Editorial

PD-1 and PD-L1 inhibitor toxicities in non-small cell lung cancer

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Immune checkpoint inhibitors (ICIs) utilize the natural programming of the immune system to initiate an antitumor response, counteracting checkpoint molecule expression on tumor cells (1). Immunotherapies that inhibit the programmed death 1 (PD-1) molecule, the programmed death ligand 1 (PD-L1) molecule, and the cytotoxic lymphocyte antigen 4 (CTLA-4) molecule have demonstrated improved survival outcomes for patients with renal cell carcinoma (2), advanced melanoma (3), and non-small cell lung cancer (NSCLC) (4-11). ICIs are a relatively recent therapeutic strategy in cancer that may produce off-target effects due to inflammation in various organ systems. These effects are defined as immune-related adverse events (irAEs), and though are rare occurrences, can be fatal (12). The toxicities associated with PD-1 and CTLA-4 inhibition reported thus far include skin rashes, diarrhea and colitis, thyroid dysfunction, type I diabetes mellitus, and pneumonitis (1). Pneumonitis is a particularly concerning adverse effect of ICI therapy because of its potentially fatal outcomes in patients treated with anti-PD-1/PD-L1 ICIs for cancer (13).

Pneumonitis is defined as a focal or diffuse inflammation of the lung parenchyma (14), and may occur as a result of treatment with a number of classes of anti-cancer agents. Symptoms of pneumonitis include dyspnea, cough, fever, or chest pain (1). The CTCAE NIH grading system stratifies the severity of a particular toxicity into five grades (15), and helps to determine appropriate treatment. In the case of pneumonitis, management can range from withholding immunotherapy until symptoms improve or resolve, to hospitalization with intravenous corticosteroids followed by secondary forms of immunosuppression. The optimum choice for additional immunosuppression remains an open question, and includes options such as infliximab, mycophenolate mofetil or intravenous immunoglobulin (1). Patients with irAEs, particularly PD-1/PD-L1 pneumonitis, comprise an important proportion of inpatient oncology admissions (16), and as the number of patients who receive immunotherapy for NSCLC and other tumor types increases, it will become increasingly important to understand the risk factors associated with pneumonitis from PD-1/PD-L1 agents. One approach to elucidating the connection between ICI therapy and pneumonitis is to understand the subtle yet key differences between PD-1 and PD-L1 inhibitors and their contribution to the risk of developing pneumonitis as an immune-related toxicity.

In published literature from clinical trials and observation studies of NSCLC patients receiving immunotherapy, the overall incidence of all-grade immune-related toxicities such as hypothyroidism and pneumonitis appear to be slightly lower in those treated with PD-L1 inhibitors (such as atezolizumab, durvalumab, and avelumab) , but is comparable to those treated with PD-1 inhibitors (such as nivolumab and pembrolizumab) (4-13). In this meta-analysis, Pillai *et al.* begin the search to further understand how PD-1 and PD-L1 inhibitors differ in their toxicity profiles (17). In "Comparison of the Toxicity Profile of PD-1 Versus PD-L1 Inhibitors in Non-Small Cell Lung Cancer: A Systematic Analysis of the Literature," the authors conduct a meta-analysis of PD-1 and PD-L1 monotherapy clinical trials in NSCLC, and identify 11 PD-L1 and 12 PD-1

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clinical trials suitable for inclusion. The primary aim of this analysis was to report the overall incidence of toxicities seen with these two groups of agents, and specifically focus on differences in high-grade toxicities, common toxicities, and the overall spectrum of irAEs across groups. In this paper, NSCLC patients enrolled in clinical trials that used PD-1 monotherapy were compared with NSCLC patients enrolled in trials that utilized PD-L1 monotherapy. The two patient populations were similar in terms of age, gender, smoking status, and overall treatment response as defined within each included trial. Many of the trials included in this study were multi-institutional as well as multi-national, providing a large and heterogeneous patient population. The PD-1 and PD-L1 groups were similar in their overall AE incidence (e.g., fatigue, diarrhea, and skin rash) as well as their incidence of grade 3+ toxicities. In both groups, fatigue was identified as the most common toxicity, and hypothyroidism was the most common irAE.

The principal finding in this study was that patients treated with PD-1 monotherapy as part of the included trials had a higher incidence of reported irAEs, as well as a higher incidence of pneumonitis, compared with those treated as part of PD-L1 monotherapy trials. Pillai *et al.* hypothesize that this finding may be due to the mechanism of action of an anti-PD-1 agent in blocking the interaction with both PD-L1 and PD-L2, while anti-PD-L1 antibodies still allow PD-1 to interact with PD-L2. The authors assert that this may result in a less 'immunogenic' response and reduced autoimmunity (17). While this study investigates potential differences in the incidence of a variety of irAEs between the groups, the only statistically significant difference in irAE incidence was found in those who developed pneumonitis, in which the incidence was double with the PD-1 as opposed to the PD-L1 agents [4% (95% CI, 3–5%) *vs.* 2% (95% CI, 1–3%); P=0.01].

Choice of anti-PD-1 *vs.* PD-L1 agents is a critical issue relevant to patients with NSCLC, since there are multiple FDA-approved agents within a variety of indications in this tumor type. Therefore, infusion time, cost, frequency of visits and toxicity profiles come to the fore as key elements in decision-making between one agent and another (18). The data from Pillai *et al.* and others highlight that receipt of either a PD-1 inhibitor or a PD-L1 inhibitor is associated with all-grade and high-grade pneumonitis when used to treat NSCLC (17,19-23), and that NSCLC patients have a higher rate of mortality after being diagnosed with PD-1/PD-L1 pneumonitis (17). However, patients treated with PD-1/PD-L1 inhibitors had no significant increased risk of pneumonitis-related death when compared to patients treated with the control standard-of-care regimens within in each (21). Reassuringly, most cases of PD-1/PD-L1 pneumonitis are low grade, and either improve or resolve with withholding immunotherapy and treatment with corticosteroids. However in some cases, PD-1/PD-L1 pneumonitis does not respond to corticosteroids or even additional immunosuppression, and can lead to death (13,24,25). Patients who present to the emergency department with PD-1/PD-L1 pneumonitis are associated with poor overall survival compared to patients who develop other irAEs from immunotherapy (26), highlighting that vigilance is key to detection and aggressive treatment of PD-1/PD-L1 pneumonitis. While these data may be interpreted to suggest that PD-L1 agents are safer from a pneumonitis perspective, the overall incidence of pneumonitis for both agents is within an acceptable range of <5%. Therefore, the incidence of pneumonitis alone may not be a sufficient criterion on which to base treatment decisions.

The article by Pillai *et al.* is based on a mainly second-line treatment setting in patients with advanced NSCLC. Since the publication of this meta-analysis, the field of immunotherapy for NSCLC has rapidly evolved such that patients with newly diagnosed NSCLC may receive first-line anti-PD-1/PD-L1 agents, with or without chemotherapy (4-7), and PD-L1 monotherapy is licensed for use after chemoradiation for stage III NSCLC (27). Data from these studies highlight the increasing complexity of discerning PD-1/PD-L1 pneumonitis from radiation pneumonitis or chemotherapy-related pneumonitis. Future work in this area will be needed, including meta-analyses that assess the risk of pneumonitis in both first-line immunotherapy-containing regimens and beyond. The need for this work is supported by newer data that suggests that treatment-naïve NSCLC patients may be more likely to experience PD-1/PD-L1 pneumonitis (19). The unique toxicity profile associated with combination ICIs is another route of investigation that should be pursued in future endeavors, as there is increased risk of pneumonitis in NSCLC patients treated with PD-1/PD-L1 based immunotherapy combinations (20,21). Certain subgroups of patients, such as those diagnosed with NSCLC who have previously been treated with targeted therapies, may also be at increased risk of developing PD-1/PD-L1 pneumonitis (28). This group should be studied in a real-world setting, as they would have been excluded from entry onto clinical trials.

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While this meta-analysis constitutes an important contribution to the literature, there are potential pitfalls in this study. These include variations between included trials of by which attribution to study therapy for each AE was assessed, and inclusion of clinical trials and associated toxicity data from studies only presented at conference proceedings rather than published in full.

In summary, Pillai and colleagues are to be congratulated on constructing a key meta-analysis aimed at comprehensively exploring the differences in toxicity between PD-1 and PD-L1 inhibitors in patients with NSCLC, and uncovering that the incidence of PD-1/PD-L1 pneumonitis may be different depending on the type of agent received. Further inquiry in this area is needed that includes individual patient data, specifically diagnostic features of specific irAEs, treatment patterns of irAEs and their resultant outcomes—which may serve as a practical guide in irAE decision-making, and hopefully inform future patient selection.

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Footnote

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

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