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Cost-effectiveness analysis of pembrolizumab versus standard-of-care chemotherapy for first-line treatment of PD-L1 positive (> 50%) metastatic squamous and non-squamous non-small cell lung cancer in France

Christos Chouaid[a,*], Lionel Bensimon[b], Emilie Clay[c], Aurélie Millier[c], Laurie Levy-Bachelot[b], Min Huang[d], Pierre Levy[e]

[a] Centre Hospitalier Intercommunal, Créteil, France
[b] MSD France, Courbevoie, France
[c] Creativ-Ceutical, Paris, France
[d] Merck & Co., Inc., Kenilworth, New Jersey, USA
[e] Université Paris-Dauphine, PSL Research University, LEDa[LEGOS], Paris, France

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ABSTRACT

Introduction: In the KEYNOTE-024 trial, pembrolizumab demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS) versus Standard-of-Care (SoC) platinum-based doublets for first-line treatment of PD-L1 -positive (≥50%) metastatic Non-Small-Cell Lung Cancer (NSCLC) patients with no EGFR mutations or ALK translocations. This study aims to assess the cost-effectiveness of pembrolizumab versus SoC platinum-based chemotherapy from the French healthcare system perspective.

Methods: A three-state partitioned-survival model was adapted to project outcomes and costs of squamous and non-squamous NSCLC patients respectively, over a 10-year time horizon. Clinical and utility data were collected from the trial. A network meta-analysis was performed to consider platinum-based triplets also used for non-squamous NSCLC. Direct medical costs were considered based on ressources identified from the trial and literature. Costs and outcomes were discounted at 4% per year. Incremental cost-effectiveness ratios (ICERs) were calculated as cost per Life Year (LY) and cost per Quality-Adjusted Life Year (QALY). Sensitivity and scenario analyses were performed to assess the robustness of results.

Results: For squamous NSCLC, pembrolizumab was projected to increase life expectancy of patients by 0.93 LY (11 months), and 0.74 QALY (9 months) for an incremental cost of €62,032 compared with platinum-based doublets. The ICER of pembrolizumab versus platinum-based doublets was €66,825/LY and €84,097/QALY. For non-squamous NSCLC, pembrolizumab was projected to increase life expectancy of patients by 0.85–1.32 LYs (10.2–15.8 months) and 0.64–1.02 QALYs (7.7–12.2 months) for an incremental cost varying from €-14,947-+47,064 depending on the specific comparator. The ICER of pembrolizumab versus platinum-based chemotherapy with paclitaxel plus bevacizumab was €62,846/LY and €78,729/QALY; regimens including pemetrexed were dominated. Results were most sensitive to extrapolations of survival outcomes and assumptions for continued effectiveness and treatment duration of pembrolizumab.

Conclusions: Pembrolizumab appears cost-effective versus SoC chemotherapy for first-line treatment of PD-L1-positive (50%) metastatic NSCLC patients in France, assuming willingness-to-pay under 100,000€/QALY (OECD threshold in the discussion section).

1. Introduction

Lung cancer is the most common cancer worldwide with 1.8 million new cases reported in 2012 [1]. Tobacco smoking including second-hand smoke remains the major risk factor for lung cancer. The prognosis of lung cancer is generally poor with a 5-year overall survival rate estimated at 10–15% worldwide [2]. In France, 5-year and 10-year survivals rates were 17% and 10% in 2015, respectively [3]. The poor prognosis of lung cancer can be explained by a diagnosis at an advanced stage of the disease. In 2012, about 1.6 million deaths due to lung

* Corresponding author.
E-mail address: christos.chouaid@chicreteil.fr (C. Chouaid).

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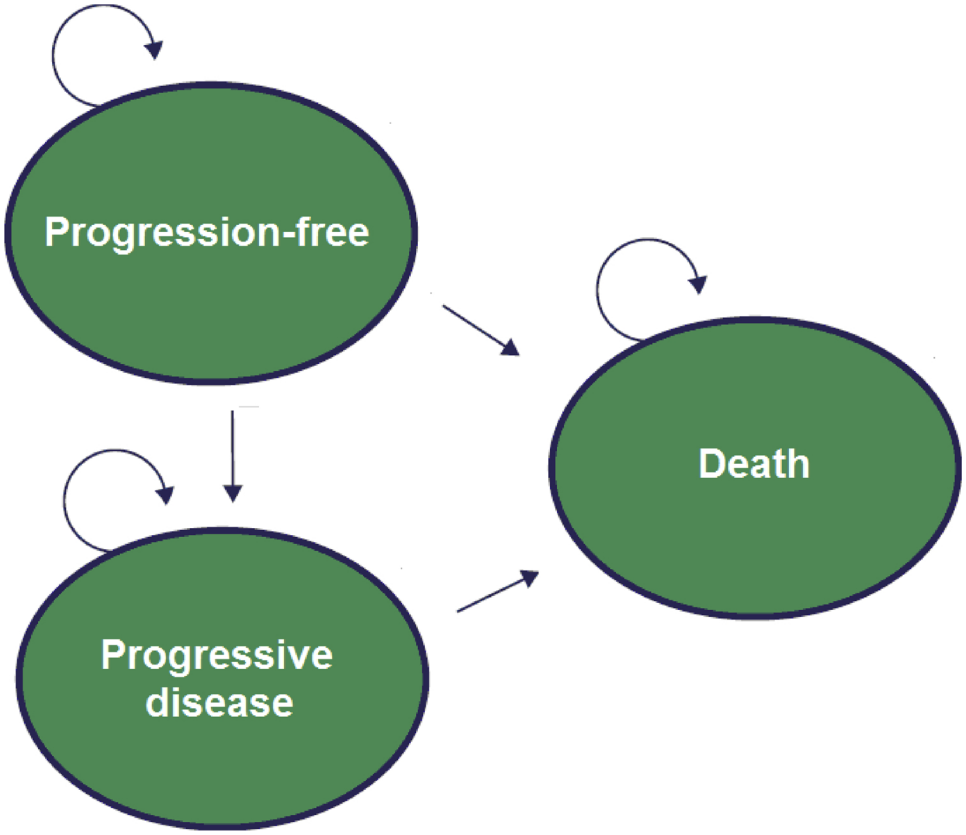

Fig. 1. Model structure and transitions.

cancer were reported worldwide, making it the leading cause of death due to cancer in men and the second one in women after breast cancer [1].

Non-small cell lung cancer (NSCLC) constitutes the most frequent histological type of lung cancers (85–90%) [4]. In this group, squamous NSCLC accounts for 25–30% of cases and non-squamous NSCLC for 70–75% [5].

At an unresectable/advanced stage, platinum-based doublets including a third-generation cytotoxic agent (gemcitabine, vinorelbine and taxanes) are recommended as first-line treatments for squamous and non-squamous NSCLC patients [4]. For non-squamous NSCLC patients, platinum-based doublets including pemetrexed or triplets with bevacizumab may also be considered. Despite these various treatment options, survival benefit remains moderate, with a 3–8 month median progression-free survival (PFS) [6,7] and a 7–17 month median overall survival (OS) reported in clinical trials [6,8,9].

In January 2017, pembrolizumab — a humanized monoclonal antibody designed to block the Programmed Death-1 (PD-1) receptor, a negative regulator of T cell anti-tumor defense — was approved by the European Commission for the first-line treatment of metastatic NSCLC. The labeling targets adults whose tumors express PD-L1 with a ≥50% tumor proportion score (TPS), with no EGFR mutations or ALK translocations [10]. Among patients with NSCLC, 30.2% have a PD-L1 tumor proportion score of 50% or greater [11] and 86.5% have no tumoral mutation of EGFR or ALK [12]. The approval was based on interim analysis of KEYNOTE-024, an international, randomized, open-label and active-controlled phase III trial. On May 9, 2016 (median duration of follow-up: 11.2 months), KEYNOTE-024 demonstrated statistically significant improvements in progression-free survival (PFS) and overall survival (OS) for patients treated with pembrolizumab 200 mg every 3 weeks (Q3W) compared with chemotherapy Q3W (five platinum-based regimens chosen by the investigator). In the intention-to-treat (ITT) population, median PFS was 10.3 months (95% confidence interval [CI], 6.7 to not reached) in the pembrolizumab arm and 6.0 months (95% CI, 4.2–6.2) in the chemotherapy arm (HR = 0.50; 95% CI 0.37-0.68; p < 0.001). The estimated rate of OS at 6 months was 80.2% in the pembrolizumab arm versus 72.4% in the chemotherapy arm (HR = 0.60; 95% CI 0.41-0.89; p = 0.005) [11].

The development of pembrolizumab appears as an innovative and promising strategy for the treatment of metastatic NSCLC patients. Therefore, healthcare spending allocated for the management of NSCLC may significantly increase compared with current clinical practice. The aim of this economic evaluation was to assess the cost-effectiveness of pembrolizumab versus SoC platinum-based chemotherapy for first-line treatment of metastatic squamous and non-squamous NSCLC patients expressing high levels of PD-L1 ≥50%) in France.

2. Methods

2.1. Model structure

A partitioned-survival model previously published by Huang et al [13] was adapted in accordance with the French Health Technology Assessment (HTA) guidelines for economic evaluation [14].

The model was used to project outcomes and costs of squamous and non-squamous NSCLC patients, respectively, within three mutually exclusive health states: "progression-free" (initial state of patient until progression); "progressive disease" (health state after progression) and "death" (absorbing state) (Fig. 1). The length of each model cycle was one week, to fit with the various dosage frequencies of interventions. At the end of each model cycle, patients were distributed within these three health states from the area under OS and PFS curves. The partitioned cohort modeling technique does not require the calculation of transition probabilities and naturally incorporates variability of treatment effect over time. This approach has previously been used for modeling in metastatic cancer [15–19].

Life-Years (LYs), Quality-Adjusted Life Years (QALYs) and costs of care were estimated at any model cycle and projected over a 10-year time horizon, long enough to capture most future costs and outcomes of the interventions. This time horizon was consistent with maximum life expectancy for most patients initiating chemotherapy according to survival data available in the literature [2,3] and previous economic studies published by the National Institute for Health and Care Excellence (NICE) [20–23]. Costs and outcomes were discounted at 4% per year. The incremental cost-effectiveness ratio (ICER) for pembrolizumab versus SoC platinum-based chemotherapy was calculated and expressed as cost per QALY gained and cost per LY gained.

Microsoft Excel 2010® was used for the development of the model (Redmond, WA, USA).

2.2. Patient population

The target population of KEYNOTE-024 was considered in the model, namely: adults, diagnosed with metastatic NSCLC, expressing high levels of PD-L1 (TPS ≥ 50%), without EGFR mutations or ALK translocations and naïve to systemic chemotherapy treatment for metastatic NSCLC. As the number of French patients included in the trial was insufficient (11 out of 305) to be considered as country-representative, baseline characteristics of the ITT population were used at the entry of the model (Table 1**).** Similar characteristics were reported for French patients in two observational studies [24,25].

Table 1
Baseline characteristics of the modeled population at the entry into the model (patients from KEYNOTE-024 trial) [11].

Characteristics	N = 305
Male gender, %	61.3
Age (years), median	65
Weight (kg), mean	70.73
Body surface area (m^2), mean	1.81
Tobacco status, %	
Former	70.8
Current	21.3
Never	7.9
ECOG score[a], %	
0	35.1
1	64.6
2	0.3
Stage, %	
IIIB	0.7
IV	99.3
Histology, %	
Squamous	18.0
Non-squamous	82.0

[a] Eastern Cooperative Oncology Group (ECOG) performance-status scores (from 0, no symptoms to 5, maximal disability).

2.3. Interventions

Interventions considered in the model were pembrolizumab and all treatments used in clinical practice according to French recommendations and market data [26,27]. No differentiation was taken into account between platinum agents (cisplatin and carboplatin) and between platinum-based doublets without pemetrexed since their equivalence was demonstrated in an indirect comparison performed by the UK National Health Service (NHS) [28]. In patients with squamous NSCLC, comparators were platinum-based doublets including a third-generation cytotoxic agent (gemcitabine, vinorelbine and taxanes). In patients with non-squamous NSCLC, comparators were platinum-based doublets including also pemetrexed or triplets including pemetrexed plus bevacizumab, paclitaxel plus bevacizumab, or gemcitabine plus bevacizumab. As no head-to-head evidence versus regimens containing bevacizumab were available in KEYNOTE-024, a network meta-analysis (NMA) of 10 randomized controlled trials was conducted [29].

2.4. Outcomes

2.4.1. Efficacy inputs

Clinical data including PFS and OS were obtained from the KEYNOTE-024 trial (data cut-off May 9, 2016) and the NMA, considering PFS as a proxy for treatment duration. Observed data in KEYNOTE-024 were then extrapolated to project outcomes to the end of the 10-year time horizon. Hazard ratios from the NMA were used to extrapolate PFS and OS for interventions not included in the trial.

Due to the low number of patients with squamous NSCLC in KEYNOTE-024 (n = 56 in squamous group and n = 249 in non-squamous group), extrapolations were performed in the ITT population and were then derived separately for squamous and non-squamous subgroups. The efficacy of pembrolizumab was assumed to be maintained after completing the 2-year maximum duration of treatment.

A piecewise modeling approach was performed, utilizing PFS and OS Kaplan-Meier curves until a cut-off point, and extrapolating data beyond with exponential, Weibull, Gompertz, log-normal or generalized gamma distributions as recommended by the NICE Decision Support Unit (DSU) [30] (Table 2). The clinical plausibility of extrapolated data was finally appraised based on visual inspection, published literature [31,32] and independent expert opinion.

For PFS, Kaplan-Meier curves were considered up to week 9, defined as the first imaging assessments date performed in KEYNOTE-024 and resulting in a drop between week 8 and 9 making modeling by standard parametric curves difficult. The best-fitting parametric models to extrapolate pembrolizumab and SoC PFS data beyond were the Weibull and the exponential distribution in the squamous subgroup and the generalized-gamma and the exponential distribution in the non-squamous subgroup, respectively.

For OS, Kaplan-Meier curves were considered up to week 22 for pembrolizumab and week 15 for SoC, as identified by the Chow test [33]. The exponential parametric function was used to extrapolate both pembrolizumab and SoC OS data beyond in the squamous and the non-squamous subgroups, respectively. The modeled analyses and extrapolation of OS reflects the cross-over permitted in KEYNOTE-024 for patients in the SoC arm to receive pembrolizumab following disease progression (43.7% of SoC arm patients crossed over).

Extrapolations of Kaplan-Meier curves in squamous and non-squamous subgroups are available in Supplementary Materials.

2.4.2. Safety inputs

Adverse events for the different strategies were identified from phase-III clinical trials: KEYNOTE-024 for pembrolizumab and chemotherapy with or without pemetrexed [11]; POINTBREAK for chemotherapy with pemetrexed and bevacizumab [34]; AVAIL for chemotherapy with gemcitabine and bevacizumab [35] and BEYOND for chemotherapy with paclitaxel and bevacizumab (Table 2) [35,36].

Grade 3–4 AEs related to treatment and reported in at least 1% of patients in one of these trials were considered in the model, via an impact on quality of life and management costs. All AEs were accounted for at the onset of treatment (first cycle of the model) for simplification purposes, and assuming the rates of AEs were independent of treatment duration, histology and time horizon. The mean duration of Grade 3–4 AEs reported in KEYNOTE-024 (31.5 days (95% CI, 26.4–36.7) was considered in the model, except for immune-mediated type 1 diabetes mellitus, that was assumed to have an impact on quality of life and cost until end of life (mean OS simulated by the model).

2.4.3. Utility inputs

In KEYNOTE-024, the EuroQoL-5 Dimensions, 3 Levels (EQ-5D 3L) was administered to elicit patient's preferences for given health states. Utility values were then estimated based on the stated preferences of

Table 2
Key input data of the model.

Inputs Efficacy	Base case value	Source
PFS		
Squamous	Pembrolizumab: KM9 weeks + Generalized gamma SoC: KM9 weeks + Exponential	KEYNOTE-024 [36]
Non-squamous	Pembrolizumab: KM9 weeks + Weibull SoC: KM9 weeks + Exponential	
OS		
Squamous	Pembrolizumab : KM22 weeks + Exponential SoC: KM15 weeks + Exponential	
Non-squamous	Pembrolizumab : KM22 weeks + Exponential SoC KM15 weeks + Exponential	
Utility		
PFS without AE	0.778	KEYNOTE-024 (EQ-5D-3 l) [36]
PFS with AE	0.687	
PD	0.641	
Unit cost (2017 Euros)		
Drug acquisition (for drugs funded on the top of DRG)		
Pembrolizumab 200 mg Q3W	€5367.62	National Tariff database (including taxes)
Pemetrexed 500 mg/m² Q3W	€1618.59	
Bevacizumab 15 mg/kg Q3W	€2490.60	
Diagnosis Related Group	€336	ATIH
Transportation	€80,48	Cour des Comptes
AEs management		
Anemia	€5,752	Chouaid et al (2017) [39]
Anorexia	€4,349	
Asthenia/Fatigue	€586	
Diarrhea	€2,879	
Nausea	€2,052	
Neutropenia	€93	
Stomatitis	€482	
Pneumonitis	€5,778	
Thrombocytopenia	207€	
Venous thromboembolism	€3,324	
Dehydration	€3,750	
Hemorrhage	€3,754	
Hypertension	€46	
Febrile neutropenia	€824	
Elevated transaminases	€3,500	
Colitis	€3,457	
Diabetes	€7742 €[a]	
Supportive care		
Erythropoietin + injection	€140,39	National Tariff database
Aprepitant	€45,81	
Test for pembrolizumab	€217	CCAM
Terminal Care	€386	Chouaid et al (2004) [40]
Treatment duration		
Pembrolizumab	Until progression with a maximum 2 years of treatment	Summary for product characteristics
Comparators	Until progression with a maximum 6 cycles of platinum, no treatment cap for bevacizumab or pemetrexed maintenance	Novello et al [4]

AE, adverse event; PFS, free-survival progression; KM, Kaplan-Meier; OS, overall survival; PD, progressive disease.
[a] Mean annual cost.

the French population using an algorithm published in the literature (Table 2) [37].

As differences in EQ-5D utility values between pembrolizumab and comparators were under a relevant difference threshold of 0.08 previously determined based on UK index scores [38], a pooled average utility value was considered for both pembrolizumab and comparators in the "progression-free" and the "progressive-disease" states, respectively. A utility decrement was applied for all AEs considered in the model based on the difference between utility values in the "progression-free state" with or without AEs.

2.4.4. Cost inputs

Resource use was derived from KEYNOTE-024, published literature and independent experts' opinions. Only direct medical costs (in 2017 Euros) were assessed, from a health system perspective, taking into account all stakeholders of the French health system (i.e. patients, compulsory and supplementary health insurance schemes, state, etc.) (Table 2) [14].

Acquisition costs for drugs reimbursed in addition to the Diagnosis-Related Group (DRG), namely expensive and in-hospital use drugs (i.e. pembrolizumab; bevacizumab and pemetrexed) were obtained from the French National Tarif database (BdM IT). Wastage was not considered for any medication. DRG cost for a chemotherapy infusion was estimated based on public and private weighted tarifs from the technical agency for hospital information database (ATIH). Transportation costs were obtained from data published by the Cour des Comptes (i.e. the supreme body for auditing the use of public funds in France). Premedication costs for drugs dispensed in retail pharmacies to prevent anemia (i.e. Erythropoietin) and nausea/vomiting (i.e. Aprepitant) were obtained from the National Tarif database and were applied at each chemotherapy infusion. It is really relevant to clarify that point. Erythropoietin cost was taken into account for only 20% of patients according to experts' opinions and included the injection by a home care nurse.

These costs were applied at each infusion up to progression (mean PFS simulated by the model) and limited to 2-year maximum treatment duration for pembrolizumab, 6 treatment cycles for platinum; no treatment cap was considered for bevacizumab or pemetrexed maintenance (34.8% of patients treated with doublets including pemetrexed and 48.4% of patients treated with triplets including pemetrexed plus bevacizumab as reported in French market data). Adverse events management costs were obtained from Chouaid et al [40].

The PD-L1 test cost was obtained using the immunohistochemistry test tariff referenced in the CCAM. The unit cost has been weighted by the prevalence of NSCLC patients expressing high levels of PD-L1 ($\geq$50%), as reported in KEYNOTE-024, to take into account the number of patients needed to detect a case. The final cost was applied at the first cycle of the model for patients treated with pembrolizumab.

After progression, second-line costs including acquisition, DRG, transportation and premedication costs were considered for 58.7% of patients in the SoC arm who switch to an anti-PD-1 in and out of the frame of the cross-over of KEYNOTE-024 and for 60.8% of patients in the pembrolizumab arm who switch to chemotherapy following progression. Terminal care costs were obtained from Chouaid et al [41].

2.5. Sensitivity analyses

The robustness of the model was assessed through sensitivity and scenario analyses.

Univariate deterministic sensitivity analysis (DSA) was performed on the following parameters: initial weight and body surface area, utilities, PD-L1 test cost, administration cost, management costs of adverse events, terminal care cost, parameters of parametric survival modeling and HRs from the NMA. Extreme values around tested parameters were defined by the variance estimates when available (i.e. 95% confidence interval) or assumptions. Results were reported in a Tornado diagram.

Multivariate probabilistic sensitivity analysis (PSA), simultaneously varying model parameters in 1000 Monte Carlo iterations, was also

Table 3
Base-case analysis results.

	Costs (2017 Euros)	QALYs	LYs	ICER
Squamous subgroup (25%)				
SoC	63,229	0.83	1.21	–
Pembrolizumab	125,261	1.57	2.14	€66,825/LY €84,097/QALY
Non-squamous subgroup (75%)				
SoC	70,790	1.04*	1.56	–
Platinum-based chemotherapy with gemcitabine plus bevacizumab	74,042	1.04**	1.51	Strictly dominated
Platinum-based chemotherapy with paclitaxel plus bevacizumab	80,330	1.38	1.98	€22,601/LY €28,448/QALY
Platinum-based chemotherapy with pemetrexed	86,902	1.23	1.80	Strictly dominated
Pembrolizumab	133,966	2.06	2.83	€62,846/LY €78,729/QALY
Platinum-based chemotherapy with pemetrexed plus bevacizumab	148,913	1.42	1.98	Strictly dominated

QALYs, Quality-adjusted life-years; LYs, life years.
* 1.04447.
** 1.0444.

performed. Results were reported in a cost-effectiveness acceptability curve (CEAC) representing the probability of an intervention being cost-effective over a range of different willingness-to-pay thresholds.

Scenario analyses assessed the impact of alternative structural assumptions on the ICER (e.g. different time horizon, discount rates, parametric model, utility values, continued treatment effect, treatment duration and exclusion of second-line treatments costs).

3. Results

3.1. Base-case analysis

Compared with chemotherapy regimens used in clinical practice, pembrolizumab was associated with a gain of LYs and QALYs for NSCLC patients, and an increase in the costs of care for NSCLC management (Table 3).

In patients with squamous NSCLC, pembrolizumab was associated with an expected gain of 0.93 LYs (11.2 months) and 0.74 QALYs (9 months) compared with SoC platinum-based chemotherapy in the KEYNOTE-024 trial. At 3 years, 29% of patients in the pembrolizumab arm were still alive compared to 9% in the SoC platinum-based chemotherapy arm according to the extrapolations of OS KM curves (Supplementary Materials). The total mean cost of pembrolizumab over a 10-year time horizon was estimated at €125,261, for an incremental cost of €62,032 in comparison to SoC. The ICER was estimated at €66,825/LY gained and €84,097/QALY gained.

In patients with non-squamous NSCLC, pembrolizumab was associated with an expected gain varying from 0.85 (10.2 months) to 1.32 (15.8 months) LYs and 0.64 (7.7 months) to 1.02 (12.2 months) QALYs gained according to the specific comparator. At 3 years, 40% of patients in the pembrolizumab arm were still alive compared to 16–25% in the SoC platinum-based comparator arms according to the extrapolations of OS KM curves (Supplementary Materials). The total mean cost of pembrolizumab for a 10-year time horizon was estimated at €133,966. The incremental cost of pembrolizumab varied from €-14,947 to €47,064. The cost-effectiveness frontier included pembrolizumab, platinum-based chemotherapy with paclitaxel plus bevacizumab and platinum-based chemotherapy without pemetrexed; other regimens, especially platinum-based chemotherapies including pemetrexed were strictly dominated. The ICER of pembrolizumab versus platinum-based chemotherapies with paclitaxel plus bevacizumab was estimated at €62,846/LY gained and €78,729/QALY gained.

3.2. Sensitivity analysis

The results from the DSA showed that uncertainty around results was mainly driven by PFS and OS estimates for pembrolizumab and comparators (Fig. 2). In the squamous subgroup, OS estimates for pembrolizumab had the highest impact on the model varying the ICER from €51,067/QALY to pembrolizumab being dominated by SoC platinum-based chemotherapy. In the non-squamous subgroup, OS estimates for platinum-based chemotherapy with paclitaxel plus bevacizumab had the highest impact on the model varying the ICER between €60,088/QALY gained and €307,094/QALY gained.

The results from the PSA demonstrated that pembrolizumab had an 80% probability of being cost-effective at a willingness-to-pay (WTP) threshold of €170,000/QALY in the squamous subgroup and €130,000€/QALY in the non-squamous subgroup (Fig. 3).

3.3. Scenario analyses

The results from the scenario analyses are presented in Supplementary Materials. Overall, these analyses led to similar ICERs compared with the base-case analysis. Nevertheless, assumptions on three variables of the model had significant consequences on the conclusions of the analysis: the efficacy duration of pembrolizumab, the treatment duration and the consideration of second-line costs.

4. Discussion

The present study assessed the cost-effectiveness of pembrolizumab versus SoC platinum-based chemotherapy for first-line treatment of PD-L1 -positive (≥50%) metastatic squamous and non-squamous NSCLC patients. Mainly based on the KEYNOTE-024 phase III trial, the economic analysis was performed for the French setting in accordance with current guidelines.

Over a 10-year time horizon, the base-case simulations confirmed significant improvements in LYs and QALYs for patients treated with pembrolizumab compared with regimens used in clinical practice. For the health system, this clinical benefit was associated with additional costs relative to NSCLC management. In the squamous subgroup, the ICER of pembrolizumab versus SoC platinum-based chemotherapy was estimated at €84,097/QALY gained and €66,825/LY gained. In the non-squamous subgroup, the ICER of pembrolizumab versus platinum-based chemotherapy with paclitaxel plus bevacizumab was estimated at €78,729/QALY gained and €62,846/LY gained. Other regimens, especially platinum-based chemotherapies with pemetrexed were strictly dominated. Comparable ICERs were documented with tyrosine kinase

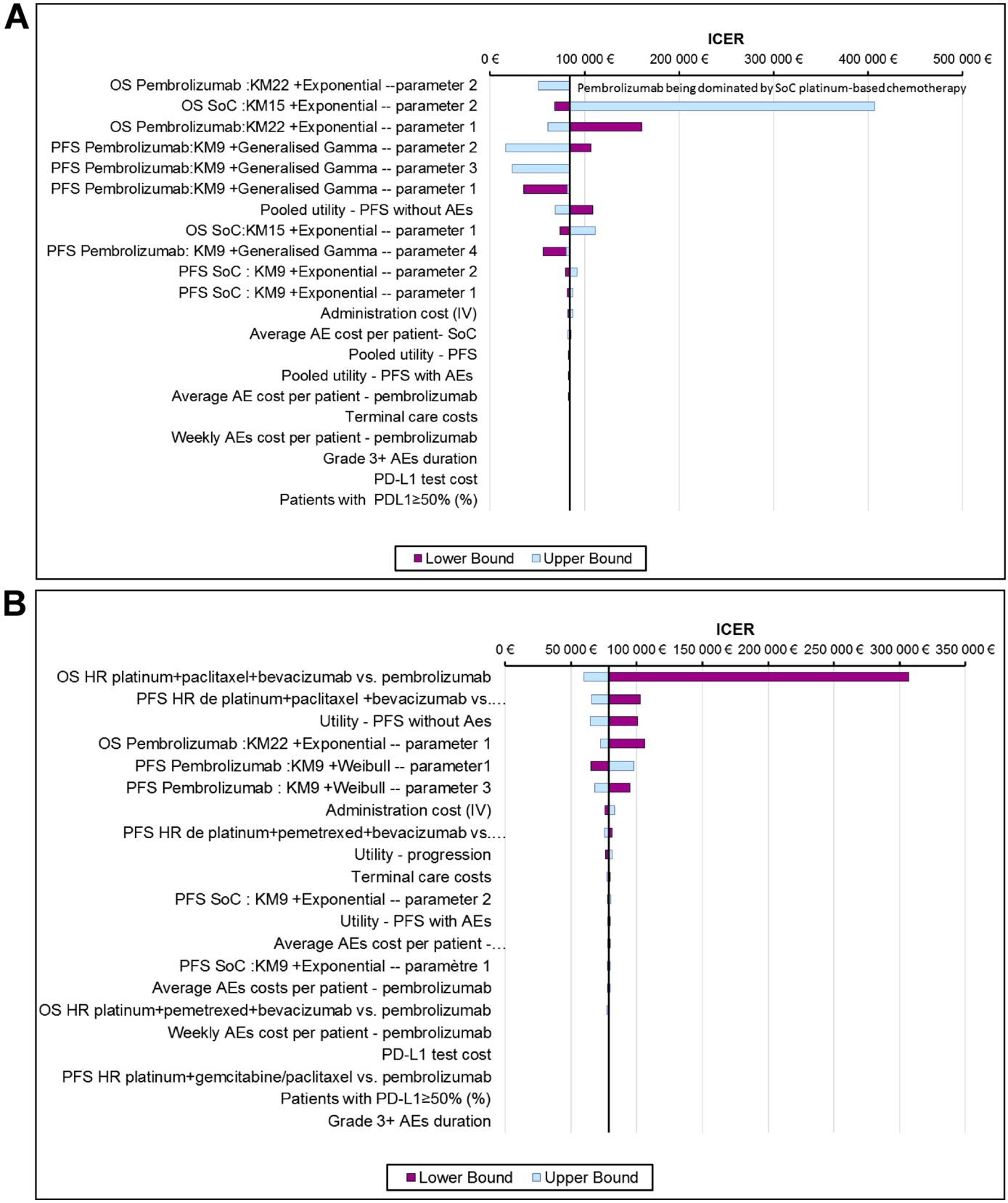

Fig. 2. Tornado diagram for the ICER per QALY of pembrolizumab versus standard-of-care chemotherapies in squamous NSCLC (A) and pembrolizumab versus chemotherapies with paclitaxel and bevacizumab in non-squamous NSCLC (B).

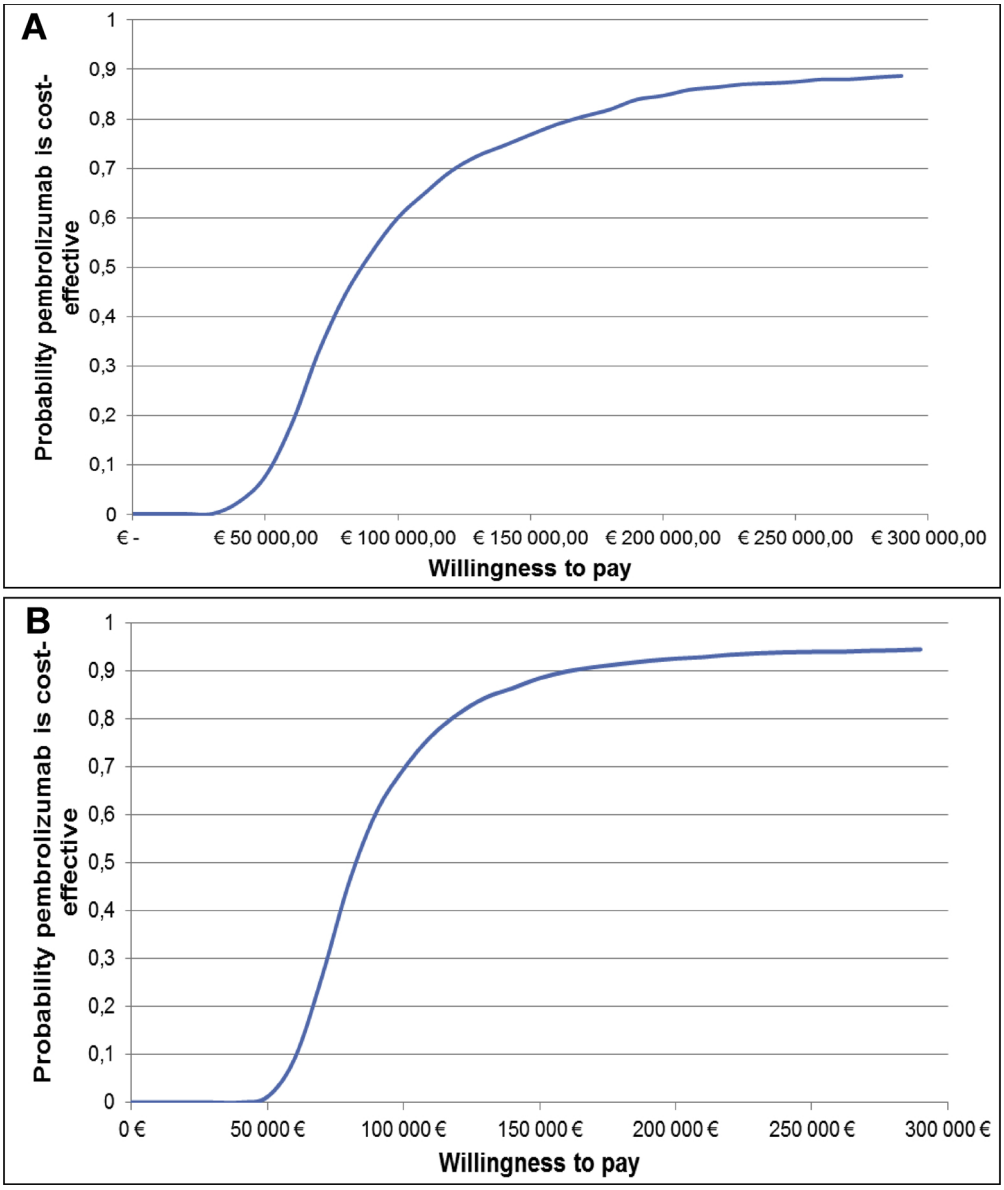

Fig. 3. Cost-effectiveness acceptability curves for squamous NSCLC (A) and non-squamous NSCLC (B).

inhibitors for first-line treatment of NSCLC patients with EGFR mutations [42,43] or ALK translocations [44].

However, the present study had several limitations due to data availability and assumptions made at the time of the analysis. First, extrapolations of survival data were based on interim analysis data from the KEYNOTE-024 trial and could change with the availability of data with longer-term follow-up. For interventions used in clinical practice and not included in the trial, extrapolations of OS and PFS were performed using HRs from indirect comparisons based on 10 trials for which there may have been uncontrolled sources of heterogeneity. The assumption of continued treatment effect after stopping pembrolizumab at 2 years was based on long-term results from the KEYNOTE-010 trial in previously treated NSCLC patients, and has not yet been documented for first-line treatment [45]. Regarding the method used to take into account some inputs, the number of AEs may be underestimated due to exclusion of lower frequency AEs. Also, it would have been preferred to apply a unique disutility related to each AE. The sensitivity and scenario analyze showed that uncertainty around results was mainly driven by these limitations.

At the time of the analysis, few elements allow robust validation of extrapolations for pembrolizumab and comparators. Long-term follow-up data for pembrolizumab (KEYNOTE-001), published literature and clinical trials for chemotherapies were used. Considering comparable populations, the model's estimates of OS and PFS for pembrolizumab and comparators seem acceptable. More recently, an updated analysis of KEYNOTE-024 conducted in the ITT population after a median follow-up of 25.2 months was published. At the time of the data cut-off (July 10, 2017,), OS estimates at 12 months were 70.3% (95% CI, 62.3%–76.9%) for the pembrolizumab group and 54.8% (95% CI, 46.4%–62.4%) for the chemotherapy group [46]. These long-term data are likely to confirm robustness of extrapolations and reduce uncertainty around results. In the ITT population, modeled OS estimates at 12 months were 69.3% (squamous: 62.8%; non-squamous: 70.8%) for the pembrolizumab arm and 54.1% (squamous: 45.4%; non-squamous: 58.9%) for the chemotherapy group.

Furthermore, results from the present analysis should be interpreted with caution with respect to other countries. Management costs of NSCLC were considered from the French health system perspective, although health benefits are thought to be generalizable. In contrast with other European countries such as the United Kingdom, economic

evaluation is appraised considering compliance to guidelines and serves as a basis for price negotiation in France ; a binary decision on reimbursement is not taken based on a willingness-to-pay threshold, as it may be the case in United Kingdom for example [47]. According to the World Health

Organization recommendation, a cost-effective strategy might have an ICER less than three times the national annual GDP per capita, namely €100,011/QALY in France (2016 OECD value). At this willingness-to-pay (WTP) threshold, pembrolizumab had a 60% probability of being cost-effective in the squamous subgroup and 70% probability of being cost-effective in the non-squamous subgroup.

A comparable study was recently reported by Huang et al in the setting of United States [13]. The authors concluded that pembrolizumab resulted in an expected gain of 1.31 LY and 1.05 QALY compared with SoC platinum-based chemotherapy; the ICER was $US97,621/QALY gained and $US78,344/LY gained. Although the conclusions of this analysis were consistent with our study, there were some differences in the design of the model. First, our analysis was performed in squamous and non-squamous NSCLC subgroups, respectively. This is an important issue since comparators differ according to tumor histology. The time horizon was 20 years in the analysis of Huang et al and 10 years in our model. Then, extrapolations of OS were not performed from the same cut-off and with the same parametric distribution. Resource use considered, and costs were adapted to the country perspective.

5. Conclusions

Pembrolizumab appears to be a promising strategy for patients with metastatic squamous and non-squamous NSCLC in comparison to SoC platinum-based chemotherapy. Improved PFS and OS demonstrated in KEYNOTE-024 and projected by the model are likely to extend life expectancy, quality-adjusted life expectancy and to increase costs associated with the NSCLC management. The present analysis suggests that first-line treatment with pembrolizumab is a cost-effective strategy compared with SoC platinum-based chemotherapy in squamous and non-squamous metastatic NSCLC patients expressing high levels of PD-L1 (≥50%) and without EGFR and ALK mutations in France although an explicit threshold is not available.

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Conflict of interest

In the past 5 years, Christos Chouaid received fees for attending scientific meetings, speaking, organizing research or consulting from AstraZeneca, Boehringer Ingelheim, GSK, Roche, Sanofi Aventis, BMS, MSD, Lilly, Novartis and Amgen

Laurie Lévy-Bachelot and Lionel Bensimon are employees of MSD France.

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