Navigating Uncertainty in Overall Survival Data: Insights from Positive Canadian HTAs on Lung Cancer Therapies

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HTA12

INTRODUCTION

- Overall survival (OS) is widely recognized by regulatory and health technology assessment (HTA) bodies as the gold standard endpoint in oncology trials.[1-4]
- However, certain limitations are associated with the use of OS, which can vary by cancer type and stage. These include:
  - Time to demonstrate OS benefit, particularly in indications with long baseline survival or in curative settings.
  - It may not be possible to attribute benefit to a new treatment in situations where patients receive subsequent therapies or due to trial design aspects (e.g., crossover).
  - Does not reflect all aspects of value (e.g., reduced side effect burden).
- Thus, manufacturers may submit OS data considered to be uncertain (i.e., immature data or non-statistically significant OS), supported by evidence from other endpoints to strengthen the submission.

OBJECTIVE

We aimed to summarize the characteristics of Canadian HTA appraisals in lung cancer treatments that received a positive reimbursement decision despite uncertainty in OS.

METHODS

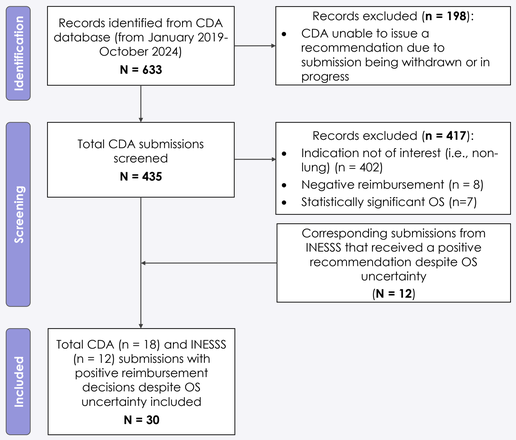
- HTA submissions for lung cancer indications with final recommendations published from January 2019 to October 2024 were retrieved from the CDA website. Submissions that were withdrawn or in progress were not retrieved. Corresponding recommendation reports for retrieved CDA submissions were obtained from the INESSS website.
- Submissions that met the PICOS (i.e., patients diagnosed with lung cancer, treated with anticancer agents where there was uncertainty in OS (immature OS or non-statistically significant OS), with positive reimbursement recommendation) were included in our review.
- The following were extracted from the included CDA and INESSS final recommendation report: treatment under review, pivotal trial characteristics and results, and rationale for recommendation from the HTA agency

RESULTS

Overall submissions

- Of 435 HTAs by CDA with a final recommendation issued between January 2019–October 2024, 18 submissions in lung oncology indications/solid tumour indications that included patients with lung cancer received a positive reimbursement decision despite OS uncertainty (**Fig. 1**).
  - Corresponding submissions were retrieved from INESSS, of which 12 submissions received a positive reimbursement decision despite OS uncertainty.
- Data from Phase 3 trials were most frequently included in CDA (n=8) and INESSS (n=6) positive submission final recommendation reports.
- RWE data was included to complement clinical evidence in 5 CDA and 5 INESSS submission reports.
- An ITC/NMA was included in 11 CDA and 7 INESSS submissions reports, of which 7 and 4 were single arm trials.
- Six of the included submissions (N=30) were for therapies with novel mechanisms of action at the time of submission.

Figure 1. Flow chart of identification and selection process for inclusion of CDA submissions and corresponding INESSS submissions



OS uncertainty

- Among the positive recommendations issued by CDA (N=18), CDA noted OS uncertainties were mainly due to immature OS data (n=7), for which most pivotal trials submitted by the sponsor were ongoing at the time of submission (n=5).
  - OS was the primary endpoint in 4/18 submissions that received a positive CDA recommendation.
  - The most frequent primary endpoints included in CDA HTA reports were ORR (9/18), DFS (3/18), and PFS (3/18).

RESULTS (*cont.*)

- In corresponding INESSS submissions that received a positive recommendation (N=12), seven submissions reported an immature OS, four submissions in which OS immaturity was unclear, and in three submissions OS was not statistically significant.
  - OS was the primary endpoint in 3/12 INESSS submissions with a positive recommendation.
  - ORR, DFS, and PFS were the most frequently reported primary endpoints in positive INESSS submission final recommendation reports (5, 3, and 2 HTAs, respectively)

Reimbursement decisions

- Nine therapies had differing recommendations between the agencies (**Fig. 2**).
  - Among these therapies with differing recommendations, majority were oral medications (n=7).
  - Submissions for majority of the therapies with differing recommendations were supported by a phase 3 pivotal trial (3/9) or multiple pivotal trials (3/9).
- Six negative recommendations were issued by CDA for submissions in lung oncology/solid tumour indications that reported OS uncertainty.
  - None of the final recommendation reports for the submissions included OS as the primary endpoint.
  - Non-comparative trial data were submitted for all HTAs that received a negative CDA recommendation.

Figure 2. Alignment and discrepancies between CDA and INESSS reimbursement decisions (N = 20 therapies)

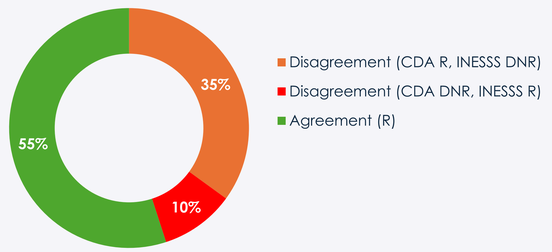
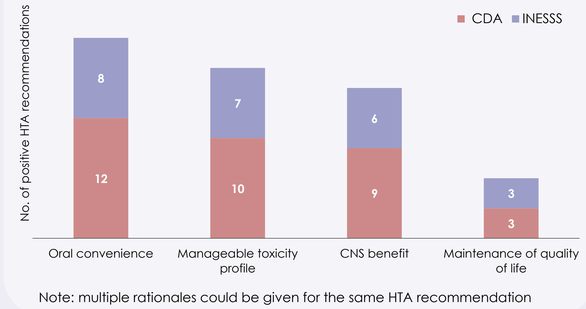


Figure 3. Rationales given for positive HTA recommendations, by HTA organization



Note: multiple rationales could be given for the same HTA recommendation

Rationale for recommendation

- Of the 30 positive HTAs (18 CDA, 12 INESSS), the HTA bodies noted oral convenience (n=20), manageable toxicity profile (n=17), CNS benefit (n=15), maintenance of quality of life (n=6) as part of their rationale for recommendation (**Fig. 3**).

DISCUSSION & CONCLUSIONS

- CDA and INESSS have issued positive recommendations in the absence of mature or non-statistically significant OS data based on results of other endpoints that were deemed important, e.g., maintenance of HRQoL or a manageable toxicity associated with the product.
- Although OS has been considered the gold standard for primary clinical endpoints in oncology, its utility is limited by several drawbacks.
  - The lengthy duration of trials focusing on OS has prompted a recent shift towards investigating surrogate clinical endpoints and their potential to provide additional data that could inform decision-making such as HRQoL endpoints which could help capture the quality of survival.[5]
- Notably, CDA has recently implemented time limited recommendations as part of modernizing their review processes, to help balance timely access to promising new therapies with considerations under high uncertainty; future investigations will provide an understanding of the impact of these changes in decision-making processes.

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