Lung Cancer 115 (2018) 84–88

Contents lists available at ScienceDirect

Lung Cancer

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

Comparative effectiveness of immune-checkpoint inhibitors for previously treated advanced non-small cell lung cancer – A systematic review and network meta-analysis of 3024 participants

Pui San Tan[a,*], Pedro Aguiar Jr.[b], Benjamin Haaland[c], Gilberto Lopes[d]

[a] Nuffield Department of Primary Care Health Sciences, University of Oxford, UK
[b] Clinical Oncology Sector, Federal University of São Paulo, São Paulo, Brazil
[c] H. Milton Stewart School of Industrial and Systems Engineering, Georgia Institute of Technology Atlanta, USA
[d] Sylvester Comprehensive Cancer Center, University of Miami, USA

ARTICLE INFO

Keywords:
Immune-checkpoint inhibitors
PD-L1
NSCLC
Meta-analysis

ABSTRACT

Introduction: Role of PD-L1 expression to guide immunotherapies in previously treated advanced NSCLC remains unclear and there is a lack of data comparing immune checkpoint inhibitors (ICIs) with each other. This network meta-analysis (NMA) aims to compare survival with ICIs to docetaxel and perform indirect comparisons between ICIs in the PD-L1 unselected population and by PD-L1 expression levels.

Methods: PubMed was searched and study screening was performed by two independent reviewers. NMA of survival outcomes in the PD-L1 unselected population and by PD-L1 expression levels < 1%, > = 1%, > = 5%, > = 10%, and > = 50% was performed. Head-to-head indirect comparisons were constructed and treatment rankings were provided. Potential survival benefits by PD-L1 expression level as compared to a PD-L1 unselected population were estimated.

Results: 5 trials with 3024 total patients were included for meta-analysis. Overall, ICIs improved survival across PD-L1 expression levels compared to docetaxel, although there was only weak evidence of benefit for individual ICI nivolumab or atezolizumab in PD-L1 < 1%. PD-L1 subgroups suggested positive dose-response relationship between PD-L1 expression levels with survival benefits. In addition, there were also survival benefits due to selecting for PD-L1 in the PD-L1 > = 10% and > = 50% subgroups as compared to the PD-L1 unselected population. Indirect comparisons of ICIs showed little evidence of differences between nivolumab, pembrolizumab and atezolizumab.

Discussion: ICIs improve survival in previously treated advanced NSCLC patients across PD-L1 expression levels compared to docetaxel. There is a positive dose-response relationship between PD-L1 expression and survival benefits, and little evidence of survival differences between nivolumab, pembrolizumab and atezolizumab.

1. Introduction

Lung cancer is the most common cause of cancer-related death worldwide with more than 1.5 million deaths in 2012 [1], more than breast, prostate, and colon cancer deaths combined [1–3]. Platinum based chemotherapy is the cornerstone of treatment for advanced non-small cell lung cancer (NSCLC) [4]. In the last decade, new strategies have been studied, but still median overall survival (OS) with chemotherapy has not surpassed 15 months [5].

The ability to avoid the immune system is one of the hallmarks of cancer [6]. Lung cancer has a high mutational burden and this may lead to a high immunogenicity [7]. There are many complex interactions between antigen presenting cells, lymphocytes, and tumor cells. The most studied is the link between the lymphocytes membrane receptor, Program Cell Death 1 (PD-1), and its ligand 1 or 2 (PD-L1 or PD-L2), which are expressed by some tumor cells [8]. This interaction inhibits lymphocytes [8]. As a consequence, in a short period of time, many PD-1 and PD-L1 inhibitors have reached late phase development in lung cancer [9–13].

Several immunotherapies have been approved by FDA in record time due to strong clinical benefits and milder side effects [9–14]. These results have rapidly reset the management of advanced non-small cell lung cancer (NSCLC). Nevertheless, some questions regarding lung cancer immunotherapy remain unclear, especially the role of PD-L1

* Corresponding author at: University of Oxford Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Rd, Oxford OX2 6GG UK.
E-mail address: puisan.tan@gmail.com (P.S. Tan).

https://doi.org/10.1016/j.lungcan.2017.11.017
Received 13 May 2017; Received in revised form 10 October 2017; Accepted 19 November 2017

expression as a biomarker, even for second-line treatment. In addition, all clinical trials that included previously treated patients compared immune checkpoint inhibitors (ICI) to docetaxel, and there is a lack of data comparing agents with one another [9–13].

Therefore, a meta-analysis assessing all relevant data published until now should endorses the benefit of immunotherapy versus docetaxel. Moreover, a meta-analysis should provide a better understanding regarding biomarkers and indirectly compare each immunotherapy agent. The current study investigates these issues, and provides evidence to improve the treatment of patients with advanced NSCLC after chemotherapy failure. A network meta-analysis will be performed to compare survival benefits of ICIs nivolumab, pembrolizumab, and atezolizumab to docetaxel in previously treated advanced NSCLC patients by PD-L1 expression levels (i) unselected, (ii) < 1%, (iii) ≥1%, (iv) ≥5%, (v) ≥10%, and (vi) ≥50%.

2. Methods

2.1. Systematic review

PubMed was searched for randomized controlled trials evaluating immunotherapy ICI in advanced NSCLC using the following search phrase with no time restrictions: (“non-small cell lung cancer” OR “non small-cell lung cancer” OR “non-small-cell lung cancer” OR “non small cell lung cancer” OR “NSCLC”) AND (“atezolizumab” OR “pembrolizumab” OR “nivolumab”) AND (randomized controlled trial[pt] OR randomized controlled trial)

Inclusion criteria was phase II/III randomized controlled trials evaluating nivolumab, pembrolizumab, or atezolizumab for the treatment of previously treated advanced NSCLC. Two independent reviewers performed study screening. Data extraction was performed using a standardized extraction sheet.

2.2. Outcomes evaluation

Treatment efficacies were evaluated in terms of overall survival (OS) for patient populations comprising of (i) PD-L1 unselected, (ii) PD-L1 < 1%, (iii) PD-L1 > = 1%, (iv) PD-L1 > = 5%, (v) PD-L1 > = 10%, and (vi) PD-L1 > = 50%. Additional subgroup analyses were performed comparing ICIs by histology and PD-L1 expression levels.

2.3. Statistical analysis

Meta-analysis was performed using a Bayesian hierarchical model. Individual treatment efficacies were meta-analyzed on the logarithmic scale centered at the mean with two components of variance; within and between study heterogeneities. Within study heterogeneity was modeled using individual studies’ reported variances while between study heterogeneity was modeled using a partially informative prior allowing treatment efficacies to vary up to two-fold study to study.

Meta-estimates for treatment efficacies were expressed as hazard ratios (HRs) with corresponding 95% credible intervals (CrIs). Indirect comparisons were constructed in terms of HR with corresponding 95% CrI and probability for an individual ICI to be best (probability best). Treatment rankings were estimated using surface under cumulative ranking curve (SUCRA) by taking the average cumulative ranking probabilities following the expression $SUCRA_j = \frac{\sum_{r=1}^{c-1} cum_{j,r}}{c-1}$ on a percent scale, where c denotes the number of treatments compared [15]. SUCRA was computed to provide summary estimates of ranking efficacies, with higher values representing better treatments [15].

3. Results

14 studies were screened and 5 trials comprised of 3024 patients were included for meta-analysis (Fig. 1) [16]. Included trials compared ICIs nivolumab, pembrolizumab, or atezolizumab to docetaxel for previously treated patients who had disease progression (Table 1, Appendix Fig. 1) [9–13]. Median survival was approximately 9–14 months for patients treated with ICIs with survival gain ranging from approximately 2–4 months versus docetaxel [9–13]. Details on characteristics of included studies are provided in Table 1.

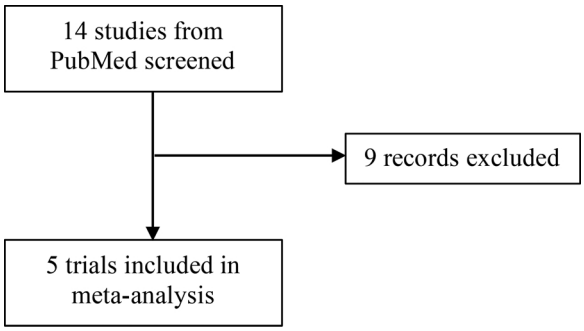

Fig. 1. Search flow diagram according to PRISMA guidelines [16].

Four trials, which evaluated nivolumab or atezolizumab, enrolled patients with no pre-defined PD-L1 biomarker status [9,10,12,13] while KEYNOTE-010, which evaluated pembrolizumab, enrolled patients with PD-L1 expression on at least 1% of tumor cells [11]. Trials which evaluated nivolumab and pembrolizumab measured PD-L1 expression using tumor cell cutoffs [9–11] while atezolizumab trials measured PD-L1 expression using both tumor cell and/or immune cell cut-offs. [12,13] PD-L1 > =50% for atezolizumab trials included patients with tumor cell PD-L1 > =50% or immune cell PD-L1 > =10% [12,13].

3.1. Overall survival by PD-L1 expression

Fig. 2 shows overall survival in individual trials and pooled meta-estimates for nivolumab, pembrolizumab, and atezolizumab compared to docetaxel by PD-L1 expression. In patients with unselected PD-L1 biomarker status, meta-estimates showed evidence of survival benefits for both nivolumab and atezolizumab compared to docetaxel with HR 0.67 (95% CrI 0.54-0.83) and 0.73 (0.59-0.90) respectively. In patients with PD-L1 < 1%, meta-estimates showed weaker evidence of survival benefits for both nivolumab and atezolizumab compared to docetaxel with HR 0.77 (0.57-1.04) and 0.81 (0.62-1.08) respectively. In patients with PD-L1 > =1%, meta-estimates showed evidence of survival benefits for nivolumab, pembrolizumab, and atezolizumab compared to docetaxel with HR 0.63 (0.47-0.84), 0.67 (0.51-0.87) and 0.69 (0.53-0.88) respectively. In patients with PD-L1 > =5%, meta-estimates showed evidence of survival benefits for nivolumab and atezolizumab compared to docetaxel with HR 0.46 (0.33-0.65) and 0.63 (0.46-0.84) respectively. In patients with PD-L1 > =10%, meta-estimates showed evidence of survival benefits for nivolumab compared to docetaxel with HR 0.43 (0.30-0.63). In patients with PD-L1 > =50%, meta-estimates showed evidence of survival benefits for pembrolizumab and atezolizumab compared to docetaxel with HR 0.53 (0.38-0.75) and 0.43 (0.28-0.65) respectively.

3.2. Indirect comparisons by PD-L1 expression

Fig. 3 shows indirect comparisons of nivolumab, pembrolizumab, and atezolizumab by PD-L1 expression for overall survival. Results showed little evidence of differences between nivolumab vs pembrolizumab, nivolumab vs atezolizumab or pembrolizumab vs atezolizumab across all compared PD-L1 expression levels. However, there was weak evidence suggesting that nivolumab could outperform atezolizumab.