White Paper

Championing Oncology Relevant Endpoints (CORE) in Canada: Surrogate endpoints in clinical trials and reimbursement decisions for early-stage cancers

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This research was conducted by the Oncology Real World Solutions team at IQVIA Canada, sponsored and funded by AstraZeneca Canada. AstraZeneca and IQVIA partnered through project CORE (Championing Oncology Relevant Endpoints) which aims to expand the acceptability of oncology relevant endpoints by regulatory authorities, HTA agencies and payers in Canada within the solid tumour space.

Introduction

Malignant neoplasms remain the leading cause of death globally and in Canada[1,2], although survival for many cancers has improved in recent years[3]. Researchers attribute the increased survival to the development of, and access to, new and more effective treatments[4]. However, the search for innovative therapies continues, with 159 novel active substances in oncology launched globally since 2012, of which 30 were launched in 2021.[5] Although most clinical trials (89%) target metastatic/advanced tumors, research focused on early-stage cancers has been increasing recently[5]. With more than 2,000 products currently in development for oncology[5], a considerable number are expected to seek market authorization in the near future and will include medicines targeted across oncology disease stages.

Given the increasing costs of cancer care[6], expert committees who are involved in drug reimbursement decisions employ deliberative frameworks to facilitate decision-making. Internationally, several frameworks exist that provide an assessment of the value of oncology therapies[7-10]. Although different in their target audience, methodology, value dimensions and items, they all include safety and clinical efficacy as essential elements. In Canada, the Canadian Agency for Drugs & Technology in Health (CADTH) uses a similar deliberative framework to review and assess oncology treatments based on four important values: clinical benefit, economic evaluation, patient-based values and adoption feasibility. Although not explicit, clinical benefit reportedly carries the greatest weight in receiving positive or negative recommendation for drug reimbursement.[11]

Clinical benefit of oncology drugs is most commonly evaluated using overall survival (OS), which is considered an appropriate traditional measure in oncology[12]. Of late, surrogate endpoints have become increasingly more common as proxy endpoints that are used as a substitute to patient-relevant endpoints, such as mortality, and known to predict clinical outcomes[12]. The most frequently used examples are recurrence-free survival (RFS), disease-free survival (DFS) or event-free survival (EFS). The rise in emphasis on surrogate endpoints in oncology clinical trials can partially be attributed to development of treatments that offer improvement at early-stage and advantages such as shorter study durations than that needed to demonstrate overall survival.[13] While there is a demonstrated acceptance by drug regulatory bodies such as FDA or EMA[15,16], the use of surrogate endpoints by HTA bodies for making reimbursement decisions and their perceptions of the concept are unclear: published guidance is scarce in many jurisdictions globally[14]. The uncertainty in the use of surrogate outcomes for decision-making is a concern in light of the upcoming large number of oncology products coming to market, many of which are expected to be for early-stage cancers.

IQVIA Canada, in partnership with AstraZeneca Canada, conducted this study to quantify and examine how traditional and surrogate endpoints used in early-stage oncology clinical trials are evaluated in Canadian reimbursement decision-making. The study had two objectives: (i) a retrospective analysis of outcomes used in early-stage oncology clinical trials to quantify the future impact of surrogate endpoints in oncology drug approval and funding recommendations, and (ii) a retrospective analysis of endpoints considered by CADTH when making informed reimbursement recommendations to provide a historical benchmark.

Methodology

SELECTION OF TRIALS AND HTA SUBMISSIONS

Data on endpoints used in phase II or III clinical trials were retrieved from the clinicaltrials.gov website. Interventional studies included for 10 pre-specified solid tumor types, based on the frequency of trials by indication, were explored. The studies were included if they were initiated between 2017 and March 2022 for early-stage, non-metastatic, non-invasive, localized (Stage I-III) disease and were not withdrawn, suspended or terminated. **Table 1** presents more detail on selection parameters. A Microsoft Excel data extraction form was created to record study characteristics from all studies, including trial design, sample size, blinding and allocation procedures, indication, intervention and comparator, basic participant characteristics (age and gender), and primary and secondary endpoints.

For HTA recommendations in Canada, data were extracted from publicly available documents of reimbursement submissions in oncology that led to a Final Recommendation issued between January 2017 and March 2022 by CADTH (www.cadth.ca). Similar to the clinical trials, submissions were selected for review if they had early-stage, non-metastatic, localized, Stage I–III cancers as an indication for the management of solid tumors. A separate Microsoft Excel data extraction form was created to systematically review Final Recommendation documents for each selected CADTH submission, which included the submission date and type, the indication, final recommendation and its date, and endpoints used in the submissions. For each endpoint, information was collected on the following: type of endpoint (primary, secondary, exploratory, not reported in trial, reported but not used in submission, reported and used in submission but not evaluated on by CADTH); data maturity status; effect size (clinically meaningful, not clinically meaningful, not stated), and statistical significance of effect size as reported in the CADTH documents.

Table 1. Selection parameters used in analysis

	PARAMETER	CONSIDERED FOR CLINICAL TRIALS	CONSIDERED FOR HTA (CADTH)
1	Trial type	Interventional clinical trials	N/A
2	Trial timing	Start date between January 2017 and March 2022	Final Recommendation between January 2017 and March 2022
3	Sponsor	Industry	N/A
4	Study Phase	Phase II or Phase III	Phase II or Phase III
5	Status	Not “Withdrawn”, “Suspended” or “Terminated”	“Completed” (i.e., not withdrawn or suspended), first submission (i.e., not resubmission)
6	Tumor types	Lung, Breast, Prostate, Melanoma, Ovarian, Colorectal, Pancreatic, Esophageal, Gastric, Bladder (single indication)	Solid tumors*
7	Indication	Early-stage, non-metastatic, non-invasive, localized, Stage I–III	Early stage, non-metastatic, localized, Stage I–III

*Selection criteria was originally limited to the 10 tumor types of focus from the clinical trial assessment but has since been expanded to all early-stage cancers. This resulted in 1 additional review being selected.

DEFINITION OF ENDPOINTS

Endpoints considered in both analyses were categorized into traditional and surrogate as previously described. For the purposes of this study, traditional endpoints included overall survival (OS), progression-free survival (PFS), complete response (CR), duration of response (DOR) and overall response rate (ORR). Surrogate endpoints included other outcomes that were commonly reported, such as pathologic complete response (pCR), disease-free survival (DFS), metastasis-free survival (MFS), time to next treatment (TTNT), quality of life (QOL), etc.

DESCRIPTIVE ANALYSIS

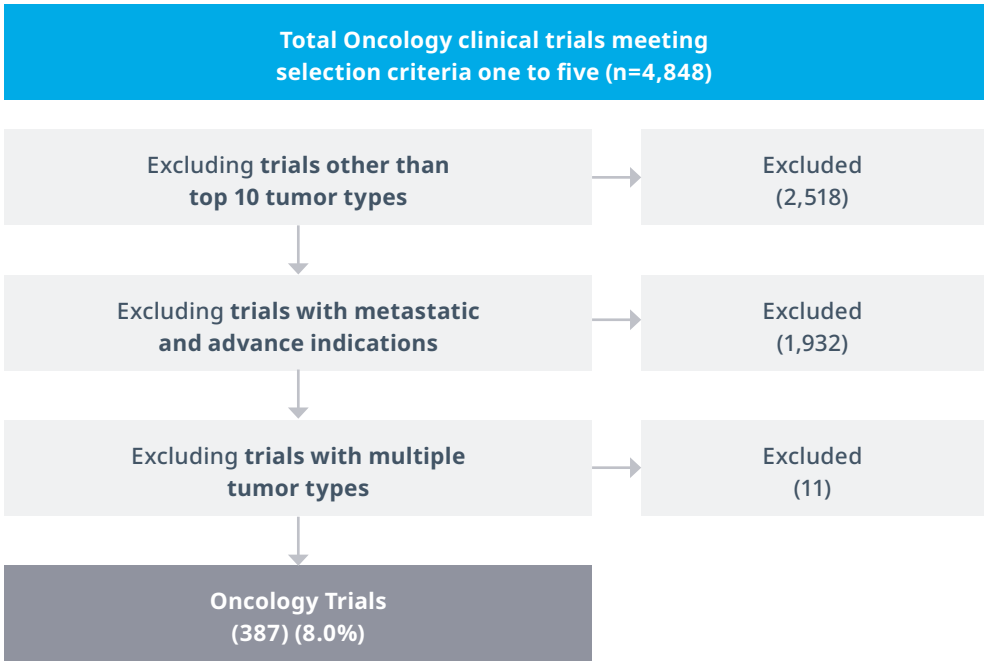
No statistical analyses were conducted. The collected data were subject to a narrative review.

Results

ASSESSMENT OF OUTCOMES USED IN TRIALS

A total of 4,848 oncology clinical trials were identified based on the trial type, timing of start date, sponsor, study phase and trial status. After restricting the search results to the top 10 tumor types and indications, 387 trials were considered eligible for this analysis (**Figure 1**).

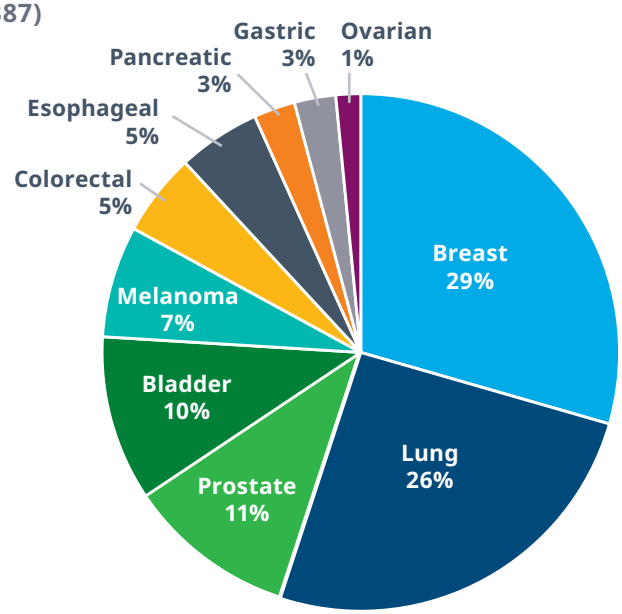
Figure 1. Selection of eligible trials



Source: clinicaltrials.gov

Breast, lung, prostate and bladder cancers were the most common tumor types, representing more than 75% (n=294) of the 387 included clinical trials (**Figure 2**). Lung, breast, colorectal, prostate and bladder cancers are the most commonly diagnosed cancers in Canada[17]. Most of the included clinical trials (n=316, 82%) were active at the time of analysis.

Figure 2. Distribution of clinical trials by tumor type (N = 387)

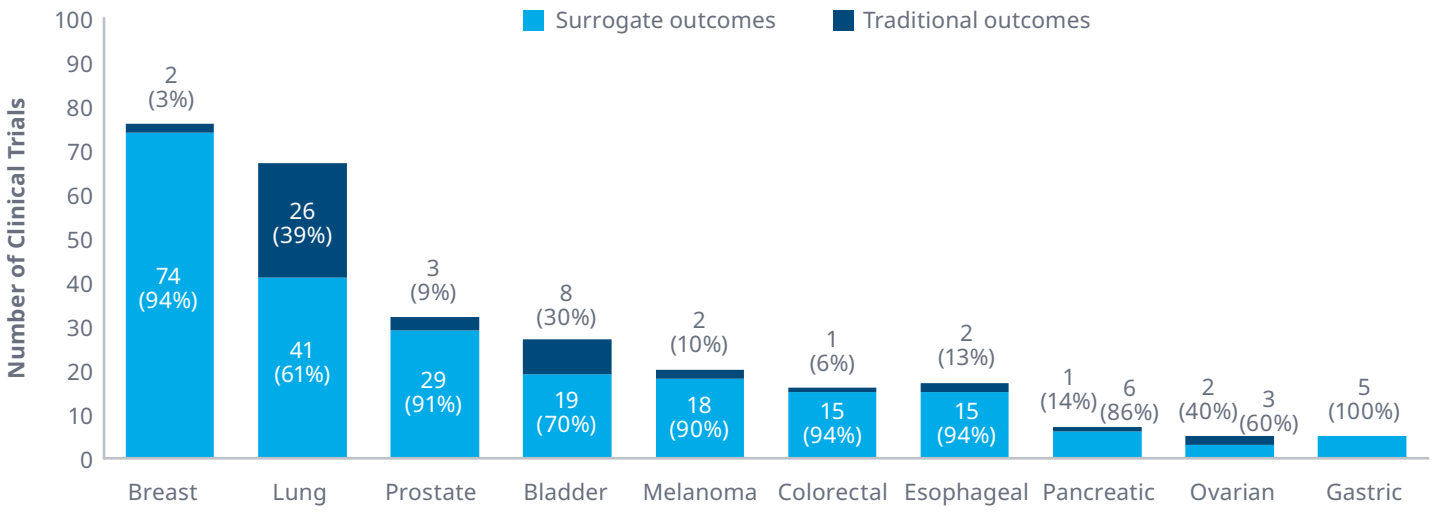


Of the 387 included trials, a majority (n=337, 87%) had both traditional and surrogate outcomes measured, 6 trials (2%) included only traditional endpoints (specifically OS, PFS and CR) and 44 trials (11%) included only surrogate outcome measures.

When examining trials by the number of primary endpoints, 70% (n=272) had a single primary endpoint, of which 225 (83%) were surrogate. Across all tumor types evaluated, trials in lung (n=26, 39%) and bladder (n=8, 30%) cancers assessed traditional outcomes most frequently (**Figure 3**). Of note, approximately 40% of trials that had surrogate primary endpoints did not include any of the traditional outcomes as co-primary or secondary endpoint.

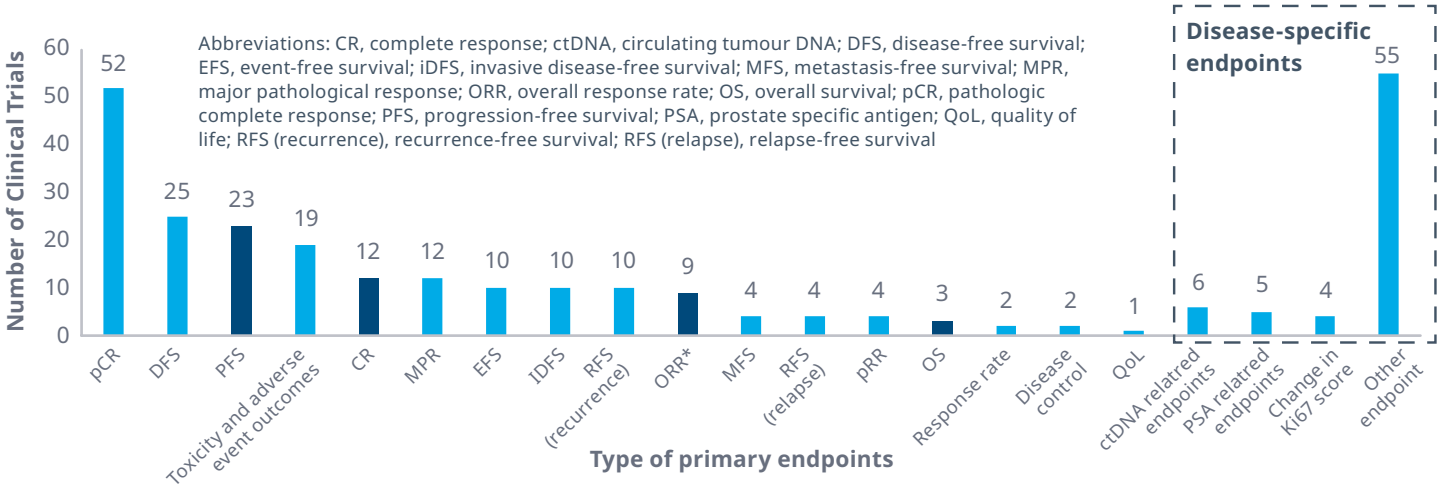
Among the trials with only one primary endpoint, pCR was the most common surrogate whereas PFS was the most common traditional outcome included. OS was the least common traditional endpoint included for assessment in trials (**Figure 4**).

Figure 3. Distribution of clinical trials by type of primary endpoint, across tumor types (n = 272)



Notes: 1 trial with gastro-esophageal cancer was merged with esophageal cancer

Figure 4. Distribution of clinical trials by type of primary endpoint (n = 272)

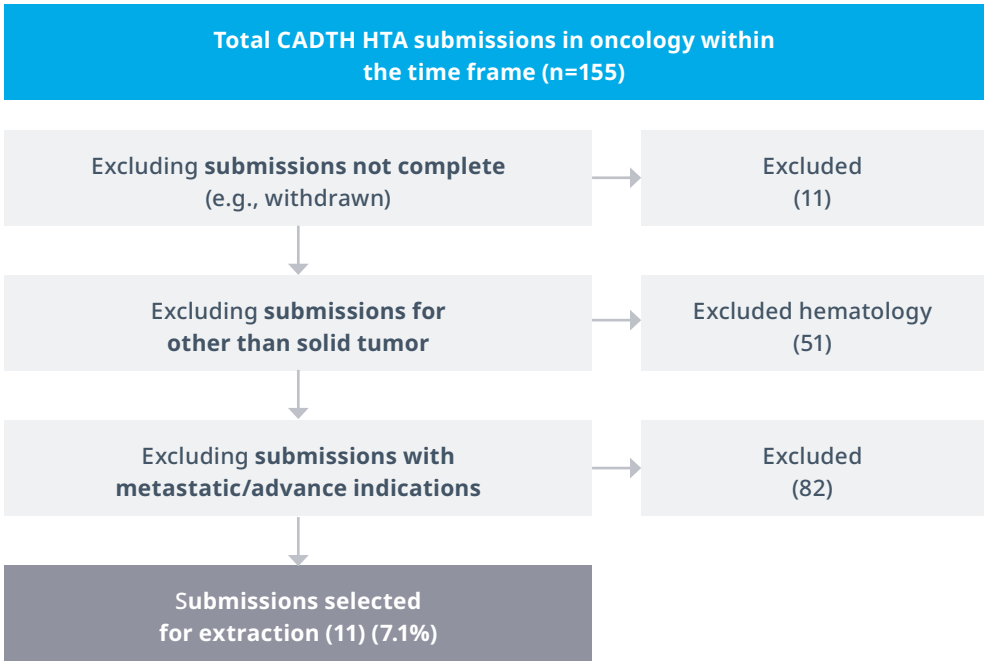


Notes: ctDNA related endpoints: clearance, change or decrease; PSA related endpoints: reduction, time to progression, undetectable, patients with response

ASSESSMENT OF ENDPOINTS CONSIDERED IN REIMBURSEMENT DECISION-MAKING

A total of 155 CADTH health technology assessment (HTA) submissions were made in oncology between January 2017 and March 2022 (**Figure 5**). After excluding incomplete submissions, resubmissions, submissions for tumors other than solid tumors and those with metastatic/advanced indications, 11 were considered for this analysis. All 11 submissions used data from double-blinded phase III trials; one submission included data from both open-label phase II and double-blinded phase III trials.

Figure 5. Selection of eligible CADTH submissions



Notes: selection criteria were originally limited to the 10 tumour types of focus from the clinical trial assessment but has since been expanded to all early-stage cancers. This resulted in 1 additional review being selected.

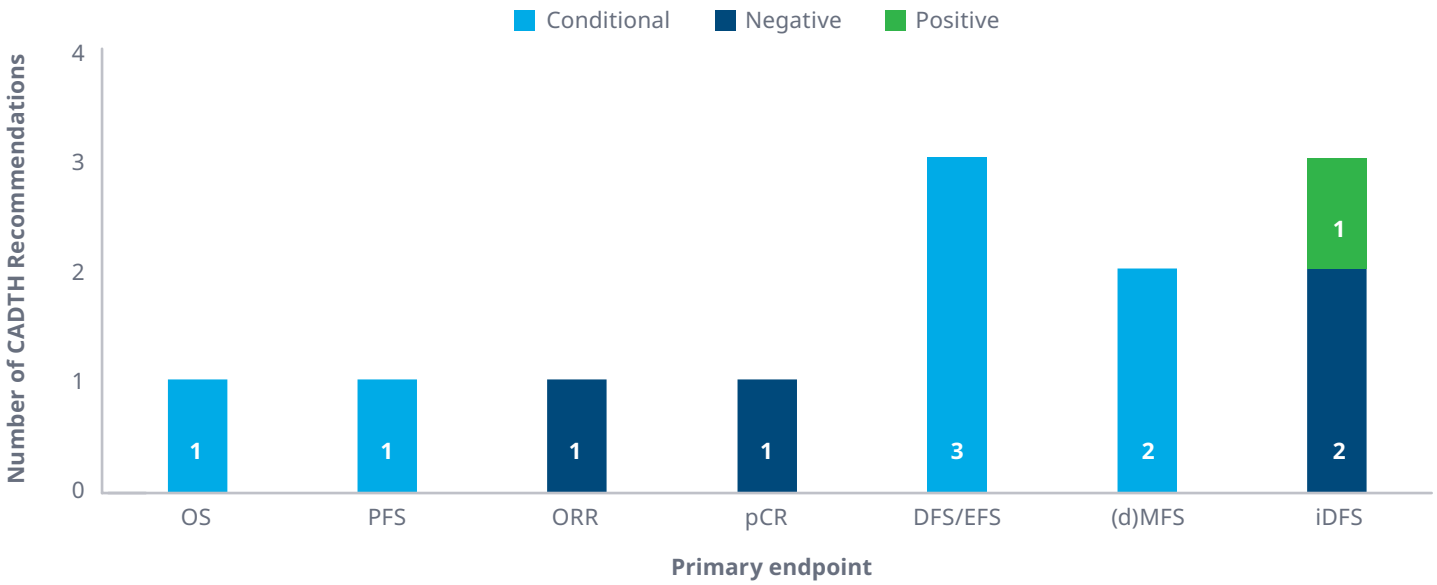
The included submissions covered 6 disease areas (breast, lung, prostate, melanoma, esophageal and skin) and were granted a positive (with/without conditions) reimbursement decision in most of the cases (7/11). Of the four negative recommendations, all cited uncertainty around clinically meaningful net benefit as the main reason, including no improvement in longer-term survival outcomes. Primary endpoints in these negative recommendations included ORR, pCR and iDFS.

For the drugs that received conditional recommendations, improving cost-effectiveness to an acceptable level was the most common condition for reimbursement.

CADTH RECOMMENDATIONS BY PRIMARY ENDPOINT

Figure 6 shows that the majority of the primary outcomes used in the included submissions were surrogate endpoints (n=9, 75%), many of which were statistically significant and clinically meaningful.

Figure 6. CADTH Recommendations by Primary Endpoint



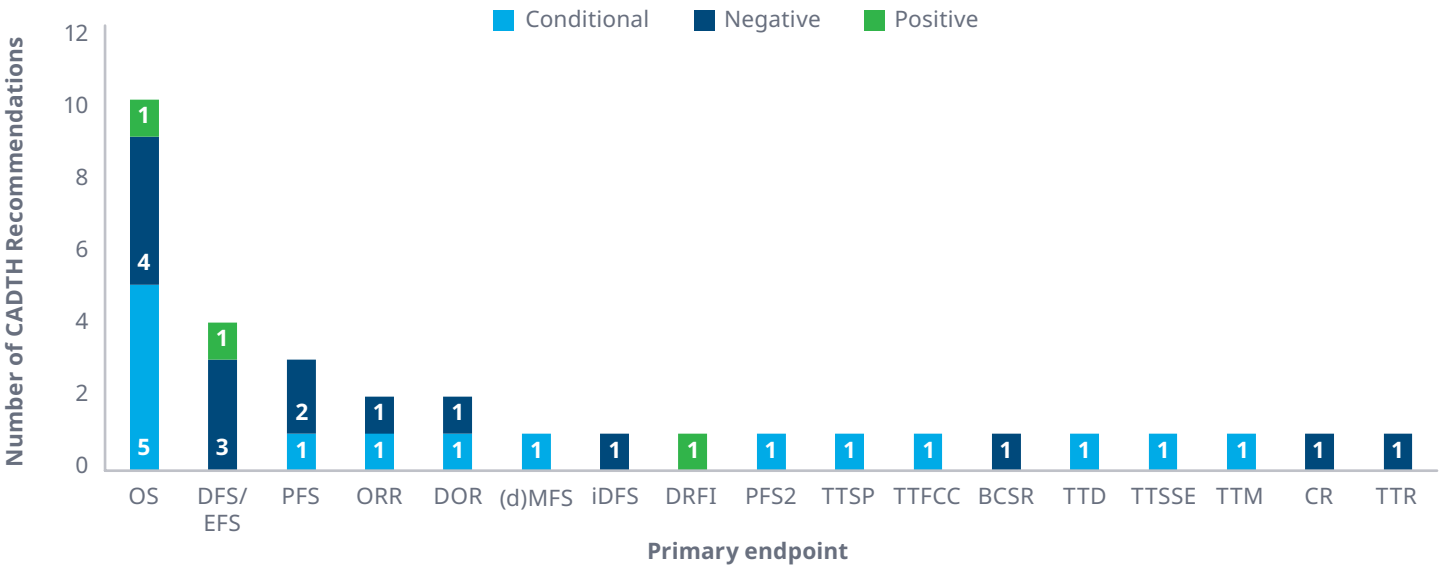
Note: One study has co-primary outcomes, hence the total number is 12
Abbreviations: DFS, disease-free survival; EFS, event-free survival; iDFS, invasive disease-free survival; (d)MFS, (distant) metastasis-free survival; pCR, pathologic complete response; OS, overall survival; PFS, progression-free survival

Three out of four CADTH submissions that received a negative recommendation had surrogate endpoints as their primary outcomes (pCR and iDFS). Reviewers commented on the lack of clinical significance of these outcomes. Specifically, for pCR it was noted that there was uncertainty that "improvements in pCR translate to clinically meaningful improvements in event-free or OS outcomes".

CADTH RECOMMENDATIONS BY SECONDARY ENDPOINT

OS was the most commonly measured secondary outcome (n=10); however, it was often not significant or mature at the time of submission. Other traditional endpoints such as PFS and ORR were also listed as secondary outcomes in the negative submissions.

Figure 7. CADTH Recommendations by Secondary Endpoint



Abbreviations: BCSR, breast-conserving surgery rate; CR, complete response; DFS, disease-free survival; DOR, duration of response; EFS, event-free survival; iDFS, invasive disease-free survival; (d)MFS, (distant) metastasis-free survival; OS, overall survival; PFS, progression-free survival; pCR, pathologic complete response; PR, partial response; RR, response rate; TTD, time to deterioration; TTDR, time to distant recurrence; TTFCC, time to first use of cytotoxic chemotherapy; TTSP, time to symptomatic progression; TTSSE, time to first serious safety event

LIMITATIONS

This analysis has few limitations. Firstly, the stringent selection criteria used in this study (e.g., focus on early-stage solid cancers) and the comparatively small sample size for the HTA analysis may limit the generalizability of results across a wider spectrum of oncologic conditions. Further, the analysis did not include exploratory outcomes. However, exploratory endpoints are rarely considered in decision-making by HTA agencies as they are not designed to provide confirmatory results and typically exclude proper statistical evaluation. Cost-effectiveness aspects from the analysis were also omitted. Although value for money is a common pillar of deliberative frameworks, clinical benefit plays a major role in decision-making: in fact, economic evaluation is hardly justifiable where no clinical superiority or equivalency is established. Lastly, the critical appraisal of trial design in relation to pre-defined endpoints selected for analysis was not evaluated from an ethical perspective and would present a potential area of future research. Overall, the limitations are unlikely to affect the conclusions.

Discussion of status quo and future directions

The selection of endpoints for clinical trials is driven by many factors. The use of surrogate endpoints in early-stage oncology clinical trials is steadily increasing, many as the primary clinical endpoint. Studies have demonstrated that surrogate endpoints may reduce clinical trial duration by approximately 11 months, and in early-stage cancer, it may be infeasible to demonstrate overall survival benefit as it would often be confounded by subsequent lines of therapy and mandatory cross-over[18]. Globally, evidence based on surrogate endpoints is increasingly being accepted to enable decision-making in regulatory and clinical settings. In an effort to increase the acceptance of surrogate outcomes, it is important to balance timely access to life-saving therapies and ensuring marketed therapies are clinically meaningful. The evaluation of surrogate endpoints in early-stage cancers should consider the immediate clinical improvements in patients with early-stage disease.

The decision to fund cancer drugs is becoming more difficult day-by-day owing to multiple factors such as substantial growth in number of drugs, high costs, and the uncertainty of their clinical benefit in the real world. Despite the increasing use of surrogate endpoints by regulatory agencies for drug approval, HTA bodies often preferentially weigh traditional clinical outcomes, which may be more serviceable to the advanced or metastatic setting, over surrogate outcomes. To improve acceptance, it would be important to clearly define surrogate endpoints, define the level at which survival data is considered mature, and establish validated instruments that demonstrate the clinical benefit of a drug through correlation between surrogate and traditional endpoints. As real-world evidence is now being considered by major HTA agencies, its broader use for surrogate outcome validation is anticipated.

Over time, there have been significant developments in CADTH processes with a demonstrated willingness to evolve and adapt. CADTH's scope of work in the early days included broad indication drugs and valued common RCT endpoints. CADTH's scope of work today includes expanded review of drugs, including generics, drugs for oncology and rare disease, guidelines for companion diagnostics, blood plasma assessment and CAR T-cell therapy. Real-world evidence may have the potential to provide CADTH the necessary evidence to evaluate the current processes and advance the acceptance of oncology-relevant endpoints.

Future work should explore the optimal use of surrogate endpoints to improve timely access to new therapies for early-stage oncology patients. Moreover, it is important for sponsors to have a clearer understanding of the factors influencing oncology reimbursement recommendations, in the context of evaluation of clinically meaningful surrogate endpoints. As a next step, roundtable discussions with stakeholders, including regulatory officials, HTA bodies and sponsors, may provide the necessary perspectives to initiate and maintain a productive dialogue and prepare for upcoming HTA submissions in early-stage oncology.

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