EE350

Cost-effectiveness of pembrolizumab for previously treated MSI-H/dMMR solid tumors in Canada

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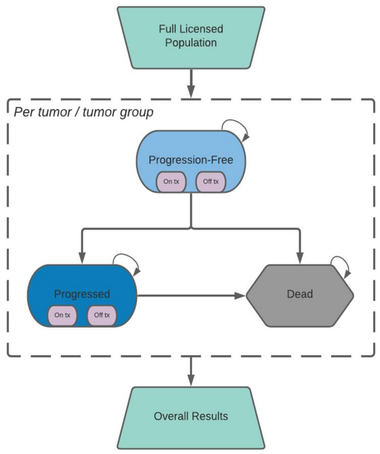
Background & Objectives

- This study evaluated the cost-effectiveness of pembrolizumab, a programmed cell death protein 1 inhibitor immunotherapy, indicated for the treatment of patients with unresectable or metastatic microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) solid tumors who have progressed following prior treatment and have no satisfactory alternative treatments, from the Canadian healthcare payer perspective
- Canada's Drug Agency (CDA-AMC) issued a specific guidance in 2021 for the economic evaluation of tumor-agnostic products[1], which notably included the following requirements: 1) analysis must be stratified by tumor types and by place in the treatment sequence; 2) results must be weighted by tumor prevalence; 3) no incremental clinical benefit is applied for "unmodeled" (i.e. without extrapolation) tumor sites
- To our knowledge, this was the first submission that aligned with these requirements

Methods

- A cost-effectiveness model with a partitioned survival analysis structure was developed with three mutually exclusive health states: progression-free, progressed disease, and death; alive states were further separated into on- and off-treatment (Figure 1)
- The model takes a Canadian healthcare payer perspective to compare the direct costs, life years (LYs), and quality-adjusted life years (QALYs). The model applies a 1-week cycle length, a lifetime time horizon (40 years), and a discount rate of 1.5% to outcomes
- The analysis included all MSI-H/dMMR tumor sites studies within the KEYNOTE-164 and KEYNOTE-158 clinical trials.[2, 3] KEYNOTE-164 is a Phase II non-randomized, open-label study of pembrolizumab in previously treated unresectable, locally advanced or metastatic MSI-H/dMMR colorectal cancer (CRC). KEYNOTE-158 is a Phase II non-randomized, open-label, multisite study of pembrolizumab in advanced unresectable and/or metastatic incurable non-colorectal solid tumors with disease progression on or intolerance to prior standard therapy

Figure 1: Cost-effectiveness model structure



- Long-term costs and clinical outcomes were explicitly modeled and stratified by tumor site where patient-level data were the most abundant: KEYNOTE-164 (colorectal) and KEYNOTE-158 (endometrial, gastric, and small intestine)
- The model evaluated pembrolizumab 200 mg, given intravenously every 3 weeks for up to 35 cycles or until progression, versus the current available treatment options (CAT). Since there are no approved treatment recommendations for MSI-H/dMMR solid tumors, relevant comparator therapies for the Canadian setting were identified using treatment guidelines for each tumor site and clinical opinion. Clinical systematic literature reviews were conducted to identify relevant published evidence for included comparators. For each tumor site, CAT was defined by weighting each constituent treatment by its respective market share:
  - **CRC:** pooled FOLFOX (leucovorin, 5-fluorouracil and oxaliplatin)/FOLFIRI (leucovorin, 5-fluorouracil and irinotecan), anti-vascular endothelial growth factor (VEGF) + chemotherapy, trifluridine/tipiracil
    - *Grouping of therapies (i.e. anti-VEGF + chemotherapy was only permitted where there was sufficient clinical rationale for a class effect)*
  - **Endometrial cancer:** paclitaxel, doxorubicin
  - **Gastric cancer:** paclitaxel, irinotecan, ramucirumab + paclitaxel, FOLFIRI, ramucirumab
  - **Small intestinal cancer:** nab-paclitaxel, anti-VEGF + chemotherapy, taxane-based treatments
    - *No clinical evidence was available for anti-VEGF + chemotherapy and taxane-based treatments; efficacy and safety therefore assumed equivalent to nab-paclitaxel*
  - **All other tumor sites:** average of the modeled CAT stated above, weighted by each tumor sites' relative prevalence
- Overall survival and progression-free survival for pembrolizumab were derived from KEYNOTE-164 and KEYNOTE-158 for each modeled tumor site using standard parametric survival models, with each final model chosen according to clinical plausibility, visual fit to the Kaplan–Meier data, and goodness-of-fit criteria
- Comparator survival outcomes were estimated using standard parametric models fitted to pseudo-individual patient-level data derived from digitized Kaplan–Meier data
- Health state utilities were derived from KEYNOTE-158 for all tumor sites except for CRC, using EQ-5D-3L questionnaires and the Canadian value set applied to derive utility values. For utilities specific to the CRC tumor site, EQ-5D utility values were obtained from Grothey et al. 2013.[4] Utilities were assumed to be the same across treatment regimens
- Cost categories included drug acquisition, drug administration, subsequent treatment, subsequent administration, testing, resource use, end-of-life, and adverse events. Cost inputs, in CAD $, were derived from available relevant Canadian sources. All drug acquisition costs were at list price
- Tumor sites for which the number of observations were not deemed suitable for explicit extrapolation of study outcomes ("unmodeled") were included in the analysis (ovarian, pancreatic, cholangiocarcinoma, brain, sarcoma, breast, cervical, neuroendocrine, prostate, adrenocortical, mesothelioma, thyroid, small cell lung cancer, urothelial, salivary, renal, and other tumors). Conservatively, to align with the CDA-AMC guidance, no incremental clinical benefit was assumed for pembrolizumab. For each of these unmodeled tumor sites, both pembrolizumab and the comparators' QALYs and LYs were set equal to the weighted modeled CAT results, despite clinical expectation that pembrolizumab would offer clinical benefits. The only incremental impact captured for these sites was acquisition costs, where pembrolizumab acquisition costs were compared to a weighted average of the modeled CAT acquisition costs
- Results are presented for pembrolizumab versus weighted CAT. Results for each site were then weighted by the tumor site prevalence to provide an overall result for the entire licensed indication
- Table 1 presents the tumor site prevalence based on the Canadian (excluding Quebec) epidemiological data

Table 1: Tumor site prevalence model inputs

Tumor site	Prevalence
CRC	33.06%
Endometrial	18.50%
Gastric	24.26%
Small intestine	4.20%
Pancreatic	2.91%
Prostate	5.32%
Adrenocortical	2.60%
Renal	2.38%
All other tumors with a prevalence lower than 2%	*6.77%*

Key: CRC, colorectal cancer.

Results

- In deterministic analysis, pembrolizumab was associated with an increase in LYs, QALYs, and costs compared with CAT (Table 2). This resulted in an incremental cost-effectiveness ratio (ICER) of $33,946 per QALY and net health benefit (NHB) of 2.21, indicating that pembrolizumab is cost-effective at a willingness-to-pay (WTP) threshold of 100,000 $/QALY

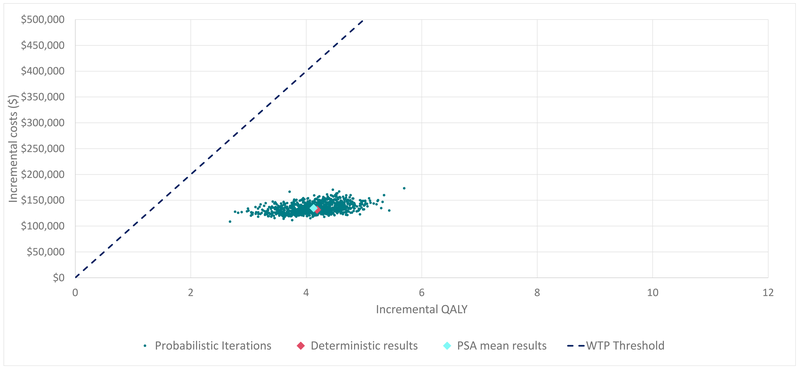
Table 2: Deterministic results for pembrolizumab vs CAT for all MSI-H/dMMR solid tumors

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER	NHB
CAT	$109,493	1.19	0.81	–	–	–	–	–
Pembrolizumab	$223,263	5.95	4.16	$113,769	4.77	3.35	$33,946	2.21

Key: CAT, current available treatment options; ICER, incremental cost-effectiveness ratio; LY, life year; NHB, net health benefit; QALY, quality-adjusted life year.

- Figure 2 presents the probabilistic results, which were well-aligned with the deterministic results (ICER = $35,618, NHB = 2.13)

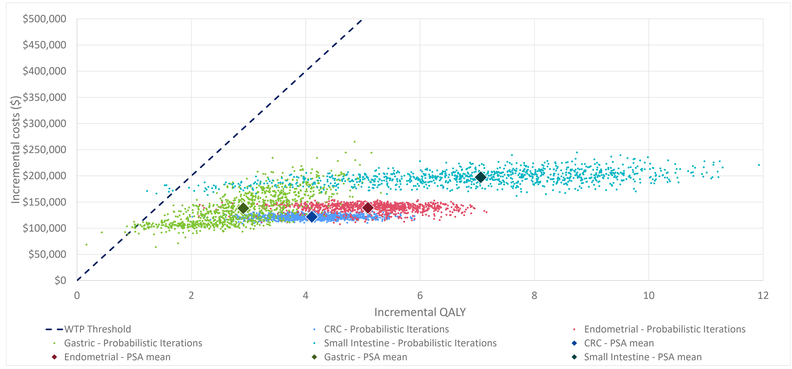
Figure 2: Probabilistic cost-effectiveness plane for all MSI-H/dMMR solid tumors



Key: MSI-H/dMMR, microsatellite instability-high/mismatch repair deficient; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; WTP, willingness-to-pay.

- Figure 3 presents the disaggregated probabilistic results for each of the tumor sites modeled explicitly. Pembrolizumab is cost-effective at a WTP threshold of $100,000/QALY within each of these specific tumors

Figure 3: Probabilistic cost-effectiveness plane for all MSI-H/dMMR solid tumors



Key: CRC, colorectal cancer; MSI-H/dMMR, microsatellite instability-high/mismatch repair deficient; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness to pay.

- Scenario analysis found that the model was most sensitive to changes in the time horizon and discount rate. One-way sensitivity analysis showed that the parameters that were associated with the greatest uncertainty were mostly those that related to the most prevalent site (i.e. CRC). However, reasonable changes to these parameters in both scenario and one-way sensitivity analysis do not influence the conclusions of the analysis

Discussion

- The analysis presents a well-founded estimation of the cost-effectiveness of pembrolizumab for MSI-H/dMMR solid tumors. Results were robust to plausible variations in parameters conducted via sensitivity analysis. However, there are several important assumptions and limitations that could not be explored in sensitivity analyses to consider when interpreting results, as they relate to the evaluation of tumor agnostic therapies
- In line with CDA-AMC guidelines, the "unmodeled" tumor sites assumed no treatment benefit for treatment with pembrolizumab, contrary to clinical expectations. While this assumption is highly conservative, the explicitly "modeled" tumor sites within this analysis represent 80% of the population, limiting the overall impact. Pembrolizumab's definitive clinical impact in these sites outweighs the uncertainties and assumptions on the "unmodeled" sites when interpreting overall results. Nonetheless, it may be more reasonable to consider inclusion of the "unmodeled" sites within sensitivity analysis rather than the base case
- Small patient numbers were the key limitations requiring many sites to be "unmodeled"; however, other statistical methods such as Bayesian hierarchical models could be explored that would capture heterogeneity between tumor sites, while allowing for the "borrowing" of information between tumor sites to mitigate the impact of small populations
- While the stratified explicit modeling attempts to capture a part of the heterogeneity between the tumor sites, the underlying clinical trial (i.e. KEYNOTE-158), having a basket trial design, was not designed to inform clinical efficacy for each individual tumor, and conclusions should not be drawn on a per-site basis
- This analysis was conducted considering the publicly available list prices of drugs. Therefore, the results may not be reflective of the true cost-effectiveness of the products to payers, where confidential pricing arrangements may be in place

Conclusion

- This study demonstrates that pembrolizumab provides a valuable and cost-effective therapy for Canadian patients with MSI-H/dMMR solid tumors who progressed following prior treatment, despite several conservative assumptions

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Disclosures:
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