Editorial Commentary

Pembrolizumab in advanced non-small cell lung cancer: safety implications of dose adjustments

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Immune checkpoint inhibitors have changed the treatment landscape for non-small cell lung cancer (NSCLC) and are often incorporated into first line therapy for advanced or metastatic NSCLC (1). Pembrolizumab is one of the many monoclonal antibodies that inhibit the programmed cell death-1 (PD-1)/programmed cell death ligand (PDL-1) axis leading to substantial clinical benefit in lung cancer.

In the recently published article in the *Journal of Thoracic Oncology* (*JTO*) by Higashiyama *et al.*, the authors retrospectively evaluated 45 patients with advanced NSCLC who were previously stable on pembrolizumab at 200 mg every 3 weeks (Q3W) and switched to an extended-dose interval of pembrolizumab at 400 mg Q6W (2). After the transition, the results show that 17 out of 45 patients (37.8%) experienced new or worsening treatment-related adverse events (TRAEs) within three cycles, including 11 patients with pneumonitis (24.4%) and 3 patients with diarrhea (6.7%). The median time after transitioning to the higher dose until the onset of the new TRAEs was 63 days, and 12 out of the 17 patients received systemic steroids for the treatment of TRAEs.

KEYNOTE-001 was the initial evaluation of pembrolizumab in advanced NSCLC that led to its accelerated approval in patients with PDL-1 tumor proportion score (TPS) of 50% or greater (3). In this pivotal trial, patients received pembrolizumab at either 10 mg per kilogram (mg/kg) Q2W, 10 mg/kg Q3W, or 2 mg/kg Q3W. The results showed that there were no significant differences with regards to safety profile between the 10 mg/kg Q2W or Q3W regimen (3).

In KEYNOTE-010, the phase 2/3 trial of pembrolizumab versus docetaxel in previously treated patients with advanced NSCLC, patients who were treated with pembrolizumab at 2 mg/kg Q3W and 10 mg/kg Q3W had similar TRAE profile. Any grade TRAE was 63% with 2 mg/kg of pembrolizumab and 66% with 10 mg/kg. Grade 3+ TRAE were 13% and 16%, respectively (4). Modeling an average sized patient weighing 75 kg using these doses from KEYNOTE-010, the average dose of pembrolizumab for a 75 kg patient would either be 150 mg Q3W (at 2 mg/kg) or 750 mg Q3W (at 10 mg/kg). Thus, pembrolizumab doses far greater than the escalated dose of 400 mg Q6W (from the JTO study) in large, prospective, single arm and randomized trials have suggested a similar degree of TRAEs compared to lower doses. Moreover, using a model-based approach evaluating pharmacokinetic parameters, a thorough study showed that the expected exposure of pembrolizumab at 400 mg Q6W versus 200 mg Q3W were similar (5). Furthermore, the 400 mg dose rapidly achieved steady state in these models. The question of whether the brief initial exposure to higher levels of pembrolizumab prior to achieving steady state correlated to the higher incidence of TRAE is hard to confirm.

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Nivolumab, another FDA-approved immune checkpoint inhibitor, has been utilized at various dosing regimens. In the Checkmate-384 phase IIIB/IV trial of nivolumab 480 mg Q4W versus 240 mg Q2W in previously treated advanced NSCLC, safety profiles were similar. Any grade TRAEs were numerically lower with 480 mg Q4W (48%) versus 240 mg Q2W (61%) (6). This suggests that patients who see physicians more regularly due to more frequent dosing of immunotherapy may endorse more adverse events to their providers than those who do not see their oncologists as frequently.

There were 4 patients in the study who received tyrosine kinase inhibitors (TKIs) before pembrolizumab. Three patients had an *EGFR* gene mutation at the time of increasing pembrolizumab, thus the assumption is that all three patients received EGFR-directed TKIs. Since these patients were dose escalated with pembrolizumab sometime between August 2020 and November 2021, it would be reasonable to deduce that all 3 patients with *EGFR* mutations received prior osimertinib, a 3rd generation EGFR inhibitor that was FDA-approved in April 2018 following the FLAURA trial (7,8). All EGFR TKIs, including osimertinib, are well characterized to cause pneumonitis as an uncommon adverse effect (9). Additionally, in an observational study of over 20,000 patients, patients who received subsequent immunotherapy (nivolumab in this case) after EGFR-TKI had statistically higher odds of pneumonitis than those who did not get prior EGFR-TKI (10).

In the article, 7 patients permanently discontinued pembrolizumab due to TRAEs and 2 patients resumed at a lower dose. In those two patients who resumed at 200 mg Q3W, one patient had pneumonitis relapse and the other developed colitis. One possible explanation is that even without the dose escalation, these patients may have ultimately developed TRAEs, but this cannot be proven. One question that arises from this study is whether you can safely de-escalate a patient from 400 mg Q6W to 200 mg Q3W after low grade TRAE.

To conclude, the authors' results are interesting, yet, should be interpreted with caution as it was a small retrospective analysis at a single institution in comparison to a large amount of data from large, prospective, multicenter trials that would provide a rational counterargument. The U.S. Food and Drug Administration approved the pembrolizumab dosing regimen of 400 mg Q6W in April of 2020, soon after the explosion of coronavirus-19 (COVID-19). And in light of our current climate with the ongoing COVID-19 pandemic and popularization of telemedicine visits, the option of Q6W dosing minimizes additional clinic visits that may not be entirely necessary and caters to a patient population who are vulnerable with underlying cancer and who may be less eager to travel outside their comfort zone.

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Footnote

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References

1. Steuer CE, Ramalingam SS. Advances in Immunotherapy and Implications for Current Practice in Non-Small-Cell Lung Cancer. JCO Oncol Pract 2021;17:662-8.
2. Higashiyama RI, Yoshida T, Yagishita S, et al. Safety Implications of Switching Pembrolizumab Dosage From 200 mg Every 3 Weeks to 400 mg Every 6 Weeks in Patients With Advanced NSCLC. J Thorac Oncol 2022;17:1227-32.
3. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
4. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387:1540-50.
5. Lala M, Li TR, de Alwis DP, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. Eur J Cancer 2020;131:68-75.
6. Garon EB, Reinmuth N, Falchero L, et al. CheckMate 384: Phase IIIb/IV Trial of Nivolumab (Nivo) 480 Mg Q4W versus 240 Mg Q2W after ≤ 12 Months of Nivo in Previously Treated Advanced NSCLC. J Clin Oncol 2019;37:abstr 100.
7. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:113-25.
8. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020;382:41-50.
9. Ma Z, Pei J, Zhang Y, et al. Interstitial pneumonitis associated with EGFR/ ALK tyrosine kinase inhibitors used in non-small cell lung cancer: an observational, retrospective, pharmacovigilance study. Expert Opin Drug Saf 2022. [Epub ahead of print]. doi: 10.1080/14740338.2022.2110235.
10. Oshima Y, Tanimoto T, Yuji K, et al. EGFR-TKI-Associated Interstitial Pneumonitis in Nivolumab-Treated Patients With Non-Small Cell Lung Cancer. JAMA Oncol 2018;4:1112-5.

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