Evaluating the Patient Burden Associated With Delayed Reimbursement: A Case Study of Pembrolizumab in the Treatment of Endometrial Cancer in Canada

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Objectives

- Access to novel efficacious therapies in oncology can meaningfully improve patient outcomes, including survival
- Geographic location may determine when patients can obtain access to novel treatments
  - For example, a phase II single-arm trial of pembrolizumab monotherapy for adult patients with unresectable, or metastatic, microsatellite instability high (MSI-H), or deficient mismatch repair (dMMR) endometrial cancer, whose tumors had progressed following prior systemic therapy (KEYNOTE-158: median overall survival 65.4 months, median follow-up 54.5 months[1]) was granted conditional regulatory approval in Canada in 2019 and a positive reimbursement recommendation from Canada's Drug Agency (CDA) in 2023.[2,3] By contrast, the therapy became available in the United States in 2017 and in parts of Europe in 2022
- Access to therapies varies between countries due to multiple reasons including: Different payer archetypes, different evidence requirements by regulatory and health technology assessment (HTA) agencies, sequential approval pathways across nations and provinces, and manufacturer submission considerations
  - When making reimbursement decisions, HTA agencies may request to see trial data based on longer follow-up where key efficacy outcomes have been reached. For example, they may wish to see statistically significant and clinically meaningful improvements in overall survival
  - Data with longer follow-up can increase certainty around a drug's risk–benefit profile, however, waiting for this data to become available delays patient access to clinical benefits. The extent to which such delays and the associated uncertainties affect patients and health systems is not well understood
- In this study we aim to capture the patient burden associated with different reimbursement timelines, and explore the impact of data uncertainty on cumulative lifetime quality-adjusted life years (QALYs) and life years (LYs)

Methods

This study uses a case-study approach that focuses on evidence from the single-arm KEYNOTE-158 trial[1] to assess the potential impact on patient outcomes of alternate access scenarios

- A previously published partitioned-survival semi-Markov model,[4] based on KEYNOTE-158, was adapted to assess the population-level impact of hypothetical access scenarios vs the 2023 real-world reimbursement recommendation[2]
- The underlying model was modified to accommodate successive annual patient cohorts entering the model. The cohort size was estimated based on the eligible population in line with estimates by the Canadian Cancer Society and the patient funnel used by Houde F-X et al. (2025).[4] Patient outcomes were then tracked through the model
  - The cohorts differed in when they were able to access novel therapies, depending on the selected reimbursement settings, which informed the market shares and access timing to pembrolizumab after regulatory approval
- The model considered three scenarios reflecting different payer archetypes to assess the impact of faster access on patient outcomes. An additional fourth scenario utilized data with shorter follow-up to examine how increased uncertainty affects estimated patient outcomes and, ultimately, an agency's decision (**Table 1**)

Table 1. Reimbursement scenarios

Scenario[a]	Real-world payer archetype mirrored	Regulatory approval year	Data cut used to inform efficacy input	Actual/Hypothetical positive reimbursement recommendation
Impact of early access on patient outcomes				
Base case: Real-world reimbursement of pembrolizumab monotherapy (3.8 years)	KEYNOTE-158 timeline[2,3]	2019	FA	2023
Scenario 1: Immediate access after Canadian regulatory approval	Germany, US[5,6]	2019	FA	2019
Scenario 2: Access 3-months post-regulatory approval	Accès Précoce scheme in France[7]	2019	FA	2019, Q2
Scenario 3: Access 1-year post-regulatory approval	Median time to access in the UK, Canada, and Italy[8,9]	2019	FA	2020
Impact of using trial data with shorter follow-up on HTA decision				
Scenario 4: Real-world reimbursement of pembrolizumab monotherapy (3.8 years), but using interim analysis data instead of final analysis data	KEYNOTE-158 timeline[2,3]	2019	IA[b]	2023

[a]Market share assumptions were consistent across all scenarios. Pembrolizumab assumed uptake of 60% in Year 1 post-reimbursement, 75% in Year 2, and 89.3% thereafter.[10] Paclitaxel and doxorubicin uptake covered the remainder of the market not occupied by pembrolizumab, split 25.8%:74.2%, respectively, in line with the ratio reported in the KEYNOTE-158 CDA submission.[11]
[b]It should be noted the IA used in the analysis had a data cut off of October 11, 2021, which is different to the interim data cut used for the initial CDA submission which had a data cut off of October 5, 2020.

CDA, Canada's Drug Agency; FA, final analysis; IA, interim analysis; HTA, health technology assessment; Q2, quarter two.

Scenarios 1-3 evaluated the impact of quicker access by considering population-level patient outcomes in the form of:

- 5-year survival
- Mortality/progression events avoided
- Cumulative lifetime quality-adjusted QALYs and LYs

All timeline scenarios used the KEYNOTE-158 final analysis (data cut off: January 12, 2022) data in alignment to the data used in the accepted CDA submission, to carry out retrospective analysis.

The impact on uncertainty from using an earlier data cut off is explored in Scenario 4:

- KEYNOTE-158 interim analysis (data cut off: October 11, 2021) and final analysis (data cut off: January 12, 2022) data were used to estimate the 95% CI, IQR, and median output of a 1,000-sample probabilistic sensitivity assessment of total LYs and QALYs
- Cumulative lifetime LYs and QALYs were estimated using interim analysis data and compared with the base case scenario, which was based on FA data

Costs were not considered in the analyses.

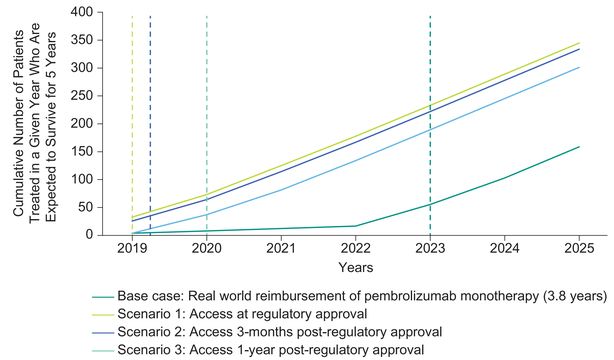
Results

Impact of delay in access on patient outcomes

5-year survival:

- In the base case, 159 patients were expected to reach the 5-year survival milestone across the 7-year exploratory range (2019-2025); this increased to 345, 334, and 301 patients in Scenarios 1, 2, and 3, respectively
- **Figure 1** presents the cumulative patient results. This demonstrates increased long-term survivorship and sustained clinical impact with early access

Figure 1. Cumulative number of patients treated in a given year who are expected to survive for 5 years

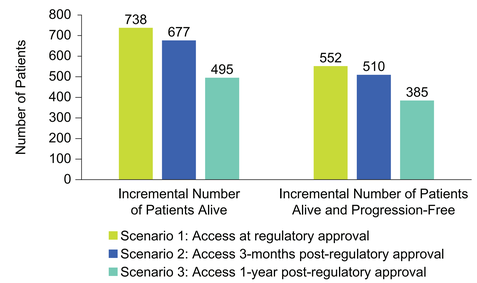


Notes: The dashed lines reflect when reimbursement occurred in each scenario. In Scenarios 1, 2, and 3, regulatory approval occurred in 2019.

Snapshot progression and survival results:

- These results present the number of patients who are modeled to have been alive at the end of 2025
- **Figure 2** shows that the progression and survival outcomes notably improve across all scenarios from the base case where 1,415 patients were alive, and 1,057 patients were alive and progression-free

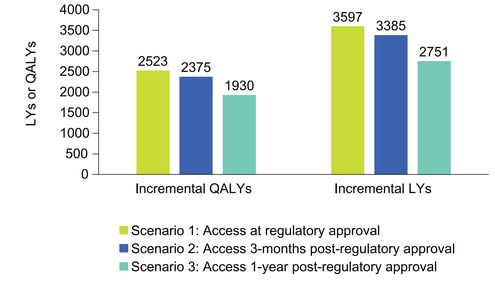
Figure 2. Incremental number of patients alive and alive and progression-free vs the base case



Cumulative lifetime LY and QALY gains:

- These results capture the lifetime QALYs and LYs for all patients with endometrial cancer, in all cohorts, between the start and end of cohorting
- The base-case results suggest patients accumulated 2,507 QALYs and 3,585 LYs over the model time horizon
  - The earlier reimbursement scenarios indicated these outcomes could be far higher if earlier access was available (**Figure 3**)

Figure 3. Incremental cumulative lifetime LY and QALY gains vs the base case

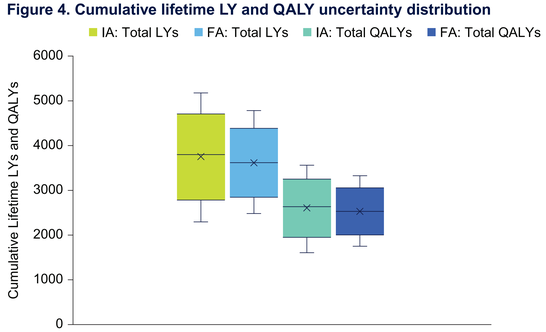


LY, life year; QALY, quality-adjusted life year.

Impact of using trial data with shorter follow-up on HTA decision

- The interim data cut results displayed more uncertainty, shown by slightly wider confidence interval and interquartile range estimates (**Figure 4**). However, mean and median estimates of LYs, and QALYs changed only marginally, with estimates changing by less than 5% between the final and interim data cuts

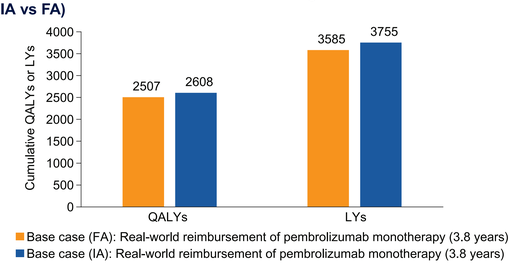
Figure 4. Cumulative lifetime LY and QALY uncertainty distribution



FA, final analysis; IA, interim analysis; LY, life year; QALY, quality-adjusted life year.

- Recalculating the base scenario using the interim data cut produced very similar estimates, with both data cuts suggesting that there are notably positive patient gains from more rapid access to pembrolizumab, and the additional four months of follow-up does not change the trend in results (**Figure 5**)
  - The opportunity cost of waiting for longer follow-up in cases like this, where interim results present an advantageous profile, is a challenging issue for HTA agencies when evaluating novel therapies. HTA agencies must try to identify if they believe early clinical results could be contradicted by longer follow-up. Further research would be required to quantify the level of certainty needed to be confident early trial read-outs reflect long-term outcomes

Figure 5. Cumulative lifetime LY and QALY gains for base case (IA vs FA)



FA, final analysis; IA, interim analysis; LY, life year; QALY, quality-adjusted life year.

Conclusions

- This model-based case study of pembrolizumab for MSI-H or dMMR endometrial cancer demonstrates that earlier access to efficacious therapies can produce meaningful population-level health gains in cancers with high unmet need
- Although longer trial follow-up can reduce uncertainty, it does not always alter positive net-benefit conclusions for efficacious therapies. In such situations, earlier reimbursement decisions may improve population-level outcomes
- As more innovative therapies are approved by regulatory agencies, striking the right balance between timeliness and evidentiary rigor will be essential to maximizing health benefits for the population

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