# Risk of pneumonitis with different immune checkpoint inhibitors in NSCLC

**Kyrillus S. Shohdy[1], Omar Abdel-Rahman[2]**

[1]Department of Clinical Oncology, Faculty of Medicine, Cairo University, Cairo, Egypt; [2]Department of Clinical Oncology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

*Correspondence to:* Omar Abdel-Rahman. Department of Clinical Oncology, Faculty of Medicine, Ain Shams University, Cairo, Egypt.
Email: omar.abdelrhman@med.asu.edu.eg.

*Provenance:* This is a Guest Editorial commissioned by Section Editor Jianrong Zhang, MD (Department of Thoracic Surgery, First Affiliated Hospital of Guangzhou Medical University, Guangzhou Institute of Respiratory Disease, Guangzhou, China).

*Comment on:* Khunger M, Rakshit S, Pasupuleti V, *et al.* Incidence of Pneumonitis With Use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis of Trials. Chest 2017;152:271-81.

Submitted Jun 17, 2017. Accepted for publication Jun 22, 2017.
doi: 10.21037/atm.2017.06.67
**View this article at:** http://dx.doi.org/10.21037/atm.2017.06.67

Having auspicious value in treating lung cancer, immune checkpoint inhibitors gained approval in the first-line therapy of advanced NSCLC as well as in many other solid tumors. In the last decade, immunotherapy is considered the second breakthrough after tyrosine kinase inhibitors in the management of lung cancer. Targeting immune checkpoint could put T-cell into action and enhance immune response against tumor cells. Those unleashed immune responses were expected to have collateral damage in the form of inducing plethora of autoimmune manifestations that virtually can affect any part of the body. Immune-related adverse events (IRAEs) have a distinctive pattern of development. Commonly involved sites include lung, gastrointestinal (GI) tract, skin, and endocrine glands. It seems that every immune checkpoint inhibitors have different toxicity profile. For instance, ipilimumab, an anti-CTLA-4, is associated with early development of mucocutaneous complications followed by GI affection. On the other hand, nivolumab, an anti-PD-1, has a relatively delayed onset of its AEs.

Much attention to pneumonitis is warranted not only because it may be rapidly fatal in some occasions but also because the diagnosis is challenging. Pneumonitis-like picture can develop spontaneously in the natural history of lung cancer due to multiple factors such as infection and malignant lung infiltrate hence, proving causality to immune checkpoint inhibitors is a daunting task (1). To complicate matters further, withholding the treating agent may flare the condition if it is disease-related rather drug-induced adverse effect. As the disease and the adverse effect affect the same anatomical site, the clinical and radiologic manifestations are difficult to be distinguishable. This issue recapitulates the well-known debate on patients with rheumatoid arthritis who develop interstitial pneumonia while they are on treatment by methotrexate. The latter is known to cause interstitial lung disease (2). Is that disease-related and the drug should be continued or drug-induced and the treatment have to be discontinued? This question is transmitted to oncology circles now. Some reports are trying to formulate a pattern of recognition to help clinicians identifying such serious condition and provide timely management (3).

Khunger and her colleagues (4) published a systematic review in *the Chest Journal* in May, 2017 under the title "incidence of pneumonitis with use of PD-1 and PD-L1 inhibitors in non-small cell lung cancer: a systematic review and meta-analysis of trials". This study continued the cumulative work of reviews and meta-analyses that have dissected the epidemiology of pneumonitis with immune checkpoint inhibitors. Before delving to the details of this interesting report we will set the scene with three important deductions regarding this challenging adverse effect. First, it was evident that immune checkpoint inhibitors were associated with higher risk of all-grade pneumonitis

compared to chemotherapy or placebo controls based on our meta-analysis of 11 trials (5). Second, pneumonitis related to PD-1 inhibitors tends to occur in NSCLC more frequently than in other tumors. For instance, compared to melanoma, the incidence of all grade and high-grade pneumonitis in NSCLC was (4.1% *vs.* 1.6%; P=0.002) and (1.8% *vs.* 0.2%; P<0.001) respectively (6). Third, immunotherapy combinations have an added risk for all and high-grade pneumonitis compared to monotherapy (6). In an analysis of 915 patients received anti-PD-1/PD-L1, the incidence of pneumonitis in those who received combination therapy versus monotherapy was (10% *vs.* 3%, P<0.001) (1). Moreover, the median time for occurrence of pneumonitis after commencing therapy was 2.6 months with wide range (0.5–11.5 months) (6). Furthermore, prospective studies to identify possible risk factors for development of pulmonary toxicity in such setting are not available yet.

Khunger *et al.* tried to solve the last piece of the puzzle. Does the type of immune checkpoint inhibitors make difference in the estimated risk and does prior chemotherapy constitute a risk factor per se? The answer came positive for the first question and negative for the second.

The meta-analysis included 19 clinical trials with a total of 5,038 patients. Twelve trials used PD-1 inhibitors (nivolumab =9, pembrolizumab =3) and seven trials used PD-L1 inhibitors (atezolizumab =5, durvalumab =1, avelumab =1). Most of them were open label, single-arm trials. A significantly higher incidence of all and high-grade pneumonitis was found with PD-1 inhibitors in comparison to PDL-1 inhibitors. To circumvent the higher heterogeneity observed in the pneumonitis rate among PD-1 inhibitors trials, the authors performed subgroup analysis that didn't reveal any statistically significant differences between Nivolumab and pembrolizumab. This is consistent with the indirect comparison of odds ratio of high-grade pneumonitis for both agents in another meta-analysis (7).

One of the strengths of this analysis that it explored the difference of rate of pneumonitis related to the use of PD-1 and PD-L1 inhibitors in treatment-naive and previously-treated advanced NSCLC patients. Although there was a higher incidence of all-grade pneumonitis in the treatment-naïve group (4.3% *vs.* 2.8%; P=0.03), high-grade pneumonitis showed no statistically significant difference between both groups. This result is quiet reassuring for use of immune check point inhibitors in the frontline setting of advanced NSCLC. Still not clear why previously treated patients have a less likelihood for development of all-grade pneumonitis. Most of these patients received multiple lines of chemotherapy and radiation. Interestingly, the authors found that all the deaths related to pneumonitis occurred with PD-1 inhibitors. Moreover, the role of smoking history and prior radiation therapy as risk factors for pneumonitis need further investigation. An additional strength of this meta-analysis is to restrict the inclusion to adverse effects termed "pneumonitis" with exclusion of unconfirmed cases of interstitial lung disease or pneumonia.

However, a point of caution is needed before over-interpreting the results of this meta-analysis. None of the studies in this analysis contained a head to head comparison between PD-1 and PD-L1 inhibitors or a head to head comparison between individual PD-1 and PD-L1 inhibitors. Thus, it would be difficult to conclude with confidence about the pulmonary safety of any of these agents compared to each others. Prospective randomized studies with head to head comparisons among these agents are needed to reach clear conclusions about comparative efficacy and safety.

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

## References

1. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. J Clin Oncol 2017;35:709-17.
2. Hallowell RW, Horton MR. Interstitial lung disease in patients with rheumatoid arthritis: spontaneous and drug induced. Drugs 2014;74:443-50.
3. Possick JD. Pulmonary Toxicities from Checkpoint Immunotherapy for Malignancy. Clin Chest Med 2017;38:223-32.
4. Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of Pneumonitis With Use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis of Trials. Chest 2017;152:271-81.
5. Abdel-Rahman O, Fouad M. Risk of pneumonitis in

 

cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Ther Adv Respir Dis 2016;10:183-93.
6. Nishino M, Giobbie-Hurder A, Hatabu H, et al. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-analysis. JAMA Oncol 2016;2:1607-16.
7. Peng TR, Tsai FP, Wu TW. Indirect comparison between pembrolizumab and nivolumab for the treatment of non-small cell lung cancer: A meta-analysis of randomized clinical trials. Int Immunopharmacol 2017;49:85-94.

**Cite this article as:** Shohdy KS, Abdel-Rahman O. Risk of pneumonitis with different immune checkpoint inhibitors in NSCLC. Ann Transl Med 2017;5(17):365. doi: 10.21037/atm.2017.06.67

 