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A Bayesian network analysis of immunotherapy and taxane chemotherapy as second- or later-line treatments in non-small cell lung cancer

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Abstract

Background: Taxane chemotherapy represents the standard of care in the second-line setting for non-small cell lung cancer (NSCLC) patients, but immunotherapy agents pose great challenges. Whether immunotherapy/chemotherapy alone or combination therapy has more benefits remains controversial. In this study, we provided comparisons to integrate the efficacy of immunotherapy and taxane chemotherapy as second- or later-line treatments in advanced NSCLC.

Methods: PubMed, Web of Science, Embase, and Cochrane Central Register of Controlled Trials were systematically searched from inception to September 1, 2020. Randomized controlled trials comparing immunotherapy and taxane chemotherapy were enrolled in the Bayesian network analysis. Overall survival (OS) and progression-free survival (PFS) with hazard ratios (HRs) were investigated.

Results: Eight trials in 13 studies with 4398 patients comparing seven treatments were identified. Pembrolizumab 10 mg/kg was associated with the best improved OS, with significant differences versus docetaxel (HR 0.81, 95% credible interval [CrI] 0.74-0.88), avelumab (HR 0.84, 95% CrI 0.75-0.95), and pembrolizumab 200 mg plus docetaxel (HR 0.75, 95% CrI 0.56-1.00). Although pembrolizumab 200 mg plus docetaxel ranked the last in terms of OS, the combination therapy showed the most favorable PFS. Additionally, the anti-programmed death-ligand 1 (PD-L1) agent, avelumab, was associated with the least improvement in PFS.

Conclusion: As second- or later-line therapeutic strategies, pembrolizumab 10 mg/kg provided the largest OS benefits and pembrolizumab 200 mg plus docetaxel improved PFS to the greatest extent. Considering that immunotherapy has been recommended to the first-line setting of NSCLC, advanced patients who have not received immunotherapy previously might be the suitable population for our findings.

Abbreviations: CrI = credible interval, HR = hazard ratio, ICI = immune checkpoint inhibitors, NSCLC = non-small cell lung cancer, OS = overall survival, PD-1 = programmed death-1, PD-L1 = programmed death-ligand 1, PFS = progression-free survival.

Keywords: Bayesian network analysis, chemotherapy, immunotherapy, non-small cell lung cancer, second- or later-line treatments

1. Introduction

For patients with previously treated, advanced or metastatic non-small cell lung cancer (NSCLC), the prognosis remains poor.[1] Among the first-line chemotherapies, platinum plus gemcitabine or pemetrexed strategies are administered. However, the median overall survival (OS) was approximately 10.3 months.[2] In the second-line treatments, taxane-based chemotherapy has been approved to be an option as one of the standard of cares.[3–5] Nevertheless, the OS had been slightly improved (10.6 months).[5] In recent five years, immune checkpoint inhibitors (ICIs) have been globally and widely used in cancer treatments. Targeting the programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) results in the restoration of antitumor T cell activity. Based on published clinical trials, immunotherapy has been certified as an effective second- or later-line treatment strategy for NSCLC patients.[6–8]

Before 2018, three ICIs (nivolumab, pembrolizumab, and atezolizumab) in five trials (CheckMate 057, CheckMate 017, POPLAR, KEYNOTE-010, and OAK) had been published. All these five trials were open-label and randomized studies, and squamous and/or non-squamous NSCLC patients who had

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The datasets generated during and/or analyzed during the current study are publicly available.

All included studies can be searched and downloaded from their official websites or PubMed.

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disease recurrence or progression during or after at least one prior line chemotherapy regimen were collected. The results found that the three ICIs significantly improved OS (over 12 months) compared with taxane docetaxel.[9–13] Following analyses synthesized these results and demonstrated that immunotherapy was associated with better OS and progression-free survival (PFS) compared with docetaxel chemotherapy.[14–17] Subsequently, trials in studying avelumab (JAVELIN Lung 200), nivolumab (CheckMate 078), and pembrolizumab plus docetaxel (PROLUNG) versus taxane docetaxel provided novel insights into the treatment for patients with previously treated NSCLC.[18–20] The availability of these strategies has improved NSCLC survival outcomes.

However, owing to the lack of head-to-head studies comparing the above treatments, clinicians hesitate to choose one therapy over others. Therefore, this study aimed to compare immunotherapy with taxane chemotherapy in NSCLC to inform decision-making.

2. Methods

This Bayesian network analysis was performed following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension statement for network meta-analysis.[21] The data used in the analysis were not original raw data but were based on the published clinical studies with ethical approvals. Therefore, ethical approval was not necessary.

2.1. Study selection

We systematically searched PubMed, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials to find relevant articles up to September 1, 2020. Search terms included "nivolumab or pembrolizumab or cemiplimab or atezolizumab or durvalumab or avelumab or ipilimumab or tremelimumab or PD-1 or PD-L1 or CTLA-4," "docetaxel or paclitaxel or taxol or taxane," and "non small cell lung cancer" within the restriction limit of "study or trial."

We included published original studies that met the following criteria: trials were prospective randomized controlled phase ≥2 studies and published in English; participants were previously treated NSCLC patients; comparisons were between any two or more ICIs or between ICIs, docetaxel, and also ICI plus docetaxel; clinical outcomes including OS (primary endpoint, time from randomization to death) and PFS (secondary endpoint, time from randomized to disease progression or death) were reported. Studies containing targeted therapies, surgery, or radiotherapy were excluded. Additionally, patients who were previously treated with immunotherapy were excluded.

Titles and abstracts were screened by two investigators (BW and XL). Subsequently, the full-text of potentially eligible articles was assessed for further inclusion.

2.2. Data analysis

Data on trial details, such as trial name, study design, number of patients, publication year, treatments, and survival outcomes, were extracted. Survival outcomes with hazard ratios (HRs) and 95% confidence intervals (CIs) were also recorded by two independent investigators (BW and XL).

Network plots were generated through STATA 14.0 software. Bayesian network analyses were performed in a Bayesian fixed-effects network analysis framework using a Markov Chain Monte Carlo method in the OpenBUGS 3.2.3 software and the results were reported as HRs with 95% credible intervals (CrIs).[22] We used noninformative uniform and normal prior distributions[23] and four different chains of initial values to fit the model. For OS and PFS effects, 300,000 sample iterations were generated with 100,000 burn-ins and a thinning interval of 10. When 95% CrI did not include the null value, the difference was considered statistically significant. The rankings of treatments within the Bayesian framework were estimated by calculating the surface under the cumulative ranking curve.[24] The convergence of the four chains established by inspection of the history was shown in Figure S1, Supplemental Digital Content, http://links.lww.com/MD/H900.

The risk of bias of individual studies was assessed according to the criteria outlined in the Cochrane Risk of Bias Tool in Review Manager 5.3.[25]

3. Results

Overall, 4036 records were identified. One thousand thirty six duplicated records were excluded. Two thousand nine hundred forty nine irrelevant records (irrelevant topic = 2897; meeting abstracts = 52) were excluded after screening the titles and abstracts. Fifty one full-text articles were assessed for eligibility. Subsequently, 18 reviews/comments/letters, 19 registered protocols, and one retrospective study were excluded. Finally, 13 studies (comprising eight trials) were eligible in the Bayesian network analyses as they met all the inclusion criteria,[9–13,18–20] with a total of 4398 patients enrolled to received seven different treatments including docetaxel (75 mg/m^2), nivolumab (3 mg/kg), pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, pembrolizumab 200 mg plus docetaxel (75 mg/m^2), atezolizumab 1200 mg, and avelumab 10 mg/kg (Fig. 1). All trials were randomized, open-label, multicenter trials. Five (62.5%) of eight trials were phase 3 studies, two (25.0%) were phase 2 studies, and the remaining one (12.5%) trial was a phase 2/3 study. Detailed characteristics of all the trials included in the Bayesian network analysis are provided in Table 1.

All treatments were compared to docetaxel since it was the standard of care of the second- or later-line treatments and the most common comparator present in the trials. All treatments were included in the Bayesian network analysis for OS and PFS (Fig. 2). Detailed assessments of the risk of bias were displayed in Figure S2, Supplemental Digital Content, http://links.lww.com/MD/H901.

Figure 3 summarizes the pooled estimates of the network analysis. In terms of OS (Fig. 3 lower), nivolumab (HR 0.85, 95% CrI 0.80-0.90), pembrolizumab 2 mg/kg (0.86, 0.79-0.94), pembrolizumab 10 mg/kg (0.81, 0.74-0.88), and atezolizumab (0.87, 0.82-0.93) were significantly better than docetaxel. Among ICIs, two regimens were better than avelumab, including nivolumab (0.89, 0.80-0.98) and pembrolizumab 10 mg/kg (0.84, 0.75-0.95). Moreover, pembrolizumab 10 mg/kg was significantly better than pembrolizumab 200 mg plus docetaxel (0.75, 0.56-1.00). Pembrolizumab 2 mg/kg and atezolizumab had comparative OS effects versus nivolumab, pembrolizumab 10 mg/kg, pembrolizumab 200 mg plus docetaxel, and avelumab.

In terms of PFS (Fig. 3 upper), pembrolizumab 200 mg plus docetaxel significantly prolonged PFS compared with other therapies. Three ant-PD-1 therapies (nivolumab (HR 0.91, 95% CrI 0.86-0.96), pembrolizumab 10 mg/kg (0.90, 0.84-0.98), and pembrolizumab 200 mg plus docetaxel (0.54, 0.41-0.71)) were shown to be better than docetaxel. Among single immune-regimens, we found significantly differences between anti-PD-1 therapy and anti-PD-L1 therapy: nivolumab versus atezolizumab (0.93, 0.86-1.00), nivolumab versus avelumab (0.85, 0.77-0.93), pembrolizumab 2 mg/kg versus avelumab (0.89, 0.79-0.99), and pembrolizumab 10 mg/kg versus avelumab (0.85, 0.76-0.94).

Figure 4 displays the distribution of probabilities of each regimen being ranked at each of the possible seven positions (the x-axis). The cumulative probabilities of being among the two most efficacious treatments in terms of OS were: pembrolizumab 10 mg/kg (70%) and nivolumab (40%). The cumulative probabilities of being among the two most efficacious treatments in improving PFS were: pembrolizumab 200 mg plus docetaxel (100%) and pembrolizumab 10 mg/kg (48%).

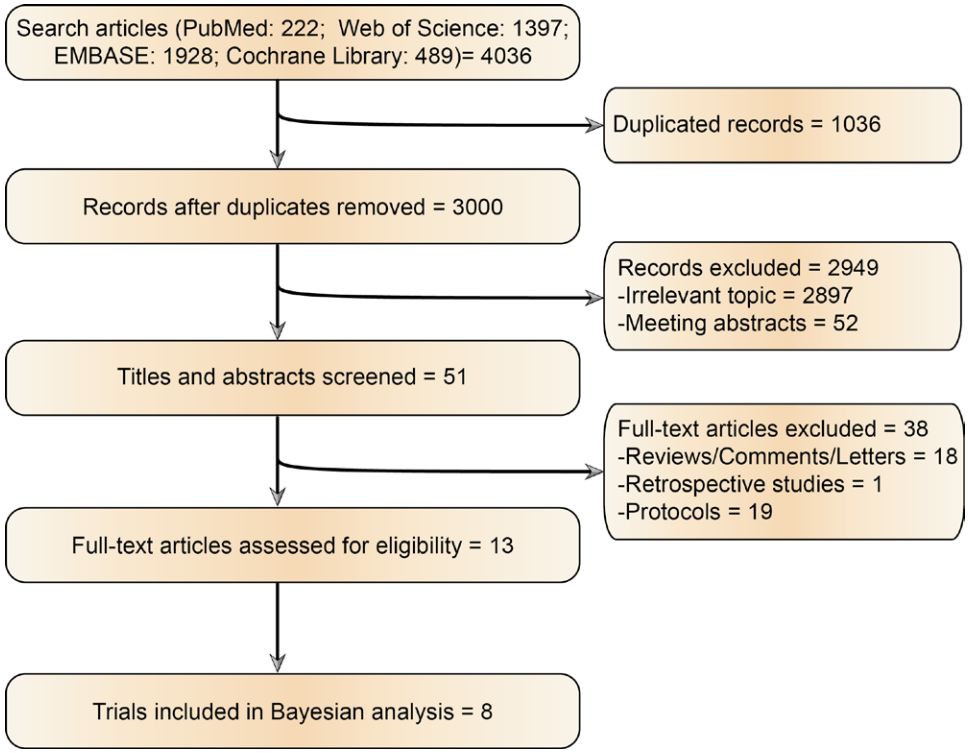

Figure 1. Selection process of the eligible studies included in the Bayesian network analysis.

4. Discussion

This Bayesian network analysis was based on eight trials, including 4398 individuals randomly assigned to seven different treatments. Our findings might help choose among immunotherapy agents, immunochemotherapy, or docetaxel for previously treated patients with NSCLC. Pembrolizumab 200 mg plus docetaxel was better efficacious than the other treatments and ranked first in terms of PFS. However, it ranked last, and no significant benefits were provided in improving OS. For prolonged OS, pembrolizumab 10 mg/kg was more efficacious than pembrolizumab 200 mg plus docetaxel, avelumab, and docetaxel, and ranked first compared with the other six treatments. These results indicate that pembrolizumab 10 mg/kg might be preferred in the second- or later-line treatment for immunotherapy-naive NSCLC patients.

Due to the median follow-up in PROLUNG trial being 8.9 months, which was much shorter than the minimum follow-up of

Table 1

Basic characteristics of the eligible clinical trials.

Study	Year	Design	NSCLC patients	Groups	No. patients	Median OS (months, 95% CI)	Median PFS (months, 95% CI)
CheckMate 057	2015	Randomized, open-label, multi-center, phase 3	Nonsquamous	1. Nivolumab: 3 mg/kg, q2w	292	12.2 (9.7-15.0)	2.3 (2.2-3.3)
				2. Docetaxel: 75 mg/m^2, q3w	290	9.4 (8.1-10.7)	4.2 (3.5-4.9)
CheckMate 017	2015	Randomized, open-label, multi-center, phase 3	Squamous	1. Nivolumab: 3 mg/kg, q2w	135	9.2 (7.3-13.3)	3.5 (2.1-4.9)
				2. Docetaxel: 75 mg/m^2, q3w	137	6.0 (5.1-7.3)	2.8 (2.1-3.5)
POPLAR	2016	Randomized, open-label, multi-center, phase 2	Nonsquamous Squamous	1. Atezolizumab: 1200 mg, q3w	144	12.6 (9.7-16.4)	2.7 (2.0-4.1)
				2. Docetaxel: 75 mg/m^2, q3w	143	9.7 (8.6-12.0)	3.0 (2.8-4.1)
KEYNOTE-010	2016	Randomized, open-label, multi-center, phase 2/3	Nonsquamous Squamous	1. Pembrolizumab: 2 mg/kg, q3w	344	10.4 (9.4-11.9)	3.9 (3.1-4.1)
				2. Pembrolizumab: 10 mg/kg, q3w	346	12.7 (10.0-17.3)	4.0 (2.7-4.3)
				3. Docetaxel: 75 mg/m^2, q3w	343	8.5 (7.5-9.8)	4.0 (3.1-4.2)
OAK	2016	Randomized, open-label, multi-center, phase 3	Nonsquamous Squamous	1. Atezolizumab: 1200 mg, q3w	425	13.8 (11.8-15.7)	2.8 (2.6-3.0)
				2. Docetaxel: 75 mg/m^2, q3w	425	9.6 (8.6-11.2)	4.0 (3.3-4.2)
JAVELIN Lung 200	2018	Randomized, open-label, multi-center, phase 3	Nonsquamous Squamous	1. Avelumab: 10 mg/kg, q2w	396	10.5 (9.2-12.9)	2.8 (2.7-3.5)
				2. Docetaxel: 75 mg/m^2, q3w	396	9.9 (8.1-11.8)	4.2 (3.3-5.2)
CheckMate 078	2019	Randomized, open-label, multi-center, phase 3	Nonsquamous Squamous	1. Nivolumab: 3 mg/kg, q2w	338	12.0 (10.4)	2.8 (2.4-3.4)
				2. Docetaxel: 75 mg/m^2, q3w	166	9.6 (7.6-11.2)	2.8 (1.6-2.9)
PROLUNG	2020	Randomized, open-label, multi-center, phase 2	Nonsquamous Squamous	1. Pembrolizumab: 200 mg, d8 plus Docetaxel: 75 mg/m^2, d1, q3w	40 38	14.6 (4.8-not reached)	9.5 (4.2-not reached)
				2. Docetaxel: 75 mg/m^2, d1, q3w		14.1 (7.9-not reached)	3.9 (3.2-5.7)

CI = confidence interval NSCLC = non-small-cell lung cancer, OS = overall survival, PFS = progression-free survival, q2w = every two weeks, q3w = every three weeks.

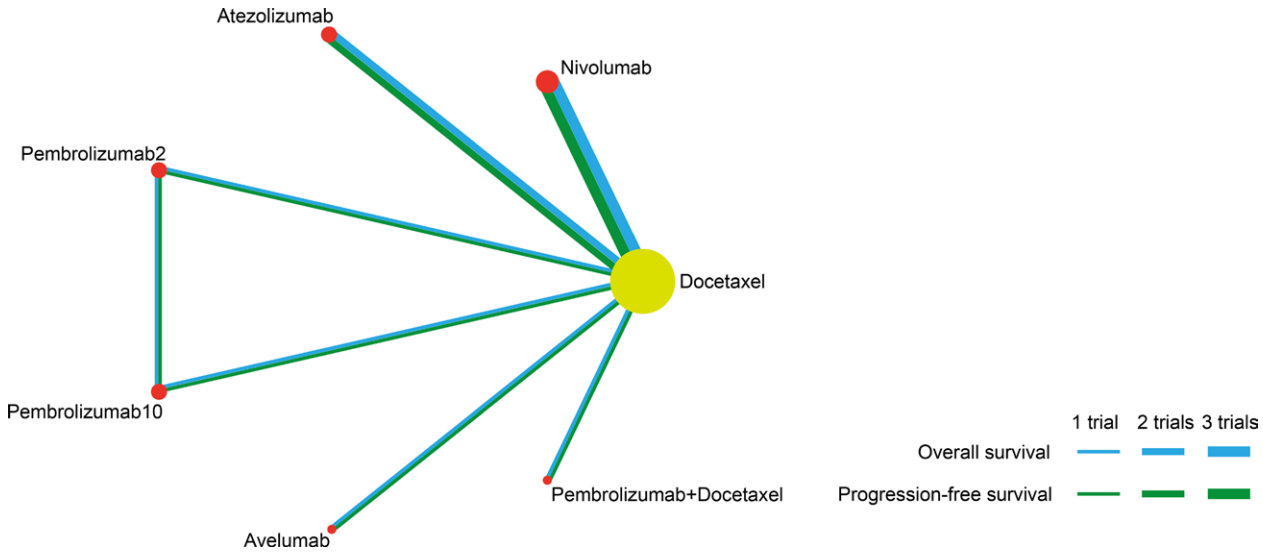

Figure 2. Network plots of comparisons on overall survival and progression-free survival of treatments in patients with advanced non-small cell lung cancer.

Progression-free survival

Overall survival						
Nivolumab	0.96 (0.87-1.05)	1.01 (0.91-1.11)	1.68 (1.27-2.22)	0.93 (0.86-1.00)	0.85 (0.77-0.93)	0.91 (0.86-0.96)
0.98 (0.88-1.10)	Pembrolizumab 2	1.05 (0.94-1.17)	1.76 (1.32-2.33)	0.97 (0.88-1.06)	0.89 (0.79-0.99)	0.95 (0.88-1.02)
1.05 (0.94-1.17)	1.07 (0.94-1.22)	Pembrolizumab 10	1.68 (1.26-2.23)	0.92 (0.84-1.02)	0.85 (0.76-0.94)	0.90 (0.84-0.98)
0.79 (0.59-1.05)	0.80 (0.59-1.07)	0.75 (0.56-1.00)	Pembrolizumab+ Docetaxel	0.55 (0.42-0.73)	0.50 (0.38-0.67)	0.54 (0.41-0.71)
0.97 (0.89-1.06)	0.99 (0.88-1.10)	0.93 (0.83-1.04)	1.24 (0.93-1.65)	Atezolizumab	0.91 (0.83-1.01)	0.98 (0.92-1.03)
0.89 (0.80-0.98)	0.90 (0.80-1.02)	0.84 (0.75-0.95)	1.13 (0.85-1.51)	0.91 (0.82-1.01)	Avelumab	1.07 (0.98-1.16)
0.85 (0.80-0.90)	0.86 (0.79-0.94)	0.81 (0.74-0.88)	1.08 (0.82-1.43)	0.87 (0.82-0.93)	0.96 (0.88-1.03)	Docetaxel

Figure 3. Hazard ratios for the Bayesian network analysis. Comparisons should be read from left to right. For overall survival and progression-free survival, a hazard ratio of less than 1 favors left treatment.

24 months, the current data analysis of OS could not fully demonstrate the inferiority of pembrolizumab 200 mg plus docetaxel in improving OS. Alternatively, docetaxel might be better against other second- or later-line treatments (gemcitabine, etoposide, and vinorelbine).[3] Thus, we consider that NSCLC patients could benefit from docetaxel after the failure of mono-immunotherapy.

Among PD-1/PD-L1 inhibitors, the efficacy of anti-PD-1 versus anti-PD-L1 remains controversial. Moreover, whether squamous or non-squamous NSCLC benefits more from immunotherapies is unclear. In our analysis, the OS and PFS values were significantly prolonged for patients treated with anti-PD-1 monotherapies compared with avelumab, a PD-L1 inhibitor. Although atezolizumab exhibited worse PFS than nivolumab, this regimen had comparative OS efficacy compared with PD-1 inhibitors as monotherapy or combination therapy. Therefore, in the overall NSCLC population, it could be hard to indicate that PD-1 inhibitors lead to significantly superior survival than PD-L1 inhibitors. One mirror-designed meta-analysis confirms our deduction and found no significant differences regarding the OS (HR 0.93, 95% CrI 0.76-1.14) and PFS (0.83, 0.52-1.27) across all NSCLC types.[26]

However, there is a solid predictive association between the expression level of PD-L1 and survival outcomes.[27–29] In the PD-L1 positive population, the mirror meta-analysis synthesized the data extracted from KEYNOTE-010 and JAVELIN Lung 200[12,18] and showed the advantage of pembrolizumab versus avelumab in curing previously treated advanced NSCLC patients.[26] This might be one of the reasons why pembrolizumab 10 mg/kg ranked first in our analysis.

Meanwhile, we focus on NSCLC subtypes because squamous cell carcinoma and adenocarcinoma might have different responses in the second- or later-line treatments. Firstly, pemetrexed plus platinum is the preferred first-line treatment for non-squamous NSCLC. For squamous NSCLC, carboplatin plus paclitaxel or albumin-bound paclitaxel is the recommended chemotherapy. Secondly, in the CheckMate 017 trial, squamous NSCLC showed no significant differences between nivolumab and docetaxel regardless of the expression PD-L1.[10] However, for the adenocarcinoma subtype in CheckMate 057, the higher the PD-L1 expression levels, the higher effects were reported.[9] In addition, Xu's study confirmed that the antitumor effects of nivolumab were positively correlated with

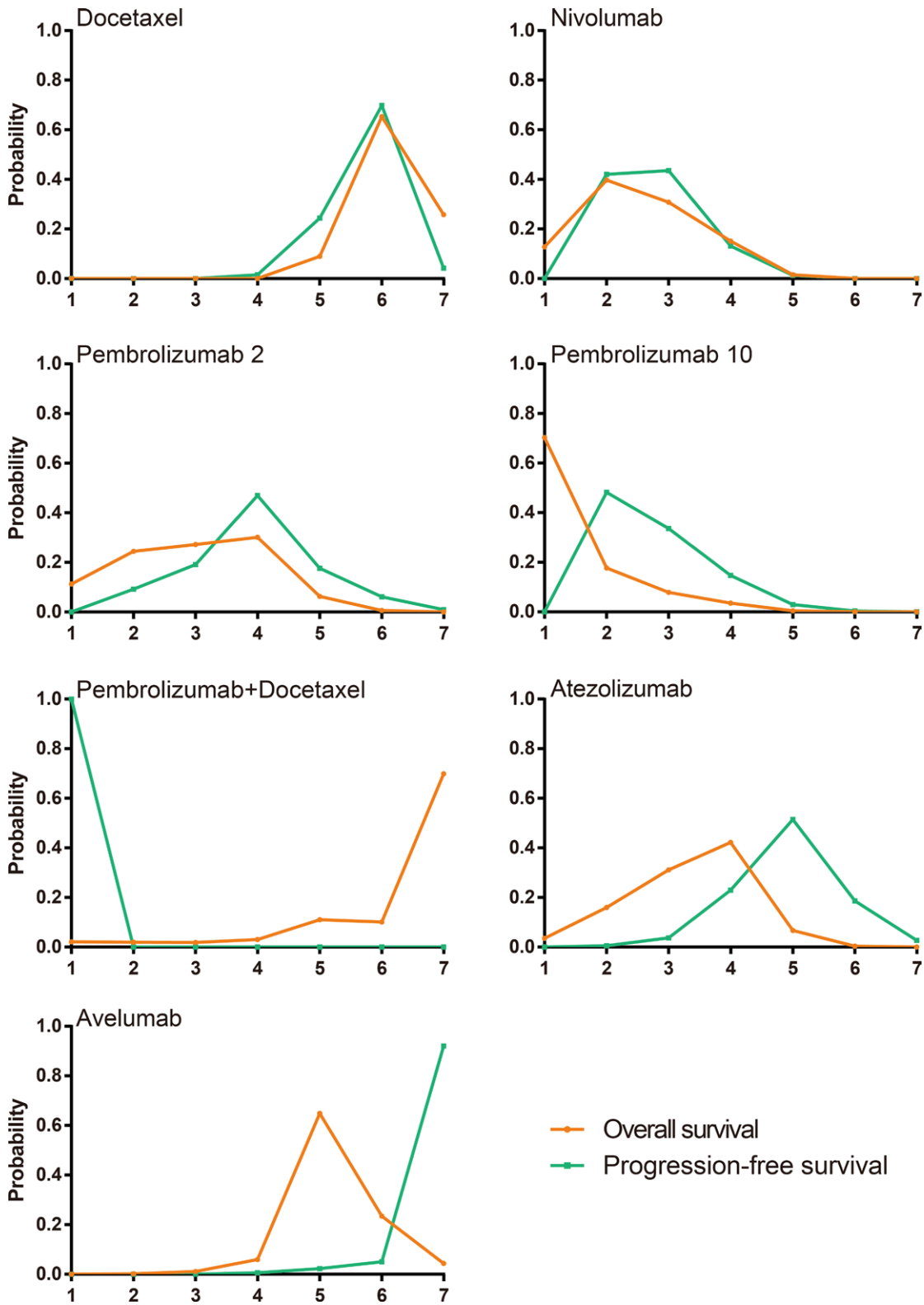

Figure 4. Bayesian ranking profiles of comparable treatments on efficacy for previously treated patients with non-small cell lung cancer. Profiles indicate the probability of each comparable treatment being ranked from first to last on overall survival and progression free survival.

the expression level of PD-L1.[30] Therefore, the effects might decrease when docetaxel is administrated as a second-line treatment after paclitaxel.

Up to now, ICI have been recommended as the first-line treatment in the National Comprehensive Cancer Network guideline of NSCLC.[31] For recurrent patients who have received immunotherapy, the results of our analysis are not applicable. Consequently, the main suitable populations could be the patients with progressed diseases after epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1 (ROS1), or B-rapidly accelerated fibrosarcoma (BRAF) target therapy, or those treated with chemotherapy alone previously.

5. Limitations

Since the tolerability of immune inhibitors has been demonstrated to be pretty well in clinical practice, we did not further investigate the toxic effects in this Bayesian network analysis. Owing to the search data remaining on September 2020 and there might be a long time from submission to publication, our results should be explained and compared with other potential published clinical trials during this period. In addition, cost-effect should be considered in the real world because the cost may highly increase when pembrolizumab is given at a dose of 10 mg/kg. All trials included in this study were open-label trials, which might undermine the validity of the findings. Another limitation was that only docetaxel was enrolled, and other taxanes might have potentially different effects. Finally, all enrolled studies comparing the immunotherapies with docetaxel were funded by the pharmaceutical companies marketing these ICIs, which might increase the bias.

6. Conclusions

As second- or later-line treatments, pembrolizumab 10 mg/kg had the highest benefit of OS, while pembrolizumab 200 mg plus docetaxel had the highest benefit of PFS in immunotherapy naive NSCLC patients. Future clinical studies and meta-analyses are needed to update our results and to explore more efficacy combination strategies.

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Author contributions

Study design: Bi-Cheng Wang; data extraction: Bi-Cheng Wang and Xin-Xiu Liu; data analysis: Bi-Cheng Wang and Xin-Xiu Liu; Manuscript writing and edition: Bi-Cheng Wang, Guo-He Lin and Xin-Xiu Liu.
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Writing – review & editing: Guo-He Lin, Xin-Xiu Liu.

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