IMPassionate about immunotherapy for TNBC: from change, to revolution and to cure?

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Comment on: Schmid P, Rugo HS, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:44-59.

Submitted May 02, 2020. Accepted for publication May 09, 2020.

doi: 10.21037/atm-20-3690

View this article at: http://dx.doi.org/10.21037/atm-20-3690

The IMPassion130 represents an important practice change study for patients with TNBC because it is the first prospective study to demonstrate an improvement in overall survival (OS) for newly recurrent TNBC resulting in the FDA-approval of atezolizumab (TECENTRIQ®). Briefly, the study was a phase III double-blind study, enrolling patients with advanced or metastatic TNBC who had received no prior treatment for their metastatic disease. Patients were randomly assigned to receive nab-paclitaxel 100 mg/m² on days 1, 8 and 15 of every 28-day cycle in combination with 840 mg atezolizumab or placebo on days 1 and 15 until disease progression or unacceptable toxicity (1). Patients who received taxanes and/or radiation as part of their curative treatment within 12 months prior to randomization were excluded from the study. The primary end points were progression-free survival (PFS) in the intention-to-treat (ITT) population and PD-L1 positive subgroup and OS in the intention to treat population. If OS would be significant, investigators would test it as well for the PD-L1 positive subpopulation (1).

The first prespecified data analysis reported with a median follow-up of 12.9 months demonstrated, in the ITT population a median PFS of 7.2 months for atezolizumab and 5.5 months for the placebo arm while in the subpopulation with PD-L1 positive tumors the median PFS were 7.5 and 5 months respectively. The median OS in the ITT population was 21.3 months in the atezolizumab arm as compared with 17.6 months for those who received placebo which was not statistically significant (P=0.08). Remarkably, in patients with PD-L1 positive tumors, the median OS was 25 and 15.5 months in the atezolizumab and placebo arm respectively.

The second prespecified OS interim analysis that was recently published confirmed the previously reported results (2). In this updated analysis, the median follow-up was 18.5 months in the atezolizumab arm and 17.5 months in the placebo arm, with a median OS of 21 months for atezolizumab group versus 18.7 in the placebo one (P=0.078). Exploratory analysis for the PD-L1 positive population confirmed a stronger and, predominant benefit restricted to this cohort, with a median OS of 25 months for the atezolizumab arm as compared with 18 months for the placebo arm (stratified HR 0.71; 0.54–0.94). Safety profile of the combination arm was not consistent with the expected toxic effects of both drugs and also no meaningful difference was observed between arms. Study authors have also published patient-reported outcomes in report with health related quality of life (HRQoL). According to this data, no difference in HRQoL was observed between arms and no significant change from baseline was reported. In addition, the frequency of side effects from treatment such as fatigue or diarrhea was similar in both arms (3).

What did we learn from this additional analysis? What was unique about the IMPassion130 compared to other trials investigating checkpoint inhibitors in TNBC? What other rationale combinations outside cytotoxic chemotherapy may be investigated in TNBC? Certainly, the most relevant conclusion from updated analysis is the confirmation of significant benefit from immunotherapy in PD-L1 positive subpopulation that persists over time.
with continued retained survival benefit, consolidating the predictive value of PD-L1 expression. In spite of such important practice changing achievement, the investigators recognized that the study had several limitations. The first and most important is that such results do not apply to the treatment of every metastatic TNBC because the study population was either treatment naïve or had only received neoadjuvant or adjuvant chemotherapy and particularly taxanes one year or more prior to randomization. Consequently, patients were more likely to respond to treatment and/or had less aggressive disease compared to those who recur during or within one year from the treatment given with curative intent in the neoadjuvant and adjuvant setting. Indeed, subset analysis showed that in the ITT population treatment naïve patients had slightly greater benefit from atezolizumab compared to those who had received prior chemotherapy (HR 0.72 vs. 0.85) while for the PD-L1 positive subgroup both exposed and unexposed patient derived significant benefit from atezolizumab (HR 0.76 and 0.45 respectively). Thus, remains unclear if the regimen can be applied outside the first-line metastatic setting or for patients with refractory disease. To answer this question, a phase III randomized, placebo-controlled study, IMpassion132, is evaluating the atezolizumab in combination with chemotherapy (carboplatin/gemcitabine or capecitabine in patient who have previously received platinum agents) in locally advanced or metastatic TNBC patients who had recurrence during or within 12 months from the curative intent treatment (4).

Other studies confirmed the superior efficacy of combination regimens with cytotoxic chemotherapy compared to single agent treatment [3-6]. The phase III trial, KEYNOTE-119, enrolled metastatic TNBC patients who had progressed on prior treatments to receive either single agent pembrolizumab or physician’s choice chemotherapy. Primary endpoint was OS and the results showed that pembrolizumab was inferior to chemotherapy in this population (5). Of note, in the phase I and II studies, KEYNOTE-012 and KEYNOTE-086 respectively, where the primary endpoint was objective response rate (ORR) in the entire and PD-L1 positive population, pembrolizumab demonstrated some antitumor activity (6,7). The most recent phase III study, KEYNOTE 355, compared either pembrolizumab or placebo in combination with chemotherapy (nab-paclitaxel, paclitaxel or gemcitabine plus carboplatin) as first line treatment in metastatic TNBC. Primary endpoints of the study were progression free survival (PFS) and OS in intention-to treat population but also in the PD-L1 positive subgroup. In contrast from the IMpassion130 study, PD-L1 positivity was measured as a positive combined score (CPS) in both immune and tumor cells and the results will be reported for PD-L1 CPS ≥1 and CPS ≥10. The investigators announced that the study achieved the primary endpoints and most likely pembrolizumab will be the second approved checkpoint inhibitor as first-line treatment in advanced or metastatic TNBC (8).

The other significant issue to highlight is the importance of PD-L1 testing and, the possibility to improve patients’ selection with investigation of other biomarkers with stronger predictive value. In the IMpassion130 study, PD-L1 expression was assessed in the tumor associated immune cells and was tested with the VENTANA SP142 assay. Along with the approval of atezolizumab, FDA approved the assay as companion diagnostic to select TNBC patient who are eligible to receive atezolizumab and nab-paclitaxel. An exploratory analysis of the biomarker-evaluable study population performed by the investigators, compared VENTANA SP142 with two other assays, VENTANA SP263 and DACO 22C3 that are currently being used for the assessment of PD-L1 expression in other tumor histologies and selection of different immunotherapy agents. According to the results, the assays were nonequivalent with the SP142. Specifically, patients who derived greater benefit by atezolizumab were those who had PD-L1 positive tumors detected by SP142 assay. In contrast, patients with PD-L1 positive tumors detected by SP263 or 22C3 assays but negative by SP142 had minimal or no benefit from atezolizumab. No clinical benefit from atezolizumab was observed in patients with PD-L1negative tumors by all three assays (9).

To date, PD-L1 expression and DNA mismatch repair instability (d-MMR) are the only biomarkers approved as predictors for response to immune CPIs. However, several other markers such as tumor mutational burden (TMB) or tumor infiltrating lymphocytes (TILs) are also suggested to indicate sensitivity to immunotherapy. Despite the progress made in this field, there are many limitations in the clinical use of the immune biomarkers (10).

As detailed above, patients with PD-L1 positive tumors are more likely to respond to immune checkpoint blockade. However, not all patients with PD-L1 positive tumors will respond to immunotherapy and most importantly, in some cases with PD-L1 negative tumors may show response. Specifically, for TNBC is not yet well established the value of PD-L1 expression on the tumor cells compared to
immune cells or a combined score of both. There is also no clear correlation between the amplitude of expression and the degree of response. As research data are suggesting, PD-L1 expression is a dynamic variable and can be affected by a large number of factors such as prior use of immune modulators, sampling timing or selection of primary versus metastatic site. Thus, more precise, reliable and reproducible biomarkers that will predict response or resistance to immune checkpoint blockade are warranted to optimize the use of immune CPIs in cancer treatment. Non-invasive methods such as liquid biopsy to assess immune biomarkers in CTCs or cfDNA should be also part of tumor assessment.

While for other tumor histologies immune CPIs have shown activity even when administered as monotherapy, their use in TNBC is limited only in combination with chemotherapy. This can be partially explained by the fact that BC has a relatively low mutational burden compared to more responsive to immunotherapy tumors such as melanoma or NSCLC. In addition, the tumor responses achieved in TNBC patients treated with immune CPIs are very modest. Thus, the discovery of new combinatorial approaches that will enhance antitumor activity and achieve durable responses is necessary to further improve immunotherapy efficacy in TNBC. The combination of immune checkpoint blockade with poly ADP ribose polymerase (PARP) inhibitors seems to be a very promising therapeutic approach (11). The complex mechanism of interaction between PARP and DNA repair pathway with the immune response is not very well understood. PARP inhibition lead to increase DNA instability and higher TMB which in turn predispose sensitivity to immunotherapy. Other implications of PARP in upregulation of PDL-1 expression, dendritic cell (DC) differentiation and promoting the inflammatory cytokines such as IL-6 or TNFα have also been reported (12).

Encouraging data are also coming from the combination of different immunotherapy agents aiming to enhance the immune response and/or overcome immune resistance.

In conclusion, the IMPassion130 is paving the way to the standard use of immunotherapy in TNBC allowing the field to expand with more accurate, predictive biomarkers and, more selective combinations with the goal to improve quality of life and prolong survival in an incurable disease.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, Annals of Translational Medicine. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-3690). MC declares personal fees from Pfizer, CytoDyn, Foundation Medicine and Lilly. EV 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: Vagia E, Cristofanilli M. IMPassionate about immunotherapy for TNBC: from change, to revolution and to cure? Ann Transl Med 2020;8(22):1537. doi: 10.21037/atm-20-3690

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