Editorial

Additive effects of atezolizumab and bevacizumab plus chemotherapy for patients with non-small cell lung cancer regardless of presence of *EGFR* mutations, *ALK* rearrangements, or PD-L1 expression

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Comment on: Socinski MA, Jotte RM, Cappuzzo F, *et al.* Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. N Engl J Med 2018;378:2288-301.

Submitted Jul 30, 2018. Accepted for publication Aug 08, 2018.
doi: 10.21037/tcr.2018.08.14
View this article at: http://dx.doi.org/10.21037/tcr.2018.08.14

The first-line treatment protocol for advanced non-small cell lung cancer (NSCLC) has improved with immune checkpoint inhibitor (ICI) development. The Food and Drug Administration (FDA) has approved three ICIs for second-line treatment of NSCLC (nivolumab, pembrolizumab, and atezolizumab), and randomized studies have shown superior overall survival (OS) with ICIs compared with second-line docetaxel (1-4). Moreover, pembrolizumab was approved as a first-line treatment because of its superior efficacy in the first-line treatment of tumors with PD-L1 ≥50% versus chemotherapy [progression-free survival (PFS) of 10.4 *versus* 6.0 months, respectively] (5). Durvalumab, another ICI, also showed a longer PFS following consolidation therapy than placebo in patients with stage III NSCLC without disease progression after ≥2 platinum-based chemoradiotherapy cycles (6). These advances for managing NSCLC are important, but a number of patients will not benefit from these single-agent therapies, and other strategies using ICIs are being evaluated. Increasing evidence from studies suggests that chemotherapy mediates its antitumor activity through cytotoxic effects and immunological effects, including T-regulatory cell activity reduction and cross-presentation enhancement of tumor antigens (7-9). Reportedly, chemotherapy induces PD-L1 expression on tumor cells (10,11). Thus, a combination of immunotherapy and chemotherapy may synergistically improve the anticancer activity of anti-PD-1 and anti-PD-L1 monotherapy. Combinations of anti-PD-1 or anti-PD-L1 antibodies with standard chemotherapy or with anti-CTLA-4 antibody are the primary approaches that are being applied. Attempting to improve survival in NSCLC patients beyond the subgroup of highly expressing PD-L1 patients, the KEYNOTE-021 study tested a combination of pemetrexed and carboplatin for treating patients with previously untreated metastatic NSCLC (12). In this randomized, open-label, phase II study, the overall response rate (ORR) and PFS for patients randomized to the pembrolizumab plus chemotherapy group was improved and the treatment-related adverse events were tolerable. These results, along with the manageable safety profile led to the FDA approval of pembrolizumab, with pemetrexed and carboplatin, as first-line combination therapy. It is possible that the use of multiple agents may enhance their effectiveness in terms of increasing OS. The results of other clinical trials of combination therapies including ICIs are being published these days.

In the June 2018 issue of *The New England Journal of Medicine*, Socinski and colleagues demonstrated a significant improvement in PFS and OS among patients with metastatic non-squamous NSCLC administered atezolizumab plus bevacizumab and chemotherapy (IMpower-150)—regardless of their PD-L1 expression and *EGFR* or *ALK* genetic alteration status (13). The following patients were included

in the study: those who had stage IV or recurrent metastatic non-squamous NSCLC and were not treated with chemotherapy, those with a baseline Eastern Cooperative Oncology Group (ECOG) performance status score of 0/1, and those with any PD-L1 immunohistochemistry status. Additionally, patients with *EGFR* or *ALK* genomic alterations were enrolled treatment with at least one approved tyrosine kinase inhibitor had previously resulted in disease progression or unacceptable side effects. The international, open-label, phase III study enrolled a total of 1,202 patients randomly assigned to 1 of 3 groups: the atezolizumab plus carboplatin plus paclitaxel, ACP group (402 patients), the atezolizumab plus bevacizumab plus carboplatin plus paclitaxel, ABCP group (400 patients), or the bevacizumab plus carboplatin plus paclitaxel, BCP group (400 patients). Induction treatments were administered for four or six 21-day cycles. After that, patients were continually administered atezolizumab, bevacizumab, or both until unmanageable toxic effects or disease progression was observed. Patients were allowed to continue atezolizumab after disease progression in case any clinical benefits were evidenced. Atezolizumab was ensured to have no crossover.

The two primary end points were PFS, among both patients in the intention-to-treat population with a wild-type (WT) population and those in the WT population with high expression of an effector T-cell (Teff) gene signature in the tumor (Teff-high WT population), and OS in the WT population. The Teff gene signature was described as *PD-L1*, *CXCL9*, and *IFN*-γ messenger RNA expression, as assessed using macro-dissected tumor tissue RNA measurements at baseline. Secondary end points included PFS and OS in the intention-to-treat population comprising all enrolled patients (including those with *EGFR* or *ALK* genomic alterations), PFS as determined at an independent review facility, investigator-assessed PFS in the PD-L1 expression subgroups, the objective response rate, and the duration of response among patients with an objective response.

The WT population comprised 1,040 patients (86.5%), and 445 of them (42.8%) had high Teff gene-signature expressions. At the time of data cutoff, the PFS of the WT population was significantly longer in the ABCP group than in the BCP group [8.3 *vs.* 6.8 months; hazard ratio (HR) 0.62; 95% confidence interval (CI), 0.52–0.74; P<0.001]. In the Teff-high WT population, the PFS was also significantly longer in the ABCP group than in the BCP group (11.3 *vs.* 6.8 months; HR 0.51; 95% CI, 0.38–0.68; P<0.001). The PFS among patients with *EGFR* mutations or *ALK* rearrangements increased with ABCP compared with that with BCP (9.7 *vs.* 6.1 months; HR, 0.59; 95% CI, 0.37–0.94). Additionally, in all intention-to-treat patients (including those with *EGFR* mutations or *ALK* rearrangements), the PFS increased with ABCP than with BCP at 8.3 *vs.* 6.8 months (HR 0.61; 95% CI, 0.52–0.72). Prolonged PFSs were observed regardless of PD-L1 status and expression of Teff gene signature. One benefit of PFS was observed with ABCP in key clinical and biomarker subgroups: in patients with liver metastasis (7.4 *vs.* 4.9 months; HR 0.42; 95% CI, 0.26–0.66) and in patients with *KRAS* mutations (8.1 *vs.* 5.8 months; HR 0.50; 95% CI, 0.29–0.84).

At the time of the interim analysis, the OS in the WT population was significantly longer in the ABCP group than in the BCP group (19.2 *vs.* 14.7 months; HR 0.78; 95% CI, 0.64–0.96; P=0.02). The investigator-assessed unconfirmed objective response rates in the WT were 63.5% in the ABCP group and 48.0% in the BCP. In the WT population, the median response durations were 9.0 and 5.7 months in the ABCP and BCP groups, respectively; in the Teff-high WT population, these were 11.2 and 5.7 months in the ABCP and BCP groups, respectively.

Grade 1 or 2 adverse events occurred in 35.9% and 45.4% of patients in the ABCP and BCP groups, respectively. The most commonly observed treatment-related adverse events (grade 3 or 4) were neutropenia and hypertension. The incidences of rash, stomatitis, febrile neutropenia, and hemoptysis were higher by <10% among patients in the ABCP group than among those in the BCP group. Deaths from treatment occurred in 11 (2.8%) and 9 (2.3%) patients in the ABCP and BCP groups, respectively. Five deaths in the ABCP group were due to pulmonary hemorrhage or hemoptysis. In all, 77.4% of the immune-related adverse events observed in the ABCP group belonged to grade 1 or 2, and none of these belonged to grade 5. The most common observed immune-related adverse events included rash, hepatitis, hypothyroidism, hyperthyroidism, pneumonitis, and colitis.

The study was the first phase III trial that reported on chemotherapy combination, immunotherapy, and antiangiogenic treatment as first-line treatment for advanced non-squamous NSCLC. The results demonstrated significantly improved PFS and OS with the inclusion of atezolizumab in the BCP regimen as a first-line treatment for non-squamous metastatic NSCLC. Compared with the results of the ECOG4599 (14), a trial of paclitaxel and carboplatin or of paclitaxel and carboplatin

Table 1 Patients characteristics and results of ECOG4599, IMpower-150, KEYNOTE-189, and CheckMate-227

Variables	ECOG4599			IMpower-150			KEYNOTE-189			CheckMate-227		
	Bev + C	C	HR (95% CI)	Bev + C + ICI	Bev + C	HR (95% CI)	C + ICI	C	HR (95% CI)	ICI + ICI	C	HR (95% CI)
N	417	433	–	400	400	–	410	206	–	139	160	–
PFS (months)	6.2	4.5	0.66 (0.57–0.77)	8.3	6.8	0.62 (0.52–0.74)	8.8	4.9	0.52 (0.43–0.64)	7.2	5.5	0.58 (0.41–0.81)
OS (months)	12.3	10.3	0.79 (0.67–0.92)	19.2	14.7	0.78 (0.64–0.96)	Not reached	11.3	0.49 (0.38–0.64)	Not reached	Not reached	–
ORR (%)	35	15	–	68.5	48	–	47.6	18.9	–	45.3	26.9	–
Treatment	CBDCA + PTX ± Bev			CBDCA + PTX + Bev ± atezolizumab			Platinum + PEM ± pembrolizumab			Nivolumab + ipilimumab *vs.* chemotherapy		
EGFR or *ALK* mt positive patients	–			Included in subgroup analysis			Excluded			Excluded		
Histologic type	Non-sq			Non-sq			Non-sq			All		
Criteria for PD-L1 and TMB	–			All comer			All comer			TMB high		

Bev, bevacizumab; C, chemotherapy; ICI, immune checkpoint inhibitor; CBDCA, carboplatin; PTX, paclitaxel; PEM, pemetrexed; HR, hazard ratio; TMB, tumor mutation burden; ORR, overall response rate; OS, overall survival; mt, mutation; sq, squamous.

with bevacizumab, the superiority of the ABCP treatment is apparent by comparing the OS, PFS, and ORR (*Table 1*). Benefits with respect to OS, PFS, and ORR were found in all subgroups examined, including those that had a PD-L1 tumor proportion score of <1%. These findings in unselected patients with metastatic NSCLC are particularly important because the effect of the PD-1 inhibitor monotherapy has only been proven in patients with positive PD-L1 expression. The inclusion of pembrolizumab to pemetrexed and a platinum-based drug (standard chemotherapy) has been shown to result in significantly longer OS and PFS than chemotherapy alone in patients with untreated metastatic non-squamous NSCLC and any PD-L1 immunohistochemistry status without *EGFR* or *ALK* mutations (KEYNOTE-189) (15). The combination of ICI treatment, nivolumab plus ipilimumab, was also shown to result in significantly longer PFS than that of chemotherapy among patients with NSCLC and a high tumor mutation burden (but without *EGFR* and *ALK* mutations) (CheckMate-227) (16). The PFSs in these three trials were similar. Each trial was conducted on the basis of the different criteria, and the best treatment in selected patients is still unknown. In all, the results so far demonstrate the success of the ICI combination therapy for NSCLC, although the IMpower-150 trial only showed benefit in patients with *EGFR* and *ALK* genetic alterations. In some clinical trials, retrospective, and meta-analysis studies, the use of PD-1 or PD-L1 inhibitors as monotherapy has shown relatively low efficacy in patients with *EGFR* or *ALK* genetic alterations (1,3,4,17,18). In particular, atezolizumab monotherapy was not effective for patients with *EGFR* or *K-RAS* genetic alterations in a phase III trial of atezolizumab versus docetaxel in patients with previously treated NSCLC (OAK trial) (4); therefore, the combination of atezolizumab and bevacizumab with chemotherapy may correct this result producing an additive effect useful against *EGFR* and *ALK* gene alterations. Another report showed that T790M-negative patients with NSCLC and positive-*EGFR* mutations are more likely to benefit from nivolumab than the T790M-positive counterparts after disease progression with EGFR-TKI (19), but the proportion of T790M-negative patients with positive *EGFR* mutations after EGFR-TKI treatment was unknown in the IMpower-150 study. Other clinical trials are being conducted for patients with *EGFR* mutations after EGFR-TKI treatment (*Table 2*) and the partial results may suggest the new combination immunotherapy which is effective for NSCLC patients with *EGFR* mutations.

Table 2 Ongoing trials of combination immunotherapy after treatment with EGFR-TKI in NSCLC

NCT	Study phase	ICI	Gene mutation	T790M	Treatment sequence
NCT03091491	II	Nivo, Ipi	*EGFR*	Allowed	EGFR-TKI, no more than 1 line chemo→Nivo or Nivo/Ipi
NCT03242915	II	Pembro	*EGFR, ALK*	Not described	EGFR-TKI→CBDCA + PEM + Pembro
NCT03256136	II	Nivo, Ipi	*EGFR, ALK*	Not described	Cohort A: 3rd generation EGFR-TKI→CBDCA + PEM + Nivo
					Cohort C: 3rd generation EGFR-TKI →platinum-based chemotherapy→Nivo/Ipi
NCT02454933 (CAURAL)	III	Durva	*EGFR*	Positive	EGFR-TKI→additional anti-cancer treatment is permitted →osimertinib or Durva/osimertinib
NCT02864251 (CheckMate-722)	III	Nivo, Ipi	*EGFR*	Negative	EGFR-TKI→platinum + PEM or platinum + PEM + Nivo or Nivo/Ipi
NCT03515837 (KEYNOTE-789)	III	Pembro	*EGFR*	Negative or treated with osimertinib	EGFR-TKI→CBDCA→PEM ± Pembro

TKI, tyrosine kinase inhibitor; Nivo, nivolumab; Pembro, pembrolizumab; Ipi, ipilimumab; Durva, durvalumab; CBDCA, carboplatin; PEM, pemetrexed; ICI, immune checkpoint inhibitor.

Detailed and extensive preclinical and clinical rationale data support the hypothesis that anti-vascular endothelial growth factor (VEGF) may act synergistically with immunotherapy benefiting patients (20). VEGF suppresses tumor-directed immune responses and promotes angiogenesis. Altering these effects in the tumor microenvironment by inhibiting angiogenesis is an appealing combination strategy for ICIs. Combination therapy promotes antitumor activity and has beneficial effects on the host antitumor immune response. Because VEGF signaling attenuates the antitumor response through the inhibition of lymphocyte adhesion (21) and the regulation of immune cells (22,23), antiangiogenic agents may bring about stimulation of the immune response and enhancement of the efficacy of immunotherapies.

To adapt the combination therapy of bevacizumab, atezolizumab, and chemotherapy for NSCLC patients, thrombosis, bleeding, gross hemoptysis, and hypertension need to be ruled out. Regardless of the existence of these restrictions and based on the IMpower-150 results, the ABCP combination therapy may be especially useful for patients who have *EGFR* or *ALK* mutations or liver metastases. The NSCLC patients who have pleural fluid or small brain metastases may be also eligible to use this regimen because of the efficacy of bevacizumab on them (24,25). Moreover, according to its better ORR compared with others (*Table 1*), this regimen may be also adequate for patients requiring tumor volume reduction, i.e., for the treatment of trachea stenosis and superior vena cava syndrome or to prevent rupture of liver metastases.

In conclusion, the Impower-150 study showed that addition of atezolizumab to the regimen of bevacizumab plus chemotherapy as first-line treatment for non-squamous metastatic NSCLC resulted in significantly improved PFS and OS. Regardless of the expression of PD-L1 or the presence of a T-effector gene signature, the combination therapy proved beneficial. In addition, the clinical benefits were clearly observed at baseline in key subgroups of patients with *EGFR* and *ALK* genomic alterations and liver metastases. The trial showed that combining chemotherapy and immunotherapy helps avoid the requirement for strict patient selection (based on the presence of biomarkers); thus, the strategy can potentially benefit large patient populations with advanced NSCLC without encountering practical difficulties involving biomarker testing. Different ICI combination therapies have shown promising results, and the IMpower-150 showed the efficacy of atezolizumab plus bevacizumab in combination as one chemotherapy regimen. Each combination therapy has its own features, and the choice of the best combination therapy needs to be based on its features and the patients' characteristics (their condition and gene profiling).

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Wei Xu (Division of Respiratory Disease, Department of Geriatrics, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.08.14). T Hida has received grants and personal fees from AstraZeneca, Ono Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, Novartis, Taiho Pharmaceutical, Nippon Boehringer Ingelheim, Pfizer, Bristol-Meyers Squibb, Clovis Oncology, MSD, and Kissei and grants from Eisai, Takeda Pharmaceutical, Dainippon Sumitomo Pharma, Abbvie, Merck Serono, Kyowa Hakko Kirin, Daiichi Sankyo, Astellas, Ignyta, and Servier. T Uemura has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Uemura T, Hida T. Additive effects of atezolizumab and bevacizumab plus chemotherapy for patients with non-small cell lung cancer regardless of presence of *EGFR* mutations, *ALK* rearrangements, or PD-L1 expression. Transl Cancer Res 2018;7(Suppl 7):S796-S801. doi: 10.21037/tcr.2018.08.14

