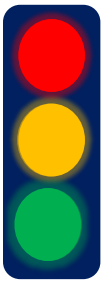

Monitoring system for updated OS results for cancer trials

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Executive summary

Recommendations for PBAC consideration

1. Consider adopting the Overall Survival (OS) monitoring system

The OS monitoring system presents a relatively low-cost, systematic method to prospectively monitor clinical trials for additional OS data for submissions where the PBAC recommendation was based on immature or interim OS results. Routinely reviewing past recommendations as updated data becomes available will assist in verifying the longer-term survival benefit of treatments and their implications for cost-effectiveness estimates.

2. Consider prospectively designating trials for cancer medicines to enter the OS monitoring system at each PBAC meeting

The time of PBAC recommendation is optimal for deciding which trials related to medicines recommended by the PBAC require further monitoring and should be entered into the system. This is because when considering submissions where the clinical claim is based on a surrogate outcome, the PBAC considers the level of uncertainty in the clinical claim and the maturity of the data presented in the submission. The designated trials would be entered into the OS monitoring system after each PBAC meeting.

3. Determine the optimal interval for continued OS monitoring

An annual literature search for new publications and additional OS reports for all trials for cancer medicines in the monitoring system is recommended to be adopted initially.

4. Determine the decision rule for medicines and related trials exiting the monitoring system with green alerts

Trials for cancer medicines where the final OS hazard ratio is consistent with PBAC expectations at the time of recommendation and for which OS data is considered mature will be allocated a green alert status and flagged to exit the system, as further monitoring is likely unnecessary. Case reports will be generated for all trials allocated to green alert status. If the PBAC is satisfied that a trial no longer requires monitoring, the trial would be removed from the system.

5. Determine further actions for medicines and related trials with red alerts

Medicines where the updated OS hazard ratio from the included trials has worsened or does not align with PBAC expectations, or where the trial has passed its registered end date and no publications of final OS analysis have been identified, will be allocated to red alert status. Case reports will be generated for all trials allocated a red alert status. The PBAC should determine any further actions after considering the case report and other relevant information. Potential actions could include re-evaluating cost-effectiveness based on the updated OS data in cases where OS has worsened over time.

Introduction

In oncology clinical trials, overall survival (OS) remains the preferred clinical endpoint for assessing the clinical effectiveness of most new interventions. However, its utility is constrained by the need for long-term patient follow-up, larger patient populations and financial outlay. In addition, OS may be confounded by the use of subsequent treatments during the follow-up and cross-over of trial interventions. Decision makers are increasingly relying on surrogate measures, such as disease progression (e.g., progression-free survival) or tumour shrinkage (e.g., response rate), to shorten the duration of clinical development, reduce sample sizes and accelerate the approval of new cancer drugs, even though there may be no demonstrated significant association between improvements in surrogate outcomes and patient-relevant outcomes such as survival and quality of life. While timely reimbursement and patient access to new treatments are important, so is robust evidence demonstrating significant patient benefit. For regulatory approvals and funding

decisions of drugs based on immature or interim data, there is a role for funders to continue to monitor emerging evidence and drug companies to continue OS data collection to provide confirmatory evidence for ongoing funding.

In July 2023, the PBAC considered a review of cancer related surrogate outcomes used for Pharmaceutical Benefits Advisory Committee (PBAC) decision-making, the "Cancer Surrogate Report" (herein CSR). The CSR focused on PBAC submissions for cancer drugs from January 2012 to May 2022, where a surrogate outcome was used in lieu of OS or if the Public Summary Document (PSD) stated that a surrogate outcome was relied upon for the clinical claim or PBAC recommendation. The CSR found that of the submissions that relied on a surrogate, 65% presented OS data based on interim results, of which 60% had not subsequently published final trial results. The Economic Sub-committee (ESC), which considered the report in June 2023, advised the PBAC to consider recommending that the Department of Health and Aged Care (Department) establish a monitoring system to report to the ESC/PBAC the final OS data for trials on cancer medicines where PBAC made a recommendation for Pharmaceutical Benefits Scheme (PBS) listing based on interim or immature OS data. In September 2023, the PBAC recommended the establishment of a monitoring system for final trial OS results for these cancer medicines.

This project will action the PBAC recommendations from the CSR to establish a system for monitoring updated and final trial OS results for cancer medicines that were PBS-listed based on interim or immature OS results.

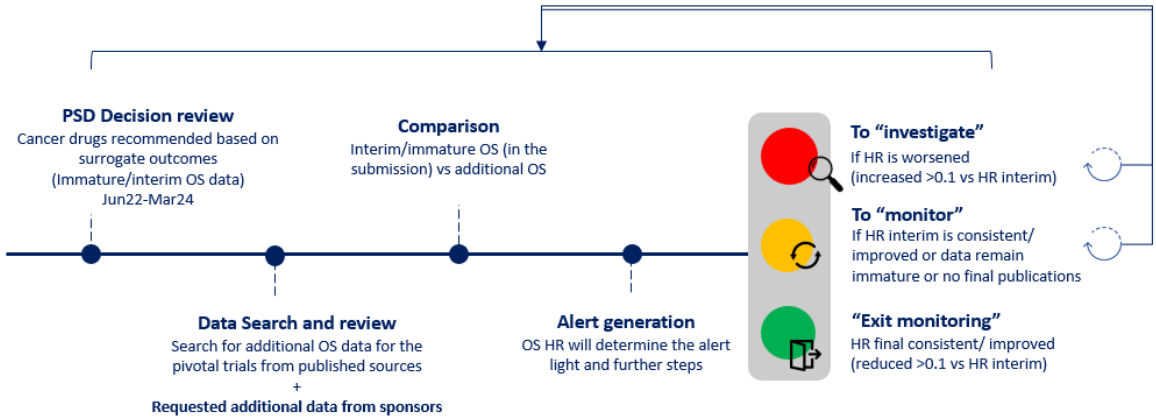
Pilot study (January 2012-May 2022 submissions)

A pilot of methods to search for and obtain (including from sponsors) additional OS data for a selected sample of eligible submissions identified in the CSR was conducted to help design a final search strategy and sponsor information requests for the whole sample. Submissions (n=24) from January 2012 to May 2022, where immature/interim OS data were used to support PBS listing and the pivotal trials (n=25) that had not yet reported their final OS data at the time of the CSR, were used for the pilot. The search of published literature for final OS data on the included pilot trials was conducted between 3 June and 1 July 2024. A broader Google search for other potential information sources, such as recent conference abstracts and publications not yet indexed in the databases, news bulletins or sponsor announcements was also conducted. Publications presenting updated OS data were identified for 21/25 (84%) trials, of which 13 publications were described as final reports. The high proportion of trials reporting updated and final OS data after being recommended by the PBAC indicated that implementing a system to prospectively monitor trials for additional OS data would be feasible.

OS monitoring project (June 2022-March 2024 submissions)

Figure ES1 presents the schematic of the project steps for the monitoring system for final OS data.

Figure ES1: Schematic of the project steps with the monitoring system for final OS data



Source: constructed during the project.
HR=hazard ratio; OS=overall survival; PSD=Public Summary Document; RCT=randomised controlled trial;

Method

For this OS monitoring project, a review was conducted on PSDs and/or PBAC Minutes for cancer medicines recommended by the PBAC for listing on the PBS between June 2022 and March 2024 (inclusive). The review used the same eligibility criteria as for the CSR to identify submissions[1] where the PBAC's recommendation was primarily based on the surrogate outcomes. Trials for cancer medicines were included in the OS monitoring system if the clinical claim relied upon surrogate outcome(s), OS data were immature at the time of consideration, and the submission received a positive PBAC recommendation. Trials included in the pilot study were eligible for inclusion in the OS monitoring system if they were also relied upon in a submission for a drug recommended for listing by the PBAC between June 2022 and March 2024. Four trials (pertaining to 5 submissions[2]) from the pilot were also included in the OS monitoring system; for these, OS data presented in the submission during the OS monitoring capture period was recorded as the baseline data in the OS monitoring system. Single-arm studies that were pivotal to the submissions' clinical claims were also included; however, additional computation to assess comparative OS at later timepoints was beyond the scope of this report. Table ES1 presents the eligibility criteria adapted from the CSR that were used to identify the relevant submissions of cancer drugs with a PSD from June 2022 to March 2024 to be included in the monitoring system.

Table ES1: Eligibility criteria for submissions* of cancer therapies in the review

Inclusion criteria	Exclusion criteria
- Submission with a PSD available, that was considered by the PBAC between June 2022 and March 2024. - Submission for a chemotherapy or other anti-cancer treatment. - Submission where a surrogate outcome was used for OS or the PSD clearly states that a surrogate outcome for another clinically meaningful outcome was relied upon for the clinical claim or PBAC recommendation. - OS data were immature at the time of the PBAC consideration. - Submission received a positive PBAC recommendation.	- Submission for a supportive treatment in a cancer population (e.g. treatments for pain, nausea or adverse events associated with anti-cancer treatments). - The OS (or the claimed clinically meaningful endpoint) was statistically significantly different between treatment and comparator.

Source: Table 1, Cancer Surrogate Report.* Includes resubmissions
Abbreviations: OS=overall survival; PBAC=Pharmaceutical Benefits Advisory Committee; PSD=public summary document.

[1] Submissions herein includes first submissions or resubmissions
[2] 4 first submissions and 1 resubmission

The relevant trial data (e.g. medicine name, indication, cancer type, PBAC meeting date, PBAC recommendation, key trial name, trial number, trial comparator, surrogate outcome, analysis dates, OS hazard ratio (HR) and confidence interval considered by the PBAC) were extracted from the PBAC submissions and entered into an Excel database of trials with interim or immature OS data at the time of the PBAC recommendation, developed during the reporting of the CSR.

A second database was established in Excel to collect the additional OS data. The additional OS data were sought first from published literature based on the method developed in the initial pilot study. Searches included publication databases (Embase, PubMed), clinical trial registries (clinicaltrials.gov and clinicaltrialsregister.eu), broader internet searches and regulatory websites. If publicly available, clinical trial protocols and statistical analysis plans were checked for scheduled OS reporting timepoints for interim and final analyses and the trial definition of final OS. We also identified any reported planned contamination points, such as crossover timepoints, in the trials if relevant. The searches included phase II/III trial results and any extended observational follow-ups from the included trials reporting OS outcomes. The search of published literature for final OS data on the included trials in the monitoring system was conducted between 9 September and 9 December 2024.

The monitoring system then compares the final or updated OS (i.e. subsequent data cuts) trial data with the assumed OS results accepted by the PBAC (i.e. interim/immature OS data at the time of the submission) to confirm whether or not they align. Corresponding alerts were generated based on the alignment between interim and updated OS data and the associated risk to cost-effectiveness.

Table ES2 summarises the OS monitoring alert criteria for the included trials.

Table ES2: OS monitoring alert criteria.

Red alert - investigate	Amber alert - monitor	Green alert – exit monitoring
• {Final/updated HR is worsened (increased >0.1 vs HR interim), AND Final/updated OS HR does not align with PBAC expectations} **OR** • {No follow-up data identified, AND • Trial registered end date has passed} **OR** • Trial terminated	• {Final/updated HR is consistent (≤0.1 difference vs HR interim), OR Final/updated HR is improved (reduced >0.1 vs HR interim)} **AND** • Final/updated OS HR aligns with PBAC expectations **AND** • {OS data remain immature, OR No final OS data available yet (i.e. registered end date not reached)}	• {Final HR is consistent (≤0.1 difference vs HR interim), OR Final HR is improved (reduced >0.1 vs HR interim)} **AND** • Final OS HR aligns with PBAC expectations **AND** • OS data are mature

Source: constructed during the project.
HR=hazard ratio; OS=overall survival; PBAC=Pharmaceutical Benefits Advisory Committee.

The alert system takes the form of a traffic light reporting system that indicates when further investigation of the evidence is required (red alert), when continued monitoring of the trial is recommended (amber alert) or when the trial can exit monitoring (green alert). The alerts include criteria for final OS HR, data maturity and PBAC expectations for the final/updated OS HR. For trials that appear to be completed but no final OS data were found, we worked with the Department to request information from the sponsor companies. Case reports are generated for each trial with a green or red alert for the PBAC to determine the next course of action.

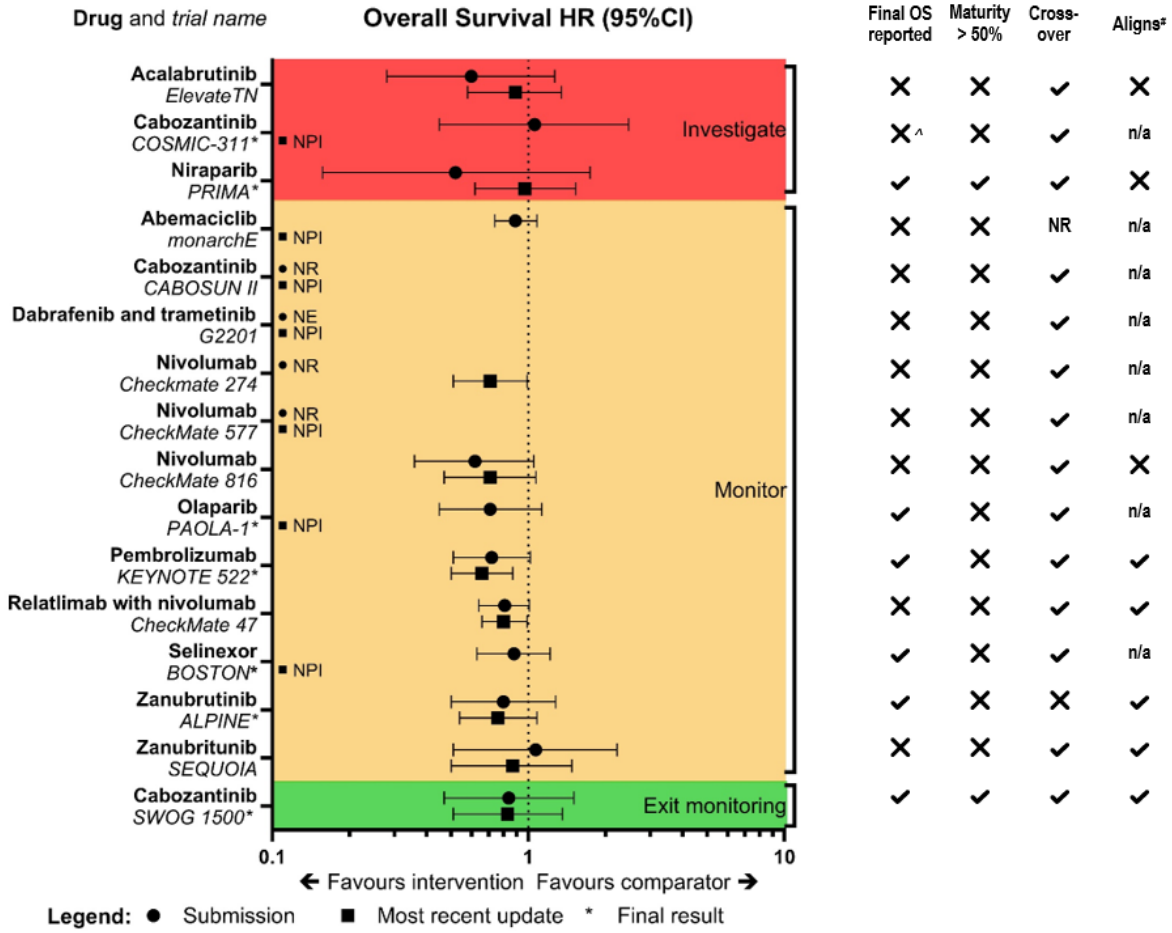
Results

From a total of 311 submissions with a PSD between June 2022 and March 2024 (inclusive), 18 submissions recommended by the PBAC relying on 21 trials (including 5 single-arm studies) reporting immature/interim OS data were included for further monitoring of OS data. The literature search identified updated OS data for 9/16 (56%) trials and 4/5 (80%) single-arm studies. Trials for cancer medicines were allocated to an alert category based on the change in OS HR from the trial/s

since PBAC consideration and other relevant information reported in the publications identified in the literature search, such as trial end date, whether OS was reported as 'final' in the publication, data maturity, extent of crossover and alignment of results with PBAC expectations.

Figure ES2 shows the HRs reported at the time of PBAC consideration (June 2022 to March 2024) for each trial of the cancer medicines included in the OS monitoring and the most recent OS data identified from published literature. The trials are grouped by the alert system category allocation.

Figure ES2. Hazard ratios for overall survival at submission and at the most recent published timepoint up to September 2024



Source: compiled during the review from OS HR reported in PSDs and publications (See Attachment 5)

✗= no; ✓ = yes; n/a = not applicable (no updated data); CI=confidence interval; HR=hazard ratio; NE=not estimable; NPI=no publications identified in the public domain; NR=not reported; OS=overall survival; PBAC=Pharmaceutical Benefits Advisory Committee.

Aligns with PBAC expectations

^ Since the primary endpoint was met, no updated OS analyses was conducted

* Final result = publication or trial protocol indicated OS analyses were final

NB Reported only where Overall Survival HRs were publicly available

OS monitoring alerts

Based on the alert system criteria summarised in Table ES2, 3 trials for cancer medicines recommended by the PBAC were identified for further investigation (red alert status), 1 trial identified to exit the monitoring system (green alert status), and 12 trials to remain in the monitoring system (amber alert status). Each of the trials allocated to red or green alert status were further reviewed and summarised in a one-page case report.

Two of the trials allocated to red alert status (ELEVATE-TN for acalabrutinib and PRIMA for niraparib) showed worse OS HR (difference of >0.1 towards the null) at subsequent data analysis compared with the interim/immature OS data at the time of the submission. Overall, the worsened OS HR from the additional data cuts after the submission were likely to impact the primary clinical and cost-effectiveness or cost-minimisation analysis relied on in the respective PBAC submissions.

For the third trial allocated red alert status (COSMIC-311), no updated OS results were identified, and a 2024 publication (Capdevila 2024[3]) claimed that further analyses on OS would not be conducted due to extensive crossover, hence, any future OS data are unlikely to be informative for decision-making purposes.

The SWOG 1500 trial for cabozantinib in renal cancer was allocated green alert status because the additional 3 years' data reported as the final OS analysis was mature (73%), and the OS HR was consistent with the interim result considered by the PBAC. Thus, further monitoring may have low value and not be necessary.

Single-arm studies

There were 3 submissions for 3 drug-indication pairs, relying on a total of 5 single-arm clinical studies, recommended by the PBAC. One recommended drug (mobocertinib) was not subsequently PBS listed due to the drug being withdrawn from the market (red alert status), thus, further monitoring of the mobocertinib study (Study 101) may not be necessary. The remaining 4 single-arm studies were allocated amber alert status and will continue to be monitored for additional OS data.

Discussion

We found that between June 2022 and March 2024, 37.8% of the submissions for cancer treatments included pivotal trials with immature/interim survival data at the time of the submission to the PBAC. Approximately half of these cancer drug submissions with immature/interim OS data received a positive recommendation from the PBAC for listing on the PBS. Trials selected for inclusion in the OS monitoring system were those where the OS data were immature at the time of PBAC consideration, the submission's clinical claim relied upon a surrogate outcome, and the submission received a positive PBAC recommendation. The literature review conducted as part of the monitoring system found that additional survival data became available for over half (56%) of the cancer drug trials and most (80%) of the single-arm studies, which contributed pivotal evidence for submissions recommended by the PBAC based on immature/interim results.

Most of the trials with published additional OS analysis showed consistent OS HR compared to the interim OS HR at the time of the submission. However, two cancer drug trials (Elevate-TN and PRIMA) were found to have worsened OS HR (>0.1) at subsequent data cuts to the submission, which could have important implications on the previously accepted evidence for the respective clinical claims, economic evaluations and any risk sharing arrangements implemented to manage uncertainties. The Elevate-TN trial is ongoing, with OS data remaining immature at the 6-year follow-up, reflecting the indolent nature of chronic lymphocytic leukaemia (CLL). Hence, ongoing monitoring of the Elevate-TN trial is required to inform whether a re-evaluation is required and whether the PBAC should revisit their recommendations. A re-evaluation of PRIMA would inform whether the PBAC recommendation for listing may have been different if mature data were available.

The majority of trials and studies of cancer medicines recommended by the PBAC were allocated to amber alert status and will remain in the monitoring system due to their trials being ongoing or OS data remaining immature. For example, the final analysis from KEYNOTE-522 showed a significant survival benefit in favour of the submission drug, but the OS data remained immature, and the registered end date of the trial had not yet been reached. Another trial, G2201, had concluded, and final OS results were provided with the Pre-Sub-Committee Response (PSCR);

[3] Capdevila J., et al Increased Progression-Free Survival with Cabozantinib Versus Placebo in Patients with Radioiodine-Refractory Differentiated Thyroid Cancer Irrespective of Prior Vascular Endothelial Growth Factor Receptor-Targeted Therapy and Tumor Histology: A Subgroup Analysis of the COSMIC-311 Study. Thyroid 2024;34(3):347-359.

however, OS data remained immature at the final planned analysis. KEYNOTE-522 and G2201 remain in the monitoring system to capture any longer-term follow-up data that may be published in the future.

One trial (SWOG 1500) was considered to have met the criteria for green alert and could exit the monitoring system based on the maturity of the additional OS data identified in the literature review and the consistency of the final OS HR with the OS HR considered by the PBAC.

Our project had limitations, including constraints from trial designs. We did not conduct adjustments for treatment switching or subsequent treatments. Long-term OS data may be confounded by significant crossover from the control group to the treatment group at the time of disease progression or the use of other subsequent therapies after treatment discontinuation, which were not consistently reported in trial publications. For submissions that relied on post-hoc subgroups or indirect treatment comparisons (ITCs) or network meta-analyses, we did not re-estimate the treatment effect and only compared the OS HR in the trial population at the time of the PBAC consideration with the updated OS HR.

Our system for monitoring OS data presents a novel approach to retrospectively review past PBAC recommendations based on immature/interim survival data against updated trial data to identify whether significant differences exist between interim and final analyses. Based on the level of difference between OS HRs (i.e. consistent, improved or worsened), three categories of alerts are triggered to determine whether the cancer medicine warrants further investigation, ongoing monitoring or exiting the monitoring system. It is envisaged that the PBAC would decide which medicines and related trials enter the system, if any further investigations are warranted for trials allocated to red alert status, including the nature of those investigations, and confirm when trials allocated to green alert status no longer require monitoring and may be removed from the system.

Our findings show that most cancer drug submissions were made with immature/interim survival data; however, additional survival data became available for nearly all the pivotal trials included in the pilot and more than half of the trials and single-arm studies for medicines included in the monitoring system. While most trials with updated or final analysis showed survival benefits consistent with the interim analysis at the time of the PBAC recommendation, a small proportion (9.5%) of trials also indicated worse long-term survival, which may impact the estimated cost-effectiveness relied on by the PBAC in the initial recommendation. As more submissions of new cancer drug indications are based on trials with immature/interim survival data, giving rise to clinical and cost-effectiveness uncertainty, future PBAC recommendations may consider prospectively including medicines and their related trials in the OS monitoring system at the time of the recommendation and routinely review past recommendations as updated data becomes available to verify longer-term survival benefit of treatments and their implications to cost-effectiveness estimates.

Future work beyond the current alerts may include:

- Developing a framework to further investigate cancer medicines where there are concerns about the validity of the evidence relied on for recommendations.
- Re-evaluation of the clinical and cost-effectiveness analysis using updated OS data for trials identified as having significantly worse OS HR than expected at the time of PBAC recommendation.
- Reviews of trials, registries, real-world observational studies, or the analysis of administrative data for any additional evidence on the long-term survival benefits of cancer drugs, where the final OS data remains immature, the trials have been terminated, or crossovers or subsequent treatments have contaminated long-term follow-up data.
- Monitor how the listings of these cancer medicines have impacted survival in Australia by using linked administrative data, such as the Person Level Integrated Data Asset (PLIDA).

- Measuring the strength of correlation between the surrogate outcome and OS between the interim and final analysis, given that the cancer drug submissions included in the monitoring system had relied on surrogate outcomes in the clinical claim or PBAC recommendation.

Introduction

In oncology clinical trials, overall survival (OS) remains the preferred clinical endpoint for assessing the clinical effectiveness of most new interventions. However, its utility is constrained by the need for long-term patient follow-up, larger patient populations and financial outlay. In addition, OS may be confounded by subsequent treatments during the follow-up and cross-over of trial interventions. Decision makers are increasingly relying on surrogate measures, such as disease progression (e.g., progression free survival) or tumour shrinkage (e.g., response rate), to shorten the duration of clinical development, reduce sample size and accelerate the approval of new cancer drugs, even though there may be no demonstrated significant association between improvements in surrogate outcomes and patient-relevant outcomes such as survival and quality of life. While timely reimbursement and patient access to new treatments are important, so is robust evidence demonstrating significant patient benefit. For regulatory approvals and funding decisions of drugs based on immature or interim data, there is a role for funders to continue to monitor emerging evidence and for drug companies to continue OS data collection to provide confirmatory evidence for ongoing funding.

In July 2023, the PBAC considered a review of cancer related surrogate outcomes used for Pharmaceutical Benefits Advisory Committee (PBAC) decision-making, the "Cancer Surrogate Report" (herein CSR). The review focused on PBAC submissions for cancer drugs from January 2012 to May 2022, where a surrogate outcome was used in lieu of OS or if the Public Summary Document (PSD) stated that a surrogate outcome was relied upon for the clinical claim or PBAC recommendation. The CSR found that of the submissions that relied on a surrogate, 65% presented OS data based on interim results, of which 60% had not subsequently published final trial results. The Economic Sub-committee (ESC), which considered the report in June 2023, advised the PBAC to consider recommending that the Department of Health and Aged Care (Department) establish a monitoring system to report to the ESC/PBAC the final OS data for trials on cancer medicines where the PBAC made a recommendation for PBS-listing based on interim or immature OS data. In September 2023, the PBAC recommended establishing a monitoring system for final trial OS results for these cancer medicines.

This project implements the PBAC recommendations from the CSR to establish a system for monitoring updated and final trial OS results for cancer medicines that were PBS-listed based on interim or immature OS results.

Method

Pilot monitoring system (January 2012-May 2022 selected submissions)

A pilot of methods to search for and obtain (including from sponsors) additional OS data for a selected sample of eligible submissions was conducted to help design the final search strategy and sponsor information requests for the whole sample. The relevant submissions identified in the CSR that have not yet reported their final OS data were used for the pilot. Submissions included in the CSR were from January 2012 to May 2022, where immature/interim OS data were used to support PBS listing. In the CSR, data and reporting were focused only on the pivotal trial supporting the submission and did not focus on any other supporting trials. In this pilot, to comprehensively capture all relevant trials relied on by the submissions to PBAC, PSDs were reviewed again to identify any additional trials reporting OS data in the submissions. Unlike the reporting in the CSR (which compared final to interim OS irrespective of the PBAC's recommendation), the OS monitoring focuses only on PBAC-recommended submissions.

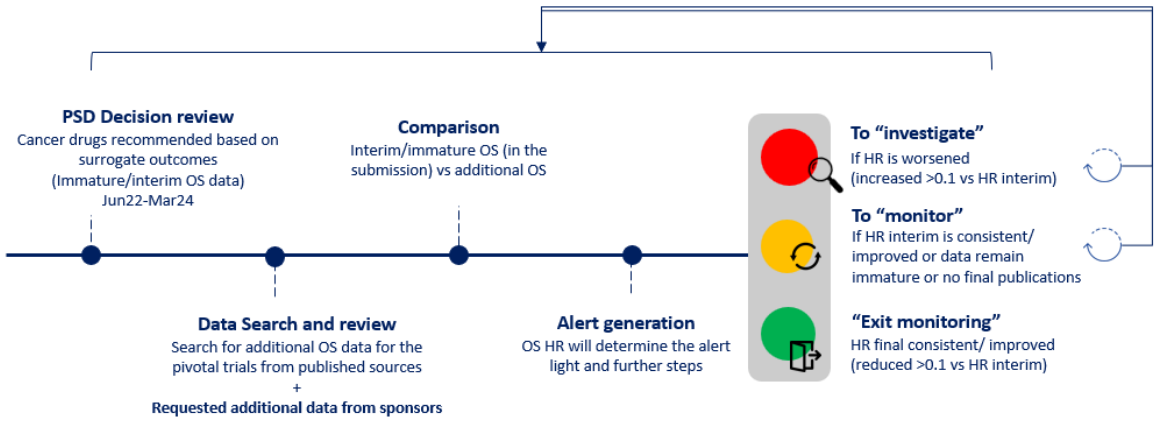
The search for final OS data on the included pilot trials was conducted between 3 June and 1 July 2024. OS data reported in the PSDs were extracted, including the hazard ratio (HR), median OS, data cut-off date, citations and associated publication dates. Then, clinicaltrials.gov was searched

for any subsequent OS results posted, including HR, median OS, data cut-off date, date of the data post, associated trial publications, and expected or actual trial completion dates. The Embase, PubMed and other relevant clinical trial registries were searched to June 2024. A supplementary search of published literature was also conducted on Google Scholar, followed by a broader Google search for other potential information sources, such as recent conference abstracts and publications not yet indexed in the databases, news bulletins or sponsor announcements.

OS monitoring project (June 2022-March 2024 submissions)

Figure 1 presents the schematic of the project steps with the monitoring system for final OS data.

Figure 1: Schematic of the project steps with the monitoring system for final OS data



Source: constructed during the project.
HR=hazard ratio; OS=overall survival; PSD=Public Summary Document; RCT=randomised controlled trial;

For this OS monitoring project, a review was conducted on PSDs for cancer medicines recommended by the PBAC for listing on the PBS between June 2022 and March 2024 (inclusive). The review used the same eligibility criteria as for the CSR to identify submissions[4] where the PBAC's recommendation was primarily based on the surrogate outcomes. Trials for cancer medicines were included in the OS monitoring system if the clinical claim relied upon surrogate outcome(s), OS data were immature at the time of consideration, and the submission received a positive PBAC recommendation. Trials included in the pilot study were eligible for inclusion in the OS monitoring system if they were also relied upon in a submission recommended by the PBAC between June 2022 and March 2024. If a trial from the pilot study was also included in the OS monitoring system, the OS data presented in the submission for the drug-indication pair recommended by the PBAC during the OS monitoring capture period was recorded as the baseline data in the OS monitoring system. Four trials (pertaining to 5 submissions[5]) from the pilot were also included in the OS monitoring system. Relevant trial data were extracted from the PSDs. This was incorporated in the Excel database developed during the CSR, of trials with interim or immature OS data at the time of the PBAC recommendation for listing between June 2022 and March 2024.

Table 1 presents the eligibility criteria adapted from the CSR used to identify the relevant submissions of cancer drugs with a PSD from June 2022 to March 2024 to be included in the monitoring system.

[4] Includes first submissions or resubmissions
[5] 4 first submissions and 1 resubmission

Table 1: Eligibility criteria for submissions* of cancer therapies in the review

Inclusion criteria	Exclusion criteria
- Submission with a PSD available, that was considered by the PBAC between June 2022 and March 2024. - Submission for a chemotherapy or other anti-cancer treatment. - Submission where a surrogate outcome was used for OS or the PSD clearly states that a surrogate outcome for another clinically meaningful outcome was relied upon for the clinical claim or PBAC recommendation. - OS data were immature at the time of the PBAC consideration. - Submission received a positive PBAC recommendation.	- Submission for a supportive treatment in a cancer population (e.g. treatments for pain, nausea or adverse events associated with anti-cancer treatments). - The OS (or the claimed clinically meaningful endpoint) was statistically significantly different between treatment and comparator.

Source: Table 1, Cancer Surrogate Report.
Abbreviations: PBAC=Pharmaceutical Benefits Advisory Committee; PSD=public summary document; OS=overall survival;
* Includes resubmissions

The relevant data variables extracted from PSDs included medicine name, indication, cancer type, PBAC meeting date, PBAC recommendation, key trial name, trial number, trial comparator, surrogate outcome and other reported clinical outcomes.

Based on the proposed eligibility criteria, we identified all funding recommendations for cancer treatments where the pivotal evidence relied upon was from a clinical trial with at least 1 treatment group. Cancer medicines were included if the clinical claim relied upon trial surrogate outcome(s), OS data were immature at the time of consideration, and the submission received a positive PBAC recommendation. Trials for the recommended cancer medicines pivotal for the submissions' clinical claim were entered into the monitoring system. Single-arm studies that were pivotal to the submissions' clinical claims were also included, however, additional computation to assess comparative OS at later timepoints was beyond the scope of this report. We collected data on the OS HR and confidence interval considered by the PBAC, as well as the expected trial completion or analysis dates or criteria.

For the included submissions between June 2022 and March 2024, where immature/interim OS data were used to support a positive PBAC recommendation, the pivotal trials with the immature/interim OS data were included in the monitoring system for additional OS data. If a clinical claim relied on more than one clinical trial of the cancer medicine, all pivotal trials of the cancer medicine included in the submission were entered into the monitoring system. Trials of comparator medicines that did not include the cancer medicine requesting PBS listing as a treatment arm (e.g. trials of comparator medicines used in indirect treatment comparisons) were not included in the monitoring system. A second database was established in Excel to collect the additional OS data. The additional OS data was sought first from published literature based on the method developed in the pilot study. Searches included publication databases (Embase, PubMed), clinical trial registries (clinicaltrials.gov and clinicaltrialsregister.eu), broader internet searches and regulatory websites. If no additional published data were found, the reason why final or additional interim trial data are not available was sought from publicly available sources. If publicly available, clinical trial protocols and statistical analysis plans were checked for scheduled OS reporting timepoints for interim and final analyses and the trial definition of final OS. We also identified any reported planned contamination points, such as crossover timepoints, in the trials if relevant. The searches included phase II/III trial results and any extended observational follow-ups reporting OS outcomes. The search of published literature for final OS data on the included trials in the monitoring system was conducted between 9 September and 9 December 2024.

The monitoring system then compares the final or updated OS (i.e. subsequent data cuts) trial data with the assumed OS results accepted by the PBAC (i.e. interim/immature OS data at the time of the submission) to confirm whether or not they align. Upon the comparison between the final or

updated trial OS and the interim/immature OS results accepted by the PBAC, corresponding alerts were generated based on the associated risk to cost effectiveness.

Table 2 summarises the OS monitoring alert criteria for the included trials.

Table 2: OS monitoring alert criteria.

Red alert - investigate	Amber alert - monitor	Green alert – exit monitoring
• {Final/updated HR is worsened (increased >0.1 vs HR interim), AND Final/updated OS HR does not align with PBAC expectations} **OR** • {No follow-up data identified, AND • Trial registered end date has passed}, **OR** • Trial terminated	• {Final/updated HR is consistent (≤0.1 difference vs HR interim), OR Final/updated HR is improved (reduced >0.1 vs HR interim)}, **AND** • Final/updated OS HR aligns with PBAC expectations, **AND** • {OS data remain immature, OR No final OS data available yet (i.e. registered end date not reached)}.	• {Final HR is consistent (≤0.1 difference vs HR interim), OR Final HR is improved (reduced >0.1 vs HR interim)} **AND** • Final OS HR aligns with PBAC expectations, **AND** • OS data are mature.

Source: constructed during the project.
HR=hazard ratio; OS=overall survival; PBAC=Pharmaceutical Benefits Advisory Committee.

The alert system takes the form of a traffic light reporting system that indicates when further investigation of the evidence is required (red alert), when continued monitoring of the trial is recommended (amber alert) or when the cancer medicine can exit monitoring (green alert). The alerts include criteria for final OS HR, data maturity and PBAC expectations for the final/updated OS HR. For trials that appear to be complete but no final OS data were found, we worked with the Department to request and obtain information from the sponsor companies. Case reports are generated for each trial with a green or red alert.

The monitoring system would signal green alerts for trials of cancer medicines where the final OS HR result is consistent or significantly improved compared to the interim/immature OS at the time of the submission, which aligns with the PBAC expectations at the time of the PBAC recommendation, and the OS data is sufficiently mature. Trials with green alerts could exit the monitoring system.

Amber alerts would be given to trials if the final or updated OS HR is consistent or improved compared to the interim/immature OS at the time of the submission. However, the OS data remains immature, or there is ongoing follow-up of the trial (e.g. registered end data not reached). The trials with amber alert status would remain in the monitoring system until final or mature OS data from the trials are reported.

A red alert is given to cancer medicines where the additional OS HR from the trial/s is significantly worse than interim/immature OS results, which do not align with PBAC expectations at the time of submission. Trials will also have a red alert if there are no further follow-up data beyond the interim/immature OS data accepted by the PBAC, for example, due to sponsor decision, extensive crossover or data maturity. A red alert would trigger a further evidence review of the trial.

Results

Pilot monitoring system (January 2012-May 2022 selected submissions)

The pilot of the methods to search for and obtain (including from sponsors) additional OS data was conducted on a sample of 26 submissions considered by the PBAC from January 2012 to May 2022 (excluding resubmissions relying on the same trials), which were identified in the CSR. These were grouped by drug-indication pairs, including the pivotal trials that had not reported their final OS data at the time of CSR in July 2023. The review of PSDs again to identify additional trials reporting OS data in the submissions identified one further relevant trial (for the July 2020 recommendation

of fulvestrant in breast cancer), thus totalling 27 trials for 26 drug-indication pairs. Table 3 summarises the number of trials by cancer type and PBAC recommendation for inclusion in the pilot.

Table 3: Number of trials by submission and cancer type considered by the PBAC and included in the pilot.

Cancer type	Submissions	Recommended	Not recommend/ deferred	Not recommend/ deferred but subsequently recommended	Trials^ with interim OS results at the time of submission	Pilot: trials^ in submissions recommended by PBAC
Blood cancer	9	4	5	4	9	8
Breast cancer	5	3	2	1	6	5
Lung cancer	2	1	1	1	2	2
Skin cancer	4	2	2	2	4	4
Other cancers*	6	2	4	4	6	6
All cancers	**26**	**12**	**14**	**12**	**27**	**25**

Source: compiled during the project.
OS=overall survival;
^ the number of trials by drug-indication pairs (exclude resubmissions relying on the same trials).
* Other cancers submissions included gastrointestinal cancer (n=1), ovarian (n=4) and renal cancer (n=1).

At the time of the CSR, only 12 of the 26 submissions included in the pilot were recommended by the PBAC, and 14 were not recommended/deferred. A search of subsequent PBAC outcomes at the start of the pilot for the 14 submissions that were not recommended/deferred at the time of the CSR found that the PBAC had subsequently recommended 12 of these submissions. Overall, a total of 24 submissions (with 25 trials) were included in the pilot monitoring of OS data.

Table 4 lists the cancer medicines and 25 related trials in the pilot attributable to 24 submissions with a positive PBAC recommendation.

Table 4: List of trials (n=25) included for pilot OS monitoring attributable to submissions (n=24) from January 2012-May 2022 with a positive PBAC recommendation.

Drug	Meeting date	Broad cancer type	Trial name
Abemaciclib	1/03/2019	Breast cancer	MONARCH-3 (NCT02246621)
Abemaciclib	1/03/2022	Breast cancer	monarchE (NCT03155997)
Acalabrutinib	1/03/2020	Blood cancer	ASCEND (NCT02970318)
Acalabrutinib	1/07/2020	Blood cancer	ELEVATE-TN (NCT02475681)
Avelumab	1/03/2020	Renal cancer	JAVELIN (NCT02684006)
Certinib	1/11/2016	Lung cancer	ASCEND 5 (NCT01828112)
Daratumumab	1/03/2019	Blood cancer	CASTOR (NCT02136134)
Encorafenib + Binimetinib	1/11/2018	Skin cancer	COLUMBUS (NCT01909453)
Fulvestrant	1/07/2020	Breast cancer	FALCON (NCT01602380), FIRST (NCT00274469)
Niraparib	1/07/2021	Ovarian cancer	PRIMA (NCT02655016)
Nivolumab	1/11/2015	Skin cancer	CA209-067 (NCT01844505)
Nivolumab	1/03/2019	Skin cancer	CA209238 (NCT02388906)
Olaparib	1/03/2016	Ovarian cancer	Study 19 (NCT00753545)
Olaparib	1/03/2018	Ovarian cancer	SOLO2 (NCT01874353)
Olaparib	1/11/2019	Ovarian cancer	SOLO1 (NCT01844986)
Osimertinib	1/11/2017	Lung cancer	AURA 3 (NCT02151981)
Pembrolizumab	1/11/2018	Skin cancer	KN054 (NCT02362594)
Pembrolizumab	1/03/2022	Gastro-intestinal cancer	KEYNOTE 590 (NCT03189719)
Pomalidomide	1/11/2019	Blood cancer	OPTIMISMM (NCT01734928)
Selinexor	1/07/2021	Blood cancer	BOSTON (NCT03110562)
Trastuzumab emtansine	1/11/2019	Breast cancer	KATHERINE (NCT01772472)
Venetoclax	1/11/2018	Blood cancer	MURANO (NCT02005471)
Venetoclax	1/07/2020	Blood cancer	CLL-14 (NCT02242942)
Zanubrutinib	1/07/2021	Blood cancer	ASPEN (NCT03053440)

Source: compiled during the project.

Based on the estimated or actual completion dates posted on clinicaltrials.gov, of the 25 trials that had not reported their final OS data at the time of the CSR in July 2023, 12 trials remain incomplete (4 have final OS published), and 13 trials appeared to be completed with final OS published for 9 of those trials at the time of the pilot. Of the 13 trials that appeared to be complete, there were 4 trials with completion dates posted on clinicaltrials.gov and no publication of final OS identified in the literature search. These were screened for suitability for a data request from the sponsor. Data requests were not considered necessary for the following 3 trials:

- KEYNOTE 590 (NCT03189719 for pembrolizumab, March 2022 PBAC meeting) had published 5-year outcomes, with the OS rate being 11% in the treated group and 3% in the control group. As such, the OS data was considered to be mature.
- CheckMate 67 (NCT01844505 for nilovumab, November 2015 PBAC meeting) had a completion date of 19th April 2024 and a record of an update being posted to clinicaltrials.gov in July 2024. However, the content of that update had not yet been verified by the website and thus was not available. A data request could be made for that trial in the future.
- KATHERINE (NCT01772472 for trastuzumab emtansine, November 2019 PBAC meeting) has a completion date of 23rd May 2024; there was conflicting information regarding the timepoint for final OS analyses. The PSD (paragraph 6.14, trastuzumab emtansine, PSD, November 2019 PBAC meeting) stated final OS analysis was expected by March 2023, however, the trial protocol stated OS would be measured up to 12 years from the first patient in (April 2013) and a recent conference abstract reported final analysis for the surrogate outcome, but interim analysis for OS, stating that OS follow-up is ongoing. According to the recent publication, OS data remain immature, with 88% and 83% of patients in the treatment and control arms, respectively, still alive. Due to the immaturity of the data and the statistically significant interim OS HR reported in the publication, this trial will remain in the monitoring system. A data request could be made to the sponsor in the future.

There was 1 trial (ASCEND 5, NCT01828112 for ceritinib, November 2016 PBAC meeting) that appeared to be completed as of June 2024, however, no evidence of the final OS data was found in the public domain. Table 5 summarises the submission recommended by the PBAC and the supporting trial (ASCEND 5 trial) with interim/immature OS data, where additional OS data was requested from the sponsor. **Redacted text.**

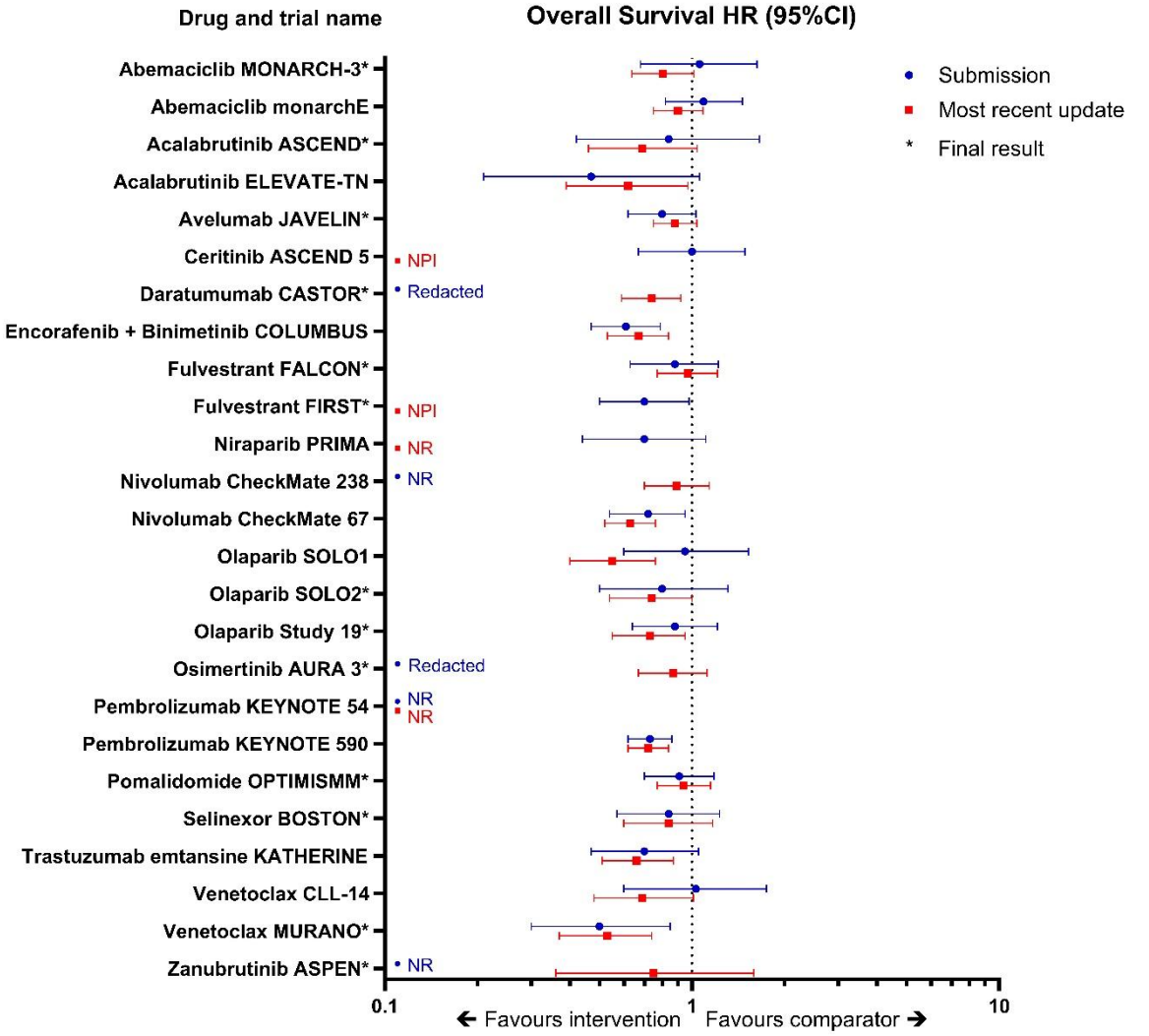
Table 5: Submissions by drug-indication pairs with trials for additional OS data request from the sponsor (pilot OS monitoring).

Drug name	Indication	broad cancer type	PBAC meeting date	Trial name	NCT	Study start date	Study end date	Date of most recent interim analysis
Ceritinib	anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic NSCLC	Lung cancer	1/11/2016	ASCEND 5	NCT01828112	28/06/2013	10/11/2023	7/6/2016 (PSD / Shaw 2017)

Source: compiled during the project.

A comparison between the OS HR reported for the pivotal trials in the submissions included in the pilot study and the most recently published OS HR identified during the literature search is presented in Figure 2.

Figure 2. Hazard ratios for overall survival at submission and at the most recent publication up to July 2024 (pilot OS monitoring).



Source: Compiled during the review from OS HR reported in PSDs and publications (see Attachment 4).
CI=confidence interval; HR=hazard ratio; NPI=no further publications identified in public domain; NR=not reported in submission/recent publication; OS=overall survival; Pending=data requested from sponsor; Redacted=redacted in Public Summary Document (PSD).
* Final result=publication indicated OS analyses were final
NB Reported only where HRs for OS were publicly available

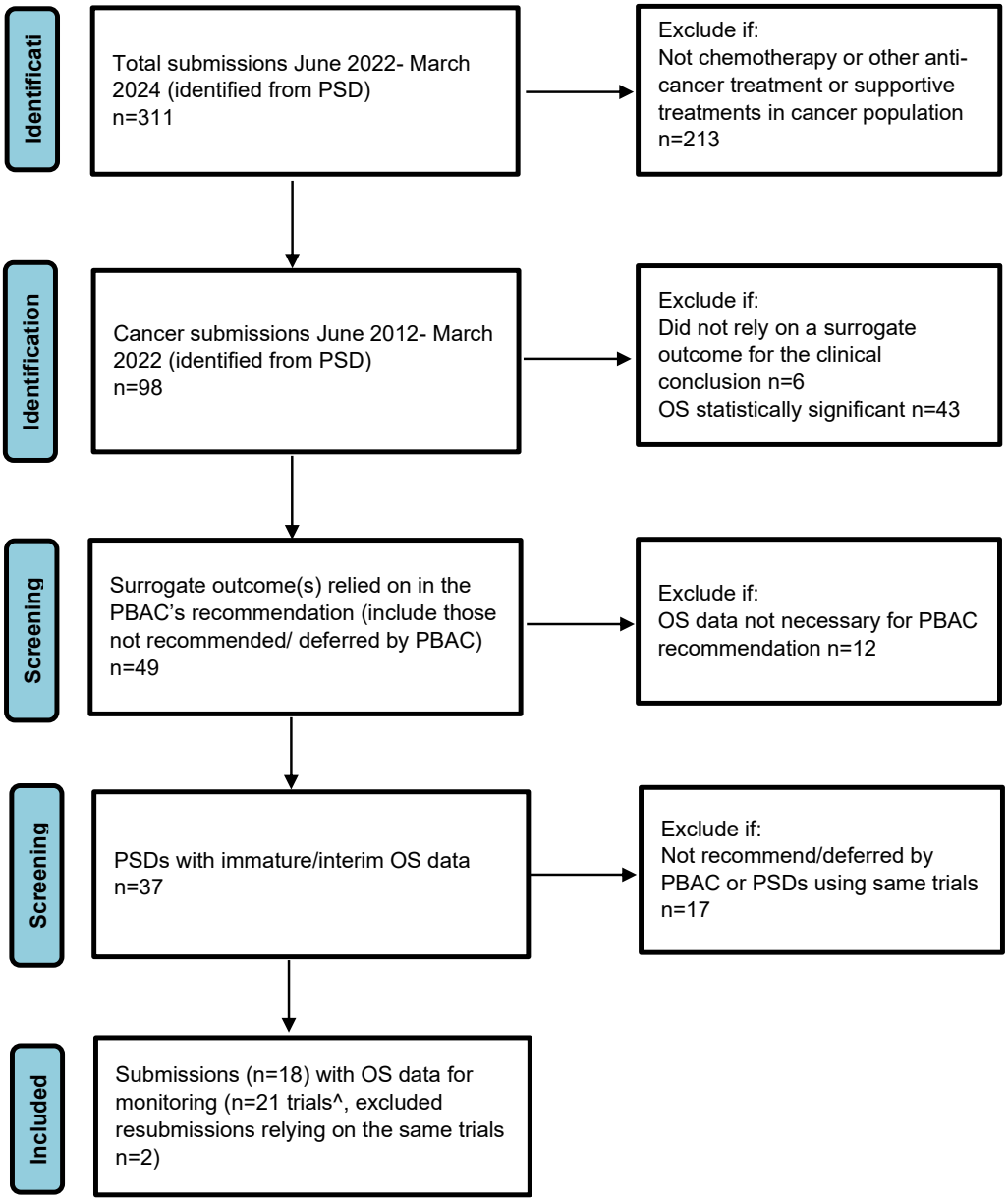
For the 13 trials with final OS data published, the interim OS at the time of submission was redacted or not reported in 3 PSDs, and the OS reported in the PSD was later deemed final for 1 trial. A comparison between the interim and final OS results for the 9 trials with accessible HRs reported for both timepoints is presented in Table A1 in Attachment 1. The comparison shows that the interim HRs were generally consistent with final HRs, with the exception of 2 trials for which HR improved >0.1, but remained statistically insignificant, and 1 trial which reported a statistically significant final OS HR. The point estimate for OS HR remained in favour of the submission drug for all trials, however there was a trend (<0.1) towards the null for 2 trials classified as 'consistent'. Of the 3 trials with OS HR redacted or not reported in the submission PSD, final OS HR reached statistical significance for 1 trial and favoured the submission drug, but was not statistically significant for the other 2 trials. A comparison including the redacted Committee in Confidence results in the PSDs is presented in the Committee In Confidence Section of the report.

OS monitoring project (June 2022-March 2024 submissions)

Review of PSDs

Figure 3 presents the PRISMA flow diagram for selection of relevant cancer drug submissions from PSDs.

Figure 3: PRISMA flow diagram



Source: complied during the review based on publication by Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. Doi: 10.1136/bmj.n71
HR=hazard ratio; OS=overall survival; PBAC=Pharmaceutical Benefits Advisory Committee; PSD=public summary documents; n=number.
^ including 5 single-arm studies

A total of 311 submissions with a PSD were identified between June 2022 and March 2024 (inclusive), of which 213 were not a chemotherapy, anti-cancer therapy or supportive treatment in a cancer population (i.e. treatments for pain, nausea or adverse events). Out of the 98 cancer submissions considered between June 2022 and March 2024, reporting in the PSDs suggested that PBAC's recommendation at least partially relied on a surrogate outcome for 92 submissions. Of these submissions, 43 provided evidence of a statistically significant impact on OS in addition to the surrogate evidence. This left 49 submissions in which the PBAC's recommendation was primarily based on the surrogate outcome. Within the 49 submissions, 12 reported no OS data, leaving 37 submissions with trials reporting immature or interim OS data. Of these, 17 submissions were deferred or not recommended, leaving 20 submissions matching the inclusion criteria for the study. Excluding resubmissions relying on the same trials, the resultant 18 submissions for cancer medicines recommended by the PBAC relying on 21 trials (including 5 single-arm studies) reporting immature/interim OS data were included for further monitoring of OS data. Attachment 2 summarises the number of submissions with interim/immature OS trial results, by cancer type and PBAC recommendations from June 2022 to March 2024.

Within the 49 submissions between June 2022 and March 2024 that relied on a surrogate, the PBAC had considered 27 drugs for 15 broad cancer indications. Of the 49 submissions, 59.2% (29/49) received a positive recommendation and 40.8% (20/49) were not recommended by the PBAC. Of the submissions with a positive PBAC recommendation 65.5% (19/29) presented immature OS data (i.e. from an interim trial analysis). Attachment 2 summarises the characteristics of the total submissions (N=49) that relied on surrogate outcomes for the clinical claim or PBAC recommendation.

Review of trial publications for additional OS data

Table 6 lists the 21 trials for cancer medicines included for OS monitoring, attributable to 15 submissions from June 2022 to March 2024 with a positive PBAC recommendation.

Table 6: List of trials (n=21) included for OS monitoring attributable to submissions (n=18) from June 2022-March 2024 with a positive PBAC recommendation based on immature/interim OS data

Drug	Meeting date	Broad cancer type	Trial name
Abemaciclib	1/11/2023	Breast cancer	monarchE (NCT03155997)
Acalabrutinib	1/07/2023	Blood cancer	ELEVATE-TN (NCT02475681)
Cabozantinib	1/03/2024	Renal cancer	SWOG 1500 (NCT02761057), CABOSUN II (NCT03541902)
Cabozantinib	1/03/2024	Thyroid cancer	COSMIC-311 (NCT03690388)
Dabrafenib and trametinib	1/03/2024	Brain/spine cancer	G2201 (NCT02684058)
Larotrectinib*	1/03/2024	Lung cancer, soft-tissue cancer	LOXO-001 (NCT02122913) NAVIGATE (LOXO-002) (NCT02576431)
Mobocertinib*	1/07/2023	Lung cancer	Study 101 (NCT02716116)
Niraparib	1/07/2023	Ovarian cancer	PRIMA (NCT02655016)
Nivolumab	1/11/2022	Gastro-intestinal cancer	CheckMate 577 (NCT02743494)
Nivolumab	1/07/2023	Lung cancer	CheckMate 816 (NCT02998528)
Nivolumab	1/03/2024	Bladder cancer	CheckMate 274 (NCT02632409)
Olaparib	1/07/2023	Ovarian cancer	PAOLA-1 (NCT02477644)
Pembrolizumab	1/07/2023	Breast cancer	KEYNOTE-522 (NCT03036488)
Pembrolizumab*	1/11/2023	Skin cancer	CARSKIN (NCT02883556) KN629 (NCT03284424)
Relatlimab with nivolumab	1/07/2023	Skin cancer	RELATIVITY-047 (NCT03470922)
Selinexor	1/11/2022	Blood cancer	BOSTON (NCT03110562)
Zanubrutinib	1/03/2023	Blood cancer	ALPINE (NCT03734016)
Zanubrutinib	1/03/2023	Blood cancer	SEQUOIA (NCT03336333)

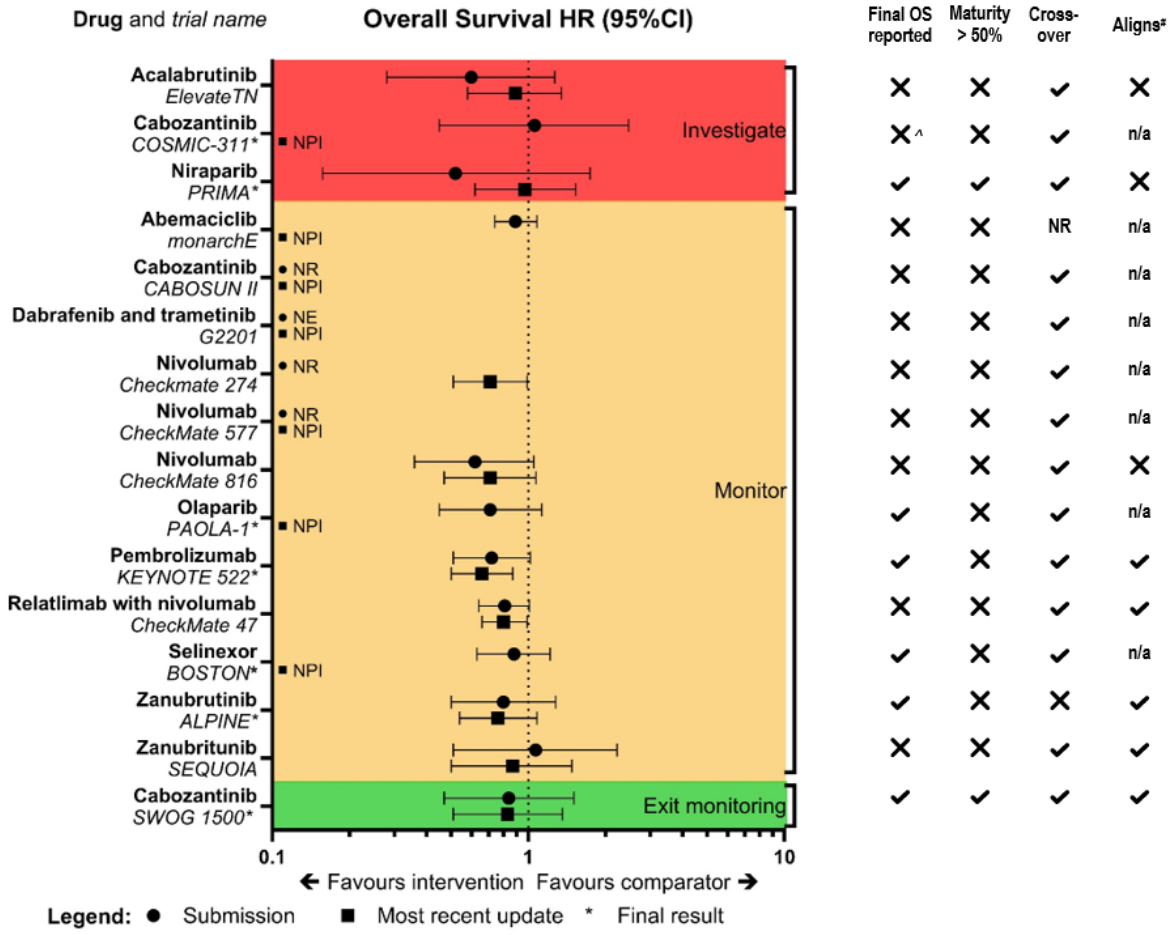
Source: compiled during the project.
Submissions include first submissions and resubmissions
* Single-arm studies.

The literature search identified final OS data for seven of the 16 included trials.

Comparison of interim/immature vs updated OS data

Figure 4 shows the HRs reported at the time of PBAC consideration (June 2022 to March 2024) for each trial of the cancer medicines included in the OS monitoring and the most recent OS data identified from published literature. The cancer medicines and trials are grouped by a traffic light alert system (denoted as red, amber or green alerts).

Figure 4. Hazard ratios for overall survival at submission and at the most recent published timepoint up to September 2024.



Source: compiled during the review from OS HR reported in PSDs and publications (See Attachment 5)

✗=no; ✓=yes; n/a = not applicable (no updated data); CI=confidence interval; HR=hazard ratio; NE=not estimable; NPI=no publications identified in the public domain; NR=not reported; OS=overall survival; PBAC=Pharmaceutical Benefits Advisory Committee.

Aligns with PBAC expectations

^ Since the primary endpoint was met, no updated OS analyses was conducted

* Final result = publication or trial protocol indicated OS analyses were final

NB Reported only where Overall Survival HRs were publicly available

Attachment 3 presents a comparison between the interim/immature OS results relied on in the submission and trials with published final OS data, as well as for trials with published updated OS results from later data cuts.

The OS HR reported at the time of PBAC consideration was later reported to be final for cancer medicines from three trials (PAOLA-1, BOSTON and COSMIC-311). Of the four trials with data available at both interim and final timepoints (PRIMA, KEYNOTE 522, ALPINE and SWOG 1500), a comparison of the interim OS results relied on in the submissions versus published final OS showed two trials (ALPINE and SWOG 1500) reported consistent final and interim OS HR. One trial reported a statistically significant result in favour of the submission drug (KEYNOTE 522). One trial (PRIMA)

reported a worse OS HR (difference of >0.1 towards the null), though the HR remained statistically insignificant.

Of the five trials reporting OS data for later data cuts, a comparison of the results for these trials with the interim OS results relied on in the submission showed two trials (CheckMate 274 and CheckMate 47) reported a statistically significant OS HR (one of which did not report OS in the submission), one trial reported improved OS HR (SEQUOIA), and two trials reported worse results (CheckMate 816 and ElevateTN), though point estimates remained in favour of the submission drug.

OS monitoring alerts

Red alert -trials for investigation

Three trials associated with three medicines were identified for further investigation. Two of the trials (ELEVATE-TN for acalabrutinib and PRIMA for niraparib) reported a worse OS HR (difference of >0.1 towards the null) at subsequent data analysis compared with the interim/immature OS data at the time of the submission. Overall, the worsened OS HR from the additional data cuts after the submission were likely to impact the primary clinical and cost-effectiveness or cost-minimisation analysis relied on in the PBAC submission.

The OS data in the COSMIC-311 trial of cabozantinib for the treatment of thyroid cancer have not been updated since submission. A 2024 publication (Capdevila 2024[6]) claimed that further analyses on OS would not be conducted due to extensive crossover. Hence, even if reported, updated OS data are unlikely to be informative for decision-making purposes.

Each of the medicines and related trials allocated to red alert status and the respective published PBAC recommendations based on these trials were further reviewed and summarised in a one-page case report. The case reports for ELEVATE-TN, PRIMA and COSMIC-311 are presented below.

[6] Capdevila J., et al Increased Progression-Free Survival with Cabozantinib Versus Placebo in Patients with Radioiodine-Refractory Differentiated Thyroid Cancer Irrespective of Prior Vascular Endothelial Growth Factor Receptor-Targeted Therapy and Tumor Histology: A Subgroup Analysis of the COSMIC-311 Study. Thyroid 2024;34(3):347-359.

Case report: ELEVATE-TN, to be investigated

In the July 2023 meeting, the PBAC recommended acalabrutinib monotherapy for the treatment of untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL). Based on ELEVATE-TN trial, comparing acalabrutinib (ACA) as monotherapy or in combination with obinutuzumab (OBIN) and obinutuzumab plus chlorambucil (OBIN+CHL), the submission claimed ACA +/- OBIN was non-inferior in effectiveness to venetoclax plus obinutuzumab (VTX+OBIN) using a matched adjusted indirect comparison (MAIC).

Analysis in the PSD

Intervention	Comparator	Broad indication	Indication	Evidence	Trials	ITC HR	95%CI
ACA	OBIN + VTX	Blood cancer	CLL, SLL	ITC	-ELEVATE-TN -CLL-14	1.13	0.56, 2.24

Trial characteristics

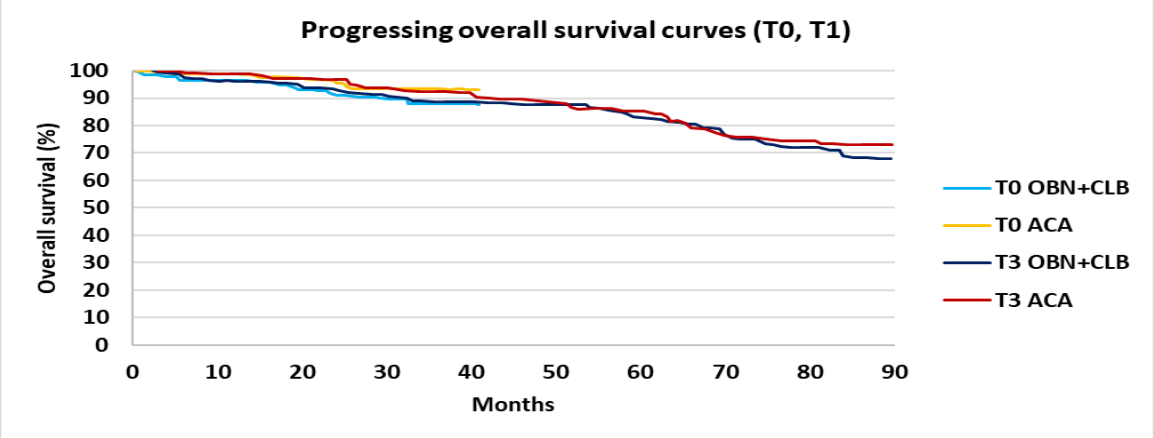
Trial name	Trial ID	Start date	End date	Group	RCT Tx1	RCT Tx2	RCT Cx
ELEVATE-TN	NCT02475681	6/26/2015	9/30/2025 *(NC)*	ITT	ACA	ACA+ OBIN	OBIN + CLB

Trial results

Time point	DCO	MFU (m)	HR (Tx/Cx)	95%CI	Alive/Tx	Alive/Cx	Final OS
Time_0 [a]	2/8/2019	28.3 [b]	**0.60**	**0.28, 1.27**	95%	92%	*No*
Time_1	NR	46.9	NR	NR	88%	88%	*No*
Time_2	10/1/2021	58.2	NR	NR	NR	NR	*No*
Time_3	3/3/2023	74.5	**0.89**	**0.58, 1.35**	72%	53%	*No*

Notes:
a Time_0 is the time of the submission.
b Kaplan-Meier curve of OS for median follow-up of 58.2 months. The submission reported HRs for median follow-up of 28.3 months.
Time_F: Not yet published.

Kaplan-Meier curves (T0, T3)



Note: Graph plotted using the KM curves presented in the PSD and Sherman et al., 2023 (refer to sources).

Findings:

- **OS outcome:** The PSD reported OS HR of 0.60 (95% CI: 0.28, 1.27) for ACA versus OBIN+CLB based on median follow-up of 28.3 months. The ESC noted the wide confidence intervals reflected the indolent nature of CLL and the small number of deaths (para 6.19, Acalabrutinib PSD, July 2023 PBAC Meeting). Additional data at 6-year follow-up (median: 74.5 months) showed a higher HR of 0.89 (95% CI: 0.58, 1.35), indicating a worsening of >0.1, though the confidence interval remained wide. Final OS has not yet been published.
- **Contamination:** Crossover to ACA was possible for OBIN+CLB patients following progression.
- **Maturity:** Not mature (<50% dead in both arms).
- **Assessment:** Given the immaturity of the data, further monitoring and investigation is necessary.
- **Impact:** These findings may alter the results of the ITC, potentially impacting the cost-effectiveness analysis.

Recommendation to the PBAC: The additional OS HR from the latest DCO worsened compared to the OS presented in the July 2023 submission. While the final OS has not yet been published, if similar result is assumed for the final OS then the PBAC may wish to re-evaluate the ITC analysis with the final OS and the CMA versus VTX+OBIN including any RSA implemented to manage risks to the cost-effectiveness.

Abbreviations: ACA=Acalabrutinib, CLB=chlorambucil, CI=confidence interval, CLL=lymphocytic leukaemia, Cx=comparator, DCO=data cut-off; HR=hazard ratio, ICER=incremental cost-effectiveness ratio, ITC=indirect treatment comparison, m=months, MFU=median follow-up, NR=not reported, OBIN=obinutuzumab, OS=overall survival, RCT=randomised clinical trial, RSA=risk sharing arrangements, SLL=small lymphocytic lymphoma, Tx=treatment, VTX=venetoclax.

References *(Date search was conducted: 07/10/2024):*

1. *Acalabrutinib PSD July 2023. https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2023-07/files/acalabrutinib-psd-july-2023.pdf.*
2. *Sharman JP, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet. 2020 Apr 18;395(10232):1278-1291.*
3. *Sharman JP, Egyed M, Jurczak W, et al Acalabrutinib +/- obinutuzumab versus obinutuzumab + chlorambucil in treatmentnaive chronic lymphocytic leukemia: Five-year follow-up of ELEVATE-TN. J. Clin. Oncol. 2022;40(16 Supplement 1):no pagination.*
4. *Sharman JP, et al. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. Leukemia. 2022 Apr;36(4):1171-1175.*
5. *Sharman JP, et al Acalabrutinib +/- Obinutuzumab Vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of Elevate-TN. Blood 2023;142(Supplement 1):636.*

Case report: PRIMA, to be investigated

In the July 2023 meeting, the PBAC recommended niraparib for the treatment of advanced epithelial ovarian, fallopian tube or primary peritoneal cancer, on a cost-minimisation basis versus olaparib (near market comparator). The PBAC considered that based on the primary evidence from PRIMA trial, niraparib had superior efficacy in terms of PFS compared to placebo, however the OS data were immature. Unanchored side-by-side comparison of niraparib (PRIMA) with olaparib + bevacizumab (PAOLA-1) was used to inform the non-inferior efficacy of niraparib vs olaparib.

Analysis in the PSD

Intervention	Comparator	Broad indication	Indication	Evidence	Trials	ITC HR	95%CI
Niraparib	placebo	Ovarian cancer	Ovarian, fallopian tube or peritoneal cancer	ITC[b]	-PRIMA -PAOLA-1	n/a[b]	n/a[b]

Trial (of interest) characteristics

Trial name	Trial ID	Start date	End date	Group	RCT Tx1	RCT Tx2	RCT Cx
PRIMA	NCT02655016	7/11/2016	9/25/2024	BRCAwt HRD+	Niraparib	-	placebo

Trial (of interest) results

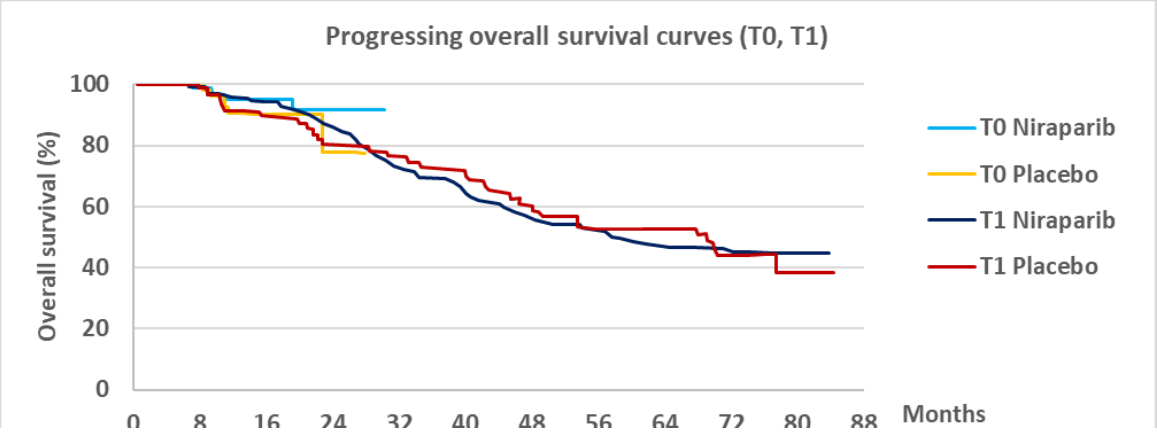
Time point	DCO	MFU (m)	HR (Tx/Cx)	95%CI	Alive/Tx	Alive/Cx	Final OS
Time_0 [a]	17/05/2019	13.8	0.52	0.16, 1.75	93.68%	89.09%	*No*
Time_F	08/04/2024	73.9	0.97	0.62, 1.53	NR	NR	*Yes*

Notes:

a Time_0 is the time of the submission.

b The comparison to olaparib, a near market comparator (considered appropriate by the PBAC) was based on an unanchored side-by-side comparison of niraparib (PRIMA trial) with olaparib + bevacizumab (PAOLA-1 trial).

Kaplan-Meier curves (T0, T1)



Findings:

- **OS outcome:** The PSD reported OS HR of 0.52 (95% CI: 0.16, 1.75) for niraparib versus placebo based on a median follow-up of 3.5 years, which was not significant, with wide confidence interval reflecting a high level of uncertainty, possibly due to significant censoring (para 6.50, niraparib PSD, July 2023). Final OS was not published at the time of the July 2023 addendum to the March 2023 PSD, but results of the final prespecified OS analysis have since been reported. The 73.9-month median follow-up at DCO of 8 April 2024 revealed a higher HR of 0.97 (95% CI: 0.62, 1.53), indicating a worsening of >0.1.
- **Contamination:** Patients who discontinued study treatment could receive subsequent therapies during follow-up, including PARP inhibitors. Subsequent poly (ADP-ribose) polymerase inhibitor therapy was received by 11.7% and 15.8% of niraparib patients and 37.8% and 48.4% of placebo patients in the overall and HRd populations, respectively. Statistical analyses were conducted to estimate the adjusted OS treatment effect, modelling scenarios where treatment switching had not occurred, but results were not reported for the HRD+ and BRCAwt subgroup.
- **Maturity:** 62.5%

- **Assessment:** At the time of submission, OS data for the HRD-positive BRCAwt subgroup (median follow-up: 13.8 months) were immature. In contrast, final mature OS data (median follow-up: 73.9 months) demonstrated a considerable shift favouring the comparator, with the HR point estimate from the submission falling outside the range of the final OS 95%CI. PFS was consistent for HRD+/BRCAwt patients between PBAC consideration, DCO November 2021, PFS HR 0.66 (95%CI: 0.437, 0.999), and the most recent data cut, April 2024, PFS HR 0.67 (95%CI: 0.45, 1.00). OS for the ITC comparator, olaparib, from PAOLA-1 trial was not significant (OS HR: 0.71, 95%CI: 0.45, 1.13). The PBAC recommended niraparib based on revised CMA versus olaparib in July 2023. The March 2023 submission presented a modelled economic evaluation (CUA) and CMA for niraparib vs olaparib. The PBAC considered that the CUA was not reliable for decision-making. In particular, the method for estimating OS in the niraparib arm based on results from the olaparib SOLO-1 trial (BRCAm population) introduced a high degree of uncertainty (para 7.15, niraparib PSD, July 2023). The estimated OS HRs were 0.69 for the HRD-positive BRCAwt and 0.80 for the HRD-negative cohorts.
- **Impact:** The additional OS findings may impact the ITC results and the accepted CMA vs olaparib.

Recommendation to the PBAC: In the July 2023 meeting, the PBAC recommended niraparib based on a revised CMA, noting that niraparib was likely to be non-inferior to olaparib in the HRD+ BRCAwt setting. Given the final mature OS HR worsened compared to the OS presented in the March 2023 and July 2023 submission, the PBAC may wish to re-evaluate the ITC analysis with the final OS and the revised CMA versus olaparib including the RSA that applies.

Abbreviations: BRCAwt=BRCA wild type, CI=confidence interval, CMA=cost minimisation analysis; CUA=cost utility analysis; Cx=comparator, DCO=data cut-off, HR=hazard ratio, HRD=homologous recombination deficiency. ICER= incremental cost-effectiveness ratio, ITC=indirect treatment comparison, NA=not applicable, NC=not completed, NR=not reported, m=months, MFU=median follow-up, OS=overall survival, PBAC=Pharmaceutical Benefits Advisory Committee; PFS=progression-free survival; PSD=Public Summary Document; RCT=randomised clinical trial, RSA=risk sharing arrangements, Tx=treatment.

References *(Date search was conducted: 16/09/2024):*

1. Niraparib PSD (July 2023). URL: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2023-03/files/niraparib-psd-march-2023-july-2023.pdf. Accessed: 16/09/2024.

2. Monk B, Barretina-Ginesta M, Pothuri B et al. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from PRIMA/ENGOT-OV26/GOG-3012 trial. Annals on Oncology. 2024. URL: https://www.annalsofoncology.org/article/S0923-7534(24)03762-1/fulltext. Accessed: 16/09/2024.

Case report: COSMIC-311

In the March 2024 meeting, the PBAC recommended cabozantinib for the treatment of locally advanced or metastatic differentiated thyroid carcinoma (DTC). Cabozantinib was considered superior in effectiveness compared to placebo in terms of ORR and PFS based on evidence from the COSMIC-311 trial, however, superiority in terms of OS was uncertain. Clinical evidence was also presented in the submission considered at the November 2023 PBAC Meeting.

Analysis in the PSD

Intervention	Comparator	Broad indication	Indication	Evidence	Trials	ITC HR	95%CI
Cabozantinib	Placebo (BSC)	Thyroid cancer	Differentiated thyroid cancer (DTC)	RCT	COSMIC-311	n/a	n/a

Trial characteristics

Trial name	Trial ID	Start date	End date	Group	RCT Tx1	RCT Tx2	RCT Cx
COSMIC-311	NCT03690388	5/10/2018	31/12/2024	Patients with prior lenvatinib	cabozantinib	n/a	placebo

Trial results

Time point	DCO	MFU (m)	HR (Tx/Cx)	95%CI	Alive/Tx	Alive/Cx	Final OS
Time_0[a]	2/2/2021	10.1	1.06	0.45, 2.47	75	76	*Yes*[b]

Notes:
a Time_0 is the time of the submission.
b OS reported at submission was not 'final', however, further analyses are unlikely due to crossover (Capdevila 2024).

Findings:

- **OS outcome:** PBAC considered that the superiority of cabozantinib in terms of OS was uncertain due to patients randomised to placebo receiving cabozantinib, the relatively short follow up and the high number of observations that were censored (para 7.10, November 2023 PSD). No updated OS reports were identified in the literature search.
- **Contamination:** 40 of 88 (45%) patients in the placebo arm crossed over to receive open label cabozantinib. For the ITT analyses, OS in the placebo arm was confounded by cross-over to active treatment with open-label cabozantinib following progression (para 6.21, November 2023 PSD). After adjusting for crossover, OS HR remained not significant (HR 0.98; 95%CI 0.24, 3.91) (Para 7.9, November 2023 PSD).
- **Maturity:** At DCO, OS data were immature. While OS was included in COSMIC-311 as an additional endpoint, the study was not powered for OS. Since the primary endpoint was met, and since the study underwent protocol approved crossover from placebo to cabozantinib, it has been determined that no meaningful results can be obtained by updated OS analyses comparing the cabozantinib arm with the placebo arm (Capdevila 2024).
- **Assessment:** The PBAC previously considered for cabozantinib that "The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies as the magnitude of the OS benefit was uncertain" (para 5.2, cabozantinib, PSD, March 2024). While it is unlikely that further OS analyses will be conducted, mainly due to the extent of crossover from the placebo arm, COSMIC-311 trial does not fullfill the requirements to exit monitoring and hence will remain in the OS monitoring system.
- **Impact:** Unclear, however, the PBAC considered that there was a clinical need for additional treatments in this setting, and that the financial impact was small (para 5.1, March 2024 PSD).

Recommendation to the PBAC: Given it is unlikely further OS analyses will be conducted due to the extent of crossover from the placebo arm, and the uncertain OS benefit, the PBAC may wish to consider whether COSMIC-311 should remain in the monitoring system.

Abbreviations: BSC=best supportive care, CI=confidence interval, Cx=comparator, DCO=data cut-off, HR=hazard ratio, ICER=incremental cost-effectiveness ratio, ITC=indirect treatment comparison, ITT=intention to treat, n/a=not applicable, NCCN=National Comprehensive Cancer Network, nccRCC=non-small cell renal cell carcinoma, NR=not reported, m=months, MFU=median follow-up; OS=overall survival; PBAC=Pharmaceutical Benefits Advisory Committee; PSD=Public Summary Document; RCT=randomised clinical trial, Tx=treatment

References *(Date search was conducted: 09/10/2024):*

1.Capdevila J., et al Increased Progression-Free Survival with Cabozantinib Versus Placebo in Patients with Radioiodine-Refractory Differentiated Thyroid Cancer Irrespective of Prior Vascular Endothelial Growth Factor Receptor-Targeted Therapy and Tumor Histology: A Subgroup Analysis of the COSMIC-311 Study. Thyroid 2024;34(3):347-359.

Amber alert – trials for further monitoring

Twelve trials have been identified for ongoing monitoring. The main reasons these trials remain in the monitoring system include that the literature search did not find updated OS data since the submission, OS data were immature, and the trial remains active with ongoing follow-up (i.e. registered end data not reached). Table 7 summarises the trials included for further monitoring.

Table 7: Trials identified for further monitoring (amber alert)

Drug name (trial), PBAC meeting^	Time	DCO date	OS HR (95%CI)	%alive - treatment	%alive - control	Trial start date#	Trial end date#
Abemaciclib (*monarchE*), Nov 2023	T0	07/03/2023	0.89 (0.74, 1.08)	92.3	91.3	07/12/2017	28/05/2029
Dabrafenib and trametinib (*G2201*), Mar 2024	T0	23/08/2021	NE	100 (LGG) 65.9 (HGG)	97.3	28/12/2017	28/04/2023
Nivolumab (*Checkmate 816*), Jul 2023	T0	14/10/2022	0.62 (0.36, 1.05)	78.0	64.0	03/04/2017	08/11/2028
As above	T1	23/02/2024	0.71 (0.47, 1.07)	71	58.0	As above	As above
Nivolumab (*Checkmate 274*), Mar 2024	T0	08/09/2022	NR	59	48.7	22/03/2016	27/05/2027
As above	T1	NR[c]	0.71 (0.51, 0.99)	59	49	As above	As above
Pembrolizumab (*KEYNOTE 522*), Jul 2023	T0	23/03/2021	0.72 (0.51, 1.02)	85.9	89.8	03/07/2017	30/09/2025
As above	T1	22/03/2024	0.66 (0.50, 0.87)	85.3	78.2	As above	As above
Selinexor (*BOSTON*), Nov 2022	T0	01/02/2021	0.88 (0.63, 1.22)	65.1	61.4	24/05/2017	12/05/2022
Olaparib (*PAOLA-1*), Jul 2023	T0	22/03/2022	0.71 (0.45, 1.13)	54.6	41.8	05/06/2015	22/03/2022
Zanubritunib (*SEQUOIA*), Mar 2023	T0	05/07/2021	1.07 (0.51, 2.22)	93	94	31/10/2017	09/2026
As above	T1	31/10/2022	0.87 (0.50, 1.48)	89.4	88.3	As above	As above
Relatlimab with nivolumab (*CA224047*), Jul 2023	T0	10/01/2021	0.81 (0.64, 1.01)	80.8	74.3	04/11/2018	16/12/2025
As above	T1	NR	0.82 (0.67, 1.02)	52	43	As above	As above
As above	T2	19/10/2023	0.80 (0.66, 0.99)	48.7	39.4	As above	As above
Zanubrutinib (*ALPINE*), Mar 2023	T0	01/12/2021	0.8 (0.5, 1.28)	89.9	87.7	11/01/2018	28/02/2024
As above	T1[a]	08/08/2022	0.76 (0.51, 1.11)	85.3	81.5	As above	As above
As above	Tx[b]	15/05/2023	0.75 (0.54, 1.05)	82.6	79.7	As above	As above
Cabozantinib (*CABOSUN II*), Mar 2024	T0	30/06/2021	NR	40	59	15/05/2018	31/07/2025
Nivolumab (*Checkmate 577*), Nov 2022	T0	01/02/2021	NR	NR	NR	14/07/2016	11/10/2025

DCO=data cut-off; HGG=high grade glioma; HR=hazard ratio; LGG=low grade glioma; NR=not reported; OS=overall survival; PBAC=Pharmaceutical Benefits Advisory Committee; T0=time of submission; Tn=data cut at subsequent timepoint n=1, 2 , 3 etc.

^ PBAC meeting date in which drug was recommended for listing on the PBS.

Expected or actual dates from clinicaltrials.gov.

a Study indicated final analysis.

b extended follow-up

c Possibly from the same data cut as the submission given the similar % alive, however the data cut-off date was not reported in the publication (conference abstract).

Amber alert – trials to remain in the monitoring system

Twelve trials were allocated to amber alert status due to the trial being ongoing or OS data remaining immature. Two examples of trials allocated amber alert status are outlined below.

KEYNOTE-522

In the July 2023 meeting, the PBAC recommended pembrolizumab for the treatment of breast cancer based on evidence from the KEYNOTE-522 trial. The PBAC accepted the claim of superior comparative effectiveness with pembrolizumab plus chemotherapy in terms of event-free survival

compared to chemotherapy alone, however overall survival was immature. The PBAC had requested that OS data from KEYNOTE-522 be provided when it is available (paragraph 5.4, pembrolizumab PSD July 2023 PBAC meeting).

At the time of the interim analysis (data cut-off date 23 March 2021), with a median follow-up of 37.8 months, the proportions alive in the treatment and control arms were 85.9% and 89.8%, respectively. In the final analysis (data cut-off date 22 March 2024), at a median follow-up of 75.1 months, median survival was not yet reached, and the proportions alive in the treatment and control arms were 85.3% and 78.2%, respectively. The September 2024 report from the KEYNOTE-522 trial reported a significantly improved final OS result (HR: 0.66, 95%CI: 0.50, 0.87) compared to the interim analysis (HR: 0.72, 95%CI: 0.51, 1.02) considered at the March 2023 and July 2023 PBAC meeting.

Given the final analysis from KEYNOTE-522 showed significant survival benefit in favour of the submission drug, but the OS data remain immature (and the registered end date of the trial has not been reached), the trial will remain in the OS monitoring system.

● *G2201*

Results from the G2201 trial were relied on in the March 2024 submission for dabrafenib and trametinib (D+T) in the treatment of paediatric patients with BRAF V600E mutation positive low grade glioma (LGG) and high grade glioma (HGG). The LGG component of the trial was an open label RCT of D+T versus carboplatin and vincristine chemotherapy. The HGG component of the trial was a single-arm study. The submission presented results from an interim data cut (August 2021), and the sponsor provided results from the final CSR (dated 28th September 2023) with the Pre-Sub-Committee Response (PSCR). OS data remained immature at the final planned analysis.

In the LGG component, no deaths had occurred in the D+T arm and 1 death in the comparator arm, hence the OS HR was not estimable (para 6.24, PSD, March 2024 PBAC meeting). PFS in the LGG component at the final analysis was consistent with PFS at interim analysis (para 6.20, PSD, March 2024 PBAC meeting).

In the HGG arm, median OS was not estimable (para 6.24, March 2024 PSD): median survival had not been reached as 17/41 patients (41.5%) had died at the final planned analysis (median follow-up 45.2 months). PFS in the HGG component was consistent at both data cuts (para 6.31, PSD, March 2024 PBAC meeting).

Redacted text. Even though G2201 has concluded, it is recommended that it remain in the monitoring system due to the immaturity of the data. Longer term follow-up data may be published in the future.

Green alert – trials to exit monitoring

One trial was identified to exit the monitoring system. In the SWOG 1500 trial of cabozantinib for renal cancer, OS was mature (73%) at Time_1 DCO (30 September 2023), which was reported as the final OS analysis. The additional 3 years' data showed OS HR (0.83, 95%CI: 0.51, 1.36) remained consistent with the OS HR (0.84, 95%CI: 0.74, 1.08) considered by PBAC. Thus, further monitoring may have low value and not be necessary.

The case report for SWOG 1500 is presented below.

Case report: SWOG 1500

In the March 2024 meeting, the PBAC recommended cabozantinib for the treatment of non-clear cell renal cell carcinoma (nccRCC). The submission was based on 'frame of reference' comparison between cabozantinib versus sunitinib in the ccRCC setting from the SWOG 1500 trial (also known as PAPMET), and cabozantinib versus sunitinib in the nccRCC setting in the CABOSUN II trial. The CABOSUN II trial remains in the OS monitoring system.

Analysis in the PSD and identified in the literature search

Intervention	Comparator	Broad indication	Indication	Evidence	Trials	ITC HR	95%CI
cabozantinib	sunitinib	Renal cancer	nccRCC	RCT	SWOG 1500	n/a	n/a

Trial (of interest) characteristics

Trial name	Trial ID	Start date	End date	Group	RCT Tx1	RCT Tx2, Tx3 [b]	RCT Cx
SWOG 1500	NCT02761057	25/7/2016	12/12/2024	ITT ccRCC	Cabozantinib	Crizotinib, savolitinib	Sunitinib

Trial (of interest) results

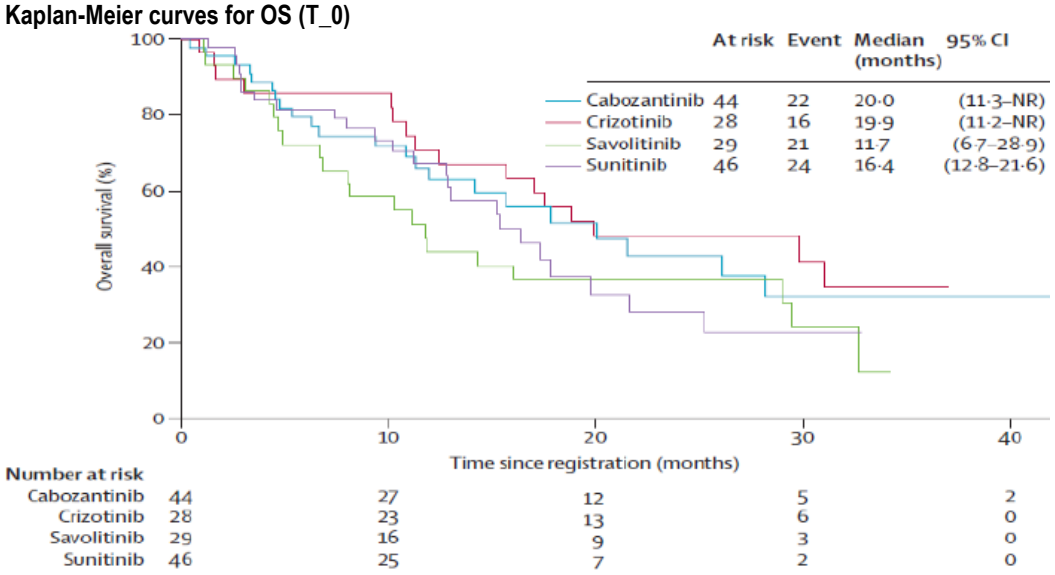
Time point	DCO	MFU (m)	HR (Tx/Cx)	95%CI	Alive/Tx	Alive/Cx	Final OS
Time_0 [a]	16/10/2020	NR	0.84	0.47, 1.51	50.00	47.83	*No*
Time_1	30/9/2023	17.5	0.83	0.51, 1.36	29.55	23.91	*Yes*

Notes:

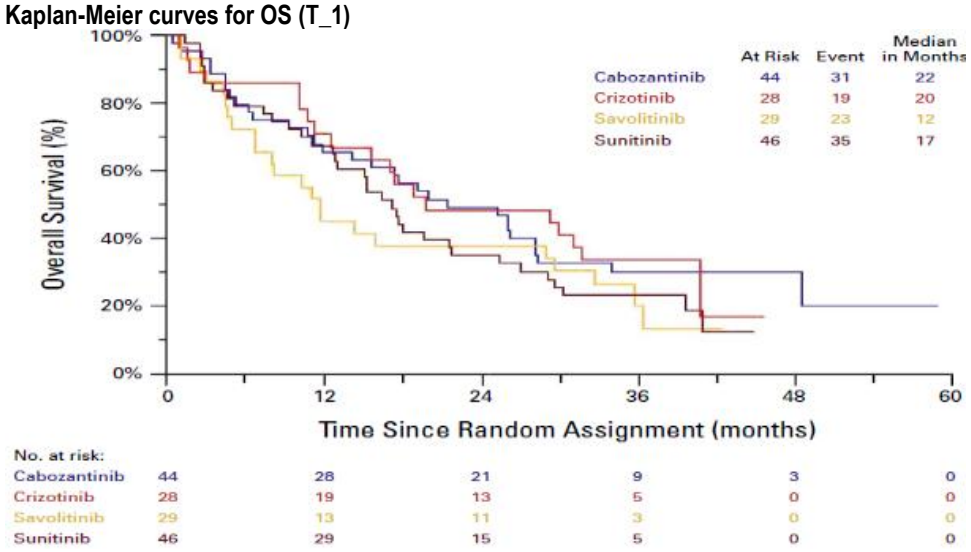
a Time_0 is the time of the submission.

b Crizotinib and Savolitinib study arms were closed due to futility.

Kaplan-Meier curves for OS (T_0)



Kaplan-Meier curves for OS (T_1)



Sources: Time_0: Figure 3, PSD (Cabozantinib – nccRCC, PSD, March 2024 PBAC Meeting); Time_1: Figure 1B, Barata 2024.

Findings:

- **OS outcome:** OS landmark estimates for cabozantinib and sunitinib were 50% versus 39% at 24 months and were 32% versus 28% at 36 months. Final OS HR was consistent with the OS HR considered by the PBAC. The PBAC considered the claim of non-inferior OS with sunitinib was reasonable (para 6.4, cabozantinib-nccRCC, PSD, March 2024 PBAC Meeting).
- **Contamination:** 17/44 patients (39%) on cabozantinib and 20/46 (43%) on sunitinib received subsequent anticancer therapy.
- **Maturity:** OS data were mature. At the time of final OS analysis, no patients remained on protocol treatment, 73% of patients in the cabozantinib and sunitinib arms had died, and the number of patients at risk was zero in both groups.
- **Impact:** The updated findings were consistent with the interim OS results, so the cost-effectiveness of cabozantinib in nccRCC patients is unlikely to be impacted.

Action for the PBAC: Given the maturity of OS data, further monitoring of SWOG 1500 trial may not be necessary.

Abbreviations: CI=confidence interval, Cx=comparator, HR=hazard ratio, ICER=incremental cost-effectiveness ratio, ITC=indirect treatment comparison, NR=not reported, m=months, MFU=median follow-up, nccRCC=non-clear cell renal cell carcinoma, OS=overall survival; PBAC=Pharmaceutical Benefits Advisory Committee; PSD=Public Summary Document; RCT=randomised clinical trial, Tx=treatment.

References *(Date search was conducted: 09/10/2024):*

1. Barata, P., et al. (2024). Final Overall Survival Analysis of S1500: A Randomized, Phase II Study Comparing Sunitinib With Cabozantinib, Crizotinib, and Savolitinib in Advanced Papillary Renal Cell Carcinoma. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology.

Review of single arm studies for additional OS data

There were 3 submissions for 3 drug-indication pairs, relying on a total of 5 single-arm clinical studies, recommended by the PBAC.

🔴 *Study 101* (red alert status)

Mobocertinib, was recommended at the July 2023 PBAC meeting based on the results of the Phase I/II Study 101 (NCT02716116). However, the drug was not subsequently PBS listed because it was voluntarily withdrawn worldwide, based on its failure to meet the primary endpoint of progression-free survival (PFS) in the phase III EXCLAIM-2 trial (NCT04129502), which compared mobocertinib to platinum-based chemotherapy.[7,8]

Action for the PBAC: Given that mobocertinib was not PBS listed due to the drug being withdrawn from the market, further monitoring of the mobocertinib study may not be necessary.

🟡 *CARSKIN and KEYNOTE-629* (amber alert status)

Both studies used to support the November 2023 submission for pembrolizumab to treat squamous cell carcinoma have since published updated results: CARSKIN has published final OS, and KEYNOTE-629 has published long-term results with a median 5-year follow-up.

Action for the PBAC: Continue to monitor for updated survival data on CARSKIN because the OS data remain immature; continue to monitor KEYNOTE-629 as the most recent publication did not specify that OS analyses were final.

🟡 *LOXO-001 and NAVIGATE* (amber alert status)

Two single-arm studies, LOXO-001 (NCT02122913) and NAVIGATE (NCT02576431), which investigated the efficacy of larotrectinib in a variety of solid tumours, were used to support the March 2024 submission for larotrectinib to treat lung cancer and soft tissue sarcoma. In the submission, results from both studies were pooled, and outcomes were reported separately for each proposed indication. A third study, SCOUT, was also included in the pooled evidence for the submission. SCOUT was not included in the OS monitoring system because it was a paediatric study from which individual–level data from two participants who had reached 18 years of age were included in the pooled analysis. Monitoring OS results for the SCOUT study was not considered informative for the PBS population. One publication reporting updated OS results for the lung cancer subgroup was identified.[9] No updated results specific for soft tissue sarcoma were identified. However, two publications using real world evidence (RWE) to compare the efficacy of larotrectinib with non-tropomyosin receptor kinase (TRK) inhibitor therapies in a range of cancers were identified. One publication reported in a matching-adjusted indirect comparison (MAIC) using individual patient data from 3 larotrectinib clinical studies with published aggregate data from a US

[7] Federal Register: Takeda Pharmaceuticals U.S.A., Inc.; Withdrawal of Approval of New Drug Application for EXKIVITY (Mobocertinib Succinate) Capsule, Equivalent to 40 Milligrams Base Docket No. FDA-2024-N-3165. July 15, 2024.

[8] Hanley MJ, Camidge DR, Fram RJ, Gupta N. Mobocertinib: Mechanism of action, clinical, and translational science. Clin Transl Sci. 2024; 17:e13766. doi:10.1111/cts.13766

[9] Lin J.J., Tan D.S.W., Kummar S., et al Updated Efficacy, Safety, and Biomarker Analysis in Patients with TRK Fusion Lung Cancer Treated with Larotrectinib. J. Thorac. Oncol. 2024;19(10 Supplement):S77. doi:10.1016/j.jtho.2024.09.138

database.[10] Another publication reported on the VICTORIA study (NCT05192642), a retrospective observational study utilising patient data from 4 databases.[11] Both RWE studies reported an overall survival benefit for larotrectinib compared to standard of care.

Action for the PBAC: Continue to monitor for updated survival data on LOXO-001 and NAVIGATE as the NAVIGATE study is ongoing.

Discussion

We found that between June 2022 and March 2024, 37.8% of the submissions for cancer treatments included pivotal trials with immature/interim survival data at the time of the submission to the PBAC. Approximately half of these cancer drug submissions with immature/interim OS data received a positive recommendation from the PBAC for listing on the PBS. Trials selected for inclusion in the OS monitoring system were those where the OS data were immature at the time of PBAC consideration, the submission's clinical claim relied upon a surrogate outcome, and the submission received a positive PBAC recommendation.

The literature review conducted as part of the monitoring system found that additional survival data became available for over half (56%) of the cancer drug trials and most (80%) of the single-arm studies, which contributed pivotal evidence for submissions recommended by the PBAC based on immature/interim results. 71.4% of the trials with published final OS analysis showed consistent OS HR compared to the interim OS HR at the time of the submission. Two cancer drug trials were found to have worsened OS HR (>0.1) at subsequent data cuts to the submission, which could have important implications on the previously accepted evidence for the respective clinical claims, economic evaluations and any risk sharing arrangements implemented to manage uncertainties. For one trial, ELEVATE-TN, the final analysis is forthcoming; however, the OS data remains immature at the 6-year follow-up, reflecting the indolent nature of the disease. Ongoing monitoring of the trial is required to inform whether a re-evaluation is required and whether the PBAC should revisit their recommendations. For the PRIMA trial, the final mature survival benefit worsened compared to the interim/immature OS at the time of the submission, which suggests that a re-evaluation of the clinical and cost-effectiveness may be warranted to estimate the difference between the analyses based on the interim and the latest final data cuts. A re-evaluation would inform whether the PBAC recommendation for listing may have been different if mature data were available.

For one trial, COSMIC-311, the OS data has not been updated since the submission, and further analysis was not likely to be conducted due to extensive crossover. Even if additional data is reported, it is unlikely to be informative for decision-making purposes. Hence, COSMIC-311 could exit the monitoring system. However, we found that for another trial, the SWOG 1500 trial, the final OS data was mature, and the OS HR remained consistent with the OS HR considered by the PBAC. Therefore, further monitoring would not be necessary for SWOG 1500, and for this reason, the trial could also exit the monitoring system.

The majority of trials for cancer medicines were allocated to amber alert status and will remain in the monitoring system due to the trials being ongoing or OS data remaining immature. For example, the final analysis from KEYNOTE-522 showed a significant survival benefit in favour of the

[10] Bokemeyer C., Paracha N., Lassen U., et al Survival Outcomes of Patients With Tropomyosin Receptor Kinase Fusion-Positive Cancer Receiving Larotrectinib Versus Standard of Care: A Matching-Adjusted Indirect Comparison Using Real-World Data. JCO Precis. Oncol. 2023;7:no pagination. doi:10.1200/PO.22.00436

[11] Brose M.S., Westphalen C.B., Kehl K.L., et al Outcomes of larotrectinib compared with real-world data from non-TRK inhibitor therapies in patients with TRK fusion cancer: VICTORIA study. J. Clin. Oncol. 2024;42(16 Supplement):no pagination.

submission drug but the OS data remained immature, and the registered end date of the trial had not yet been reached. Another trial, G2201, had concluded, and final OS results were provided with the Pre-Sub-Committee Response (PSCR), however, OS data remained immature at the final planned analysis. KEYNOTE-522 and G2201 remain in the monitoring system to capture any longer-term follow-up data that may be published in the future.

The four single-arm studies, which comprised the pivotal evidence for the two drug-indication pairs which have subsequently been PBS listed were also allocated to amber alert status due to the immaturity of the data, and two of the studies are ongoing. While a comparison of the OS data in the single-arm studies was beyond the scope of this project, the literature search identified two publications using real world evidence to compare the efficacy of larotrectinib to standard of care in the treatment of solid tumours, in addition to publications arising from the studies. Both of these observational studies reported a survival benefit for larotrectinib compared to standard of care.

Our findings reflect those of a recent retrospective study by Naci et al 2024, who reported that between 2001 and 2018, 41% of new cancer drug indications with an OS outcome had immature survival data in the pivotal trials at the time of initial FDA approval. While additional survival data became available for nearly all cancer drug indications initially approved with immature data, 63% of these indications showed no statistically significant survival benefit in their approved indications. Additional survival data from pivotal trials became available after a median of 8.2 (range 5.3, 12.0) years since FDA approval. In another study, Tai et al 2021 reviewed published cancer technology appraisals by the National Institute of Health and Care Excellence (NICE) between 2015 and 2017 and found that 41% of these appraisals used immature data to inform reimbursement decisions. Tai et al 2021 also found that analyses of cancer treatments using immature survival data may result in incorrect estimates of survival benefits. A case study reconstructed the modelled economic evaluation using more mature data, showing that the ICER was halved compared to the original immature data cut.

Our project had limitations, including constraints from trial designs. We did not conduct adjustments for treatment switching or the use of subsequent treatments. Long-term OS data may be confounded by significant crossover from the control group to the treatment group at the time of disease progression or the use of other subsequent therapies after treatment discontinuation, which were not consistently reported in trial publications. While single-arm studies were included in the monitoring system, a comparison of the OS data was not performed, as additional computation to assess comparative OS was beyond the scope of this project. For submissions that relied on post-hoc subgroups, ITC, or network meta-analyses, we did not redo the analysis in the submission. We only compared the OS HR in the trial population at the time of the PBAC consideration with the updated OS HR.

Our system for monitoring OS data presents a novel approach to retrospectively review past PBAC recommendations based on immature/interim survival data compared against updated trial data to identify whether significant differences existed between interim and updated analyses. Based on the level of difference between OS HRs (i.e. consistent, improved or worsened), three categories of alerts are triggered to determine whether the cancer medicine warrants further investigation, ongoing monitoring or exit from the monitoring system. It is envisaged that the PBAC would decide which medicines and related trials enter the system, if any further investigations are warranted for trials allocated to red alert status, including the nature of those investigations, and confirm when trials allocated to green alert status no longer require monitoring and may be removed from the system.

Future work beyond the current alerts may incorporate re-evaluation of the clinical and cost-effectiveness analysis using updated OS data for trials identified. Further reviews of trials, registries, real-world observational studies or analysis of linked administrative data may be required to

provide further evidence on the long-term survival benefits of cancer drugs, where the final OS data remains immature, and the trial/s have been terminated, or crossovers or subsequent treatments contaminated long-term follow-up data. This could include a pilot re-evaluation of the change in cost-effectiveness for one of the medicines allocated to red alert status. Other studies may include investigating the frequency of reporting of survival data from clinical trials to estimate the optimal interval for monitoring. It may also be useful to measure the strength of correlation between the surrogate outcome and OS and how these change between the interim and final analysis, given that the cancer drug submissions included in the monitoring system had relied on surrogate outcomes in the clinical claim or PBAC recommendation. In addition, there may be value in using linked administrative data available in Australia, such as the Person Level Integrated Data Asset (PLIDA) to monitor the change in survival related to the listing of the cancer medicine.

Conclusion

Our findings show that most cancer drug submissions were made with immature/interim survival data. However, additional survival data became available for nearly all the pivotal trials included in the pilot and more than half of the trials and single-arm studies for medicines included in the monitoring system. While most trials with updated or final analysis showed a survival benefit for the cancer medicine consistent with the interim analysis at the time of the PBAC recommendation, a small proportion (9.5%) of trials also indicated worse long-term survival, which may impact the estimated cost-effectiveness relied on by the PBAC in the initial recommendation. As more submissions for cancer drugs are based on trials with immature/interim survival data, giving rise to clinical and cost-effectiveness uncertainty, future PBAC recommendations may consider prospectively including medicines and related trials into the OS monitoring system at the time of the recommendation and routinely review past recommendations as updated data becomes available to verify longer-term survival benefit of treatments and their implications for cost-effectiveness estimates.

Committee in Confidence Information

Text redacted.

Attachment 1: Comparison of the published final OS results versus interim OS results relied on in the submissions (pilot monitoring)

Table A1: Comparison of the published final OS results versus interim OS results relied on in submissions included in the pilot study (submissions from January 2012 to May 2022).

Cancer type	Trials^[a] with interim OS results at the time of submission and published final OS	HR consistent[c] (number of trials)	HR improved[c] (number of trials)	HR worsened[c] (number of trials)	HR reached statistical significance[b] (number of trials)
Blood cancer	4	3	1	0	0
Breast cancer	3	2	1	0	0
Lung cancer	0	-	-	-	-
Skin cancer	0	-	-	-	-
Other cancers*	3	2	0	0	1
All cancers	10	7	2	0	1

Source: compiled during the project.

^ the number of trials by drug-indication pairs (exclude resubmissions relying on the same trials).

* Other cancers submissions included ovarian (n=2) and renal cancer (n=1).

a excluding trials for which the HR for OS were not reported in the PSD and trials for which this variable was not applicable (e.g. single arm studies used as the key clinical evidence).

b in favour of the drug.

c HR consistent = HR within 0.1 difference compared to interim; HR improved = HR reduced >0.1 compared to interim; HR worsened = HR increased >0.1 compared to interim.

Attachment 2: Characteristics of cancer PSDs that relied on surrogates and included in OS monitoring project

Table A3: Number submissions with interim/immature OS trial results, by cancer type and PBAC recommendations from June 2022-March 2024.

Cancer type	Submissions	Recommended	Not recommend/ deferred	Trials^ with interim OS results at the time of submission	OS monitoring: trials^ in submissions recommended by PBAC
Bladder cancer	3	1	2	1	1
Blood cancer	5	4	1	5	4
Breast cancer	4	3	1	2	2
Ovarian cancer	5	2	3	2	2
Skin cancer	3	2	1	1	1
Other cancers*	8	5	3	6	6
All cancers	**28**	**17**	**11**	**17**	**16**

Source: compiled during the project.
OS=overall survival;
^ the number of trials by drug-indication pairs (exclude resubmissions relying on the same trials).
* Other cancers submissions included gastrointestinal cancer (n=2), lung (n=2), thyroid (n=2), brain/spine (n=1) and renal cancer (n=1).

Table A4: Descriptive statistics of all cancer PSDs that relied on surrogates (N=49) from June 2022-March 2024 (including those not recommended/ deferred by PBAC).

Variables	N (%)
Total cancer submissions that relied on surrogates (number of PSDs)	49 (100)
Total drugs	27 (55.1)
Drug-indication pairs	39 (79.6)
Recommendation	
not recommended	20 (40.8)
recommended	29 (59.2)
Recommendation	
do not list	18 (36.7)
list at price	19 (38.8)
list with Criteria	5 (10.2)
list similar in class	0
list at lower price	4 (8.2)
defer	3 (6.1)
PBAC recommend list with RSA	5 (10.2)
PBAC recommend list with managed access	0
RCT appropriate nominated comparator	30 (61.2)
Main comparator in pivotal trial	
no comparator	11 (22.4)
active comparator	16 (32.7)
placebo comparator	16 (32.7)
same drug, different dose or schedule	4 (8.2)
Bioequivalence (field left blank)	2 (4.1)
PBAC considered trial comparator appropriate:	
no	6 (12.2)
yes	30 (61.2)
not sure (NA)	11 (22.4)
Bioequivalence (field left blank)	2 (4.1)
Submission's clinical claim rely on final clinical endpoint	36 (73.5)
Surrogate	49 (100)
OS maturity	
mature	0

Variables	N (%)
immature	35 (71.4)
not reported	2 (4.1)
not applicable	12 (24.5)
OS significant	0
OS based on interim results	34 (69.4)
Submission based on ITC	21 (42.9)
PBAC accepted the ITC comparator	21 (100)
RCTs reporting OS data	44 (89.8)
Final OS results available	1 (2.3)
Final OS results significant	0

Source: compiled during the project.
ITC=indirect treatment comparison; OS=overall survival; RSA=risk sharing arrangement;

Table A5: Descriptive statistics of all cancer PSDs that relied on surrogates (N=49) from June 2022-March 2024 by recommendation.

PSDs that relied on surrogates	Not recommended N=17	Recommended N=29	Deferred N=3
If not recommended or deferred, reason for decision:			
clinical uncertainty	7 (41.2%)	0	1 (33.3%)
cost uncertainty	2 (11.85%)	0	1 (33.3%)
both	8 (47.1%)	0	1 (33.3%)
NA	0	29 (100%)	0
OS maturity:			
mature	0	0	0
immature^	13 (76.5%)	19 (65.5%)	3 (100%)
not reported	1 (5.9%)	1 (3.4%)	0
not applicable	3 (17.6%)	9 (31.0%)	0
OS based on interim results	12 (70.6%)	19 (65.5%)	3 (100%)
Final trial OS results available	1 (5.9%)	0	0
Final trial OS results available by OS maturity in the submission:			
mature OS	*0*	*0*	*0*
- Final trial OS results available	*0*	*0*	*0*
immature OS	*16*	*19*	*3*
- Final trial OS results available	*1*	*0*	*0*

Source: compiled during the project
NA=not applicable; OS=overall survival; PBAC=Pharmaceutical Benefits Advisory Committee; PSD=Public Summary Document
^ Considered 'immature' if the PSD stated that the data were immature.

Attachment 3: Comparison of the published final OS results versus interim OS results relied on in the submissions (OS monitoring project)

Table A6: Comparison of the published final OS results versus interim OS results relied on in the submission from June 2022 to March 2024

Cancer type	Trials^[a] with interim OS results at the time of submission	HR consistent[c] (number of trials)	HR improved[c] (number of trials)	HR worsened[c] (number of trials)	HR reached statistical significance[b] (number of trials)
Blood cancer	2	2	0	0	0
Breast cancer	1	0	0	0	1
Ovarian cancer	2	1	0	1	0
Other cancers*	2	2	0	0	0
All cancers	7	5	0	1	1

Source: compiled during the project.
cf=compared to; HR=hazard ratio; OS=overall survival
^ the number of trials by drug-indication pairs (exclude resubmissions relying on the same trials).
* Includes broad cancer areas, namely: renal (n=1) and thyroid (n=1).
a excluding trials for which the HR for OS were not reported in the PSD and trials for which this variable was not applicable (e.g. single arm studies used as the key clinical evidence).
b OS HR in final analysis reached statistical significance.
c HR consistent = HR within 0.1 difference compared to interim; HR improved = HR reduced >0.1 compared to interim; HR worsened = HR increased >0.1 compared to interim.

Table A7: Comparison of the published updated OS results from later data cuts versus interim OS results relied on in the submission from June 2022 to Mach 2024

Cancer type	Trials^[a] with interim OS results at the time of submission	HR consistent[c] (number of trials)	HR improved[c] (number of trials)	HR worsened[c] (number of trials)	HR reached statistical significance[b] (number of trials)
Lung cancer	1	0	0	1	0
Blood cancer	2	0	1	1	0
Skin cancer	1	0	0	0	1
Bladder cancer	1	0	0	0	1
All cancers	5	0	1	2	2

Source: compiled during the project.
cf=compared to; HR=hazard ratio; OS=overall survival
^ the number of trials by drug-indication pairs (exclude resubmissions relying on the same trials).
a excluding trials for which the HR for OS were not reported in the PSD and trials for which this variable was not applicable (e.g. single arm studies used as the key clinical evidence).
b for our sample OS in final analysis reached statistical significance.
c HR consistent = HR within 0.1 difference compared to interim; HR improved = HR reduced >0.1 compared to interim; HR worsened = HR increased >0.1 compared to interim.

Attachment 4: Relevant publications identified in the pilot literature search

Table A8: Most recent publications identified in the pilot literature search which included relevant, updated interim or final OS results

Drug	Trial name	Publication
Acalabrutinib	ASCEND (NCT02970318)	No new publication identified
Acalabrutinib	ELEVATE-TN (NCT02475681)	Sharman, J. P., Egyed, M., Jurczak, W., et al. (2023). Acalabrutinib ± Obinutuzumab Vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of Elevate-TN. Blood., 142(Supplement 1), 636–636. https://doi.org/10.1182/blood-2023-174750
Avelumab	JAVELIN (NCT02684006)	Motzer, R.J. et al. Avelumab + axitinib vs sunitinib in patients (pts) with advanced renal cell carcinoma (aRCC): Final overall survival (OS) analysis from the JAVELIN Renal 101 phase 3 trial.. *JCO* **42**, 4508-4508(2024). DOI:10.1200/JCO.2024.42.16_suppl.4508
Certinib	ASCEND 5 (NCT01828112)	No new publication identified. Sponsor contacted: no new publications to date.
Daratumumab	CASTOR (NCT02136134)	Sonneveld, P.et al., Overall Survival With Daratumumab, Bortezomib, and Dexamethasone in Previously Treated Multiple Myeloma (CASTOR): A Randomized, Open-Label, Phase III Trial. JCO 41, 1600-1609(2023). DOI:10.1200/JCO.21.02734
Encorafenib + Binimetinib	COLUMBUS (NCT01909453)	Schadendorf D., Dummer R., Flaherty K.T., et al COLUMBUS 7-year update: A randomized, open-label, phase III trial of encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF V600E/K-mutant melanoma. Eur. J. Cancer 2024;204:no pagination. doi:10.1016/j.ejca.2024.114073
Fulvestrant	FALCON (NCT01602380)	Robertson, J., Shao, Z., Noguchi, S., et al. (2023). 384MO Final overall survival analysis for fulvestrant vs anastrozole in endocrine therapy (ET)-naïve, hormone receptor-positive (HR+) advanced breast cancer (FALCON). Annals of Oncology, 34, S339–S340. https://doi.org/10.1016/j.annonc.2023.09.561
Fulvestrant	FIRST (NCT00274469)	Ellis, M.J. et al., Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRST Study. JCO 33, 3781-3787(2015). DOI:10.1200/JCO.2015.61.5831
Niraparib	PRIMA (NCT02655016)	González-Martín, A., et al., Progression-free survival and safety at 3.5 years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer, European Journal of Cancer, Volume 189, 2023, 112908. https://doi.org/10.1016/j.ejca.2023.04.024.
Nivolumab	CA209-067 (NCT01844505)	Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al., Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol. 2022 Jan 10;40(2):127-137. doi: 10.1200/JCO.21.02229.
Nivolumab	CA209238 (NCT02388906)	Ascierto, P., Del Vecchio, M., Merelli, B., et al., (2023). 1089P Adjuvant nivolumab (NIVO) vs ipilimumab (IPI) in resected stage III/IV melanoma: 7-y results from CheckMate 238. Annals of Oncology., 34. https://doi.org/10.1016/j.annonc.2023.09.2223
Olaparib	Study 19 (NCT00753545)	Friedlander, M., Matulonis, U., Gourley, C., et al., Spencer, S., Rowe, P., Mann, H., & Parry, D. (2018). Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. The British Journal of Cancer /, 119(9), 1075–1085. https://doi.org/10.1038/s41416-018-0271-y
Olaparib	SOLO2 (NCT01874353)	Poveda, A., Floquet, A., Ledermann, J. A., et al. (2021). Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Oncology., 22(5), 620–631. https://doi.org/10.1016/S1470-2045(21)00073-5

Drug	Trial name	Publication
Olaparib	SOLO1 (NCT01844986)	DiSilvestro, P. et al., Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. JCO 41, 609-617(2023). DOI:10.1200/JCO.22.01549
Osimertinib	AURA 3 (NCT02151981)	Papadimitrakopoulou VA, Mok TS, Han JY, et al. Osimertinib versus platinum-pemetrexed for patients with EGFR T790M advanced NSCLC and progression on a prior EGFR-tyrosine kinase inhibitor: AURA3 overall survival analysis. Ann Oncol. 2020 Nov;31(11):1536-1544. doi: 10.1016/j.annonc.2020.08.2100.
Pembrolizumab	KN054 (NCT02362594)	No new publication identified
Pembrolizumab	KEYNOTE 590 (NCT03189719)	Manish A. Shah et al., First-line pembrolizumab (pembro) plus chemotherapy (chemo) for advanced esophageal cancer: 5-year outcomes from the phase 3 KEYNOTE-590 study.. JCO 42, 250-250(2024). DOI:10.1200/JCO.2024.42.3_suppl.250
Pomalidomide	OPTIMISMM (NCT01734928)	https://clinicaltrials.gov/study/NCT01734928?a=84&tab=results#outcome-measures
Selinexor	BOSTON (NCT03110562)	Mateos, M., Engelhardt, M., Leleu, X., et al. (2024). Impact of prior treatment on selinexor, bortezomib, dexamethasone outcomes in patients with relapsed/refractory multiple myeloma: Extended follow-up subgroup analysis of the BOSTON trial. European Journal of Haematology., 113(2), 242–252. https://doi.org/10.1111/ejh.14223
Trastuzumab emtansine	KATHERINE (NCT01772472)	Loibl, S., et al., Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis [abstract]. In: Proceedings of the 2023 San Antonio Breast Cancer Symposium; 2023 Dec 5-9; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2024;84(9 Suppl):Abstract nr GS03-12.
Venetoclax	MURANO (NCT02005471)	https://clinicaltrials.gov/study/NCT02005471?a=83&tab=results#outcome-measures
Venetoclax	CLL-14 (NCT02242942)	Al-Sawaf, O. et al., VENETOCLAX-Obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized CLL14 study. (Abstract release date: 06/09/23) EHA Library. 06/08/2023; 387845; S145
Zanubrutinib	ASPEN (NCT03053440)	Dimopoulos M.A., Opat S., D'Sa S., et al Zanubrutinib Versus Ibrutinib in Symptomatic Waldenstrom Macroglobulinemia: Final Analysis from the Randomized Phase III ASPEN Study. J. Clin. Oncol. 2023;41(33):5099-5106. doi:10.1200/JCO.22.02830

Attachment 5: Relevant publications identified in the literature search

Table A9: Most recent publications identified in the literature search which included relevant, updated interim or final OS results

Drug	Trial name	Publication
Abemaciclib	monarchE (NCT03155997)	No relevant publications identified for PBS cohort
Acalabrutinib	ELEVATE-TN (NCT02475681)	Sharman J.P., Egyed M., Jurczak W., et al Acalabrutinib +/- Obinutuzumab Vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of Elevate-TN. Blood 2023;142(Supplement 1):636. doi:10.1182/blood-2023-174750
Cabozantinib	SWOG 1500 (NCT02761057),	Barata P, Tangen C, Plets M, et al. Final Overall Survival Analysis of S1500: A Randomized, Phase II Study Comparing Sunitinib With Cabozantinib, Crizotinib, and Savolitinib in Advanced Papillary Renal Cell Carcinoma. J Clin Oncol. 2024 Sep 10:JCO2400767. doi: 10.1200/JCO.24.00767.
Cabozantinib	CABOSUN II (NCT03541902)	No publications identified
Cabozantinib	COSMIC-311 (NCT03690388)	Capdevila J., Krajewska J., Hernando J., et al Increased Progression-Free Survival with Cabozantinib Versus Placebo in Patients with Radioiodine-Refractory Differentiated Thyroid Cancer Irrespective of Prior Vascular Endothelial Growth Factor Receptor-Targeted Therapy and Tumor Histology: A Subgroup Analysis of the COSMIC-311 Study. Thyroid 2024;34(3):347-359. doi:10.1089/thy.2023.0463
Dabrafenib and trametinib	G2201 (NCT02684058)	No publications identified. Sponsor states analyses presented in PSCR were final.
Larotrectinib^	LOXO-001* (NCT02122913) NAVIGATE (LOXO-002)* (NCT02576431)	Lin J.J., Tan D.S.W., Kummar S., et al Updated Efficacy, Safety, and Biomarker Analysis in Patients with TRK Fusion Lung Cancer Treated with Larotrectinib. J. Thorac. Oncol. 2024;19(10 Supplement):S77. doi:10.1016/j.jtho.2024.09.138+
Mobocertinib#	Study 101* (NCT02716116)	Federal Register :: Takeda Pharmaceuticals U.S.A., Inc.; Withdrawal of Approval of New Drug Application for EXKIVITY (Mobocertinib Succinate) Capsule, Equivalent to 40 Milligrams Base Docket No. FDA-2024-N-3165. July 15, 2024.
Niraparib	PRIMA (NCT02655016)	Monk B, Barretina-Ginesta M, Pothuri B et al. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarianc cancer: final overall survival results from PRIMA/ENGOT-OV26/GOG-3012 trial. Annals on Oncology 2024
Nivolumab	CheckMate 577 (NCT02743494)	No publications identified
Nivolumab	CheckMate 816 (NCT02998528)	Spicer, J. et al., Meeting Abstract: 2024 ASCO Annual Meeting , Neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) vs chemo in patients (pts) with resectable NSCLC: 4-year update from CheckMate 816
Nivolumab	CheckMate 274 (NCT02632409)	https://www.urotoday.com/conference-highlights/eau-2024/eau-2024-bladder-cancer/150967-eau-2024-extended-follow-up-from-checkmate-274-including-the-first-report-of-overall-survival-outcomes.html
Olaparib	PAOLA-1 (NCT02477644)	No publications identified
Pembrolizumab	KEYNOTE-522 (NCT03036488)	Schmid P, Cortes J, Dent r, et al. Overall Survival with Pembrolizumab in Early-Stage Triple-Negative Breast Cancer NEJM DOI: 10.1056/NEJMoa2409932 (Published 15/9/2024 no pagination as yet)
Pembrolizumab	CARSKIN* (NCT02883556)	Maubec, E., et al. "1139P Final results of a phase II study of pembrolizumab as first-line treatment in advanced cutaneous squamous cell carcinomas (CSCCs)." Annals of Oncology 34 (2023): S682-S683.
Pembrolizumab	KEYNOTE-629* (NCT03284424)	Muñoz Couselo, E. et al., Pembrolizumab (pembro) for locally advanced (LA) or recurrent/metastatic (R/M) cutaneous squamous cell carcinoma (cSCC): Long-term results of the phase 2 KEYNOTE-629 study.. JCO 42, 9554-9554(2024). DOI:10.1200/JCO.2024.42.16_suppl.9554
Relatlimab with nivolumab	RELATIVITY-047 (NCT03470922)	Tawbi, H. A., Schadendorf, D., Lipson, E. J., et al. (2022). Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. The New England Journal of Medicine., 386(1), 24–34. https://doi.org/10.1056/NEJMoa2109970

Drug	Trial name	Publication
Selinexor	BOSTON (NCT03110562)	No publications identified
Zanubrutinib	ALPINE (NCT03734016)	Brown JR, Eichhorst B, Lamanna N et al. Extended Follow-up of ALPINE Randomized Phase 3 Study Confirms Sustained Superior Progression-free Survival of Zanubrutinib Versus Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL). Presented at: 65th ASH Annual Meeting and Exposition, December 9-12, 2023. San Diego, California. Available at: https://www.onclive.com/view/extended-follow-up-of-alpine-randomized-phase-3-study
Zanubrutinib	SEQUOIA (NCT03336333)	Munir T, Shadman M, Tobak T et al. Zanubrutinib (zanu) vs bendamustine + rituximab (br) in patients (pts) with treatment-naive chronic lymphocytic leukemia / small lymphocytic lymphome (CLL/SLL): Extended follow-up of the SEQUOIA study. HemaSphere, 2023;7(S3)

Not PBS listed because drug was withdrawn from the market
*Single-arm study
^Pooled results reported
+Lung cancer cohort