#EE416

Cost-effectiveness of pembrolizumab monotherapy for the first-line treatment of adult patients with microsatellite instability high/mismatch repair-deficient metastatic colorectal cancer in France

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Background

- Keytruda® (pembrolizumab) is a humanized monoclonal antibody designed to block the Programmed Death-1 (PD-1) receptor, a negative regulator of T-cell anti-tumor defense.
- Pembrolizumab was recently approved by EMA for the treatment of patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) unresectable or metastatic colorectal cancer (mCRC) in the first-line setting.
- Approval was based on the results of the KEYNOTE-177 study (data cutoff Feb 19, 2020), a phase III trial that included patients with MSI-H/dMMR unresectable or mCRC[1]. Patients were randomized to receive either pembrolizumab monotherapy or chemotherapy ± targeted therapy. The median follow-up was 32.4 months (range, 24.0 to 48.3).
- There was a statistically significant improvement in progression-free survival (PFS) in favor of the pembrolizumab arm (HR 0.60, 95% CI 0.45-0.80; p=0.0002), and a doubling of the median PFS with a clinically relevant gain of 8.3 months with pembrolizumab (16.5 months for pembrolizumab versus 8.2 months for SoC).
- The French Health Technology Assessment (HTA) agency requires to assess the cost-effectiveness for innovative therapies, in order to help decision making regarding drug price.

Objective

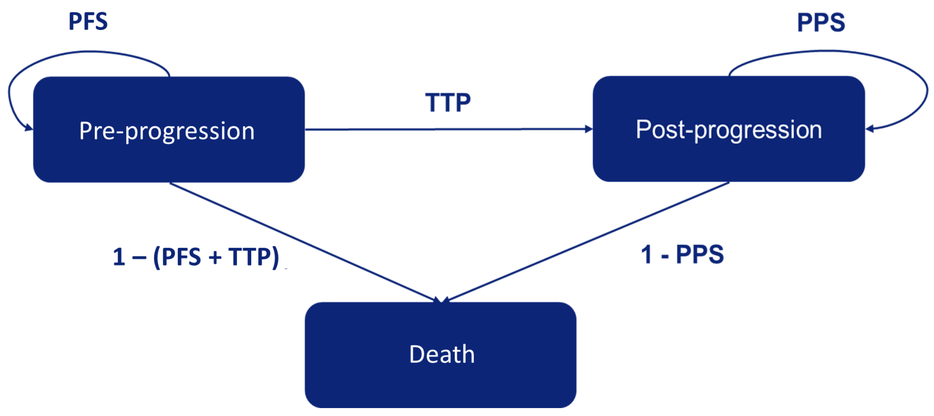
- The aim of the present analysis was to evaluate the cost-effectiveness of pembrolizumab vs. standard-of-care (SoC, i.e. chemotherapy ± targeted therapy) as first-line treatments in adult patients with MSI-H/dMMR mCRC from the French Health system perspective.

Method

Economic model

A three-health-state transition model (pre-progression, post-progression and death) was developed and adapted to the perspective of the French Health system (Figure 1) to estimate the incremental cost-effectiveness ratio (ICER) of pembrolizumab versus chemotherapy +/- targeted therapy, following French HTA guidelines[3].

Figure1. Model structure



PFS: progression free survival, PPS : post-progression survival, TTP : time to progression

- The duration of each cycle of the model was one week
- Costs and health outcomes were projected over a 15-year time horizon (based on a trade-off between expected proportion of surviving patients in each treatment arm and uncertainty generated by extrapolations, following HAS guidelines) and were discounted at 2.5% per year

Efficacy, safety and QoL parameters

- Transitions between health states were extrapolated from PFS, TTP, PPS and OS Kaplan-Meier curves from the KEYNOTE-177 study based on parametric methods.
- Grades 3+ adverse events with an incidence equal to or over 5%, as observed in KEYNOTE-177, were considered.
- Utility data were derived from the KEYNOTE-177 study and were converted to French population-based utilities using the French value set[2]:
  - Utility scores of "pre-progression" state, were higher for pembrolizumab compared to SOC.
  - Utility score of “post-progression” state, were common for pembrolizumab and SoC
- Mean disutility values related to grades 3+ adverse events (5% threshold) were applied; they were different for pembrolizumab vs. comparators.

Cost parameters

- Medical costs (in 2019 Euros) were assessed, from a health system perspective, taking into account all French health system stakeholders.
- Costs included drug acquisition and administration of first and second-line treatment, transportation, follow-up, adverse events management, surgery and end of life[4-6].
- Resource use was derived from KEYNOTE-177, published literature and independent experts' opinions.

Robustness of the results was assessed using deterministic, probabilistic and scenario analyses.

Results

Base Case analysis

- Over a 15-year time horizon, pembrolizumab was projected to increase average life expectancy by 1.62 years (19,4 months) compared to SoC (with absolute gain of 1,52 QALYs (18,2 months in perfect health))
- The average total cost of care over a 15-year time horizon for pembrolizumab was €138,084 (discounted) vs. €66,331 for SoC (incremental cost of €71,753)
- These costs are mainly attributable to the higher acquisition costs of pembrolizumab vs. SOC, partially offset by lower costs for treatment administration, AEs and end of life for pembrolizumab vs. SoC.
- ICER of pembrolizumab vs. SoC was €44,385/LY and €47,333/QALY (Table 1).

Table 1. Base case analysis results

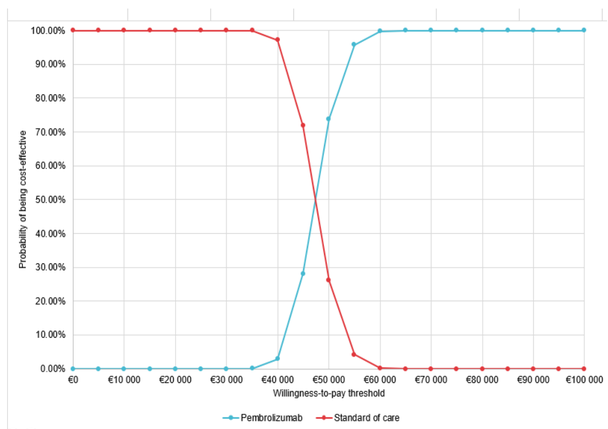
	Cost (€)	LYs	QALYs	ICER (€/LYs)	ICER (€/QALY)
Pembrolizumab	138,084	4.728	3.808	44,385	47,333
SoC	66,331	3.111	2.292	-	-

Sensitivity analyses

Deterministic sensitivity analyses highlighted the low uncertainty of these results relative to the input data with variations of 3% or less in the estimated ICER. The numerical parameter with the greatest impact on the ICER was the estimated pre-progression utility for pembrolizumab.

- Probabilistic sensitivity analysis estimated a mean ICER of pembrolizumab vs. SoC at €47,451/QALY (+0.2%).
- Figure 2 shows the cost-effectiveness acceptability curve for pembrolizumab compared with SoC. For a willingness to pay of €54,000/QALY, pembrolizumab had a 90% chance of being the most efficient strategy.
- These cost-effectiveness acceptability curves reflect the low uncertainty in the estimated baseline ICER.

Figure 2. Cost-effectiveness acceptability curves



Scenario analyses

- Results were robust to scenario analyses testing structural and methodological assumptions
- The scenario with the greatest impact on the ICER used alternative assumptions regarding the second-line treatment distribution and efficacy according to KEYNOTE-177 data (€21,920/QALY; -54% compared to the basecase analysis).

Conclusion

Pembrolizumab is cost-effective vs. SoC treatments for the first-line treatment of adult patients with MSI-H/dMMR mCRC in France based on a willingness-to-pay of €54,000/QALY.

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