CHALLENGES IN EVALUATING AND PAYING FOR COMBINATION THERAPIES IN ONCOLOGY – A CANADIAN PERSPECTIVE

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BACKGROUND

- Cancer is characterized by a breakdown of multiple biological pathways. This has led to the development of therapies to target various individual pathways alone or in combination[1].
- Currently, there are several combination therapy (CT) regimens in oncology with clinical benefits beyond monotherapy that have become the standard for clinical treatment.
- Yet, combining multiple targeted treatments poses varied challenges wherein existing health technology assessment (HTA) processes limit the ability to demonstrate incremental value of such CTs that is commensurate with observed clinical benefits, particularly when payers are challenged to accommodate the total cost of expensive CTs[2, 3].
- Similar to many healthcare systems (HCS) worldwide, the Canadian HCS includes HTA that utilize willingness-to-pay (WTP) approaches for assessing value of single manufacturer submissions[4]. However, some agencies such as in Sweden and UK, employ flexible WTP thresholds for conditions of greater need[2].
- If left unaddressed clinically effective CT regimens are deemed not cost-effective even if add-on therapies were available at zero cost[5], resulting in patients facing significant delays to access, and in some cases being denied, clinically superior treatments
- Payers are generally not willing to pay more per health unit gained for combination regimens than for single technology interventions. Combinations with off-patent products are likely avoid this challenge, as it allows for the company to present a total cost of regimen that is satisfactory to the payer and price the constituent medications accordingly.

OBJECTIVE

- This study seeks to describe and highlight the reimbursement challenges associated with evaluating and paying for CTs in the context of the Canadian HCS.

METHODS

- The findings in this study were obtained via a focused literature review and supported by Canada-specific review of HTA recommendations for oncology CTs and non-CTs in the last two years.
- IQVIA's Market Access Metrics database was used to identify CADTH recommendations for oncology CTs issued between January 2020 – December 2021 based on the following selection criteria.

Inclusion criteria:

- Be for a new combination of targeted therapies OR new add-on therapy combined with back-bone therapy (or therapies) including but not limited to immunotherapy, biosimilars or generics
- Be latest final recommendation for the drug and indication, if resubmitted
- Be initiated *by drug sponsor*

Exclusion criteria:

- Be for a monotherapy
- Be for fixed dose combinations
- Be for an innovative therapy combined with chemotherapy only
- Be for an innovative therapy combined with hormone therapy such as androgen depriv*ation therapy*

- Final recommendations were reviewed based on predefined variables: recommendation decision / conditions, price recommendation, percentage price reduction recommended, willingness-to-pay threshold referenced made for CTs.
- CADTH recommendations for oncology products not identified as CT (non-CT) issued during the same time-period of January 2020 – December 2021 were also analyzed separately based on the same variables.

RESULTS

FOCUSED LITERATURE REVIEW

Reimbursement challenges of oncology CTs identified in focused literature review:

- The challenges of assessing CTs for reimbursement are exacerbated in the Canadian HCS due to:
  - lack of defined frameworks (i.e., through clinical trials, HTA and beyond) for attributing value to each constituent therapy,
  - lack of mechanisms to revisit prices for existing therapies to accommodate add-on therapies,
  - involvement in price determination by multiple agencies, including the pan-Canadian Pharmaceutical Alliance, and the Patented Medicine Prices Review Board, and
  - legal challenges of different CT patent holders negotiating collectively with payers.

CADTH RECOMMENDATION ANALYSIS:

Recommendation outcome:

- A total of 15 CTs met the inclusion criteria and were assessed based on predefined variables.
- Thirteen (87%) of the CTs included in the analysis received recommendation to 'reimburse with condition/criteria', one (7%) received recommendation 'do not reimburse', and one (7%) received recommendation 'reimburse with condition/ criteria' for only part of the requested indication.
- In the last instance, the reimbursement request was for the innovative medication with or without the existing targeted therapy. However, CADTH only recommended to 'reimburse with conditions/criteria' the add-on innovative medication as a monotherapy, while issuing a 'do not reimburse' recommendation for the combination with back-bone therapy.
- Three out of 15 CTs (20%) included add-on innovative medication combined with only back-bone medications which were biosimilars or generics at the time of recommendation (See appendix). In some other cases, generics or biosimilars of the back-bone treatments became available after CADTH recommendations were issued which may have implications on negotiations with pCPA. (see appendix)
- On the other hand, 40 non-CTs were identified and assessed separately. Three (8%) received recommendation to 'reimburse', 29 (73%) received recommendation to 'to reimburse with condition/criteria', and eight (20%) received recommendation 'do not reimburse'.

Price reduction recommendations:

- In all 13 'reimburse with condition/criteria' recommendations for CTs issued by CADTH price reductions to achieve variable WTP thresholds were noted. One of the two CT recommendations that did not specify percentage of price reduction, indicated that price should not exceed other existing combination treatment with the same mechanism of action.
- The percentage of price reduction recommended was specified in 11 CT recommendations, with an average reduction of 76% for the innovative medications. Specifically, the three CTs with biosimilar or generic back-bone medications recommended average price reduction of 60% for the innovative add-on medications.
- In contrast, only 25 out of 32 non-CT recommendations with 'reimburse' or 'reimburse with condition/criteria' stated a price reduction required to meet a specific WTP threshold, with an average reduction of 67%.
- Thirty six percent (4 out of 11) of CT recommendations and only 12% (3 out of 25) of non-CT recommendations requested price reduction of 95% or greater.

More than 80% (9 out of 11) of CT recommendations requested a price reduction of 70% or greater for the innovator medications. While only 52% (13 out of 25) of non-CT recommendations requested price reduction of 70% or greater. (Different price reduction categorization than Figure 1).

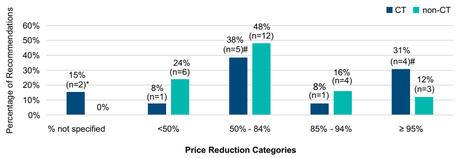
Price reduction recommendation for innovative medications and back-bone combination medications:

- Four CT recommendations requested price reduction for the add-on innovative medications only.
- Seven CT recommendations had price reduction conditions for both constituent parts of the combination.
  - Four CT recommendations had a single percentage reduction for both the constituent parts of the CT medications combined. Notably, three of these recommendations included combinations of two innovative medications, and one included add-on innovative medication combined with two back-bone medications.
  - The remaining three CTs had different percentage reductions recommended for the constituent parts of the combination. Prices of the add-on innovative medications were recommended to be reduced by 99% on average. However, the back-bone treatments they were combined with were recommended to be reduced by only 60% on average.
- Notably in an example, CADTH states that the add-on innovative medication would not be cost-effective even if it was offered at zero price and price reductions were offered for the back-bone medication[6]. Interestingly, CADTH recommendation for the back-bone therapy was issued in July 2014[7], and it had also been through pCPA negotiations twice for the same indication, once in 2015 once again (details unknown) in 2018. Both of these negotiations concluded with letter of intent[8, 9]. This highlights that recommendations for add-on innovative medications should potentially be able to consider confidential rebates already in place for backbone.

Manufacturer of the combination medications and price reduction recommendations:

- Seven CTs with the 'reimburse with condition/criteria' recommendations included the back-bone medication from a different manufacture than the submitting sponsor. Contrastingly, the remaining six CTs included both constituent parts of the CT regimen from the same sponsor.
- Recommendations for six CTs with different manufacturers specified price reduction percentage for add-on innovative medications, with an average of 81%. On the other hand, recommendations for five CTs with same sponsor specified price reduction percentage for add-on innovative medications, with an average of 69%.

Figure 1. Percentage price reduction in 'reimburse with conditions/criteria' recommendations for CTs (N=11) and non-CTs (N=25)

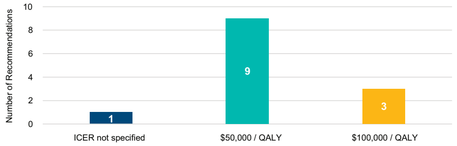


* Price reduction category includes one CT with medications from different manufactures
\# Price reduction categories include three CTs each with medications from different manufacturers (n=7 total across all categories)

Willingness-to-pay (WTP) thresholds:

- Most (8 out of 11) of the CT recommendations with price reduction recommendations considered the willingness-to-pay threshold of $50,000/QALY.
- Remaining three recommendations considered the $100,000 / QALY threshold to recommend price reductions. All three of these recommendations were issued in March or April 2020.
- Average price reduction for CT recommendations with $50,000/QALY threshold was 77% (n=8), while the same for CT recommendations with $100,000/QALY threshold was 73% (n=3).
- Binder et al, reports that CADTH reduced the WTP threshold for oncology products starting in late 2020[10].
- Similar trends were seen in the CT recommendations, wherein WTP thresholds have shifted from $100,000/QALY to $50,000/QALY after April 2020.

Figure 2. ICER thresholds considered in 'reimburse with conditions/criteria' recommendations for combination oncology products (n=13)



pCPA Status and time from CADTH recommendation:

- Two of the 15 CTs were under consideration for negotiations, three were undergoing negotiations, and negotiations were not pursued for one CT at the time of this analysis. Remaining nine CT negotiations (60% of 15 reviewed) concluded with a letter of intent (LOI), On average, it took approximately 10 months from CADTH recommendation to LOI.
- Among 40 non-CT recommendations issued during the same 2020-2021 time period, three were under consideration for negotiations, five were undergoing negotiations, and negotiations were not pursued for six non-CTs. Remaining 26 (65% of 40 reviewed) non-CT negotiations concluded with a LOI, On average, it took 7.5 months from CADTH recommendation to LOI.
- On average, pCPA negotiations for CTs with both medications from the same sponsor concluded faster than CTs with back-bone medication from a different manufacturer than the submitting sponsor (data not shown). This was based on a small number of observations.
- In an interesting case, a CT product which received CADTH recommendation in August 2019 took approximately 2 years and 6 months to conclude pCPA negotiation with LOI in February 2022. One of the constituent parts became genericized during the intervening time period between CADTH recommendation and LOI [11, 12].

DISCUSSION

- This review of HTA recommendations for oncology CTs focused only on CADTH recommendations issued in last two years. As this data was used only to support the findings from literature review and provide Canadian context, a more in-depth analysis with extended time-period can be conducted in the future. The COVID-19 pandemic's impact on Canada's HCS should also be considered while interpreting results of this review.
- Recent trends and upcoming clinical trials suggest that oncology CTs have become mainstay and increasingly important for the cancer patient. An urgent dialogue between all stakeholders is recommended to address these challenges in order to optimize patient care.
- While the WTP threshold as it relates to CADTH reporting of price reductions for considerations of cost-effectiveness has recently changed, in 2020, to $50,000/QALY, some backbone therapy components of recently evaluated CTs were previously assessed as monotherapies according to a WTP threshold of $100,000/QALY. This could pose specific reimbursement challenges within Canada by holding new CTs to a different standard for evaluation than the individual component therapies within that CT regimen.
- No announcement or public consultation with stakeholders was undertaken by CADTH prior to the reduction in the WTP threshold[10, 13].
- Absence of consistent or explicitly stated frameworks for flexible WTP thresholds being applied to CTs may locally disincentivize new drug development and inconsistently limit patient access to life saving therapies.
- Potential solutions to addressing these challenges discussed in the past are reducing cost, improving value and increasing WTP[3].
  - Reduced cost can be achieved by revisiting price of the existing back-bone medications proportional to their value in the CT.
- Agencies in Sweden and UK have provision of flexible WTP thresholds and reflect the judgement of society's willingness to pay more for conditions of greater need. To assign a priority to diseases of higher severity, a similar WTP flexibility can be introduced for CTs in terms of WTP threshold.
- The expected clinical benefit of using the medicines in combination is superior to that of using either constituent as monotherapy, but the duration of treatment increases by the same amount of time as the expected increase in overall survival (OS). Adaptive trial designs, dosing schedule and supportive care requirements could improve value of the CT without increasing cost.

CONCLUSION

- Newly aligned reimbursement frameworks addressing both near- and long-term implementation issues, and acknowledging opportunity costs for patients and HCS, should be explored to ensure that optimal health benefits from global innovations in oncology can be accessed by Canadian patients in a timely manner.
- All stakeholders in the healthcare ecosystem (payers, manufacturers, and health review agencies) need to acknowledge the shared problem and work towards pragmatic consensus solutions.

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APPENDIX

CADTH recommendations for CTs:
PC0189-000, Darzalex (combined with branded backbone therapy, but generic options became available after recommendation was issued); PC0185-000, Keytruda; PC0195-000, Kisqali (combined with one generic back-bone therapy); PC0155-000, Tecentriq & Avastin; PC0210-000 (combined with back-bone therapy where recommendation refers to originator biologic but biosimilar options were available), Calquence; PC0212-000, Venclexta; PC0217-000, Tecentriq & Avastin (combined with back-bone therapy where recommendation refers to originator biologic but biosimilar options were available); PC0218-000, Opdivo in combination with Yervoy; PC0220-000, Sarclisa; PC0227-000, Poliv (combined with one generic and one biosimilar back-bone therapy); PC0226-000, Tafinlar & Mekinist in combo; PC0229-000, Opdivo-Yervoy; PC0233-000, Braftovi; PC0232-000, Braftovi and Mektovi; PC0243-000, Tukysa (combined with one generic and one biosimilar back-bone therapy)

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