Lung Cancer 124 (2018) 248–254

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Cost-effectiveness of pembrolizumab as first-line therapy for advanced non-small cell lung cancer

Mina Georgieva[a], Joao P. da Silveira Nogueira Lima[b], Pedro Aguiar Jr.[c], Gilberto de Lima Lopes Jr.[d,1], Benjamin Haaland[a,e,*,1]

[a] Industrial and Systems Engineering, Georgia Institute of Technology, Atlanta, USA
[b] Medical Oncology Department, A. C. Camargo Cancer Center, Sao Paulo, Brazil
[c] Clinical Oncology Sector, Faculdade de Medicina do ABC, Santo André, Brazil
[d] Sylvester Comprehensive Cancer Center, University of Miami, Miami, USA
[e] Department of Population Health Sciences and Huntsman Cancer Institute, University of Utah, Salt Lake City, USA

ARTICLE INFO

Keywords:
Bayesian Markov model
Cost-effectiveness
First-line therapy
Immunotherapy
NSCLC
Pembrolizumab

ABSTRACT

Background: Anti-PD-1 immunotherapy has dramatically shifted therapeutic perspectives for advanced non-small cell lung cancer (NSCLC). We assessed cost-effectiveness of anti-PD-1 antibody pembrolizumab compared to platinum-doublet chemotherapy as first-line therapy for advanced NSCLC.

Methods: We retrieved survival, progression, and safety data comparing first-line pembrolizumab to platinum-doublets for advanced NSCLC patients with PD-L1 expression ≥50%, non-mutated EGFR, and non-translocated ALK, from KEYNOTE-024. Published United Kingdom (UK) and United States (US) costs informed incremental cost-effectiveness ratios (ICERs). Our analysis was based on a Bayesian Markov model of disease with full lifetime horizon. We estimated costs in USD and summarized effectiveness as quality-adjusted life-years (QALYs).

Results: Patients treated with pembrolizumab accumulated 1.80 QALYs (95% CrI 1.56–1.89), for moderate dependency between outcomes, compared to 1.06 QALYs (0.94–1.13) with chemotherapy. From a British National Health System (NHS) perspective, the ICER was $52k ($43k–$69k) per end-of-life (EoL) adjusted QALY gained, above the 42k USD threshold, while from a US cost perspective, the ICER was $49k ($40k-67k) per EoL adjusted QALY, below the hypothetical 100k USD threshold.

Conclusions: Evidence suggests first-line pembrolizumab for NSCLC may be cost-effective in the US but not the UK, in spite of very similar ICER values in both countries.

1. Background

In the last two decades, systemic therapy has brought meaningful clinical improvements for non-small cell lung cancer (NSCLC) patients, more than doubling life expectancy of patients with metastatic disease. Precision medicine and targeted therapy have become a reality responsible for increasingly high response rates and prolonged disease control for selected patients [1–5]. Notwithstanding these gains, lung cancer remains the most common cause of cancer-related death, claiming more lives than breast, prostate, and colon cancer combined [6–8]. Patients lacking actionable targets - the majority - or those who inevitably progress after personalized therapy still rely upon palliative chemotherapy, with median overall survival not exceeding 16 months [7,9,10].

New therapies are urgently required and immunotherapy has shown enormous potential to further improve prognosis for lung cancer patients. With elevated neo-antigen expression and active mechanisms of immune surveillance evasion, lung cancer is an ideal setting for current PD-1, PD-L1, and CTLA-4 therapies [11,12]. Recently, several PD-1, PD-L1, and CLTA-4 drugs have reached late phase development for lung cancer, in a quest for betterment of prognosis and patient selection [13–16].

Some immunotherapies have received FDA and EMA approval in record time due to strong clinical results, with superior, and for some patients durable, survival and more tolerable side effects. These results have largely reset standard management of advanced NSCLC.

* Corresponding author at: Population Health Sciences, University of Utah, 295 Chipeta Way, Salt Lake City, UT, 84108, USA.
E-mail address: ben.haaland@hci.utah.edu (B. Haaland).
[1] Joint senior authors.

https://doi.org/10.1016/j.lungcan.2018.08.018
Received 22 June 2018; Received in revised form 6 August 2018; Accepted 20 August 2018

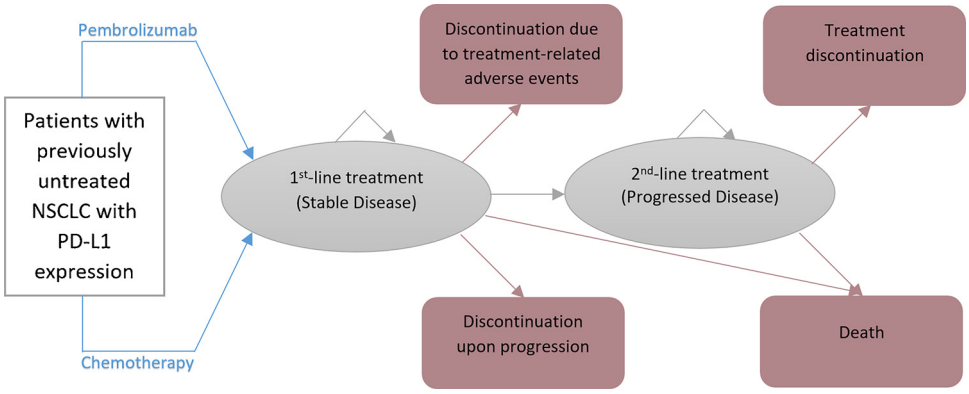

Fig. 1. Diagram of Markov model used to compare platinum doublet chemotherapy to pembrolizumab as first-line therapy for advanced NSCLC.

Nevertheless, there is a price tagged to these breakthrough treatments that cannot be overlooked [17].

Analysis of cost-effectiveness of new therapies is imperative to ensure appropriate and sustainable use of targeted treatments in NSCLC. The current study investigates cost-effectiveness of pembrolizumab treatment for previously untreated patients with advanced NSCLC and PD-L1 expression in ≥50% of tumor cells.

2. Methods

2.1. Data

Overall survival (OS) and progression-free survival (PFS) time-to-event data were extracted from published Kaplan-Meier (KM) curves, numbers at risk, and censoring times from the KEYNOTE-024 study. In brief, KEYNOTE-024 compared first-line platinum-doublets versus pembrolizumab for EGFR wild-type, ALK non-translocated, chemo-naive advanced lung cancer patients whose tumors expressed PD-L1 in ≥50% of cancer cells [18–20]. The most up-to-date KM curves [19] for OS and PFS were digitized using WebPlotDigitizer [21], and raw time-to-event data was recovered by inverting the KM equations, extending techniques in Guyot et al [22]. Details on frequency and severity of side effects for both intervention arms were also abstracted. Quality of data recovery is examined in Appendix A1.

2.2. Bayesian survival and progression model

Distributions of OS and PFS times were modeled using a Bayesian semi-parametric framework. Specifically, we modeled discrete-time event probabilities until last follow-up time using a hierarchical Dirichlet Process (DP). Time until last follow-up was discretized into one-month intervals. This approach avoids assumptions about the shape of the survival distributions, allows incorporation of censored data, and accommodates study-to-study heterogeneity. Further, the DP model is particularly well-suited to situations where relative efficacy measures such as hazard and odds ratios are not sufficient, such as cost-effectiveness analyses requiring patient-level disease trajectories as a basic ingredient. The tail of the survival distribution (after last follow-up time) was modeled using a Weibull distribution. The parametric nature of the Weibull model is well-suited to making inferences about the survival curve after last follow-up.

Detailed description of the DP and Weibull models is provided in Appendix A2. Model validation, sensitivity to priors, and sensitivity to heterogeneity parameters are described in Appendices A3, A4, and A5, respectively. Samples from the posterior distribution were generated via Markov chain Monte Carlo (MCMC) implemented in JAGS and called via the rjags package in R [23–25]. Posterior distributions summarize uncertainty about the model after examining the data. Five MCMC chains were used with the first 10,000 iterations of each discarded while the Markov chain stabilized. Posterior inference was based on 100,000 iterations from each chain, thinned at a lag of 50.

For constructing patient trajectories in the pembrolizumab and chemotherapy arms, quantities of interest were posterior probabilities of death and progression within particular one-month time intervals until last follow-up, and posterior probabilities of death and progression on the continuous truncated time-line after last follow-up. Notably, the probability that a progression event occurred in a particular time interval was taken as the difference between the corresponding PFS and OS probabilities. Pembrolizumab and chemotherapy were compared based on 10,000 OS and progression times *for each* of the 10,000 draws from the posterior distributions.

2.3. Disease model

Cost-effectiveness of pembrolizumab relative to chemotherapy was assessed using simulated patient trajectories in the pembrolizumab and chemotherapy arms over a full lifetime horizon. Patients could transition from stable disease to one transition state, (1) progressive disease, and three absorbing states, (2) death, (3) discontinuation due to treatment-related adverse events, or (4) discontinuation upon progression. Probabilities for treatment discontinuation due to adverse events and probabilities for continuation after progression were obtained from Reck et al [18–20]. In particular, patients in the model discontinued treatment due to adverse events with probability 13.6% in the pembrolizumab group, and 10.7% in the chemotherapy group. Upon progression, 44% of patients in the pembrolizumab group, and 54% of patients in the chemotherapy group underwent second-line treatment. From a progressive disease state, patients could transition to absorbing states, (1) death or (2) treatment discontinuation. We assumed post-progression therapy discontinuation occurred after a median of 4 cycles for the pembrolizumab arm, and a median of 5 cycles for the chemotherapy arm. The state-transition diagram in Fig. 1 illustrates how patients flowed through the model.

Our analysis explored several levels of dependency between each simulated patient's hypothetical disease trajectories in the pembrolizumab and chemotherapy arms, as well as between their progression and OS times. Intuitively, we might expect that patients with longer time to progression would also have longer survival time, and patients with extended survival on pembrolizumab might also have longer than typical survival time had they instead been treated with chemotherapy. The dependency model controlled the extent to which these event times were *positively* associated. Dependencies between each simulated patient's four associated event times (progression and death for each of pembrolizumab and chemotherapy) were modeled via a Gaussian copula. Detailed description of the dependency model is provided in Appendix A6. Two scenarios, no and moderate dependency between hypothetical outcomes, are reported in the main manuscript. A high dependency scenario is reported in Appendix A7.