Protocol: Estimating overall survival in people receiving PBS-listed cancer medicines in Australian clinical practice

Final Report

MI-CRE

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Medicines Intelligence CRE
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Executive Summary

The Australian Government Department of Health and Aged Care contracted the Medicines Intelligence Centre of Research Excellence (MI-CRE) to develop and test a protocol to robustly estimate overall survival (OS) in people receiving Pharmaceutical Benefits Scheme (PBS) listed medicines for the treatment of advanced solid tumour cancers. This protocol details a framework for the assessment of survival outcomes associated with PBS-listed cancer medicines and focuses on medicines indicated for the treatment of advanced solid tumour cancers (i.e., metastatic and locally advanced indications without curative intent). These medicines have been chosen as they will likely be used last-line or late in the cancer treatment algorithm, thus reducing the confounding effect on OS that may occur if a medicine was initiated earlier in the treatment pathway. Specifically, this report is divided into three parts relating to distinct activities of the overall protocol:

- Part 1: Selecting and evaluating candidate medicines
- Part 2: Assessing the feasibility of estimating OS using available data sources
- Part 3: Estimating OS using fit-for-purpose methods

Part 1: Selecting and evaluating candidate medicines

Estimating OS for people receiving specific PBS-listed cancer treatments begins by identifying and selecting candidate medicines. This process considers the amount of time a medicine has been PBS-listed; the number of people predicted to be treated with a medicine; and the wider treatment landscape of the cancer for which a medicine is indicated:

- Time of PBS listing: the medicine should be listed on the PBS for a period equal to or longer than the expected median OS reported in the pivotal clinical trial/s.
- Predicted PBS treatment population: the number of people predicted to be treated with the PBS-listed medicine should be similar to the number of people in the clinical trial population.
- Treatment landscape: the potential impact of contamination of OS estimates from other PBS-listed medicines with the same indication or listing of the same medicine for an earlier phase of treatment should be negligible. For instance, if Medicine A is listed on the PBS for first-line treatment of metastatic breast cancer but then two years later Medicine B is listed for the same indication and Medicine A moves to a second- or later-line treatment, different patient populations will receive Medicine A and any conclusions drawn from OS estimates for patients receiving Medicine A will be unreliable.

The Pharmaceutical Benefits Advisory Committee (PBAC) Public Summary Documents (PSDs) and the pivotal clinical trial publication/s contain information on the key factors to consider when determining the suitability of specific medicines and their effect on OS in the treated PBS population. The *Selection and Evaluation Worksheet* presented in Attachment B can assist in extracting relevant information from these sources.

This protocol details the evaluation of 12 PBS-listed medicines, of which six candidate medicines were selected to undergo feasibility assessment in Part 2: ipilimumab, lanreotide, olaparib, panitumumab, trastuzumab emtansine, and trifluridine-tipiracil.

Part 2: Assessing the feasibility of estimating OS using available data sources

Once relevant medicines have been evaluated and selected in Part 1, fit-for-purpose data sources must be identified to determine whether OS estimation is feasible in the candidate medicines.

To generate robust OS estimates the *minimum data required* for analysis are unit level PBS dispensing records for people treated with the PBS-listed medicine of interest, linked with fact of death (FOD) records. More complex estimation methods are possible if the *minimum data* are linked with additional datasets such as cancer notifications or hospitalisations and these will be discussed in Part 3.

This protocol details the feasibility assessment of the six candidate medicines identified in Part 1 above, using PBS dispensing records linked with FOD records (i.e., *minimum data*). Based on the feasibility assessments, four of the six medicines were deemed suitable to progress to a study estimating OS. Two medicines were not considered feasible candidates due to an insufficient proportion of observed deaths in the treated cohort. Trastuzumab emtansine for treatment of metastatic breast cancer (one of the four suitable medicines) was selected to pilot the study methods for estimating OS outlined in Part 3.

Part 3: Estimating OS using fit-for-purpose methods

Once relevant medicines have been selected (Part 1) and assessed as to the feasibility of generating OS estimates for the medicines in available data, appropriate methods are required to carry out the analyses. To identify the best methods of estimating OS in real world patients, a literature review was conducted. Two common approaches were identified to estimate OS in the peer-reviewed literature:

- All-comers analysis: estimates OS from the entire population dispensed the medicine of interest. The benefit of this approach is that it aligns with the funder-perspective in that the payer is subsidising treatment for everyone in the treated population. *All-comers analysis* is also feasible when minimum data are available but can also be undertaken with enhanced data collections.

- Trial emulation: estimates OS by only including patients treated in clinical practice who have characteristics that match those of clinical trial participants. This approach is more sophisticated than *all-comers analysis* in that it uses additional patient and disease information to select real-world patients who more closely resemble the characteristics of the patients treated in the clinical trial. *Trial emulation* uses advanced statistical methods to adjust for population characteristics and requires enhanced data collections that include more detailed clinical information to match real-world patients to trial populations.

  As the characteristics of real-world patients will likely differ from clinical trial participants—particularly older patients and those with complex comorbidity profiles—this approach to OS estimation will exclude some people treated with the medicine of interest.

Based on the literature review, the following analyses are recommended for estimating OS associated with PBS-listed medicines:

- As the primary analysis, calculate median OS (all-cause mortality) using unadjusted Kaplan-Meier (K-M) curves (*all-comer analysis*)
- As a sensitivity analysis to the primary analysis, exclude the first three months after PBS-listing to remove people who may have received treatment with the medicine through

special access programs prior to its PBS listing. If a new medicine for the same indication has subsequently been listed on the PBS, end follow-up when the new medicine was listed. Finally, it may be of interest to censor patients at the end of their treatment.

- If enhanced data collections are available, secondary analyses should include stratifying K-M curves by relevant demographic and clinical factors, such as disease stage; censoring at the end of treatment and weighting K-M curves by inverse probability of censoring weights; identifying the risk factors for all-cause mortality using Cox proportional hazards models; and analysing cause-specific mortality.
- While it is possible to explore factors associated with all-cause mortality using *minimum data*, the analysis will be incomplete. Conclusions drawn from analyses including only those patient factors typically included in minimum data collections (i.e., age and gender) will be confounded by missing data such as disease stage and ECOG status.

Trastuzumab emtansine pilot study:

Trastuzumab emtansine for metastatic breast cancer was listed on the PBS on 1 July 2015. The median overall survival estimated from the pivotal trial (and included in the PBAC submission) was 30.9 months (N = 991). In this pilot study, OS was estimated in a cohort of patients receiving trastuzumab emtansine for metastatic breast cancer using PBS dispensing data linked to FOD data.

Follow-up lasted from July 2015 through December 2021 and the cohort for primary analysis included all treated patients (*all-comers*). Sensitivity analyses were conducted, restricting the cohort to patients initiating treatment from 1 October 2015 (three months after trastuzumab emtansine's PBS-listing) to 31 March 2020. Trastuzumab emtansine for early-stage breast cancer was listed on the PBS on 1 April 2020, so the cohort was closed on 31 March 2020 to avoid potential contamination of the cohort by people treated for early-stage breast cancer.

The results:

- 1,027 patients initiated trastuzumab emtansine; median age 59 years (IQR: 50 – 68); 62% died during follow-up
- Median OS, primary analysis: 28.9 months (95%CI: 26.1 – 32.0)
- Median OS, sensitivity cohort: 23.5 months (95%CI: 21.2 – 27.1)

The difference between the median OS estimates from the primary and sensitivity analyses is likely due to cohort contamination from 1 April 2020. Patients initiating trastuzumab emtansine from this time included those receiving treatment for early-stage disease and early-stage patients have longer expected survival times than late-stage/metastatic patients. It is likely the case that OS estimates including early-stage patients are biased longer. In this instance, the sensitivity analyses estimate is likely closer to the true OS for patients treated with trastuzumab emtansine for metastatic disease.

The difference between the median OS estimate, derived from the sensitivity analysis and the clinical trial estimate cited in the PSD, is likely due to differences in patient characteristics (e.g., the real-world cohort was older than the trial cohort). The median age of patients in the pilot study was six years older than that reported in the pivotal clinical trial (53 years). Relapse after treatment for early-stage disease is a known negative prognostic indicator and while staging data were not available for the pilot study, it is likely the case that a substantially larger proportion of real-world patients had previously been treated with trastuzumab for early-stage disease than had been previously treated in the trial (reported at 16% of trial participants).

Further stratification to determine reasons for the discrepancy would require linkage with enhanced datasets with more detailed clinical information.

Protocol Summary

The table below details the steps for estimating OS of people dispensed PBS-listed cancer medicines for advanced solid tumours. From selecting relevant medicines, ascertaining the feasibility of estimating OS for those medicines in available data, and to employing the appropriate methodologies to generate robust OS estimates, detailed rationales for each of these steps are provided in the full report. A link to the specific section of the report for each step is included in the table below.

Step	Action	Full description
Part 1: Determining the suitability of PBS-listed medicines for estimating OS		
1	Complete the *Medicine Selection and Evaluation* worksheet by extracting the relevant information from the PBAC PSD. The worksheet collates key information about uncertainties at the time of listing, data availability and the treatment landscape. Ideally this process should be undertaken by two people independently.	Attachment B, Section 1.2
2	Seek clinician input about the use of the medicine in routine care and clarify any uncertainties identified in the data extracted from the PSD.	
3	If a medicine is selected to proceed to feasibility analysis (i.e., the medicine has been PBS-listed at least as long as the expected median OS reported in the pivotal clinical trial/s AND the number of people treated with the PBS-listed medicines is predicted to be similar to the number of people in the trial population), complete the *Trial Data Worksheet* by extracting the relevant data from the pivotal clinical trials.	Attachment B, Section 1.2
Part 2: Assessing the feasibility of estimating OS using available data sources		
4	Identify potential datasets to use for OS estimation. The minimum data required to estimate the OS of people dispensed PBS-subsidised cancer medicines include: - Unit record PBS dispensing records (with authority codes) linked with - Unit record fact of death (FOD) records (at least mm/yyyy, preferably dd/mm/yyyy) Enhanced data collections (i.e., minimum data linked with additional data sources) such as cancer notifications, hospitalisations, and cause of death data can facilitate more complex estimation methods.	Section 2.2
5	Determine the ethical and governance requirements for accessing the identified data source for OS estimation. Consult with ethics governance bodies as required to access the desired data.	Section 2.2

Step	Action	Full description
6	Once the datasets have been obtained, determine whether adequate numbers of people have been dispensed the medicine of interest. The adequate number of people required to estimate OS will vary by medicine and indication and is likely to be informed by clinician input. A reasonable rule-of-thumb is the number of people dispensed the PBS medicine of interest should be similar to the number enrolled in the clinical trial. Determine the number of deaths observed during the follow-up period. Seek clinician input around the interpretation of the feasibility results.	Section 2.3
7	Consider potential external factors that may impact or bias OS estimates. For instance, have new indications for the medicine of interest been subsidised on the PBS since the original listing? Or, has the medicine been listed for an earlier stage of cancer treatment for the same indication?	Section 2.3
8	Examine the distributions of patient factors in the patient population (if data are available to do so; similar to Table 1 of Section 2.4). Examples of feasibility analyses are included in section 2.4 and Attachment E	Section 2.4, Attachment E
Part 3: Estimating OS using fit-for-purpose methods		
9	If a medicine is selected in Part 1 and deemed feasible for OS estimation in Part 2, perform the *all-comers analysis* (i.e., all people dispensed the medicine of interest through the PBS) as detailed in Part 3. If enhanced data sources are available, a *trial emulation* analysis (i.e., a cohort of people dispensed the medicine of interest restricted to match trial participants based on demographic and clinical factors) may also be undertaken.	Section 3.2
10	As a sensitivity analysis, exclude patients initiating treatment within the first 90 days after PBS listing. Prior to a medicine being PBS-listed, patients may have received the medicine via other mechanisms such as compassionate access schemes. When these patients continue their treatment on the PBS, they will appear to be medicine initiators and their inclusion will likely bias OS estimates shorter.	Section 3.2
11	Account for potential external factors identified in Parts 1 or 2. For instance, when there is a new indication listed for the same medicine, limit cohort inclusion dates to avoid potential misclassification.	

Step	Action	Full description
	Calculate median OS using Kaplan–Meier (K-M) methods	
12	If enhanced data sources are available, more sophisticated analyses may be employed, such as inverse probability of censoring weighting (IPCW) before calculating median OS.	Section 3.2
13	If required, estimate median OS using K-M methods stratified by relevant factors (e.g., patient sex, age groups, state of residence, number of comorbidities).	Section 3.2
14	Perform additional analyses to investigate the source of potential differences between the real-world OS estimate and that reported in the pivotal trial. For instance, examine age distributions, treatment duration and/or patterns of treatment with the medicine of interest.	Section 3.2

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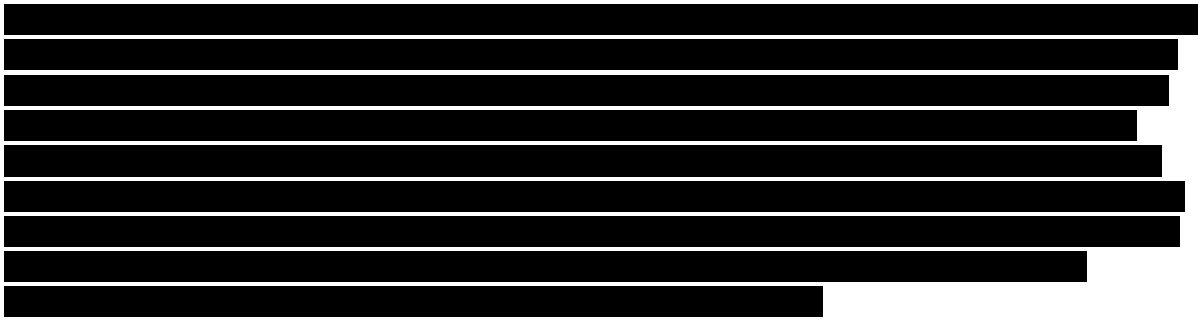
Background

Cost-effectiveness analyses underpin decisions to subsidise health technologies in many health jurisdictions globally and quantifying the benefits of new treatments, such as estimating overall survival (OS) associated with treatment, is a key component of these analyses. OS is a commonly reported metric that measures the period of time from a specific start point (often cancer diagnosis or treatment initiation) until the date of death or the end of follow-up for a cohort. The advantage of OS as a clinical trial outcome is that it represents an unequivocal endpoint that can be assessed with 100% accuracy both for its occurrence and timing, provided the number of patients with incomplete follow-up times is not substantial. Median OS—the amount of time by which 50% of the cohort have died and, necessarily, 50% survive beyond—with a corresponding 95% confidence interval or interquartile range is often reported to characterise survival in patients treated for cancer.

Sponsor submissions for health technology reimbursement typically rely on estimates derived from clinical trials. However, these estimates often differ substantially from real-world OS estimates. These differences have implications for the ongoing cost-effectiveness of these medicines or technologies post-subsidy.



The protocol that follows details the Medicines Intelligence Centre for Research Excellence (MI-CRE's) advice to the Pharmaceutical Benefits Advisory Committee (PBAC), focusing on medicines indicated for advanced solid cancers, i.e., metastatic and locally advanced indications without curative intent.

1. Selecting and evaluating candidate medicines

1.1 Introduction

The medicine selection and evaluation process was designed by reviewing PBS listings for cancer medicines over a five-year period from 2014-2019 (Attachment A). To determine which specific PBS-listed cancer medicines could be selected for the subsequent steps described in this protocol, a process was developed based on key information from the PBAC submissions as reported in the Public Summary Documents (PSDs Attachment B). The key selection and evaluations are discussed, as well as the strengths and limitations of the process.

1.2 Key selection issues

Availability of data for the required length of follow up

If only a short period of time has passed since the medicine of interest was PBS-listed, it will likely be difficult to estimate median OS, as sufficient numbers of patients receiving the treatment may not have died. As a rule of thumb, the medicine should have been PBS-listed for at least as long as the expected OS (as estimated in the submission). If the length of time since listing is too short, then median OS must be extrapolated, and the resulting estimate will be more uncertain.

Number of patients treated

While there is not a specific number of treated patients that can be defined as sufficient to facilitate a robust OS estimation, when very few patients have been treated with the medicine of interest, precise estimation of OS may not be possible. Therefore, in situations where the PSD reports that the estimated number of patients treated each year after listing is likely small, further analysis of the medicine may not be worthwhile, as the resulting OS estimates will likely be unreliable. Clinician input will also be valuable in deciding on an adequate number of treated patients to proceed to the subsequent parts of this protocol.

Treatment landscape

The availability of alternative PBS treatments for the same cancer indication could reduce the number of patients initiating the medicine of interest and/or result in switching between the medicine of interest and other treatments. High rates of switching will increase the uncertainty associated with the OS estimates, as any survival benefit may be difficult to attribute to a particular medicine. Medicines used as last-line therapy, or late in the treatment algorithm, will be less impacted by these issues compared to medicines initiated earlier in the pathway. A listing of the medicine of interest for an earlier stage of cancer treatment may also contaminate analyses due to misclassification of treatment stage based on PBS item codes.

1.3 Key evaluation issues

The selection and evaluation process draws on key information extracted from the PBAC PSDs and published clinical trials and builds on the existing review process for PBAC submissions. In particular, the process identifies and documents uncertainties regarding cost-effectiveness or financial impact to the PBS, as highlighted in the PBAC assessment process.

The issues of uncertainty can be categorised as:

- Uncertainty about effectiveness at an individual level, e.g., because of imprecise or uncertain estimates of benefits.
- Uncertainty about effectiveness at a population level, e.g., because of uncertainty about how trial results will generalise to the actual clinical population.
- Uncertainty related to the financial impact of listing, e.g., because of uncertainty about the eligible population.

The selection and evaluation process also considers key information available after the PBAC's positive recommendation. This includes:

- Subsequent clinical trial results that update OS estimates or provide them for the first time.
- Changes such as subsequent listings of other medicines for the same indication that may impact on uptake.

A ***Selection and Evaluation Worksheet*** was developed to collate this key information (Attachment B). This worksheet is intended to assist in prioritising listings for further analysis. For medicines that pass this initial selection and evaluation process, the worksheet includes an additional section for data extraction from key clinical trials. This is to inform further data analysis.

1.4 Discussion

Broader applicability of the medicine suitability assessment framework

The selection and evaluation process was initially developed to estimate OS in patients treated for cancer. However, the information extracted from the PSDs is also suitable for estimating OS in patients treated with medicines for non-cancer indications and the framework could be adapted for use in these areas. Post-market analysis of real-world data is most likely to be of interest for conditions with high mortality rates, where there is significant unmet clinical need, and therefore where the PBAC may recommend listing despite substantial uncertainty in terms of cost-effectiveness.

Strengths and weaknesses of the process

Strengths

- Uses publicly available information only, enabling a transparent process
- PSDs are the primary source of data and appraisal, streamlining the process and ensuring consistency with PBAC deliberation
- Qualitative synthesis of data allows for adaptable prioritisation
- Clinician input highlights practical and clinical considerations
- Allows for an early consideration of feasibility without the need for data analysis

Weaknesses

- Qualitative shortlisting criteria may be assessor-dependent, and results may not be reproducible
- Clinical input may be subjective
- No critical appraisal of evidence beyond the PBAC assessment as reported in the PSD

Practical issues

The selection and evaluation process (Part 1) was applied to 12 PBS-listed cancer medicines and six were selected to proceed to feasibility assessment (Part 2). Key details from the pivotal clinical

trials for these six medicines were extracted from published journal manuscripts (Attachment C) and summarised for each medicine (Attachment D).

This first application also identified aspects of the selection and evaluation process that could be improved. For simplicity, medicines of interest were restricted to those that were PBS-listed between two to seven years ago, however, older listings, such as ipilimumab, may remain of interest.

Identifying issues for the *Selection and Evaluation Worksheet* required some subjective judgement, as did the selection of key points from the worksheet. For example, information on the likely number of patients to be treated was usually redacted in the PSD, and qualitative statements about this were difficult to interpret. Further sources of information on the current prevalence of different cancers by stage of cancer in Australia may be helpful.

2. Assessing the feasibility of estimating OS using available data sources

2.1 Introduction

The process outlined in Part 1 draws information from publicly available sources to identify PBS-listed cancer medicines best suited to estimating OS using real-world data. This section details a framework for determining the feasibility of estimating OS using Australian data sources. Key considerations are:

1) Whether fit-for-purpose Australian data are available to estimate OS for people treated with the PBS-listed cancer medicine of interest (Section 2.2).

2) Whether, based on exploratory analyses of these data, there is sufficient use, follow-up time and mortality rates reported in people treated with the medicine of interest to feasibly estimate median OS (Section 2.3).

2.2 Assessment of potential data sources

Table 2.2.1 identifies the minimum data requirements for estimating OS in people treated with the PBS-listed cancer medicines of interest, as identified in Part 1. As a minimum, unit record PBS dispensing claims linked with unit record fact of death (FOD) records are required to identify the patients dispensed a specific treatment and to generate OS estimates for those patients. The additional data sources presented under 'enhanced data' can be linked to the minimum required data and used to increase certainty about a patient's cancer treatment (e.g., cancer notifications can be used to ensure a medicine is being dispensed for a particular indication). Enhanced data also allow for a more robust characterisation of a patient's sociodemographic and health profile (particularly in relation to how they compared to clinical trial populations). These additional data can be used to refine OS estimates, facilitate more complex statistical methods, and match real-world patient populations to trial participants (all discussed in Part 3).

Table 2.2.1: Data requirements for estimating OS

Minimum data requirements	Unit record PBS claims (with authority codes) linked to • Unit record fact of death (FOD) records (at least mm/yyyy, preferably dd/mm/yyyy)
Enhanced data	Minimum data requirements, linked with at least one of the following: • Cancer notifications (cancer diagnosis, fact and cancer-specific death) (if diagnosis and/or cancer stage is uncertain), or • Hospitalisation (if outcomes other than death are required), or • Electronic health records, (if cancer severity or clinical data are required), or • Cause of death records, (if cause-specific mortality is important), or • Other collection (e.g., MBS, emergency department)

A range of Australian data sources were identified that meet the minimum requirements outlined above. Table 2.2.2 outlines further key details about these data sources that impact their utility for estimating OS associated with PBS-listed cancer medicines. Consideration of these details may be applied to any potential data source in determining feasibility for OS estimation. While not included in this protocol, these considerations extend to oncology-specific electronic health records linked with other data sources.

Ethics and governance requirements must be considered when accessing these and other Australian health datasets. Each data source and data custodian has specific requirements and approvals for data access and linkage, plus additional project and output approvals. These requirements vary on a range of factors including, but not limited to, the group seeking data access (e.g., government vs. independent research organisations), the project being undertaken (e.g., monitoring and evaluation vs. research) and the nature of the outputs (e.g., government reports vs. peer-reviewed publications). The time frame in which the data are available for analysis is also dependent on the maturity of the data access and governance processes.

Table 2.2.2: Examples of Australian data sources that could be leveraged to estimate OS of PBS-listed medicines

Data Source	Population		Outcome			Sociodemographic characteristics		
	Coverage	Sample size	Date of death	Cause of death	Other medicine records	Hospital records	Postcode of residence	PBS Beneficiary status
Basic								
PBS & date of death extracts From 2002	All PBS-eligible Australians	25 million	Yes	No	Yes	No	Can be mapped to socioeconomic and other indices	Yes
PBS 10% sample 2005-current	10% sample of PBS-eligible Australians	2.5 million	Perturbed by +/- 180 days, rounded to year	No	Yes	No	No Pharmacy State only	Yes
Enhanced								
NIHSI[*] From 2010	Australian residents	25 million	Yes	Yes	Yes	Yes for jurisdictions other than WA & NT	Mapped to socioeconomic and other indices	Yes
MADIP[†] From 2006	Australian residents	25 million	Yes	Yes	Yes	Not available routinely	Individual measures of sociodemographic status	Yes
Medicines Data Platform[‡] From 2002	NSW residents	9 million	Yes	Yes	Yes	NSW only	Mapped to socioeconomic and other indices	Yes

[*]National Integrated Health Services Information. [†]Multi Agency Data Integration Project. [‡]A researcher-led, cross-jurisdictional data linkage.

2.3 Feasibility analyses of PBS-listed medicines identified in Part 1

Once an appropriate data source has been obtained, the feasibility of generating OS estimates from that data source must be assessed. This is accomplished through exploratory data analyses to determine the number of people treated with the medicine of interest, the number of people who died during the follow-up, and a crude estimate of median OS. It is also important to examine trends in dispensings to identify potential anomalous patterns of medicine use in the data.

The Department of Health and Aged Care provided PBS data linked with fact of death data for this project. The data was supplied under the condition that the data be stored securely, be accessed only by the named personnel completing the review and be used solely to investigate the feasibility of this data for estimating OS for the six medicines identified in Part 1. Feasibility assessment summaries for these six medicines are presented below. The full feasibility assessments are detailed in Attachment E.

2.4 Feasibility assessment

2.4.1 Ipilimumab

Indication: Unresectable stage III or stage IV malignant melanoma in patients who have not responded to, or were intolerant to, prior systemic therapy for metastatic disease

PBS item codes - form and strength

02638W, 02643D - Injection concentrate for I.V. infusion 50 mg in 10 mL

02641B, 02663E - Injection concentrate for I.V. infusion 200 mg in 40 mL

PBS Listed: 1 August 2013

Time period of analysis: 1 February 2013 to 31 December 2021

Summary of findings

- 6,189 patients treated (31% female); median age 64 years (IQR: 54 – 72)
- 38% dispensed antineoplastics in the 6 months prior to IPILIMUMAB initiation (3% chemotherapy; 20% targeted therapy; 19% immunotherapy)*
- Crude median overall survival: 23.1 months (95%CI: 21.3 – 25.7)

Feasibility assessment

- There is sufficiently long follow-up and number of deaths to produce robust and meaningful median survival estimates.
- IPILIMUMAB is currently indicated for four different cancers; check for sufficient follow-up time to estimate OS if patients are censored before additional indications were listed.
- There is an unusual decrease in PBS dispensings from August 2015 to December 2016. This event requires further research to determine what, exactly, caused the decrease in use during this time period.

* Antineoplastic treatments—chemotherapy, targeted therapy, immunotherapy—are not exclusive and patients may receive any/all during the six months prior to initiating the medicine of interest.

- **IPILIMUMAB is a feasible candidate for full analysis but requires a strong caveat due to the decrease in dispensings in 2015/2016.**
- **The time period for analysis should be restricted to 2013 – 2019, when IPILIMUMAB was listed for melanoma only.**

2.4.2 Lanreotide

Indication: Non-functional gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults with unresectable locally advanced or metastatic disease

PBS item codes - form and strength

11513Y, 11527Q - Injection 120 mg (as acetate) in single dose pre-filled syringe

PBS Listed: 1 December 2018

Time period of analysis: 1 June 2018 to 31 December 2021

Summary of findings

- 578 patients treated (45% female); median age 66 years (IQR: 56 – 74)
- 7% dispensed antineoplastics in the 6 months prior to lanreotide initiation (6% chemotherapy; 1% targeted therapy; <1% immunotherapy)*
- There was insufficient follow up time to estimate crude median overall survival.

Feasibility assessment

- LANREOTIDE has insufficient follow-up time and number of deaths to produce a precise confidence interval for median overall survival.
- There is an increase in dispensings around August 2019 in line with the listing of the medicine for a different indication.
- **LANREOTIDE is not a feasible candidate for full analysis.**

2.4.3 Olaparib

Indication: high grade serous ovarian cancer, high grade serous fallopian tube cancer and high grade serous primary peritoneal cancer with evidence of a germline class 4 or 5 BRCA1 or BRCA2 gene mutation. The condition must be platinum sensitive.

PBS item codes - form and strength

11034R, 11050N - Capsule, 50mg

11522K, 11503K - Tablet, 100mg

11528R, 11539H - Tablet, 150mg

PBS Listed: 1 February 2017

Time period of analysis: 1 August 2016 to 31 December 2021

* Antineoplastic treatments—chemotherapy, targeted therapy, immunotherapy—are not exclusive and patients may receive any/all during the six months prior to initiating the medicine of interest.

Summary of findings

- 673 patients treated (99% female); median age 62 years (IQR: 55 – 70)
- 79% dispensed antineoplastics in the 6 months prior to olaparib initiation (69% chemotherapy; 24% targeted therapy; <1% immunotherapy) *
- Unable to calculate crude median overall survival

Feasibility assessment

- There is insufficient follow-up time and number of deaths to produce robust and meaningful median survival estimates.
- There is a notable increase in patients initiating PBS listed OLAPARIB after November 2020. This is likely due to the introduction of a new population after the listing of OLAPARIB as a first line treatment in November 2020.
- **OLAPARIB is a not a feasible candidate for full analysis.**

2.4.4 Panitumumab

Indication: K-RAS wild-type (WT) metastatic colorectal cancer (mCRC) in patients who have failed first-line chemotherapy

PBS item codes - form and strength

10069Y, 10082P - 100 mg/5 mL injection, 5mL vial; or 400 mg/20 mL injection, 20mL vial

PBS Listed: 1 April 2014

Time period of analysis: 1 October 2013 to 31 December 2021

Summary of findings

- 2,064 patients treated (37% female); median age 65 years (IQR: 55 – 73)
- 86% dispensed antineoplastics in the 6 months prior to panitumumab initiation (84% chemotherapy; 42% targeted therapy; <1% immunotherapy)*
- Crude median overall survival: 16 months (95%CI: 15.0 – 17.0)

Feasibility assessment

- There is sufficiently long follow-up and number of deaths to produce robust and meaningful median survival estimates.
- There is a notable increase in dispensings during 2017 but no apparent reason for the increase (i.e., no new indications listed). From 2018 dispensings return to trend.
- **PANITUMUMAB is a feasible candidate for full analysis, including sensitivity analyses, which can then be benchmarked against pivotal trial estimates.**

* Antineoplastic treatments—chemotherapy, targeted therapy, immunotherapy—are not exclusive and patients may receive any/all during the six months prior to initiating the medicine of interest.

2.4.5 Trastuzumab emtansine

Indication: HER2 positive metastatic breast cancer patients who have received prior treatment with trastuzumab and a taxane and whose disease has progressed despite treatment with trastuzumab for metastatic disease.

PBS item codes - form and strength

10281D, 10282E - 100 mg injection, 1 x 100 mg vial; or 160 mg injection, 1 x 160 mg vial

PBS Listed: 1 July 2015

Time period of analysis: 1 January 2015 to 31 December 2021

Summary of findings

- 1770 patients treated (99% female); median age 58 years (IQR: 50 – 68)
- 85% dispensed antineoplastics in the 6 months prior to TRASTUZUMAB EMTANSINE initiation (33% chemotherapy; 81% targeted therapy; <1% immunotherapy)*
- Crude median overall survival: 28.9 months (95%CI: 26.1 – 32.0)

Feasibility assessment

- There is sufficiently long follow-up and number of deaths to produce robust and meaningful median survival estimates.
- There is a small increase in dispensings from April 2020 after the listing for the treatment of early breast cancer. There is sufficient data to censor at this point if required.
- **TRASTUZUMAB EMTANSINE is a feasible candidate for full analysis, including sensitivity analyses, which can then be benchmarked against pivotal trial estimates.**

2.4.6 Trifluridine with tipiracil

Indication: Metastatic colorectal cancer (mCRC) in patients who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy.

PBS item codes - form and strength

11507P - Tablet, 15 mg trifluridine with 6.14 mg tipiracil

11524M - Tablet, 20 mg trifluridine with 8.19 mg tipiracil

PBS Listed: 1 December 2018

Time period of analysis: 1 June 2018 to 31 December 2021

Summary of findings

- 2,356 patients treated (59% female); median age 65 years (IQR: 56 – 73)

* Antineoplastic treatments—chemotherapy, targeted therapy, immunotherapy—are not exclusive and patients may receive any/all during the six months prior to initiating the medicine of interest.

- 92% dispensed antineoplastics in the 6 months prior to trifluridine initiation (90% chemotherapy; 58% targeted therapy)*
- Crude median overall survival: 10.1 months (95%CI: 9.3 – 11.0)

Feasibility assessment

- There is sufficiently long follow-up and number of deaths to produce robust and meaningful median survival estimates.
- There were no discernible external factors that would indicate concerns over data quality and interpretability of the survival results.
- **TRIFLURIDINE with TIPIRACIL is a feasible candidate for full analysis, including sensitivity analyses, which can then be benchmarked against pivotal trial estimates.**

2.5 Summary

The most important factor determining the feasibility for estimating OS using Australian health data is the number of deaths observed during follow-up. If the maximum observed follow-up time is shorter than the median survival time, OS cannot be estimated. This factor is intimately connected to the time since the medicine was PBS-listed, the number of people initiating a medicine, and the medicine's indication (i.e., treatments for early-stage disease will be accompanied by fewer deaths than those for late-stage disease). However, these latter considerations relate more to the robustness of the OS estimate rather than the feasibility of deriving an estimate.

Shorter periods of time since PBS listing may result in a small number of patients receiving a medicine and, therefore, smaller numbers of observed deaths; while longer periods of time since PBS listing may be more susceptible to bias. For instance, if a new treatment indication for the medicine is subsidised by the PBS after the initial PBS listing, a materially different patient population may begin using the medicine and OS estimates would be confounded by the heterogeneous treatment population. In the case of TRASTUZUMAB EMTANSINE, such a confounding event occurred in April 2020, when TRASTUZUMAB EMTANSINE—previously listed solely for late-stage breast cancer—was also listed on the PBS for early-stage disease.

It should be noted that while PBS item codes contain information about the treatment indication of the dispensed medicine, prescribers and pharmacists do not always select the correct item code at the time of prescribing/dispensing, resulting in some misclassification in the dispensing data. As early-stage patients have far lower mortality rates than late-stage patients it is likely the case that the median OS estimate of 28.9 months reported in the feasibility analysis above is higher than the true estimate for patients receiving TRASTUZUMAB EMTANSINE for late-stage disease. If enhanced data collections containing cancer notifications are available, it may be possible to more accurately ascertain which patients are receiving treatment for early- and late-stage disease. As in Part 1, seeking clinician advice around the interpretation of feasibility results may help identify issues like this and other anomalous findings.

Part 3 presents an analytical template detailing the methods for estimating OS using minimum data requirements and enhanced data. Those methods are then applied to TRASTUZUMAB EMTANSINE as a pilot study, demonstrating the full analysis estimating OS using the minimum data used in the feasibility assessment.

* Antineoplastic treatments—chemotherapy, targeted therapy, immunotherapy—are not exclusive and patients may receive any/all during the six months prior to initiating the medicine of interest.

3. Estimating OS using fit-for-purpose methods

3.1 Introduction

A scoping review was conducted of the recent literature around methods for estimating OS for patients treated with cancer medicines and comparisons to the original clinical trials. The findings of the literature review (summarised below), as well as the identification and feasibility assessments conducted in Parts 1 and 2, were used to inform the development of an analytical template in Part 3, the methodology for which is presented using the START-RWE template (Attachment G).

3.2 Narrative literature review

The purpose of the literature review was to identify recent literature that may inform the analytical template. Articles were selected if they investigated how estimates from observational studies of OS for patients dispensed cancer medicines compare with estimates of OS reported in the pivotal trials.

The aims of the literature review were to:

1. Identify peer-reviewed and grey literature comparing OS in cancer patients treated in routine clinical care with estimates reported in pivotal clinical trials.
2. Identify the methodology used to estimate OS using real world data.

Methods

Peer-reviewed articles and grey literature were searched on 7 February 2022 for studies that compared OS in real-world data (RWD) and randomised controlled trials (RCTs) and/or described the methodology for doing so. Search terms included “cancer”, “medicine”, “overall survival” and “real world”. Using information provided in the abstract, a sample of studies that provided real-world OS estimates for people treated with at least one cancer medicine, with a focus on those studies that compared real-world estimates to RCT estimates, were selected. Additionally, studies of medicines identified in Part 1 of this report were searched for using the terms “overall survival”, “real world” and the name of the medicine.

Results

A complete summary of the reviewed articles can be found in Attachment F. Studies comparing real-world estimates of OS to RCT estimates fell into two distinct types. The first type assessed survival in all patients who were prescribed or dispensed at least one cancer medicine (“all-comers”). The second type applied the RCT eligibility criteria to real-world patients prior to estimating real-world OS (“trial emulation”).

All-comer studies

All-comer studies use unadjusted analysis to estimate OS in the population of interest. An example is the study by Green et al. (2021) that examined 22 medicines—including immunotherapies, targeted therapies and chemotherapies—for 29 indications for metastatic solid cancers. In general, patients included in the real-world studies were older than those included in the RCTs and estimates of median OS were shorter in real-world studies than those reported from RCTs for 28 of

the 29 indications (median difference: −6.3 months; range: −28.7 to 2.7 months). Treatment duration was also shorter in real-world studies for 23 of the 27 indications (median difference: −1.9 months; range: −12.4 to 1.4 months). Another study investigating the overall survival of patients treated with trastuzumab emtansine for metastatic breast cancer in Australia found patients were older and real-world median OS was shorter than the pivotal trial: 19.3 months (interquartile range: 7.9 to 29.5) compared with 29.9 months reported in the RCT (Daniels 2021). Other smaller studies found real-world median OS was comparable to RCTs (Yu 2021, ipilimumab for melanoma; Stewart 2019, PD-(L)1 inhibitors for advanced non–small-cell lung cancer). Notably, Daniels et al.'s analysis excluded patients initiating trastuzumab emtansine within 90 days of the medicine's availability on the PBS (1 July 2015). This was done in an attempt to better capture typical real-world patients as those initiating treatment within the first three months of trastuzumab emtansine being PBS listed may have been receiving the medicine through special access programs prior to 1 July 2015 and their inclusion would have biased OS estimates lower.

All-comer studies are useful because they provide OS estimates from the actual population treated in real-world clinical care. These studies perhaps best align with the perspective of the funder of the treatment in that the payer is subsidising treatment for all those in the population who meet the clinical criteria to receive the treatment. All-comer studies also have an advantage of being feasible when only basic data are available. At an absolute minimum, these studies require only medicine supply data and date of death to produce valid OS estimates. In general, all-comer studies analysed data using an intention to treat (ITT) approach and ignored treatment switching and discontinuation. However, some studies, such as Petito 2020, attempted to adjust for instances of treatment switching by weighting OS estimates using more advanced methods like inverse probability of censoring weights (Willems 2018).

Trial Emulation studies

Trial emulation studies restrict the population used to estimate real-world OS to people who more closely reflect the population treated in the RCTs. Often, the primary purpose of these studies is to estimate the treatment effect between the active group and the comparator in real-world data, with a secondary aim being a comparison between real-world vs RCT active arm OS. Examples of studies that have attempted to emulate RCTs include a study of ceritinib in non-small-cell lung cancer (Davies 2018) and erlotinib added to gemcitabine (Petito 2020). These studies found better agreement between real-world and RCT OS estimates using either median OS (ceritinib real-world median OS 16 months vs RCT 15 months, Davies 2018), 1- and 2-year survival rates (ipilimumab real-world 2-year survival rates range from 23.9% to 43.5% vs 23.5% from the RCT, Kim 2018), or hazard ratios (HR; erlotinib added to gemcitabine compared to gemcitabine alone real-world adjusted HR 1.04, (95% CI 0.86-1.42) vs RCT HR 0.96 (95% CI 0.74 to 1.24), Petito (2020). Petito et al. also conducted an all-comers analysis that resulted in a discordant HR (HR 0.68 [95% CI 0.54-0.87]).

Trial emulation studies require more detailed data on patient and clinical characteristics to identify patients in real-world data who match the RCT inclusion criteria conditions. Additionally, trial emulation studies tend to use more advanced methods and statistical techniques to adjust for population characteristics. These methods included the use of target trial designs (Petito 2020), Kaplan-Meier (K-M) curves weighted by inverse propensity scores (Davies 2018), or multivariable Cox proportional hazards models (Dalle 2021, Kim 2018).

Summary

The studies reviewed highlight the potential for heterogeneity in OS estimates using real-world data and their discordance with RCT OS estimates. In general, all-comer analyses use an ITT approach in all patients receiving the treatment of interest in the real world. Real-world treatment populations can differ substantially from those included in RCTs. As such, in the sample of real-world studies examined in this report, median OS estimated based on all-comers analyses were generally shorter than RCT estimates, with the median difference approximately 6 months (Green 2021). However, the real-world patients in Green 2021 were more than 10 years older than RCT participants. Additionally, real-world treatment duration was generally shorter than RCT treatment duration. These findings highlight that differences in survival between real-world and RCT populations may be due to differences in population, such as age, and treatment characteristics, such as treatment duration, and treatment switching. Methods to adjust for patient and treatment differences, such as inverse probability of censoring weights, may be warranted when the goal of analysis is to emulate trial settings.

Trial emulation studies—where real-world populations are adjusted to match RCT populations—had better agreement with RCT median OS estimates than those using all-comer analysis.

Recommendations for estimating OS in PBS populations following literature review

- Calculate median OS using K-M methods in an unadjusted, all-comers analysis.
- Perform additional analyses to investigate potential differences between real-world OS and RCT estimates. Differences in OS estimates are likely if the treatment population is different to that included in the RCTs. Real-world populations are often older and may be treated with cancer medicines differently to trial protocols (e.g., shorter treatment durations than in the RCTs).
- When limited data on patient characteristics are available (such as in the case of minimum required data collections), stratify analyses by important patient characteristics that are available (e.g., age groups, gender).
- It is often the case that patients receiving treatment with a medicine immediately following its PBS listing may have received the therapy via other mechanisms—such as compassionate access programs—prior to the listing date. Or, they may be sicker than those indicated for treatment (e.g., patients with existing and more advanced cancers as opposed to those with recently diagnosed cancers). To account for this potential issue, exclude patients initiating treatment within the first 90 days after PBS listing.
- To address the potential issue of shorter treatment durations in real-world patients, censor patients at the end of treatment and use inverse probability of censoring weighting to account for switching and early discontinuation.

3.3 Analytical template

Following the recommendations from the literature review, and the selection, evaluation, and feasibility assessments developed in Parts 1 and 2, a template containing methodologies for estimating real-world OS was assembled using the START-RWE template. Assuming that data meeting the minimum data requirements—as detailed in Section 2.2—are available, with a maximum observed follow up time at least as long as the median survival time reported in the clinical trial, the primary analysis described in the analytical template is to calculate median OS in the PBS population using unadjusted Kaplan-Meier curves (all-comer analysis).

As detailed above, the unadjusted median OS estimate from the entire treated population (all-comers) is likely the estimate most relevant to the payer. This estimate reflects the survival of the population receiving PBS-subsidised treatment.

Parts 1 and 2 of this protocol highlighted that external events may impact and/or bias OS estimates. A common (and unobserved) event is patients receiving treatment with a medicine of interest prior to the medicine's PBS listing, as patients often access cancer medicines in trials or through compassionate access programs. Due to this early access, OS estimates will be biased shorter as the first observed dispensing in PBS data—when the follow-up period for OS estimation begins—will not be the first treatment the patient received. As mentioned in Parts 1 and 2, the listing of new indications for the same medicine of interest, or listings of new medicines with a similar indication may also bias OS estimates by changing the patient population dispensed the medicine of interest. Similarly, patients initiating a medicine of interest may quickly cease treatment or switch to a different medicine, complicating the interpretation of resulting OS estimates. To mitigate the impacts of such events, sensitivity analyses were included in the analytical template to:

1. Exclude patients initiating treatment during the first three months after PBS listing to eliminate patients who appear to be initiating treatment but who may have started the medicine before PBS listing.
2. End cohort enrolment when there is a new indication listed for the same medicine or a new medicine listed for a similar indication, to avoid potential misclassification.
3. Censor follow-up at the end of treatment for each patient, to assess the effect of differences in treatment duration from stopping treatment early and/or switching to another medicine.

For cases where enhanced data (as discussed in Part 2) are available, secondary analyses using trial emulation methods identified in the literature were included in the analytical template. These approaches can be used to investigate the reasons for potential discrepancies between real-world and RCT OS estimates; to potentially obtain more precise OS estimates; and to estimate factors associated with mortality and they include:

- Stratifying the K-M curves by patient or disease factors, where appropriate.
- Censoring follow-up at the end of treatment and weight Kaplan-Meier curves by inverse probability of censoring weights. The weighted OS estimates can be compared with the unweighted, censored estimates.
- Identifying risk factors for all-cause mortality using Cox proportional hazards models which may affect OS estimates compared to RCTs, depending on population characteristics.
- Using cause specific mortality (if cause of death information is included in the enhanced data collection being used) as the outcome, rather than all-cause mortality.

In addition to the methods outlined in the analytical template (Attachment G), descriptive statistics should be used to summarise patient characteristics for comparison with the patient characteristics of the pivotal trial(s).

3.4 START-RWE Format

The template to estimate OS in the PBS population is formatted to the *structured template for planning and reporting on the implementation of real-world evidence* (START-RWE) found in Attachment G.

The next section of the report comprises a pilot study, where the considerations, processes, and methods detailed in this report (Parts 1, 2, and 3) have been applied to generate OS estimates for trastuzumab emtansine.

4. Pilot study based on the proposed protocol: Trastuzumab emtansine

TRASTUZUMAB EMTANSINE

100 mg injection, 1 x 100 mg vial

160 mg injection, 1 x 160 mg vial

Purpose

The purpose of this pilot study is to assess the findings of the feasibility analyses (Part 2) and apply the methods detailed in the analytical template (Part 3), notably the sensitivity analyses, to address some of the issues that were identified during the feasibility analysis.

It should be noted that patients may have received treatment of TRASTUZUMAB EMTANSINE prior to its PBS listing on 1 July 2015 and, therefore, the full length of treatment for these individuals was not captured in the PBS data. Further, on 1 April 2020, TRASTUZUMAB EMTANSINE (previously listed solely for late-stage breast cancer) was listed for the treatment of early-stage breast cancer. Feasibility analyses showed a corresponding spike in patients initiating TRASTUZUMAB EMTANSINE from this date, suggesting that early-stage patients were likely being dispensed TRASTUZUMAB EMTANSINE with PBS item codes indicated for late-stage disease. The potential mixing of patient cohorts would impact the survival estimates, likely biasing the OS estimate higher. To address both issues, sensitivity analyses were implemented in this pilot study. While the primary analysis examined all patients initiating TRASTUZUMAB EMTANSINE between 1 July 2015 through 31 December 2021, a second cohort of patients was also examined, limited to those initiating treatment with TRASTUZUMAB EMTANSINE between 1 October 2015 (three months following PBS listing) and 1 April 2020 (to exclude any patients who may actually have been dispensed the medicine for early-stage disease).

The results presented in this pilot study refer to the sensitivity cohort unless otherwise stated. Full results for the primary analysis are presented in Attachment E.

These survival estimates are based on the PBS data that are available for this project, which includes dispensing records and fact-of-death data (minimum required data). Overall survival estimates could be further refined with the availability of enhanced datasets including PBS data (including the full medicine dispensing history) linked with cancer registration for accurate diagnosis data, death registrations including cause of death, MBS data, and hospitalisation data.

Summary of findings

- Primary analysis cohort: 1,770 patients treated (99% female); median age 58 years (IQR: 50 – 68)
- Primary analysis median OS: 28.9 months (95%CI: 26.1 – 32.0)
- Sensitivity analysis cohort: 1,027 patients treated (99% female); median age 59 years (IQR: 50 – 68)
- Sensitivity analysis median OS: 23.5 months (95%CI: 21.2 – 27.1)

Listing on the Pharmaceutical Benefits Scheme (PBS)

Date of PBAC Consideration: November 2014

TRASTUZUMAB EMTANSINE was PBS listed on 1 July 2015.

PBS listing details (as of 20 January 2022)

PBS listing: **https://www.pbs.gov.au/medicine/item/10281D-10282E-11951B-11956G**

TRASTUZUMAB EMTANSINE (T-DM1) was listed for the treatment of a patient with HER2 positive metastatic breast cancer who has received prior treatment with trastuzumab and a taxane and whose disease has progressed despite treatment with trastuzumab for metastatic disease. (Table 4.1)

Table 4.1: PBS listings of TRASTUZUMAB EMTANSINE

Item code	Name, form & strength	Date of listing	Schedule	Authority required?
10281D	Trastuzumab emtansine Powder for I.V. infusion 160 mg Powder for I.V. infusion 100 mg	1 July 2015	S100	Authority written
10282E	Trastuzumab emtansine Powder for I.V. infusion 160 mg Powder for I.V. infusion 100 mg	1 July 2015	S100	Authority written

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Public Summary document – November 2014 – 7.8 TRASTUZUMAB EMTANSINE available at https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2014-11/pertuzumab-trastuzumab-psd-11-2014

TRASTUZUMAB EMTANSINE was also listed for early-stage breast cancer on 1 April 2020. (Table 4.2) This listing is not part of this analysis.

Table 4.2: PBS listings of TRASTUZUMAB EMTANSINE not included in analysis.

Item code	Name, form & strength	Date of listing	Schedule	Authority required?
11951B	Trastuzumab emtansine Powder for I.V. infusion 160 mg Powder for I.V. infusion 100 mg	1 April 2020	S100	Authority written
11956G	Trastuzumab emtansine Powder for I.V. infusion 160 mg Powder for I.V. infusion 100 mg	1 April 2020	S100	Authority written

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Public Summary document – November 2019 – 6.07 TRASTUZUMAB EMTANSINE available at https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2019-11/trastuzumab-emtansine-powder-for-i-v-infusion-100-mg-powder

4.1 Data source & methods

Dispensing data were extracted from the PBS claims database by the Department of Health for all PBS and RPBS items for TRASTUZUMAB EMTANSINE (item codes 10281D, 10282E) for the period 1 July 2015 to 31 December 2021 (based on date of supply). To exclude patients who may have received initial treatment outside the PBS prior to PBS listing, as well as those initiating treatment for early-stage disease, the cohort was restricted to patients initiating with TRASTUZUMAB EMTANSINE from 1 October 2015 until 31 March 2020 (TRASTUZUMAB EMTANSINE was listed for early-stage disease on 1 April 2020).

Patient sex, date of birth, date of death and postcode of residence at time of dispensing were merged with PBS dispensing data by the Department of Health. For this cohort, all antineoplastic medicine dispensings (medicines whose ATC codes begin with 'L01') were also extracted for the time period 1 April 2015 to 1 July 2020.

Initiating patients were identified from their first dispensing of TRASTUZUMAB EMTANSINE in the PBS data between 1 October 2015 and 31 March 2020. Prevalent patients were those who had at least one dispensing of TRASTUZUMAB EMTANSINE during each calendar year from 1 October 2015 to 31 March 2020.

Demographic characteristics of initiating patients were measured at the date of first PBS dispensing of TRASTUZUMAB EMTANSINE. Patients were considered to have had prior use of antineoplastic medicines (L01) if those medicines were dispensed in the 6 months prior to TRASTUZUMAB EMTANSINE initiation. Antineoplastic medicines dispensed in the 3 months after the first TRASTUZUMAB EMTANSINE dispensing were also summarised.

Overall survival was estimated from the date of first TRASTUZUMAB EMTANSINE dispensing to the date of death or censoring (censor date: 31 December 2021) using Kaplan-Meier methods.

Sensitivity analyses were conducted limiting the follow-up time to 2 years, 3 years, 4 years, and 5 years post listing on the PBS. Overall survival was estimated from the date of first TRASTUZUMAB EMTANSINE dispensing to the date of death or censoring (censor dates: 30 June 2017/2018/2019/2020) using Kaplan-Meier methods.

4.2 Results

Table 4.2.1: Patient characteristics at the time of first PBS dispensing of TRASTUZUMAB EMTANSINE (1 October 2015 to 30 March 2020)

	n (%)
Patients	1027
Sex	
Female	1014 (98.7)
Male	16 (1.1)
Missing	2 (0.2)
Age at first PBS dispensing	
Median (IQR)	59 (50-68)
State of residence at first PBS dispensing	
ACT	14 (1.4)
NSW	327 (31.8)
NT	9 (0.9)
QLD	198 (19.3)
SA	74 (7.2)
TAS	31 (3.0)
VIC	280 (27.3)
WA	93 (9.1)
Missing	1 (0.1)
Antineoplastic (L01) medicines dispensed in 6 months prior to first PBS dispensing	
Overall	953 (92.8)
Chemotherapy	338 (32.9)
Immunotherapy	2 (0.2)
Targeted therapy (excluding medicine of interest)	939 (91.4)
Antineoplastic (L01) medicines dispensed within 3 months after first PBS dispensing	
Overall	124 (12.1)
Chemotherapy	87 (8.5)
Immunotherapy	1 (0.1)
Targeted therapy (excluding medicine of interest)	83 (8.1)

Table 4.2.2: Initiating and prevalent patients by year of PBS dispensing

Year	Initiating patients	Prevalent patients
2015 (Oct-Dec)	82	82
2016	242	303
2017	220	382
2018	214	402
2019	216	432
2020 (Jan-Mar)	53	290

Of the 1014 patients initiating TRASTUZUMAB EMTANSINE, 635 (61.8%) died prior to the end of follow-up. Median overall survival was estimated as 706 days (95% CI 635-812). Median number of dispensings per person was 10 (IQR 5-23).

Table 4.2.3: Median survival estimate in days (months) since first PBS dispensing of medicine

	Median survival Days (months)	95% confidence interval
Primary analysis	866 (28.9)	782 – 959 (26.1-32.0)
Sensitivity analysis*	706 (23.5)	635 – 812 (21.2-27.1)

* Sensitivity analysis restricts the cohort to patients initiating treatment between 1 October 2015 and 31 March 2020.

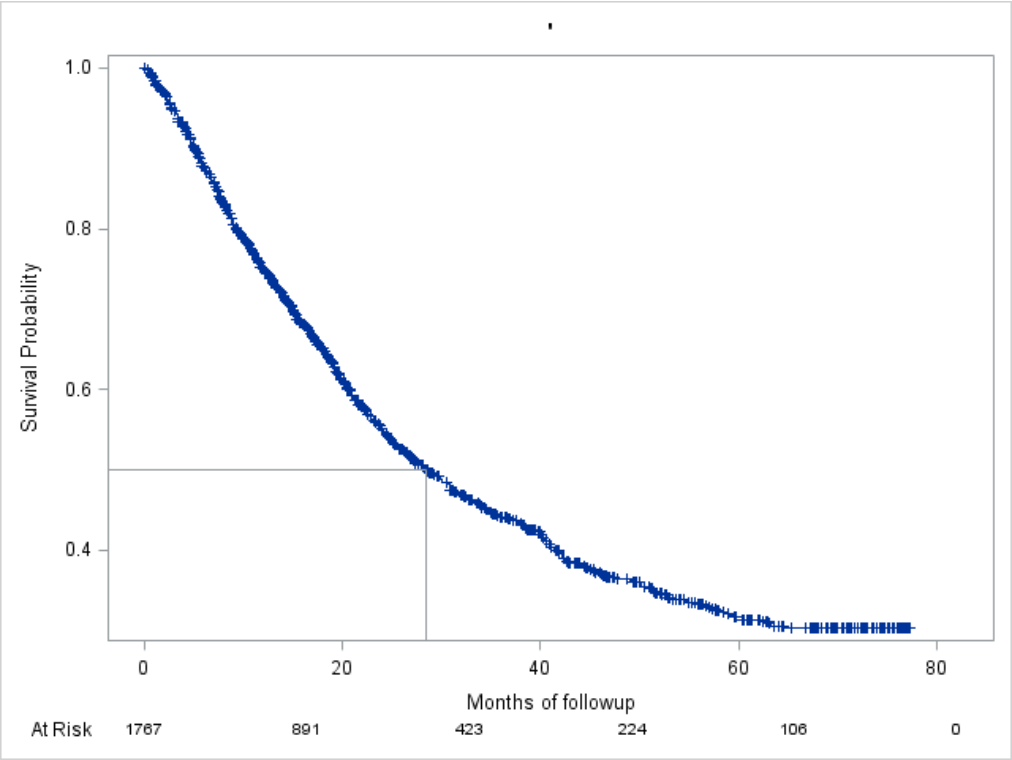


Figure 4.2.3: Kaplan Meier survival curve: primary analysis. [Note: this figure also appears in the Feasibility Assessments, Attachment E]

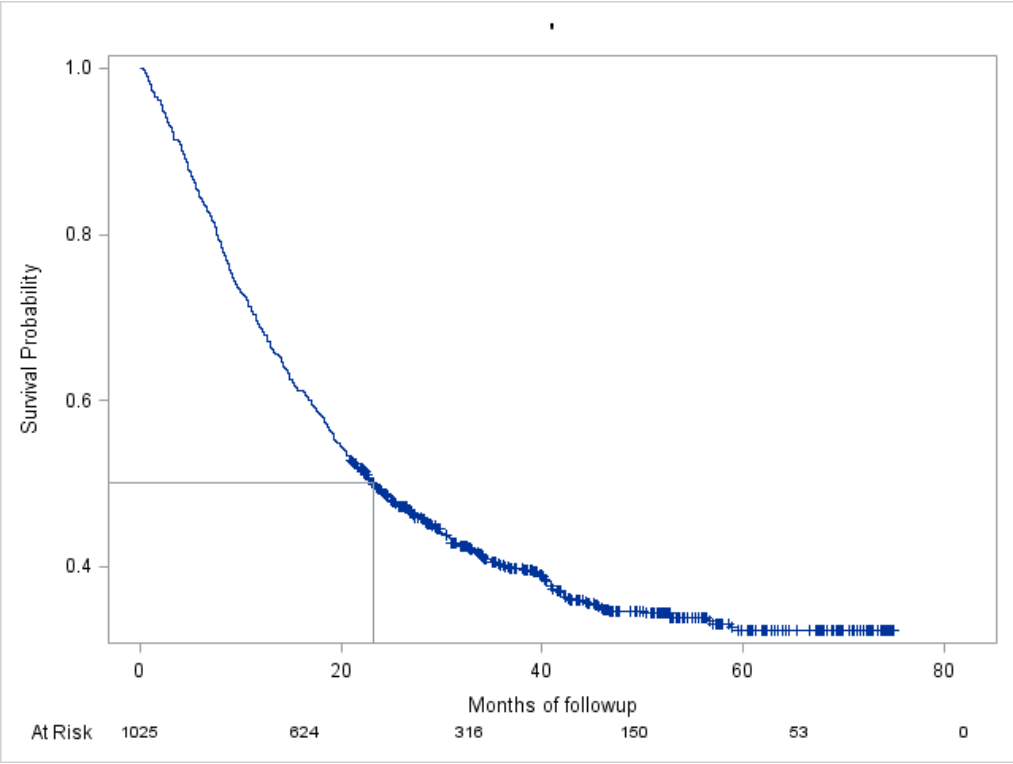


Figure 4.2.4: Kaplan Meier survival curve: sensitivity analysis

Table 4.2.4: Median survival estimates stratified by years of follow-up.

Follow-up end date	Number of Patients initiating*	Number of deaths n (%)	Median survival Days (months)	95% confidence interval
2 years (30 June 2017)	436	132 (30.3)	583 (19.4)	452 (15.1) – insufficient
3 years (30 June 2018)	655	255 (38.9)	623 (20.8)	570 – 725 (19.0 – 24.2)
4 years (30 June 2019)	855	399 (46.7)	650 (21.7)	583 – 715 (19.4 – 23.8)
5 years (30 June 2020)	1027	544 (53.0)	679 (22.6)	616 – 741 (20.5 – 24.7)
6.5 years (31 Dec 2021)	1027	635 (61.8)	706 (23.5)	635 – 812 (21.2 – 27.1)

*Patients initiating trastuzumab emtansine from 1 October 2015 to follow-up end date (31 March 2020 for 5 and 6.5 years) used to generate each OS estimate.

4.3 Summary and discussion

Patients treated with TRASTUZUMAB EMTANSINE for late-stage disease had a median overall survival of 23.5 months. This estimate is five and half months shorter than the OS estimate generated in the primary analysis (28.9 months).

The sensitivity analyses undertaken in the pilot study excluded patients initiating treatment in the first three months of the medicine's PBS listing (sensitivity analysis 1) as well as those initiating treatment following the PBS listing of TRASTUZUMAB EMTANSINE for early-stage disease in April 2020 (sensitivity analysis 2). The OS estimate from the sensitivity analyses is much closer to other real-world OS estimates from the recent literature. A previous Australian study reported a median OS of 19.3 months (Daniels 2021), while two Canadian studies reported median OS estimates of 15.4 and 19.0 months (Gong 2020, Lupichuck 2019). This finding highlights the importance of beginning follow-up from several months following the initial PBS listing as well as the need to account for potential external events that may materially change cohort composition and bias OS estimates. While the primary analysis OS estimate is closer to that reported in the pivotal trial (30.9 months), the estimate is very likely biased. TRASTUZUMAB EMTANSINE is a good example of a new indication altering the characteristics of the cohort receiving the medicine—in this case resulting in healthier, early-stage breast cancer (EBC) patients entering the cohort and likely biasing the OS estimate longer.

Additional cohort restrictions were able to be applied in this pilot study because there was a sufficient time (nearly 5 years) between the PBS listing of TRASTUZUMAB EMTANSINE for late-stage disease (July 2015) and the PBS listing of the medicine for early-stage disease (April 2020). This amount of time also allowed for exploration of how various follow-up durations impact on OS estimates. Table 4.2.4 shows that early initiators may have been comprised of sicker patients, as median OS is four months shorter than the OS estimate based on the full follow-up period. As more time passed since PBS listing, the robustness of the estimates improved, as did the estimate itself.

The pilot study found that 93% of the cohort had received prior anti-neoplastic therapy. This is not unexpected for a medicine like TRASTUZUMAB EMTANSINE, which, during the study period (2015 – 2020) was primarily used as a second-line treatment for metastatic breast cancer. EBC patients who progressed to metastatic disease within 6 months of completing trastuzumab (note,

trastuzumab is a distinct medicine from ‘trastuzumab emtansine’) for EBC were eligible to receive TRASTUZUMAB EMTANSINE as first-line metastatic treatment during the study period. Their inclusion may inflate OS estimates somewhat, however, previous research has shown this group of patients to be a small proportion of those treated with TRASTUZUMAB EMTANSINE (Daniels 2021). The impact of these patients on the median OS estimate is likely small, but approved treatment pathways and where different medicines sit on those pathways are additional external factors that should be considered—and potentially accounted for—when undertaking these analyses. Clinician input will be helpful in identifying issues such as this.

Ultimately, the median OS estimate from Australian patients treated with TRASTUZUMAB EMTANSINE is seven months shorter than the 31 months reported in the pivotal trial. Previous research on real-world outcomes associated with trastuzumab (not ‘emtansine’) have found similar survival discrepancies. This discrepancy in OS is likely due to differences between the characteristics of real-world patients and trial participants. The median age of patients in the pilot study was six years older than that reported in the pivotal clinical trial (53 years). The trial reported that 16% of participants had been treated with trastuzumab for early-stage disease prior to receiving TRASTUZUMAB EMTANSINE. Patients treated with trastuzumab for early-stage disease who relapse and again receive treatment for late-stage disease with trastuzumab and then TRASTUZUMAB EMTANSINE are known to have a worse prognosis than those who are treatment-naïve when beginning treatment for late-stage disease. Staging data were not available for the pilot study, but it is likely the case that a substantially larger proportion of real-world patients had previously been treated with trastuzumab for early-stage disease, which would likely result in a shorter OS estimate. In the case of TRASTUZUMAB EMTANSINE, it may be possible to identify patients treated for early-stage disease with longer lookback periods in the data. For instance, most relapses for HER2-positive breast cancer occur within three years of ending treatment for early-stage disease. Several years of data prior to TRASTUZUMAB EMTANSINE initiation would allow for identification of patients who may have been treated for early-stage disease (if not all of those patients diagnosed with early-stage disease). Clinician input will help in identifying issues such as this and designing strategies to mitigate them.

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A Attachment: Summary of positive PBAC recommendations for cancer treatments for advanced solid tumours (2014-2019)

#	Medicine	PBS Listing Date	Indication	Line of therapy
1	Avelumab	1 May 2019	Merkel cell carcinoma in patients progressed after chemotherapy (or contraindication/intolerance)	Second
2	Bevacizumab	1 Aug 2014	Epithelial ovarian, fallopian tube or primary peritoneal cancer, in combination with paclitaxel and carboplatin	First
3	Bevacizumab	1 Sep 2016	Cervical cancer, in combination with platinum-based chemotherapy or topotecan + paclitaxel	Second
4	Cetuximab	1 Jun 2015	Colorectal cancer (RAS wild-type) in combination with chemotherapy	First
5	Crizotinib	1 Jul 2015	NSCLC (ALK positive)	First
6	Crizotinib	1 Jan 2019	NSCLC c-ROS proto-oncogene 1 (ROS1) positive	First
7	Enzalutamide	1 Dec 2014	Prostate cancer	Second
8	Eribulin	1 Oct 2014	Breast cancer	Third
9	Eribulin	1 Dec 2017	Liposarcoma	Second
10	Erlotinib	1 Jan 2014	NSCLC	First
11	Everolimus	1 Sep 2014	Renal cell carcinoma (clear cell variant)	Second
12	Lanreotide	1 Apr 2018	Non-functional gastroenteropancreatic neuroendrocrine tumours (GEP-NETs)	First
13	Nivolumab	1 Aug 2017	Squamous NSCLC	Second
14	Nivolumab	1 Aug 2017	Non-squamous NSCLC	Second
15	Nivolumab	1 Aug 2017	Renal cell carcinoma (clear cell variant)	Second

16	Nivolumab + Ipilimumab	1 Mar 2019	Renal cell carcinoma (clear cell variant), IMDC intermediate to poor risk	First
17	Osimertinib	1 Feb 2019	NSCLC (EGFR T790 mutation positive)	Second
18	Paclitaxel-nanoparticle albumin bound	1 Nov 2014	Adenocarcinoma of the pancreas, in combination with gemcitabine	First
19	Palbociclib	1 May 2019	Breast cancer (HR+/HER2-), endocrine-based therapy, in non-premenopausal patients, in combination with a non-steroidal aromatase inhibitor (NSAI)	First
20	Panitumumab	1 Apr 2014	Colorectal cancer (K-RAS wild-type)	Second
21	Pazopanib	1 Mar 2014	Soft tissue sarcoma	Second
22	Pembrolizumab	1 Sep 2015	Melanoma	First and second
23	Pembrolizumab	1 Mar 2019	Urothelial cancer	Second
24	Pembrolizumab	1 Nov 2018	NSCLC (EGFR wildtype and ALK translocation negative), PD-L1 tumour proportion score (TPS) >=50%.	First
25	Pertuzumab + Trastuzumab + Trastuzumab Emtansine	1 Jul 2015	Breast cancer (HER2+)	First and second
26	Ribociclib	1 Jul 2018	Breast cancer (HR+/HER2-), endocrine-based therapy, in non-premenopausal patients, in combination with a NSAI	First
27	Sorafenib	1 Apr 2015	Renal cell carcinoma (clear cell variant)	Second
28	Trastuzumab	1 Apr 2016	Adenocarcinoma of the stomach or gastro-oesophageal junction HER2 positive, in combination with cisplatin and either capecitabine or 5-fluorouracil.	First
29	Trifluridine/ tipiracil	1 Dec 2018	Colorectal cancer	Last
30	Vismodegib	1 Apr 2017	Basal cell carcinoma	Second

B Attachment Cancer medicine selection and evaluation worksheet

Selection and evaluation worksheet

The cancer medicines short-listed for review will be based on the key and additional criteria listed in this document. The information relating to the criteria will be identified in the Pharmaceutical Benefits Advisory Committee (PBAC) Public Summary Documents (PSD) and published clinical trials.

Abbreviations

DoH: Department of Health

DUSC: Drug Utilisation Sub-Committee

ESC: Economics Sub-Committee

ICER: Incremental Cost-Effectiveness Ratio

PFS: Progression free survival

PBAC: Pharmaceutical Benefits Advisory Committee

PBS: Pharmaceutical Benefits Scheme

PSD: Public Summary Document

OS: Overall survival

Listing characteristics	Description	Extracted Data
Medicine and dose form	Medicine name and method of delivery	
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	
Place in therapy relative to progression	Indicate first-line or late/last-line	
Date of positive recommendation	Date on PSD	
Date of PBS listing	Date listed, PBS Summary of changes	
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate outcome such as progression free survival • Name the trial(s) reported in the PSD	
Comparator in trial(s) supporting case for listing	• Placebo or active comparator? • For primary comparison only	

Key considerations	Description	Extracted data
Median overall survival (OS)	As stated in PSD for key trial or pooled analysis	
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	
Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	
Large or uncertain budgetary impact	As mentioned in the PSD, for example: • risk-sharing agreement • uncertain incidence of disease • large/uncertain anticipated uptake • large/uncertain size of eligible population	
Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD: Y/N • In most current list of PSDs Additional information may be found at https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets	
Area of unmet need	Mentioned in the PSD Y/N	
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD • Indicated (and/or required by listing) • Anticipated	
Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	
Other significant issues noted in PSD	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	

Additional considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	
Anticipated significant uptake	Was concern raised in the PSD?	
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	
Nature of PBS listing and restriction	• S85 or S100 • written or telephone authority	
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	
Chosen for DUSC review	Mentioned in PSD Y/N	
Analysis methods	• Will analysis be complicated e.g., treatment switching?	
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within same in class. Considerations might include: • testing/monitoring requirements • adverse events • method of delivery (IV vs oral vs injection)	

Trial data worksheet

Key trial data	Description	Extracted Data
Study design	RCT, single arm, etc	
Comparator(s) (if any)		
Trial name and other identifiers	May include informal trial name, internal sponsor identifiers and/or registry numbers (e.g., CT.gov) Date(s) main results published	
Citation(s)		
Inclusion criteria		
Exclusion criteria		
Companion testing		
Prior and concurrent treatments	As specified by the trial protocol	
Subgroup for pharmacoeconomic analysis	If submission was based on data taken from a subgroup rather than the complete trial population.	
Baseline characteristics of trial participants	Age, Sex, Performance Status, Staging, ... Attach a copy of relevant table(s) from PSD or RCT publication	
Endpoint definition e.g., surrogate	List only endpoints discussed in PSD	
Duration of treatment	As reported (days, cycles etc)	
Method used to calculate or extrapolate OS	Refers to methods in submission, not necessarily in publication(s)	
Median OS (or equivalent)	Note if results in PSD differ from those published elsewhere	
Trial quality	As assessed in PSD only	

B.1 Completed worksheets for 12 PBS-listed medicines

B.1.1 Crizotinib (PBS Listed January 2019)

Listing characteristics	Description	Extracted Data
Medicine, dose form	Medicine name and method of delivery	Crizotinib capsules
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	Locally advanced (Stage IIIB) or metastatic (Stage IV) c-ROS proto-oncogene 1 (ROS1) positive non-small cell lung cancer (NSCLC). Performance state <=2
Place in therapy relative to progression	Indicate first-line or late/last-line	Late
Date of positive recommendation	Date on PSD	July 2018
Date of PBS listing	Date listed, PBS Summary of changes	January 2019
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate outcome such as progression free survival • Name the trial(s) reported in the PSD	OS. A8081001 (PROFILE 1001) and OO12-01 -- pooled results (n=53 and n=127). Pooled n=53 (?)
Comparator in trial(s) supporting case for listing	• Placebo or active comparator? • For primary comparison only	Single arm results, naive comparison with pemetrexed arm of second line RCT.

Key considerations	Description	Extracted data
Median overall survival		51.4 months
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	Yes. The ESC considered that incremental OS was likely to be overestimated, as (i) crizotinib studies employed censoring practices resulting in patients being censored for reasons other than loss to follow-up; and (ii) the magnitude of OS benefit with crizotinib was unknown as only 31% of patients had died in the pooled crizotinib analysis. Also, ESC considered the extrapolated PFS and OS for crizotinib were overestimated because substantial post-progression survival was assumed.
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	Naive comparison did not allow for AE rates to be compared with comparator. The PBAC considered that the submission's claim of non-inferior safety compared with pemetrexed was reasonable but noted that the fatal adverse event rate in the crizotinib studies (17% and [redacted]%) appeared to be greater than for pemetrexed (1%).
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	Yes. Unselected pemetrexed population (re: c-ROS status); differences in proportion of patients with performance status 2, metastatic disease at baseline, prior use of chemotherapy and ethnicity. Exponential extrapolation.
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	No
Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	https://pubmed.ncbi.nlm.nih.gov/30980071/ (extension of PROFILE 1001): Median OS 51.4 months

		https://www.jto.org/article/S1556-0864(19)30276-X/fulltext (EUCROSS) Median OS not reached https://pubmed.ncbi.nlm.nih.gov/31416808/ (METROS) Median OS not reached High VTE rates in ROS1 NSCLC (tx related?): https://www.clinical-lung-cancer.com/article/S1525-7304(19)30154-8/fulltext
Large or uncertain budgetary impact	As mentioned in the PSD, for example: • risk-sharing agreement • uncertain incidence of disease • large/uncertain anticipated uptake • large/uncertain size of eligible population	No. No RSA. The ESCs considered that the financial implications of ROS1 testing and crizotinib treatment were modestly underestimated
Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD: Y/N • In most current list of PSDs Additional information may be found at https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets	Entrectinib, August 2020
Area of unmet need	Mentioned in the PSD Y/N	Y
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD • Indicated (and/or required by listing) • Anticipated	No (sole therapy)
Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	June 2015, ALK-positive NSCLC
Other significant issues noted in PBAC review	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	Transitivity issues with indirect comparisons. The ESCs considered that improvements in clinical practice since Hanna et al. 2004 was conducted would have resulted in improvements in NSCLC survival in the chemotherapy arm.

Other considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	Y
Anticipated significant uptake	Was concern raised in the PSD?	No
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	No
Nature of listing and restriction	• S85 or S100 • written versus telephone authority	S85 written authority
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	3
Chosen for DUSC review	Mentioned in PSD Y/N	N
Analysis methods	To consider after PSD review • Will analysis be complicated e.g., treatment switching? • Will there be data on a suitable comparator? • Is data available for OS estimates?	
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within same in class. Considerations might include: • testing/monitoring requirements • adverse events • method of delivery (IV vs oral vs injection)	This treatment is only indicated in a very rare subtype of lung cancer (ROS1), so sufficient patient numbers may be a feasibility consideration. Access is also contingent on availability of ROS1 testing (not performed at every hospital), which may reduce the study population further if not widely undertaken. Oral medication and generally well-tolerated. No specific testing/monitoring

		requirements outside usual blood tests and scans.

B.1.2 Ipilimumab (PBS Listed August 2013)

Listing characteristics	Description	Extracted Data
Medicine and dose form	Medicine name and method of delivery	Ipilimumab Concentrate solution for IV infusion
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	• unresectable stage III or stage IV malignant melanoma • not responded to or were intolerant to prior systemic therapy for metastatic disease
Place in therapy relative to progression	Indicate first-line or late/last-line	Second-line • Induction treatment (4 doses) after failure of prior therapy • Re-induction in patients who progressed after initial response
Date of positive recommendation	Date on PSD	November 2012
Date of PBS listing	Date listed, PBS Summary of changes	August 2013
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate outcome such as progression free survival • Name the trial(s) reported in the PSD	Direct Phase III RCT CT-20 Multiple Phase II trials: CR-004, CT-007, CT-008, CT-022, CT-024
Comparator in trial(s) supporting case for listing	• Placebo or active comparator? • For primary comparison only	CT-20 glycoprotein 100 (gp100) peptide vaccine CT-024 ipilimumab alongside dacarbazine vs dacarbazine and placebo No comparator for other trials

Key considerations	Description	Extracted data
Median overall survival (OS)	As stated in PSD for key trial or pooled analysis	10.1 months (8.0-13.8)
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	PSD mentioned small numbers at end of survival curves and uncertainty about magnitude of benefit. Plateau effect noted
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	Large proportion in trial discontinued due to adverse events
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	
Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	Pooled median OS 11.4 months (95% CI, 10.7 to 12.1 months) www.ncbi.nlm.nih.gov/pmc/articles/PMC5089162/
Large or uncertain budgetary impact	As mentioned in the PSD, for example: risk-sharing agreement uncertain incidence of disease large/uncertain anticipated uptake large/uncertain size of eligible population	Risk-sharing agreement Small numbers of patients in trial at end of study, may be too small to extrapolate economic models Uncertain eligibility and uptake, likely to be substantially higher
Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD: Y/N • In most current list of PSDs Additional information may be found at https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets	Pembrolizumab Sept 2015
Area of unmet need	Mentioned in the PSD Y/N	Y
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD Indicated (and/or required by listing) Anticipated	monotherapy

Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	Stage IV clear cell variant renal cell carcinoma Stage IV (metastatic) non-small cell lung cancer (NSCLC) Unresectable malignant mesothelioma
Other significant issues noted in PBAC review	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	No comparator in most trials Patient populations and/or dosing in trials was different to listing

Additional considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	First in class
Anticipated significant uptake	Was concern raised in the PSD?	Y
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	Patient population under three trial protocols differed from listing Dosing in trials was different from listing
Nature of listing and restriction	S85 or S100 written or telephone authority	S100
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	4
Chosen for DUSC review	Mentioned in PSD Y/N	N
Analysis methods	Will analysis be complicated e.g., treatment switching?	May be difficult to distinguish between induction and re-induction
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within same in class. Considerations might include: testing/monitoring requirements adverse events	

	method of delivery (IV vs oral vs injection)	

B.1.3 Ipilimumab–Nivolumab (PBS Listed March 2019)

Listing characteristics	Description	Extracted Data
Medicine, dose form	Medicine name and method of delivery	Ipilimumab and nivolumab (both medicines given in combination) Injection concentrate for IV infusion
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	For Stage IV clear cell variant renal cell carcinoma (solid tumour) Palliative treatment Other criteria: WHO performance status 0-2, IMDC intermediate to poor risk group
Place in therapy relative to progression	Indicate first-line or late/last-line	First-line
Date of positive recommendation	Date on PSD	November 2018
Date of PBS listing	Date listed, PBS Summary of changes	March 2019 (combination for current indication)
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate outcome such as progression free survival • Name the trial(s) reported in the PSD	Co-primary endpoints were OS, ORR and PFS among patients with intermediate or poor prognostic risk CA209-214 trial (CheckMate 214)
Comparator in trial(s) supporting case for listing	• Placebo or active comparator? • For primary comparison only	Sunitinib (active comparator)

Key considerations	Description	Extracted data
Median overall survival		47 months (press release)
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	Data are indicative of an important improvement in OS. However, the absolute magnitude of the treatment effect could not be reliably estimated because the OS were immature (median OS not reached for intervention arm). Trial may have overestimated effectiveness, and underestimated toxicity as the trial population may have been healthier than the likely PBS population.
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	Trial may have overestimated effectiveness, and underestimated toxicity as the trial population may have been healthier than the likely PBS population.
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	
Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	Updated follow-up 2020: OS HR 0.65, mOS still not reached for intervention arm (Ref: Albiges L, et al Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO Open. 2020 Nov;5(6):e001079. doi: 10.1136/esmoopen-2020-001079. Press release 2021: mOS 47 vs 27m, HR 0.68 (URL: https://news.bms.com/news/corporate-

		financial/2021/Five-Year-Data-from-CheckMate--214-Show-Opdivo-nivolumab-Plus-Yervoy-ipilimumab-Demonstrates-Longest-Median-Overall-Survival-Currently-Reported-in-Phase-3-Trial-of-Patients-with-Previously-Untreated-Advanced-or-Metastatic-Renal-Cell-Carcinoma/default.aspx)
Large or uncertain budgetary impact	As mentioned in the PSD, for example: • risk-sharing agreement • uncertain incidence of disease • large/uncertain anticipated uptake • large/uncertain size of eligible population	Proposed RSA with 100% rebate beyond estimated utilisation (Less than 10,000 in Year 1, less than 10,000 in Year 6)
Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD: Y/N • In most current list of PSDs Additional information may be found at https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets	Nivolumab August 2017
Area of unmet need	Mentioned in the PSD Y/N	"There is a high clinical need for effective first-line therapies for RCC, especially in the poor prognostic risk patient population for whom no PBS-subsidised therapies are available"
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD • Indicated (and/or required by listing) • Anticipated	Ipilimumab and nivolumab to be given concomitantly
Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	Nivolumab/ipilimumab for Stage III/IV melanoma Ipilimumab monotherapy for Stage III/IV melanoma Nivolumab/ipilimumab+chemotherapy for Stage IV non-small cell lung cancer Nivolumab/ipilimumab for malignant mesothelioma

Other significant issues noted in PBAC review	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	

Other considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	First in class for this indication
Anticipated significant uptake	Was concern raised in the PSD?	
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	
Nature of listing and restriction	• S85 or S100 • written versus telephone authority	S100 Streamlined
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	4 (substantial benefit)
Chosen for DUSC review	Mentioned in PSD Y/N	No
Analysis methods	To consider after PSD review • Will analysis be complicated e.g., treatment switching? • Will there be data on a suitable comparator? • Is data available for OS estimates?	
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within same in class. Considerations might include: • testing/monitoring requirements • adverse events	IV delivery High rate of adverse events (Grade 3-4 adverse events requiring hospitalisation in 46% of ipilimumab/nivolumab recipients) “Adverse events may be challenging to manage outside major tertiary centres,

	• method of delivery (IV vs oral vs injection)	where there a need for improved access to immune-modulating rescue therapies." It is only indicated for intermediate-poor risk patients; however, this is a clinical classification so we would not be able to ascertain whether clinicians followed these guidelines, or whether they extended it to patients with good prognosis. If the latter, it may result in higher-than-expected patient numbers and/or artificially inflate survival estimates due to better prognosis of patients.

B.1.4 Lanreotide (PBS Listed April 2018)

Listing characteristics	Description	Extracted Data
Medicine, dose form	Medicine name and method of delivery	Lanreotide Form: Injection 120 mg (as acetate) in single dose pre-filled syringe (120mg/0.5mL injection)
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	Gastroenteropancreatic neuroendrocrine tumours (GEP-NETs) Stage: Stage III-IV Adults (18+) with unresectable locally advanced or metastatic non-functional GP-NETs. 13 injections per year (6.5 scripts for 2x120mg)
Place in therapy relative to progression	Indicate first-line or late/last-line	First
Date of positive recommendation	Date on PSD	November 2017

Date of PBS listing	Date listed, PBS Summary of changes	1 April 2018 (medicine first listed 1 Feb 2004)
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate outcome such as progression free survival • Name the trial(s) reported in the PSD	PFS Median OS not achieved Trial: CLARINET lanreotide vs placebo (Watchful Waiting) n=204 Long-term data from post-trial n=88
Comparator in trial(s) supporting case for listing	• Placebo or active comparator? • For primary comparison only	Placebo – watchful waiting (WW) Long-term data from open-label extension study (n=88)

Key considerations	Description	Extracted data
Median overall survival		38.5 months (PFS)
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	Yes. PFS was statistically significant for lanreotide. Clinical significance of gain in PFS was uncertain as it was based on radiologic progression & may not change clinical symptoms. Median PFS was 72 weeks for placebo group and not reached for lanreotide group.
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	No. Inferior with respect to adverse-events. PBAC considered claim for superior efficacy for PFS and inferior safety to be appropriate.
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	No

Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	2021 CLARINET results https://pubmed.ncbi.nlm.nih.gov/33052555/ Median PFS 38.5 months
Large or uncertain budgetary impact	As mentioned in the PSD, for example: • risk-sharing agreement • uncertain incidence of disease • large/uncertain anticipated uptake • large/uncertain size of eligible population	Yes. Decision deferred until price & cap were negotiated to adequately off-set the uncertainty about the cost-effectiveness. RSA with annual cap. RSA to mitigate against: - higher than expected number of patients converting to lanreotide from WW - uncertain rates of utilisation in patients with post-progressive disease.
Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD: Y/N • In most current list of PSDs Additional information may be found at https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets	No Potentially relevant comparators in the post-progression setting include octreotide, sunitinib, everolimus, interferon alfa-2b, cytotoxic chemotherapy, peptide receptor radionuclide therapy.
Area of unmet need	Mentioned in the PSD Y/N	Y
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD • Indicated (and/or required by listing) • Anticipated	No, must be monotherapy
Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	None
Other significant issues noted in PBAC review	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	

Other considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	Y
Anticipated significant uptake	Was concern raised in the PSD?	Yes. Concerned patient population will be higher as more switch from WW and it gets used for post-progressive disease.
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	No
Nature of listing and restriction	• S85 or S100 • written versus telephone authority	S100 Highly specialised drug program Streamlined authority
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	
Chosen for DUSC review	Mentioned in PSD Y/N	N
Analysis methods	To consider after PSD review • Will analysis be complicated e.g., treatment switching? • Will there be data on a suitable comparator? • Is data available for OS estimates?	
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within same in class. Considerations might include: • testing/monitoring requirements • adverse events • method of delivery (IV vs oral vs injection)	Subcutaneous injectable drug can be administered by nurses in outpatient/GP settings. Well-tolerated. This drug is primarily used to control symptoms and delay progression.

B.1.5 Nivolumab (PBS Listed August 2017)

Listing characteristics	Description	Extracted Data
Medicine and dose form	Medicine name and method of delivery	Nivolumab Injection concentrate for I.V. infusion
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	Advanced squamous and non-squamous non-small cell lung cancer (solid tumour) Palliative intent Stage IV Following progression after treatment with platinum-based chemotherapy
Place in therapy relative to progression	Indicate first-line or late/last-line	Second-line therapy
Date of positive recommendation	Date on PSD	March 2017
Date of PBS listing	Date listed, PBS Summary of changes	August 2017
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate outcome such as progression free survival • Name the trial(s) reported in the PSD	OS primary endpoint for both trials CA209-017 (CheckMate 017) CA209-057 (CheckMate-057)
Comparator in trial(s) supporting case for listing	• Placebo or active comparator? • For primary comparison only	Active comparator (docetaxel chemotherapy)

Key considerations	Description	Extracted data
Median overall survival		12.2 months
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	The PBAC queried the effectiveness of nivolumab in patients aged 75 years or older, and also regarding difference in clinical benefit based on predictive biomarkers (e.g., PD-L1). Resubmission included age-based subgroup analyses and additional data examining the treatment effect of PD-L1 status to address show that

		nivolumab had clinical benefit irrespective of age or PD-L1 status.
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	
Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	5-year outcomes published 2021 https://ascopubs.org/doi/full/10.1200/JCO.20.01605 Five-year pooled OS rates were 13.4% versus 2.6%
Large or uncertain budgetary impact	As mentioned in the PSD, for example: • risk-sharing agreement • uncertain incidence of disease • large/uncertain anticipated uptake • large/uncertain size of eligible population	Yes "A rebate for greater than expected use in older patients, that being use in more than xx% of patients aged 75 years or older, with the minor re-submission suggesting that greater than expected use is attributable to patients with an ECOG performance-status>1 (i.e., use outside the proposed PBS restriction)." "A risk sharing arrangement proposed by the sponsor adequately addressed concerns regarding the possible variation in the extent of effectiveness in patients 75 years or older, and uncertainties regarding the ICERs presented in the November 2016 submissions, the overall numbers using nivolumab in NSCLC, the risk of leakage of nivolumab outside of the intended restriction, and the duration of nivolumab treatment."

Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD: Y/N • In most current list of PSDs Additional information may be found at https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets	Yes, for Stage IV NSCLC, not specifically for second-line Atezolizumab Atezolizumab + bevacizumab in combination with platinum doublet chemotherapy
Area of unmet need	Mentioned in the PSD Y/N	No
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD • Indicated (and/or required by listing) • Anticipated	
Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	Nivolumab/ipilimumab for Stage IV renal cell carcinoma Nivolumab for unresectable, recurrent head and neck squamous cell carcinoma Nivolumab/ipilimumab for Stage III/IV melanoma Nivolumab/ipilimumab+chemotherapy for Stage IV non-small cell lung cancer Nivolumab/ipilimumab for malignant mesothelioma
Other significant issues noted in PBAC review	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	

Other considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	First in class for this indication
Anticipated significant uptake	Was concern raised in the PSD?	
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	Trial population and PBS restriction require ECOG WHO 0-1. However, it was anticipated that there would be use outside

		this population “greater than expected use is attributable to patients with an ECOG performance-status>1”
Nature of listing and restriction	• S85 or S100 • written versus telephone authority	S100 Streamlined
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	5 (substantial benefit)
Chosen for DUSC review	Mentioned in PSD Y/N	No
Analysis methods	To consider after PSD review • Will analysis be complicated e.g., treatment switching? • Will there be data on a suitable comparator? • Is data available for OS estimates?	
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within same in class. Considerations might include: • testing/monitoring requirements • adverse events • method of delivery (IV vs oral vs injection)	Now likely uncommonly used as current treatment algorithm for advanced NSCLC recommends immunotherapy as first-line treatment

B.1.6 Nivolumab (PBS Listed August 2018)

Listing characteristics	Description	Extracted Data
Medicine and dose form	Medicine name and method of delivery	Medicine: Nivolumab Dose: Injection concentrate for I.V. infusion, 40 mg in 4 mL and 100 mg in 10 mL
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	Recurrent/metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx (RM SCCHN) in patients who have progressed within 6 months after platinum-based chemo (CT) Last considered by PBAC in November 2017.
Place in therapy relative to progression	Indicate first-line or late/last-line	Second-line
Date of positive recommendation	Date on PSD	March 2018
Date of PBS listing	Date listed, PBS Summary of changes	August 2018
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate outcome such as progression free survival • Name the trial(s) reported in the PSD	Outcomes: OS, PFS Trial name: CheckMate (https://www.nejm.org/doi/full/10.1056/nejmoa1602252)
Comparator in trial(s) supporting case for listing	• Placebo or active comparator? • For primary comparison only	Random 2:1 assignment to nivolumab alone (TREATMENT) or physician's choice of docetaxel, methotrexate, or cetuximab (CONTROL).

Key considerations	Description	Extracted data
Median overall survival		7.5 months
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	'Applicability of the results to the Australian setting remained uncertain.' The PBAC remained particularly uncertain about the consequence of replacing cetuximab with capecitabine as a comparator on the incremental effectiveness of nivolumab.' (ß not addressed in 2018 submission) 'The PBAC was concerned that the results of a subgroup analysis showed that OS HR was more favourable when nivolumab was compared to cetuximab, than to methotrexate or docetaxel, noting that this disparity in comparators contributed to uncertainty in estimating the magnitude of incremental clinical benefit derived with nivolumab in the Australian clinical setting' (ß not addressed in 2018 submission) 'The PBAC was also concerned regarding the likely reduced effectiveness of nivolumab in the older patient population (>75 years).' (ß not addressed in 2018 submission)
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	• PBAC noted the log-logistic function used to extrapolate OS was the "least conservative choice" and that exponential curves "would have been

		the most appropriate method for extrapolation".
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	NA
Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	NA
Large or uncertain budgetary impact	As mentioned in the PSD, for example: • risk-sharing agreement • uncertain incidence of disease • large/uncertain anticipated uptake • large/uncertain size of eligible population	• risk-sharing agreement • Concerns around comparators and likely Australian population using nivolumab; still concerned about efficacy in 75+ Australia population
Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD: Y/N • In most current list of PSDs Additional information may be found at https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets	cetuximab was subsequently listed as first-line treatment for this cancer. Not mentioned in the PSD (listed in 2019)
Area of unmet need	Mentioned in the PSD Y/N	PBAC note uncertainty to the degree nivolumab meets an unmet need but, ultimately, they imply they do believe an unmet need is met by nivolumab.
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD • Indicated (and/or required by listing) • Anticipated	nivolumab alone
Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	renal cell carcinoma, malignant melanoma, NSCLC, mesothelioma
Other significant issues noted in PBAC review	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	

Other considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	First in class for this indication
Anticipated significant uptake	Was concern raised in the PSD?	overestimation of the uptake rate
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	Concerns over efficacy in older patients.
Nature of listing and restriction	• S85 or S100 • written versus telephone authority	• S100 • Streamlined authority
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	ESMO-MCBS for nivolumab for RM SCCHN: 5
Chosen for DUSC review	Mentioned in PSD Y/N	N
Analysis methods	To consider after PSD review • Will analysis be complicated e.g., treatment switching? • Will there be data on a suitable comparator? • Is data available for OS estimates?	• Suitable comparator would be any one of several CTs alone and it would be difficult to determine who was getting which CT without nivolumab for RM SCCHN • Should be sufficient data for OS estimates
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within same in class. Considerations might include: • testing/monitoring requirements • adverse events	IV infusion PBS listing restricts use to patients with performance status ECOG 0-1. Anecdotally clinicians may use this in patients with poor performance status (ECOG 2+). This may increase the study population and also result in shorter OS estimates due to inclusion of poorer prognosis patients.

	• method of delivery (IV vs oral vs injection)	

B.1.7 Olaparib (PBS Listed February 2017)

Listing characteristics	Description	Extracted Data
Medicine and dose form	Medicine name and method of delivery	Olaparib Capsule 50 mg
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	High grade serous ovarian cancer High grade serous fallopian tube cancer High grade serous primary peritoneal cancer Platinum sensitive, after relapse of Pt containing regimen Patient must have evidence of a germline class 4 or 5 BRCA1 or BRCA2 gene mutation
Place in therapy relative to progression	Indicate first-line or late/last-line	Initial/continuing after platinum therapy
Date of positive recommendation	Date on PSD	November 2016
Date of PBS listing	Date listed, PBS Summary of changes	Feb 2017
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate such as progression free survival • Name the trial(s) used in the PBAC assessment	PFS (BRCA subgroup analysis) Randomized, double-blind, placebo-controlled, phase 2 study (Study 19)
Comparator in trial(s) supporting case for listing	• Placebo or active comparator? • For primary comparison only	Placebo

Key considerations	Description	Extracted data
Median overall survival (OS)	As stated in PSD for key trial or pooled analysis	Interim analysis BRCA1/2 subgroup 34.9 months (29.2-NC) (from March 2016 PSD), no sig diff with placebo
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	Economic model changed from March 2016 initial submission; horizon reduced from 10 years to 7.5 years. Missing data on BRCA status noted in subgroup analysis, request for test of interaction between subgroups for PFS (p=0.03)
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	Inferior comparative safety noted
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	Planned BRCAm subgroup analysis did not account for crossover to Olaparib in placebo arm (Ledermann 2014), post hoc analysis did (Matulonis 2015). Missing data on BRCA status noted in subgroup analysis Log-logistic model used to extrapolate OS, no sig diff between groups in interim analysis
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	Uncertain risk of bias
Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	OS 34.9 months in BRCAm group (Ledermann 2016) https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(16)30376-X/fulltext
Large or uncertain budgetary impact	As mentioned in the PSD, for example: • risk-sharing agreement • uncertain incidence of disease • large/uncertain anticipated uptake • large/uncertain size of eligible population	Risk-sharing agreement/Special pricing arrangements Uncertainty around duration of use: PSD mentioned that results might not be generalisable to Australian clinical practice which would monitor for progression less frequently.

Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD or among listings table	Bevacizumab (1 August 2014)
Area of unmet need	Mentioned in the PSD Y/N	Orphan drug designation by TGA Jan 2015
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD • Indicated (and/or required by listing) • Anticipated	None
Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	None
Other significant issues noted in PBAC review	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	Most concerns over missing BRCA status and implications for cost-effectiveness

Additional considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	Orphan drug (first in class?)
Anticipated significant uptake	Was concern raised in the PSD?	N
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	
Nature of listing and restriction	• S85 or S100 • written or telephone authority	Written or telephone authority
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	3 (metastatic) 4 (advanced)
Chosen for DUSC review	Mentioned in PSD Y/N	N

Analysis methods	• Will analysis be complicated e.g., treatment switching?	In 2020, listing changed to initial treatment as well as after progression following Pt chemotherapy
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within same in class. Considerations might include: • testing/monitoring requirements • adverse events • method of delivery (IV vs oral vs injection)	

B.1.8 Panitumumab (PBS Listed April 2014)

Listing characteristics	Description	Extracted Data
Medicine and dose form	Medicine name and method of delivery	Panitumumab 100 mg/5 ml and 400 mg/20 ml injection
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	Colorectal cancer K-RAS wild-type metastatic colorectal cancer in patients who have failed first-line chemotherapy
Place in therapy relative to progression	Indicate first-line or late/last-line	Second
Date of positive recommendation	Date on PSD	November 2013
Date of PBS listing	Date listed, PBS Summary of changes	1 April 2014
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate outcome such as progression free survival • Name the trial(s) reported in the PSD	• OS (Non-inferior, NI margin 50%) • ASPECCT trial
Comparator in trial(s) supporting case for listing	• Placebo or active comparator?	Cetuximab (non-inferior)

	• For primary comparison only	

Key considerations	Description	Extracted data
Median overall survival (OS)	As stated in PSD for key trial or pooled analysis	10.4 months
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	ASPECCT was non-inferiority trial of third line monotherapy treatment, uncertainty over use as second line therapy either alone or in combination with chemotherapy Variable treatment effect with different RAS mutations mentioned
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	Higher incidence of adverse events grade 3 (drug related or any) than cetuximab, hypomagnesaemia and hypokalaemia but lower rate of infusion reactions (IRs), pyrexia, constipation and abdominal pain Difference in IRs not considered to affect healthcare resources provided to patients
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	Non-inferiority assessed using a historical trial (CO.17) of cetuximab over best supportive care (BSC) but no there was no BSC arm in ASPECCT so similar relative treatment effect assumed
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	
Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	Median OS 10.2 months https://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.3586

Large or uncertain budgetary impact	As mentioned in the PSD, for example: • risk-sharing agreement • uncertain incidence of disease • large/uncertain anticipated uptake • large/uncertain size of eligible population	• Cost-minimisation basis compared with cetuximab (comparator in non-inferiority trial) • Risk-sharing agreement with cetuximab • Cost savings to other budget lines considered to be over-estimates
Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD: Y/N • In most current list of PSDs Additional information may be found at https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets	Cetuximab
Area of unmet need	Mentioned in the PSD Y/N	No
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD • Indicated (and/or required by listing) • Anticipated	Monotherapy OR in combination with an irinotecan-based therapy
Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	Initial treatment for wild type RAS metastatic colorectal cancer in combination with first-line chemotherapy
Other significant issues noted in PBAC review	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	

Additional considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	Follow-up medicine
Anticipated significant uptake	Was concern raised in the PSD?	N
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	Patients must have a WHO performance status of 2 or less Restricted to wild type K-RAS mutations (now RAS on PBS website)

Nature of listing and restriction	• S85 or S100 • written or telephone authority	S100 Streamlined
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	3 (for wild-type RAS)
Chosen for DUSC review	Mentioned in PSD Y/N	N
Analysis methods	• Will analysis be complicated e.g., treatment switching?	Possible switching to/from cetuximab Was listing condition changed from wild type K-RAS in November 2013 to wild-type RAS at a later date? Now listed for initial treatment in combination with chemo
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within same in class. Considerations might include: • testing/monitoring requirements • adverse events • method of delivery (IV vs oral vs injection)	

B.1.9 Pembrolizumab (PBS Listed March 2019)

Listing characteristics	Description	Extracted Data
Medicine and dose form	Medicine name and method of delivery	Pembrolizumab Solution concentrate for IV infusion 100 mg in 4 mL
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
Place in therapy relative to progression	Indicate first-line or late/last-line	Second line after failure of a platinum-based therapy
Date of positive recommendation	Date on PSD	July 2018
Date of PBS listing	Date listed, PBS Summary of changes	March 2019
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate outcome such as progression free survival • Name the trial(s) reported in the PSD	• overall survival (OS) and progression-free survival • KEY-NOTE 045
Comparator in trial(s) supporting case for listing	• Placebo or active comparator? • For primary comparison only	Standard of care; paclitaxel 175 mg/m2 IV, once every 3 weeks, or docetaxel 75 mg/m2, IV once every 3 weeks

Key considerations	Description	Extracted data
Median overall survival		10.3 months
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	• Modest but statistically significant OS gain • PFS not higher than comparator • A difference in OS but no difference in PFS suggested that pembrolizumab may be effective in some patients and

		not others, indicating that better targeting of this treatment may be useful • Concerns raised regarding costs of fixed dose vs dosing by weight • Time horizon changed in modelling
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	• A warning included for a higher risk of death in the pembrolizumab arm than the chemotherapy arm • Lower risk of AEs for pembrolizumab in trials
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	• Not all Kaplan-Meier data was used in the extrapolation of survival benefit • PBAC requested time on treatment be used instead of PFS for duration of treatment • Different parametric distributions used across arms for PFS and OS • PBAC requested conservative extrapolation be used due to limited follow-up data
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	Moderate risk of bias noted, mainly due to open label trial Patients could continue therapy beyond progression if there was clinical benefit, up to 24 months of treatment
Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	>2–year follow-up reported in 2019 https://www.sciencedirect.com/science/article/pii/S0923753419312104
Large or uncertain budgetary impact	As mentioned in the PSD, for example: • risk-sharing agreement • uncertain incidence of disease • large/uncertain anticipated uptake	• risk sharing agreement/Special pricing arrangement • Uncertainty about number of eligible patients (restriction to after failure of platinum-based therapy only)

	• large/uncertain size of eligible population	• PBAC considered the number of patients used in economic modelling was an underestimate • Uncertain incidence of disease noted
Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD: Y/N • In most current list of PSDs Additional information may be found at https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets	Not in PSD Not in current list
Area of unmet need	Mentioned in the PSD Y/N	N
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD • Indicated (and/or required by listing) • Anticipated	None
Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	• Unresectable Stage III or Stage IV malignant melanoma • Relapsed or Refractory Hodgkin lymphoma • Stage IV (metastatic) non-small cell lung cancer (NSCLC) • Resected Stage IIIB, Stage IIIC or Stage IIID malignant melanoma • Relapsed or refractory primary mediastinal B-cell lymphoma • Unresectable or metastatic deficient mismatch repair (dMMR) colorectal cancer
Other significant issues noted in PBAC review	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	TGA approval restriction also includes treatment for cisplatin ineligible patients first line. The ESC noted that if a patient was not able to use cisplatin, then carboplatin would be the alternative therapy, and it was therefore likely that the risk of use outside the requested indication was mostly in

		patients who were ineligible for any chemotherapy. ESC raised uncertainty over treatment switching and time horizons
Other considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	First in class
Anticipated significant uptake	Was concern raised in the PSD?	Yes, numbers in submission considered an underestimate
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	Unknown if patients have • WHO performance status of 2 or less • progression after failure of platinum-based therapy
Nature of listing and restriction	• S85 or S100 • written versus telephone authority	• S100 • Streamlined authority
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	ESMO 4
Chosen for DUSC review	Mentioned in PSD Y/N	Resubmission not reviewed by DUSC
Analysis methods	To consider after PSD review • Will analysis be complicated e.g., treatment switching? • Will there be data on a suitable comparator? • Is data available for OS estimates?	• Time on chemo before switching may differ between patients • OS < 12 months so enough data in PBS • Comparator is standard of care (including paclitaxel or docetaxel)
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within same in class. Considerations might include:	• Delivery by IV infusion • No additional adverse events or monitoring considerations

	• testing/monitoring requirements • adverse events • method of delivery (IV vs oral vs injection)	

B.1.10 Ribociclib (PBS Listed July 2018)

Listing characteristics	Description	Extracted Data
Medicine and dose form	Medicine name and method of delivery	Ribociclib 200mg tablet
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	non premenopausal hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2-) locally advanced, metastatic, inoperable breast cancer
Place in therapy relative to progression	Indicate first-line or late/last-line	First line
Date of positive recommendation	Date on PSD	March 2018
Date of PBS listing	Date listed, PBS Summary of changes	July 2018
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate outcome such as progression free survival • Name the trial(s) reported in the PSD	• Progression free survival • MONALEESA-2 trial (comparison with placebo + letrozole) • PALOMA-2 trial, indirect comparison with palbociclib + letrozole
Comparator in trial(s) supporting case for listing	• Placebo or active comparator? • For primary comparison only	ribociclib + letrozole vs • Placebo + letrozole (direct) • palbociclib + letrozole (indirect)

Key considerations	Description	Extracted data
Median overall survival		63.9 months
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	PBAC noted that gain in life years from the economic model was highly uncertain due to OS estimates not yet available. Concerns over time horizons used, truncated to 7 years
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	PBAC noted high rate of adverse events in MONALEESA-2 trial leading to dose changes or interruption. Particularly mentioned the rate of Grade 3+ AEs and the prolongation of the QTc interval, which may be greater in the PBS population
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	Only a Weibull function used to extrapolate the OS showed a benefit, a sensitivity analysis using other functions increased the ICER
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	Median OS not reached, difference in OS was in favour of ribociclib but not statistically significant, PBAC noted that if there is no survival gain for patients treated with ribociclib, then gains in PFS would appear to be at the expense of reduced post-progression survival
Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	Yes, OS published in 2021 (63.9 months) https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/overall-survival-os-results-from-the-phase-iii-monaleesa-2-ml-2-trial-of-postmenopausal-patients-pts-with-hormone-receptor-positive-human-epi
Large or uncertain budgetary impact	As mentioned in the PSD, for example: • risk-sharing agreement	• risk-sharing agreement

	• uncertain incidence of disease • large/uncertain anticipated uptake • large/uncertain size of eligible population	• uncertain uptake, budgetary impact considered an underestimate • possible difference in dose intensity • uncertain population size, mentioned excluding patients with ECOG ≥2, potential use beyond progression
Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD: Y/N • In most current list of PSDs Additional information may be found at https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets	• Palbociclib • abemaciclib
Area of unmet need	Mentioned in the PSD Y/N	N
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD • Indicated (and/or required by listing) • Anticipated	• must be in combination with a non-steroidal aromatase inhibitor (anastrozole or letrozole) • none anticipated, but current PBS listing also lists fulvestrant
Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	None
Other significant issues noted in PBAC review	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	• Noted to have inferior AE rate compared with letrozole • Concerns raised over indirect comparison with palbociclib + letrozole, economic modelling approach used. • Appropriate comparator considered to be letrozole • DUSC (July 2017) considered that the adherence to ribociclib in practice may be lower than observed in the trial

Other considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	Palbociclib described as near market comparator
Anticipated significant uptake	Was concern raised in the PSD?	Y - cost estimates considered to be an underestimate
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	PSD has highly restricted criteria (e.g., ECOG status, non-menopausal, inoperable, no uncontrolled brain metastases
Nature of listing and restriction	• S85 or S100 • written versus telephone authority	• S85 • telephone
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	The PBAC noted that MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for ribociclib as 3 compared to letrozole alone. MOGA noted that the score may increase to 4 when OS data matures (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement). 3 on website
Chosen for DUSC review	Mentioned in PSD Y/N	Y
Analysis methods	To consider after PSD review • Will analysis be complicated e.g., treatment switching? • Will there be data on a suitable comparator? • Is data available for OS estimates?	• Comparator letrozole or palbociclib + NSAI? • Possible switching
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within	EviQ protocol guidelines indicates that QT interval monitoring is required – this involves fortnightly ECGs for the first 6 weeks, which may influence clinicians'

	same in class. Considerations might include: • testing/monitoring requirements • adverse events • method of delivery (IV vs oral vs injection)	choice of drug from within the same class of CDK inhibitors (including palbociclib and abemaciclib)

B.1.11 Trastuzumab emtansine (PBS Listed July 2015)

Listing characteristics	Description	Extracted Data
Medicine and dose form	Medicine name and method of delivery	Trastuzumab Emtansine (T-DM1) 100 mg injection, 1 x 100 mg vial, 160 mg injection, 1 x 160 mg vial
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	HER2+ metastatic breast cancer who has received prior treatment with trastuzumab and a taxane and whose disease has progressed despite treatment with trastuzumab for metastatic disease
Place in therapy relative to progression	Indicate first-line or late/last-line	Second
Date of positive recommendation	Date on PSD	November 2014
Date of PBS listing	Date listed, PBS Summary of changes.	1 July 2015
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate outcome such as progression free survival • Name the trial(s) reported in the PSD	PFS + OS EMILIA
Comparator in trial(s) supporting case for listing	• Placebo or active comparator? • For primary comparison only	lapatinib + capecitabine

Key considerations	Description	Extracted data
Median overall survival (OS)	As stated in PSD for key trial or pooled analysis	30.9 months
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	Previous treatment in EMILIA trial varied, so the efficacy of T-DM1 in patients who progress on a pertuzumab combination therapy is unknown
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	Lower AEs than comparator in trial PBAC noted that some of the toxicity profile of T-DM1 was less favourable than that of its comparator
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	
Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	OS 29.9 months https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30312-1/fulltext
Large or uncertain budgetary impact	As mentioned in the PSD, for example: • risk-sharing agreement • uncertain incidence of disease • large/uncertain anticipated uptake • large/uncertain size of eligible population	Unchanged from March 2013 submission PBAC had concerns regarding post-progression costs in the economic models Drug prices were a key driver in the models The financial estimates may not adequately account for increased prevalence of HER2+ metastatic breast cancer. Due to the survival gains from the newer treatments, there is likely to be a much larger pool of patients eligible for third-line trastuzumab in the future. Decision on T-DM1 was initially deferred due to uncertainties in the economic model by omitting post-progression costs, the nature

		of the treatment effect and the place of T-DM1 once pertuzumab is available. Sponsor presented new pricing proposal out of session
Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD: Y/N • In most current list of PSDs Additional information may be found at • https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets	Listed together with trastuzumab and pertuzumab as part of treatment pathway
Area of unmet need	Mentioned in the PSD Y/N	All three medicines mentioned as only treatment for HER+ breast cancer
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD • Indicated (and/or required by listing) • Anticipated	Monotherapy
Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	None
Other significant issues noted in PBAC review	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	PBAC was concerned by the issues around the use in clinical practice and the applicability of the evidence i.e., in the key T-DM1 trial, patients had progressed on trastuzumab + taxane and not pertuzumab + trastuzumab + taxane as would occur in clinical practice once pertuzumab is listed. The PBAC noted the use of pertuzumab in the EMILIA trial, but considered that the number of patients in the trial was too small to substantiate this claim and the treatment effect of T-DM1 in patients who have progressed following pertuzumab + trastuzumab is not yet known

Additional considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	Follow-up
Anticipated significant uptake	Was concern raised in the PSD?	Yes – due to survival gains in HER2+ metastatic breast cancer
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	Patient must have a WHO performance status of 0 or 1 Condition must have progressed after previous therapy
Nature of listing and restriction	• S85 or S100 • written or telephone authority	S100
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	4
Chosen for DUSC review	Mentioned in PSD Y/N	Y
Analysis methods	• Will analysis be complicated e.g., treatment switching?	Part of treatment pathway algorithm with trastuzumab and pertuzumab - second of three treatments
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within same in class. Considerations might include: • testing/monitoring requirements • adverse events • method of delivery (IV vs oral vs injection)	

B.1.12 Trifluridine–Tipiracil (PBS Listed December 2018)

Listing characteristics	Description	Extracted Data
Medicine and dose form	Medicine name and method of delivery	Trifluridine with tipiracil tablets
PBS Listing/indication	Include cancer type, category (Haematological/solid tumour), indication (including curative intent) and stage e.g., metastatic, locally advanced, including specific staging category(s)	Metastatic colorectal cancer (solid tumour), stage III-IV, performance status <=1
Place in therapy relative to progression	Indicate first-line or late/last-line	Last-line
Date of positive recommendation	Date on PSD	July 2018
Date of PBS listing	Date listed, PBS Summary of changes	Dec 2018
Primary endpoint in trial(s) supporting case for listing	• OS or surrogate such as progression free survival • Name the trial(s) used in the PBAC assessment	OS RECOURSE
Comparator in trial(s) supporting case for listing	• Placebo or active comparator? • For primary comparison only	Placebo

Key considerations	Description	Extracted data
Median overall survival		7.2 months
Uncertainty about magnitude of benefit	As mentioned in the PSD, list specific concerns	Median gain in OS was modest
Uncertainty about magnitude of adverse effects	As mentioned in the PSD, list specific concerns	Toxicity may be significant in context of modest benefit
Uncertainty about methods used to estimate OS	As mentioned in the PSD, list specific concerns	(no, although sponsor suggested mean rather than median survival more relevant, PBAC considered median)
Uncertainty about trial quality	As mentioned in the PSD, list specific concerns	no
Important new data published since PBAC assessment	Have new data been published that may change estimates of benefits and adverse effects? *This will require a literature search*	No. Several RWD studies published.
Large or uncertain budgetary impact	As mentioned in the PSD, for example: • risk-sharing agreement • uncertain incidence of disease • large/uncertain anticipated uptake • large/uncertain size of eligible population	RSA
Other medicines listed for the same/overlapping indication within a 2-year time window	• Mentioned in PSD: Y/N • In most current list of PSDs Additional information may be found at https://www.pbs.gov.au/info/industry/pricing/pbs-items/therapeutic-relativity-sheets	Pembrolizumab Aug 2021
Area of unmet need	Mentioned in the PSD Y/N	Y
Any indicated or anticipated concomitant treatments	List concomitant treatments in PSD • Indicated (and/or required by listing) • Anticipated	None
Listings of medicine for other indications	List other indications if any, either in PSD or in later PSDs	Metastatic (Stage IV) adenocarcinoma of the stomach or gastro-oesophageal junction (Nov 2019)

Other significant issues noted in PBAC review	e.g., DUSC or ESC concerns. For example: concern over adverse event rate, appropriate comparator	N

Other considerations	Description	Extracted Data
First in class or follow-up medicine for this indication	Indicate first in class or follow-up medicine	First in class
Anticipated significant uptake	Was concern raised in the PSD?	No
Expected differences between key RCT population and post-listing population	As mentioned in PSD. For example: highly restrictive inclusion/exclusion criteria that may not be met in PBS population	PBS populations are likely to have additional and/or more extensive comorbidities compared with the trial patients.
Nature of listing and restriction	• S85 or S100 • written versus telephone authority	S85 Streamlined
Formal clinical benefit scale (ESMO or ASCO)	May provide a useful independent assessment of the drug/indication. *ESMO scales can be found at* https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?filterType=agent	2: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-25-1 3: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-300-1
Chosen for DUSC review	Mentioned in PSD Y/N	N
Analysis methods	To consider after PSD review • Will analysis be complicated e.g., treatment switching? • Will there be data on a suitable comparator? • Is data available for OS estimates?	No difficulties noted
Clinical considerations	To consider after PSD review with clinical input e.g., for prioritising medicine within	Oral tablets PBS indication restricts use to those with ECOG 0-1, anecdotally patients with ECOG

	same in class. Considerations might include: • testing/monitoring requirements • adverse events • method of delivery (IV vs oral vs injection)	2+ may be prescribed this drug as they are typically heavily pre-treated and at very advanced states of disease (as reflected in mOS of 5.3 months in the trial). This would increase the study population and shorten the estimated OS.

C Attachment: Key clinical trial data for medicines deemed suitable for feasibility assessment

C.1. Ipilimumab (PBS Listed August 2013)

Key trial data	Description	Extracted Data
Study design	RCT, single arm, etc	Phase III RCT
Comparator(s) (if any)		Ipi + gp100 Gp100 alone
Trial name and other identifiers	May include informal trial name, internal sponsor identifiers and/or registry numbers (e.g., CT.gov) Date(s) main results published	CT-20 NCT00094653 Sponsors Medarex and Bristol-Myers Squibb
Citation(s)		Hodi (2010) https://www.nejm.org/doi/full/10.1056/nejmoa1003466
Inclusion criteria		• diagnosis of unresectable stage III or IV melanoma and had received a previous therapeutic regimen containing one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2 • at least 18 years • life expectancy of at least 4 months • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 • positive status for HLA-A*0201 • normal hematologic, hepatic, and renal function • no systemic treatment in the previous 28 days
Exclusion criteria		• any other cancer from which the patient had been disease-free for less than 5 years (except treated and cured basal-cell or squamous-cell skin cancer, superficial bladder cancer, or treated carcinoma in situ of the cervix, breast, or bladder) • primary ocular melanoma

		• previous receipt of anti–CTLA-4 antibody or cancer vaccine; autoimmune disease • active, untreated metastases in the central nervous system • pregnancy or lactation • concomitant treatment with any nonstudy anticancer therapy or immunosuppressive agent • long-term use of systemic corticosteroids
Companion testing		positive status for HLA-A*0201
Prior and concurrent treatments	As specified by the trial protocol	previous therapeutic regimen containing one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2
Subgroup for pharmacoeconomic analysis	If submission was based on data taken from a subgroup rather than the complete trial population.	
Baseline characteristics of trial participants	Age, Sex, Performance Status, Staging, ... Attach a copy of relevant table(s) from PSD or RCT publication	See article
Endpoint definition e.g., surrogate	List only endpoints discussed in PSD	OS
Duration of treatment	As reported (days, cycles etc)	64% in IPI alone group received all 4 doses
Method used to calculate or extrapolate OS	Refers to methods in submission, not necessarily in publication(s)	
Median OS (or equivalent)	Note if results in PSD differ from those published elsewhere	Ipilimumab alone: 10.1 months
Trial quality	As assessed in PSD only	

C.2. Lanreotide (PBS Listed April 2018)

Key trial data	Description	Extracted Data
Study design	RCT, single arm, etc	Phase 3 parallel, randomized, double-blind, placebo-controlled
Comparator(s) (if any)		Placebo (sodium chloride)
Trial name and other identifiers	May include informal trial name, internal sponsor identifiers and/or registry numbers (e.g., CT.gov) Date(s) main results published	CLARINET NCT00353496 Sponsor Ipsen
Citation(s)		https://www.nejm.org/doi/full/10.1056/nejmoa1316158
Inclusion criteria		• adults • sporadic neuroendocrine tumours that were confirmed centrally to be well differentiated or moderately differentiated and measurable according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.0 • tumours had a centrally assessed proliferation index (on staining for the Ki-67 antigen) of less than 10% (or a mitotic index of ≤2 mitoses per 10 high-power fields, if the Ki-67 index could not be quantified reliably) • unresectable locally advanced tumour or metastatic disease (or the patient declined surgery) • target lesion or lesions that were classified on somatostatin-receptor scintigraphy as grade 2 or higher within the previous 6 months

		• score of 2 or less on the World Health Organization (WHO) performance scale
Exclusion criteria		• had received treatment with interferon, chemoembolization, or chemotherapy within 6 months before study entry, a radionuclide at any time , or a somatostatin analogue at any time (unless they had received it >6 months previously and for <15 days) • major surgery related to the neuroendocrine tumour within 3 months before study entry • multiple endocrine neoplasia • previous cancer (except in the case of patients with treated or untreated in situ cervical or uterine carcinoma or basal-cell skin carcinoma or patients with other cancers who had been treated with curative intent and had been disease-free for >5 years) • baseline abnormalities or medical conditions that could jeopardize the patient's safety or interfere with the study
Companion testing		biopsy of the neuroendocrine tumour within 6 months before study entry was required for patients who had previous cancer and those with evidence of clinical progression
Prior and concurrent treatments	As specified by the trial protocol	None
Subgroup for pharmacoeconomic analysis	If submission was based on data taken from a subgroup rather than the complete trial population.	
Baseline characteristics of trial participants	Age, Sex, Performance Status, Staging, ... Attach a copy of relevant table(s) from PSD or RCT publication	See article

Endpoint definition e.g., surrogate	List only endpoints discussed in PSD	PFS, OS
Duration of treatment	As reported (days, cycles etc)	Median 24 months (range 1.0-25.3)
Method used to calculate or extrapolate OS	Refers to methods in submission, not necessarily in publication(s)	Kaplan-Meier/Log-rank test
Median OS (or equivalent)	Note if results in PSD differ from those published elsewhere	Not reached. PFS rate at 24 months: 65.1% (95%CI: 54.0%, 74.1%). PFS HR: 0.47 (95%CI: 0.30, 0.73)
Trial quality	As assessed in PSD only	

C.3. Olaparib (PBS Listed February 2017)

Key trial data	Description	Extracted Data
Study design	RCT, single arm, etc	Randomised, double-blind, placebo-controlled phase II
Comparator(s) (if any)		Placebo
Trial name and other identifiers	May include informal trial name, internal sponsor identifiers and/or registry numbers (e.g., CT.gov) Date(s) main results published	Phase 2 “Study 19” AstraZeneca Published between 2012-2016 NCT00753545
Citation(s)		(From March 2016 PSD) PFS Ledermann (2012) https://www.nejm.org/doi/full/10.1056/nejmoa1110553 OS (Ledermann 2014 primary source) Ledermann (2014) https://pubmed.ncbi.nlm.nih.gov/24882434/ Matulonis (2015) https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.29995 https://clinicaltrials.gov/ct2/show/results/NCT00753545
Inclusion criteria		• 18 or older • recurrent ovarian or fallopian-tube cancer or primary peritoneal cancer with high-grade (grade 2 or 3) serous features or a serous component, which was platinum-sensitive • completed at least two courses of platinum-based chemotherapy, and their most recent regimen induced an objective response • CA-125 measurements before treatment that were below the upper limit of the normal range
Exclusion criteria		
Companion testing		BRCA mutation status (not required for trial)

Prior and concurrent treatments	As specified by the trial protocol	completed at least two courses of platinum-based chemotherapy, and their most recent regimen induced an objective response
Subgroup for pharmacoeconomic analysis	If submission was based on data taken from a subgroup rather than the complete trial population.	BRCA 1 or 2 with placebo to Olaparib crossover sites excluded from Matulonis (2015)
Baseline characteristics of trial participants	Age, Sex, Performance Status, Staging, ... Attach a copy of relevant table(s) from PSD or RCT publication	See article
Endpoint definition e.g., surrogate	List only endpoints discussed in PSD	PFS OS modelled
Duration of treatment	As reported (days, cycles etc)	Median 206.5 days (range 3-469 days)
Method used to calculate or extrapolate OS	Refers to methods in submission, not necessarily in publication(s)	Log-logistic model (March 2016 submission)
Median OS (or equivalent)	Note if results in PSD differ from those published elsewhere	In Lederman 2012, median OS was 29.7 months for all patients. Retrospective subgroup analysis for BRCAm was 34.9 months, confirmed in updated analysis of 2016.
Trial quality	As assessed in PSD only	Unclear risk of bias noted in March 2016 PSD. Subgroup analysis by BRAC status noted as possible not being appropriate due to missing data on BRCA types

C.4. Panitumumab (PBS Listed April 2014)

Key trial data	Description	Extracted Data
Study design	RCT, single arm, etc	Parallel, non-inferiority, open-label
Comparator(s) (if any)		Cetuximab Historical trial of best supportive care for non-inferiority
Sample size		Panitumumab (N=499) Cetuximab (N=500)
Trial name and other identifiers	May include informal trial name, internal sponsor identifiers and/or registry numbers (e.g., CT.gov) Date(s) main results published	ASPECCT Sponsor Amgen Inc Clinical trials NCT01001377 Published May 2014
Citation(s)		https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)70118-4/fulltext
Inclusion criteria		• 18 years + • ECOG 2 or less • chemotherapy-refractory metastatic colorectal cancer • previously received a thymidylate synthase inhibitor (including fluorouracil, capecitabine, raltitrexed, or fluorouracil-uracil) for colorectal cancer • Wild type KRAS exon 2 tumour status • measurable or non-measurable disease according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1
Exclusion criteria		• previous anti-EGFR therapy • antitumour therapy within 30 days • symptomatic brain metastases needing treatment, history of other unresolved malignancies • major surgery within 28 days • significant cardiovascular disease or myocardial infarction • history of interstitial lung disease

		• active or uncontrolled infections within 14 days • serum magnesium concentrations below lower limit of normal • inadequate haematological function (absolute neutrophil count <1·5 × 109 per L, platelet count <75 × 109 per L, or haemoglobin <80 g/L) • inadequate renal function (creatinine >1·5 × upper limit of normal) • inadequate hepatic function (total bilirubin >1·5 × upper limit of normal, or aspartate aminotransferase or alanine aminotransferase >3 × upper limit of normal [>5 × upper limit of normal if the patient had liver metastases])
Companion testing		KRAS testing
Prior and concurrent treatments	As specified by the trial protocol	Prior • previously received a thymidylate synthase inhibitor (including fluorouracil, capecitabine, raltitrexed, or fluorouracil-uracil) for colorectal cancer
Subgroup for pharmacoeconomic analysis	If submission was based on data taken from a subgroup rather than the complete trial population.	Full population
Baseline characteristics of trial participants	Age, Sex, Performance Status, Staging, ... Attach a copy of relevant table(s) from PSD or RCT publication	See article
Endpoint definition e.g., surrogate	List only endpoints discussed in PSD	OS and PFS
Duration of treatment	As reported (days, cycles etc)	Median duration 14.3 weeks (IQR 6.1-29.3) Median number of infusions 7 (IQR 3-13.5)
Follow-up time	Including definition	Time from randomisation to the last on-study or long-term follow-up visit 41.4 weeks (IQR 22.1-71.6)
Method used to calculate or extrapolate OS	Refers to methods in submission, not necessarily in publication(s)	Cox model stratified by randomisation factors (geographic region and ECOG status)
Median OS (or equivalent)	Note if results in PSD differ from those published elsewhere	OS 10.4 months (IQR 9.4-11.6) PFS 4.1 months (IQR 3.2-4.8)

Trial quality	As assessed in PSD only	Indirect comparison of best supportive care raised

C.5. Trastuzumab emtansine (PBS Listed July 2015)

Key trial data	Description	Extracted Data
Study design	RCT, single arm, etc	Open label parallel RCT
Comparator(s) (if any)		lapatinib + capecitabine
Sample size		Trastuzumab Emtansine (N=495) lapatinib + capecitabine (N=496)
Trial name and other identifiers	May include informal trial name, internal sponsor identifiers and/or registry numbers (e.g., CT.gov) Date(s) main results published	EMILIA Sponsor Roche Products Clinical Trials NCT00829166 Published November 2012
Citation(s)		https://www.nejm.org/doi/full/10.1056/nejmoa1209124
Inclusion criteria		• documented progression of unresectable, locally advanced or metastatic HER2-positive breast cancer (progression during or after the most recent treatment for locally advanced or metastatic disease or within 6 months after treatment for early-stage disease) • previously treated with a taxane and trastuzumab • centrally confirmed HER2-positive status • a left ventricular ejection fraction of 50% or more • ECOG 0 or 1
Exclusion criteria		• prior treatment with T-DM1, lapatinib, or capecitabine • peripheral neuropathy of grade 3 or higher • symptomatic central nervous system (CNS) metastases or treatment for these metastases within 2 months before randomization • a history of symptomatic congestive heart failure or serious cardiac arrhythmia requiring treatment

		• a history of myocardial infarction or unstable angina within 6 months before randomization
Companion testing		• centrally confirmed HER2-positive status assessed by means of immunohistochemical analysis (with 3+ indicating positive status), fluorescence in situ hybridization (with an amplification ratio ≥2.0 indicating positive status), or both • ventricular ejection fraction of 50% or more (determined by echocardiography or multiple-gated acquisition [MUGA] scanning) at baseline and during follow-up
Prior and concurrent treatments	As specified by the trial protocol	Prior • Trastuzumab and taxane
Subgroup for pharmacoeconomic analysis	If submission was based on data taken from a subgroup rather than the complete trial population.	All + subgroup who received prior pertuzumab
Baseline characteristics of trial participants	Age, Sex, Performance Status, Staging, ... Attach a copy of relevant table(s) from PSD or RCT publication	See article
Endpoint definition e.g., surrogate	List only endpoints discussed in PSD	PFS and OS and safety
Duration of treatment	As reported (days, cycles etc)	Until end of follow-up?
Follow-up time	Including definition	median duration of follow-up, approximately 19 months
Method used to calculate or extrapolate OS	Refers to methods in submission, not necessarily in publication(s)	Kaplan-Meier
Median OS (or equivalent)	Note if results in PSD differ from those published elsewhere	OS 30.9 months PFS 9.6 months
Trial quality	As assessed in PSD only	

C.6. Trifluridine–Tipiracil (PBS Listed December 2018)

Key trial data	Description	Extracted Data
Study design	RCT, single arm, etc	Randomised, parallel double-blind
Comparator(s) (if any)		Placebo
Sample Size		Trifluridine with tipiracil (N=534), placebo (N=266)
Trial name and other identifiers	May include informal trial name, internal sponsor identifiers and/or registry numbers (e.g., CT.gov) Date(s) main results published	RECOURSE Sponsor Taiho Oncology–Taiho Pharmaceutical Clinical Trials NCT01607957 May 2015
Citation(s)		https://pubmed.ncbi.nlm.nih.gov/25970050/
Inclusion criteria		• biopsy-documented adenocarcinoma of the colon or rectum • knowledge of tumour status with regard to *KRAS* • 18 years or older • have adequate bone-marrow, liver, and renal function • ECOG status < 2 • had received at least two prior regimens of standard chemotherapies, which could have included adjuvant chemotherapy if a tumour had recurred within 6 months after the last administration of this therapy • had either tumour progression within 3 months after the last administration of chemotherapy or clinically significant adverse events from standard chemotherapies
Exclusion criteria		
Companion testing		KRAS tumour status (for subgroup analysis only)

Prior and concurrent treatments	As specified by the trial protocol	required to have received chemotherapy with each of the following agents: a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and — for patients with *KRAS* wild-type tumours — cetuximab or panitumumab
Subgroup for pharmacoeconomic analysis	If submission was based on data taken from a subgroup rather than the complete trial population.	Sensitivity analysis assumed no benefit of treatment in patients who received granulocyte colony stimulating factors, placebo effect treatment effect applied to these patients
Baseline characteristics of trial participants	Age, Sex, Performance Status, Staging, ... Attach a copy of relevant table(s) from PSD or RCT publication	See article
Endpoint definition e.g., surrogate	List only endpoints discussed in PSD	Median overall survival
Duration of treatment	As reported (days, cycles etc)	Mean 12.7 (SD 12) weeks Median 6.7 weeks (IQR 0.1-78)
Follow-up time	Including definition	19 months
Method used to calculate or extrapolate OS	Refers to methods in submission, not necessarily in publication(s)	reverse Kaplan–Meier
Median OS (or equivalent)	Note if results in PSD differ from those published elsewhere	Median OS 7.2 months in trial 10.0 months after removal of patients who received granulocyte colony stimulating factors
Trial quality	As assessed in PSD only	

D Attachment: Implementation of the suitability assessment

Step-by-step process

For the purposes of this report, the assessment was implemented as follows:

1. Eligible listings were selected from listing dates between 7 and 2 years prior to December 2021 and for the indication of interest e.g., treating late-stage solid tumours with non-curative intent (Appendix B).
2. One cancer medicine ***selection and evaluation worksheet*** per listing was completed.
3. A second person checked details of each worksheet.
4. A shortlist was created by eliminating medicines that had serious feasibility issues or minimal issues of uncertainty.
5. Clinician input was sought to complete clinical considerations for all shortlisted medicines.
6. Key issues and uncertainty were highlighted.
7. The shortlist was prioritised in collaboration with the Department of Health (DoH).
8. Key trial data worksheets were completed for selected listings (Attachment C).

Selection, evaluation and shortlisting outcomes

A longlist of 30 medicines was considered (see Appendix B). From that list, the DoH nominated four additional medicines to be considered after internal consultation (see Box below). Olaparib for ovarian cancer was selected to test the methodology for streamlined and telephone authority medicines. Ipilimumab was selected as there was a Managed Access Program for this medicine and additional data could be used for the review. Lanreotide was suggested, however, there may be an insufficient number of patients exposed to this medicine as it was only listed at the end of 2018 and has a long estimated median OS. Ibrutinib was suggested as it is one of the early chronic lymphocytic leukemia (CLL) treatments and it is likely that there would be sufficient follow up data available for this medicine. However, ibrutinib for CLL has a haematological cancer listing, as opposed to a solid tumour indication, and it was deemed out of scope for this review.

Table D.1: Shortlist

Listing	Listing Date	Source
Ipilimumab for metastatic melanoma	Aug 2013	DoH nominated
Lanreotide for GEP-NET	Apr 2018	DoH nominated
Olaparib for BRCAm relapsed ovarian, fallopian and peritoneal cancer	Feb 2017	DoH nominated
Panitumumab for colorectal cancer	Apr 2014	Longlist
Trastuzumab emtansine for breast cancer	Jul 2015	Longlist
Trifluridine with tipiracil for colorectal cancer	Dec 2018	Longlist

Summary of evaluation for shortlisted listings

Key issues identified in the cancer medicine selection and evaluation worksheets for the shortlisted medicines are summarised in the table 1.7.2 below. For three of the medicines immature data

meant that real-world median survival was unlikely to have been reached. Listing changes and subsequent listing of alternative treatments for the same indication were identified for many of the medicines which may limit the interpretability of observations beyond the date of the changes. In some cases, the PSD identified scenarios where the PBS population was likely to differ from the population used in the submission, with potential impact on cost-effectiveness, e.g., for trifluridine with tipiracil, "PBS population are likely to have additional and/or more extensive comorbidities compared with the trial patients."

Table D.2: Key issues for the shortlisted medicines

Listing	Issues
Ipilimumab	• Pembrolizumab listed for same indication Sept 2015 • Patient population under three trial protocols differed from listing • Dosing in trials were different from listing • Results from PBS Managed Access Program evaluation of OS published as Kim et al (2018)
Lanreotide	• Long survival times (median progression-free survival (PFS) 38.5 months) • Clinical significance of gain in PFS was uncertain as it was based on radiologic progression & may not change clinical symptoms. • Concerned patient population will be higher as more switch from watchful waiting and it gets used for post-progressive disease.
Olaparib	• Long survival times (median OS 35 months) • Listed for first-line in Nov 2020 • Uncertainty around duration of use: PSD mentioned that results might not be generalisable to Australian clinical practice which would monitor for progression less frequently.
Panitumumab	• Follow-up to cetuximab. Possible switching to/from cetuximab • Changes to KRAS testing criteria in Jan 2015 • Changed to streamlined authority in Feb 2015 • Cetuximab listed June 2015 for first-line in metastatic colorectal cancer (mCRC) • Listed for first line in combination with chemotherapy in Oct 2015 • Feb 2018 DUSC review of targeted therapies for mCRC
Trastuzumab emtansine	• Long survival times (median OS 30.9 months) • Listed together with trastuzumab and pertuzumab as part of treatment pathway • PBAC was concerned by the issues around the use in clinical practice and the applicability of the evidence, i.e., in the key T-DM1 trial, patients had progressed on trastuzumab + taxane and not pertuzumab + trastuzumab + taxane as would occur in clinical practice once pertuzumab is listed. The PBAC noted the use of pertuzumab in the EMILIA trial (Verma 2012), but considered that the number of patients in the trial was too small to substantiate this claim and the treatment effect of T-DM1 in patients who have progressed following pertuzumab + trastuzumab is not yet known
Trifluridine with tipiracil	• Pembrolizumab listed for same indication in Aug 2021 • PBS populations are likely to have additional and/or more extensive comorbidities compared with the trial patients. • PBS indication restricts use to those with ECOG 0-1, anecdotally patients with ECOG 2+ may be prescribed this drug as they are typically heavily pre-treated and at very advanced states of disease (as reflected in median OS of 5.3 months in the trial). This would increase the study population and shorten the estimated OS.

E Attachment: Feasibility Assessments

E.1 Ipilimumab

Injection concentrate for I.V. infusion 50 mg in 10 mL

Injection concentrate for I.V. infusion 200 mg in 40 mL

Purpose

The purpose of this document is to determine the feasibility of calculating robust and meaningful survival estimates for people initiating IPILIMUMAB through the PBS. Analytical issues under consideration include: time since IPILIMUMAB was PBS-listed; the number of people initiating treatment; the number of deaths observed during the available follow-up time; and potential external factors that may impact/bias survival estimates (e.g., a new indication being listed on the PBS that may result in a different patient population receiving IPILIMUMAB during the observation period).

Summary of findings

- 6,189 patients treated (31% female); median age 64 years (IQR: 54 – 72)
- 38% dispensed antineoplastics in the 6 months prior to IPILIMUMAB initiation (3% chemotherapy; 20% targeted therapy; 19% immunotherapy)*
- Crude median overall survival: 23.1 months (95%CI: 21.3 – 25.7)

Feasibility assessment

- There is sufficiently long follow-up and number of deaths to produce robust and meaningful median survival estimates.
- IPILIMUMAB is currently indicated for four different cancers; check for sufficient follow-up time to estimate OS if patients are censored before additional indications were listed.
- There is an unusual decrease in PBS dispensings from August 2015 to December 2016. This event requires further research to determine what, exactly, caused the decrease in use during this time period.
- **IPILIMUMAB is a feasible candidate for full analysis but requires a strong caveat due to the decrease in dispensings in 2015/2016.**
- **The time period for analysis should be restricted to 2013 – 2019, when IPILIMUMAB was listed for melanoma only.**

* Antineoplastic treatments—chemotherapy, targeted therapy, immunotherapy—are not exclusive and patients may receive any/all during the six months prior to initiating the medicine of interest.

Listing on the Pharmaceutical Benefits Scheme (PBS)

Date of PBAC Consideration: November 2012

IPILIMUMAB was PBS listed on 1 AUGUST 2013

PBS listing details (as of 20 January 2022)

https://www.pbs.gov.au/medicine/item/11628B-11644W-12304N-12308T-12322M-12324P-12583G-12601F-2638W-2641B

IPILIMUMAB was listed for the patients with unresectable stage III or stage IV malignant melanoma who have not responded to or were intolerant to prior systemic therapy for metastatic disease (Table 1).

Table 1: PBS listings of IPILIMUMAB

Item code	Name, form & strength	Date of listing	Schedule	Authority required?
02638W 02641B	IPILIMUMAB Injection concentrate for I.V. infusion 50mg in 10mL Injection concentrate for I.V. infusion 200mg in 40mL	1 August 2013	S100	Streamlined
02643D 02663E	IPILIMUMAB Injection concentrate for I.V. infusion 50mg in 10mL Injection concentrate for I.V. infusion 200mg in 40mL	1 August 2013 Ends Dec 2016	S100	Streamlined

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Public Summary Document – November 2012 - PBAC Meeting - 7.19 IPILIMUMAB available at https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-11/ipilimumab

IPILIMUMAB was also listed for Stage IV clear cell variant renal cell carcinoma (RCC), Stage IV (metastatic) non-small cell lung cancer (NSCLC) and Unresectable malignant mesothelioma. (Table 2) These listings are not part of this analysis.

Table 2: PBS listings of IPILIMUMAB not included in analysis.

Item code	Name, form & strength Indication	Date of listing	Schedule	Authority required?
11628B 11644W	IPILIMUMAB Injection concentrate for I.V. infusion 50 mg in 10 mL; Injection concentrate for I.V. infusion 200 mg in 40 mL Stage IV clear cell variant renal cell carcinoma (RCC)	1 March 2019	S100	Streamlined
11647B 11641Q	IPILIMUMAB	1 March 2019	S100	Streamlined

	Injection concentrate for I.V. infusion 50 mg in 10 mL; Injection concentrate for I.V. infusion 200 mg in 40 mL Stage IV clear cell variant renal cell carcinoma (RCC)	Ends 30 Sep 2020		
12304N 12308T 12322M 12324P	IPILIMUMAB Stage IV (metastatic) non-small cell lung cancer (NSCLC)	Not in DUSC map	S100	Streamlined
12583G 12601F	IPILIMUMAB Unresectable malignant mesothelioma	Not in DUSC map	S100	Streamlined

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Data Source/methodology

Dispensing data were extracted from the PBS claims database by the Department of Health for all PBS and RPBS items for IPILIMUMAB (item codes 02638W, 02641B, 02643D, 02663E) for the period 1 August 2013 to 31 December 2021 (based on date of supply). Patient sex, date of birth, date of death and postcode of residence at time of dispensing were merged with dispensing data by the Department of Health. For this cohort, all antineoplastic medicine dispensings (medicines whose ATC codes begin with 'L01') were also extracted for the time period 1 February 2013 to 31 December 2021.

Initiating patients were identified from their first dispensing of IPILIMUMAB in the PBS data. Prevalent patients were those who had at least one dispensing of IPILIMUMAB during the calendar year.

Demographic characteristics of initiating patients were measured at the date of first PBS dispensing of IPILIMUMAB. Patients were considered to have had prior use of antineoplastic medicines (L01) if those medicines were dispensed in the 6 months prior to IPILIMUMAB initiation. Antineoplastic medicines dispensed in the 3 months after the first IPILIMUMAB dispensing were also summarised.

Overall survival was estimated from the date of first IPILIMUMAB dispensing to the date of death or censoring (censor date: 31 December 2021) using Kaplan-Meier methods.

Results

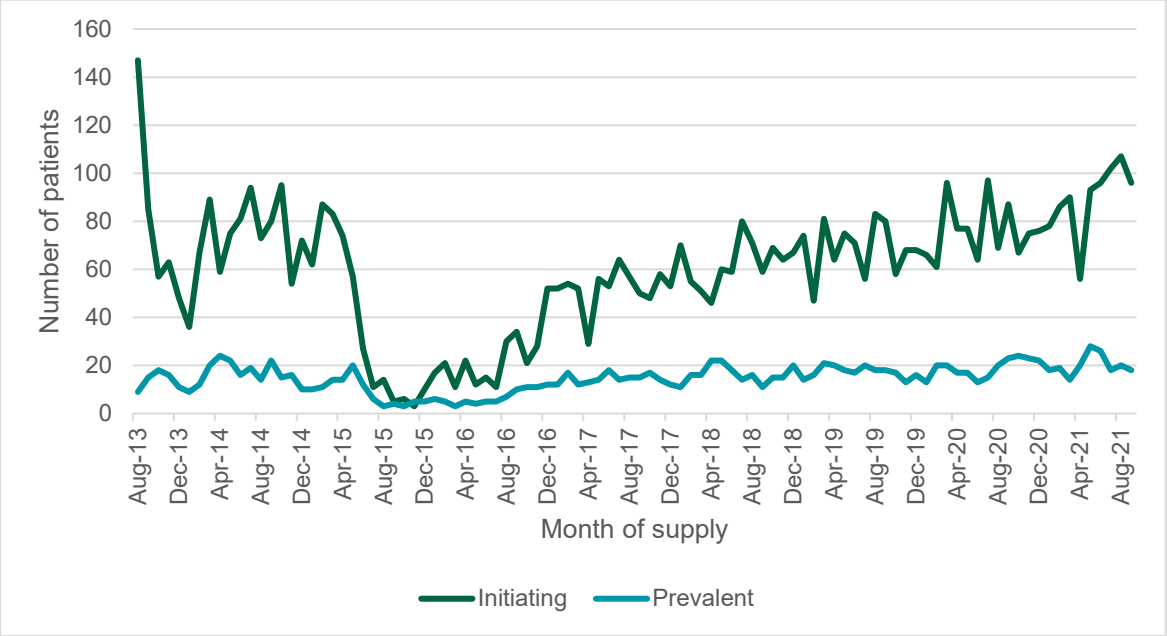


Figure 1: Initiating and prevalent patients for PBS medicine use, by month of supply

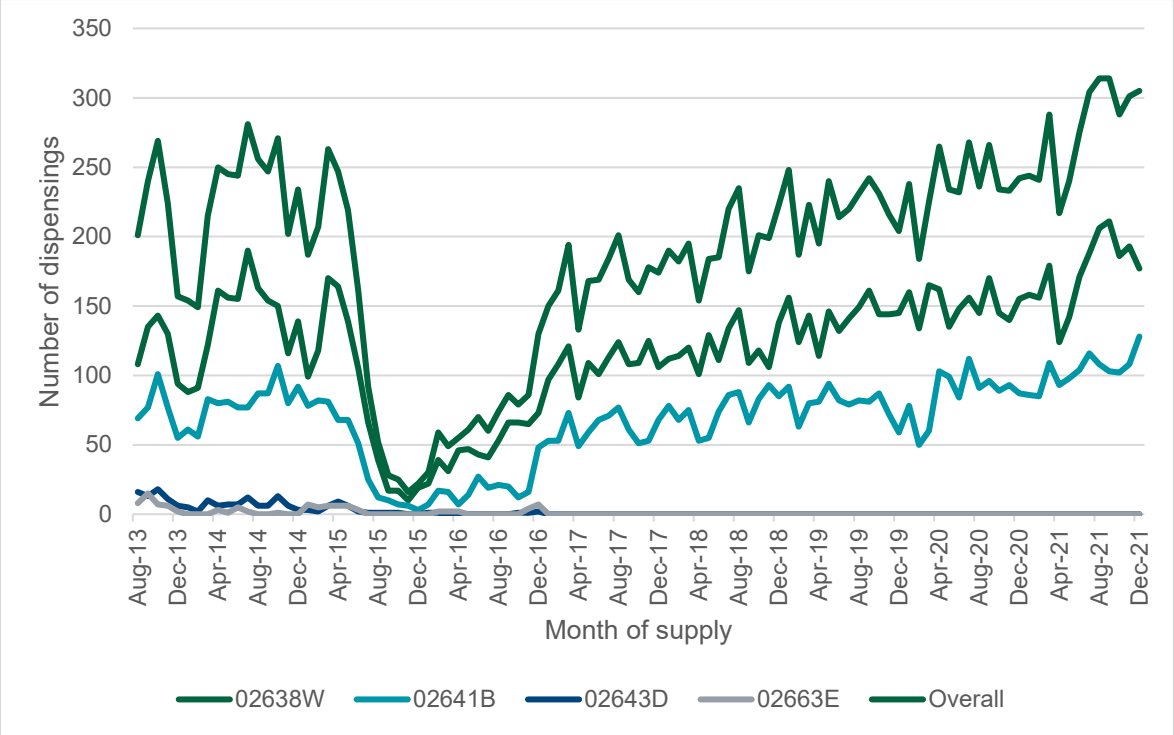


Figure 2: PBS dispensings for IPILIMUMAB by item code and overall

Table 3: Patient characteristics at the time of first PBS dispensing of IPILIMUMAB (1 August 2013 to 31 December 2021)

	n (%)
Patients	6189
Sex	
Female	1944 (31.4)
Male	4243 (68.6)
Missing	2 (0.0)
Age at first PBS dispensing	
Median (IQR)	64 (54-72)
State of residence at first PBS dispensing	
ACT	129 (2.1)
NSW	1948 (31.5)
NT	48 (0.8)
QLD	1398 (22.6)
SA	322 (5.2)
TAS	159 (2.6)
VIC	1354 (21.9)
WA	829 (13.4)
Missing	2 (0.0)
Antineoplastic (L01) medicines dispensed in 6 months prior to first PBS dispensing	
Overall (excluding medicine of interest)	2362 (38.2)
Chemotherapy	169 (2.7)
Immunotherapy (excluding medicine of interest)	1154 (18.6)
Targeted therapy	1215 (19.6)
Antineoplastic (L01) medicines dispensed within 3 months after first PBS dispensing	
Overall (excluding medicine of interest)	2663 (43.0)
Chemotherapy	76 (1.2)
Immunotherapy (excluding medicine of interest)	2509 (40.5)
Targeted therapy	246 (4.0)

Table 4: Initiating and prevalent patients by year of PBS dispensing

Year	Initiating patients	Prevalent patients
2013 (Aug-Dec)	400	400
2014	875	968
2015	439	571
2016	274	323
2017	626	734
2018	751	882
2019	825	987
2020	912	1069
2021	1087	1259

Of the 6189 patients initiating IPILIMUMAB, 3025 (49%) died prior to the end of follow-up. Median overall survival was estimated as 694 days (95% CI 638-772). Median number of dispensings per person was 3 (IQR 2-4).

Table 5: Median survival in days (months) since first PBS dispensing of medicine

	Median survival days (months)	95% confidence interval
Survival estimates	694 (23.1)	638 – 772 (21.3-25.7)

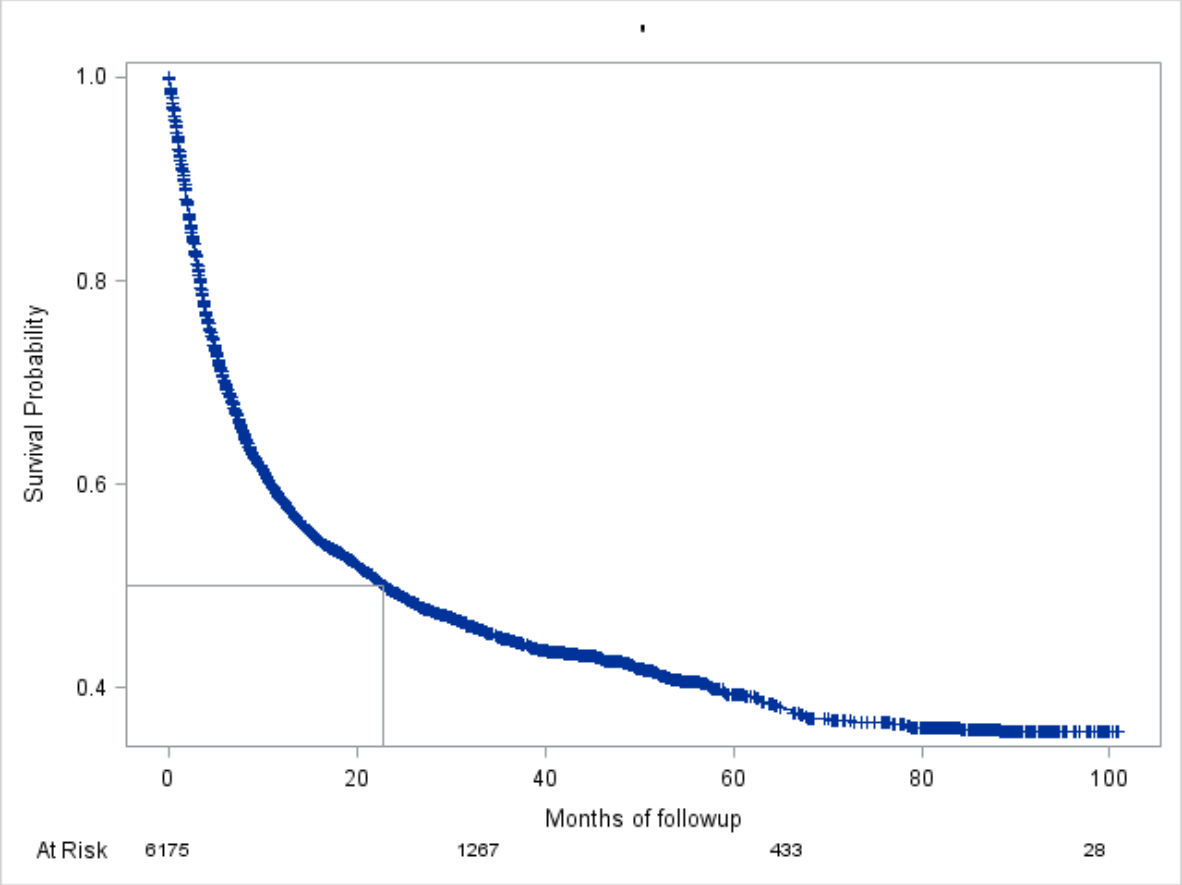


Figure 3: Kaplan Meier survival curve of people initiating PBS treatment from 1 August 2013 to 31 December 2021.

Feasibility outcome

IPILIMUMAB has a sufficiently long follow-up and number of deaths to produce a precise confidence interval for median overall survival. IPILIMUMAB is indicated for four different cancers; check for sufficient follow-up time to estimate OS if patients are censored before additional indications were listed. There is an unusual decrease in PBS dispensings from August 2015 to December 2016. This event requires further research to determine what, exactly, caused the decrease in use during this time period. IPILIMUMAB is a feasible candidate for full analysis but requires a strong caveat due to the decrease in dispensings in 2015/2016. The time period for analysis should be restricted to 2013 – 2019, when IPILIMUMAB was listed for melanoma only.

E.2 Lanreotide

Injection 120 mg (as acetate) in single dose pre-filled syringe

Purpose

The purpose of this document is to determine the feasibility of calculating robust and meaningful survival estimates for people initiating LANREOTIDE through the PBS. Analytical issues under consideration include: time since LANREOTIDE was PBS-listed; the number of people initiating treatment; the number of deaths observed during the available follow-up time; and potential external factors that may impact/bias survival estimates (e.g., a new indication being listed on the PBS that may result in a different patient population receiving LANREOTIDE during the observation period).

Summary of findings

- 578 patients treated (45% female); median age 66 years (IQR: 56 – 74)
- 7% dispensed antineoplastics in the 6 months prior to lanreotide initiation (6% chemotherapy; 1% targeted therapy; <1% immunotherapy)*
- There was insufficient follow up time to estimate crude median overall survival.

Feasibility assessment

- LANREOTIDE has insufficient follow-up time and number of deaths to produce a precise confidence interval for median overall survival.
- There is an increase in dispensings around August 2019 in line with the listing of the medicine for a different indication.
- **LANREOTIDE is not a feasible candidate for full analysis.**

* Antineoplastic treatments—chemotherapy, targeted therapy, immunotherapy—are not exclusive and patients may receive any/all during the six months prior to initiating the medicine of interest.

Listing on the Pharmaceutical Benefits Scheme (PBS)

Date of PBAC Consideration: November 2017

LANREOTIDE was PBS listed on 1 December 2018.

PBS listing details (as of 20 January 2022)

https://www.pbs.gov.au/medicine/item/11289E-11315M-11316N-11513Y-11527Q-11736Q-5777C-5778D-5779E-6423C-6424D-6425E

LANREOTIDE was listed on the PBS for the treatment of non-functional gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults with unresectable locally advanced or metastatic disease (Table 1).

Table 1: PBS listings of LANREOTIDE

Item code	Name, form & strength	Date of listing	Schedule	Authority required?
11513Y	Lanreotide 120 mg/0.5 mL injection, 0.5 mL syringe	1 December 2018	S100	Streamlined 10061
11527Q	Lanreotide 120 mg/0.5 mL injection, 0.5 mL syringe	1 December 2018	S100	Streamlined 10077

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Public Summary Document – November 2017 PBAC Meeting - LANREOTIDE available at

https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2017-11/lanreotide-gep-nets-psd-november-2017

LANREOTIDE was also listed for (Table 2) This listing is not part of this analysis.

Table 2: PBS listings of LANREOTIDE not included in analysis.

Item code	Name, form & strength	Date of listing	Schedule	Authority required?
11736Q	Lanreotide 120 mg/0.5 mL injection, 0.5 mL syringe	1 August 2019	S100	Streamlined
11315M	Lanreotide 120 mg/0.5 mL injection, 0.5 mL syringe	1 April 2018	S100	Streamlined
11316N	Lanreotide 120 mg/0.5 mL injection, 0.5 mL syringe	1 April 2018	S100	Streamlined
11289E	Lanreotide 120 mg/0.5 mL injection, 0.5 mL syringe	1 April 2018	S100	Streamlined

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Public Summary Document – March 2019 PBAC Meeting - LANREOTIDE available at

https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2019-03/lanreotide-psd-march-2019

Data Source/methodology

Dispensing data were extracted from the PBS claims database by the Department of Health for all PBS and RPBS items for LANREOTIDE (item codes 11513Y, 11527Q) for the period 1 December 2018 to 31 December 2021 (based on date of supply). Patient sex, date of birth, date of death and postcode of residence at time of dispensing were merged with dispensing data by the Department of Health. For this cohort, all antineoplastic medicine dispensings (medicines whose ATC codes begin with 'L01') were also extracted for the time period 1 June 2018 to 31 December 2021.

Initiating patients were identified from their first dispensing of LANREOTIDE in the PBS data. Prevalent patients were those who had at least one dispensing of LANREOTIDE during the calendar year.

Demographic characteristics of initiating patients were measured at the date of first PBS dispensing of LANREOTIDE. Patients were considered to have had prior use of antineoplastic medicines (L01) if those medicines were dispensed in the 6 months prior to LANREOTIDE initiation. Antineoplastic medicines dispensed in the 3 months after the first LANREOTIDE dispensing were also summarised.

Overall survival was estimated from the date of first LANREOTIDE dispensing to the date of death or censoring (censor date: 31 December 2021) using Kaplan-Meier methods.

Results

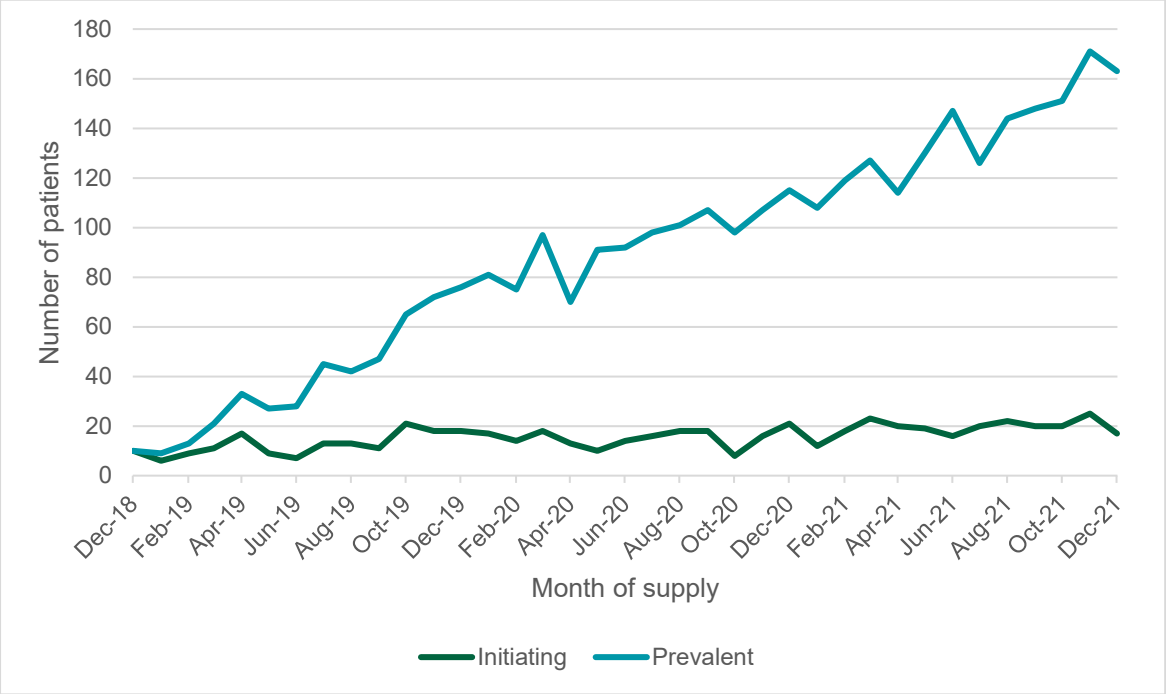


Figure 1: Initiating and prevalent patients for PBS medicine use, by month of supply

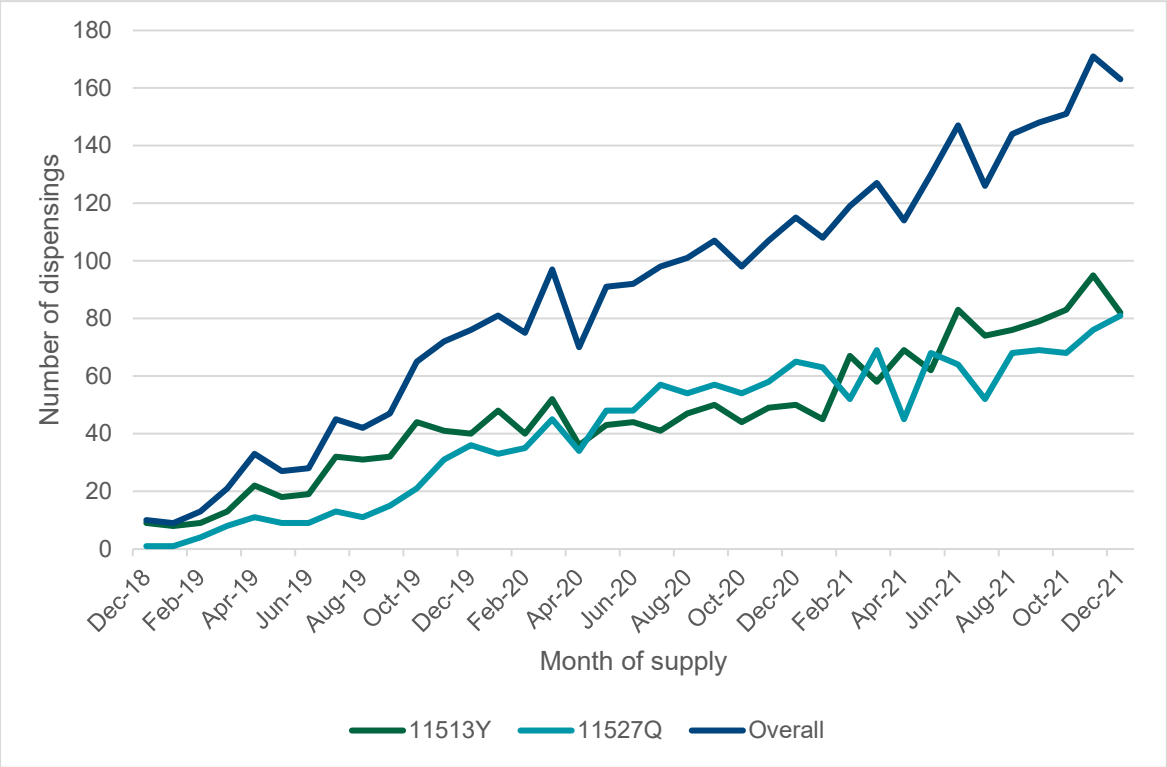


Figure 2: PBS dispensings for LANREOTIDE by item code and overall

Table 3: Patient characteristics at the time of first PBS dispensing of LANREOTIDE (1 December 2018 to 31 December 2021)

	n (%)
Patients	578
Sex	
Female	259 (44.9)
Male	318 (55.1)
Missing	1 (0.0)
Age at first PBS dispensing	
Median (IQR)	66 (56-74)
State of residence at first PBS dispensing	
ACT	12 (2.1)
NSW	173 (29.9)
NT	2 (0.4)
QLD	95 (16.4)
SA	55 (9.6)
TAS	44 (7.6)
VIC	149 (25.8)
WA	47 (8.1)
Missing	1 (0.0)
Antineoplastic (L01) medicines dispensed in 6 months prior to first PBS dispensing	
Overall	43 (7.4)
Chemotherapy	36 (6.2)
Immunotherapy	3 (0.5)
Targeted therapy	7 (1.2)
Antineoplastic (L01) medicines dispensed within 3 months after first PBS dispensing	
Overall	42 (7.3)
Chemotherapy	33 (5.7)
Immunotherapy	2 (0.3)
Targeted therapy	9 (1.6)

Table 4: Initiating and prevalent patients by year of PBS dispensing

Year	Initiating patients	Prevalent patients
2018 (Dec)	10	10
2019	153	160
2020	183	285
2021	232	418

Of the 578 patients initiating LANREOTIDE, 32 (5.5%) died prior to the end of follow-up. There was insufficient follow up time to estimate median overall survival. Median number of dispensings per person was 5 (IQR 2-7).

Table 5: Median survival in days (months) since first PBS dispensing of medicine

	Median survival Days (months)	95% confidence interval
Survival estimates		insufficient follow up time

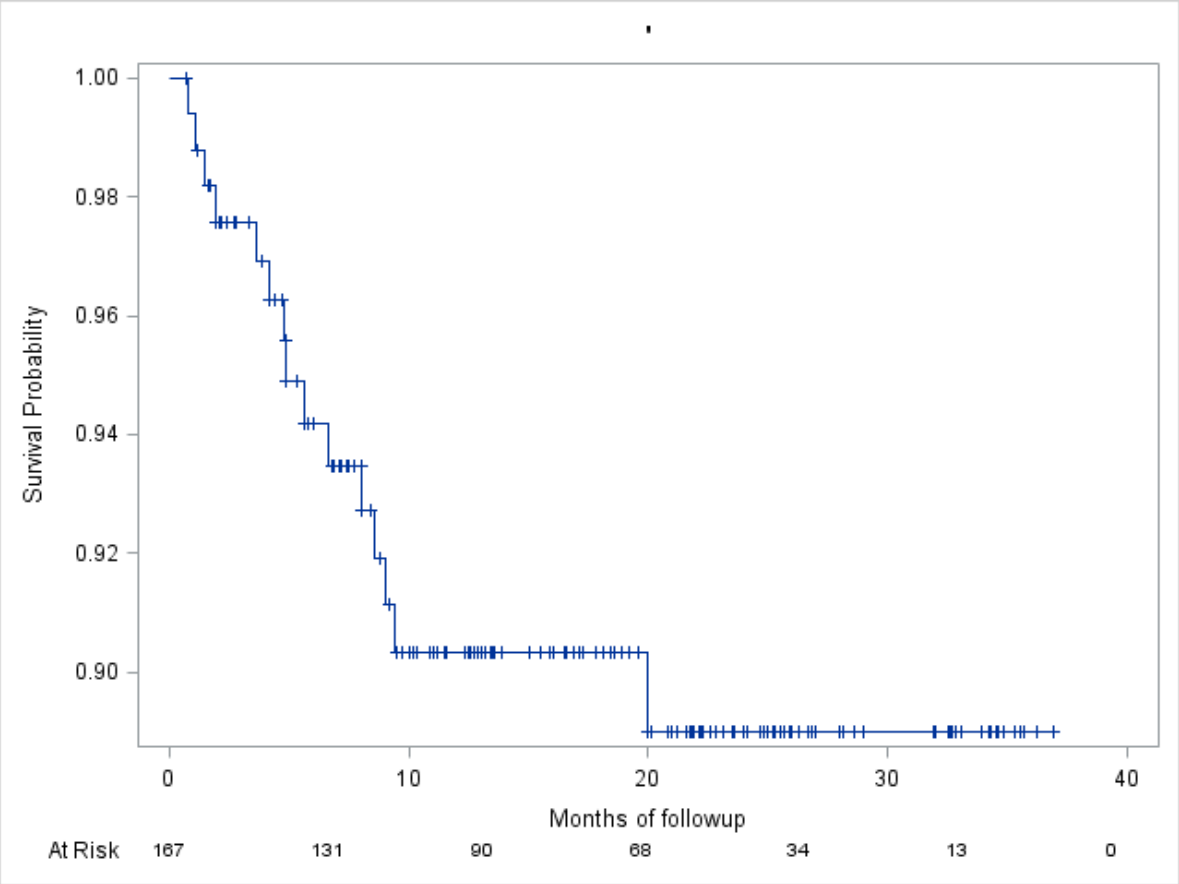


Figure 3: Kaplan Meier survival curve of people initiating PBS treatment from 1 December 2018 to 31 December 2021.

Feasibility outcome

LANREOTIDE has insufficient follow-up time and number of deaths to produce a precise confidence interval for median overall survival. There is an increase in dispensings around August 2019 in line with the listing of the medicine for a different indication. LANREOTIDE is not a feasible candidate for the full analysis.

E.3 Olaparib

Capsule, 50mg; Tablet 100mg; Tablet 150mg

Purpose

The purpose of this document is to determine the feasibility of calculating robust and meaningful survival estimates for people initiating OLAPARIB through the PBS. Analytical issues under consideration include: time since OLAPARIB was PBS-listed; the number of people initiating treatment; the number of deaths observed during the available follow-up time; and potential external factors that may impact/bias survival estimates (e.g., a new indication being listed on the PBS that may result in a different patient population receiving OLAPARIB during the observation period).

Summary of findings

- 673 patients treated (99% female); median age 62 years (IQR: 55– 70)
- 79% dispensed antineoplastics in the 6 months prior to olaparib initiation (69% chemotherapy; 24% targeted therapy; <1% immunotherapy)[*]
- Unable to calculate crude median overall survival

Feasibility assessment

- There is insufficient follow-up time and number of deaths to produce robust and meaningful median survival estimates.
- There is a notable increase in patients initiating PBS listed OLAPARIB after November 2020. This is likely due to the introduction of a new population after the new listing of OLAPARIB as first line treatment in November 2020.
- **OLAPARIB is a not a feasible candidate for full analysis.**

[*] Antineoplastic treatments—chemotherapy, targeted therapy, immunotherapy—are not exclusive and patients may receive any/all during the six months prior to initiating the medicine of interest.

Listing on the Pharmaceutical Benefits Scheme (PBS)

Date of PBAC Consideration: November 2016 (tablets March 2018)

OLAPARIB was PBS listed on 1 FEBRUARY 2017 (tablets 1 DECEMBER 2018)

PBS listing details (as of 20 January 2022)

https://www.pbs.gov.au/medicine/item/11503K-11522K-11528R-11539H-12157W-12161C-12169L-12170M

OLAPARIB was listed for the treatment of high grade serous ovarian cancer, high grade serous fallopian tube cancer and high grade serous primary peritoneal cancer. Patient must have evidence of a germline class 4 or 5 BRCA1 or BRCA2 gene mutation. The condition must be platinum sensitive; patients must have received at least two previous platinum-containing regimens. Patients must have relapsed following a previous platinum-containing regimen and must be in partial or complete response to the immediately preceding platinum-based chemotherapy regimen. The treatment must be as monotherapy and must be maintenance therapy (Table 1).

Table 1: PBS listings of OLAPARIB

Item code	Name, form & strength, pack size	Date of listing	Schedule	Authority required?
11034R 11050N	OLAPARIB Capsule 50mg	1 Feb 2017 (no longer on PBS)	General	Initial- in writing Continued- Streamlined
11522K 11503K	OLAPARIB Tablet 100mg, 56	1 Dec 2018	General	Initial- in writing Continued- Streamlined
11528R 11539H	OLAPARIB Tablet 150mg, 56	1 Dec 2018	General	Initial- in writing Continued- Streamlined

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Public summary document – November 2016 – 4.04 OLAPARIB available at https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2016-11/olaparib-psd-november-2016

Public summary document – March 2018 – 5.08 OLAPARIB for same indication, tablets: https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2018-03/Olaparib-psd-march-2018

OLAPARIB was also listed as the first-line treatment of high grade serous ovarian cancer, high grade serous fallopian tube cancer and high grade serous primary peritoneal cancer in November 2020 (Table 2). This listing is not part of this analysis.

Table 2: PBS listings of OLAPARIB not included in analysis.

Item code	Name, form & strength, pack size	Date of listing	Schedule	Authority required?
12169L 12170M	OLAPARIB Tablet 100mg, 56	1 November 2020	General	Initial- in writing Continued- Streamlined
12157W 12161C	OLAPARIB Tablet 150mg, 56	1 November 2020	General	Initial- in writing Continued- Streamlined

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Public summary document – July 2020 – 7.05 OLAPARIB available at: https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2020-07/olaparib-tablet-100-mg-tablet-150-mg-lynparza

Data Source/methodology

Dispensing data were extracted from the PBS claims database by the Department of Health for all PBS and RPBS items for OLAPARIB (item codes 11034R, 11050N, 11528R, 11503K, 11522K, 11539H) for the period 1 February 2017 to 31 December 2021 (based on date of supply). Patient sex, date of birth, date of death and postcode of residence at time of dispensing were merged with dispensing data by the Department of Health. For this cohort, all antineoplastic medicine dispensings (medicines whose ATC codes begin with 'L01') were also extracted for the time period 1 August 2016 to 31 December 2021.

Initiating patients were identified from their first dispensing of OLAPARIB in the PBS data. Prevalent patients were those who had at least one dispensing of OLAPARIB during the calendar year.

Demographic characteristics of initiating patients were measured at the date of first PBS dispensing of OLAPARIB. Patients were considered to have had prior use of antineoplastic medicines (L01) if those medicines were dispensed in the 6 months prior to OLAPARIB initiation. Antineoplastic medicines dispensed in the 3 months after the first OLAPARIB dispensing were also summarised.

Overall survival was estimated from the date of first OLAPARIB L dispensing to the date of death or censoring (censor date: 31 December 2021) using Kaplan-Meier methods.

Results

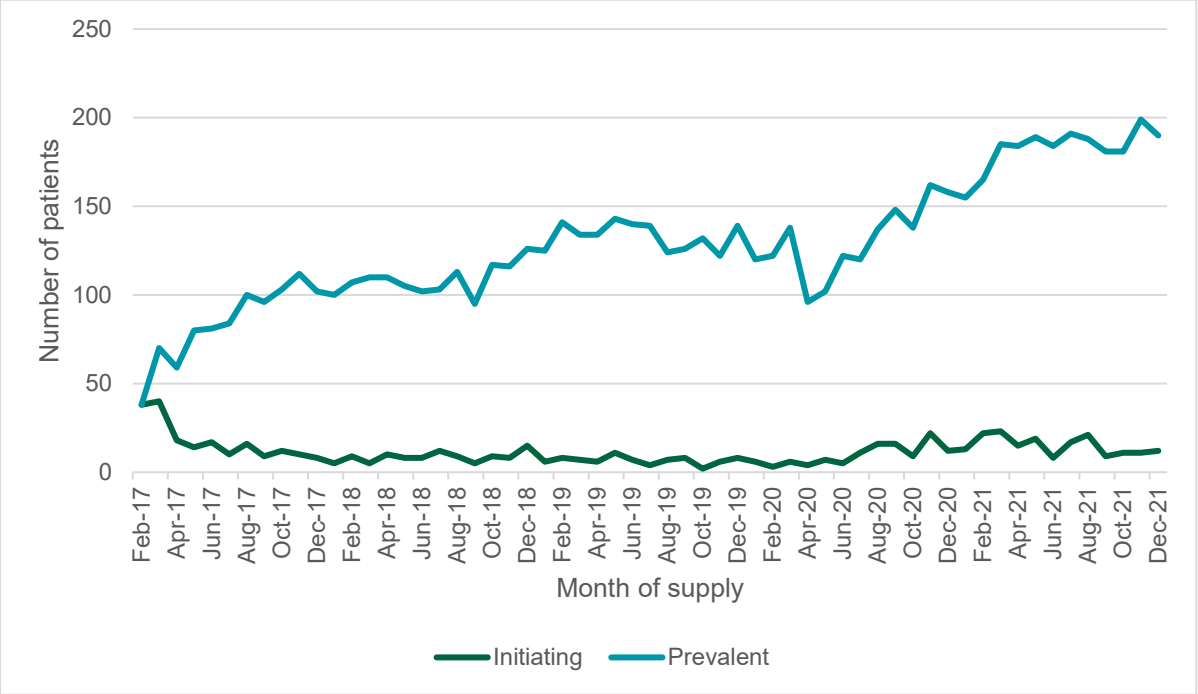


Figure 1: Initiating and prevalent patients for PBS medicine use, by month of supply

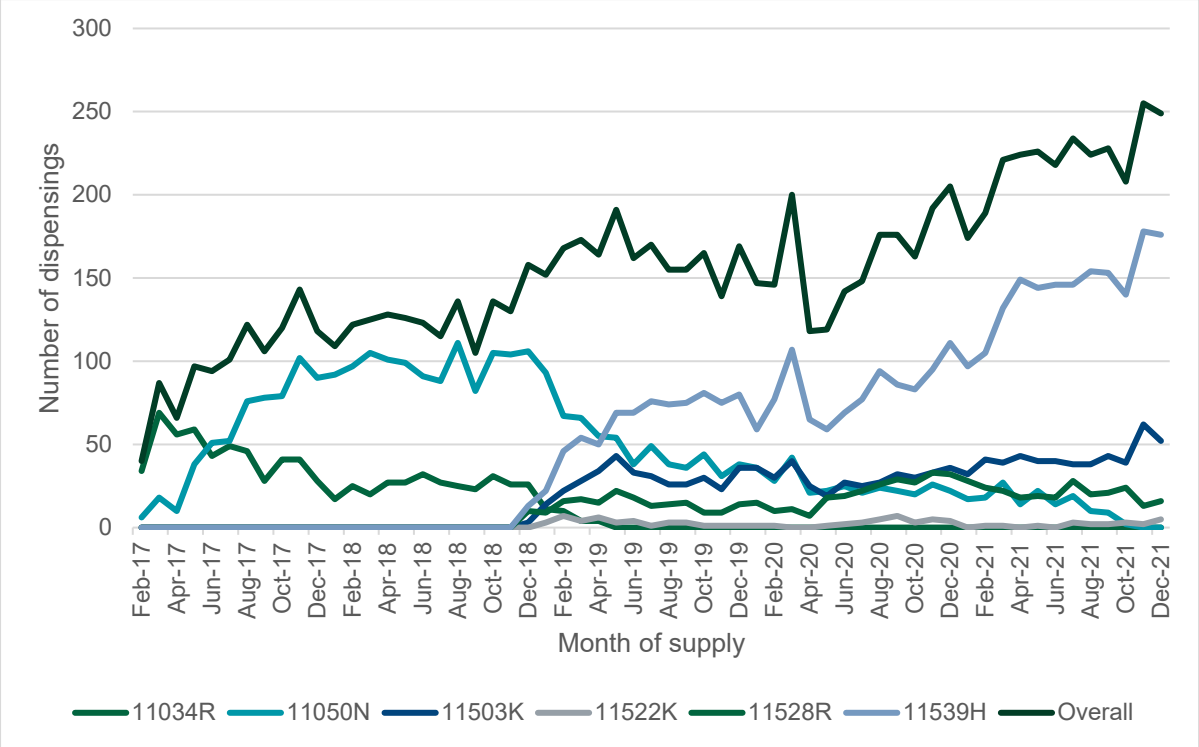


Figure 2: PBS dispensings for OLAPARIB by item code and overall

Table 3: Patient characteristics at the time of first PBS dispensing of OLAPARIB (1 February 2017 to 31 December 2021)

	n (%)
Patients	673
Sex	
Female	663 (98.7)
Male	9 (1.3)
Missing	1 (0.0)
Age at first pbs dispensing	
Median (IQR)	62 (55-70)
State of residence at first PBS dispensing	
ACT	10 (1.5)
NSW	213 (31.7)
NT	3 (0.5)
QLD	128 (19.0)
SA	43 (6.4)
TAS	7 (1.0)
VIC	197 (29.3)
WA	71 (10.6)
Missing	1 (0.0)
Antineoplastic (L01) medicines dispensed in 6 months prior to first PBS dispensing	
Overall (excluding medicine of interest)	531 (78.9)
Chemotherapy	463 (68.8)
Immunotherapy	3 (0.4)
Targeted therapy (excluding medicine of interest)	159 (23.6)
Antineoplastic (L01) medicines dispensed within 3 months after first PBS dispensing	
Overall (excluding medicine of interest)	553 (82.2)
Chemotherapy	70 (10.4)
Immunotherapy	2 (0.3)
Targeted therapy (excluding medicine of interest)	529 (78.6)

Table 4: Initiating and prevalent patients by year of PBS dispensing

Year	Initiating patients	Prevalent patients
2017 (Feb-Dec)	192	192
2018	103	251
2019	80	258
2020	117	285
2021	181	385

Of the 673 patients initiating OLAPARIB, 177 (26%) died prior to the end of follow-up. There was insufficient follow up time to estimate median overall survival. Median number of dispensings per person was 8 (IQR 4-17).

Table 5: Median survival in days (months) since first PBS dispensing of medicine

	Median survival Days (months)	95% confidence interval
Survival estimates		Lower = 1409 (insufficient follow up time)

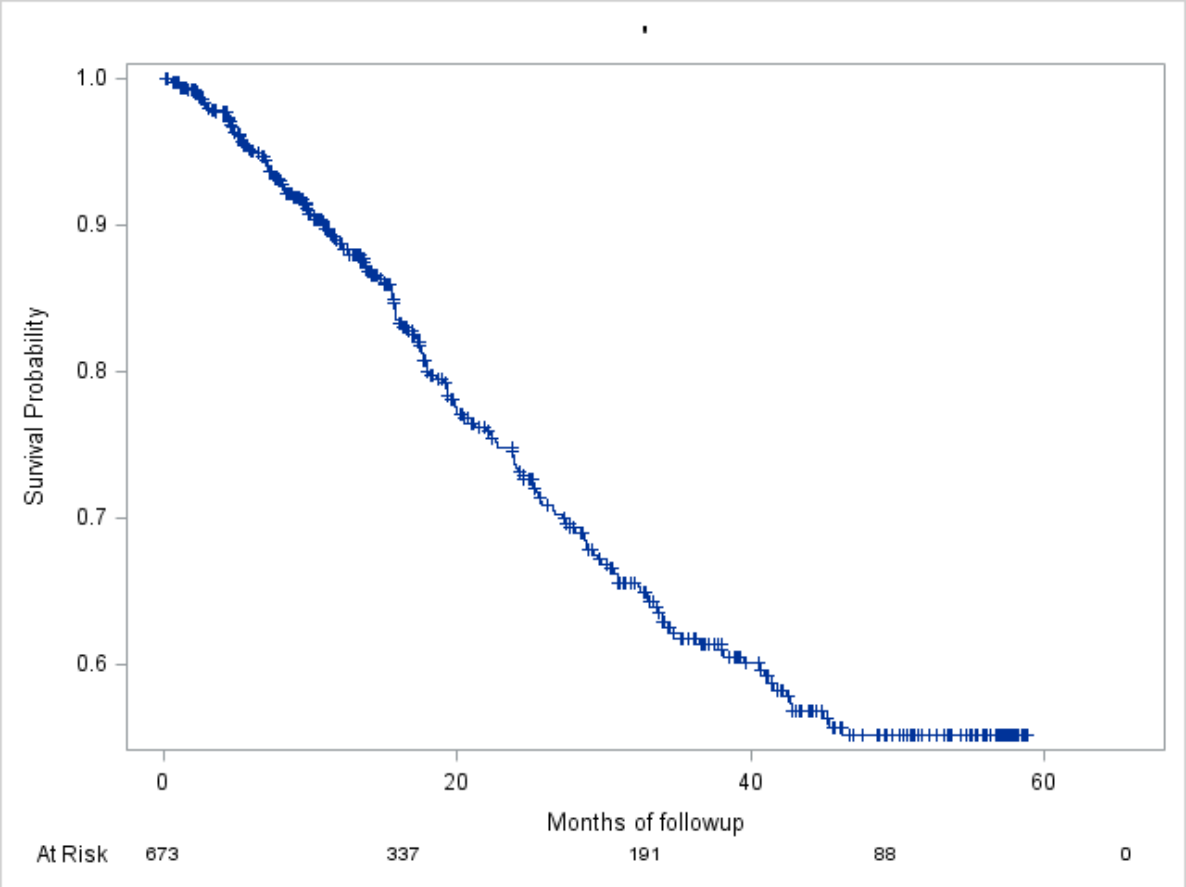


Figure 3: Kaplan Meier survival curve of people initiating PBS treatment from 1 February 2017 to 31 December 2021.

Feasibility outcome

OLAPARIB does not have sufficient follow-up time and number of deaths to produce robust and meaningful median survival estimates. There is a notable increase in patients initiating PBS listed OLAPARIB after November 2020. This is likely due to the introduction of a new population after the listing of OLAPARIB as a first line treatment in November 2020. OLAPARIB is not a feasible candidate for the full analysis.

E.4 Panitumumab

100 mg/5 ml injection, 5mL vial

400 mg/20 ml injection, 20mL vial

Purpose

The purpose of this document is to determine the feasibility of calculating robust and meaningful survival estimates for people initiating PANITUMUMAB through the PBS. Analytical issues under consideration include: time since PANITUMUMAB was PBS-listed; the number of people initiating treatment; the number of deaths observed during the available follow-up time; and potential exogenous factors that may impact/bias survival estimates.

Summary of findings

- 2,064 patients treated (37% female); median age 65 years (IQR: 55 – 73)
- 86% dispensed antineoplastics in the 6 months prior to panitumumab initiation (84% chemotherapy; 42% targeted therapy; <1% immunotherapy)*
- Crude median overall survival: 16 months (95%CI: 15.0 – 17.0)

Feasibility assessment

- There is sufficiently long follow-up and number of deaths to produce robust and meaningful median survival estimates.
- There is a notable increase in dispensing during 2017 but no apparent reason for the increase (i.e., no new indications listed). From 2018 dispensings return to trend.
- **PANITUMUMAB is a feasible candidate for full analysis, including sensitivity analyses, which can then be benchmarked against pivotal trial estimates.**

* Antineoplastic treatments—chemotherapy, targeted therapy, immunotherapy—are not exclusive and patients may receive any/all during the six months prior to initiating the medicine of interest.

Listing on the Pharmaceutical Benefits Scheme (PBS)

Date of PBAC Consideration: November 2013

PANITUMUMAB was PBS listed on 1 April 2014.

PBS listing details (as of 20 January 2022)

www.pbs.gov.au/medicine/item/10069Y-10082P-10508C-10513H

PANITUMUMAB was listed as a Section 100 (Efficient Funding of Chemotherapy) Authority Required medicine for the treatment of K-RAS wild-type (WT) metastatic colorectal cancer (mCRC) in patients who have failed first-line chemotherapy (Table 1).

Table 1: PBS listings of PANITUMUMAB

Item code	Name, form & strength	Date of listing	Schedule	Authority required?
10069Y	PANITUMUMAB Solution concentrate for I.V. infusion 100 mg in 5 mL or 400 mg in 20 mL	1 Apr 2014	S100	Streamlined
10082P	PANITUMUMAB Solution concentrate for I.V. infusion 100 mg in 5 mL or 400 mg in 20 mL	1 Apr 2014	S100	Streamlined

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Public Summary Document – November 2013 PBAC Meeting - PANITUMUMAB available at https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-11/panitumumab

PANITUMUMAB was also listed as first-line treatment for metastatic colorectal cancer on 1 October 2015 (Table 2). This listing is not part of this analysis.

Table 2: PBS listings of PANITUMUMAB not included in analysis.

Item code	Name, form & strength	Date of listing	Schedule	Authority required?
10508C	PANITUMUMAB Solution concentrate for I.V. infusion 100 mg in 5 mL or 400 mg in 20 mL	1 Oct 2015	S100	Streamlined
10513H	PANITUMUMAB Solution concentrate for I.V. infusion 100 mg in 5 mL or 400 mg in 20 mL	1 Oct 2015	S100	Streamlined

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Public Summary Document – March 2015 PBAC Meeting – 7.08 PANITUMUMAB available at https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2015-03/panitumumab-vectibix-psd-03-2015

Data Source/methodology

Dispensing data were extracted from the PBS claims database by the Department of Health for all PBS and RPBS items for PANITUMUMAB (item codes 10069Y, 10082P) for the period 1 April 2014 to 31 December 2021 (based on date of supply). Patient sex, date of birth, date of death and postcode of residence at time of dispensing were merged with dispensing data by the Department of Health. For this cohort, all antineoplastic medicine dispensings (medicines whose ATC codes begin with 'L01') were also extracted for the time period 1 October 2013 to 31 December 2021.

Initiating patients were identified from their first dispensing of PANITUMUMAB in the PBS data. Prevalent patients were those who had at least one dispensing of PANITUMUMAB during the calendar year.

Demographic characteristics of initiating patients were measured at the date of first PBS dispensing of PANITUMUMAB. Patients were considered to have had prior use of antineoplastic medicines (L01) if those medicines were dispensed in the 6 months prior to PANITUMUMAB initiation. Antineoplastic medicines dispensed in the 3 months after the first PANITUMUMAB dispensing were also summarised.

Overall survival was estimated from the date of first PANITUMUMAB dispensing to the date of death or censoring (censor date: 31 December 2021) using Kaplan-Meier methods.

Results

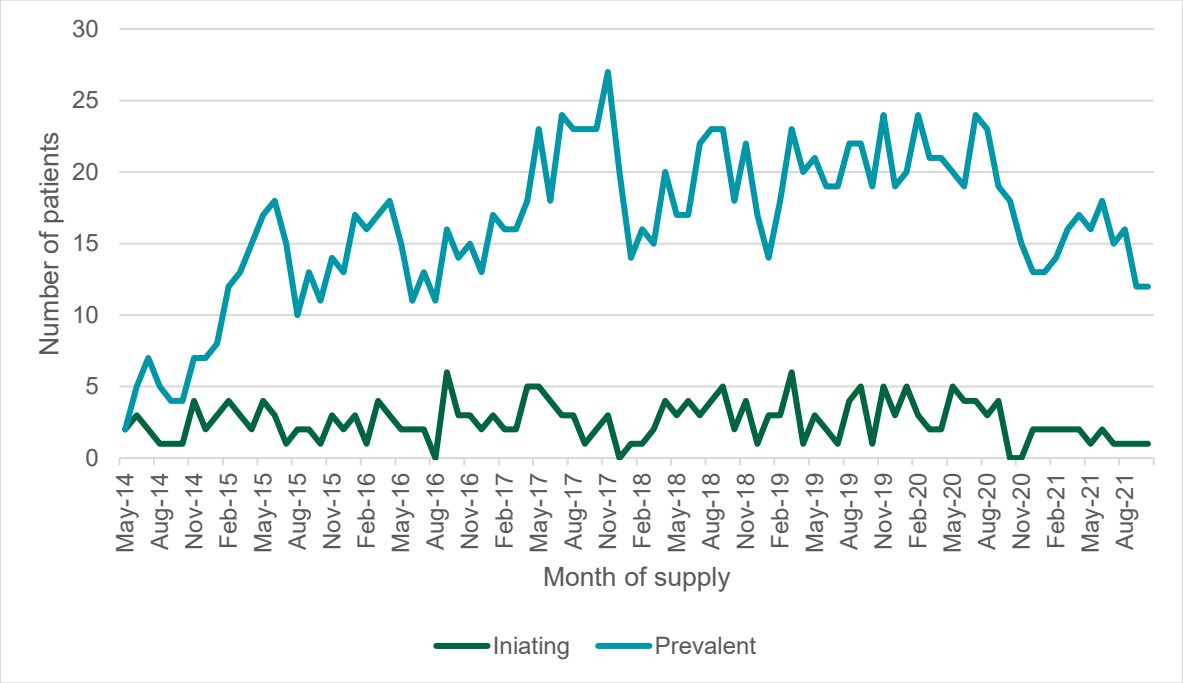


Figure 1: Initiating and prevalent patients for PBS medicine use, by month of supply

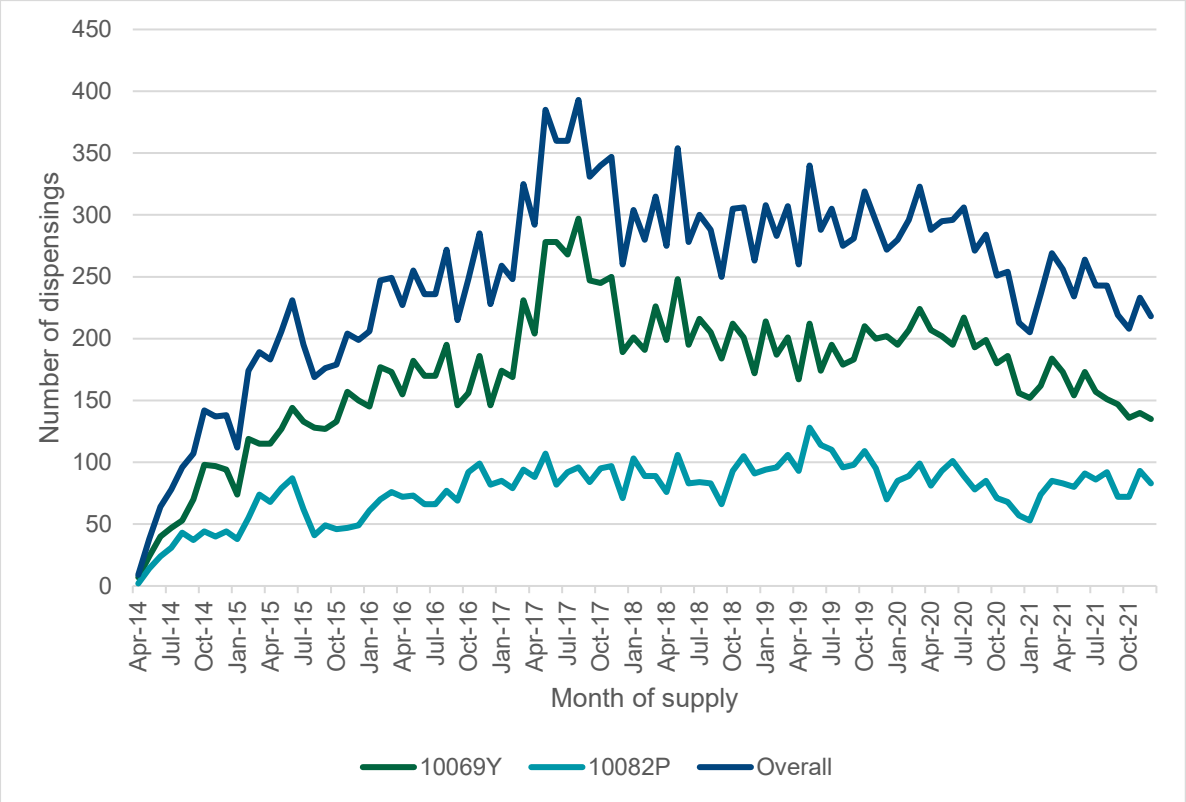


Figure 2: PBS dispensings for PANITUMUMAB by item code and overall

Table 3: Patient characteristics at the time of first PBS dispensing of PANITUMUMAB (1 April 2014 to 31 December 2021)

	n (%)
Patients	2064
Sex	
Female	758 (36.7)
Male	1305 (63.3)
Missing	1 (0.0)
Age at first PBS dispensing	
Median (IQR)	65 (55-73)
State of residence at first PBS dispensing	
ACT	25 (1.2)
NSW	637 (30.9)
NT	14 (0.7)
QLD	488 (23.6)
SA	210 (10.2)
TAS	71 (3.4)
VIC	367 (17.8)
WA	251 (12.2)
Missing	1 (0.0)
Antineoplastic (L01) medicines dispensed in 6 months prior to first PBS dispensing	
Overall (excluding medicine of interest)	1767 (85.6)
Chemotherapy	1736 (84.1)
Immunotherapy	2 (0.1)
Targeted therapy (excluding medicine of interest)	864 (41.9)
Antineoplastic (L01) medicines dispensed within 3 months after first PBS dispensing	
Overall (excluding medicine of interest)	1488 (72.1)
Chemotherapy	1471 (71.3)
Immunotherapy	1 (0.0)
Targeted therapy (excluding medicine of interest)	110 (5.3)

Table 4: Initiating and prevalent patients by year of PBS dispensing

Year	Initiating patients	Prevalent patients
2014 (Apr-Dec)	140	140
2015	225	291
2016	284	387
2017	336	473
2018	325	505
2019	304	484
2020	263	443
2021	187	340

Of the 2064 patients initiating PANITUMUMAB, 1341 (65%) died prior to the end of follow-up. Median overall survival was estimated as 480 days (95% CI 449-511). Median number of dispensings per person was 7 (IQR 4-15).

Table 5: Median survival in days (months) since first PBS dispensing of medicine

	Median survival Days (months)	95% confidence interval
Survival estimates	480 (16.0)	449 – 511 (15.0-17.0)

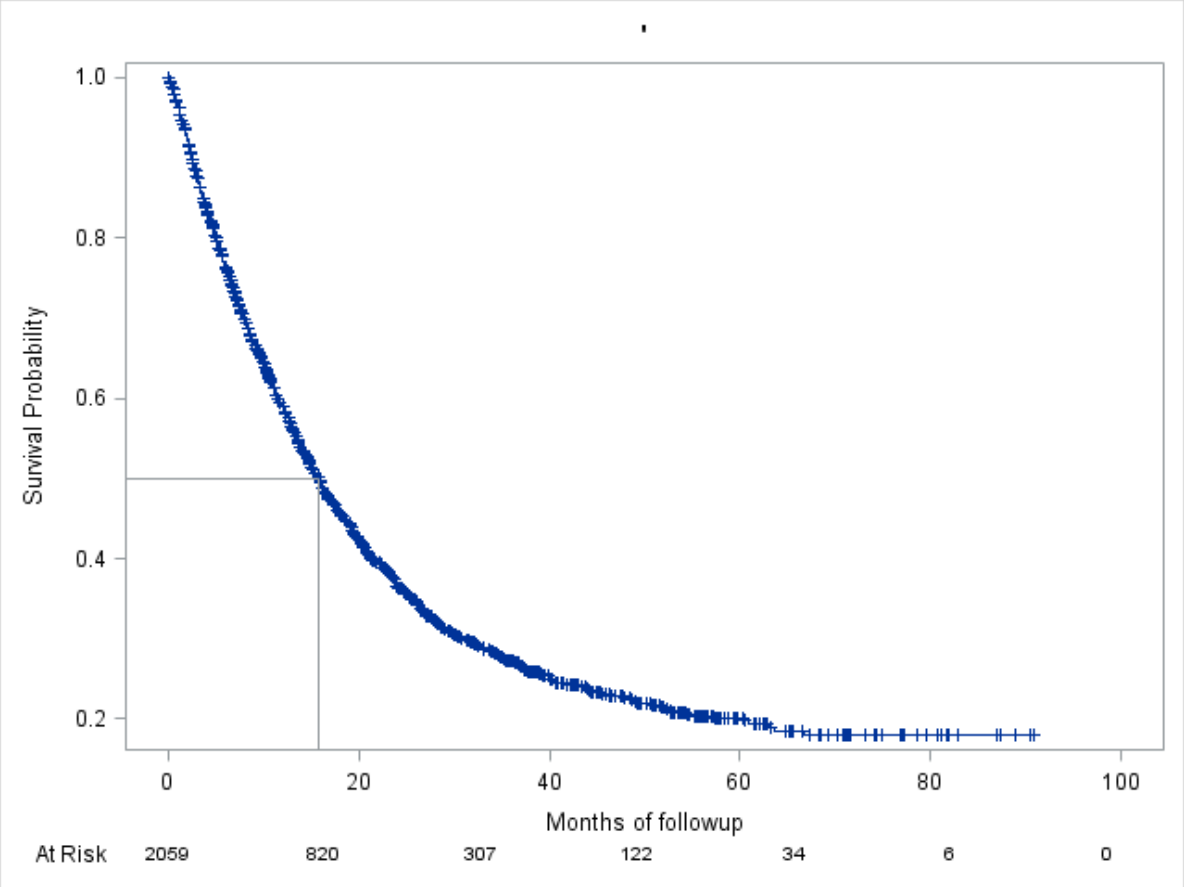


Figure 3: Kaplan Meier survival curve of people initiating PBS treatment from 1 April 2014 to 31 December 2021

Feasibility outcome

PANTIMUMUAB has sufficiently long follow-up and number of deaths to produce robust and meaningful median survival estimates. There is a notable increase in dispensing during 2017 but no apparent reason for the increase (i.e., no new indications listed). From 2018 dispensings return to trend. PANTIMUMUAB is a feasible candidate for the full analysis.

E.5 Trastuzumab emtansine

100 mg injection, 1 x 100 mg vial; 160 mg injection, 1 x 160 mg vial

Purpose

The purpose of this review is to determine the feasibility of calculating robust and meaningful survival estimates for people initiating TRASTUZUMAB EMTANSINE (TDM-1) through the PBS. Analytical issues under consideration include: time since TRASTUZUMAB EMTANSINE was PBS-listed; the number of people initiating treatment; the number of deaths observed during the available follow-up time; and potential external factors that may impact/bias survival estimates (e.g., a new indication being listed on the PBS that may result in a different patient population receiving TRASTUZUMAB EMTANSINE during the observation period).

Summary of findings

- 1770 patients treated (99% female); median age 58 years (IQR: 50 – 68)
- 85% dispensed antineoplastics in the 6 months prior to TRASTUZUMAB EMTANSINE initiation (33% chemotherapy; 81% targeted therapy; <1% immunotherapy)*
- Crude median overall survival: 28.9 months (95%CI: 26.1 – 32.0)

Feasibility assessment

- There is sufficiently long follow-up and number of deaths to produce robust and meaningful median survival estimates.
- There is a small increase in dispensings from April 2020 after the listing for the treatment of early breast cancer. There is sufficient data to censor at this point if required.
- **TRASTUZUMAB EMTANSINE is a feasible candidate for full analysis, including sensitivity analyses, which can then be benchmarked against pivotal trial estimates.**

* Antineoplastic treatments—chemotherapy, targeted therapy, immunotherapy—are not exclusive and patients may receive any/all during the six months prior to initiating the medicine of interest.

Listing on the Pharmaceutical Benefits Scheme (PBS)

Date of PBAC Consideration: November 2014

TRASTUZUMAB EMTANSINE was PBS listed on 1 July 2015.

PBS listing details (as of 20 January 2022)

PBS listing: https://www.pbs.gov.au/medicine/item/10281D-10282E-11951B-11956G

TRASTUZUMAB EMTANSINE (T-DM1) was listed for the treatment of a patient with HER2 positive metastatic breast cancer who has received prior treatment with trastuzumab and a taxane and whose disease has progressed despite treatment with trastuzumab for metastatic disease. (Table 1)

Table 1: PBS listings of TRASTUZUMAB EMTANSINE

Item code	Name, form & strength	Date of listing	Schedule	Authority required?
10281D	Trastuzumab emtansine Powder for I.V. infusion 160 mg Powder for I.V. infusion 100 mg	1 July 2015	S100	Authority written
10282E	Trastuzumab emtansine Powder for I.V. infusion 160 mg Powder for I.V. infusion 100 mg	1 July 2015	S100	Authority written

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Public Summary document – November 2014 – 7.8 TRASTUZUMAB EMTANSINE available at https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2014-11/pertuzumab-trastuzumab-psd-11-2014

TRASTUZUMAB EMTANSINE was also listed for early-stage breast cancer on 1 April 2020. (Table 2) This listing is not part of this analysis.

Table 2: PBS listings of TRASTUZUMAB EMTANSINE not included in analysis.

Item code	Name, form & strength	Date of listing	Schedule	Authority required?
11951B	Trastuzumab emtansine Powder for I.V. infusion 160 mg Powder for I.V. infusion 100 mg	1 April 2020	S100	Authority written
11956G	Trastuzumab emtansine Powder for I.V. infusion 160 mg Powder for I.V. infusion 100 mg	1 April 2020	S100	Authority written

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Public Summary document – November 2019 – 6.07 TRASTUZUMAB EMTANSINE available at https://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2019-11/trastuzumab-emtansine-powder-for-i-v-infusion-100-mg-powder

Data Source/methodology

Dispensing data were extracted from the PBS claims database by the Department of Health for all PBS and RPBS items for TRASTUZUMAB EMTANSINE (item codes 10281D, 10282E) for the period 1 July 2015 to 31 December 2021 (based on date of supply). Patient sex, date of birth, date of death and postcode of residence at time of dispensing were merged with dispensing data by the Department of Health. For this cohort, all antineoplastic medicine dispensings (medicines whose ATC codes begin with 'L01') were also extracted for the time period 1 January 2015 to 31 December 2021.

Initiating patients were identified from their first dispensing of TRASTUZUMAB EMTANSINE in the PBS data. Prevalent patients were those who had at least one dispensing of TRASTUZUMAB EMTANSINE during the calendar year.

Demographic characteristics of initiating patients were measured at the date of first PBS dispensing of TRASTUZUMAB EMTANSINE. Patients were considered to have had prior use of antineoplastic medicines (L01) if those medicines were dispensed in the 6 months prior to TRASTUZUMAB EMTANSINE initiation. Antineoplastic medicines dispensed in the 3 months after the first TRASTUZUMAB EMTANSINE dispensing were also summarised.

Overall survival was estimated from the date of first TRASTUZUMAB EMTANSINE dispensing to the date of death or censoring (censor date: 31 December 2021) using Kaplan-Meier methods.

Results

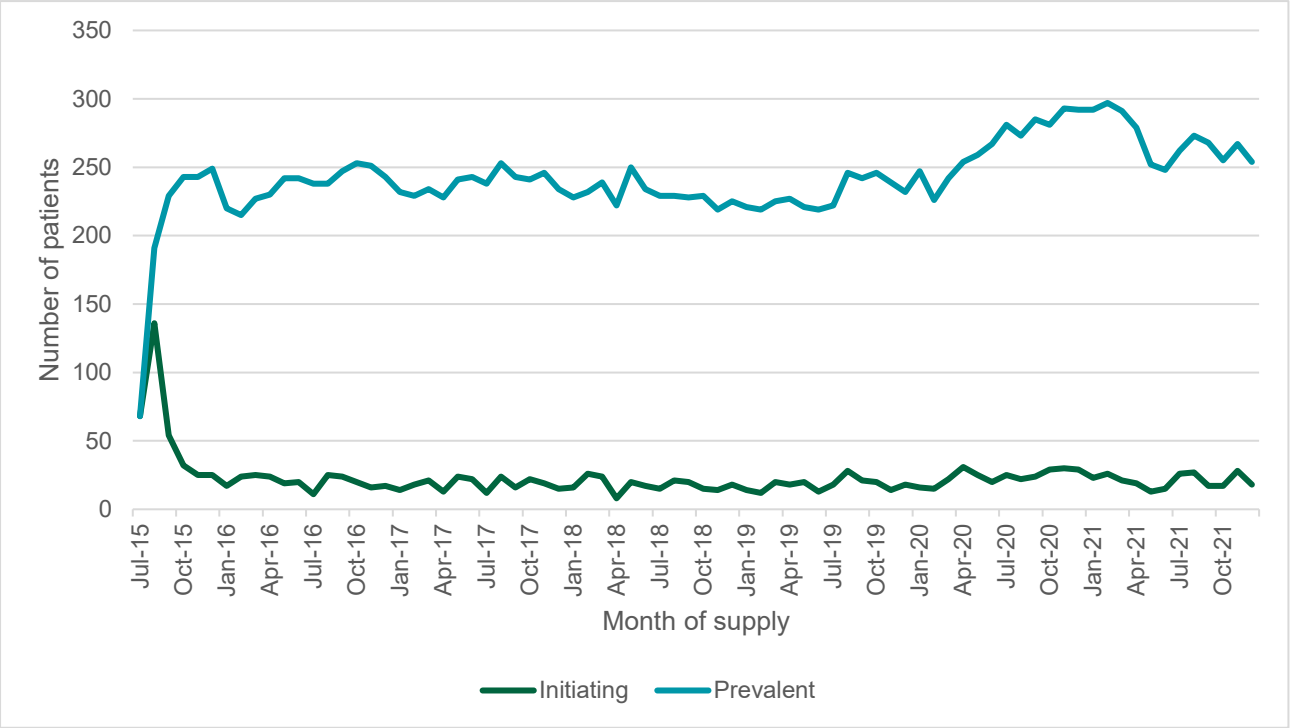


Figure 1: Initiating and prevalent patients for PBS medicine use, by month of supply

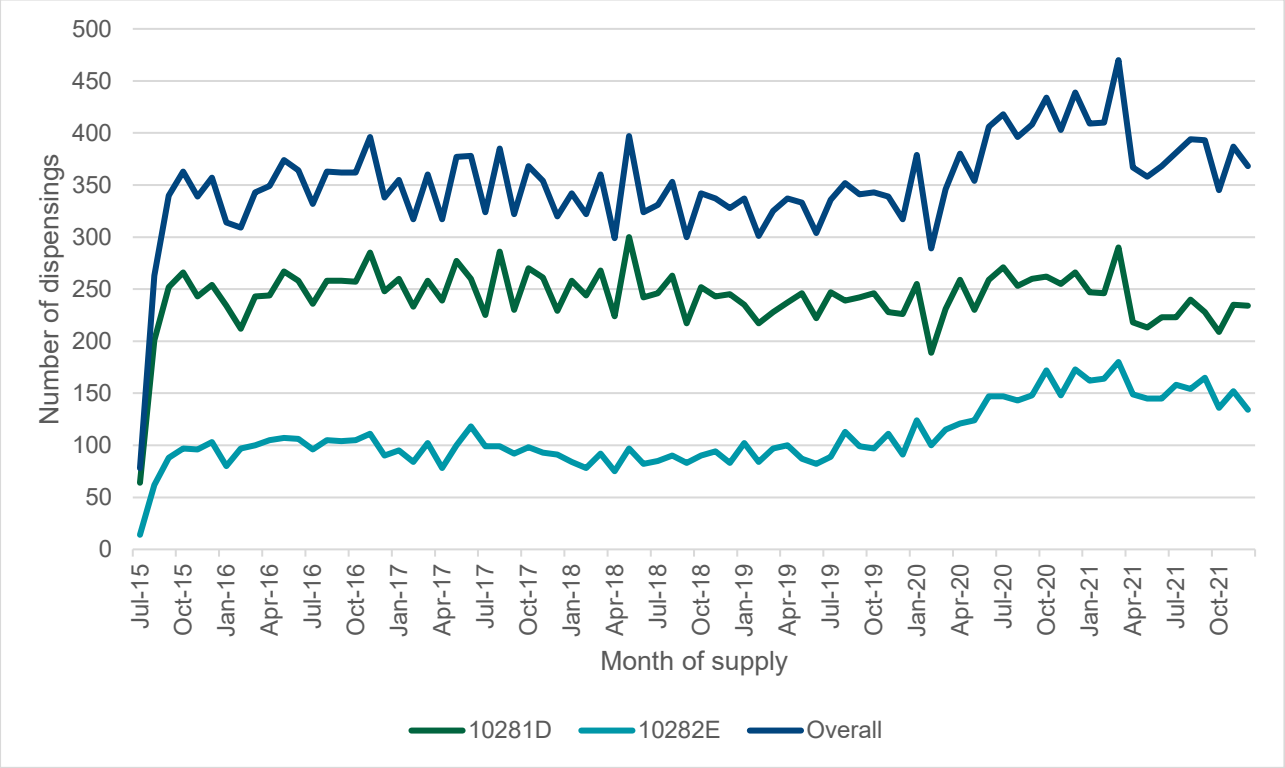


Figure 2: PBS dispensings for TRASTUZUMAB EMTANSINE by item code and overall

Table 3: Patient characteristics at the time of first PBS dispensing of TRASTUZUMAB EMTANSINE (1 July 2015 to 31 December 2021)

	n (%)
Patients	1770
Sex	
Female	1752 (99.0)
Male	16 (0.9)
Missing	2 (0.1)
Age at first PBS dispensing	
Median (IQR)	58 (50-68)
State of residence at first PBS dispensing	
ACT	27 (1.5)
NSW	548 (31.0)
NT	14 (0.8)
QLD	316 (17.9)
SA	138 (7.8)
TAS	48 (2.7)
VIC	505 (28.5)
WA	173 (9.8)
Missing	1 (0.0)
Antineoplastic (L01) medicines dispensed in 6 months prior to first PBS dispensing	
Overall	1506 (85.1)
Chemotherapy	578 (32.7)
Immunotherapy	2 (0.1)
Targeted therapy (excluding medicine of interest)	1438 (81.2)
Antineoplastic (L01) medicines dispensed within 3 months after first PBS dispensing	
Overall	182 (10.3)
Chemotherapy	125 (7.1)
Immunotherapy	1 (0.1)
Targeted therapy (excluding medicine of interest)	131 (7.4)

Table 4: Initiating and prevalent patients by year of TRASTUZUMAB EMTANSINE PBS dispensing

Year	Initiating patients	Prevalent patients
2015 (Jul-Dec)	340	340
2016	242	477
2017	220	468
2018	214	460
2019	216	465
2020	288	543
2021	250	545

Of the 1770 patients initiating TRASTUZUMAB EMTANSINE, 861 (48.6%) died prior to the end of follow-up. Median overall survival was estimated as 866 days (95% CI 782-959). Median number of dispensings per person was 9 (IQR 5-19).

Table 5: Median survival estimate in days (months) since first PBS dispensing of TRASTUZUMAB EMTANSINE

	Median survival days (months)	95% confidence interval
Survival estimates	866 (28.9)	782 – 959 (26.1-32.0)

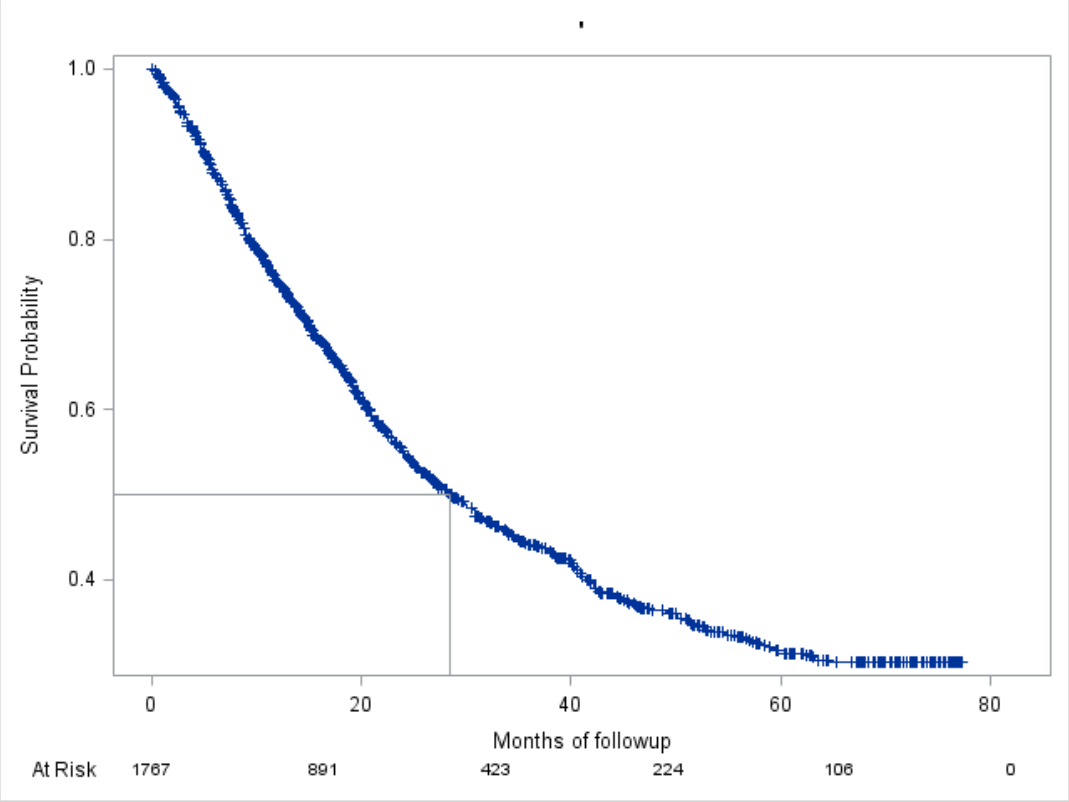


Figure 3: Kaplan Meier survival curve of people initiating PBS treatment from 1 July 2015 to 31 December 2021

Feasibility outcome

TRASTUZUMAB EMTANSINE has sufficiently long follow-up and number of deaths to produce robust and meaningful median survival estimates. There is a small increase in dispensings from April 2020 after the listing for the treatment of early breast cancer. There is sufficient data to censor at this point if required. TRASTUZUMAB EMTANSINE is a feasible candidate for the full analysis.

E.6 Trifluridine with tipiracil

Tablet, 15 mg trifluridine with 6.14 mg tipiracil

Tablet, 20 mg, trifluridine with 8.19 mg tipiracil

Purpose

The purpose of this document is to determine the feasibility of calculating robust and meaningful survival estimates for people initiating TRIFLURIDINE with TIPIRACIL through the PBS. Analytical issues under consideration include: time since TRIFLURIDINE with TIPIRACIL was PBS-listed; the number of people initiating treatment; the number of deaths observed during the available follow-up time; and potential external factors that may impact/bias survival estimates (e.g., a new indication being listed on the PBS that may result in a different patient population receiving TRIFLURIDINE with TIPIRACIL during the observation period).

Summary of findings

- 2,356 patients treated (59% female); median age 65 years (IQR: 56 – 73)
- 92% dispensed antineoplastics in the 6 months prior to trifluridine initiation (90% chemotherapy; 58% targeted therapy)[*]
- Crude median overall survival: 10.1 months (95%CI: 9.3 – 11.0)

Feasibility assessment

- There is sufficiently long follow-up and number of deaths to produce robust and meaningful median survival estimates.
- There were no discernible external factors that would indicate concerns over data quality and interpretability of the survival results.
- **TRIFLURIDINE with TIPIRACIL is a feasible candidate for full analysis, including sensitivity analyses, which can then be benchmarked against pivotal trial estimates.**

[*] Antineoplastic treatments—chemotherapy, targeted therapy, immunotherapy—are not exclusive and patients may receive any/all during the six months prior to initiating the medicine of interest.

Listing on the Pharmaceutical Benefits Scheme (PBS)

Date of PBAC Consideration: July 2018

TRIFLURIDINE with TIPIRACIL was PBS listed on 1 December 2018

PBS listing details (as of 20 January 2022)

https://www.pbs.gov.au/medicine/item/11507P-11524M-12033H-12056M

TRIFLURIDINE with TIPIRACIL was listed for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy on 1 December 2018 (Table 1).

Table 1: PBS listings of TRIFLURIDINE with TIPIRACIL

Item code	Name, form & strength, pack size	Date of listing	Schedule	Authority required?
11507P	TRIFLURIDINE with TIPIRACIL, Tablet, 15mg trifluridine with 6.14mg tipiracil, 20	1 Dec 2018	General	Streamlined
11524M	TRIFLURIDINE with TIPIRACIL, Tablet, 20mg, trifluridine with 8.19mg tipiracil, 20	1 Dec 2018	General	Streamlined

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

Public Summary Document – July 2018 PBAC Meeting - 7.19 TRIFLURIDINE with TIPIRACIL available at https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2018-07/Trifluridine-psd-july-2018

TRIFLURIDINE with TIPIRACIL was also listed for Metastatic (Stage IV) adenocarcinoma of the stomach or gastro-oesophageal junction in June 2020 (Table 2). This listing is not part of this analysis.

Table 2: PBS listings of TRIFLURIDINE with TIPIRACIL not included in analysis.

Item code	Name, form & strength, pack size	Date of listing	Schedule	Authority required?
12056M	TRIFLURIDINE with TIPIRACIL Tablet, 15mg trifluridine with 6.14mg tipiracil, 20	1 June 2020	General	Streamlined
12033H	TRIFLURIDINE with TIPIRACIL, Tablet, 20mg, trifluridine with 8.19mg tipiracil, 20	1 June 2020	General	Streamlined

Source: Australian Government Department of Health, The Pharmaceutical Benefits Scheme (PBS) online, available at www.pbs.gov.au/pbs/home (accessed 20 January 2022).

PBAC Public Summary Document – November 2019 PBAC Meeting – 6.08 TRIFLURIDINE with TIPIRACIL available at https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2019-11/trifluridine-with-tipiracil-tablet-containing-15-mg-trifluridine

Data Source/methodology

Dispensing data were extracted from the PBS claims database by the Department of Health for all PBS and RPBS items for TRIFLURIDINE with TIPIRACIL (item codes 11507P, 11524M) for the period 1 December 2018 to 31 December 2021 (based on date of supply). Patient sex, date of birth, date of death and postcode of residence at time of dispensing were merged with dispensing data by the Department of Health. For this cohort, all antineoplastic medicine dispensings (medicines whose ATC codes begin with 'L01') were also extracted for the time period 1 June 2018 to 31 December 2021.

Initiating patients were identified from their first dispensing of TRIFLURIDINE with TIPIRACIL in the PBS data. Prevalent patients were those who had at least one dispensing of TRIFLURIDINE with TIPIRACIL during the calendar year.

Demographic characteristics of initiating patients were measured at the date of first PBS dispensing of TRIFLURIDINE with TIPIRACIL. Patients were considered to have had prior use of antineoplastic medicines (L01) if those medicines were dispensed in the 6 months prior to TRIFLURIDINE with TIPIRACIL initiation. Antineoplastic medicines dispensed in the 3 months after the first TRIFLURIDINE with TIPIRACIL dispensing were also summarised.

Overall survival was estimated from the date of first TRIFLURIDINE with TIPIRACIL dispensing to the date of death or censoring (censor date: 31 December 2021) using Kaplan-Meier methods.

Results

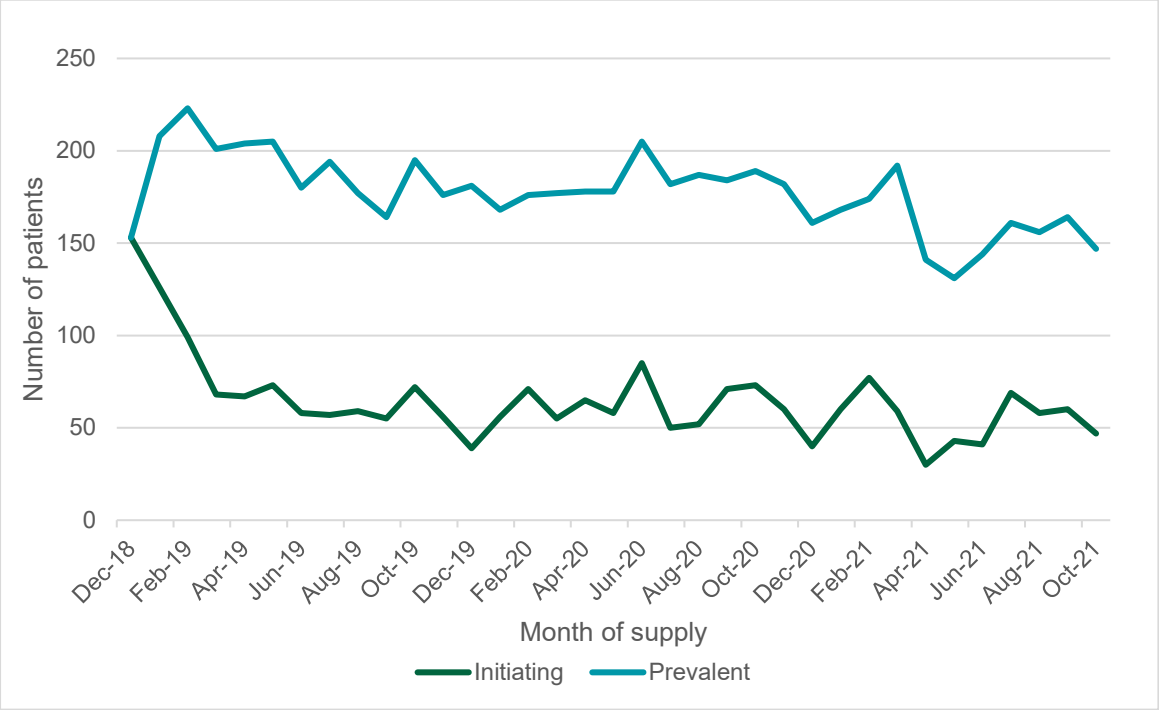


Figure 1: Initiating and prevalent patients for PBS medicine use, by month of supply

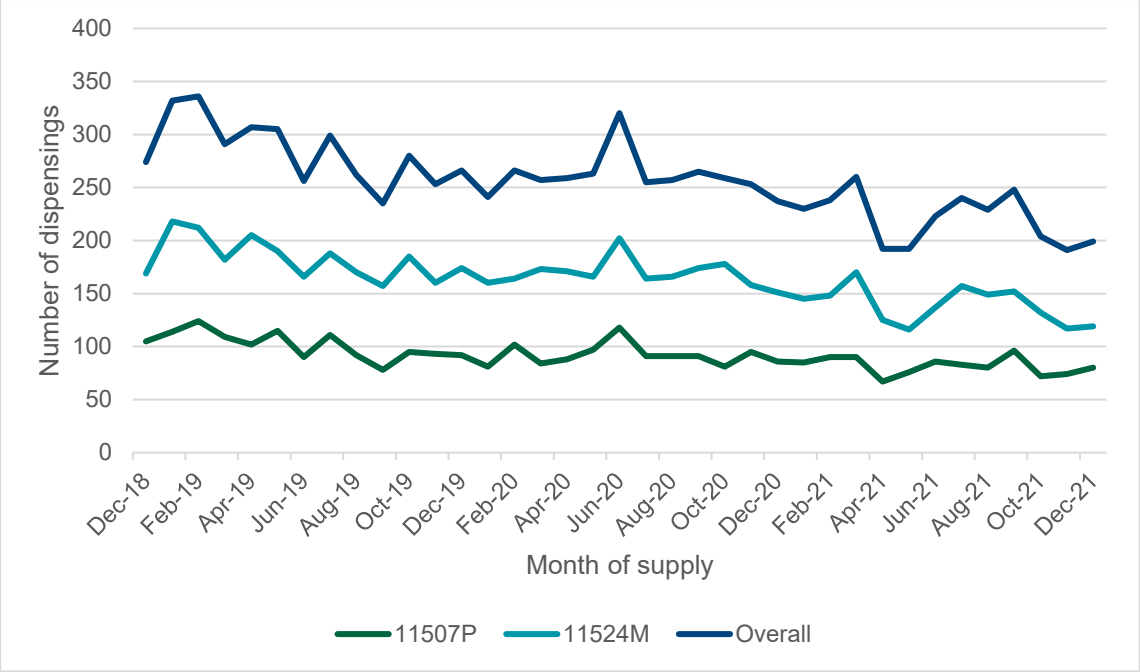


Figure 2: PBS dispensings for TRIFLURIDINE with TIPIRACIL by item code and overall

Table 3: Patient characteristics at the time of first PBS dispensing of TRIFLURIDINE with TIPIRACIL (1 December 2018 to 31 December 2021)

	n (%)
Patients	2356
Sex	
Female	965 (41.0)
Male	1390 (59.0)
Missing	1 (0.0)
Age at first PBS dispensing	
Median (IQR)	65 (56-73)
State of residence at first PBS dispensing	
ACT	38 (1.6)
NSW	670 (28.4)
NT	12 (0.5)
QLD	445 (18.9)
SA	200 (8.5)
TAS	85 (3.6)
VIC	653 (27.7)
WA	252 (10.7)
Missing	1 (0.0)
Antineoplastic (L01) medicines dispensed in 6 months prior to first PBS dispensing	
Overall (excluding medicine of interest)	2173 (92.2)
Chemotherapy (excluding medicine of interest)	2118 (89.9)
Immunotherapy	1 (0.0)
Targeted therapy	1371 (58.2)
Antineoplastic (L01) medicines dispensed within 3 months after first PBS dispensing	
Overall (excluding medicine of interest)	418 (17.7)
Chemotherapy (excluding medicine of interest)	333 (14.1)
Immunotherapy	1 (0.0)
Targeted therapy	181 (7.7)

Table 4: Initiating and prevalent patients by year of PBS dispensing

Year	Initiating patients	Prevalent patients
2018 (Dec)	153	153
2019	829	931
2020	736	899
2021	638	780

Of the 2356 patients initiating TRIFLURIDINE with TIPIRACIL, 1246 (53%) died prior to the end of follow-up. Median overall survival was estimated as 303 days (95% CI 278-331). Median number of dispensings per person was 3 (IQR 2-5).

Table 5: Median survival in days (months) since first PBS dispensing of medicine

	Median survival Days (months)	95% confidence interval
Survival estimates	303 (10.1)	278 – 331 (9.3-11.0)

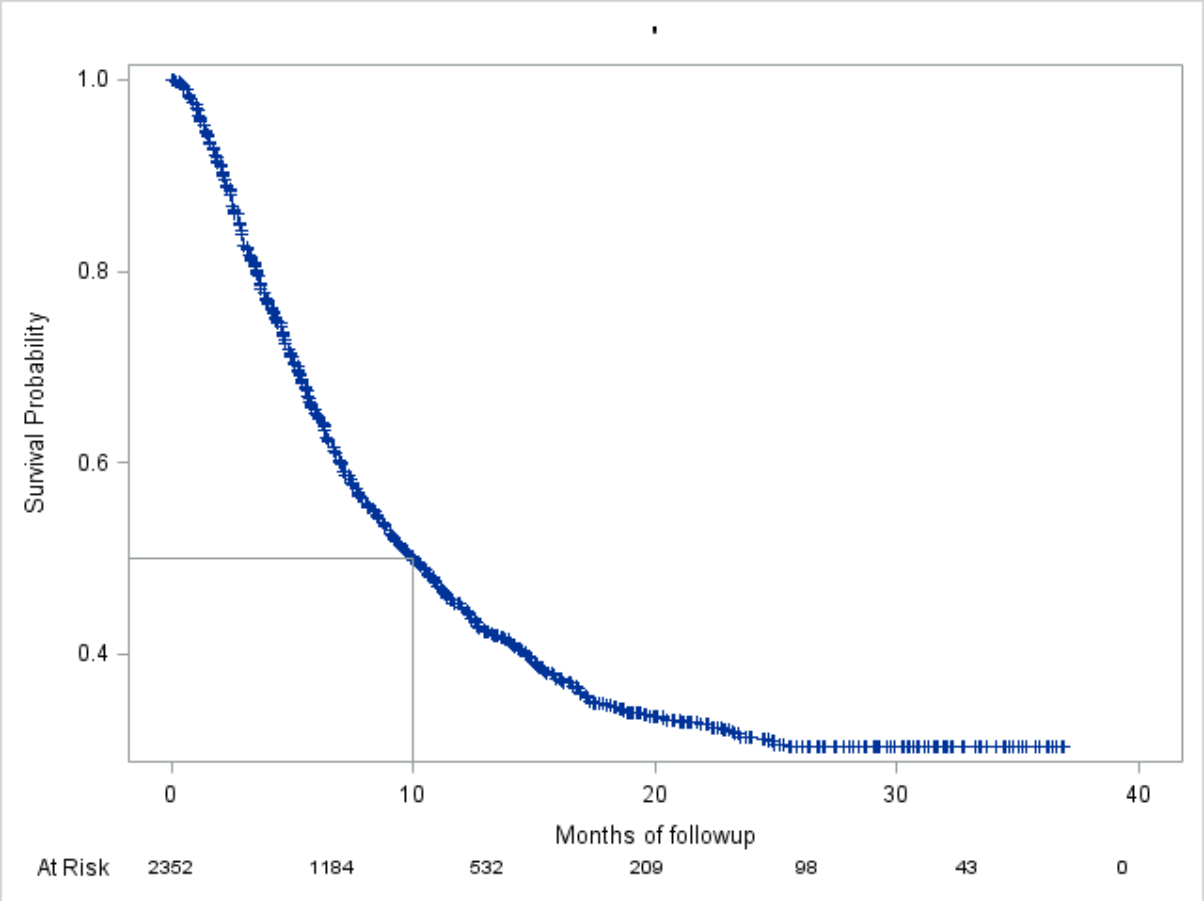


Figure 3: Kaplan Meier survival curve of people initiating PBS treatment from 1 December 2018 to 31 December 2021

Feasibility outcome

TRIFLURIDINE with TIPIRACIL has sufficiently long follow-up and number of deaths to produce robust and meaningful median survival estimates. There were no discernible external factors that would indicate concerns over data quality and interpretability of the survival results. TRIFLURIDINE with TIPIRACIL is a feasible candidate for the full analysis.

F Attachment: Summary of Literature Review

Summary of articles with general comparisons of real-world evidence (RWE) and randomised controlled trials (RCT); opinions or commentaries

Study	RW Data source	Summary	Outcome measure	Relevant to Part 3
General comparisons of RWE and RCT				
Green (2021)	Surveillance, Epidemiology and End Results - Medicare linked data (SEER) Locally advanced or metastatic solid cancers	Food and Drug Administration (FDA)-approved cancer drugs only Median OS: real world (RW) < RCT OS for 28/29 indications (median difference, −6.3 months; range, −28.7 to 2.7months) Median duration: RW < RCT for 23/29 indications (median difference, −1.9 months; range, −12.4 to 1.4 months)	Median overall survival (OS) Duration of treatment Dose reduction	Yes
Kim (2015)	FDA approvals Published studies	Literature review/Assessment of cancer drugs approved using surrogate endpoints (PFS or rate of response). FDA approvals compared to subsequent studies measuring OS	OS	No
Yu (2021)	Melanoma patients from QLD oncology electronic health records (EHR)	3 classes of drugs Median OS from Kaplan – Meier (K-M).	OS	Yes

		RW median OS ~ RCT median OS for two trials		
Stewart (2019)	6 United States (US) administrative claims and EHR databases Patients with advanced non–small-cell lung cancer treat with PD-(L)1 inhibitors	RW OS fell within the range of RCT median OS Moderate correlation between progression-free survival (PFS; treatment discontinuation) and RW OS	Time to treatment discontinuation Time to next treatment Median OS (K-M)	Yes

Summary of articles of medicine specific comparisons of RWE and RCTs

Medicine specific studies				
Study	**RWD source**	**Medicine/Summary**	**Outcome measure**	**Agreement?**
Petito (2020)	SEER-Medicare linked data Emulated target trial for advanced pancreatic adenocarcinoma	erlotinib added to gemcitabine (another emulated RCT surgery + adjuvant fluorouracil) RW patients older and more males, less prior chemo. Inverse probability of censoring weights (IPCW) used in target trial. Weighted pooled logistic regression used for hazard ratios (HR).	HR	Unadjusted RW HR < RCT HR, adjusted HRs in agreement
Davies (2018)	Patient data from clinical trial US Flatiron Health electronic health record non-small-cell lung cancer	Alectinib (pooled 2 single arm trials) vs ceritinib (external RW control arm). K-M & multivariable Cox model. Propensity scores used to balance baseline covariates.	Median OS (compared with log-rank test) HR	Consistent RW and RCT OS estimates for ceritinib after modelling

Kazmi (2020)	Cancer Treatment Centers of America Patients with metastatic breast cancer and visceral metastases (liver or lung)	Treated in the third-line setting with eribulin, gemcitabine or capecitabine Eribulin had a numerically higher median overall survival than other drugs, consistent with RCT results	Median OS (Kaplan-Meier) OS at landmark survival times	eribulin RW median OS < RCT median OS
Svensson (2016)	Retrospective data from 3 Swedish hospitals Patients with prostate cancer	abiraterone acetate	Median OS (Kaplan-Meier) Treatment duration	RW median OS similar to RCT OS
Liposits (2020)	Retrospective data from 2 Danish departments of oncology (20 patients)	Olaparib PFS only, 15 month follow-up not long enough to measure median OS (35 months for Olaparib) Large number of toxicities reported	Median PFS	RW PFS < RCT PFS
Borrelli (2020)	Systematic review of RWE for Olaparib (5 studies)	Olaparib	Median OS Median PFS	RW OS approx. equal to RCT OS
Daniels (2021)	Australian PBS Patients with metastatic breast cancer	Trastuzumab emtansine initiators First and second line therapy Patients older, more prior pertuzumab	Median OS Median duration of treatment (Kaplan-Meier)	RW median OS < RCT median OS
Nakayama (2021)	EHRs from 5 sites in Japan	Trastuzumab emtansine	PFS OS	RW Median OS <= RCT

	128 patients with metastatic breast cancer	Median OS 22.8 months (18.2-32.4) Median OS 30.4 months reported in PBAC public summary document	Time to treatment failure Objective response rate Clinical benefit rate	
Hardy-Werbin (2019)	Single Spanish hospital records (15 patients only)	Trastuzumab emtansine	Median PFS Median OS (Kaplan-Meier)	RW median OS >= RCT OS
Kim (2018)	Patients in Australian PBS with unresectable stage IIIc / IV metastatic melanoma treated with at least 1 dose of ipilimumab were invited to participate (prospective study)	Ipilimumab 751 patients with outcomes collected via oncologist after 2 years Median OS from K-M plus subgroup analyses by ECOG status, cancer stage etc…	2-year survival rate	RW OS similar to pivotal trial - lower before 1 year, higher after
Cramer-van der Welle (2021)	Patients with non-small-cell lung cancer in 6 large Dutch teaching hospitals	1st line pembrolizumab or 2nd line nivolumab Digitized survival curves from RCTs to compare survival Similar PFS	Median PFS/OS from unadjusted K-M HR	Pembrolizumab RW median OS < RCT median OS
Andersen (2019)	Systematic review 9 observational studies compared with 3 trials	trifluridine/tipiracil for metastatic colorectal cancer	Median PFS Median OS	RW median OS similar to RECOURSE trial but < Asian trials

Patt (2019)	US oncology records of patients with advanced melanoma	Ipilimumab Sponsored by Bristol-Myers Squibb	Median OS 1 year OS	Results consistent with RCTs
Dalle (2021)	IMAGE multinational prospective observational study (phase IV) of patients with advanced melanoma	Ipilimumab Sponsored by Bristol-Myers Squibb	Adjusted OS curves based on multivariate Cox models HR	Results consistent with RCTs
Yamazaki (2020)	Japanese patients with advanced melanoma in prospective multinational observational study	Ipilimumab Sponsored by Bristol-Myers Squibb	Median OS (Kaplan-Meier)	RW median OS <= RCT OS (depending on trial)
Hebart (2019)	Pooled data from 2 observational studies in Europe Patients with wild-type KRAS for metastatic colorectal cancer	Panitumumab + chemo Funded by Amgen	Duration of treatment Response rate	Results consistent with RCTs

Summary of articles describing statistical methods for survival estimates

Methods				
Study	**RW Data source**	**Summary**	**Outcome measure**	**Relevant**
Gebski (2018)	Numerous studies	Methods to determine minimum number of subjects at risk after which K-M plots should be curtailed	Survival estimates	Yes
Therneau (2015)	Adjusted survival curves	Methods for producing adjusting survival curves for a reference population	Survival estimates	Yes
Willems	Inverse probability of censoring weights	Method and code for inverse probability of censoring weighting of Kaplan-Meier curves	Survival estimates	Yes

G Attachment: START-RWE documents

Structured Template and Reporting Tool for Real World Evidence (START-RWE)

Contents

Table G1. Administrative Information

Title:			
	Comparing overall survival for patients accessing cancer medicines through the Pharmaceutical Benefits Scheme with overall survival reported in pivotal randomised controlled trials		
Objective: *Include PICOTS (Patient, Intervention, Comparator, Outcome, Time-Horizon, Setting)*			
	Primary:		
	To evaluate median overall survival in patients initiating cancer medicines identified in Part 1 under the Pharmaceutical Benefits Scheme, where overall survival is defined as the time from initiation to death from any cause and compare it to median overall survival in the pivotal trial(s). The study period is from the first date of listing until most recent date in available data (31 December 2021 is used in this analytical template).		
	Secondary:		
	To identify patient characteristics associated with overall survival.		
Registration:	**Registration identifier**	**Registration date**	**Registration site**
	n/a		
Version:	**Version number**	**Version date**	
	V1	21 March 2022	
Contributors:	**Name**	**Role**	**Affiliation**
	Prof Sallie Pearson	Project Lead	University of New South Wales
	Prof Nicole Pratt	Project Lead	University of SA
	Dr Benjamin Daniels	Co-investigator	University of NSW
	Ms Melisa Litchfield	Data Manager	University of NSW
	Dr Monica Tang	Medical Oncologist	University of NSW
	Dr Malcolm Gillies	Co-investigator	University of NSW
	Dr Lan Kelly	Co-investigator	University of SA

Funding:	Grant identifier	Source	
	RG213559	Australian Commonwealth Dept of Health	
Data Use Agreement (DUA)	**DUA identifier**	**Data provider**	**Data provider contact for data use agreements**
	Not applicable	Protected Pharmaceutical Benefits Scheme	michael.burtt@health.gov.au
Human Subjects/Ethics Approval	**Submission identifier**	**Date of approval**	**Name of human subjects/ethics approval committee**

Conflict of Interest Disclosures

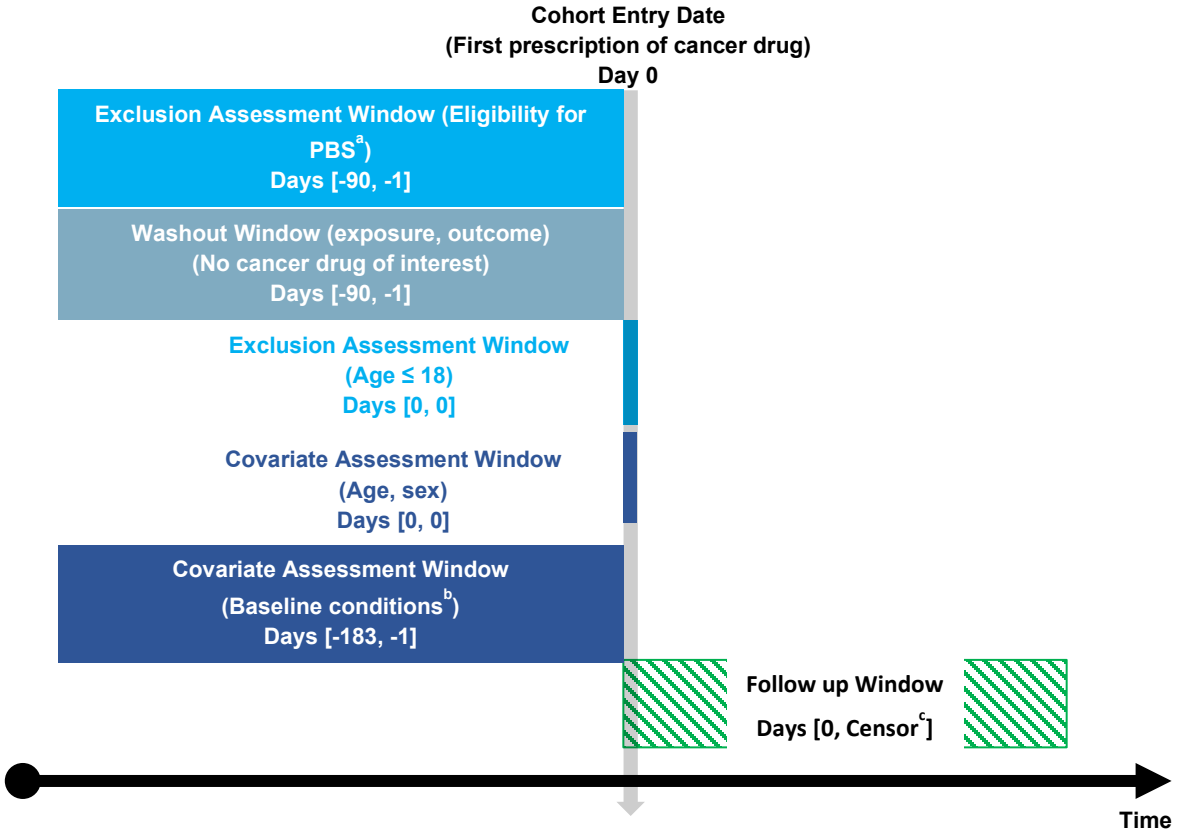
There are no conflicts of interest to disclose.

Table G2. Version History

Version date	Version number	Change log	Rationale for change
05/07/2022	1.0		Creation of START-RWE analytical template

Figure G1. Design Diagram

Exposure-based cohort entry where the cohort entry date is selected prior to application of exclusion criteria



a. Patient must have been eligible for the PBS during this window
b. Baseline conditions included: prior treatment with cancer medicines, number of co-morbidities (Rx-Risk)
c. Earliest of: death or end of the study period. Censor at switching or discontinuation of study medicines for sensitivity

Table G3. Summary of Study Population Parameters

A. Meta-data about data source and software

	Data Source 1 (basic)	Data Source 2 (enhanced)
Data Source(s):	Pharmaceutical Benefits Scheme	Pharmaceutical Benefits Scheme
Study Period:	January 1, 2013 – December 31, 2021	January 1, 2013 – December 31, 2021
Eligible Cohort Entry Period:	January 1, 2013 - September 30, 2020	January 1, 2013 - September 30, 2020
Data Extraction Date/Version:	TBD	TBD
Data sampling/extraction criteria:	All patients in data source between January 1, 2013 - December 31, 2021	All patients in data source between January 1, 2013 -December 31, 2021
Type(s) of data:	Government claims	Government claims
Data linkage:	Medicare consumer directory (fact of death)	Death registry data, cancer registry, hospitalisations, EHRs, etc…
Data conversion:	None	
Software to create study population:	SAS Statistical software version 9.4	

B. Index Date (day 0) defining criterion

The criteria that define the date of entry to the cohort(s) is specified in this section. There should be one row for each unique definition of study population entry. If the study is descriptive, there may only be one row filled out. An active comparator study may have 2 rows, one for the exposure of interest and one for the comparator.

Check the pre-specified box if the exclusion criterion was specified before beginning data analyses, check the varied for sensitivity box if it was modified as part of sensitivity analyses. Specify the source of algorithms to define study entry criteria.

Study population name(s)	Day 0 Description	Number of entries	Type of entry	Washout window	Care Setting	Code Type	Diagnosis position[2]	Incident with respect to…	Pre-specified	Varied for sensitivity	Source of algorithm
Exposure	Date of incident dispensing for Part 1 candidate medicines	Single	Incident	[-90, 0]	n/a	PBS item code	n/a	Part 1 candidate medicines (as specified by item codes)	Yes	No	
Comparator	Date of randomisation (pivotal trial)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	

C. Inclusion Criteria

Describe what the criterion is conceptually. Specify the order of application of the inclusion criteria is relative to selection of the index date (day 0) for study entry. For example, specify “after selection of index date” if you plan to 1) select the index date based on first time the study entry defining criterion is met in the study period, 2) then apply inclusion-exclusion criteria, 3) keep the selected index date for study entry if all inclusion-exclusion criteria are met. Alternatively, you can specify “before selection of index date” if you plan to 1) identify all potential index dates meeting the study entry criterion, 2) apply inclusion-exclusion criteria, 3) select one or more of the study entry dates that meet all inclusion-exclusion criteria. Define the assessment window relative to the index date, whether there are restrictions on care setting or diagnosis position in the algorithm to define each inclusion criterion and specify which study populations (defined in Table 3B) the criterion is applied to.

Defining “observable” patient time in the healthcare data source is almost always required as an inclusion criterion. When using administrative claims data, this can be measured with dates of enrolment in insurance coverage, with or without bridging of short gaps in enrolment. When using electronic health record data, defining observable patient time may require making some strong assumptions. For example, assuming that patient encounters are always observable, that patients are observable between the first and last recorded encounter in the record, that patients are observable for X days before and after any recorded encounter, etc. Alternatively, one could specify inclusion based on algorithms to measure “loyalty” to a healthcare provider or EHR system.

Check the pre-specified box if the exclusion criterion was specified before beginning data analyses, check the varied for sensitivity box if it was modified as part of sensitivity analyses. Specify the source of algorithms to define inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Pre-specified	Varied for sensitivity	Source for algorithm
Observable time	Eligibility for PBS	After selection of time zero	[-90, 0]	n/a	n/a	n/a	Exposure	Yes	Yes	n/a
Age 18+ yrs	(Cohort entry date-date of birth)/365	After selection of time zero	[0, 0]	n/a	n/a	n/a	Exposure	Yes	No	n/a
Initiation of medicine	Medicine initiation	After selection of time zero	[0-90]	n/a	n/a	n/a	Exposure	Yes	Yes (Sensitivity 1)	n/a

D. Exclusion Criteria

Describe what the criterion is conceptually. Specify the order of application of the exclusion criteria is relative to selection of the index date (day 0) for study entry. Define the assessment window relative to the index date, whether there are restrictions on care setting or diagnosis position in the algorithm to define each exclusion criterion and specify which study populations (defined in Table 3B) the criterion is applied to.

Check the pre-specified box if the exclusion criterion was specified before beginning data analyses, check the varied for sensitivity box if it was modified as part of sensitivity analyses. Specify the source of algorithms to define exclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Pre-specified	Varied for sensitivity	Source for algorithm
Days supply < 0		Before selection of time zero	[0, 0]	n/a	n/a	n/a	Exposure	Yes	No	n/a
Gender (unknown)		Before selection of time zero	[0, 0]	n/a	n/a	n/a	Exposure	Yes	No	n/a
Indications not part of original PBS listing		After selection of time zero	[0, 0]	n/a	PBS item codes	n/a	Exposure	Yes	No	n/a
Indications not part of original PBS listing + cancer diagnosis[1]		After selection of time zero	[0, 0]	n/a	PBS item codes + topography codes	Any	Exposure	Yes	No	n/a

[1] When multiple indications are PBS-listed, utilise cancer diagnosis data to reduce errors in item codes.

E. Predefined Covariates

Define the covariate conceptually, with accompanying details as necessary. Specify which planned analyses adjust for the covariate, and how it is specified in the analysis (e.g., continuous, categorical, binary). Define the assessment window relative to the index date (day 0), whether there are restrictions on care setting or diagnosis position in the algorithm, and which study populations defined in Table 3B the covariate is measured for. Specify the source of algorithms to define covariates.

Check the pre-specified box if the covariate was specified before beginning data analyses, check the varied for sensitivity box if it was modified as part of sensitivity analyses. Specify the source of algorithms to define covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Pre-specified	Varied for sensitivity	Source for algorithm
Age	(Time zero - Date of birth) OR included in dataset	Continuous	[0, 0]	n/a	n/a	n/a	Exposure	Yes	No	n/a
Sex	Male, Female	Categorical	[0, 0]	n/a	n/a	n/a	Exposure	Yes	No	n/a
Type of prior treatment	Chemotherapy, immunotherapy, targeted therapy or multiple	Categorical	[-183, 0]	any	PBS item or ATC codes	n/a	Exposure	Yes	No	n/a
Length of prior treatment	Number of months of prior treatment, any type	Continuous	[-183, 0]	n/a	PBS item or ATC codes	n/a	Exposure	Yes	No	n/a
Additional patient and disease risk factors	Data from cancer registry, MBS, hospitalisations, etc…	Various	Various	Any	Various	Any	Exposure	Yes; different for every medicine	Potentially	n/a

F. Empirically Defined Covariates

Empirical identification of covariates to use in confounding control may not be relevant to all study populations or analyses, however if such methods are used, this section includes fields to describe what the algorithm for covariate identification is, as well as specification of the settings or parameters used to empirically identify covariates. In this section, specify the assessment window relative to the index date (day 0), which analyses adjust for empirically identified covariates, how the covariates are specified in a model, whether there are restrictions on care setting or diagnosis position, and which study populations (defined in section 3B) to measure the empirical covariates.

Check the pre-specified box if the empirical covariate selection parameters were specified before beginning data analyses, check the varied for sensitivity box if the parameters were modified as part of sensitivity analyses. Specify the source for the method and/or software used for empirically defined covariates.

Algorithm	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Pre-specified	Varied for sensitivity	Source/code for algorithm
Number of co-morbidities	Continuous	[-183, -1]	n/a	ATC code	n/a	Exposure	Yes	No	Rx-Risk
Number of co-morbidities	Continuous	[-183, -1]	n/a	ICD10	n/a	Exposure	Yes	No	Charlson

G. Outcome

Define the outcome conceptually and whether it is the primary outcome of interest. Specify whether the type of outcome is incident (if so, there is a field to specify the washout window to define "incident" occurrences), prevalent or other. Specify whether there are restrictions on care setting or diagnosis position, and which groups or analyses the outcome is measured for. If there are measurement characteristics for the outcome algorithm (e.g., PPV, sensitivity, specificity) from publications, or from outcome validation within the study population (e.g., medical record review), provide this information.

Check the pre-specified box if the outcome parameters were specified before beginning data analyses, check the varied for sensitivity box if the parameters were modified as part of sensitivity analyses. Specify the source of algorithms to define outcomes.

Outcome name	Outcome measurement characteristics	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Category	Diagnosis Position[2]	Applied to study populations:	Pre-specified	Varied for sensitivity	Source of algorithm
All-cause mortality (Australian Population)	Data linkage to death registries, month and year	Yes	Time-to-event	[0, 0]	any	n/a	n/a	Exposure	Yes	Yes (sensitivity analysis 2)	n/a
End of treatment (secondary outcome)	3 months with no dispensings	Yes	Time-to-event	[0, 90]	any	n/a	n/a	Exposure	Yes	No	n/a
Cause-specific mortality	Data linkage to death registries, month and year	Yes	Time-to-event	[0, 0]	any	n/a	n/a	Exposure	Yes	Yes (sensitivity analysis 2)	n/a

H. Follow up

Specify when follow up begins relative to time zero (day 0) and select each criterion that ends follow up.

Check the pre-specified box if the outcome parameters were specified before beginning data analyses, check the varied for sensitivity box if the parameters were modified as part of sensitivity analyses.

				Pre-specified	**Varied for sensitivity**
Begins	Day 0			Yes	No
Ends	**Select all that apply**	**Specify**			
Date of Outcome	Yes	Death		Yes	Yes
Date of Death	Yes	Death		Yes	No
Day X following index date *(specify day)*	No			Yes	No
End of study period (specify date)	Yes	31-Dec-2021		Yes	No
End of exposure *(specify operational details,* *e.g., stockpiling algorithm,* *grace period)*	Yes	**Stockpiling algorithm:** For oral medicines, if refill occurs before end of days supply, count overlapping days at the end of the subsequent dispensing's day supply For intravenous (IV) medicines, if a new dispensing is received within 30 days of the previous dispensing, exposure will be held at 30 days from the last	**Grace period:** Bridge gaps of ≤30 days between dispensation + days supply and refill. Add 30 days to last dispensation + days supply in a treatment episode.	Yes	No

		dispensing (i.e., no exposure is carried over from the previous IV dispensing and added to the current dispensing)			
Date of Add to/switch from exposure *(specify algorithm)*	Yes	Censor at time of switching in a sensitivity analysis	Weight by inverse probability of censoring weights	Yes	Yes
Other date *(specify)*	No			Yes	No

Code algorithms for cohort entry date are provided in Appendix A, study entry criteria in Appendix B, covariates in Appendix C and D, outcomes in Appendix E (a * in code algorithm indicates use of a wildcard)

All temporal windows anchored on study population entry date (Day 0) unless otherwise specified.

( ) represent open intervals that do not include the end points

[ ] represent closed intervals that do include the end points

[1] Please enter all that apply. Valid entries: IP = inpatient, OP = outpatient, ED = emergency department, any, other, n/a = not applicable. See Appendix E for details on how care setting is defined

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Table G4. Primary, Secondary and Subgroup Analysis Specification

A. Primary Analysis Specify the study populations (defined in 3B) included in the analysis, the outcome being evaluated, the software that is used, the type of confounding adjustment, missing data methods and subgroup analyses.	
Hypothesis:	The median overall survival in the Australian population is shorter than the median OS in the pivotal RCT population
Study population(s):	All Australian PBS eligible population, dispensed at least one cancer medicine of interest through the PBS
Outcome:	All-cause mortality
Software:	R 'survival' package: survfit SAS: PROC LIFETEST
Model(s):	*Outcome model:* Kaplan-Meier 95% CI for median overall survival in PBS data will be compared to the point estimate for median OS in the trial(s). Unweighted, intention-to-treat analyses surv <- survfit(Surv(Tstart, Tstop, death) ~ 1, data=PBS.long)

A. Primary Analysis

Specify the study populations (defined in 3B) included in the analysis, the outcome being evaluated, the software that is used, the type of confounding adjustment, missing data methods and subgroup analyses.

	Sensitivity: see Table 5, Sensitivity Analyses 1, 2 & 3
Confounding adjustment method ***(check all that apply and provide details where requested)***	None
Bivariate	☐
Multivariable	☐
Propensity score matching ***(specify matching algorithm, ratio and calliper)***	☐
Propensity score weighting ***(specify weight formula, trimming, truncation decisions)***	☐
Propensity score stratification ***(specify strata definition)***	☐
Other ***(specify details)***	☐

A. Primary Analysis Specify the study populations (defined in 3B) included in the analysis, the outcome being evaluated, the software that is used, the type of confounding adjustment, missing data methods and subgroup analyses.	
Missing data methods *(check all that apply, provide relevant details)*	
Missing indicators	☐
Complete case	☒ Patients with missing or unknown gender are excluded
Last value carried forward	☐
Multiple imputation	☐
(specify variables)	
Other (please specify)…	☒ Assumption that if no relevant claims diagnoses/procedures are present, the condition is not present It is possible to stratify analyses by patient factors typically included in (e.g., patient sex and year of birth) or derived from (e.g., Rx-Risk comorbidities) minimum data collections such as PBS data.
Subgroup Analysis	More robust stratification by relevant demographic and clinical factors is best undertaken in enhanced data collections.

B.1 Secondary Analysis 1	
Hypothesis:	Treatment switching shortens median OS
Study population(s):	Australian PBS
Outcome:	All-cause mortality
Software:	SAS 9.4: LIFETEST, PHREG R survival package: survfit, coxph
Model(s):	*Outcome model:* - Intention-to-treat analysis - Kaplan-Meier weighted by inverse probability of censoring weights (IPCW)
Confounding adjustment method *(check all that apply and provide details where requested)*	
Bivariate	☐
Multivariable	☐
Propensity score matching	☐

(specify matching algorithm, ratio and calliper)	
Propensity score weighting	☒
(specify weight formula, trimming, truncation decisions)	IPCW using Willems (2018) Uses Cox proportional hazards model to create the weights using censoring from switching as the event. Covariates include age, gender, type and length of prior treatment, Rx-Risk co-morbidities. See R code from https://doi.org/10.1177/0962280216628900
Propensity score stratification	☐
(specify strata definition)	
Other	☐
(specify details)	

Missing data methods

(check all that apply, provide relevant details)

Missing indicators	☐
Complete case	☒ Patients with missing or unknown gender are excluded
Last value carried forward	☐
Multiple imputation	☐
(specify variables)	
Other (please specify)…	☒ Assumption that if no relevant claims diagnoses/procedures are present, the condition is not present

Subgroup Analysis

B.2 Secondary Analysis 2	
Hypothesis:	Real-world patients more closely resembling those enrolled in clinical trials will have survival outcomes more similar to those reported in clinical trials
Study population(s):	Australian PBS-eligible population; where data allow, stratified by patients who do and do not meet trial eligibility criteria
Outcome:	All-cause mortality
Software:	SAS 9.4: LIFETEST, PHREG R survival package, survfit
Model(s):	*Outcome model:* - Intention-to-treat analysis - Kaplan-Meier weighted with IPCW - Stratified by whether patients met trial eligibility criteria (yes/no), depending on data availability

Confounding adjustment method *(check all that apply and provide details where requested)*	
Bivariate	☐
Multivariable	☐
Propensity score matching	☐
(specify matching algorithm, ratio and calliper)	
Propensity score weighting	☒
(specify weight formula, trimming, truncation decisions)	IPCW using Willems (2018) Same model as secondary analysis 1 https://doi.org/10.1177/0962280216628900
Propensity score stratification	☐
(specify strata definition)	
Other	☐
(specify details)	
Missing data methods	
(check all that apply, provide relevant details)	
Missing indicators	☐
Complete case	☒ Patients with missing or unknown gender are excluded
Last value carried forward	☐
Multiple imputation	☐

(specify variables)	
Other (please specify)…	☒ Assumption that if no relevant claims diagnoses/procedures are present, the condition is not present
Subgroup Analysis	

B.3 Secondary Analysis 3	
Hypothesis:	Some patient characteristics are associated with increased risk of mortality
Study population(s):	Australian PBS
Outcome:	All-cause mortality
Software:	SAS 9.4: PHREG R survival package, coxph
Model(s):	*Outcome model:* - as-treated analysis - Cox proportional hazards regression

	- adjustment for length of treatment / on-treatment (yes/no), age, gender, Rx-Risk co-morbidities, length and type of prior treatment Sensitivity: Re-run analyses, censoring at treatment switching (Sensitivity Analysis 3)
Confounding adjustment method *(check all that apply and provide details where requested)*	
Bivariate	☐
Multivariable	☒
Propensity score matching	☐
(specify matching algorithm, ratio and calliper)	
Propensity score weighting	☐
(specify weight formula, trimming, truncation decisions)	
Propensity score stratification	☐
(specify strata definition)	
Other	☐
(specify details)	

Missing data methods	
(check all that apply, provide relevant details)	
Missing indicators	☐
Complete case	☒ Patients with missing or unknown gender are excluded
Last value carried forward	☐
Multiple imputation	☐
(specify variables)	
Other (please specify)…	☒ Assumption that if no relevant claims diagnoses/procedures are present, the condition is not present

B.4 Secondary Analysis 4	
Hypothesis:	The median overall survival in the Australian population is shorter than the median OS in the pivotal RCT population
Study population(s):	All Australian PBS eligible population, dispensed at least one cancer medicine of interest through the PBS
Outcome:	Cause-specific mortality
Software:	R cumulative incidence package

B.4 Secondary Analysis 4	
Model(s):	*Outcome model:* Cumulative incidence Unweighted, intention-to-treat analyses Sensitivity: See Table 5 below
Confounding adjustment method *(check all that apply and provide details where requested)*	None
Bivariate	☐
Multivariable	☐
Propensity score matching	☐
(specify matching algorithm, ratio and calliper)	
Propensity score weighting	☐
(specify weight formula, trimming,	

B.4 Secondary Analysis 4

truncation decisions)

Propensity score stratification	☐
(specify strata definition)	
Other	☐
(specify details)	

Missing data methods

(check all that apply, provide relevant details)

Missing indicators	☐
Complete case	☒ Patients with missing or unknown gender are excluded
Last value carried forward	☐
Multiple imputation	☐
(specify variables)	
Other (please specify)…	☒ Assumption that if no relevant claims diagnoses/procedures are present, the condition is not present

Subgroup Analysis

Table G5. Sensitivity Analyses

	What is the parameter being varied? (be clear what it is changing from)	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary?	Weaknesses of the sensitivity analysis compared to the primary?
Sensitivity Analysis 1	Study start, exclude initiators in the first 3 months after PBS listing	Include/exclude grandfathered patients who may already be on treatment, and those who start early may be sicker	Effect of prevalent users on estimate of median OS, will reduce the impact of short survival in those initiating treatment who are unlikely to benefit (e.g., patients at the end of life attempting a new treatment) and those who may have been accessing the treatment prior to PBS listing (we cannot observe their true treatment start date)	May bias estimate and reduce sample size (precision)
Sensitivity analysis 2	End follow-up when a new medicine for the same indication is PBS-listed	To test whether there is data contamination by incorrect listings	To ensure patients who are analysed were treated for the correct indication	Smaller sample size, wider confidence intervals
Sensitivity analysis 3	Censoring at treatment switching	To test how sensitive the survival estimates are to treatment switching	RW effect of switching	Fewer events (deaths) and less power

Table G6. Attrition Table

This Table will show the number of patients remaining after applying each inclusion/exclusion criterion, sequentially.

	Cancer Drug	
	Excluded Patients	**Remaining Patients**
All patients		
Did not meet cohort entry criteria (dispensation of drug)		
Excluded due to insufficient PBS eligibility (<183 days)		
Excluded due to prior use of exposure		
Excluded because patient qualified in >1 exposure category		
Excluded based on Age <18		
Excluded based on Gender (unknown)		
Excluded based on Drug supply <=0 days		
Excluded based on Drug (additional formulations and combinations not included in exposure)		
Excluded if censored on day 1		
Final cohort		

Table G7. Power and Sample Size Calculation

No power/sample size calculations will be performed since all those treated will be analysed.

Table G8. Glossary of Terminology

Term	Definition
Confounder	Variable other than the exposure of interest or outcome under investigation that is 1) associated with exposure, 2) a risk factor for the outcome, and 3) not on the causal pathway between the exposure and the outcome. A confounder can artificially inflate or reduce the magnitude of association between an exposure and outcome.
Covariates	Variables that are neither exposure nor outcome of interest, but are measured to describe a population or because they may be a confounder to account for in analyses
Data Extraction Date	The date when the data were extracted from the dynamic healthcare database
Days Supplied	Number of days supplied for a dispensed prescription
Eligible cohort entry period	Calendar time frame during which cohort entry dates are identified
Empirically defined covariates	Covariates that are not prespecified by the investigator. The selection of these covariates is based on applying algorithms to the data. The algorithms for covariate selection may be tuned by investigator specified parameters.
Observable Time	For insurance claims data, this may refer to periods of enrolment in medical and/or drug plans. For electronic health record databases, this may refer to algorithms designed to identify patients whose healthcare contacts are likely to be covered within the healthcare system.
Observable Time Gap	Maximum number of days allowed between two consecutive observable time windows to still be considered “continuously observable”.
Follow up window	The interval during which occurrence of the outcome of interest in the study population will be included in the analysis.
Grace Window	Number of days added to days supply to allow for non-adherence or account for the hypothesized biologic exposure risk window. Operationally, this could be defined as the number of extra days added to the end of a days supply to extend time counted as "exposed". This grace may bridge the gap between dispensations where the days supply dispensed does not cover all days until the refill.
Index Date	The date when subjects enter the study population (cohort entry date, outcome event date). It is defined based on events in the patient's longitudinal timeline, other windows are defined relative to the index date.
Assessment Window	Interval during which a patient is required to have evidence of a pre-existing condition (diagnosis/procedure/drug dispensing). May be used for washout of exposure or outcome, exclusion assessment or covariate assessment.
Predefined Covariates	Covariates that are prespecified and defined by the investigator in the template.
Principal Diagnosis	Diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital.
Source Data Range	The calendar time range covered by a data source that is available

Stockpiling Algorithm	Algorithm defining how early refills are handled when determining length of exposure follow up
Study Period	Calendar time interval of data available for study, including pre-index date assessment windows and post-index follow up
Treatment Episode	Continuous period of exposure defined using by dispensation date + days supply and applying stockpiling algorithms and/or grace windows
Washout Window	Minimum number of days a patient is required to have no evidence of prior exposure and/or outcome
Wildcard	Symbol used to represent any single alphanumeric digit in code algorithms. For example, 410.*1, where * is the wildcard.

Table G9. Abbreviations

ATC = Anatomical Therapeutic Chemical

CI = Confidence Interval

ECOG = Eastern Cooperative Oncology Group (Performance Status Scale)

EHR = Electronic Health Record

FDA = Food and Drug Authority (United States of America)

PBAC = Pharmaceutical Benefits Advisory Committee

PBS = Pharmaceutical Benefits Scheme

PFS = Progression Free Survival

HR = Hazard Ratio

IPCW = Inverse Probability of Censoring Weights

ITT = Intention To Treat

K-M = Kaplan-Meier

OS = Overall Survival

RCT = Randomised Controlled Trial

RW = Real World

RWD = Real World Data

RWE = Real World Evidence

START-RWE = Structured Template And Reporting Tool for Real World Evidence

US = United States of America

n/a = not applicable

Appendices G

n/a