Cost-effectiveness of pembrolizumab as an adjuvant treatment for renal cell carcinoma post-nephrectomy 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 approved by the European Medicines Agency (EMA) for the adjuvant treatment of adults with renal cell carcinoma (RCC) at increased risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.
- Approval was based on the results of the KEYNOTE-564 trial (data cutoff Dec 14, 2020), a phase III trial that included a total of 994 patients with RCC who were at high risk of recurrence after nephrectomy or following nephrectomy and resection of metastatic lesions. Patients were randomized to receive either pembrolizumab or placebo intravenously in a 1:1 ratio. The median follow-up was 24.0 months (range 2.5 to 41.5) in the pembrolizumab arm.
- The clinical benefit of pembrolizumab was confirmed by an updated analysis (data cutoff Jun 14, 2021) that showed a statistically significant improvement in disease-free survival in favor of pembrolizumab with a 37% reduction in the risk of recurrence or death (HR=0.63, IC95%: [0.50;0.80]) after an additional 6-months follow-up.
- The French Health Technology Assessment (HTA) agency requires to assess the cost-effectiveness for innovative therapies, in order to help decision making regarding the drug price.

Objective

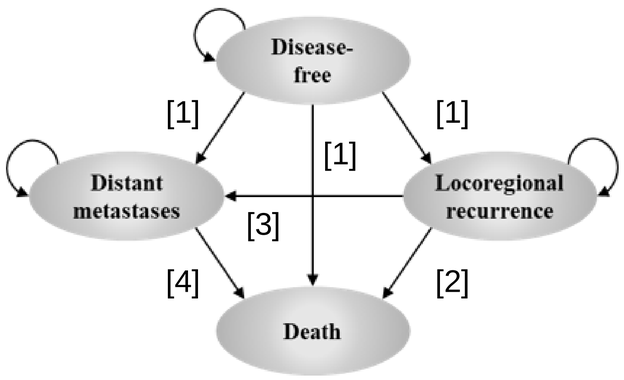
- To evaluate the cost-effectiveness of pembrolizumab vs. routine surveillance for the adjuvant treatment of adults with RCC at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions, from the French healthcare system perspective.

Method

Economic model

- A four-state Markov model (disease-free [DF], locoregional recurrence [LR], distant metastases [DM], and death) was developed to estimate, costs, effectiveness, and incremental cost-effectiveness ratio (ICER) of pembrolizumab vs. routine surveillance following French HTA (Haute Autorité de Santé (HAS)) guidelines[1] (Figure 1).

Figure 1. Model structure



[1] : KEYNOTE-564
[2] : Assumed equal to DF to Death
[3] : Brassier et al. 2021[2]
[4] : Network meta-analysis including metastatic treatments reimbursed in France for RCC*

**In the base case analysis, patients who transition to DM state ≥24 months from adjuvant pembrolizumab initiation can be retreated with an immunotherapy (IO).*

- Costs and health outcomes were projected over a 30-year time horizon (based on a trade-off between available robust data and uncertainty generated by extrapolations following HAS guidelines) and were discounted at 2.5% per year. The duration of each cycle was 1 week.

Clinical parameters – efficacy, safety and utility scores

- Transition probabilities from the DF state were estimated from the KEYNOTE-564 trial, using parametric models to extrapolate the cause-specific hazards of each transition over time. A treatment-effect waning as explored by NICE after 47.5 months (observation period) was considered.
- Transitions starting from LR state were obtained from the trial and literature considering only chirurgical treatment of those LR.
- Transition from DM state were estimated from a network meta-analysis including metastatic treatments reimbursed in France for RCC.
- Grade 3+ adverse events (AE) that occurred at least 2 times were considered for the pembrolizumab arm, by considering recurrence.
- For the DM state, EQ-5D-3L data from KEYNOTE-426 (metastatic RCC trial) were used. Utility for DF and LR states were estimated through EQ-5D-5L data collected in the KEYNOTE-564 trial mapped to EQ-5D-3L to fit with the utility scores for DM state. Utility scores were estimated using the French value sets[3]. Mixed models for repeated measures (MMRM) were used. QALY loss related to the tolerance of pembrolizumab and its administration were considered.

Cost parameters

- Direct medical costs (in €2022) were assessed, from a health system perspective, taking into account all French health system stakeholders.
- Costs included drug costs of adjuvant and later line treatments (acquisition and administration), follow-up, AE management, surgery, transportation and end of life.

Results

Base case analysis

- After 5 years the model suggests that pembrolizumab reduces risk of progression to severe stages with a proportion of patients remaining DF increased by 21% with pembrolizumab versus routine surveillance.
- Over a 30-year time horizon, pembrolizumab was projected to increase (discounted) average life expectancy of 1.21 years (14.56 months) with an absolute gain of 0.97 QALYs (11.59 months spent in perfect health).
- The average additional cost of care over a 30-year time horizon with adjuvant pembrolizumab was €28,339 (discounted). These costs are mainly attributable to the adjuvant drug cost, partially offset by savings in metastatic treatment (€48,966).
- ICER of pembrolizumab vs. routine surveillance was €29,342/QALY.

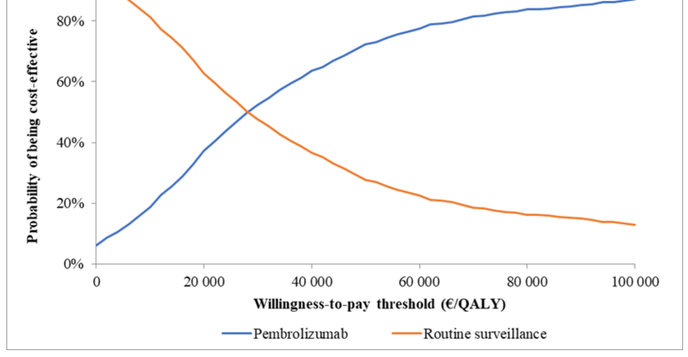
Table 1. Results of the base case analysis (Time horizon : 30 years)

Therapeutic strategy	Costs	LYs	QALYs	ICER (€/LY)	ICER (€/QALY)
Routine surv.	€172,599	11.14	9.17		
Pembrolizumab	€200,938	12.36	10.14	€23,355/LY	€29,342/QALY

Sensitivity analyses

- More than 80% of the deterministic sensitivity analyses on structural choices and model hypotheses gave an ICER inferior to €40,000/QALY.
- Probabilistic sensitivity analysis estimated a mean ICER of pembrolizumab vs. routine surveillance at €28,540/QALY (-2.7%).
- Figure 2 shows the cost-effectiveness acceptability curve for pembrolizumab compared to routine surveillance. These cost-effectiveness acceptability curves reflect the low uncertainty in the estimated baseline ICER.

Figure 2. Cost-effectiveness acceptability curves



- The results were most sensitive to the retreatment hypothesis. Adjuvant pembrolizumab becomes the dominant strategy if retreating with an IO after initial IO adjuvant treatment is not possible

Conclusion

- Model-based analysis suggests that pembrolizumab improves life expectancy and has more than 80% probability of being cost-effective versus routine surveillance assuming a WTP under €67,000/QALY. Results were robust to scenario analyses testing structural and methodological assumptions. The model and the methodology of the evaluation have been accepted by the French HTA agency.

1. HAS. Methodological recommendation – Methodological choices for cost-effectiveness assessment2020.
2. Brassier et al. Percutaneous Ablation Versus Surgical Resection for Local Recurrence Following Partial Nephrectomy for Renal Cell Cancer: A Propensity Score Analysis (REPART Study—UroCCR 71)
3. Andrade, L.F., et al., A French Value Set for the EQ-5D-5L. Pharmacoeconomics, 2020. 38(4): p. 413-425

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