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First-line pembrolizumab in PD-L1 positive non-small-cell lung cancer: A cost-effectiveness analysis from the UK health care perspective

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ABSTRACT

Background: Pembrolizumab has shown significant survival benefits in treating chemotherapy-naïve non-small-cell lung cancer patients (NSCLC) with increased level of PD-L1 expression. This analysis aimed to evaluate the cost-effectiveness of pembrolizumab as a first-line treatment for patients with PD-L1 positive NSCLC from the UK health care perspective.

Methods: A Markov model with progression-free, progressive disease and death states was developed. Clinical parameters were informed by the KEYNOTE-024 trial. Utility values were sourced from published literature. Cost data including drug acquisition costs, disease management costs, and adverse event costs were derived from British National Formulary and published literature. The model was run until 99% patients died. Both health outcomes and costs were discounted at an annual rate of 3.5%. Deterministic and probabilistic sensitivity analyses were performed to address the uncertainties around model parameters.

Results: In the base case, pembrolizumab is projected to increase patient's life expectancy by 1.32 life-years over chemotherapy (2.45 vs. 1.13) and 0.83 QALYs (1.55 vs. 0.71) at an additional cost of £72,465, yielding an incremental cost-effectiveness ratio of £86,913/QALY. When parameters were varied in the deterministic sensitivity analyses, results are most sensitive to duration of median overall survival in both groups. Probability sensitivity analyses showed that using a willingness-to-pay threshold of £50,000 per QALY, the probability of pembrolizumab being cost-effective is 29.4%.

Conclusion: Using a willingness-to-pay threshold of £50,000, pembrolizumab is not cost-effective at its current list price and a discount of 50% or more is required for it to be cost-effective comparing to commonly prescribed chemotherapy. Risk-sharing contracts may be helpful in resolving some of the underlying uncertainty associated with the long-term survival and varying extent of patient response.

1. Introduction

Pembrolizumab is the first immune check-point inhibitor approved as an initial therapy for patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) expressing high level of PD-L1. Before the introduction of immune check-point inhibitors, first-line treatment options for patients with locally advanced or metastatic NSCLC were primarily cytotoxic chemotherapies. A small portion of patients who have mutations of epidermal growth factor receptor (EGFR) or abnormal fusion of the anaplastic lymphoma kinase (ALK) are also eligible for tyrosine kinase inhibitors (TKI). Pembrolizumab is a humanized monoclonal antibody works by blocking the interaction between the programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) [1–3]. In January 2017, the European Medicine Agency granted marketing authorization for pembrolizumab as a first-line treatment for adult patients with locally advanced or metastatic NSCLC, whose tumors express PD-L1 tumor proportion score of 50% or higher with no EGFR or ALK positive tumor mutations [4].

The incremental survival benefits and better safety profile associated with pembrolizumab was demonstrated in KEYNOTE-024, an international, randomized, phase III clinical trial, comparing pembrolizumab to platinum-based chemotherapy in patients with untreated PD-L1 positive NSCLC [5]. In October 2017, an updated analysis of KEYNOTE-024 trial reported data from a longer follow-up time (median follow-up = 25.2 months). Over half of patients have had overall survival events at time of the analysis in both groups and patients treated with pembrolizumab had significantly longer overall survival compared to those treated with chemotherapy [6]. Although only a small

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proportion of advanced NSCLC patients, approximately 23–28% [2,3], may be eligible in the real-world, results from the clinical trial showed that it has the potential to provide significant and durable benefits for this targeted patient population, which could transfer into considerable survival benefits.

The development of this kind of new immunotherapies and targeted therapies marked the exciting new era that cancer research has come into. The hefty price tags that come along with these novel therapies, however, have posed a major challenge to the health care systems and have thus attracted extensive criticisms from health policy makers globally. A 2015 study analyzed the price trend of cancer drugs from 1995 to 2013 in the United States, and observed an annual increase of 10% after adjusting for inflation and median survival benefits reported in the clinical trials [7]. Although this type of study signals the potential unsustainability of cancer drug prices, benefits spanned over patient's lifetime that cannot be demonstrated in clinical trials and the value associated with the quality of life improvement still need to be accounted for. To enable patient access and assess economic implications, cost-effectiveness analyses are useful in quantifying the societal benefits as well as the potential cost associated with the new therapies through making use of the best available evidence.

In the UK, pembrolizumab is currently priced at £1,315 per 50 mg vial [8]. It will cost £5,260 per cycle for each patient at its recommended dose of 200 mg per 21 days. Taking in to account the huge unmet need for an effective treatment for metastatic NSCLC and increased patient survival, this could transfer into significant financial burden on the UK health care system. After an initial rejection due to concerns of high cost, pembrolizumab is now recommended by the National Institute for Health and Care Excellence (NICE) for use within the Cancer Drugs Fund, under a special patient access scheme in which the manufacturer will provide a discounted price to the UK government [9]. In the manufacturer's submission to NICE, an incremental cost-effectiveness ratio (ICER) of £41,213 of pembrolizumab vs. chemotherapy was reported in the base case analysis. However, the model was criticized for several key assumptions including the extrapolation of overall survival data, choice of utility values, and a 2-year treatment stopping rule in the pembrolizumab group [9]. Therefore, in this analysis, we sought to address some of these issues and to further evaluate the cost-effectiveness of pembrolizumab in patients with untreated PD-L1 positive NSCLC using the most recently reported survival data from a longer follow-up of patients enrolled in KEYNOTE-024.

2. Material and methods

2.1. Model overview

We used a Markov model with three mutually exclusive health states, progression-free, progressive disease, and death, to simulate the course of disease. Patients start receiving pembrolizumab or chemotherapy in the progression-free state, and can stay in or move to progressive disease or death state at a cycle length of 21 days based on their assigned transition probabilities. Treatment decision following an event occurrence (progression or adverse event) were based on the KEYNOTE-024 trial or published literature. Only direct medical costs were considered in the model and are presented in 2017 British pounds. Both costs and health outcomes were discounted an annual rate of 3.5% according to NICE guidelines. The model was run until 99% patients die.

The primary outputs of the model are quality-adjusted life-years (QALYs), total costs, and ICERs. The model was developed and run in Excel 2013. (Microsoft Corporation, Redmond, WA, USA)

2.2. Clinical parameters

Patient characteristics and treatment assignments were based on the KEYNOTE-024 trial [5]. We calculated the between-state transition probabilities using the DEALE methods by assuming a declining exponential function for survival [10]. The transition probabilities between progress-free and progressive disease states were based on the median progression-free survival (PFS) reported in KEYNOTE-024 (10.3 [95% CI: 6.7 – not reached] vs. 6.0 [95% CI: 4.2–6.2] months, pembrolizumab vs. chemotherapy) [5]. The probability of death is the sum of the probabilities of transitioning from either state to death state, and was calculated based on the median OS data (30.0 [95% CI: 18.3 – not reached] vs. 14.2 [95% CI: 9.8–19.0] months, pembrolizumab vs. chemotherapy) [6].

Currently there is no clinical guideline on subsequent treatment options for patients failing immune check-point inhibitors. Thus, we assumed that patients failing first-line pembrolizumab received docetaxel as their second-line treatment. This assumption is based on the NHS clinical guidance that docetaxel should be considered standard-of-care after disease progression on first-line chemotherapy [11]. For patients on chemotherapy, in KEYNOTE-024 trial, those who failed first-line chemotherapy could switch to receiving pembrolizumab upon physician's approval as their second-line treatment. During a median follow-up time of 25.2 months, 54.3% of patients in the chemotherapy group crossed over to pembrolizumab. Therefore, in this model, we assumed that 54.3% patients who progressed on first-line chemotherapy received pembrolizumab as their second-line treatment, and the rest received docetaxel as their second-line treatment. Of note, this may have diminished the incremental benefits of pembrolizumab as a first-line therapy in the model, because pembrolizumab had been demonstrated to be superior to docetaxel as a treatment of relapsed or recurrent NSCLC [3]. Nevertheless, we did not account for additional benefits from the second-line pembrolizumab in the chemotherapy group, i.e. we attributed the survival benefits from subsequent pembrolizumab to the first-line chemotherapy in the model. As pembrolizumab is now recommended for advanced NSCLC patients who have failed a chemotherapy, this likely reflects the real-world prescribing pattern in advanced NSCLC management. Fig. 1 presents the treatment assignment in this model.

Adverse events of ≥ grade 3 and frequency ≥5% as reported in KEYNOTE-024 were included in the model. Non-immune-mediated adverse events considered in the model included anemia, neutropenia, decreased platelet count and thrombocytopenia. Immune-mediated adverse events of grader 3 or higher were infrequent (< 5%) in both pembrolizumab and chemotherapy groups in the clinical trial, thus excluded from this analysis.

Utility values measuring individual's quality of life were assigned to patients by health state as well as by line of treatment. Utility values by line of treatment were obtained from published literature [12–14]. Disutilities associated with adverse events were also applied based on the frequency reported in KEYNOTE-024 [14,15]. Utility values used in the base case are presented in Table 1.

2.3. Cost inputs

Direct medical costs of treating the disease were considered in this model. Specific cost components included drug acquisition cost, drug

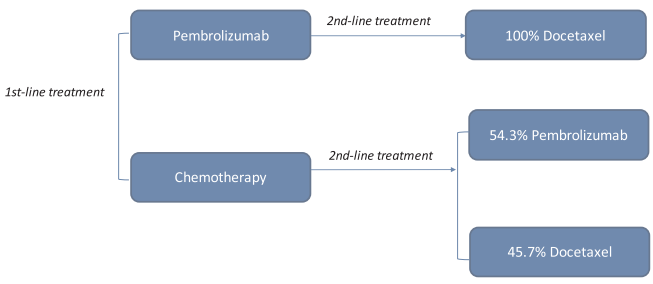

Fig. 1. Treatment assignment by line of therapy.