PCN12: COST-EFFECTIVENESS OF PEMBROLIZUMAB COMPARED TO CHEMOTHERAPY AS A TREATMENT FOR PATIENTS WITH PREVIOUSLY TREATED ADVANCED MELANOMA IN CHINA

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BACKGROUND AND OBJECTIVES

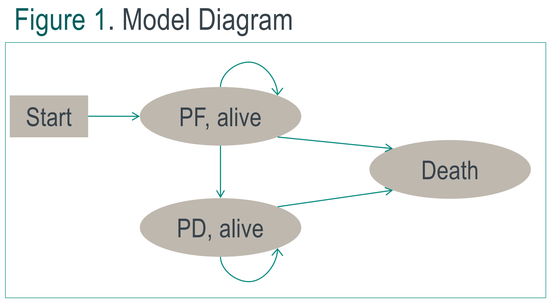
- It is estimated that the crude incidence of melanoma in China was 0.49/100,000, while the crude mortality rate was 0.27/100,000 in 2014 (Chen WQ, 2018). Among all melanoma patients, 25.1% and 12.8% of them were diagnosed with stage III and IV, compared with 9% and 4% in the US, respectively (Chi Z, 2011). 5-year survival for patients with stage IV was only 4.6% (Chi Z, 2011).
- Pembrolizumab was approved in China in July 2018 for the treatment of adult patients with advanced (unresectable or metastatic) melanoma after one prior line of therapy. With very promising survival benefit (Robert, 2014), pembrolizumab has become the new standard of care based on clinical guideline (CSCO, 2019).
- This study aimed to evaluate the cost-effectiveness of pembrolizumab compared with chemotherapy in the treatment of second line advanced melanoma in the Chinese healthcare context.

METHODS

Model structure

- A 3-state partitioned survival model was developed to compare treatment with pembrolizumab versus chemotherapy from a Chinese healthcare system perspective, accounting for patient co-pay as well.
- As illustrated in Figure 1, the three mutually exclusive health states include progression-free state (PF, alive), post-progression disease state (PD, alive) and death.

Figure 1. Model Diagram



- The model was run for 20 years, to reflect a lifetime horizon. The outcomes assessed were costs, life years, quality-adjusted life years (QALYs), and incremental cost effectiveness ratios (ICERs) in terms of incremental cost per life year gained and incremental cost per QALY gained. A discount rate of 5% per year was used for both costs and health outcomes (Chinese Pharmacoeconomics Guideline, Version 2019)

Model input

Clinical efficacy

- The analyses on progression free survival (PFS) and overall survival (OS) extrapolation in this model were based on the data cutoff as of December 3, 2015 (representing the final OS analysis) from the Phase III trial KEYNOTE-006; the median follow-up time at this data cutoff was 22.9 months.
- For the pembrolizumab arm, clinical data such as PFS, OS and incidence of adverse events (AEs) were taken from data on previously treated patients in the KEYNOTE-006 10 mg/kg Q3W arm.
- For the chemotherapy arm:
  - Carboplatin + paclitaxel was selected as the relevant comparator since it is widely used in second line advance melanoma in China and it is one of the recommended chemotherapies in clinical practice (CSCO, 2019). However, there is no head-to-head trial data comparing pembrolizumab versus carboplatin + paclitaxel.
  - As reported in the clinical guideline for melanoma in China, dacarbazine (DTIC) results in the best clinical efficacy among all chemotherapies. Therefore, it was recommended as first line treatment before pembrolizumab was approved in China (Guideline of Melanoma Diagnosis and Treatment, 2018). Carboplatin + paclitaxel was conservatively assumed to be similar to DTIC in terms of PFS and OS. Consequently, to derive the clinical efficacy for the chemotherapy arm, the results of a network meta-analysis (NMA) comparing pembrolizumab versus DTIC were utilized (CORE, MSD, 2017).

Safety

- The inclusion of AEs was based on a combination of the relative prevalence (3% or higher) and the severity (grade 3+) of each event to quantify the AE-related costs throughout the model time horizon. In addition, grade 2+ diarrhea was included based on clinical expert's feedback, due to its economic impact. The AE incidence was derived from KEYNOTE-006 in the pembrolizumab cohort, and from a phase III trial (Flaherty KT, 2013) in the chemotherapy cohort.

Utilities

- The utilities, based on a time-to-death approach for both pembrolizumab and chemotherapy cohorts, were derived from pooled EQ-5D data from KEYNOTE-006, focusing on patients previously treated, and using a Chinese utility tariff (Liu GG, 2014). Average disutility caused by Grade 3+ AEs was applied based on the incidence of AE for each treatment cohort. The utility associated to death was assumed to be 0.

Cost

- Costs were reported in 2018 prices in Chinese currency. Four major categories of costs were considered in the model:
  - Drug acquisition and drug administration costs:
    The cost of pembrolizumab in China is ¥17,918 per 100 mg vial (GBI Source database) and it is administered at a dose of 2 mg/kg Q3W for second line advanced melanoma. The cost of carboplatin + paclitaxel regimen was sourced from the median bidding price across several regions in China, including Shanghai, Beijing, Tianjin, Jiangsu, Hubei, Zhejiang, Sichuan and Guangdong (GBI Source database). The model assumed that 80% of patients received two 100 mg vial and 20% of patients received one 100 mg vial of pembrolizumab based on the conservative opinion from a clinical expert, derived from an interview conducted for this study. According to the median tendering price from 8 provinces/cities, the cost per mg for carboplatin and paclitaxel was ￥1.12 and ￥3.34, respectively. Carboplatin + paclitaxel is administered Q3W for a total of 6 doses. The administration cost per cycle for pembrolizumab and chemotherapy was ¥56.25 and ¥152.25, respectively.
  - Health state-specific disease management costs: Patients incur regular costs for routine oncology office visits, lab tests, and scans in PF and PD health states. The data for the resource use frequency and costs were provided by expert opinion.
  - Costs associated with managing adverse events: The unit costs of the different AEs were derived from published literature, a database analysis and the aforementioned physician interview. The AE-related management costs were implemented as a one-off cost in the first cycle of the model.
  - Terminal care costs. The cost of terminal care relates to the cost incurred during the last 3 months of life and was estimated to be ￥3,650 for the pembrolizumab arm and ￥5,354.00 for the carboplatin + paclitaxel arm, according to expert opinion derived from the physician interview.

Survival analysis

Pembrolizumab:

- PFS: a two-part piecewise approach was used to extrapolate PFS. Namely, Kaplan–Meier (KM) curves for pembrolizumab were used until week 13 and then a parametric curve fitting approach was used beyond this time point. After week 13, log-logistic, Weibull and log-normal distributions were very close as best fitted models. The Weibull was used in the base case, because it aligns with the OS projection for pembrolizumab.
- OS: For the first 100 weeks of the model, KM estimates of previously treated patients in the pembrolizumab 10mg Q3W arm from the KEYNOTE-006 trial (Schachter J, 2017) were used. Beyond 100 weeks, a long-term ipilimumab study (Schadendorf J, 2015) was utilized in order to capture the plateau in the OS curve found in immunotherapy until week 515, then a hazard ratio function of pembrolizumab vs. ipilimumab estimated from the KEYNOTE-006 trial was applied to the aforementioned long-term ipilimumab study to derive the OS curve for pembrolizumab until week 515. Thereafter, the hazard rates from the American Joint Committee on Cancer (AJCC) melanoma registry were used to estimate OS in the pembrolizumab arm (Agarwala SS, 2009).

Chemotherapy:

- An NMA was conducted to estimate the hazard ratio between pembrolizumab and DTIC through indirect comparison with ipilimumab. The hazard ratio was applied to pembrolizumab survival data to estimate the PFS and OS for carboplatin + paclitaxel, reflecting the model comparator.

Parameter uncertainty analysis

One-way deterministic sensitivity analyses (DSA) and a probabilistic sensitivity analysis (PSA) were performed to test the robustness of results.

RESULTS

Base-case results

- Pembrolizumab was associated with an average QALY gain of 2.26 over chemotherapy (Table 1).
- The base-case analysis results indicated a difference of ¥397,788 in the total average per-patient direct cost of treatment with pembrolizumab versus chemotherapy (Table 1).

Table 1. Base-Case Cost-Effectiveness Results

	Pembrolizumab	Chemotherapy	Difference
Average # of doses per patient	12.4	3.8	-
Life years	4.14	1.51	2.63
QALYs	3.41	1.15	2.26
Total cost	¥456,677	¥58,890	¥397,788
ICER (¥ per LY gained)			¥151,470
ICER (¥ per QALY gained)			¥176,187

Model scenario analysis results

- Model variability analysis results showed that model results were robust to variation in model parameters as shown below (Table 2).

Table 2. Scenario Analyses Results

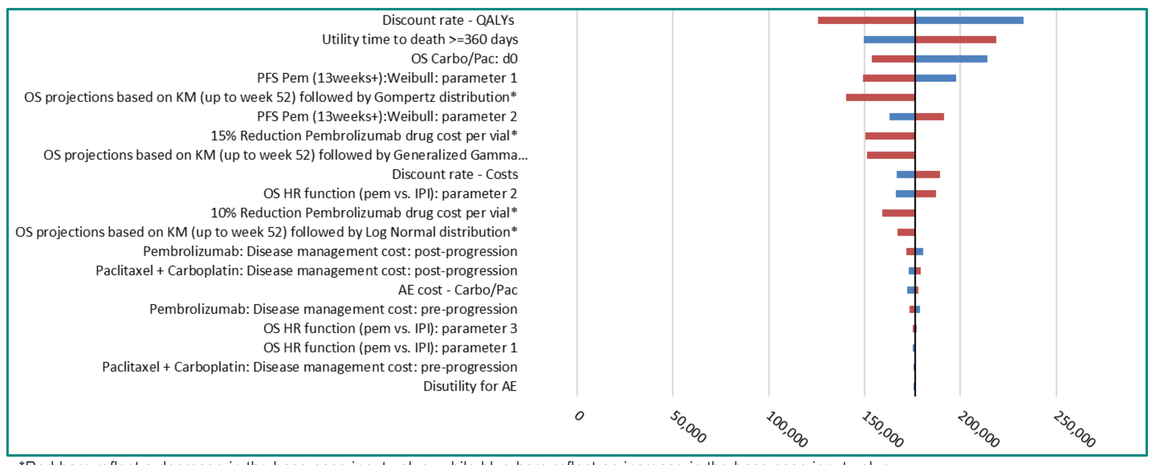
Model variability	ICER
10 years time horizon	¥ 218,790
30 years time horizon	¥ 175,598
3% discount rate for both costs and benefits	¥ 159,318
8% discount rate for both costs and benefits	¥ 202,415
Piecewise parametric model: log-normal*	¥ 166,991
Piecewise parametric model: Gompertz*	¥ 140,466
Piecewise parametric model: Generalized Gamma*	¥ 151,452
Utility approach by progression status	¥ 184,571

* These scenario analyses relate to an alternative approach to extrapolate OS, consisting on using KM data up to week 52, followed by parametric fitting. The three parametric models tested above are the only ones that resulted in clinically plausible results in the long term

Parameter uncertainty analysis results

- Cost-effectiveness key drivers included: the discount rate on QALYs, the utility approach used and the assumptions around the proportion of patients requiring 2 vials. Results are also sensitive to OS and PFS extrapolation methods (Figure 2).
- The cost-effectiveness acceptability curve suggested that pembrolizumab has an 84% probability of being cost-effective compared to carboplatin + paclitaxel under the expected threshold of 3 times the GDP per capita in China in 2018 (¥ 193,932) (Figure 4).

Figure 2. Tornado Diagram for the ICER (¥ per QALY gained) of Pembrolizumab vs. Chemotherapy*



*Red bars reflect a decrease in the base case input value, while blue bars reflect an increase in the base case input value

Figure 3. PSA Results for Pembrolizumab vs. Chemotherapy

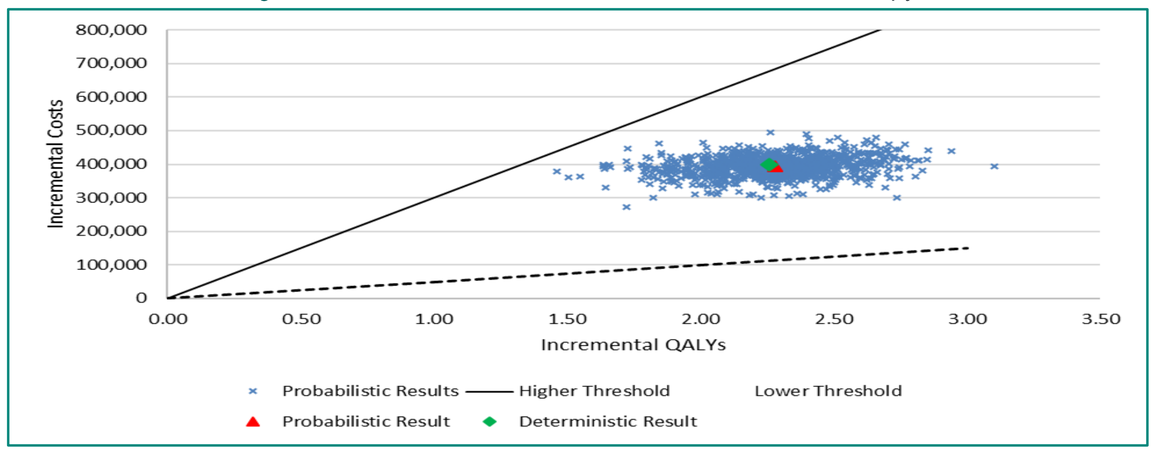
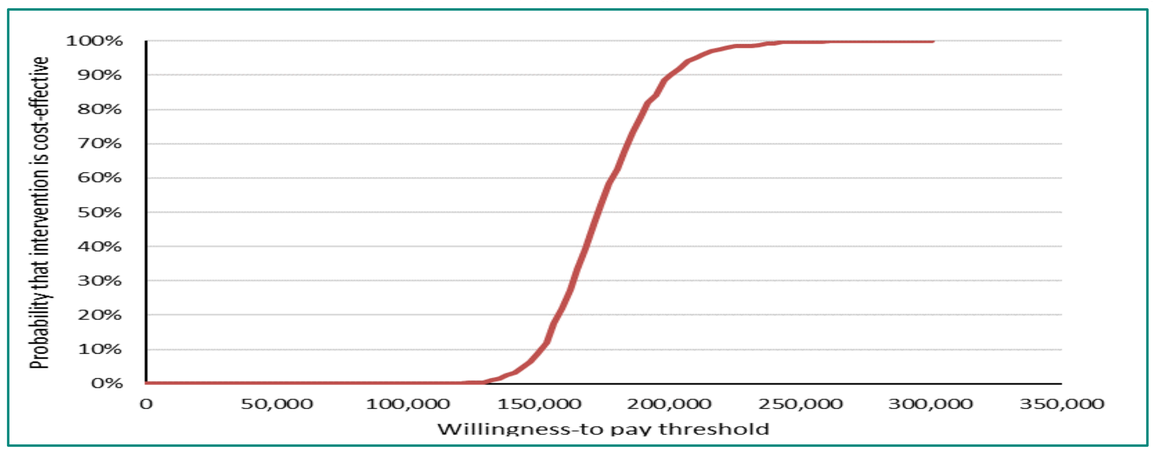


Figure 4. Cost-Effectiveness Acceptability Curve (¥ per QALY gained) for Pembrolizumab vs. Chemotherapy



DISCUSSION AND CONCLUSIONS

- This is the first economic evaluation of an immuno-oncology drug for the treatment of advanced melanoma in China.
- From a Chinese healthcare system perspective, pembrolizumab was cost-effective for the second line treatment of advanced melanoma under the threshold of 3 times the GDP per capita.
- The model evaluated a wide range of scenarios and input parameters, and the results were robust, demonstrating the economic value of pembrolizumab versus chemotherapy for the second line treatment of advanced melanoma in China.
- These results are expected to be informative for Chinese healthcare decision makers to make value-based and scientific decisions.

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