Moving Beyond Partitioned Survival Models in Oncology Submissions: Incorporation of Canada's Drug Agency Guidance on Model Structure

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Objective

To assess how 2023 Canada's Drug Agency (CDA-AMC) guidance, which highlights limitations of partitioned survival models (PSMs), has influenced model structure choice in oncology health technology assessment submissions.

Background

- CDA-AMC is a pan-Canadian organization designed to provide healthcare decision makers with independent evidence and advice to make informed drug, health technology, and health system decisions.[1]
- On 1 May 2023, CDA-AMC released new guidance for extrapolating clinical evidence within economic evaluations.[2] The report highlighted that economic models should consider causal relationships between time, health status, treatment, and mortality, which are not explicitly accounted for in PSMs, but can be included in models with a Markov structure.

Methods

- A list of Reimbursement Review Reports from the CDA-AMC website was extracted on 26 November 2024.
- Reports that were marked as "complete" for oncology drugs that were submitted after 1 May 2023, were downloaded. An equal number submitted before this date were downloaded to facilitate comparison of reports submitted pre-and post-published guidance.
- The following information was extracted: assessment details (disease area, intervention and comparators, and CDA-AMC recommendation), the sponsor's model structure, its adequacy in addressing the decision problem (used as a proxy for acceptance of model structure), and any additional comments by CDA-AMC relating to model structure.

Results

Model Structures Pre- and Post-Guidance

- Fifty CDA-AMC submissions were reviewed (25 before and 25 after the threshold date; **Table 1**). Two non-sponsored submissions (pre-May 2023 guidance) without manufacturer models were excluded. Of the remaining 48 submissions, 29/48 (60%), 4/48 (8%), and 15/48 (31%) were PSMs, (semi-)Markovs, and other model structures, respectively. Other model structures included cost-comparison, cost-minimization, hybrid (decision tree and PSM), and patient-level microsimulation models.
  - Pre-guidance, 16/23 (70%), 3/23 (13%), and 4/23 (17%) were PSMs, (semi-)Markovs, and other model structures, respectively. Post-guidance, 13/25 (52%), 1/25 (4%), and 11/25 (44%) were PSMs, (semi-)Markovs, and other model structures, respectively (**Figure 1**).

Model Structure Acceptance Pre- and Post-Guidance

- The acceptance rate of model structures pre-and post-guidance was also assessed (**Figure 1**).
  - Pre-guidance, 6/16 (38%) PSMs and 0/3 (0%) (semi-)Markov models were accepted. Post-guidance, 7/13 (54%) PSMs and 1/1 (100%) (semi-)Markov models were accepted.

Feedback from CDA-AMC on Model Structure

- In their comments pre-and post-guidance, CDA-AMC consistently highlighted limitations of PSMs, including independence of progression-free and overall survival and challenges in modeling subsequent therapies, suggesting that alternative modeling approaches may be more appropriate in some circumstances (**Figure 2**).
- Submissions that used (semi-)Markov models pre-guidance did not receive comments regarding these structural assumptions and biases, and the submission with a (semi-)Markov model post-guidance release did not receive any comments on model structure at all.

Conclusion

Based on the reviewed submissions, the use of (semi-)Markov structures did not increase following the 2023 guidance; however, sample size may limit interpretation. Comments from CDA-AMC align with their guidance, with (semi-)Markov models receiving fewer comments about structural concerns than other model types.

However, there were PSMs both pre-and post-guidance that were accepted, indicating that there are circumstances where a PSM is considered suitable. Overall, CDA-AMC feedback indicates that model structure should be carefully considered based on the disease area being modeled to maximize likelihood of acceptance.

TABLE 1

CDA-AMC oncology submissions reviewed

Appraisals included pre-guidance release

Date submission received	Disease/condition	Intervention of interest
19 August, 2021	Basal cell carcinoma	Cemiplimab
15 December, 2021	Advanced endometrial cancer	Pembrolizumab
24 February, 2022	Metastatic small cell lung cancer	Lurbinectedin
21 April, 2022	NSCLC	Amivantamab
21 April, 2022	Unresectable or metastatic uveal melanoma	Tebentafusp
9 June, 2022	Diffuse large B-cell lymphoma or high-grade B-cell lymphoma	Axicabtagene ciloleucel + third-line therapy
16 June, 2022	Metastatic castration-sensitive prostate cancer	Darolutamide + docetaxel + ADT
20 June, 2022	Triple-negative breast cancer	Pembrolizumab + chemotherapy
14 July, 2022	Biliary tract cancer	Durvalumab + gemcitabine + cisplatin
3 August, 2022	Germline BRCA-mutated, HER2– high-risk early breast cancer	Olaparib
19 August, 2022	KRAS G12C-mutated advanced NSCLC	Sotorasib
13 September, 2022	Resectable NSCLC	Nivolumab + platinum doublet chemotherapy + surgery
15 September, 2022	Acute lymphoblastic leukemia	Brexucabtagene autoleucel
23 September, 2022	Relapsed or refractory multiple myeloma	Ciltacabtagene autoleucel
13 December, 2022	Unresectable or metastatic HER2-low breast cancer	Trastuzumab deruxtecan
15 December, 2022	Unresectable hepatocellular carcinoma	Tremelimumab + durvalumab
20 January, 2023	Chronic lymphocytic leukemia/small lymphocytic lymphoma	Zanubrutinib
1 February, 2023	Relapsed or refractory follicular lymphoma	Tisagenlecleucel
17 February, 2023	Advanced or metastatic renal cell carinoma	Cabozantinib + nivolumab
1 March, 2023	Large B-cell lymphoma	R-CHP
6 March, 2023	T-cell acute lymphoblastic leukemia	Nelarabine + standard of care
13 April, 2023	Relapsed or refractory follicular lymphoma	Axicabtagene ciloleucel
21 April, 2023	Chronic lymphocytic leukemia	Ibrutinib + venetoclax
NA*	High-risk non-metastatic prostate cancer	Abiraterone + prednisone ± enzalutamide + ADT
NA*	Metastatic castration-sensitive prostate cancer	Abiraterone + docetaxel + ADT

*Non-sponsored submission without a manufacturer model.

Appraisals included post-guidance release

Date submission received	Disease/condition	Intervention of interest
12 May, 2023	Acute lymphoblastic leukemia	Calaspargase pegol
19 May, 2023	Metastatic castration-resistant prostate cancer	Olaparib + abiraterone
19 May, 2023	Left-sided metastatic colorectal cancer	Panitumumab + FOLFOX; panitumumab + FOLFIRI; panitumumab + XELOX
14 June, 2023	Metastatic castration-resistant prostate cancer	Niraparib + abiraterone acetate
20 June, 2023	Waldenström's macroglobulinemia	Ibrutinib monotherapy; ibrutinib + rituximab
10 July, 2023	Unresectable or metastatic melanoma	Nivolumab-relatlimab
14 July, 2023	Acute myeloid leukemia or myelodysplastic syndromes	Treosulfan + fludarabine
18 July, 2023	Relapsed or refractory diffuse large B-cell lymphoma	Glofitamab
15 August, 2023	Metastatic colorectal cancer	Trifluridine-tipiracil + bevacizumab
31 August, 2023	Relapsed or refractory multiple myeloma	Teclistamab
27 September, 2023	Locally advanced or metastatic NSCLC	Cemiplimab + platinum-based chemotherapy
18 October, 2023	Endometrial cancer	Dostarlimab + carboplatin-paclitaxel
24 October, 2023	Anti–PD-1 resistant advanced melanoma	Nivolumab + ipilimumab
24 October, 2023	Stage III or stage IV melanoma	Pembrolizumab
24 October, 2023	Patients with solid tumours experiencing hypersensitivity reactions to taxanes	Nab-paclitaxel
6 November, 2023	Adjuvant stage IIB or IIB melanoma	Nivolumab
9 November, 2023	Relapsed or refractory multiple myeloma	Elranatamab
14 November, 2023	Relapsed or refractory diffuse large B-cell lymphoma	Epcoritamab
14 November, 2023	Advanced prostate cancer	Relugolix
22 November, 2023	Gastric or gastroesophageal junction adenocarcinoma	Pembrolizumab + trastuzumab + chemotherapy
7 December, 2023	Biliary tract carcinoma	Pembrolizumab + chemotherapy
21 December, 2023	Previously treated advanced (locally advanced unresectable or metastatic) pancreatic cancer	Nab-paclitaxel + gemcitabine
12 February, 2024	Pancreatic cancer	Nab-paclitaxel + gemcitabine
30 April, 2024	Genito-urinary cancer (prostate cancer)	Enzalutamide ± ADT
18 July, 2024	HR+, HER2– advanced or metastatic breast cancer	Sacituzumab govitecan

Reimburse | Reimburse with clinical criteria and/or condition | Time-limited reimbursement recommendation | Do not reimburse

FIGURE 1

Model structure and structure acceptance in oncology submissions pre- and post-guidance

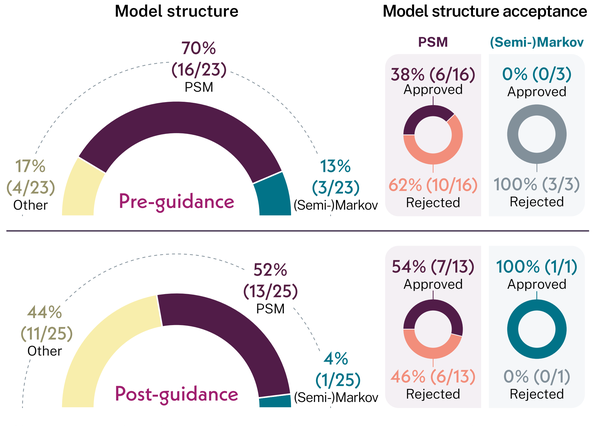

FIGURE 2

Key CDA-AMC feedback on PSMs

> *The sponsor's use of a PSM introduces structural assumptions about the relationship between PFS and OS that likely do not accurately reflect causal relationships within the disease pathway*

> *The Sponsor's base case used a Monte Carlo simulation to characterize the uncertainty of relevant input parameters, however, the absence of a structural relationship between these parameters in the PSM model structure limits the usefulness of this approach*

> *The structural assumption of a PSM is that membership of mutually exclusive health states must be determined from non–mutually exclusive survival curves. Unlike a Markov model, which can combine inputs from a variety of sources, a PSM is more restrictive*

> *Although PSMs are routinely used to model oncology treatments, this approach was not suitable for this decision problem where the primary goal of both first-line and subsequent treatments is to achieve a cure*

> *PSMs are not suitable to capture changes in response on subsequent lines of therapy, as this model structure only accounts for the costs of subsequent therapies in the progressed state but has limited flexibility to capture their clinical benefits*

Abbreviations: ADT: androgen deprivation therapy; **BRCA:** breast cancer gene; **CDA-AMC:** Canada's Drug Agency; **FOLFIRI:** folinic acid + fluorouracil + irinotecan; **FOLFOX:** folinic acid + fluorouracil + oxaliplatin; **G12C:** glycine-to-cysteine mutation; **HER2:** human epidermal growth factor receptor 2; **HR:** hormone receptor; **KRAS:** Kirsten rat sarcoma virus; **NA:** not applicable; **NSCLC:** non-small cell lung cancer; **OS:** overall survival; **PD-1:** programmed cell death protein 1; **PFS:** progression free survival; **PSM:** partitioned survival model; **R-CHP:** rituximab + cyclophosphamide + doxorubicin + prednisone; **XELOX:** capecitabine + oxaliplatin.

References: [1]CDA-AMC (2025). About Us. Available at: https://www.cda-amc.ca/about-us. [Last accessed 17 Mar 25]; [2]Coyle D. et al. Can J Health Technol 2023;3(5):6–19. **Acknowledgements:** The authors thank Jon Green, Costello Medical, for graphic design assistance. We also thank Shubhi Pathak, Costello Medical for their contributions to the preparation of this poster.
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