How have Canada's Drug Agency guidelines impacted choice of model structure and use of partitioned survival models in oncology submissions?

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INTRODUCTION

- In May 2023, Canada's Drug Agency (CDA) issued methods guidelines for extrapolating clinical evidence within economic evaluations. [1]
- Within these guidelines, CDA stated that partitioned survival models (PSMs) were not recommended given the assumption of independence between progression-free survival (PFS) and overall survival (OS).
- The objective of this study was to assess the impact of these guidelines on choice of model structure submitted by manufacturers, acceptance and critiques of the model structure from CDA, and the impact on reimbursement recommendations.

METHODS

- All sponsored submissions to CDA across oncology indications submitted after May 2023 were reviewed.
- Only submissions with a recommendation available as of December 2024 were reviewed. If available, the Clinical and Pharmacoeconomic Combined Report was reviewed, otherwise the Recommendation Report was reviewed.
- Data were extracted for the intervention, indication, line of therapy, model type, CDA's assessment of model structure including noted limitations, and the reimbursement recommendation.

RESULTS

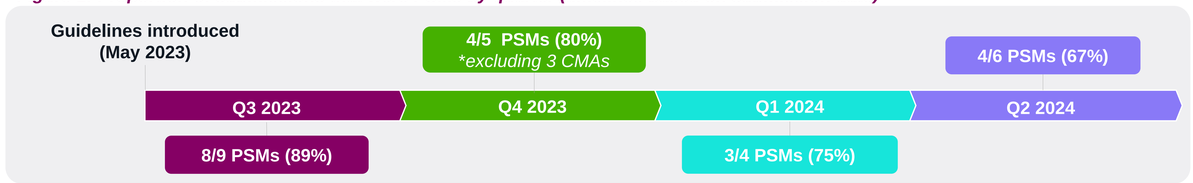
- 27 oncology submissions with recommendations available were identified between May 2023 and December 2024 (**Table 1**). [2] The proportion of submissions that were PSMs since the introduction of the CDA guidelines are presented by quarter in **Figure 1**.
- Of these, 19 were PSMs, 5 were state transition models (STMs), and 3 were cost-minimization analyses (CMAs) (**Figure 2**). For adjuvant indications (N=3), PSM was not used; however, for other indications, including first or later lines for advanced disease, the PSM was predominantly used.
- Among PSMs with completed reports, the structure was deemed adequate in over half the submissions, suggesting variability across reviewers (**Figure 3**).

Table 1: Summary of model structures used in CDA oncology submissions

Date Submission	Generic Name	Cancer type	Therapeutic area	Line of therapy	Model structure	Structure appropriate?	Reimbursed with CCC?
Complete submissions (Clinical and Pharmacoeconomic and Stakeholder Input Combined Report available)							
Q3 2023	niraparib abiraterone acetate	Prostate	Met castration-resistant prostate cancer	1L	**PSM**	Yes	Yes
Q3 2023	ibrutinib	Lymphoma	R/R Waldenström's Macroglobulinemia	2L+	STM[a]	Yes	Yes
Q3 2023	nivolumab and relatlimab	Melanoma	Unresectable or met melanoma	1L	**PSM**	Yes	Yes
Q3 2023	treosulfan	Leukemia	Acute myeloid leukemia	Conditioning	**PSM**	No	Yes
Q3 2023	sacituzumab govitecan	Breast	Adv/met HR+/HER2- breast cancer	3L+	**PSM**	Yes	Yes
Q3 2023	glofitamab	Lymphoma	R/R DLBCL	3L+	**PSM**	No	Yes
Q3 2023	trifluridine and tipiracil	Colorectal	Met colorectal cancer	3L+	**PSM**	No	Yes
Q3 2023	teclistamab	Leukemia	R/R multiple myeloma	4L+	**PSM**	Yes	Yes
Q3 2023	cemiplimab	Lung	Locally adv/met NSCLC	1L	**PSM**	No	Yes
Q4 2023	dostarlimab	Endometrial	Met endometrial cancer	1L	**PSM**	Yes	Yes
Q4 2023	nivolumab	Melanoma	Stage IIB/IIC melanoma	Adjuvant	CMA	NA	Yes
Q4 2023	elranatamab	Leukemia	R/R multiple myeloma	4L+	**PSM**	Yes	Yes
Q4 2023	epcoritamab	Lymphoma	R/R DLBCL	3L+	**PSM**	No	Time-limited
Q4 2023	relugolix	Prostate	Adv prostate cancer	1L	CMA	NA	Yes
Q4 2023	pembrolizumab	Gastric	Adv/met gastric/gastroesophageal junction	1L	**PSM**	Yes	Yes
Q4 2023	pembrolizumab	Biliary tract	Met biliary tract carcinoma	1L	CMA	NA	Yes
Incomplete submissions (only Recommendation document issued at time of review)							
Q4 2023	osimertinib	Lung	Adv/met NSCLC	1L	STM[a]	NA	Yes
Q1 2024	abemaciclib	Breast	HR+/HER2- breast cancer	Adjuvant	STM[a]	NA	Yes
Q1 2024	capivasertib	Breast	Adv/met HR+/HER2- breast cancer	2L+	**PSM**	NA	Yes
Q1 2024	pembrolizumab	Gastric	Adv/met gastric/gastroesophageal junction	1L	**PSM**	NA	Yes
Q1 2024	ivosidenib	Leukemia	Newly diagnosed acute myeloid leukemia	1L	**PSM**	NA	Yes
Q2 2024	Brentuximab vedotin	Lymphoma	High-risk Hodgkin lymphoma	1L	STM[a]	NA	Yes
Q2 2024	alectinib	Lung	NSCLC	Adjuvant	STM[a]	NA	Yes
Q2 2024	ciltacabtagene autoleucel	Leukemia	R/R multiple myeloma	2L+	**PSM**	NA	Yes
Q2 2024	avapritinib	Mastocytosis	Advanced systemic mastocytosis	1L, 2L+	**PSM**	NA	Yes
Q2 2024	lisocabtagene maraleucel	Lymphoma	R/R large B-cell lymphoma	2L	**PSM**	NA	Yes
Q2 2024	Fruquintinib	Colorectal	Metastatic colorectal cancer	2L+	**PSM**	NA	Yes

Notes: a) *Manufacturers referred to them as Markov or semi-Markov models;* ***Abbreviations:*** *adv, advanced; CCC, clinical criteria and/or conditions; CMA, cost-minimization analysis; DLBCL, diffuse large B cell lymphoma; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; L, line; met, metastatic; NA, not applicable/not available; NSCLC, non-small cell lung cancer; PSM, partitioned survival model; Q, quarter; R/R, relapsed/refractory; STM, state transition model.*

Figure 1: Proportion of submissions that were PSMs by quarter (timelines based on submission date)



- In those submissions where the PSM structure was deemed inadequate, reviewers noted limitations such as:
  - Structural assumptions about the **relationship between PFS and OS**,
  - Inability to **capture causal relationships** between patient characteristics and probability of events,
  - Not capturing **response to subsequent lines** of therapy.
- 26 of the submissions received a "reimburse with clinical criteria and/or conditions" (CCC) and 1 submission received a "time-limited reimbursement recommendation" (first ever issued by CDA).
  - Although CDA considered the PSM structure not to be appropriate, the time-limited stipulation of this recommendation was made due to the CDA determining that there was insufficient clinical evidence to justify the price premium for the drug.

Figure 2: Model structures used by line of therapy

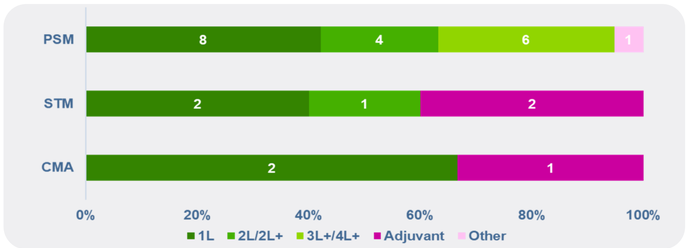
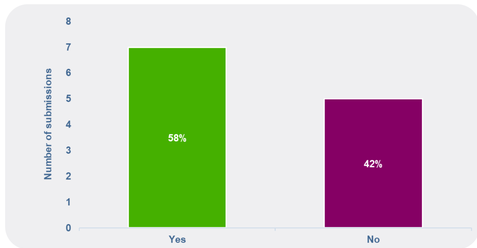


Figure 3: PSMs deemed acceptable (n=12)



CONCLUSIONS

- Whether a PSM structure was deemed adequate for the decision problem was variable and was not related to line of therapy. Typically, reviewers noted similar limitations across submissions.
- The use of a PSM did not seem to impact the reimbursement recommendation, as no negative recommendations were issued, even when the model structure was deemed inadequate.
- To date, the new guidance has not impacted the manufacturer's choice of model structure submitted or CDA's recommendations in oncology. However, this might change in the future, as more time elapses from the CDA guidelines being issued.

***References**: **1.** CDA guidelines for economic evaluation of health technologies: Canada, 2023. **2.** CDA, https://www.cda-amc.ca/, accessed Dec 2024.*

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