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Factors including Real-World Evidence (RWE) that play a role in the HTA recommendation of oncology drug submissions based on Phase II and/or Single arm trial data

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BACKGROUND

- From a health technology assessment (HTA) perspective, phase III randomized controlled trials with an active / placebo comparator are the "gold standard" for demonstrating efficacy and safety.
- However, an increased number of innovative oncology therapies are being introduced, with pivotal trials containing phase II/single arm trial data.
- With this shift in oncology, HTA agencies have expressed difficulties in decision making due to the level of uncertainty.
- Manufacturers have taken this into consideration, and are including various supplemental analyses, including real-world evidence (RWE) to help address the uncertainty.

OBJECTIVE

- The objective of this research is to perform a descriptive analysis to understand influential factors including RWE in HTA decision-making when assessing oncology submissions with phase II/single arm trial data.

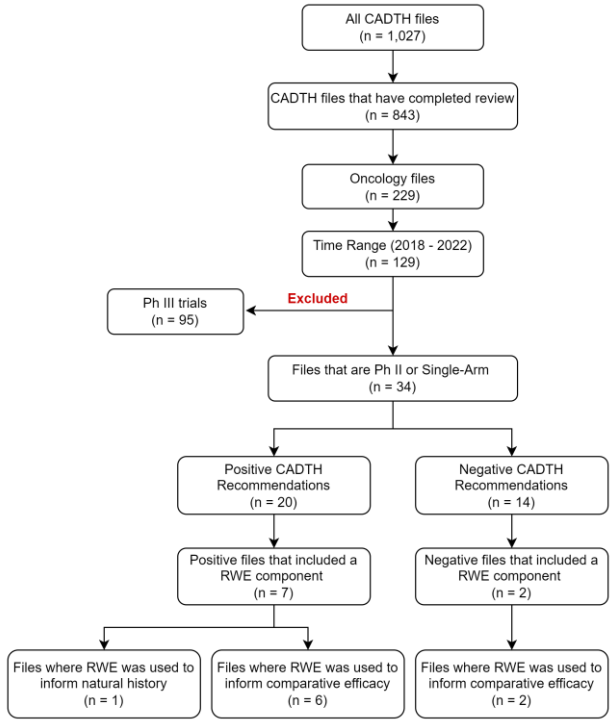
METHODS

- Health Technology Assessment (HTA) submissions for oncology drugs to the Canadian Agency for Drugs and Technologies in Health (CADTH) that contained phase II/single arm trial data between 2018 and 2022 were obtained and analyzed from the CADTH website [1]
- Specifically, the final recommendation, and clinical and economic reviewer's reports were analyzed to determine factors that likely influenced the HTA recommendations for drugs who submitted with phase II/single arm trial evidence.
- Upon completing this preliminary analysis, certain files were further investigated to understand the methodology of RWE used, any learnings that could be used for future RWE submissions by manufacturers
- Outcomes and assessments of these RWE-containing dossiers were also explored in HTA jurisdictions outside of Canada

CADTH Reimbursement Review Dossiers Filtering Process

- All CADTH files were pulled from the online reimbursement review database[1]
- The files were filtered for those that had completed HTA review
- Of all the completed review files, the oncology files were filtered
- A time range of 2018-2022 was deemed appropriate for this analysis
- In order to assess dossiers containing phase II/single arm trial data, Phase III files were excluded
- Phase II/single arm data dossiers were filtered for positive vs. negative CADTH recommendations and were assessed for HTA perceptions on clinical benefit, unmet need and supportive evidence used
- Phase II/single arm data dossiers containing RWE as supportive evidence were filtered for, while those without RWE were excluded
- Files were assessed for types of RWE used in the HTA submission (indirect comparison vs. natural history)

Figure 1 – Filtering Process for CADTH Reimbursement Review dossiers



RESULTS

Oncology files submitted to CADTH with either Phase II or single-arm trial data

- A total of 34 oncology submissions with phase II or single-arm trial data were identified on the CADTH website between 2018-2022.
  Of these, 20 (59%) received a positive recommendation (i.e., list or list with conditions) while 14 (41%) received a negative recommendation (i.e., do not list).
- Positive recommendations often (85%) recognized a net clinical benefit and acknowledged an unmet need for better treatments.
- The negative recommendations were associated with uncertain net clinical benefit or lack of satisfaction with the evidence even though an unmet need may have been recognized. Files with negative recommendations noted high uncertainty in net clinical benefit and a majority of these noted that conducting a phase III trial was feasible.

Phase II, single-arm trial data HTA dossiers utilizing RWE as supportive evidence

- Of the 9 submissions that utilized RWE as supportive evidence, 8 used international data sources while 1 used Canadian data. 7 of these received a positive recommendation, while 2 received a negative recommendation. Mostly, RWE was used to inform comparative efficacy.
- Of the 9 CADTH files using RWE, NICE and PBAC recommendations were explored to understand assessment of RWE across varying HTA jurisdictions and subsequent recommendations. HTA agencies were mostly aligned in recommendations.
- Many manufacturers had submitted to CADTH but not to NICE and PBAC.
- HTA agencies shared similar comments on RWE included in the dossier, including: (1) risks for bias, (2) high levels of uncertainty in analyses which should be interpreted with extreme caution considering the many limitations, (3) challenges in comparability, (4) critiquing the RWE methodology and (5) variability of data sources (combination of real-world, registry database and other clinical trials).

CONCLUSIONS

- Despite phase III randomized controlled trials being the "gold standard" for demonstrating efficacy and safety of therapies in HTA, submitting evidence from phase II/single arm trials can still lead to positive decisions from CADTH.
- It is important for sponsors to note that submitting a dossier with phase II/single arm trial data when conducting a phase III clinical trial is deemed feasible will likely receive a negative HTA recommendation from CADTH.
- Uncertainty from phase II/single arm trials may be mitigated if a "positive net clinical benefit" is recognized by CADTH but it is unclear whether inclusion of RWE is able to mitigate this uncertainty.
- RWE was usually heavily critiqued, especially when used in the context of informing comparative efficacy and was often noted to be interpreted with caution due to poor methodology, limitations and bias – these criticisms were consistent for CADTH, NICE and PBAC assessments.
- In 2022, NICE developed a RWE framework[2] while CADTH had also recently launched a consultation on guidance for RWE reporting[3] so it remains to be seen how these will evolve and impact RWE acceptability for HTA decision making.
- There is a continuous need for standardized guidance from HTA agencies and opportunities for engagement between sponsors and agencies on how RWE will be evaluated so that sponsors can appropriately design RWE generation activities to meet the rigor required for HTA decision making.

Table 1 - CADTH dossiers including Phase II, single-arm trials utilizing RWE as supportive evidence & other HTA jurisdictions' reimbursement outcomes

Product	Unmet Need (as per CADTH)	CADTH	NICE[4]	PBAC[5]	RWE Used
ABECMA	unmet need recognized	✗	–	–	Synthetic control arm
BAVENCIO	substantial unmet need recognized	✓	✓	✓	Observational control arm
BREYANZI	unmet need recognized	✓	–	–	ITC
FOLOTYN	substantial unmet need recognized	✓	✗	–	ITC
JEMPERLI	substantial unmet need recognized	✗	✓	✗	ITC
RETEVMO	unmet need recognized	✓	✓	–	ITC
ROZLYTREK	substantial unmet need recognized	✓	✓	✓	ITC
TAFINLAR & MEKINIST	unmet need for better tx	✓	–	–	ITC
VITRAKVI	unmet need recognized	✓	✓	✓	Natural History

Legend: ✓ positive recommendation ✗ negative recommendation – in progress/not submitted

REFERENCES

1. https://www.cadth.ca/reimbursement-review-reports
2. https://www.nice.org.uk/corporate/ecd9/chapter/overview
3. https://www.cadth.ca/news/cadth-launches-consultation-real-world-evidence-reporting-guidance
4. https://www.nice.org.uk/guidance
5. https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes