Editorial

Atezolizumab plus platinum-based regimen and bevacizumab: is it time to consider immunotherapy in a concurrent approach for lung cancer?

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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 Aug 21, 2018. Accepted for publication Nov 08, 2018.
doi: 10.21037/tcr.2018.11.06
View this article at: http://dx.doi.org/10.21037/tcr.2018.11.06

Targeting adaptive immunity is a game changer for cancer treatment, revolutionizing lung cancer management. Chemotherapy has been the standard treatment for lung cancer (1-4) until recently when molecular targets including genes harbouring cancer-driving mutations and immune check-points have emerged as targets for new therapies (5-12). With the increasing relevance of ICIs, clinical research is required to define which combination regimens provide the greatest benefits in lung cancer patients.

Immune checkpoints are pathways that can be exploited by cancer cells, preventing T cells from attacking healthy tissue; cancers are able to express checkpoint blockade molecules and therefore disrupt immune recognition pathways thus activating resistance mechanisms (10-13).

Two checkpoint, proteins, cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) are expressed by T cells themselves whilst programmed cell death ligand 1 (PD-L1) is produced by tumour cells (10-13).

PD-L1 (CD274, B7-H1) controls T cell responses by blocking PD-1 mediated T cell activity receptor resulting in the downregulation of immune response against cancer cells (10-13).

Antibodies that interact with these proteins remove the immune system's "brake" enabling a substantial immune-response against cancer cells. Interfering with the PD-1 and PD-L1 pathway has demonstrated efficacy in advanced non-small cell lung cancer (NSCLC) patient subsets (10-13).

Since the first immune checkpoint inhibitor (ICI) Food and Drug Administration (FDA) approval in 2015 (Nivolumab) for lung cancer, several clinical trials have been launched exploring the efficacy of additional checkpoint inhibitors in different disease settings (14).

A recent original article by Socinski *et al.* for IMpower Study Group (15), published on *NEJM*, has reported the results of the first phase III, open-label, randomized study of Atezolizumab in combination with chemotherapy plus Bevacizumab for first-line treatment of metastatic nonsquamous NSCLC.

Atezolizumab (Tecentriq, F. Hoffmann-La Roche/Genentech), an ICI which blocks binding of PD-L1 to PD-1 and CD80, has already shown overall survival benefit in individuals previously treated for NSCLC stage IV, irrespective of PD-L1 (16) and to be effective and safe in combination with platinum-based chemotherapy regimens (17).

Socinski *et al.* randomly allocated patients with metastatic non-squamous NSCLC in three different groups: Atezolizumab + Carboplatin + Paclitaxel (ACP); Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel (ABCP); Bevacizumab + Carboplatin + Paclitaxel (BCP). Patients were eligible regardless of PD-L1 immunohistochemistry status; EGFR or ALK genomic alterations were allowed when patients experienced disease progression or unacceptable side effects following treatment with a tyrosine kinase inhibitor (15).

Primary endpoints were progression-free survival (in accordance with RECIST criteria) and overall survival within wild-type population.

Median progression-free survival was better in Atezolizumab (ABCP) arm compared to BCP (8.3 *vs.* 6.8 months) and median overall survival significantly prolonged in the ABCP arm compared to BCP (19.2 *vs.* 14.7 months) (15).

Progression-free survival was also longer in ABCP arm within intention-to-treat population which included EGFR mutations and ALK rearrangements (15). Previous studies have not shown conclusive results regarding survival and response rate in lung cancer patients with EGFR or ALK alteration when immune checkpoint blockade treatment was administered; Lee *et al.* (18) found no benefits in terms of OS in lung cancer patients exhibiting EGFR mutations treated with ICIs over docetaxel [hazard ratios (HR) 1.05, 95% CI: 0.70–1.55, P<0.81]; other investigations have shown a lower response rate to ICIs in presence of EGFR or ALK alterations compared to EGFR wild type/ALK negative (19).

The finding by Socinski *et al.* of an improved progression-free survival and overall survival regardless of EGFR or ALK genetic alteration status among patients with metastatic nonsquamous NSCLC is an important observation which may offer additional potential therapeutic perspectives to patients already treated with a tyrosine kinase inhibitor for EGFR and ALK mutations. Further studies are required to better define response and efficacy in this specific patient subset.

Interestingly, Atezolizumab plus BCP treatment resulted in prolonged progression-free survival within all patient subgroups for expression of PD-L1, even low/negative PD-L1 (15).

Only PDL1 expression is approved for NSCLC patient assessment although, it is not mandatory for treatment with Immune check-point therapy except for Pembrolizumab where PD-L1 diagnostic test is required for first line treatment (13).

The patient population participating in the study was also investigated for Teff gene expression, a marker of pre-existing immunity reflecting mRNA expression of PD-L1, CXCL9, and IFN-γ, determined by the use of RNA isolated by real-time quantitative polymerase-chain-reaction assay from baseline tumor (15).

With ABCP regimen longer progression-free survival was achieved in all Teff gene signature subgroups, including Teff-low patients. Teff-high conferred a greater progression-free survival with benefits similar to that for high PD-L1 expression. As the majority of patients with stage IV NSCLC exhibit low, absent, or unknown PD-L1 and first line monotherapy is restricted to patients with high PD-L1 this finding may have a relevant therapeutic implication for these patients (15).

Adverse events in the Socinski study were similar in both treatment arms, occurring in 94.4% of ABCP arm and in 95.4% in the BCP. The majority of grade 3 or 4 toxicities linked to therapy included neutropenia, low neutrophils, febrile neutropenia, and hypertension. In ABCP arm, there were 11 deaths linked to therapy (2.8%) compared to 9 (2.3%) in the BCP arm; in ABCP arm pulmonary hemorrhage or hemoptysis were responsible for five deaths. Hypothyroidism, hyperthyroidism, pneumonitis, rash, hepatitis and colitis (15) were the most common immune-associated toxicities.

Other studies such as the Keynote-189 have already demonstrated that the addition of immune check-point blockade to standard chemotherapy results in significantly longer overall survival and progression-free survival without increase of toxicities (20).

The study by Socinski confirms the efficacy and safety of ICIs combined with chemotherapy in a nonsquamous metastatic NSCLC patient population irrespective of PD-L1 as well as EGFR mutations or ALK rearrangements.

Until now clinical investigations on ICIs have focused on treatment of advanced lung cancer. There is evidence to suggest that combined targeted and conventional cancer therapy, including surgery, with immunotherapy may have a relevant implication in early disease setting (21,22).

Studies like that by Socinski have demonstrated clear benefits in terms of survival with concurrent ICI platinum-based regimens in subsets of lung cancer patients. To optimize integration of ICIs and standard therapies the next steps will involve research based on molecular, immunological and clinical investigations.

Further understanding of ICIs action on patient immune system, together with well-designed trials to establish optimal sequencing for combination therapy including immune checkpoint blockade has the potential to make significant advances in lung cancer management.

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.2018.11.06). The authors have 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: Bianco A, Campbell SF. Atezolizumab plus platinum-based regimen and bevacizumab: is it time to consider immunotherapy in a concurrent approach for lung cancer? Transl Cancer Res 2019;8(Suppl 2):S103-S105. doi: 10.21037/tcr.2018.11.06