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Cost-Effectiveness of Pembrolizumab as an Adjuvant Treatment for Adults and Adolescents Aged 12 Years and Older with Resected Stage IIb/IIc Melanoma in France

Saiag P[1], Meyer N[2] , Zhang S[3] , Jiang R[3], Mamane C[4] , Chaker O[4] , Bensimon L[4] , Babonneau A[4] , Hidra R[5] , Rey L[5] , Leproust S[5] , Rai A[6] , Vohra D[6] , Khatri G[6], de Pouvourville G[7]

1. Ambroise Pare Hospital, Boulogne Billancourt, France
2. Toulouse Cancer Institute (IUC) and University Hospital (CHU), Toulouse, France
3. Merck & Co, Rahway, NJ, USA
4. MSD, Paris, France
5. IQVIA, Courbevoie, France
6. Complete HEOR Solutions (CHEORS) North Wales, PA, USA
7. ESSEC Business School, Cergy Pontoise, France

Background

- Patients with localized, stage IIB and IIC melanoma may have poor prognosis, given its high risk of recurrence[1].
- 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 as adjuvant treatment of resected stage IIB/IIC melanoma (June, 22, 2022) based on the results of the **KEYNOTE-716 study** (data cutoff Jan, 04, 2022), a phase III trial comparing the efficacy and safety of pembrolizumab to active surveillance in 976 patients with stage IIB and IIC melanoma after surgical resection based on a median follow-up time of 14.3 months[2].
- The superiority of pembrolizumab was demonstrated on the primary endpoint, with a **35% reduction in the risk of first recurrence or death** (HR=0.65, 95%CI [0.46 ; 0.92], p=0.0066) and the second hierarchical endpoint with a **36% reduction in the risk of first distant metastasis** (HR=0.64, 95%CI [0.47 ; 0.88], p=0.00292).
- The French Health Technology Assessment (HTA) agency requires the assessment of cost effectiveness for innovative therapies, in order to help decision making regarding drug price.

Objective

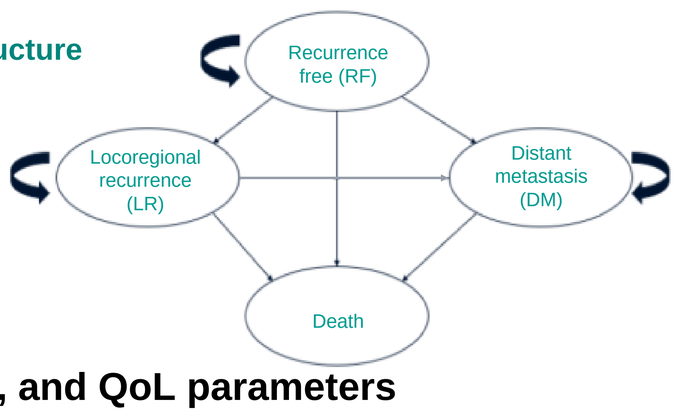
- To assess the cost-effectiveness of adjuvant pembrolizumab versus active surveillance for adults and adolescents aged 12 years and older with resected stage IIB/IIC melanoma, from the French healthcare system perspective, over a 30-year time horizon.

Method

Economic model

- A **four-state Markov transition model** (recurrence-free (RF), locoregional recurrence (LR), distant metastasis (DM), and death) was developed to determine the cost-effectiveness of pembrolizumab versus active surveillance (*Figure 1*), with one-week cycles.
- Costs and health outcomes were projected over a **30-year time horizon** and were discounted at 2.5% per year.

Figure 1. Model structure



Efficacy, safety, and QoL parameters

- Clinical data were **derived from the KEYNOTE-716** randomized trial for RF and LR states. **Extrapolations by parametric distributions** specific to each observed event were conducted for RF and a constant risk over time was supposed for LR.
- For DM state, clinical data were **derived from KEYNOTE-006** for pembrolizumab and a **network meta-analysis (NMA)** for other 1st line treatments.
- Grades 3+ adverse events (AE) with an incidence ≥ 1% and chronic AE grade 2+, as observed in KEYNOTE 716, were considered.
- Utility data from KEYNOTE-716 (EQ-5D-5L) and from KEYNOTE-006 (EQ-5D-3L) were used to populate RF/LR and DM utility scores, respectively. Utilities were mapped into EQ-5D-3L and weighted with the French value sets (*Table 1*).

Table 1. Utility values

State	RF	LR	DM pre-progression	DM post-progression
Utility value	0.887	0.849	0.80	0.69
Source	KEYNOTE-716		KEYNOTE-006	

Acronyms : AE : adverse events; DM : distant metastasis; HTA : health technology assessment; HR : hazard ratio; ICER : incremental cost-effectiveness ratio; LR : locoregional recurrence; NMA: network meta-analysis; RF : recurrence-free

Cost parameters

Only direct medical costs (in €2021) were considered, including acquisition and administration, transportation, follow-up, adverse events, subsequent treatments and end-of-life care costs

Results

Base case analysis

- Model simulations demonstrated that pembrolizumab as an adjuvant treatment for resected stage IIB/IIC melanoma versus active surveillance in France is associated with **1.06 life years (LYs) gained and 0.82 additional quality adjusted life years (QALYs)** as well as incremental costs of €27,258. **Incremental cost-effectiveness ratios were €33,110/QALY and €25,706/LY** (*Table 2*).
- Based on the model, 5 years after pembrolizumab adjuvant treatment (period with the highest risk of recurrence), **the proportion of patients remaining RF increased by 27% versus active surveillance**, and **progression to stage III or IV melanoma decreased by 65% versus active surveillance**.

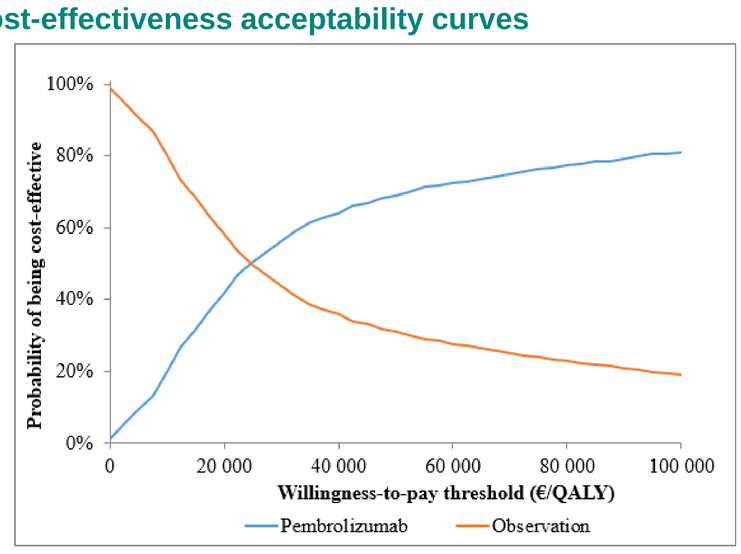
Table 2. Base case analysis results

Therapeutic strategy	Costs (€)	LYs	QALYs	ICER (€/LY)	ICER (€/QALY)
SoC	228,044	9.25	7.50	-	-
Pembrolizumab	255,302	10.31	8.33	25,706	33,110

Sensitivity analysis

- The univariate deterministic sensitivity analysis showed the parameter with the greatest impact on the ICER was the annual discount rate.
- Probabilistic sensitivity analysis estimated mean ICER of pembrolizumab vs. active surveillance at **€26,211/QALY** (-21% vs base case result) due to a higher QALY gain. With a willingness-to-pay (WTP) threshold up to €93,000/QALY, pembrolizumab has at least an 80% probability of being cost-effective relative to active surveillance (*Figure 2*).

Figure 2. Cost-effectiveness acceptability curves



Scenario analysis

- A majority of modeling assumptions tested in scenario analysis led to an ICER of less than **€40,000/QALY** for pembrolizumab versus active surveillance, attesting to limited parametric uncertainty.

Conclusion

Model-based analysis in the French context suggests that pembrolizumab as an adjuvant treatment has 80% probability of being cost-effective at a WTP of €93,000/QALY, **improves life expectancy, QALYs and reduces risk of recurrence and progression** to more severe stages.

The result is considered robust, due to the moderate variability of the sensitivity and probabilistic analyses. This model has been evaluated and accepted by French HTA agency.

1. Lee AY, Droppelmann N, Panageas KS, Zhou Q, Ariyan CE, Brady MS, et al. Patterns and Timing of Initial Relapse in Pathologic Stage II Melanoma Patients. Ann Surg Oncol. avr 2017;24(4):939-46.
2. Luke JJ, Rutkowski P, Queirolo P et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomized, double-blind, phase 3 trial. Lancet. 2022; S0140-6736(22)00562-1