

Pembrolizumab for urothelial carcinoma: 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

October 2021

Abstract

Purpose

Analysis of the predicted versus actual utilisation of pembrolizumab 24 months following its addition to the Pharmaceutical Benefits Scheme (PBS) for the treatment of urothelial carcinoma on 1 March 2019.

Data Source / methodology

PBS dispensing data for pembrolizumab was extracted from the PBS data maintained by the Department of Health, processed by Services Australia. This data was used to establish the number of prevalent and incident patients utilising pembrolizumab for urothelial carcinoma and time on therapy.

Key Findings

- 483 prevalent patients were supplied pembrolizumab in its first year of listing, 680 prevalent patients in Year 2 and 564 prevalent patients in 2021 to the data cut-off date of 31 July 2021.
- Since its listing, the utilisation of pembrolizumab has increased steadily with up to 50 first initiating (incident) patients per month and the number of prevalent patients was continuing to increase.
- The patient numbers were substantially underestimated in the submission with a [REDACTED] number in Year 1, [REDACTED] in Year 2 and [REDACTED] so far in Year 3 of listing.
- The number of patients who are platinum therapy-ineligible is approximately 8% which is less than the disparity in the predicted versus actual utilisation.
- The PBAC stated at the November 2017 meeting that the duration of pembrolizumab use may be longer than estimated. However the Kaplan-Meier analysis of treatment duration, both with breaks and without breaks, indicates that the median time on treatment for patients utilising pembrolizumab is 110 days or 101 days, respectively. This suggests that the duration of pembrolizumab treatment from the submission is overestimated.

- The number of prescriptions were overestimated where actual numbers are [REDACTED] in Years 1 and 3 despite greater patient numbers than predicted. In Year 2 there was a [REDACTED] patient number than predicted however this resulted in only a [REDACTED] prescription count.

Purpose of analysis

Analysis of the predicted versus actual utilisation of pembrolizumab 24 months following its addition to the Pharmaceutical Benefits Scheme (PBS) for the treatment of urothelial carcinoma on 1 March 2019.

Background

Clinical situation

Urothelial carcinoma is the most common type of bladder cancer and occurs in approximately 80-90% of cases.¹ The Australian Institute of Health and Welfare (AIHW) estimated the incidence of bladder cancer in Australia in 2017 was 2,777 persons, equivalent to approximately 9.4 cases per 100,000 persons, and a 5-year relative survival rate of 55.3% from 2013 to 2017.² The major risk factor for urothelial carcinoma is tobacco smoking followed by pelvic radiation, genetic predisposition, and occupational exposure.³

Currently platinum based therapies using either cisplatin or carboplatin are preferred first line treatments followed by immunotherapy with pembrolizumab. There has also been research into using immunotherapies such as atezolizumab and pembrolizumab in the first-line setting in those patients who are ineligible for platinum based therapies.³

Immunotherapy in this setting is not currently approved under the Pharmaceutical Benefits Scheme (PBS), however the Pharmaceutical Benefits Advisory Committee (PBAC) in March 2021 recommended avelumab for maintenance therapy following first line treatment on a platinum based regimen.⁴

Pharmacology

¹ Understanding Bladder Cancer, Cancer Council Australia © 2020. Last medical review of source booklet: February 2020. Australian Institute of Health and Welfare. ACIM (Australian Cancer Incidence and Mortality) Books. Canberra: AIHW.

² The Australian Institute for Health and Welfare. Cancer summary data visualisation.

<<https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation>> Last Accessed 19/8/21.

³ Kim TJ, Cho KS, Koo KC. Current Status and Future Perspectives of Immunotherapy for Locally Advanced or Metastatic Urothelial Carcinoma: A Comprehensive Review. *Cancers (Basel)*. 2020;12(1):192. Published 2020 Jan 13. doi:10.3390/cancers12010192

⁴ Pharmaceutical Benefits Advisory Committee. Public Summary Document: Avelumab (Urothelial carcinoma). March 2021. Available at < <https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2021-03/avelumab-urothelial-carcinoma-solution-concentrate>>

Pembrolizumab is an antibody that binds to the PD-1 immune-checkpoint receptor. By inhibiting the PD-1 receptor pembrolizumab is able to reactivate tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates anti-tumour immunity.

Therapeutic Goods Administration (TGA) approved indications

Pembrolizumab is approved for multiple therapeutic indications. The details of these indications can be found in [the TGA \(Product Information\)](#). Briefly, pembrolizumab is approved for use in melanoma, non-small cell lung cancer, squamous cell head and neck cancer, classical Hodgkin lymphoma, primary mediastinal B-cell lymphoma, endometrial carcinoma, and urothelial carcinoma.

In urothelial carcinoma pembrolizumab is indicated as monotherapy for locally advanced or metastatic PD-L1 expressing urothelial carcinoma in patients who are not eligible for cisplatin-containing therapy, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status or failure of prior platinum-containing therapy.

Pembrolizumab is also indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in-situ with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy.

Dosage and administration

The recommended dose of pembrolizumab is 200 mg every 3 weeks administered as an intravenous infusion over 30 minutes.

Treatment should continue until disease progression or unacceptable toxicity with the sponsor recommending to withhold or discontinue treatment to manage adverse reactions rather than dose modifications. Patients without disease progression in urothelial carcinoma can be treated for up to 24 months

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA \(Product Information\)](#) and [the TGA \(Consumer Medicines Information\)](#).

PBS listing details (as at 30 August 2021)

Table 1: PBS listing of pembrolizumab for urothelial carcinoma

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
11632F Private	pembrolizumab 100 mg/4 mL injection, 4 mL vial	200mg	6	\$7881.87	KEYTRUDA Merck Sharp & Dohme (Australia) Pty Ltd
11646Y Public	pembrolizumab 100 mg/4 mL injection, 4 mL vial	200mg	6	\$7733.78	

Source: the [PBS website](#). Note: Special Pricing Arrangements apply.

Restriction

Authority Required (STREAMLINED) listing for locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer

Clinical criteria:

The treatment must be the sole PBS-subsidised therapy for this condition,

AND

The condition must have progressed on or after prior platinum based chemotherapy; OR
The condition must have progressed on or within 12 months of completion of adjuvant platinum-containing chemotherapy following cystectomy for localised muscle-invasive urothelial cancer; OR

The condition must have progressed on or within 12 months of completion of neoadjuvant platinum-containing chemotherapy prior to cystectomy for localised muscle-invasive urothelial cancer,

AND

Patient must have a WHO performance status of 2 or less,

AND

The treatment must not exceed a total of 7 doses under this restriction.

Note

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.

For details of the current PBS listing refer to the [PBS website](#).

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

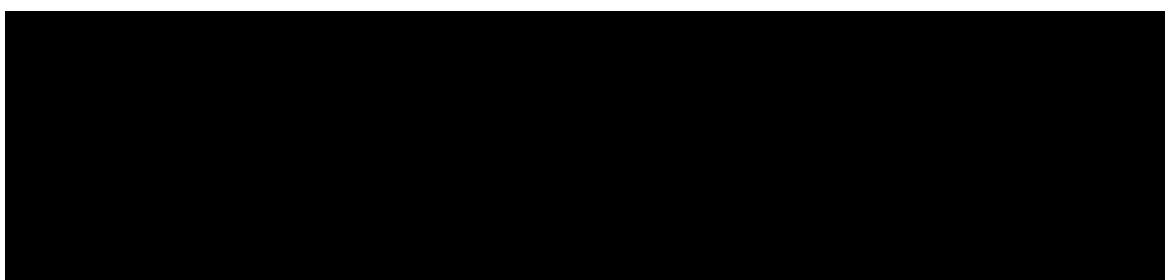
The sponsor made its first submission for pembrolizumab for locally advanced or metastatic urothelial cancer to the PBAC in November 2018. The submission used an epidemiological approach for the estimation of the total number of patients likely to be diagnosed with locally advanced or metastatic urothelial carcinoma. This approach was based on bladder cancer mortality data available from the Australian Institute of Health and Welfare (AIHW). PBAC considered the financial impact of pembrolizumab was highly uncertain. PBAC considered that the patient numbers were likely underestimated and there was a risk of

use outside the requested restriction into first-line treatment for cisplatin-ineligible patients. PBAC also considered that the duration of pembrolizumab use may be longer than estimated as some patients in the trial KN045 were treated beyond disease progression, and some were allowed to access an additional 12 months of treatment if they progressed after 24 months of pembrolizumab.

For further details refer to the [Public Summary Document](#) from the November 2017 PBAC meeting.

The sponsor made a resubmission in July 2018 and retained the epidemiological approach from the previous submission however noted the reduced effective price and proposed Risk-Sharing Arrangement.

Commercial-in-confidence



End Commercial-in-confidence

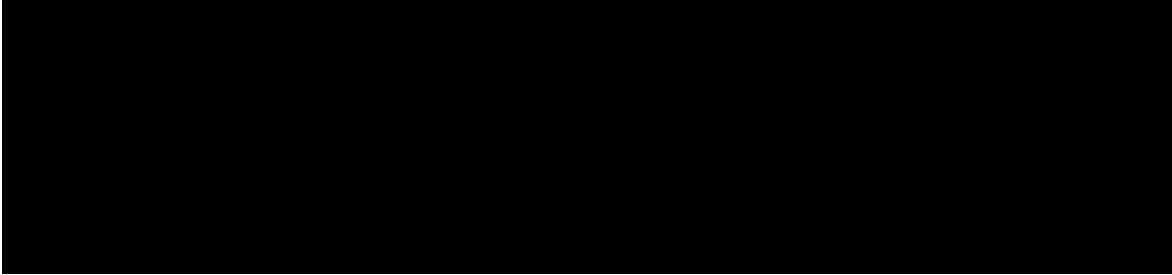
For further details refer to the [Public Summary Document](#) from the July 2018 PBAC meeting.

Approach taken to estimate utilisation

The sponsor used an epidemiological approach to estimate utilisation of pembrolizumab for locally advanced or metastatic urothelial carcinoma. This approach was based on bladder cancer mortality data available from the Australian Institute of Health and Welfare (AIHW). This was used to establish the baseline incidence of bladder cancer in Australia and it was estimated that 90% of these cases would be urothelial in nature. This proportion was obtained from the Cancer Council of Australia. The proportion of these urothelial carcinomas that would be locally advanced or metastatic at diagnosis was obtained from Tracey et al (2014) where 69.57% of patients who died of bladder cancer having previously undergone cystectomy were assessed as having regional, distant or unknown disease staging.⁵

Commercial-in-confidence

⁵ Tracey, E., Watt, H., Currow, D., Young, J. and Armstrong, B. (2014), Investigation of poorer bladder cancer survival in women. BJU Int, 113: 437-448. <https://doi.org/10.1111/bju.12496>



End Commercial-in-confidence

Methods

Data from 1 March 2019 to 31 July 2021 were extracted from the PBS data maintained by Department of Health, processed by Services Australia on or before 10 August 2021 for the PBS item codes 11632F and 11646Y which corresponds to the treatment of locally advanced or metastatic urothelial carcinoma. The data was extracted based on the date of supply.

PBS prescription data were used to determine the number of prescriptions supplied and the PBS expenditure. These data were also used to count the number of patients, both incident (new to treatment) and prevalent (number treated in each time period, i.e. year or quarter).

A breakdown of incident patients by age and gender from date of 1 March 2019 until 31 July 2021 was undertaken.

The Kaplan-Meier method was used to determine the length of treatment for patients on pembrolizumab. A break in treatment was defined as a gap of more than three times the median time between supplies. A patient was deemed to be continuing on treatment (classified as censored in the Kaplan-Meier analysis) at the end of the data period (i.e. the end of July 2021) if their last prescription was within three times the median time to resupply of this end date. Otherwise the patient was deemed to have ceased treatment with the treatment coverage end date being the supply date of their last prescription plus a median time to resupply. If a patient's supply was after a gap of more than three times the median time to resupply, then the patient was deemed to have been re-treated.

The PBS restriction for pembrolizumab states that it is to be used for second-line therapy on or after prior platinum-based therapy. Patients initiating onto pembrolizumab were then also assessed for prior use of carboplatin or cisplatin. A time between therapies was also established by comparing the difference between the starting date of pembrolizumab therapy and the last dispensing date of their prior episode of treatment.

The estimates model used to present the estimated cost to the PBS/RPBS was a model that was agreed upon by both the Department of Health and the Sponsor. Refer to the 'Approach to estimate utilisation' section for further details on the development of the financial estimates.

Results

Analysis of drug utilisation

Overall utilisation

Pembrolizumab was listed on the PBS on 1 March 2019 for locally advanced or metastatic urothelial carcinoma with 483 prevalent patients supplied this drug in its first year of listing (Table 2). Utilisation increased in its second year with 680 prevalent patients and this trend is likely to continue with 564 prevalent patients in 2021 to the data cut-off date of 31 July 2021.

Table 2: Summary of overall utilisation of pembrolizumab since listing on the PBS on 1 March 2019 for locally advanced or metastatic urothelial carcinoma

Year	Prevalent Patients	Incident Patients	Dispensings
2019 ^a	483	483	2,392
2020	680	467	4,283
2021 ^b	564	278	2,943

^aPart-year data beginning in 1 March 2019 to 31 December 2019

^bPart-year data for the period 1 January 2021 to 31 July 2021

Since its listing, the utilisation of pembrolizumab has increased steadily with up to 50 first initiating (incident) patients per month and the number of prevalent patients is increasing (Figure 1). Figure 2 shows the breakdown of dispensed prescriptions by authority type and illustrates a slowly increasing number of Streamlined Authority Initial prescriptions while Streamlined Authority Continuing prescriptions have plateaued.

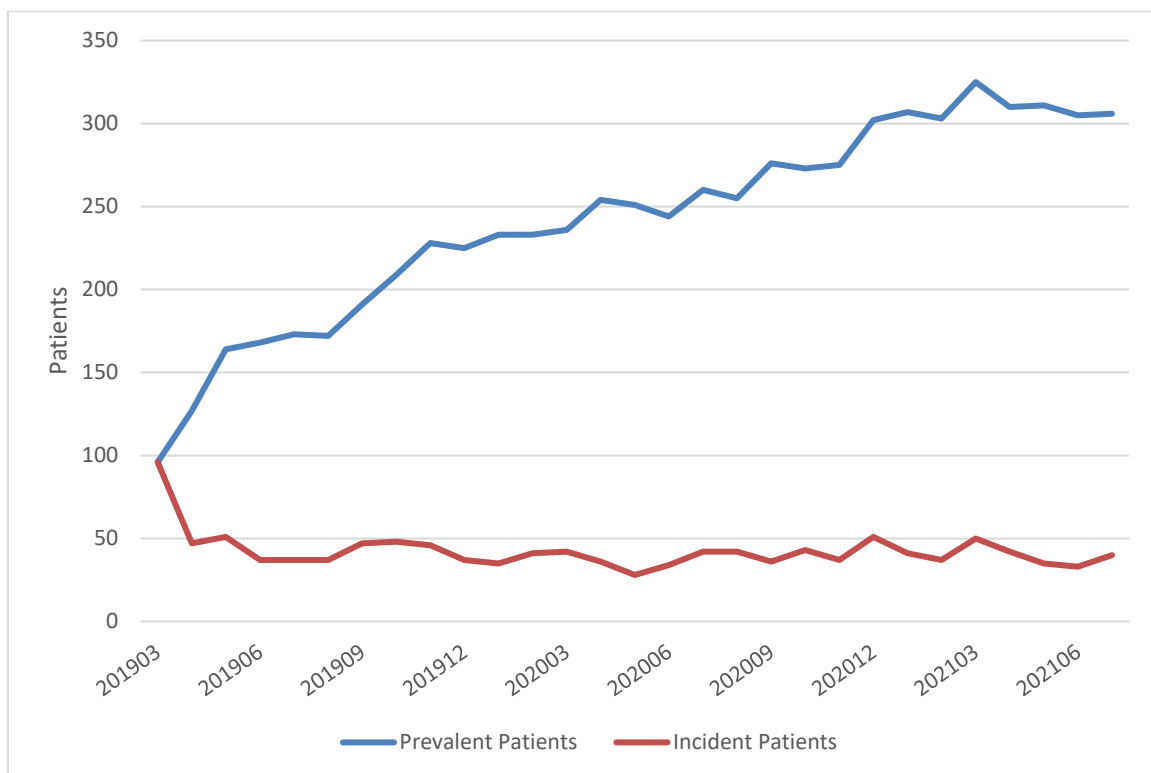


Figure 1: Number of incident and prevalent patients supplied pembrolizumab since listing on the PBS in March 2019

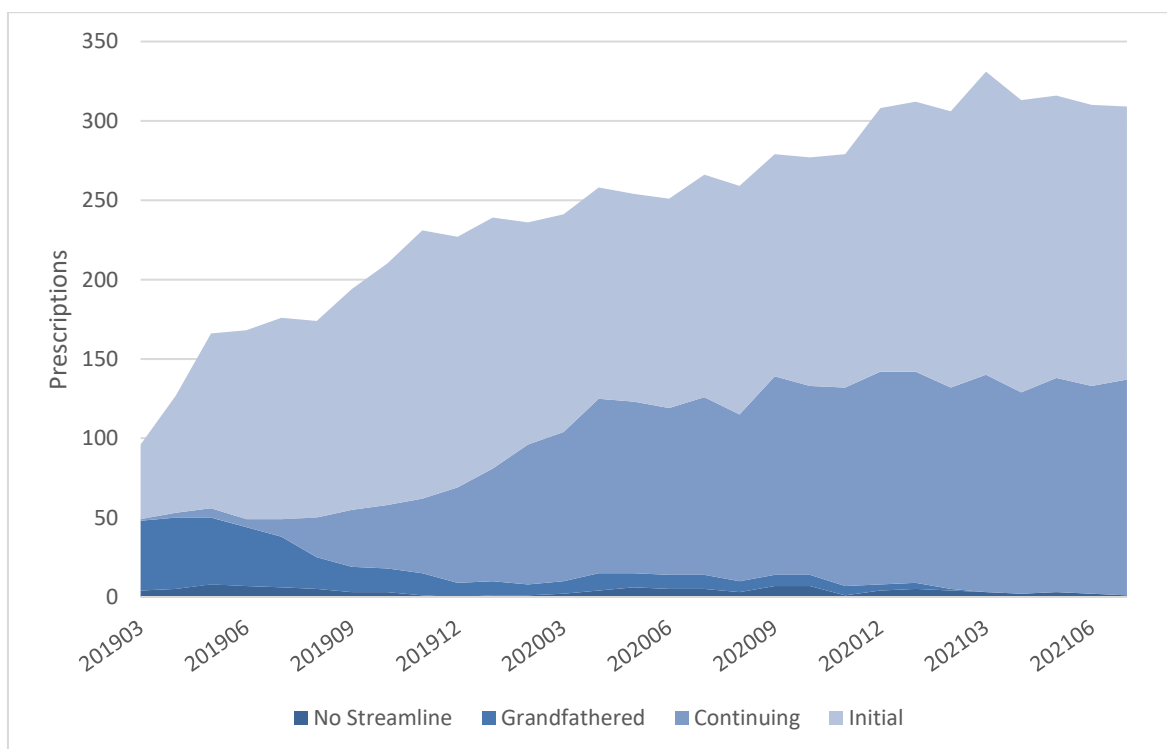


Figure 2: Pembrolizumab prescriptions by application type since listing on the PBS in March 2019

Patient level analysis

The breakdown of pembrolizumab first initiators from 1 March 2019 to 31 July 2021 by age and gender can be seen in Figure 3. The boxplot (Figure 3) indicates that the interquartile range of patients, whether female or male, are beginning pembrolizumab treatment between 65 to 80 years with a median at 73 years. The number of males undergoing treatment with pembrolizumab for locally advanced or metastatic urothelial carcinoma is almost three-fold greater than the number of females with a total of 898 males and 330 females since listing in March 2019.

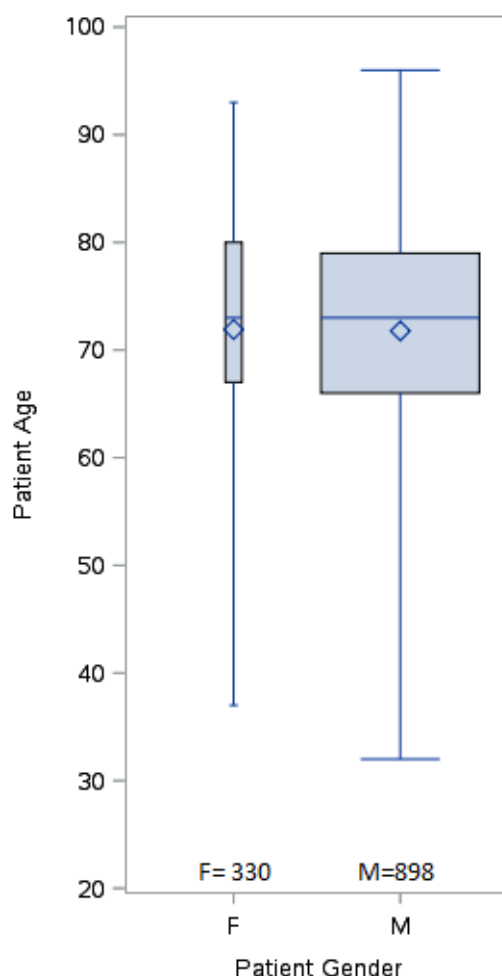


Figure 3: Boxplot of the age of first initiators on to pembrolizumab since 1 March 2019 grouped by gender

Pembrolizumab is listed for the second-line treatment of locally advanced or metastatic urothelial carcinoma after prior platinum-based therapy. The PBS history of those who initiated on to pembrolizumab for this indication was examined for records of also being supplied platinum therapy. Figure 4 illustrates that the majority of incident patients had undergone prior platinum-based therapy. However approximately 8% of patients since listing had not been supplied prior platinum-based therapy through the PBS.

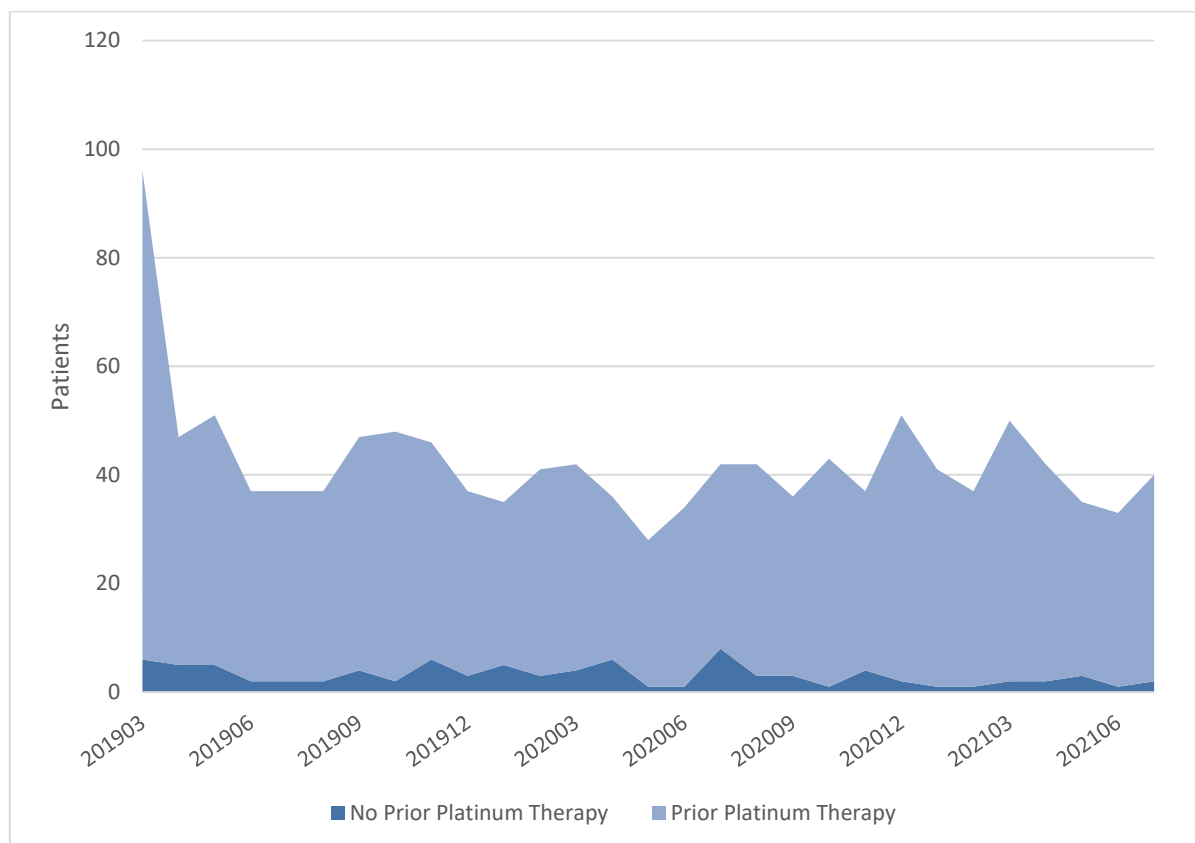


Figure 4: History of prior PBS supplied platinum therapy in incident patients of pembrolizumab for locally advanced or metastatic urothelial carcinoma since listing in 1 March 2019

The difference in time between when a patient ceased their first episode of treatment, which was assumed to be first line treatment for urothelial carcinoma, and when they began pembrolizumab as subsequent treatment was also examined (Figure 5). The results from this analysis indicate that approximately 75% of patients move on to treatment with pembrolizumab within 15 months of prior therapy and that the median time between treatment was 7 months in the case of carboplatin and 9 months with cisplatin. The results of this analysis are positively skewed however with the upper quartile range extending to 100 months.

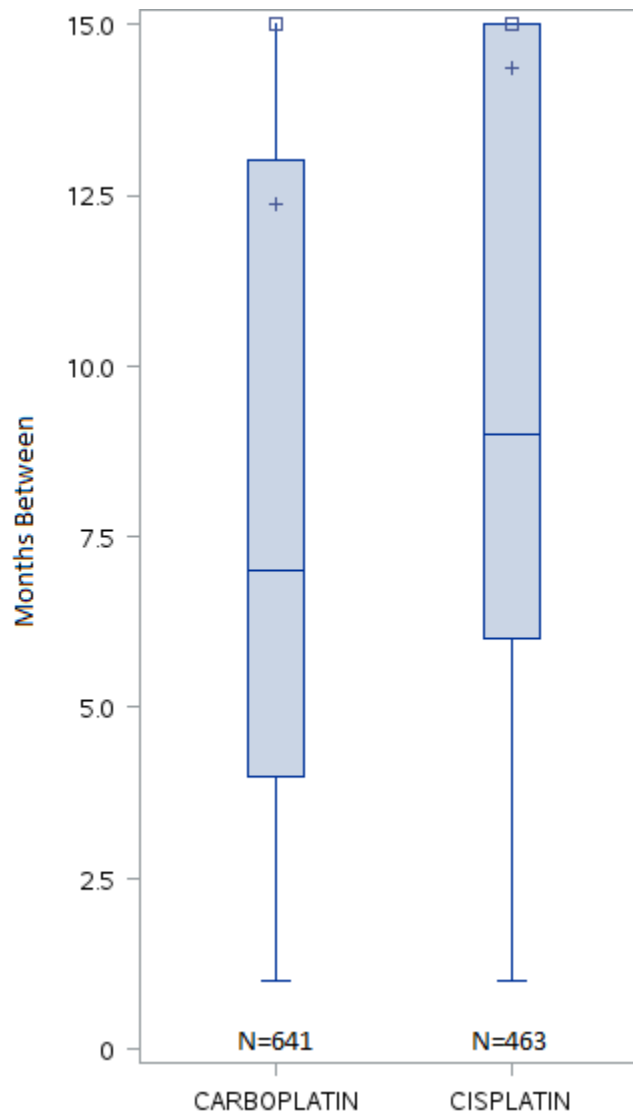


Figure 5: Months between assumed first-line treatment with platinum therapy and second-line treatment with pembrolizumab for urothelial carcinoma

Time on treatment

A Kaplan-Meier analysis was done to estimate the time on treatment for patients utilising pembrolizumab. A patient was deemed to be continuing treatment (classified as censored in the Kaplan-Meier analysis) at the end of the data period (i.e. the end of July 2021) if their last prescription was within three times the median time to resupply of this end date. The median time to resupply was 21 days resulting in a 63 day interval. The patient was deemed to have ceased treatment with the treatment coverage end date being the supply date of their last prescription plus a median time to resupply. This results in a Kaplan-Meier analysis where patients who have treatment breaks are included. Figure 6 shows this analysis where 30% of patients were censored and the median time on treatment for the remaining 863 patients was 110 days (97-126 days 95% CI).

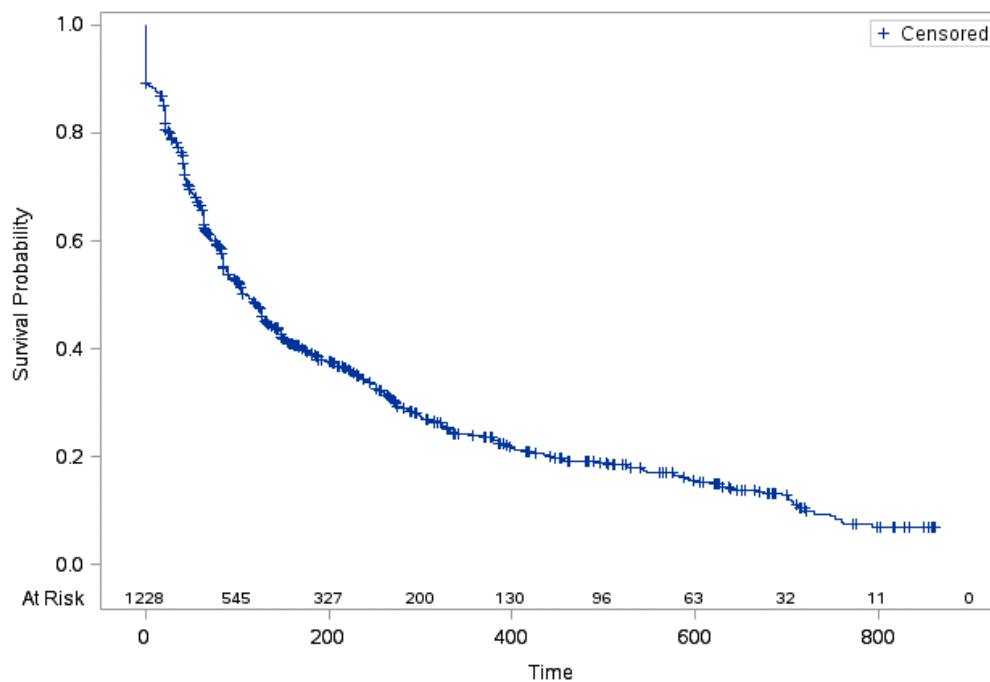


Figure 6: Kaplan-Meier analysis of the time on treatment of patients supplied pembrolizumab including treatment breaks

If a patient's supply was after a gap of more than three times the median time to resupply, then the patient was deemed to have been re-treated. Figure 7 represents this analysis for each patient's first episode of treatment. The median time on treatment in Figure 7 is 101 days (85-112 days 95% CI) for 893 patients where 27% were censored.

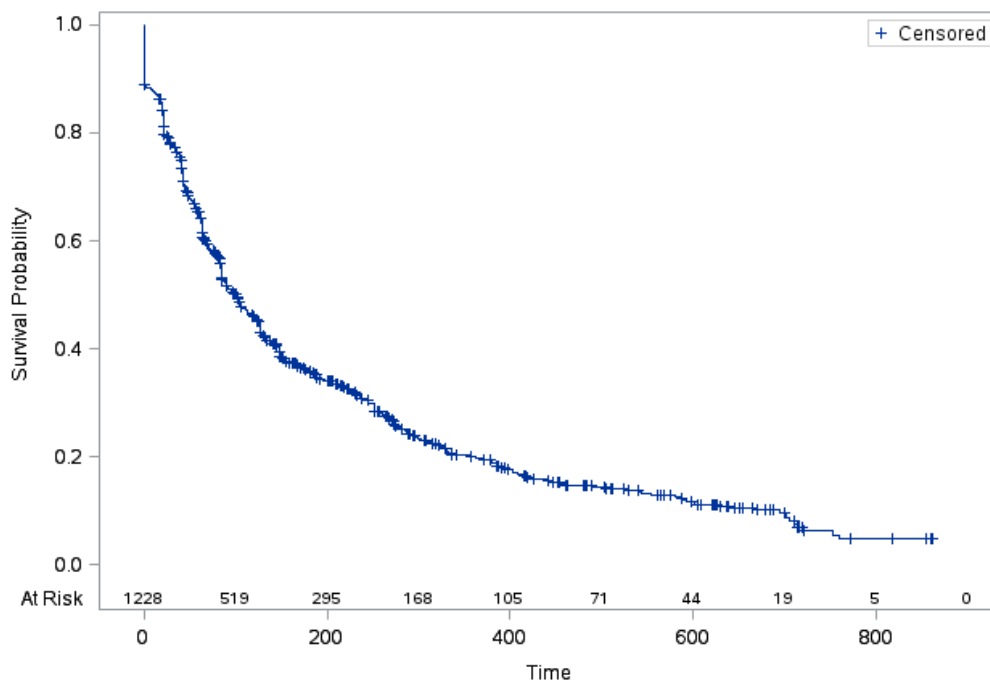


Figure 7: Kaplan-Meier analysis of the time on treatment of first episode of therapy in those supplied pembrolizumab (excludes treatment breaks)

Analysis of actual versus predicted utilisation

Table 3 presents a comparison of the predicted versus actual utilisation and expenditure of pembrolizumab for locally advanced or urothelial carcinoma since listing in March 2019. In the first year of listing the number of initiating patients was 483 which is [REDACTED] than what was predicted. The number of patients in Year 2 and Year 3 are also [REDACTED] than predicted at [REDACTED] and [REDACTED] respectively. The number of prescriptions dispensed in Year 1 and in Year 3 (year-to-date of 31 July 2021) are less than what was predicted however in Year 2 there was a slight increase. The cost to the PBS/RPBS mirror the amount of prescriptions that were dispensed in the respective years where Year 1 was 23% less than predicted, a slight increase in Year 2 and Year 3 with part-year data was less than predicted.

Table 3: Actual versus predicted utilisation and cost to the PBS/RPBS

Pembrolizumab listing years		Year 1	Year 2	Year 3
		January 2019-December 2019 ^a	January 2020 - December 2021	January 2021-December 2021 ^b
Patients	Predicted	[REDACTED]	[REDACTED]	[REDACTED]
	Actual	483	680	564
	Difference	[REDACTED]	[REDACTED]	[REDACTED]
Prescriptions	Predicted	[REDACTED]	[REDACTED]	[REDACTED]
	Actual	2,392	4,283	2,942
	Difference	[REDACTED]	[REDACTED]	[REDACTED]
Net Cost PBS/RPBS	Predicted	[REDACTED]	[REDACTED]	[REDACTED]
	Actual	\$21,834,210	\$39,095,286	\$26,854,618
	Difference	[REDACTED]	[REDACTED]	[REDACTED]

^aPart-year data beginning in 1 March 2019 to 31 December 2019

^bPart-year data for the period 1 January 2021 to 31 July 2021

Note: Predicted figures represent full-year values and have not been adjusted for any part-years.

DUSC consideration

DUSC noted the predicted utilisation of pembrolizumab for locally advanced or metastatic urothelial carcinoma was underestimated with regards to the number of patients treated. However, the dispensing and cost to the PBS/RPBS was overestimated.

DUSC noted that at the November 2017 meeting, PBAC considered that the patient numbers presented in the pembrolizumab submission were likely underestimated. This analysis confirms that

the patient numbers were underestimated in the submission with a [REDACTED] greater patient number in Year 1, [REDACTED] greater in Year 2 and [REDACTED] greater in Year 3 (based on part-year figures) of listing. DUSC noted that the number of patients who may be platinum therapy-ineligible is approximately 8% which is less than the disparity in the predicted versus actual utilisation. DUSC noted that the Pre-Sub-Committee Response (PSCR) from the sponsor who suggested that patient numbers would have been accurately estimated if AIHW mortality data for all bladder cancer patients was used in the estimates as 'coding of cause of death in the AIHW mortality data reflects the underlying cause...' (PSCR, p4). The PSCR noted (p3) that the application of a [REDACTED] reduction in AIHW data based on Tracey et al, 2014 as suggested by the PBAC unreasonably reduced the size of the eligible patient pool. DUSC did not agree with the PSCR and noted that AIHW mortality data for bladder cancer would include non-muscle invasive bladder cancer patients who would die with the disease and not from the disease.

DUSC noted that the PBAC (November 2017) acknowledged that there was a risk of use outside the requested restriction into first-line treatment for cisplatin-ineligible patients. The analysis of prior PBS subsidised platinum therapy in patients who went on to access pembrolizumab shows that potential use in first-line is low and overall usage is consistent with the current restriction. DUSC suggested investigating how long patients were taking platinum-based therapies as that information could also be used to inform estimates.

DUSC noted that 75% of patients taking platinum-based therapy who move on to pembrolizumab do so within 15 months of ceasing treatment with a median time between treatment of 7 months for carboplatin and 9 months for cisplatin. DUSC suggested that there may be a correlation between time on platinum-based therapy and time between treatments. DUSC suggested that further investigation may be useful to help clinicians and also assess inappropriate use of pembrolizumab.

DUSC noted that the PBAC (November 2017) considered that the duration of pembrolizumab use may be longer than estimated. PBAC noted some patients in the trial KN045 were treated beyond disease progression, and some were allowed to access an additional 12 months of treatment if they progressed after 24 months of pembrolizumab. In the July 2018 resubmission the sponsor increased the treatment duration estimation from [REDACTED] cycles to [REDACTED] cycles of pembrolizumab. DUSC noted the Kaplan-Meier analysis both with breaks and without breaks indicates that the median time on treatment for patients utilising pembrolizumab is 110 days or 101 days respectively. DUSC noted that this suggests that the duration of pembrolizumab treatment in practice was less than estimated by the submission. DUSC noted that the PSCR (p2) suggests that mean time on treatment is a more appropriate measure of treatment duration as the data used by DUSC suggests an estimated mean time on treatment of 7.37 months which is consistent with trial data. DUSC did not agree with the PSCR and noted that the shorter median time on treatment likely reflects the median age on treatment in practice being 73 as opposed to 67 and 65 years old in the pembrolizumab and chemotherapy arms respectively of KEYNOTE-045. DUSC noted that this represents a frailer population in practice and pembrolizumab would be a more favourable alternative to chemotherapy, especially during the COVID-19 pandemic.

DUSC noted that prescription numbers were overestimated in the submission where actual numbers are [REDACTED] less in Years 1 and 3 despite greater patient numbers than predicted and noting that the actual prescription numbers in Year 3 represent part year data until 31 July 2021. DUSC noted that in Year 2 there was a [REDACTED] higher patient number than predicted however this resulted in only a [REDACTED] greater prescription count. DUSC acknowledged the PSCR (p4) which noted that increased treatment of eligible patients can be attributed to the COVID pandemic as the recommendations for treating metastatic urothelial cancer patients in Australia changed to

“consider single agent immunotherapy in preference to chemotherapy given lower risk toxicity”. DUSC agreed with the PSCR, however noted the possibility that an increase in use may also be due to inappropriate ‘early’ use of pembrolizumab in those patients who have used a short course of chemotherapy which is not consistent with the restriction and that further investigation may be needed.

DUSC actions

DUSC requested that the report be provided to the PBAC for consideration.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors’ comments

The DUSC has considered that the overall usage of Pembrolizumab is consistent with the current restriction and that the increased treatment of eligible patients can be attributed to the COVID pandemic. This highlights the importance of having mechanisms in place to rapidly review and adjust subsidisation caps in the event of unexpected environmental events (e.g. the COVID pandemic) or other new information becoming available. Direction on the updating of risk sharing agreements to reflect eligible patient numbers, given the clear DUSC analysis and the immediacy of the impact on sponsors, would be appropriate for PBAC to provide at the earliest opportunity

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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