

Single-Arm Trials Can Be Used for Meta-analysis to Compare PD-1 Inhibitor With PD-L1 Inhibitors on the Incidence of Pneumonitis?



To the Editor:

We read with great interest the meta-analysis for non-small cell lung cancer by Khunger et al¹ in the August 2017 issue of *CHEST*. The authors searched online databases for clinical trials to explore the difference between programmed death 1 (PD-1) inhibitors and programmed death-ligand 1 (PD-L1) inhibitors on the incidence of pneumonitis in the treatment of non-small cell lung cancer. The authors found that patients treated with PD-1 inhibitors had a higher incidence of pneumonitis compared with patients treated with PD-L1 inhibitors. We congratulate and applaud the authors on important work on this topic. However, the conclusion is unstable due to lack of randomized controlled trials directly comparing PD-1 inhibitors with PD-L1 and cannot be supported.

The authors' conclusion was affected by numerous factors and thus not convincing:

1. None of the studies included by the authors is a randomized controlled trial comparing PD-1 inhibitors and PD-L1 inhibitors directly.
2. Various single-arm trials treated patients with non-small cell lung cancer with different doses.
3. The follow-up time of each study was different. Baseline levels such as age and sex in PD-1 trials and PD-L1 trials were not taken into account.
4. The authors neglected the risk of bias assessment of single-arm trials. In addition, we found that the risk of bias assessment of single-arm trials in another meta-analysis conducted by the authors was also not assessed.² The nonrandomized studies assessment tools included the methodological tools summarized by Slim et al,³ Deeks et al,⁴ and Reisch et al.⁵ The authors included up to 13 single-arm trials. Therefore, the risk of bias assessment of single-arm trials was very necessary in this meta-analysis.
5. The incidence of pneumonitis in patients treated with PD-1/PD-L1 inhibitors was too low. The highest incidence of all-grade pneumonitis was only 4.3% (provided by the authors), not to mention high-grade pneumonitis. These analyses were limited by the small number of pneumonitis events in each trial.

Therefore, comparing the difference between PD-1 inhibitors and PD-L1 inhibitors on the incidence of pneumonitis was of no clinical significance.

Considering these facts, we find it hard to accept the authors' conclusion that patients treated with PD-1 inhibitors had a higher incidence of pneumonitis compared with patients treated with PD-L1 inhibitors.

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Response



To the Editor:

We thank Zhang and colleagues for their correspondence regarding our article¹ assessing the incidence of pneumonitis in patients with non-small cell lung cancer (NSCLC) treated with programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors. We present our responses to the queries raised by the correspondence:

1. There have been no randomized controlled trials that have compared PD-1 inhibitors directly with PD-L1 inhibitors. These agents are approved for similar indications. Patients with metastatic NSCLC whose disease has progressed following chemotherapy have the option of treatment with PD-1 inhibitors

(nivolumab and pembrolizumab) and a PD-L1 inhibitor (atezolizumab). Our article¹ was one of the first efforts aimed at comparing the incidence of pneumonitis, a serious life-threatening adverse effect, among PD-1 and PD-L1 inhibitors.

2. Before the dosage of PD-1/PD-L1 inhibitors was standardized by the US Food and Drug Administration, different clinical trials included patients with varying doses. However, this fact should not adversely affect the outcomes of our study because similar rates of adverse events have been observed across different doses of PD-1/PD-L1 inhibitors in clinical trials. For instance, the KEYNOTE-010 trial evaluated two different doses of pembrolizumab (2 mg/kg and 10 mg/kg) every 3 weeks, and similar results, including similar rates of adverse events, were observed.²
3. Table 1 of our meta-analysis¹ summarizes all the included clinical trials. The median age, sex of patients, and follow-up time across each included clinical trial are defined in Table 1 of the meta-analysis.
4. Risk of bias assessment was performed by using the Cochrane risk of bias assessment³ and is provided as Figure 2 in our published meta-analysis.¹ It is also included as a supplement in our other meta-analysis comparing the efficacy and adverse events of PD-1/PD-L1 inhibitors among treatment-naïve and previously treated patients with NSCLC.⁴ Most of the studies had high risk of selection bias, performance bias, and detection bias because most were open-label, single-arm trials. All or most of the included trials had a low risk of reporting bias, attrition bias, and other bias.
5. Both PD-1 inhibitors (nivolumab and pembrolizumab) and the PD-L1 inhibitor (atezolizumab) are approved by the US Food and Drug Administration for the treatment of NSCLC in patients whose disease has progressed following chemotherapy. Pembrolizumab has been approved in the front-line setting in patients with PD-L1 expression > 50% as a single agent. In addition, the combination of chemotherapy and pembrolizumab is approved in the front-line setting for patients with metastatic NSCLC without any targetable mutations. The annual incidence of NSCLC in the United States is 234,030; approximately 75% of these patients present with advanced/metastatic disease at the time of diagnosis, and a vast majority of these patients may be treated with PD-1/PD-L1 inhibitors during their disease course. The clinical trials only included a fraction of these patients, and our meta-analysis observed a small but significant difference in the incidence of

pneumonitis among PD-1 and PD-L1 inhibitors included in the clinical trials.

As more and more patients are being treated with these agents, it is imperative to understand the differences between rates of serious, life-threatening adverse events such as pneumonitis to guide treatment selection.

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Pigtail Catheter Drainage Can Be Considered as the Initial Treatment Option for Patients With Pneumothorax Not Yet Determined



To the Editor:

We read with great interest the article by Chang et al¹ in a recent issue of *CHEST* (May 2018). The authors found that pigtail catheter drainage may be considered