Cost-effectiveness of pembrolizumab plus lenvatinib for treatment of advanced endometrial carcinoma in women who have progressed following prior systematic therapy and are not candidates for curative surgery or radiation 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 in association with lenvatinib (receptor tyrosine kinase inhibitor) was recently approved by the EMA for the treatment of adult patients with advanced endometrial cancer (aEC) who have progressed after receiving at least one platinum-based chemotherapy regimen and are not candidates for curative surgery or radiation. Approval was based on the results of the 1st interim analysis (October 26th, 2020) of KEYNOTE-775 study, which is a phase-III trial that includes a total of 827 patients randomized in a 1:1 ratio to receive either pembrolizumab plus lenvatinib (PEM+LEN) or chemotherapy of the treating physician's choice[1].

There was a statistically significant improvement in progression-free survival (PFS) and in overall survival (OS) in favor of the PEM+LEN arm with a 38% reduction in the risk of death compared to the chemotherapy arm (HR 0.62, IC95%: [0.51 ; 0.75], p<0.0001); and a clinically relevant gain of 6.9 months in OS (18.3 vs.11.4 months in chemotherapy arm).

French HTA agency granted an ASMR III to Keytruda®. In order to help decision making regarding drug price of innovative therapies, it also requires to assess the cost-effectiveness.

Objectives

To evaluate cost-effectiveness of PEM+LEN for treatment of aEC in women who have progressed following prior systemic therapy and are not candidates for curative surgery or radiation, from the French healthcare system perspective.

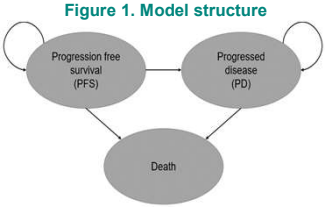
Methods

Economic model

A three-state partitioned survival model (pre-progression, post-progression and death) was developed to estimate incremental cost-effectiveness ratio (ICER) of PEM+LEN versus standard of care (SoC) chemotherapy (doxorubicin or paclitaxel) (Figure 1) for treatment of aEC in women who have progressed following prior systemic therapy and are not candidates for curative surgery or radiation. The duration of each cycle of the model was one week and patients were distributed within the three health states according to the area under the curves for probability of OS and PFS with time.

Costs and health outcomes were projected over a 10-year time horizon (to consider all expected costs and results) and were discounted at 2.5% per year.

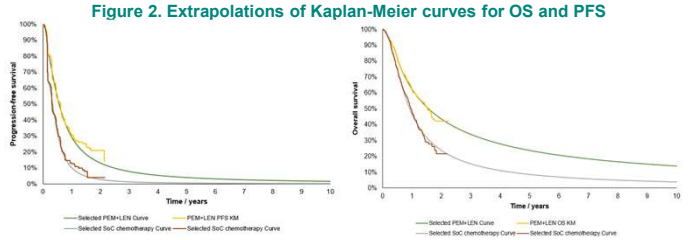
Figure 1. Model structure



Clinical parameters

- Efficacy, safety and quality of life data were derived from the phase 3 study KEYNOTE-775. All grade 3+ adverse events (AE) with an incidence ≥ 1% were considered in the model.
- PFS and OS (*Figure 2*) were extrapolated using a piecewise approach : KM + parametric function (log-logistic for OS and PFS, both arms). Time on treatment (ToT) was extrapolated with a generalized gamma curve in both treatment arms.

Figure 2. Extrapolations of Kaplan-Meier curves for OS and PFS



- State utility scores were estimated by a mixed effects linear regression model implementing EQ-5D-5L data converted to French population-based utilities using the French value set[2].
- Different utility scores were used for each health state (pre- and post-progression). QALY loss related to the tolerance profile of each treatment was a function of mean disutility value related to AE/year/episode, of the duration and frequency of each AE.

Cost parameters

- Only direct medical costs were considered, based on public sources (including drug acquisition and administration of first and second-line treatment, transportation, follow-up, AE management and end of life care). Resource use was derived from KEYNOTE-775, published literature, medico-administrative databases and independent clinical experts' opinions.
- Medical costs (in 2021 €) were assessed, from a health system perspective, considering health insurance and out-of-pocket.
- ICER was calculated as cost per quality-adjusted life year (QALY) gained and per life year gained (LYG).

Results

Base case analysis

- Over a 10-year time horizon, the model projected that PEM+LEN is associated with an increased average life expectancy of 1.25 years (15 months), an absolute gain of 1.04 QALYs (12.5 months spent in perfect health) and an incremental cost of €131,293 (discounted) compared to SoC (*Table 1*). This cost is mainly attributable to the costs of drugs (acquisition and administration) and is partly offset by the savings in terms of subsequent therapy and palliative care.

Table 1. Results of base case analysis

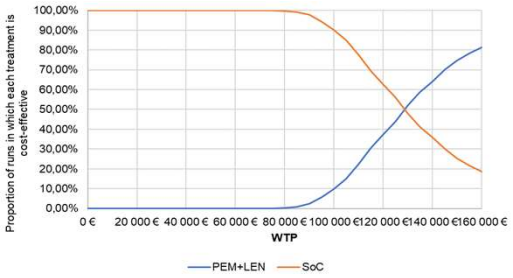
Therapeutic strategy	Costs (€)	LYs	QALYs	Δ Costs	Δ QALYs	ICER (€/LY)	ICER (€/QALY)
SoC	€20,688	1.71	1.42			-	-
PEM+LEN	€151,982	2.96	2.46	€131,293	1.04	€104,607/LY	€126,247/QALY

Sensitivity Analyses

Deterministic and probabilistic sensitivity analyses and scenarios analyses were conducted to assess robustness of results.

- The univariate deterministic sensitivity analysis showed that the different numerical parameters of the model had a limited impact on the ICER (<2%). The parameter with the greatest impact on the ICER was the pembrolizumab proportions of doses received.
- Probabilistic sensitivity analysis estimated mean ICER of pembrolizumab plus lenvatinib vs. SoC at €129,470/QALY (+3%). The acceptability curve shows that PEM+LEN has more than 80% probability of being cost-effective beyond the willingness-to-pay (WTP) threshold of €160,000/QALY compared with SoC *(Figure 3)*.

Figure 3. Cost-effectiveness acceptability curves



- Scenario analyses of the model's structuring choices showed its robustness. Results were mostly sensitive to parametric survival functions chosen to extrapolate overall survival, with an ICER varying from €107,532/QALY (-15%) with log-normal to €144,565/QALY (+14%) with Weibull.

Conclusion

Model-based analysis suggests that PEM+LEN improves life expectancy and has more than 80% probability of being cost-effective versus chemotherapy assuming a WTP under €160,000/QALY. Results were robust to scenario analyses testing structural and methodological assumptions. This model has been evaluated and adopted by French HTA agency.

1.Makker, V. et al. Lenvatinib plus pembrolizumab for advanced endometrial cancer. N. Engl. J. Med. https://doi.org/10.1056/NEJMoa2108330 (2022)
2.Andrade, L.F., et al., A French Value Set for the EQ-5D-5L. Pharmacoeconomics, 2020. 38(4): p. 413-425