Editorial

Combination chemotherapy and immunotherapy in metastatic non-small cell lung cancer: a setback for personalized medicine?

Monica S. Chatwal[1], Tawee Tanvetyanon[2]

[1]Division of Medicine, Division of Hematology/Oncology, University of South Florida/H. Lee Moffitt Cancer Center, Tampa, FL, USA; [2]Division of Thoracic Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA

Correspondence to: Dr. Tawee Tanvetyanon. Division of Thoracic Oncology, H. Lee Moffitt Cancer Center, 12902 USF Magnolia Drive, Tampa, FL 33612, USA. Email: Tanvett@moffitt.org.

Provenance: This is an invited Editorial commissioned by Section Editor Dr. Hengrui Liang (Nanshan Clinical Medicine School, Guangzhou Medical University, Guangzhou, China).

Comment on: Gandhi L, Rodriguez-Abreu D, Gadgeel S, *et al.* Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.

Submitted Jul 12, 2018. Accepted for publication Jul 26, 2018.
doi: 10.21037/tlcr.2018.07.15
View this article at: http://dx.doi.org/10.21037/tlcr.2018.07.15

The management landscape for metastatic non-small cell lung cancer (NSCLC) has changed considerably beyond chemotherapy alone. This is due to the introduction of targeted therapies for patients with targetable mutations and the advent of immune checkpoint inhibitors. The inhibitors, anti-programmed death 1 (PD-1) and anti-programmed death ligand 1 (PD-L1) agents, were initially approved by the US Food and Drug Administration (FDA) for use in the subsequent line setting after progression on first line platinum-doublet chemotherapy (1,2). Pembrolizumab, nivolumab and atezolizumab have all been approved as single-agent treatments (3). Subsequently, in the first-line setting, pembrolizumab becomes the only agent that has gained regulatory approval as single agent therapy specifically for patients with a PD-L1 tumor proportion score (TPS) ≥50%. The approval was based on results from the KEYNOTE-024 study showing higher overall survival (OS) than chemotherapy [survival rate 80.2% *vs.* 72.4%, hazard ratio (HR) for death 0.6; 95% CI, 0.41–0.89, P=0.005] (3,4). In addition, in this study, the incidence of serious grade ⩾3 toxicities were reduced by about half with pembrolizumab treatment compared with chemotherapy. Although this treatment option is available to only about 30% of patients with metastatic NSCLC who have TPS ≥50%, it can be considered as the standard of care for this group of patients and it can be viewed as a progress for personalized therapy in lung cancer. Nonetheless, for others with unknown TPS or TPS <50%, chemotherapy has remained the standard of care first line therapy.

This has recently changed, however. Gandhi *et al.* have reported promising results for the combination of pembrolizumab with chemotherapy (KEYNOTE-189) (5). In this double-blind, phase III trial, patients with previously untreated metastatic non-squamous NSCLC without targetable mutations (*EGFR* or *ALK*) were randomly assigned to receive pemetrexed and platinum-based drug plus either 200 mg of pembrolizumab or placebo, regardless of PD-L1 status. Treatment was given every 3 weeks for 4 cycles, followed by pembrolizumab or placebo plus pemetrexed maintenance therapy for up to a total of 35 cycles (approximately 2 years). Crossover to pembrolizumab monotherapy was permitted if disease progression on placebo-combination was confirmed. There was a significant OS benefit noted for the pembrolizumab combination group over the chemotherapy alone group at 12 months (69.2% *vs.* 49.4%, HR for death 0.49, 95% CI, 0.38–0.64, P<0.001). This was despite the 41.3% crossover seen from the placebo group to pembrolizumab monotherapy. Progression free survival (PFS) also favored the pembrolizumab combination (8.8 *vs.* 4.9 months, HR for disease progression or death 0.52, 95% CI, 0.43–0.64, P<0.001). Of note, statistically significant benefits in OS, PFS and response rates were seen across all PD-L1 subgroup populations, including those with TPS ≤1% (5). More encouraging was the toxicity

profile in this trial. Grade 3 or higher adverse events were quite similar between the two groups with 67.2% seen in the pembrolizumab-combination and 65.8% in the placebo-combination. However, there was a higher rate of nephritis and acute kidney injury noted with the addition of pembrolizumab (5.2% *vs.* 0.5%), possibly because more patients were exposed to prolonged pemetrexed treatment. The FDA has now granted an approval of this combination of chemotherapy and immunotherapy regimen for non-squamous NSCLC irrespective of PD-L1 status (6).

The investigators should be congratulated for their success in significantly improving outcomes of patients with metastatic NSCLC, historically a very challenging disease. Nevertheless, despite the positive results of this study, it is still questionable whether every patient will benefit from this combination therapy in the same way. We are raising this question since healthcare system in each country can be quite different. The approach of providing immunotherapy and chemotherapy to every patient, while convenient to use and profitable to pharmaceutical manufacturers, may not necessarily always be the best answer.

First, those with higher PD-L1 TPS, if choosing to have the combination treatment, will be subjected to increased toxicity due to chemotherapy, which is about twice as frequent as immunotherapy monotherapy. Furthermore, in this population, one can especially argue that the control arm in this trial—chemotherapy alone arm—is no longer an acceptable standard of care in this setting. Indeed, single-agent pembrolizumab should have been used as a reference standard.

Second, patients with lower PD-L1 TPS, if choosing to have the combination treatment, may be subjected to unnecessary immunotherapy which is very costly. The exploratory analysis obtained from a small subgroup of patients with low or negative PD-L1 TPS may not be an adequate evidence that pembrolizumab really has a therapeutic role in this population. This is especially true when the bulk of treatment benefit is more pronounced among patients with higher PD-L1 TPS.

To be fair, we are faced with the problem that available predictive biomarkers for patient selection including the TPS are not completely reliable. PD-L1 TPS results are variable between different assays as there is no single lab test used between studies, and there are a variety of cutoffs used. Some note a benefit to checkpoint inhibitor therapy with PD-L1 TPS ≥50% and others with a score ≥1% (2,5,7). To address this issue, other biomarkers are now being evaluated, such as the tumor mutational burden or expression of effector T-cell (8). Moreover, as more drugs get added to the treatment paradigm, cost is an area that should not be overlooked given the substantial impact this can play based on a patient's overall care and society.

While single-agent pembrolizumab treatment as a standard first line therapy for selected patients with PD-L1 TPS ≥50% can be viewed as an advance for personalized medicine, the combination chemotherapy and immunotherapy for unselected patients, therefore, may be viewed as a setback. Since most insurance carriers in the United States are required to pay for this combination, there is no longer any need to know PD-L1 status in order to prescribe pembrolizumab, as long as it is prescribed together with pemetrexed and carboplatin. Nevertheless, an argument in favor of this setback can be made on the ground that some patients will never make it to subsequent-line therapies once first-line therapy has failed, so it may be more practical to prescribe everything upfront. Others may also argue that chemotherapy can be immunogenic, thus helping immunotherapy work better. While the combination treatment may be less personalized, the authors agree that for now we should focus on a means to an end. Perhaps this one-size-fit-all approach will have to stay for now, but in the near future, we may find a better way to personalize immunotherapy.

In summary, this simple, pragmatic and positive study evaluated the use of combination checkpoint inhibitor and chemotherapy in non-squamous lung cancers. Results from studies testing this combination in other histological subtypes including squamous cell histology are also upcoming and have so far shown early promise (9-11). In summary, the results of this KEYNOTE-189 study have caused yet another shift in the management of metastatic NSCLC. Though questions remain to be answered, this will no doubt have a more or less positive impact on the care of patients with an otherwise dismal disease.

Acknowledgements

None.

Footnote

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

References

1. Nivolumab (Opdivo) label information. NIH U.S. National

Library of Medicine. Available online: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f570b9c4-6846-4de2-abfa-4d0a4ae4e394&audience=consumer. Accessed July 2, 2018.
2. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
3. More Immunotherapy Options Approved for Lung Cancer. NIH National Cancer Institute. 2016. Available online: https://www.cancer.gov/news-events/cancer-currents-blog/2016/fda-atezolizumab-pembrolizumab-lung. Accessed July 2, 2018.
4. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
5. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.
6. FDA Expands Approval of Pembrolizumab for First-Line Treatment of Non-Small Cell Lung Cancer. NIH National Cancer Institute. 2017. Available online: https://www.cancer.gov/news-events/cancer-currents-blog/2017/fda-pembrolizumab-lung-expanded. Accessed July 2, 2018.
7. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer. N Engl J Med 2017;376:2415-26.
8. Yarchoan M, Hopkins A, Jaffee EM. Tumor Mutational Burden and Response Rate to PD-1 Inhibition. N Engl J Med 2017;377:2500-1.
9. Jotte RM, Cappuzzo F, Vynnychenko I, et al. IMpower131: Primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. J Clin Oncol 2018;36:LBA9000-LBA.
10. A Study of Atezolizumab in Combination With Carboplatin + Paclitaxel or Carboplatin + Nab-Paclitaxel Compared With Carboplatin + Nab-Paclitaxel in Participants With Stage IV Squamous Non-Small Cell Lung Cancer (NSCLC) [IMpower131]. ClinicalTrials.gov. Available online: https://clinicaltrials.gov/ct2/show/NCT02367794. Accessed July 2, 2018.
11. Paz-Ares LG, Luft A, Tafreshi A, et al. Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel (Chemo) with or without pembrolizumab (Pembro) for patients (Pts) with metastatic squamous (Sq) non-small cell lung cancer (NSCLC). J Clin Oncol 2018;abstr 105.

Cite this article as: Chatwal MS, Tanvetyanon T. Combination chemotherapy and immunotherapy in metastatic non-small cell lung cancer: a setback for personalized medicine? Transl Lung Cancer Res 2018;7(Suppl 3):S208-S210. doi: 10.21037/tlcr.2018.07.15

