEs, SAEs, and deaths due to AEs in the subgroup with low PD-L1 expression, which could be attributable to poorer tumour control, but this cannot be established in the absence of a control arm to provide comparative safety data. The PBAC noted that the delegate noted an early survival detriment with pembrolizumab, however due to the single-arm nature of study 1108 it was not possible to assess whether a similar risk was present for durvalumab in this setting. The pre-PBAC response noted that the delegate concluded the ORR, durability of response and safety profile of durvalumab appear similar to other PD-L1/PD-1 inhibitors in the 2L post-chemotherapy setting. The delegate noted that there was a lower ORR in patients with low/negative PD-L1 expression tumours, but also that the confidence interval was wide. The delegate reasoned that the data did not warrant restricting the indication based on PD-L1 status, but that the subgroup information should be included in the PI. [redacted] and that an MSAC application for PD-L1 expression testing to allow access to durvalumab has been initiated, to allow a co-dependent submission if the results of DANUBE indicate PD-L1 testing is necessary.

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

4 Population and disease

4.1 Urothelial cancers are cancers that arise from urothelial cells (transitional cells) lining the renal pelvis, ureter, urinary bladder, and urethra. The majority of urothelial cancers (>90%) originate in the bladder. Around 8% originate in the renal pelvis, with the remainder occurring in the ureter and urethra.

4.2 Bladder cancer is associated with advancing age, with over 90% of new diagnoses occurring in individuals aged over 55 years. The incidence of bladder cancer is substantially higher in males than females. The 2015 age-standardised incidence rate in Australia was 16.7 cases per 100,000 in males, compared to 4.3 cases per 100,000 in females (AIHW, 2018). Patients with advanced or metastatic disease have a poor prognosis with a median survival of approximately 14 months (Bellmunt et al., 2014).

4.3 The submission positioned durvalumab as an alternative to pembrolizumab for patients with locally advanced or metastatic urothelial carcinoma who have disease progression after platinum-containing chemotherapy.

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

5 Comparator

5.1 The submission nominated pembrolizumab as the main comparator. The main arguments provided in support of this nomination were:

- Pembrolizumab, a monoclonal antibody that binds to PD-1 (programmed cell death 1), has a similar pharmacological action to durvalumab;
- Pembrolizumab is the only PD-1/PD-L1 immune checkpoint inhibitor listed on the PBS for treatment of patients with urothelial cancer;
- Pembrolizumab is the treatment most likely to be replaced by durvalumab.

5.2 The PBAC considered pembrolizumab was the appropriate main comparator.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (1), and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with durvalumab including being more energetic and

interested in life, a significant reduction in tumour size, and considerably fewer side effects in comparison to chemotherapy.

6.3 The PBAC noted the advice received from BEAT Bladder Cancer Australia in support of PBS-listing of durvalumab to provide an additional treatment option for patients with bladder cancer.

6.4 The PBAC noted that the Medical Oncology Group of Australia (MOGA) did not include the durvalumab submission for the treatment of patients with locally advanced or metastatic urothelial cancer in its letter to the PBAC regarding anti-cancer submissions considered at the July 2019 meeting.

Clinical trials

6.5 No head-to-head trials comparing durvalumab to pembrolizumab were identified.

6.6 The submission was based on one single-arm study of durvalumab (Study 1108), and one randomised, open-label trial of pembrolizumab versus investigator's choice of chemotherapy (Keynote-045).

6.7 The submission's claim was based on the results of an indirect comparison of durvalumab versus pembrolizumab. Evidence for durvalumab versus chemotherapy was generated using an unanchored matching adjusted indirect comparison (MAIC) of individual patient data from Study 1108, and aggregate results for the chemotherapy arm of Keynote-045. The results of the MAIC were then compared with the results of the Keynote-045 trial in an indirect comparison using chemotherapy as the common reference.

6.8 Details of the studies presented in the submission are provided in Table 2.

Table 2: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Durvalumab studies		
Study 1108 (NCT01693562)	A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects With Advanced Solid Tumors.	Clinical Study Report (final), 24 May 2018.
	Massard, C., et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer.	Journal of Clinical Oncology 2016; 34(26): 3119-3125.
	Powles, T., et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: Updated results from a phase 1/2 open-label study.	JAMA Oncology 2017; 3(9): e172411.
Pembrolizumab studies		
Keynote-045 (NCT02256436)	Bellmunt, J., et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma.	New England Journal of Medicine 2017; 376(11): 1015-1026 and online Supplementary Appendix and Study Protocol.
	Bellmunt, J., 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).	Journal of Clinical Oncology 2018; 36(6) Suppl. Feb 20 Abstract 410.
	Vaughn, D. J., et al. Health-Related Quality-of-Life Analysis From KEYNOTE-045: A Phase III Study of Pembrolizumab Versus Chemotherapy for Previously Treated Advanced Urothelial Cancer.	Journal of Clinical Oncology 2018; 36(16):1579-1587.
	Bajorin, D. F., 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 Suppl. May 20): Abstract 4501.
	De Wit, R., 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; 42nd ESMO Congress, 28(Supplement 5): v623.
	Necchi, A., et al. Pembrolizumab vs investigator-choice chemotherapy for previously treated advanced urothelial cancer: Phase 3 KEYNOTE-045 study.	European Journal of Cancer 2017; 72 (Suppl. 1): S2 (LBA3).
	Petrylak, D., 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; Conference: 42nd ESMO congress, ESMO 2017. Spain 28(Supplement 5): v298 Abstract 851PD

Selected conference abstract citations omitted.
Source: Table 2.2.2, p.35 of the submission.

6.9 The key features of the included studies are summarised in Table 3.

Table 3: Key features of the included evidence

Study	N	Design/ duration	Risk of bias	Patient population	Outcomes
Study 1108	1022 (urothelial cancer cohort: 201)	Phase 1/2, multi-centre (international), open-label, single-arm study (12-month treatment phase with additional 12-month follow-up).	High	Adults with inoperable or metastatic urothelial cancer who have progressed on or are refractory following 1 to 2 prior lines of systemic therapy, including a standard platinum-based regimen.	Objective response (co-primary), safety (co-primary); duration of response; time to response; PFS; OS; HRQOL.
Keynote-045	542	Phase 3, multi-centre (international), open-label, RCT (24-month treatment phase).	Moderate	Adults with urothelial cancer with progression or recurrence following a first-line platinum-containing regimen (cisplatin or carboplatin). No more than two prior lines of systemic chemotherapy for urothelial cancer.	OS (co-primary); PFS (co-primary); objective response rate; duration of response; safety and tolerability; HRQOL.

Source: Table 2.4.1, p.46; Table 2.4.2, p.47; Table 2.4.6, pp59-64 of the submission.
Abbreviations: HRQOL, health-related quality of life; PFS, progression-free survival; OS, overall survival; RCT, randomised controlled trial.

6.10 Study 1108 was a Phase 1/2 dose-escalation/exploration and dose expansion study designed to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and anti-tumour activity of durvalumab in adult subjects with advanced solid tumours. The dose expansion phase comprised 980 patients across 17 different tumour-specific cohorts, and included a cohort of 201 patients with urothelial cancer. Study 1108 had a high risk of bias as it was a single-arm study.

6.11 Patients in the dose expansion phase received durvalumab 10 mg/kg administered every 2 weeks. The submission was based on the results reported for the second-line post-platinum urothelial cancer cohort, a subset of the urothelial cancer cohort, which excluded nine patients who did not meet the inclusion criteria for prior treatments.

6.12 Keynote-045 was a randomised, open-label trial comparing pembrolizumab 200 mg administered every 3 weeks to investigator's choice of chemotherapy (paclitaxel 175 mg/m^2, docetaxel 75 mg/m^2, or vinflunine 320 mg/m^2) administered every three weeks. The data and safety monitoring committee recommended early termination of the trial at the second interim analysis because pembrolizumab had met the superiority thresholds for overall survival in the co-primary populations.

6.13 The submission noted that there were differences between the Study 1108 and Keynote-045 study populations in geographical location, in the proportion of patients who had received prior treatments, in the proportion of patients with visceral metastases, in the primary tumour location, in the Bellmunt risk score, in the proportion of patients with less than 3 months since the completion of their most recent prior therapy, in the proportion with prior Bacillus Calmette–Guérin therapy, and in the proportion of patients with a baseline haemoglobin of <10 g/dL. The PBAC considered that Study 1108 and Keynote-045 appeared to be reasonably matched with regard to demographic and disease characteristics, noting that, overall, patients in Study 1108 did not have a noticeably worse prognosis that those included in Keynote-045.

6.14 There were differences in the PD-L1 assays used in each of the studies, and in the algorithms that were used to estimate the percent PD-L1 expression. As a result, PD-L1 expression could not be compared between the studies. The PBAC considered that PD-L1 status was an important factor, and noted that the DANUBE trial that is currently underway may provide additional information regarding the impact of PD-L1 status on the safety and efficacy of durvalumab in patients with UC.

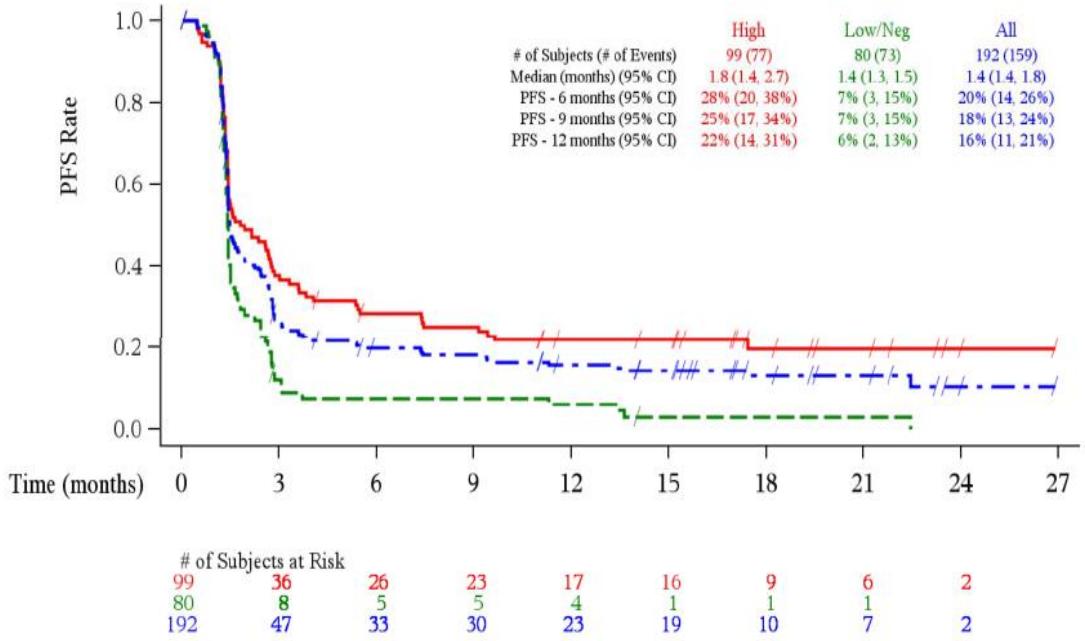
6.15 In Study 1108, the initial 20 patients with urothelial cancer were enrolled regardless of their PD-L1 expression. A protocol amendment required subsequent patients to have a minimum of 5% PD-L1 expression on tumour cells. A subsequent protocol amendment after a further 43 patients were recruited removed this requirement. Given the association of high PD-L1 expression with improved overall survival in Study 1108, this potential enrichment may have positively influenced the results for Study 1108. However, the significance of the 5% tumour cell PD-L1 expression cut-off was unclear.

6.16 In Study 1108, subjects received durvalumab treatment for a maximum of 12 months. In the event of confirmed disease progression, subjects could continue to receive durvalumab in the absence of clinical deterioration at the discretion of the investigator. Patients treated with pembrolizumab in Keynote-045 were to receive treatment for up to 24 months. Patients with disease progression and a clinically stable status could continue to receive the therapy at the discretion of the investigator.

Comparative effectiveness

6.17 Figure 1 and Table 4 present the results for the outcome of progression-free survival assessed by blinded independent central review for the second-line post-platinum urothelial cohort in Study 1108.

Figure 1: Kaplan Meier plot of progression-free survival for Study 1108 (second-line post-platinum urothelial cancer cohort) by PD-L1 expression level



Source: Figure 2.5.1, p.70 of the submission.
Abbreviations: CI, confidence interval; PFS, progression-free survival.

Table 4: Progression-free survival results for Study 1108 (second-line post-platinum urothelial cancer cohort)

Parameter	Study 1108 (second-line post-platinum UC cohort)		
	Durvalumab PD-L1 high N=99	Durvalumab PD-L1 low/negative N=80	Durvalumab all patients N=192[1]
Events, n (%)	77 (77.8)	73 (91.3)	159 (82.8)
Median PFS, months (95% CI)	1.8 (1.4, 2.7)	1.4 (1.3, 1.5)	1.4 (1.4, 1.8)
KM estimate of PFS			
-3 months, % (95% CI)	36.7 (27.3, 46.2)	11.9 (5.8, 20.4)	26.0 (19.9, 32.5)
-6 months, % (95% CI)	28.5 (19.9, 37.6)	7.4 (2.8, 15.1)	19.9 (14.5, 26.0)
-9 months, % (95% CI)	25.2 (17.0, 34.1)	7.4 (2.8, 15.1)	18.1 (12.9, 24.0)
-12 months, %, (95% CI)	21.9 (14.2, 30.6)	6.0 (2.0, 13.2)	15.6 (10.7, 21.3)
-18 months, %, (95% CI)	19.7 (12.0, 28.8)	3.0 (0.6, 9.1)	13.0 (8.2, 18.8)

Source: Table 2.5.3, p.69 of the submission; Table 100, p.267 of the durvalumab clinical study report.
Abbreviations: CI, confidence interval; KM, Kaplan Meier; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; UC, urothelial cancer.
[1] Includes 13 patients with unknown PD-L1 status.

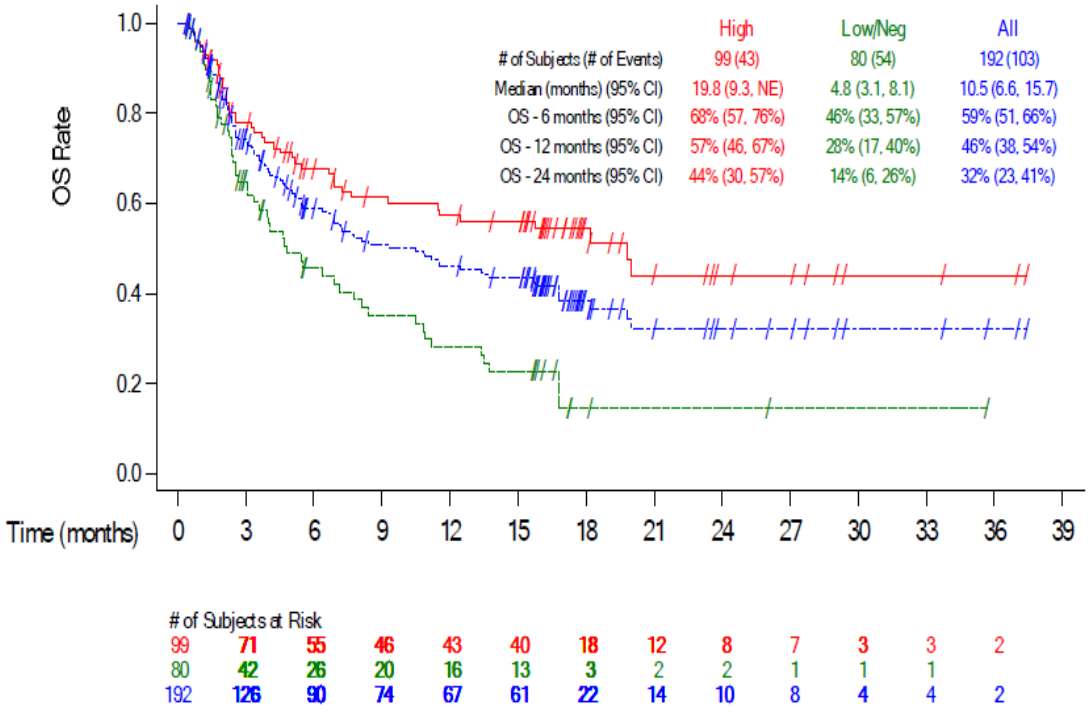
6.18 Treatment with durvalumab was associated with a median progression-free survival of 1.4 months (95% CI: 1.4, 1.8) across all patients in the second-line post-platinum subgroup. At 12 months, 15.6% of patients did not have disease progression. The proportion of patients who were progression-free at 12 months was numerically higher among patients with high PD-L1 expression (21.9%) compared to those with

low/negative expression (6.0%).

6.19 The PBAC previously commented that progression-free survival may not be a meaningful surrogate for clinical benefit for the post-platinum urothelial cancer indication (Paragraph 7.6, November 2017 pembrolizumab PSD).

6.20 Figure 2 and Table 5 present the results for the outcome of overall survival for the second-line post-platinum urothelial cohort in Study 1108.

Figure 2: Kaplan Meier plot of overall survival for Study 1108 (second-line post-platinum urothelial cancer cohort) by PD-L1 expression level



Source: Figure2.5.3, p.72 of the submission.
Abbreviations: CI, confidence interval; OS, overall survival.

Table 5: Overall survival results for Study 1108 (second-line post-platinum urothelial cancer cohort)

Parameter	Study 1108 (second-line post-platinum UC cohort)		
	Durvalumab PD-L1 High N=99	Durvalumab PD-L1 low/negative N=80	Durvalumab All patients N=192[1]
Death, n (%)	43 (43.4)	54 (67.5)	103 (53.6)
Median OS, months (95% CI)	19.8 (9.3, NE)	4.8 (3.1, 8.1)	10.5 (6.6, 15.7)
KM estimate of OS			
-6 months, % (95% CI)	67.6 (33.4, 56.9)	45.6 (33.4, 56.9)	58.9 (51.2, 65.9)
-12 months, %, (95% CI)	57.3 (46.1, 66.9)	28.0 (17.5, 39.6)	46.1 (38.2, 53.5)
-24 months, %, (95% CI)	43.9 (30.1, 57.0)	14.2 (6.0, 25.8)	32.0 (22.9, 41.4)

Source: Table 2.5.4, p.73 of the submission; Table 102, p.272 of the durvalumab clinical study report.
Abbreviations: CI, confidence interval; KM, Kaplan Meier; PD-L1, programmed cell death ligand-1; OS, overall survival; UC, urothelial cancer.
[1] Includes 13 patients with unknown PD-L1 status.

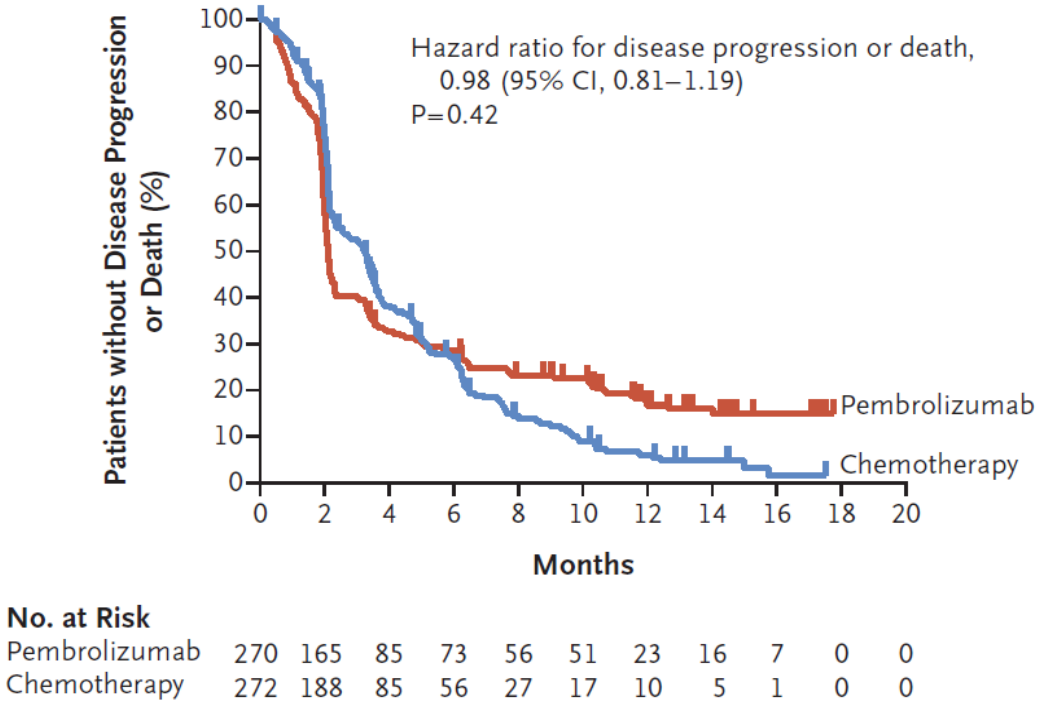
6.21 At the October 2017 data cut-off, with a median follow-up of 16.76 months (range, 0.4 to 37.7 months), the median overall survival in the second-line post-platinum urothelial cancer cohort was 10.5 months (95% CI: 6.6, 15.7). Median overall survival was numerically higher in the PD-L1 high subgroup (19.8 months; 95% CI: 9.3, not estimable) compared to the PD-L1 low/negative subgroup (4.8 months; 95% CI: 3.1, 8.1), suggesting that PD-L1 expression may be a predictor of overall survival for patients treated with durvalumab. The proportion of patients alive at 24 months was 43.9% in the PD-L1 high subgroup compared to 14.2% in the PD-L1 low/negative group. The overall survival results are likely to have been affected by the use of post-progression treatments, including post-progression use of durvalumab. The PSCR (p1) acknowledged the difference in overall survival between the PD-L1 high and PD-L1 low/negative subgroups in Study 1108, but argued that pembrolizumab was listed on the PBS for use irrespective of PD-L1 status, and that the durvalumab TGA indication is also irrespective of PD-L1 status. The ESC considered that this was not sufficient justification for not addressing this apparent treatment effect modifier. The ESC noted that the median overall survival for patients with PD-L1 low/negative status treated with durvalumab (4.8 months) was lower than that observed in the chemotherapy arm of the Keynote-045 trial (7.4 months), raising the possibility that chemotherapy would be a preferable treatment for these patients. The PBAC noted that Keynote-045 had been previously considered in November 2017 where "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" (Paragraph 6.13, July 2018 PSD for pembrolizumab). The PBAC considered that there was insufficient data addressing the effect modification of PD-L1 status in durvalumab treatment. The PBAC considered that, while it was clear that PD-L1 status was an effect modifier for durvalumab, it was unclear whether patients should be selected based on PD-L1 status.

6.22 Based on available results for the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, patients reported a relatively high level of functioning at

baseline, with scores ranging from 64.4 (role functioning) to 81.1 (cognitive functioning). Subjects reported moderate levels of fatigue, pain, insomnia, dyspnoea, constipation and appetite loss. Post-baseline, functioning scores fluctuated around the baseline values, however, some general oncology symptoms such as dyspnoea worsened.

6.23 Figure 3 and Table 6 present the results for the outcome of progression-free survival assessed by a blinded central review for Keynote-045.

Figure 3: Kaplan Meier plot of progression-free survival for the Keynote-045 trial



Source: Figure 2.5.2, p.70 of the submission.
Abbreviations: CI, confidence interval.

Table 6: Progression-free survival results for the Keynote-045 trial

Parameter	Keynote-045 Study (ITT population)	
	Pembrolizumab 200 mg every 3 weeks N=270	Chemotherapy every 3 weeks N=272
Events, n	218	219
Median PFS, months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)
Hazard ratio (95% CI)	0.98 (0.81, 1.19)	
KM estimate of PFS 12 months, %, (95% CI)	16.8% (12.3, 22.0)	6.2% (3.3, 10.2)

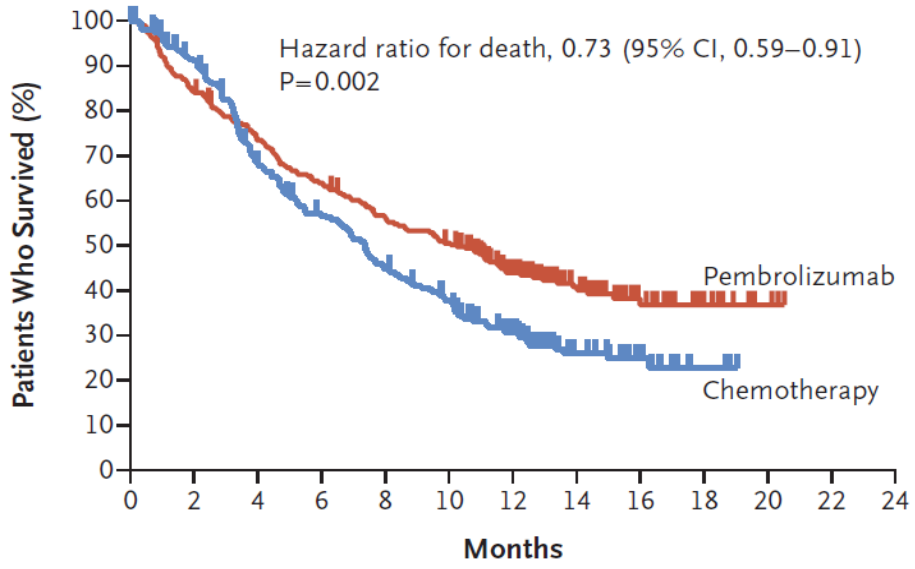
Hazard ratio <1 favours pembrolizumab.
Source: Table 2.5.3, p.69 of the submission; Table 1, p.1 of Necchi et al. (2017) conference abstract.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; KM, Kaplan Meier; PFS, progression-free survival.

6.24 Treatment with pembrolizumab was associated with a median progression-free survival of 2.1 months (95% CI: 2.0, 2.2), compared with 3.3 months (95% CI: 2.3, 3.5)

in the chemotherapy arm. Treatment with pembrolizumab did not appear to be associated with an improvement in progression-free survival compared to chemotherapy (HR 0.98; 95% CI: 0.81, 1.19). However, inspection of the Kaplan Meier curves for pembrolizumab and chemotherapy suggest that the proportional hazards assumption is violated, and therefore, the reported hazard ratio should be interpreted with caution.

6.25 Figure 4 and Table 7 present the results for the outcome of overall survival for Keynote-045.

Figure 4: Kaplan Meier plot of overall survival for the Keynote-045 trial



Source: Figure 2.5.4, p.73 of the submission.
Abbreviations: CI, confidence interval.

Table 7: Overall survival results for the Keynote-045 trial

Parameter	Keynote-045 Study (ITT population)	
	Pembrolizumab 200 mg every 3 weeks N=270	Chemotherapy every 3 weeks N=272
Death, n	155	179
Median OS, months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio (95% CI)	0.73 (0.59, 0.91)	
KM estimate of OS -12 months %, (95% CI) -18 months %, (95% CI)	 43.9 (37.8, 49.9) 36.1 (30.1, 42.0)	 30.7 (25.0, 36.7) 20.5 (15.2, 25.8)

Hazard ratio <1 favours pembrolizumab.
Source: Table 2.5.4, p.73 of the submission; Table 1, p.1 of Necchi et al. (2017) and Bajorin et al. (2017) conference abstracts.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; KM, Kaplan Meier; OS, overall survival.

6.26 At the September 2016 data cut-off, with a median duration of follow-up of 14.1 months, the median overall survival was 10.3 months (95% CI: 8.0, 11.8) in the pembrolizumab arm and 7.4 months (95% CI: 6.1, 8.3) in the chemotherapy arm. The October 2017 cut-off (abstract by Bellmunt et al, 2017) with median follow-up of 27.7 months showed very similar outcomes. Treatment with pembrolizumab was associated with a statistically significant reduction in mortality compared with chemotherapy (HR: 0.73; 95% CI: 0.59, 0.91). However, inspection of the Kaplan Meier curves for pembrolizumab and chemotherapy suggest that the proportional hazards assumption is violated, and therefore, the reported hazard ratio should be interpreted with caution. The results are likely to have been affected by differential use of post-progression treatments between arms, including use of pembrolizumab beyond disease progression in some patients.

6.27 Baseline EORTC QLQ-C30 global health status/quality-of-life scores were similar for the pembrolizumab arm (mean: 61.5; SD: 23.1) and chemotherapy arm (mean: 59.2; SD: 22.1). The EORTC QLQ-C30 global health status/quality-of-life score was stable over time for the pembrolizumab arm, but worsened over time for the chemotherapy arm, with a mean difference in change from baseline to Week 15 of 9.05 points (95% CI: 4.61-13.50).

6.28 The submission presented the results of an indirect comparison (Bucher method) of durvalumab versus pembrolizumab for the outcome of overall survival using chemotherapy as a common reference. The indirect comparison was constructed using the following treatment estimates:

- Pembrolizumab versus chemotherapy based on the published results for pembrolizumab versus chemotherapy in Keynote-045 trial.
- Durvalumab versus chemotherapy based on the results of an unanchored matching adjusted indirect comparison (MAIC) using individual level data from Study 1108 with aggregate data from the chemotherapy arm in Keynote-045.

6.29 The approach used in the submission was not based on established methods for demonstration of non-inferiority, and is considered highly uncertain. It may be more appropriate to directly compare pembrolizumab and durvalumab using an unanchored MAIC. However, differences in trial design, evidence maturity, treatment durations and PD-L1 expression assessment between Study 1108 and Keynote-045 suggest that an indirect comparison with an unanchored MAIC may not be feasible. The ESC considered that the submission's approach was not appropriate and increased uncertainty in the estimates produced in the indirect comparison. The ESC agreed with the evaluation that an unanchored MAIC to directly compare pembrolizumab and durvalumab is unlikely to be feasible due to the differences between the trials in terms of trial design. The ESC considered that, for the same reason, the unanchored MAIC of durvalumab versus chemotherapy is unreliable.

6.30 The unanchored MAIC estimate for durvalumab versus chemotherapy was obtained

from a conference abstract published by Hoyle et al. (2018). The submission provided a technical report outlining the methodology and results of an alternative unanchored MAIC of durvalumab versus chemotherapy, as well as an unanchored MAIC of durvalumab versus pembrolizumab. The submission stated that the results reported by Hoyle et al. were based on more mature data for durvalumab compared to the technical report. The PSCR confirmed that the analysis by Hoyle et al. used an identical methodology to that described in the technical document, but included updated survival analysis from Study 1108 (final data cut-off 16 October 2017) and the published Keynote-045 study data in Bellmunt 2017.

6.31 Table 8 presents the results of the Bucher method indirect comparison of durvalumab and pembrolizumab, based on the naïve (unadjusted) and MAIC (adjusted) treatment estimates for durvalumab versus chemotherapy.

Table 8: Results of the indirect comparison of overall survival for durvalumab and pembrolizumab

Durvalumab vs chemotherapy analysis	Durvalumab vs chemotherapy HR (95% CI)	Pembrolizumab vs chemotherapy HR (95% CI)	Indirect comparison of durvalumab vs pembrolizumab HR (95% CI)
Naïve (unadjusted)	0.73 (0.57, 0.92)	0.73 (0.59, 0.91)	1.0 (0.72, 1.38)[1]
MAIC (adjusted)	0.68 (0.48, 0.97)	0.73 (0.59, 0.91)	0.93 (0.62, 1.41)[1]

Source: Table 2.6.1, p82 of the submission.
Abbreviations: CI, confidence interval; HR, hazard ratio.
[1] Hazard ratio < 0 favours durvalumab.

6.32 Based on the unadjusted (naïve) result for durvalumab versus chemotherapy, the indirect comparison of durvalumab versus pembrolizumab was associated with a hazard ratio of 1.0 (95% CI: 0.72, 1.38). Based on the matching adjusted result for durvalumab versus chemotherapy, the indirect comparison of durvalumab versus pembrolizumab was associated with a hazard ratio of 0.93 (95%: CI: 0.62, 1.41). The PBAC noted that the results of this comparison appeared to indicate that durvalumab was non-inferior to pembrolizumab, however, the PBAC also considered that there was a high level of uncertainty in the results of the comparison, as the statistical validity of the approach used to conduct the indirect comparisons was unclear and the MAIC was unreliable.

6.33 There were insufficient details regarding the methodology of the MAIC, especially details about the prognostic factors chosen and the likely bias resulting from unobserved prognostic factors and effect modifiers that may be distributed differently in the trials. Furthermore, the distribution of weights plot to enable assessment of the extent of overlap between the trial populations was not provided. The technical document indicated a large loss of effective sample size following matching of the chosen variables, suggesting a lack of overlap between Study 1108 and Keynote-045 patient characteristics. The ESC noted the 62% reduction in effective sample size following matching of durvalumab to the chemotherapy arm of Keynote-045, indicative of the relatively poor overlap of populations between trials.

6.34 PD-L1 expression could not be compared due to the differences in PD-L1 expression assays and scoring systems used between the studies. This was a major limitation for

the comparisons, given that all effect modifiers and prognostic variables should be adjusted for in an unanchored MAIC in order to reliably predict absolute outcomes (NICE Technical Support Document 18; Phillippo et al. 2016), yet the results for durvalumab suggest that PD-L1 expression was a strong predictor of progression-free survival and overall survival in Study 1108. The ESC noted that failure to adjust for all prognostic and effect modifier variables leads to an unknown amount of bias in the unanchored estimate. The ESC noted the advice in the NICE technical support document for MAIC, and considered that because the degree of bias due to the imbalance in unaccounted-for covariates was not provided in the submission and is therefore unknown, the amount of systematic error is likely to be substantial and could even exceed the magnitude of treatment effects which are being estimated.

6.35 Other between-trial differences that cannot be accounted for in the MAIC include differences in trial design (Phase 1/2 non-comparative versus Phase 3 randomised comparative, timing of tumour assessments), use of post-progression treatments, protocol-defined durations of treatment, duration of follow-up, and treatment beyond disease progression. The PBAC agreed with the ESC that this severely compromised the validity of the MAIC analysis and subsequent indirect comparison with pembrolizumab using chemotherapy as a common comparator.

Comparative harms

6.36 Table 9 presents an overall summary of the adverse events associated with durvalumab, pembrolizumab and chemotherapy for Study 1108 and Keynote-045.

Table 9: Summary of adverse events across the included studies

Event	Study 1108 (second-line post-platinum cohort)	Keynote-045 Study (as treated population)	
	Durvalumab 10 mg/kg every 2 weeks N=192	Pembrolizumab 200 mg every 3 weeks N=266	Chemotherapy every 3 weeks N=255
Any AE, n (%)	189 (98.4%)	248 (93.2%)	250 (98.0%)
Treatment related AE, n (%)	115 (59.9%)	162 (60.9%)	230 (90.2%)
Any Grade 3 or 4 AE, n (%)	114 (59.4%)	NR	NR
Any Grade 3, 4 or 5 event, n (%)	NR	139 (52.3%)	160 (62.7%)
AE leading to death, n (%)[1]	68 (35.4%)	13 (3.9%)	8 (3.1%)
Serious AE, n (%)	111 (57.8%)	NR	NR
Discontinuation due to AE, n (%)	12 (6.3%)	22 (8.3%)	32 (12.5%)

Event	Study 1108 (second-line post-platinum cohort)	Keynote-045 Study (as treated population)	
	Durvalumab 10 mg/kg every 2 weeks N=192	Pembrolizumab 200 mg every 3 weeks N=266	Chemotherapy every 3 weeks N=255
Any grade, incidence ≥15%			
Fatigue	69 (35.9%)	69 (25.9%)	86 (33.7%)
Constipation	54 (28.1%)	50 (18.8%)	81 (31.8%)
Decreased appetite	48 (25.0%)	56 (21.1%)	53 (20.8%)
Bladder cancer	44 (22.9%)	0	0
Nausea	43 (22.4%)	55 (20.7%)	73 (28.6%)
Anaemia	38 (19.8%)	46 (17.3%)	91 (35.7%)
Urinary tract infection	37 (18.8%)	39 (14.7%)	34 (13.3%)
Diarrhoea	34 (17.7%)	43 (16.2%)	48 (18.8%)
Back pain	34 (17.7%)	37 (13.9%)	21 (8.2%)
Pyrexia	30 (15.6%)	36 (13.5%)	33 (12.9%)
Peripheral oedema	27 (14.1%)	26 (9.8%)	40 (15.7%)
Asthenia	24 (12.5%)	30 (11.3%)	53 (20.8%)
Pruritus	15 (7.8%)	62 (23.3%)	14 (5.5%)
Alopecia	0	2 (0.8%)	99 (38.8%)
Neutropenia	0	0	43 (16.9%)

Source: Table 2.5.6, p.76 of the submission.
Abbreviations: AE, adverse event; NR, not reported.
[1] Disease progression was included as an adverse event in Study 1108.

6.37 Almost all patients in the second-line post-platinum urothelial cancer cohort of Study 1108 experienced at least one adverse event. The most frequently reported adverse events (≥15%) in the urothelial cancer cohort were fatigue, constipation, decreased appetite, bladder cancer, nausea, anaemia, urinary tract infection, diarrhoea, back pain and pyrexia. The most common Grade 3-4 adverse events (≥4%) were anaemia, fatigue, general physical health deterioration, sepsis, urinary tract infection, hyponatraemia, back pain and acute kidney injury. The most common treatment related adverse events (≥5%) were hypothyroidism, diarrhoea, nausea, pyrexia, decreased appetite, arthralgia, pruritus and rash.

6.38 In the urothelial cancer cohort, 13 (6.5%) subjects had at least one adverse event that resulted in permanent discontinuation of durvalumab. Six (3.0%) subjects had adverse events resulting in permanent discontinuation of durvalumab that were considered by the investigator to be treatment-related.

6.39 The submission claimed that, when comparing durvalumab and pembrolizumab, both the type and incidence of adverse events that were reported were similar. However, the results of the naïve comparison of safety results should be interpreted with caution due to differences between the studies (trial design, eligibility criteria, baseline characteristics, and treatment durations). The PSCR (p3) acknowledged the inability to conduct statistical comparisons of safety outcomes, but highlighted the similar findings in the nature and frequency of adverse events reported for durvalumab and pembrolizumab.

Clinical claim

6.40 The submission described durvalumab 10 mg/kg every two weeks as non-inferior in terms of clinical effectiveness and safety/tolerability to pembrolizumab 200 mg every three weeks.

6.41 The clinical claim presented in the submission was not adequately supported;

- There is no available head-to-head trial evidence for durvalumab versus pembrolizumab. The evidence for durvalumab was based on one, single-arm study. In comparison to the evidence base for pembrolizumab, the PBAC considered that the clinical evidence for durvalumab was inadequate.
- There was a large numerical difference in overall survival between patients with low/negative PD-L1 expression and those with high PD-L1 expression (based on the Ventana PD-L1 assay). Treatment with durvalumab appears to be less effective in patients with low/negative PD-L1 expression.
- The Bucher method indirect comparison relied upon a treatment estimate for durvalumab versus chemotherapy that was derived using an unanchored MAIC of durvalumab (Study 1108) versus chemotherapy (Keynote-045). The statistical validity of using the MAIC result as a treatment estimate for durvalumab versus the common comparator in the indirect comparison was not appropriate and increased uncertainty in the estimates produced in the indirect comparison.
- The comparison between the studies was hampered by the lack of a common PD-L1 expression assay to assess PD-L1 expression status, and also by changes in the Study 1108 enrolment criteria related to PD-L1 expression. PD-L1 expression appeared to be a strong predictor of progression-free survival and overall survival for durvalumab in Study 1108.
- Other between-trial differences that cannot be accounted for in the MAIC include differences in trial design (Phase 1/2 non-comparative versus Phase 3 randomised comparative, timing of tumour assessments), use of post-progression treatments, protocol-defined durations of treatment, duration of follow-up, and treatment beyond disease progression.
- There was a lack of comparative safety data to enable comparison of safety across the trials. The submission claim was based on the results of a naïve comparison of safety.

6.42 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.

6.43 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.44 The submission presented a cost-minimisation analysis of durvalumab every 2 weeks versus pembrolizumab every 3 weeks based on the claim of non-inferior efficacy and safety presented in Section 1.2 of the submission.

6.45 The equi-effective doses were based on the administration frequency and median duration of treatment for durvalumab and pembrolizumab reported in Study 1108 and Keynote-045, respectively. The submission claimed that the median duration of treatment was the only published estimate of treatment exposure for pembrolizumab. However, during the evaluation, alternative measures of treatment duration for pembrolizumab (mean number of administrations; mean duration of treatment) were identified in the TGA AusPAR for pembrolizumab.

6.46 The submission proposed the following equi-effective doses:

- Durvalumab 10 mg/kg administered every 2 weeks for a median of 12.00 weeks is equi-effective to pembrolizumab 200 mg administered every 3 weeks for a median of 15.21 weeks.

6.47 Based on the median duration of treatment reported for pembrolizumab in the AusPAR (3.45 months), the median duration of treatment for pembrolizumab in Keynote-045 was 15.00 weeks.

6.48 The cost-minimisation analysis includes the costs associated with the administration of durvalumab (every 2 weeks) and pembrolizumab (every 3 weeks). The administration costs were based on MBS item 13915 (cytotoxic chemotherapy, administration of, either by intravenous push technique or by intravenous infusion of not more than 1 hour's duration).

6.49 The following issues are likely to impact the cost-minimisation:

- Due to the relatively short duration of progression-free survival in the studies, the median (and mean) durations of treatment are likely to have been affected by the protocol-determined timing of radiological assessments. Scheduling of the second radiological tumour assessment at 12 weeks in Study 1108 (compared to 15 weeks in Keynote-045) is likely to have contributed to the shorter median duration of treatment reported for durvalumab.
- Differences in the maximum treatment durations between the studies; in Study 1108, patients received treatment with durvalumab for a maximum of 54 weeks whereas patients received treatment with pembrolizumab for up to 2 years in Keynote-045.

- The cost-minimisation analysis was based on a median duration of follow-up of 16.8 months (range: 0.4-37.7 months) for durvalumab, and a median duration of follow-up of 14.1 months for pembrolizumab (based on the results of the second interim analysis). Additional follow-up is likely to affect treatment duration parameters (mean duration of treatment; mean treatment administrations).
- The proposed PBS restriction requires continuing patients to have stable or responding disease. However, patients in the clinical studies who experienced disease progression could continue treatment beyond progression at the discretion of the investigator.
- Dosing for pembrolizumab is based on a fixed dose of 200 mg, whereas durvalumab treatment is a weight-based dose (10 mg/kg). The cost-minimisation analysis assumes a weight of 76.6kg based on the average patient weight in Study 1108, which would require one 500 mg and three 120 mg ampoules of durvalumab per dose (sufficient for patients weighing up to 86 kg).
- The July 2018 pembrolizumab resubmission proposed a risk sharing arrangement (RSA) in the form of expenditure caps, and a rebate for a percentage of treatment costs above the annual caps.
- The proposed dose relativity does not account for potential differences in dose intensity between durvalumab and pembrolizumab. There were no available measures of dose intensity for pembrolizumab.
- The PBAC noted that the large number treatment discontinuations in the early stages of the trials impacted on the median durations of treatment.

6.50 The PBAC agreed with the ESC that the claim of non-inferiority was not well supported by the evidence which made the calculation of equi-effective doses problematic. The PBAC also considered that the clinical data presented did not provide a good basis for calculation of equi-effective doses due to differences between the trials and immaturity of the data. The ESC considered that there was no convincing evidence that the treatment duration in practice would be likely to differ between durvalumab and pembrolizumab. Therefore based on the evidence provided, it would be inappropriate to assume different treatment durations in the calculation of equi-effective doses.

6.51 The submission did not present a cost-minimised price for durvalumab based on the published price of pembrolizumab. The proposed published prices for durvalumab included in the submission (AEMP of [redacted] per 500 mg/mL vial; AEMP of $[redacted] per 120 mg/mL vial) were the same as the requested price for the durvalumab NSCLC indication. A cost-minimised price for durvalumab based on the published price of pembrolizumab was calculated during the evaluation using the equi-effective doses proposed in the submission. The PSCR requested that the cost-

minimisation analysis be used to derive the net (effective) vial prices but that published durvalumab vial prices be the same as for durvalumab for NSCLC.

6.52 A cost-minimised price was also derived using the mean number of drug administrations. However, the comparison based on mean drug administrations had many of the same limitations as the comparison based on medians. The PSCR (p4) expressed a preference for this approach over the use of median durations. The ESC noted that this approach resulted in a slightly higher price for durvalumab. The PBAC agreed with the ESC that neither approach was well supported by the evidence as the claim of non-inferiority was not supported and treatment duration in both trials was influenced by the trial design and duration of follow-up.

6.53 Table 10 presents the results of the cost-minimisation analyses conducted during the evaluation, based on the published price of pembrolizumab.

Table 10: Cost-minimised price of durvalumab

	Cost-minimisation based on median treatment duration[1]	Cost-minimisation based on mean administrations[2]
Pembrolizumab AEMP per 100 mg vial	$4,460.00	$4,460.00
Pembrolizumab administration costs	$325.28	$573.09
Total cost per treatment course	$44,929.26	$79,158.29
Durvalumab administration costs	$	$
Derived durvalumab price per mg	$	$
Durvalumab AEMP per 500 mg vial	$	$
Durvalumab AEMP per 120 mg vial	$	$

Source: Constructed during the evaluation with reference to '2019_03_05 Imfinzi (durvalumab) 2L UC Section 4 model FINAL' excel workbook.

Abbreviations: AEMP, approved ex-manufacturer price.

[1] Calculated using median treatment duration of 15.00 weeks for pembrolizumab and 12.00 weeks for durvalumab. Median duration of treatment reported in the pembrolizumab AusPAR (3.45 months), converted from months to weeks assuming 365.25 days per year.

[2] Calculated using mean administrations of 8.81 for pembrolizumab and 10.05 for durvalumab.

Drug cost/patient/course: $

6.54 The drug cost per patient for durvalumab and pembrolizumab is summarised in Table 11.

Table 11: Drug cost per patient for durvalumab and pembrolizumab

	Durvalumab	Pembrolizumab
Treatment regimen	10 mg/kg every 2 weeks	200 mg every 3 weeks
Median duration of treatment	12 weeks	15 weeks[1]
Cost/patient/dose	$[2]	$9,055.06[3]
Cost/patient/course	$	$45,275

Source: Section 3B.4.1, p.96 of the submission.

[1] Calculated using the median duration of treatment reported in the pembrolizumab AusPAR (3.45 months), converted from months to weeks assuming 365.25 days per year.

[2] Based on an average patient weight of 76.6 kg, requiring 1×500 mg vial and 3×120 mg vials every 2 weeks and accounting for a split of 69.2% for private hospitals and 30.8% for public hospitals

[3] Based on 2×100 mg vials per patient every 3 weeks and accounting for a split of 69.2% for private hospitals and 30.8% for public hospitals

Estimated PBS usage & financial implications

6.55 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the eligible patient population with locally advanced or metastatic urothelial cancer after platinum-based therapy.

6.56 The estimated utilisation and budget impact estimates are summarised in Table 12. These budget impact estimates are based on the published prices for both durvalumab and pembrolizumab, and therefore may not reflect the effective budget impact.

Table 12: Estimated utilisation and cost (published prices) of durvalumab to the PBS/RPBS in the first six years of listing for locally advanced or metastatic urothelial cancer after platinum-based therapy

	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
Patients with locally advanced or metastatic urothelial cancer	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with prior platinum based therapy (54%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients eligible for PD-1 treatment (81%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible patients treated with PD-1/PD-L1 inhibitors (100%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Durvalumab uptake rate	20%	30%	40%	50%	50%	50%
Durvalumab patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Durvalumab scripts (6.00 / patient)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Published cost of durvalumab scripts ($[redacted] / script) less co-pay	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Substituted pembrolizumab scripts (5.07 / patient)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Published cost of pembrolizumab scripts ($9,055 / script) less co-pay	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to PBS/RPBS	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**
Additional cost for durvalumab administration ($65.05 / patient)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to government	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**

Source: Tables 4.2.1, p.101; Table 4.5.3, p.125 of the submission; 2019_03_05 Imfinzi (durvalumab) 2L UC Section 4 Model Excel workbook.
Abbreviations: MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

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

6.57 The net saving from listing durvalumab on the PBS/RPBS at the proposed published price for the treatment of patients with locally advanced or metastatic urothelial cancer after platinum-based therapy was estimated to be up to less than $10 million

in the sixth year of listing. The estimated cumulative net saving over six years was less than $10 million. The proposed listing was associated with a small additional cost to the MBS as durvalumab requires more visits for drug administration compared to pembrolizumab (this has minimal impact on estimated savings).

6.58 The utilisation/financial estimates were uncertain due to the following issues:

- The size of the eligible patient population is unclear due to misinterpretation of data from the BLADDA registry and assumptions of similar downstream pathways between recurrent disease and metastatic disease. Additionally, the eligible population estimates did not account for patients undergoing chemoradiotherapy.
- The submission assumed that all patients eligible for PD-1/PD-L1 inhibitors would be treated with a PD-1/PD-L1 inhibitor. This assumption may not be appropriate as pembrolizumab was only recently subsidised on the PBS for urothelial cancer (March 2019) and therefore the PD-1/PD-L1 market is immature.
- The submission assumed that durvalumab would capture 50% of the PD-1/PD-L1 market. This assumption was inadequately justified and may overestimate uptake in clinical practice given that pembrolizumab remains the preferred treatment option in guidelines (due to its stronger evidence base), pembrolizumab requires less frequent infusion, pembrolizumab has a longer subsidised duration of treatment, pembrolizumab has a first-to-market advantage and additional PD-1/PD-L1 inhibitors are likely to enter the market in the next six years.
- The submission estimated treatment durations based on the median exposure for Study 1108 and Keynote-045 due to the lack of other available data. However, given the large number of early discontinuations in Study 1108 and Keynote-045, and the lack of available dose intensity measures for pembrolizumab, it may be more appropriate to derive the budget impact estimates using the mean number of administrations, though both approaches are problematic.
- Under the proposed restrictions there may be growth in the PD-1/PD-L1 market due to sequential use of pembrolizumab and durvalumab.

Quality Use of Medicines

6.59 The submission stated that the sponsor is working with patient support groups to improve resourcing for patient support services and is working with healthcare professionals to provide high quality information resources for their urothelial cancer patients.

6.60 There was a large numerical difference in overall survival between patients with

low/negative PD-L1 expression and those with high PD-L1 expression (based on the Ventana PD-L1 SP263 assay). It is unclear whether PD-L1 expression testing should be used to guide selection of patients for durvalumab treatment. PD-L1 testing is not currently reimbursed through the MBS for this indication and the ESC noted that developing a standard assay for PD-L1 is difficult.

Financial Management – Risk Sharing Arrangements

6.61 The submission noted that the PBS listing of pembrolizumab is subject to a special pricing arrangement and stated that durvalumab would also require a special pricing arrangement. The submission also stated that the sponsor is willing to consider a risk sharing arrangement to reduce the uncertainty associated with budget impact estimates (the submission noted that pembrolizumab may already be subject to a risk sharing arrangement).

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

7 PBAC Outcome

7.1 The PBAC did not recommend durvalumab for the treatment of patients with locally advanced or metastatic urothelial cancer who have disease progression during or following platinum-based chemotherapy. The PBAC considered that the clinical need for durvalumab was limited, given the availability of pembrolizumab, which has a more robust evidence base. The PBAC considered the data presented did not adequately establish non-inferiority between durvalumab and the nominated comparator, pembrolizumab.

7.2 The PBAC noted that pembrolizumab is the preferred treatment post-chemotherapy for patients with urothelial cancer in the version 3.2019 NCCN guidelines for bladder cancer, and considered that there was limited clinical need for another second-line PD-L1 inhibitor in patients with urothelial cancer, particularly given the less robust evidence base for durvalumab, and its requirement for more frequent infusions. [redacted] and that the UK National Institute for Health and Care Excellence (NICE) had suspended evaluation of durvalumab because the sponsor advised they will not be pursuing a licencing application from the European Medicines Authority for this indication. The PBAC also noted that ongoing trials may show that there is a clinical place for durvalumab in combination with other agents or in first line treatment of patients with high PD-L1 expression status.

7.3 The PBAC considered that durvalumab should not be used following treatment with pembrolizumab and noted that flow-on restriction changes to pembrolizumab would also be necessary to prevent sequential use if durvalumab was to be listed.

7.4 The PBAC considered that pembrolizumab was the appropriate comparator.

7.5 The PBAC noted that the submission was based on one single-arm study of durvalumab (Study 1108), and one randomised, open-label trial of pembrolizumab versus investigator's choice of chemotherapy (Keynote-045). The PBAC considered that both studies were associated with a low level of certainty, due to the open-label nature of the studies, however the data from study 1108 provided less certainty as it was a non-comparative study. The PBAC considered that study 1108 did not provide compelling evidence that durvalumab was likely to be superior to chemotherapy in terms of overall survival in the full population.

7.6 The PBAC noted that the TGA approved durvalumab for the treatment of urothelial cancer irrespective of the PD-L1 status, but the PBAC considered that Study 1108 results indicated that PD-L1 status could be a treatment effect modifier for durvalumab, and/or a prognostic marker, as the median overall survival was numerically higher in the PD-L1 high subgroup (19.8 months; 95% CI: 9.3, not estimable) compared to the PD-L1 low/negative subgroup (4.8 months; 95% CI: 3.1, 8.1) and the proportion of patients alive at 24 months was 43.9% in the PD-L1 high subgroup compared to 14.2% in the PD-L1 low/negative group. The PBAC noted that when it considered pembrolizumab in November 2017 it "concluded that, based on results stratified by PD-L1 status, there was no strong signal to consider selecting patients based on PD-L1 expression" (Paragraph 6.13, July 2018 PSD for pembrolizumab). The PBAC noted that the Phase III RCT DANUBE trial is currently underway and would provide additional data on the impact of PD-L1 status on the efficacy of durvalumab in patients with UC.

7.7 The submission used a non-standard approach to compare durvalumab with pembrolizumab. Evidence for durvalumab versus chemotherapy was generated using an unanchored MAIC of individual patient data from Study 1108 and aggregate results for the chemotherapy arm of Keynote-045. The results of the MAIC were then compared with the results of the Keynote-045 trial in an indirect comparison using chemotherapy as the common reference. The PBAC considered that this approach was not appropriate and although the MAIC appeared to indicate that durvalumab was non-inferior to pembrolizumab, the methodological issues with this approach meant that the comparison was not reliable.

7.8 The PBAC considered that Study 1108 and Keynote-045 appeared to be reasonably matched with regard to demographic and disease characteristics, noting that, overall, patients in Study 1108 did not have a noticeably worse prognosis that those included in Keynote-045. However, the PBAC noted that both the MAIC and the indirect comparison were limited by between-trial differences that could not be accounted for such as a lack of common PD-L1 expression assay to assess PD-L1 expression status, differences in the trial design, timing of tumour assessments, use of post-progression treatments, and duration of follow-up. The PBAC considered that the unanchored MAIC and naïve (unadjusted) indirect comparison presented did not adequately support the claim of non-inferiority with pembrolizumab.

7.9 The submission claimed that durvalumab was non-inferior to pembrolizumab in terms of safety and noted the type and incidence of adverse events that were reported in the trials were similar between durvalumab and pembrolizumab. The PBAC noted that this claim was based on the results of a naïve comparison of safety as no comparative safety data was available for durvalumab. The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

7.10 The PBAC agreed with the ESC that the claim of non-inferiority was not well supported by the evidence which made the calculation of equi-effective doses problematic. The PBAC also considered that the clinical data presented did not provide a good basis for calculation of equi-effective doses due to differences between the timing of assessments, differences in the protocol-driven durations of treatment, treatment beyond progression and the overall low level of certainty in the efficacy data for durvalumab.

7.11 The PBAC considered that the utilisation estimates for durvalumab were inadequately justified. The PBAC considered that the assumed duration of treatment was uncertain due to limitations in the clinical evidence as described above. The PBAC also considered that the uptake of durvalumab was likely to be overestimated given that pembrolizumab has a more robust clinical evidence base, is already listed and has a dosing convenience advantage and because the estimates inappropriately assumed that all eligible patients will be treated with a PD-1/PD-L1 inhibitor.

7.12 The PBAC noted a recent editorial published in *Journal of Clinical Oncology*[1], which stated that "the lack of ongoing or planned RCTs to evaluate definitively the efficacy of three IO [immuno-oncology] agents in the second-line setting … represents a worrisome departure from the paradigm of evidence development and challenges the compromise inherent in accelerated drug approval".

7.13 The PBAC anticipated that it would be unlikely to recommend PBS listing of durvalumab without additional clinical data, including comparative evidence from an adequately powered randomised phase III trial demonstrating a benefit for overall survival for durvalumab over standard treatment. The PBAC noted that this may be in a different patient population or in combination with other agents.

Outcome:
Rejected

[1] Vera-Badillo et al, JCO 2019 Jul 1 doi: 10.1200/JCO.18.02257

8 Context of 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 Comments

The sponsor had no comment.