

## **A review of cancer related surrogate outcomes used for PBAC decision making**

### **1 Purpose of Item**

That the Pharmaceutical Benefits Advisory Committee (PBAC):

- 1.1 **CONSIDER** and comment on the draft report, 'A review of cancer related surrogate outcomes used for PBAC decision making' (the Report), prepared by Monash University.
- 1.2 **NOTE** the ESC advice.
- 1.3 **ADVISE** the Department on any actions that should be taken because of the Report or any suggestions for further research.
- 1.4 **ADVISE** the Department on whether the Report, and associated PBAC consideration, should be published on the PBS website.

### **2 Background**

- 2.1 Surrogate outcome measures have an increasingly important role in cancer medicine research providing evidence to support registration and subsidy of new medicines. Where validated, surrogate outcome measures may allow researchers to extrapolate short-term trial results into long-term clinically relevant patient outcomes.
- 2.2 At the May 2022 PBAC Intracycle meeting, the PBAC supported a proposal for a research project on surrogate outcome measures in PBAC submissions for cancer medicines. The PBAC suggested that the research could be expanded in the future to include other indications.
- 2.3 In September 2022, the Department contracted Monash University to collate a report on the surrogate measures included in PBAC submissions for cancer medicines between 2012 and 2021 (inclusive). PBAC members were consulted on the scope.
- 2.4 Consistent with other post-market review research projects, sponsors of cancer medicines and consumers were not consulted on this item prior to the ESC or PBAC meetings.
- 2.5 A separate research project on methods to estimate overall survival (OS) outcomes for cancer medicines using Pharmaceutical Benefits Scheme (PBS)/real-world data was contracted to the Medicines Intelligence Centre of Research Excellence (MI-CRE). This project aimed to estimate OS for certain cancer medicine-indication pairs and compare these results to the OS results in the pivotal trial evidence considered by the PBAC at the time of listing. This research was presented to the PBAC in May 2023.

### **3 Report summary**

#### ***Methods***

- 3.1 All PBAC Public Summary Documents (PSDs) from the PBS website for cancer medicines (excluding treatments for pain, nausea, or adverse events) considered between January 2012 and May 2022 were reviewed. Submissions (including resubmissions) were included for detailed data extraction if a surrogate outcome was used in lieu of OS or if the PSD stated that a surrogate outcome was relied upon for the clinical claim or PBAC decision.
- 3.2 A data extraction form was created to record relevant data characteristics from the PSDs, including:
- cancer type
  - oncology medicine class
  - surrogate measure
  - surrogate outcome as primary, secondary, or other outcome in key trials
  - surrogate effect size (including confidence interval)
  - other reported clinical outcomes
  - type of economic model and whether the surrogate(s) were used as inputs
  - PBAC recommendation
  - PBAC advice on the validity of the surrogate and comments on the link between the surrogate and clinical outcomes relied on by the PBAC
  - OS data immature or from an interim analysis.
- 3.3 A narrative review was conducted to describe the use of surrogate outcomes in PBAC decisions for cancer medicines and content analysis using NVivo software was used to summarise trends in the use of surrogate measures within and across cancer types.
- 3.4 Final OS data, limited to Phase II/III clinical trials, was sought for trials where the PBAC had considered immature or interim OS data. These data were compared to the OS data considered by the PBAC.
- 3.5 A literature review was conducted to identify recent high-quality meta-analyses that assessed the validity of surrogate outcomes in cancer therapies. The studies were grouped by cancer type and surrogate measure, and a qualitative comparison was made to the evidence considered or accepted by the PBAC on surrogate validity or effect size.

#### ***Key Findings***

- 3.6 Key findings from the Report are:
- 50% (247 out of 498) of submissions (including resubmissions) for cancer medicines between January 2012 and May 2022, were based primarily on a surrogate outcome. These included 91 medicines for 22 broad cancer types.

- The most common cancer types for submissions that relied on a surrogate outcome during the study period were for blood, lung, skin, and breast cancers.
- Of the submissions that relied on a surrogate, 44% received a positive recommendation, 12% were deferred and 44% were not recommended.
- For submissions that relied on a surrogate outcome and were not recommended by the PBAC, in 62% (67 out of 108) of cases this was due to immature OS data.
- Breast cancer had the highest proportion of submissions that relied on a surrogate outcome measure (65%), but these submissions were also the most likely not to be recommended (55%).
- Progression-free survival (PFS) was the most common surrogate outcome, used in 76% (187/247) of submissions, and measured as either a primary or secondary outcome in the supporting clinical trial(s). Other commonly used surrogates include overall/objective response rate, clinical/complete response in blood cancer, relapse/recurrence free survival (RFS) in skin cancer, and invasive disease-free survival (iDFS) in breast cancer.
- Of the submissions that relied on a surrogate, 65% presented OS data based on interim results. Of the trials with interim OS results, 41% (41 out of 101) have now published final results. Final OS results were generally consistent with the interim results. The Hazard Ratio (HR) for final OS was worse (HR increased >0.1) compared to the interim OS results in 4 trials. However, none of the submissions with worse final OS results had received a positive recommendation for PBS listing.
- In submissions that presented modelled economic evaluations, surrogate outcomes were used in 85% (140 out of 165) of cases. The cost-effectiveness was likely heavily dependent on the assumed relationship between the surrogate outcome and OS or other clinically meaningful outcomes.

3.7 Key findings from the literature review of surrogate measure validation studies:

- Validation studies have presented mixed results with most studies showing low to moderate correlation between PFS or objective/overall response rate and OS. For example, studies have reported PFS to be a validated surrogate for OS in diffuse large B cell lymphoma and non-Hodgkin lymphoma but inconclusive across many other cancers (e.g., bowel, ovarian, prostate).
- Regarding the validation of surrogate endpoints in various cancer types, the Report found:
  - Event-free survival (EFS) and PFS were possible surrogates for OS in blood cancers
  - PFS was a possible surrogate for OS in glioblastoma
  - Disease free survival (DFS) was strongly correlated with OS in HER2+ breast cancer
  - PFS and DFS were possible surrogates for OS in adjuvant lung cancer
  - Metastasis-free survival (MFS) was a possible surrogate for OS in prostate cancer.
- Issues with the validation studies include:

- use of different criteria for assessing correlation between the surrogate and OS
- inconsistent thresholds to establish that a surrogate is sufficiently validated
- thresholds that may not be robust enough for health technology assessment and economic modelling purposes
- unclear disease stage and type.

3.8 The Report noted the following issues with the use of surrogate measures:

- Surrogate outcome definitions and how they are measured vary across trial protocols, making it difficult to compare outcomes across trials and elicit a reliable estimate of treatment effect.
- Standardised guidelines for measuring outcomes in clinical trials are available for many cancers but are not universally adopted in clinical trials. Guidelines and criteria are updated periodically, making comparisons to older trials more difficult.
- The potential for bias in the measurement of surrogate outcomes.
- Lack of evidence for validation of the surrogate outcomes used.
- Issues with clinical trial design, including sample size, confounding from crossover to the active arm, and use of single-arm studies in rare cancers.

3.9 The Report found that it was difficult to characterise surrogate outcomes (level of evidence, strength of association and quantification of the expected effect on the patient centred outcome) based on information in the PSDs and found limited use and mention of the PBAC's guidance on surrogate outcomes (i.e., Appendix 5 of the PBAC Guidelines).

## **4 ESC Advice**

A summary of the ESC Advice follows.

### ***Relevant publications***

- 4.1 The ESC noted a recent publication that referenced several studies where the trial results for surrogate outcome measures were discordant with OS results, particularly for haematological cancers. The paper noted that the US Food and Drug Administration (FDA) Accelerated Approval Program provides a mechanism where approved indications can be rapidly withdrawn.<sup>1</sup>
- 4.2 The ESC noted a published review of cancer medicines approved by the US FDA from 2006-2018. The review showed that around a third of cancer medicines were approved based on the surrogate endpoint of response rate (RR) and concluded that many medicines were approved based on numerically low or modest RRs (median RR for the 85 indications was 41% (interquartile range: 27-58%), with 33% having an RR <30%). Of the medicines granted accelerated approval, that were later converted to regular FDA approval, only 21% demonstrated an OS benefit, 55% demonstrated a

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<sup>1</sup> Merino M (2023), 'Irreconcilable Differences: The Divorce Between Response Rates, Progression-Free Survival, and Overall Survival', *Journal of Clinical Oncology*, 41(15):2706-12.

PFS benefit and 24% were approved based on RR.<sup>2</sup>

- 4.3 The ESC advised that the PBAC consider the Report in the broader context of the paucity of evidence provided to support some submissions, including the use of indirect comparisons, as evidenced by a recent article by the Adelaide Health Technology Assessment group. This paper indicates that the quality of evidence for cancer medicine submissions to the PBAC, based on a review of PSDs between 2005 and 2020, had declined over time. Key findings from this study were:
- 37% of studies lacked direct comparative evidence
  - 78% of indirect comparisons had transitivity issues
  - 41% of PSDs reporting on head-to-head studies had moderate, high, or unclear risk of bias, and risk of bias concerns increased by a third over the last 7 years of the study (OR 1.30, 95% CI: 0.99-1.70).<sup>3</sup>

**Comments on the Report**

- 4.4 The ESC considered the Report of value for informing health technology assessment.
- 4.5 The ESC noted that the Report showed some correlation between greater use of surrogate endpoints in submissions and lower rates of positive PBAC recommendation (e.g., breast cancer submissions had the highest use of surrogate measures in submissions and the lowest rate of PBAC recommendation).
- 4.6 The ESC noted that the Report showed that interim OS results from clinical trials for cancer medicines were generally consistent with the final OS results, where these data are available, but not in all cases. The ESC expressed concern that in many cases final OS results were not available and that this may be due to either the trials being ongoing, or to publication bias in the case of trials reporting negative or statistically inconsistent results. The ESC noted that the Report did not explore the reasons why final trial OS data were not available and further noted that some trials do not extend to the point of mature OS data.
- 4.7 The ESC was also concerned that there was substantial use of early phase clinical trials in PBAC submissions when proper studies were underway and due to report results soon.
- 4.8 The ESC noted that there was the potential for significant financial wastage and harm to patients from provisional and accelerated approval pathways, in cases where the final outcome data were worse than expected, as these pathways often provided around six years to provide additional data.
- 4.9 The ESC considered that the Report demonstrates that the PBAC is familiar with considering the inter-related issues of surrogate outcome measures, immature and early entry data, and other uncertainties, balanced against the need to make recommendations despite these uncertainties.

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<sup>2</sup> Chen EY, Raghunathan V, Prasad V (2019), 'An Overview of Cancer Drugs Approved by the US Food and Drug Administration Based on Surrogate End Point of Response Rate', *JAMA Internal Medicine*, 179(7):915-21.

<sup>3</sup> Gao Y, Laka M and Merlin T (2023), 'Is the quality of evidence in health technology assessment deteriorating over time? A case study on cancer drugs in Australia', *International Journal of Technology Assessment in Health Care*, 39(1):1-9.

- 4.10 The ESC noted that surrogate endpoints may be clinically meaningful and patient-relevant in some circumstances and that this is reflected in the PBAC's comments in the Report. For example, time without disease progression may be important to the quality of life of patients. However, the ESC considered that asymptomatic progression may be difficult to measure in clinical trials and to quantify economically.

***Suggested actions***

- 4.11 The ESC considered that it may be useful for the Department to set up active monitoring for final clinical trial OS results, where PBAC has recommended a listing based on immature or interim data, and reporting of these results to ESC and/or PBAC.
- 4.12 The ESC considered that it may be useful for the PBAC and the Australian Government to have a mechanism for rapidly changing PBS listings to withdraw subsidisation or to renegotiate price in circumstances where final trial results are worse than, or inconsistent with, the trial results used to support a listing. The ESC considered that it may be possible to incorporate this into Risk Sharing Arrangements (RSAs), along with a mechanism to compel sponsors to provide final trial OS data within an agreed timeframe. The ESC noted that for medicines granted full Therapeutic Good Administration (TGA) registration it was difficult to remove this registration based on updated data showing a lack of clinical efficacy without clear evidence of a significant safety issue.
- 4.13 The ESC advised that it would be worthwhile to explore options to enhance the information on surrogate measures in the PBAC Guidelines for submissions (Appendix 5 - Translating comparative treatment effects of proposed surrogate measures to target clinical outcomes).<sup>4</sup> The ESC considered that there had been a decline in number of submissions that comprehensively completed this data, as requested in the guidelines.
- 4.14 The ESC advised that copies of the Report be provided to the HTA Policy and Methods Review Committee and the PBAC evaluation groups, following PBAC consideration. The ESC considered that the evaluation groups may also be able to provide advice on any revision to the PBAC Guidelines - Appendix 5.
- 4.15 The ESC advised that the PBAC should consider improvements to the reporting of surrogate outcomes and surrogate measure validity in PSDs, highlighting when decisions have been made with a high degree of uncertainty. The ESC also considered that it would be useful for ESC Advice, PBAC Outcomes and PSDs to highlight when information on surrogate outcomes was not satisfactorily completed in submissions, to improve provision of this information by sponsors.
- 4.16 The ESC considered that it would be appropriate to publish a copy of the Report on the PBS website to aid in discussion of the topic, along with the PBAC's comments on the Report. The ESC considered that it would be useful to share the Report with relevant patient representative groups and with the Medical Oncology Group of Australia (MOGA). The ESC considered that it was important to understand public

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<sup>4</sup> Department of Health and Aged Care, The Pharmaceutical Benefits Advisory Committee Guidelines (Version 5.0, September 2016), [Appendix 5 – Translating comparative treatment effects of proposed surrogate measures to target clinical outcomes](#).

perceptions of the trade-off between accelerated access to medicines and less evidence to demonstrate safety and comparative effectiveness. The ESC considered that clinical need in indications with limited treatment options was an important factor for patients when considering accelerated access to medicines.

***Suggested further research***

- 4.17 The ESC noted that the Report provided a comprehensive review of current cancer surrogate validation studies. However, as this was an evolving area of research, the ESC considered that updating the literature review of validation studies across all cancer subtypes every few years may be beneficial. The ESC further considered that a more detailed systematic review of validation studies of surrogate outcome measures for some specific tumour subtypes may be of use now.
- 4.18 The ESC considered that it may be useful to perform a literature review to confirm the reliability of the surrogate outcome measures used to support first-in-class cancer medicines, to which subsequent PBS listings have been cost-minimised, focusing on programmed death-(ligand)1 (PD-[L]1) inhibitors and tyrosine kinase inhibitors (TKIs).
- 4.19 The ESC suggested that reviews of the use of surrogate measures in the following conditions could be considered:
- cystic fibrosis (CF)
  - spinal muscular atrophy (SMA), considering updated trial compared to registry data
  - Alzheimer's disease (AD)
  - pulmonary fibrosis
  - cardiac amyloidosis.

## **5 PBAC Outcome**

- 5.1 The PBAC considered the Report, 'A review of cancer related surrogate outcomes used for PBAC decision making', which included a comprehensive literature review of surrogate measure validation studies and noted the key findings.
- 5.2 The PBAC noted the Report showed that 50% (247 out of 498) of PBAC submissions (including resubmissions) for cancer medicines between January 2012 and May 2022, were based primarily on a surrogate outcome. Forty-four per cent of these were not recommended for PBS-listing by the PBAC, and in 62% (67 out of 108) of cases this was due to immature overall survival (OS) data. In submissions that presented modelled economic evaluations, surrogate outcomes were used in 85% (140 out of 165) of cases. However, a literature review of surrogate outcome measure validation studies presented mixed results with most studies showing low to moderate correlation between OS and the most common surrogate measures, including progression-free survival (PFS) and objective/overall response rate.

- 5.3 The PBAC noted the ESC Advice which included suggested actions and areas for further research. The PBAC considered that any additional research projects would need further consideration through the Post-market Review Workplan.
- 5.4 The PBAC considered that the Report was informative for health technology assessment and recommended that the Report, and the PBAC's consideration, be published on the PBS website and shared with relevant stakeholders, including the Health Technology Assessment Policy and Methods Review Committee. The PBAC emphasised the importance of communicating the substance of the Report to consumer groups and in understanding the importance of surrogate outcome measures to consumers.
- 5.5 The PBAC considered that surrogate endpoints may be clinically meaningful and important patient-relevant outcomes in some circumstances, particularly for some haematological cancers which due to longer life expectancy may be more likely to rely on surrogate measures in submissions. The PBAC noted that this is reflected in the extracts from the PBAC Minutes included in the Report.
- 5.6 Regarding a potential indirect relationship between reliance on surrogate outcome measures in PBAC submissions and a positive PBAC recommendation for PBS-listing, the PBAC considered these results may be affected by prognosis. The PBAC noted that more mature OS data may be available from studies of cancers associated with poorer prognosis and patient outcomes.

**Outcome:**

Noted