**9.01 Estimating overall survival in people receiving PBS-listed cancer medicines in Australian clinical practice**

1. Purpose of item

That the Pharmaceutical Benefits Advisory Committee (PBAC):

* 1. Consider the findings of the ‘Protocol: Estimating overall survival (OS) in people receiving Pharmaceutical Benefits Scheme (PBS)-listed cancer medicines in Australian clinical practice’ final report (herein referred to as ‘the Protocol’).
  2. Advise the Department if any further research should be undertaken on survival outcomes relating to PBS-listed cancer medicines or other medicines for non-cancer indications using the methods outlined in the Protocol.

1. Background
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   2. In September 2021, the Department of Health and Aged Care contracted the Medicines Intelligence Centre of Research Excellence (MI-CRE) to complete a two-stage research project to:

*‘Investigate how OS estimated in patients taking certain PBS-listed cancer medicines in Australia compares to the OS of patients taking the same medicines reported in the pivotal trials included in sponsor submissions to the PBAC.’*

* 1. The first stage of this project was to develop a comprehensive research protocol and methodology to conduct a similar study to Green et al. (2021)[[1]](#footnote-1) using PBS data initially, and ultimately linked health data available in Australia. The second stage of the project was to conduct the analysis in a pilot medicine and review the results for applicability and comparability with the pivotal trial results.
  2. The Department received the final report of the Protocol on 26 October 2022. The Protocol is summarised below and details the MI-CRE’s advice to the PBAC relating to the assessment of survival outcomes for PBS-listed cancer medicines using PBS data.
  3. Section 3 below is summarised from the report.

1. Protocol: Estimating overall survival in people receiving PBS-listed cancer medicines in Australian clinical practice
   1. The 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 were 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. The report is divided into three parts relating to distinct activities of the overall Protocol as follows:

* 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

* 1. 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 as follows:
* 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 at least 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.
  1. The 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’ of the Protocol was used to assist in extracting the relevant information from these sources.
  2. The Protocol details the evaluation of 12 PBS-listed medicines, of which six candidate medicines (ipilimumab, lanreotide, olaparib, panitumumab, trastuzumab emtansine [TDM-1] and trifluridine-tipiracil) were selected to undergo feasibility assessment in Part 2.

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

* 1. 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.
  2. 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.
  3. The 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. TDM-1 for treatment of metastatic breast cancer (one of the four suitable medicines) was selected to pilot the study methods for estimating OS.

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

* 1. Once relevant medicines have been selected (Part 1) and assessed as to the feasibility of generating OS estimates for the medicines in available data (Part 2), 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.
  1. Based on the literature review, the following analyses were 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) methods (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 (or other means) 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 Eastern Cooperative Oncology Group (ECOG) status.

### Trastuzumab emtansine (TDM-1) pilot study

* 1. The purpose of this pilot study was 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.
  2. TDM-1 for metastatic breast cancer was listed on the PBS on 1 July 2015. The median OS estimated from the pivotal trial (and included in the November 2014 PBAC submission) was 30.9 months (N = 991). In this pilot study, OS was estimated in a cohort of patients receiving TDM-1 for metastatic breast cancer using PBS dispensing data linked to FOD data.
  3. 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 TDM-1’s PBS-listing) to 31 March 2020. TDM-1 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.
  4. The summary of findings from this analysis are as follows:

1. 1,027 patients initiated TDM-1; median age 59 years (IQR: 50 – 68); 62% died during follow-up.
2. Median OS, primary analysis: 28.9 months (95%CI: 26.1 – 32.0).
3. Median OS, sensitivity analysis: 23.5 months (95%CI: 21.2 – 27.1).
   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 TDM-1 from this time under PBS item codes indicated for late-stage disease may have erroneously included those receiving treatment for early-stage disease who are likely to have longer expected survival times than late-stage/metastatic patients. Therefore, it is likely that OS estimates including early-stage patients are biased and the estimate from the sensitivity analysis more closely reflects the true OS for patients treated with TDM-1 for metastatic disease.
   2. The difference between the median OS estimate, derived from the sensitivity analysis and the clinical trial estimate cited in the PSD (30.9 months), 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 (not ‘emtansine’) for early-stage disease than had been previously treated in the trial (reported at 16% of trial participants). Further stratification to determine the reasons for the discrepancy would require linkage with enhanced datasets with more detailed clinical information.
   3. The findings from this study suggest the median OS estimate for Australian patients treated with TDM-1 is more than seven months shorter than the 30.9 months reported in the pivotal trial considered by the PBAC. This is consistent with previous research on real-world outcomes associated with trastuzumab (not ‘emtansine’) that have found similar discrepancies in survival outcomes.
4. Medical Officer review/input and MI-CRE advice
   1. The Protocol was provided to Departmental Medical Officers (MOs) for review/input in November 2022.
   2. The key feedback from the MO was that the metric of importance, when assessing clinical and cost-effectiveness, is the relative incremental difference in OS between the intervention and the comparator (as opposed to the absolute OS of the intervention). Therefore, it was suggested that the analysis conducted by the MI-CRE to estimate OS for TDM-1 be extended to estimate the OS of the comparator used in the November 2014 TDM-1 PBAC submission (i.e., lapatinib + capecitabine). This analysis would then allow a comparison of the incremental gain in OS for TDM-1 versus lapatinib + capecitabine based on the clinical trial data and real-world/PBS data.
   3. The MI-CRE reviewed the request and applied the assessment framework outlined above.
   4. The MI-CRE advised that they do not believe they can meaningfully estimate OS for lapatinib + capecitabine for the purposes of comparing the estimate to that from the pivotal trial used in the November 2014 TDM-1 PBAC submission for the following reasons:
5. Initially listed on the PBS in May 2008, lapatinib was not widely adopted in Australian clinical practice. Prescribing restrictions made to the initial listing between 2008 and 2010 appear to have minimised its use. Whilst there was a slight increase after the restrictions were relaxed in 2010, the number of dispensings and initiations for lapatinib from this time remained low. It appears that most Australian clinicians preferred to retain trastuzumab (not ‘emtansine’) and switch the concomitant cytotoxic agent for second- and later- line treatment. When T-DM1 was listed on the PBS in 2015 lapatinib dispensings fell to near zero and have remained there since.
6. As a flow-on effect from point number 1 above, the cohort of patients treated with lapatinib in Australia are materially different from those treated in the TDM-1 pivotal trial. The pivotal trial of TDM-1 evaluated second-line therapy, following treatment with trastuzumab (not ‘emtansine’) + chemotherapy. In Australia, lapatinib has been largely used as third- or later-line therapy, and often as a treatment of last resort. This means that, in general, only the sickest patients in Australia receive lapatinib.
   1. Because of the low use and the substantive differences between the Australian real‑world and trial patients, any OS estimates produced for lapatinib + capecitabine using PBS data would be far lower than that observed in the clinical trial and used for the November 2014 TDM-1 submission (25.1 months). The MI-CRE advised that based on previous research they have conducted, the median OS estimate would likely be less than 10 months. This in turn would have the effect of greatly inflating the incremental gain in OS for TDM-1 versus lapatinib + capecitabine from that accepted by the PBAC in November 2014.
7. PBAC Outcome
   1. The PBAC considered the Protocol detailing the MI-CRE’s advice to the committee relating to the assessment of survival outcomes for PBS-listed cancer medicines using PBS data, and noted the following key findings from the TDM-1 pilot study for metastatic breast cancer:
8. 1,027 patients initiated TDM-1; median age 59 years (IQR: 50 – 68); 62% died during follow-up.
9. Median OS, primary analysis: 28.9 months (95%CI: 26.1 – 32.0).
10. Median OS, sensitivity analysis: 23.5 months (95%CI: 21.2 – 27.1).
    1. The PBAC noted that the difference between the median OS estimates from the primary and sensitivity analyses above is likely due to cohort contamination from 1 April 2020 when TDM-1 was PBS-listed for early-stage breast cancer. Patients initiating TDM-1 from this time under PBS item codes indicated for late-stage disease may have erroneously included those receiving treatment for early-stage disease who are likely to have longer expected survival times than late-stage/metastatic patients. Therefore, it is likely that OS estimates including early-stage patients are biased and the estimate from the sensitivity analysis more closely reflects the true median OS for patients treated with TDM-1 for metastatic breast cancer.
    2. The PBAC noted that the estimate for the median OS attributed to TDM-1 from the sensitivity analysis based on PBS data (23.5 months) was more than seven months shorter than the median OS estimated in the pivotal trial used in the November 2014 TDM-1 PBAC submission (30.9 months). The PBAC agreed with the MI-CRE that this discrepancy in survival outcomes was likely due to differences in patient characteristics between the real-world and trial cohorts. For example, the real-world cohort was six years older (59 years) than that reported in the pivotal clinical trial (53 years). Furthermore, the PBAC considered that randomised controlled trials (RCTs) typically recruit patients with fewer co-existing disease(s). Therefore, the patients receiving TDM-1 in the pivotal trial were likely healthier than the patients who access TDM-1 for metastatic breast cancer via the PBS.
    3. The PBAC noted that the TDM-1 pilot study relied exclusively on median OS to determine the survival outcomes associated with this medicine in patients with metastatic breast cancer. The PBAC considered that whilst median OS is the most common measure used in the outcome reporting of cancer medicine research, the committee typically considers a range of measures of survival outcomes (such as response rates, duration of response, progression free survival [PFS] and mean OS) when making determinations regarding the clinical and cost-effectiveness of these medicines. The PBAC made the following comments regarding the limitations of relying on median OS alone to determine the patient relevant outcomes associated with a particular cancer medicine:

* Median OS describes the outcome at a single time point (i.e., when 50% of the patients have died and 50% have survived). Therefore, it does not capture the long‐term survival profile well, especially in cases in which a minority of patients have the potential to gain a durable survival.
* Median OS is sensitive to the length of follow-up used in the analysis. This was demonstrated by the results of the TDM-1 pilot study where median OS varied from 19.4 months (95%CI: 15.1 – insufficient) after 2 years of follow-up, to 23.5 months (95%CI: 21.2 – 27.1) after 6.5 years of follow-up. This raises uncertainty regarding the most appropriate follow-up length to apply when using median OS to estimate the survival outcomes associated with a particular medicine.
* Median OS does not account for qualitative factors associated with survival outcomes such as quality of life considerations.
  1. The PBAC agreed with feedback from Departmental MO’s that the metric of importance, when assessing clinical and cost-effectiveness, is the relative incremental difference in survival outcomes, such as OS, between the intervention and the comparator (as opposed to the absolute OS of the intervention). Therefore, the PBAC supported applying the methods detailed in the Protocol to alternative cancer medicines to allow a comparison of the incremental gain in survival outcomes based on the clinical trial data considered by the PBAC, with that observed in PBS data.
  2. The PBAC advised that overall, the Protocol was informing regarding the methods that are considered ‘best-practice’ when using PBS data to derive estimates of the survival outcomes attributed to specific cancer medicines. The PBAC considered that the methods detailed in the protocol may inform other health technology assessment (HTA) research by contributing to the robust analysis of OS using PBS data linked to other clinical data in the future.
  3. The PBAC was supportive of further exploration into how this research could be extended to other cancer medicines and/or different medicine classes. The PBAC supported publication of the Protocol as it may be informative to sponsors and evaluation groups involved in HTA research on the real-world use of medicines.

**Outcome:**

Noted

1. Green AK, Curry M, Trivedi N, Bach PB, Mailankody S. Assessment of Outcomes Associated With the Use of Newly Approved Oncology Drugs in Medicare Beneficiaries. JAMA Netw Open. 2021;4(2): e210030. doi:10.1001/jamanetworkopen.2021.0030

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