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Atezolizumab in metastatic triple-negative breast cancer: IMpassion130 and 131 trials - how to explain different results?

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Metastatic triple-negative breast cancer (TNBC) is a devastating disease with a historical median overall survival of approximately 17 months for all comers[1] and up to 22 months for patients with germline *BRCA* mutations treated with PARP inhibitors.[2 3] This patient population is also considered an unmet medical need due to the lack of effective targeted therapies (eg. endocrine or anti-HER2 therapies).

TNBC is the breast cancer subtype with the higher rates of tumour-infiltrating lymphocytes (TILs), programme death ligand 1 (PD-L1) expression, and tumour mutational burden, thus, being the perfect candidate for the use of immunotherapy.[4] Initial trials investigating immunotherapy given as a single agent for this subtype showed low response rates in the overall population, but some patients experienced impressive long-lasting responses,[5–7] which is unprecedented in the history of TNBC.

In 2018, the IMpassion130 trial paved the official entrance of immunotherapy in combination with chemotherapy (nab-paclitaxel) as a new first-line treatment for patients with metastatic TNBC whose tumour express PD-L1.[8] This phase III trial randomised 902 patients with previously untreated metastatic TNBC to receive treatment with nab-paclitaxel combined with atezolizumab or placebo.[8] The co-primary endpoints of the trial were progression-free survival and overall survival in the intent-to-treat (ITT) population as well as in the PD-L1 positive population provided that the results for the ITT population were statistically superior.[8]

Initial results demonstrated a benefit in progression-free survival in the ITT population (7.2 vs 5.5 months; HR 0.80; 95% CI 0.69 to 0.92; p=0.002) and in the PD-L1 positive population (7.5 vs 5.0 months; HR 0.62; 95% CI 0.49 to 0.78; p<0.001).[8] The overall survival analysis did not reach statistical significance in the ITT population and showed a clinically meaningful improvement of 7.5 months in overall survival (25.0 vs 18.0 months HR 0.71; 95% CI 0.54 to 0.94) in the PD-L1 positive population, although this hypothesis was formally not allowed to be tested according to the statistical plan of the study.[8] Based on these data, the combination of nab-paclitaxel and atezolizumab received the approval from the health authorities for the use in first-line therapy of metastatic TNBC with PD-L1 positive expression in 2019.[8]

The mature overall survival analysis presented at ESMO 2020 after 3-year follow-up upheld the benefit of atezolizumab plus nab-paclitaxel in patients with PD-L1 positive disease, reducing the risk of deaths by 33% in this subgroup when compared with placebo (benefit of 7.5 months in the PD-L1 positive population).[9]

Due to several issues regarding the availability and the use of nab-paclitaxel worldwide, a confirmatory subsequent phase III trial investigating the combination of atezolizumab and weekly paclitaxel in a similar patient population seemed like the logical way to go. However, it was disappointing and at the same time puzzling when the discrepant results of the IMpassion131 trial were presented at ESMO 2020.

THE IMPASSION131 TRIAL

This phase III, double-blind, placebo-controlled study enrolled 651 patients with metastatic or unresectable locally advanced TNBC and no prior chemotherapy or targeted therapy for advanced disease.[10] Patients were randomised between weekly paclitaxel plus atezolizumab or placebo in a 28-day schedule.[10] Differing from the IMpassion130, the primary endpoint was investigator assessed progression-free

Table 1 Impassion130 and Impassion131 trials

	IMpassion130 (n=902)		IMpassion131 (n=651)	
Disease setting	1st line metastatic TNBC		1st line metastatic TNBC	
Trial design	Phase III, randomised (1:1), placebo controlled		Phase III, randomised (2:1), placebo controlled	
PD-L1 testing	SP142		SP142	
Intervention	Atezolizumab or placebo combined with nab-paclitaxel		Atezolizumab or placebo combined with paclitaxel	
Primary endpoint	PFS and OS ITT and PD-L1+ (hierarchical)		PFS PD-L1+ and ITT (hierarchical)	
PFS PD-L1+ (intervention vs control)	7.5 vs 5.0 months (HR: 0.62; 95% CI 0.49 to 0.78)		6.0 vs 5.7 months (HR: 0.82; 95% CI 0.60-1-12 p=0.20)	
PFS ITT (intervention vs control)	7.2 vs 5.5 months (HR 0.80; 95% CI 0.69 to 0.92)		5.7 vs 5.6 months (HR: 0.86; 95% CI 0.70 to 1.05)	
OS PD-L1+ (intervention vs control)	25.4 vs 17.9 months (HR: 0.67; 95% CI 0.53 to 0.86)		22.1 vs 28.3 months (HR: 1.12; 95% CI 0.76 to 1.65)	
OS ITT (intervention vs control)	21.0 vs 18.7 months (HR: 0.87; 95% CI 0.75 to 1.02)		19.2 vs 22.8 months (HR 1.11; 95% CI 0.87 to 1.42)	
Study population (reported)				
Trial arms (ITT)	**Atezolizumab**	**Placebo**	**Atezolizumab**	**Placebo**
Median age	55 (20–82)	56 (26–86)	54 (22–85)	53 (25–81)
PD-L1+	41%	41%	44%	46%
Liver metastases	28%	26%	27%	28%
>3 metastatic sites	26%	24%	24%	22%
Prior taxane	51%	51%	48%	49%
Prior anthracycline	54%	54%	49%	50%
De novo metastatic TNBC	37%	37%	30%	31%
Use of concomitant steroids	Not required		8–10 mg dexamethasone or equivalent for at least the first two infusions	

CI, Confidence interval; HR, Hazard ratio; ITT, Intention-to-treat; ITT, intention to treat; OS, Overall survival; PD-L1, programme death ligand 1; PFS, Progression-free survival; TILs, tumour-infiltrating lymphocytes; TNBC, triple-negative breast cancer.

survival following hierarchical testing, first in the PD-L1 positive population and after in the ITT population.[10] Secondary endpoints included overall survival that would be formally tested only if the primary endpoint was positive.[10]

The trial showed no improvement in progression-free survival with the addition of atezolizumab to paclitaxel in either the PD-L1 positive (6.0 vs 5.7 months; HR 0.82; 95% CI 0.60 to 1.12; p=0.20) or in the ITT population (5.7 vs 5.6 months HR=0.86; 95% CI 0.70 to1.05; p=0.86). In the subgroup analysis, no identified subgroup derived additional benefit from the use of atezolizumab.[10] In addition, treatment with atezolizumab showed a numerically worse overall survival compared with placebo in both PD-L1 positive (22.1 vs 28.3 months; HR=1.12; 95% CI 0.76 to 1.65) and the ITT (19.2 vs 22.8 months; HR=1.11; 95% CI 0.87 to 1.42) populations[10] Table 1 summarises the study population and the results of IMpassion130 and IMpassion 131 trials.

WHAT IS TO BLAME?

The 'invisible differences' within the study population:

Superficially speaking, both trials enrolled a very similar study population with respect to disease setting, median age, performance status, metastatic sites, PD-L1 expression, prior chemotherapy with taxanes and anthracyclines as well as the proportion of de novo metastatic breast cancer.

However, we have learnt over the years that TNBC is a remarkably heterogeneous disease in a transcriptomic level that can be further classified into several subtypes (eg, luminal androgen receptor, immunomodulatory, basal-like immune suppressed, and mesenchymal).[11] These subtypes present unique biological pathways and different compositions of the immune microenvironment that go beyond PD-L1 expression, and thus may present different responses to immunotherapy.

For example, compelling data have demonstrated the better prognosis associated with high levels of TILs in TNBC both in the early and metastatic disease settings.[5 12–14] Although stromal TILs are not a specific biomarker of response to immunotherapy, using them as a stratification factor could help us to ensure a more homogenous population in both arms of the study. Moreover, although follow-up is still immature, it is curious to observe the extremely good median overall survival reported in the control arm of the IMpassion131 trial (28.3 months in the PD-L1

positive population and 22.8 months in the ITT population) and perhaps, a higher proportion of TILs in the control arm of this trial could further justify these findings. Other important aspects to be studied include potential differences related to immune gene signatures and tumour mutational burden within the arms that might confer distinct responses to immunotherapy and chemotherapy.

Furthermore, the proportion of patients with *BRCA* mutations was not yet explored in the IMpassion131 trial. These patients may present a better prognosis in comparison with BRCA wild-type patients and the optimal management for patients with metastatic TNBC with *BRCA* mutation and PD-L1 positive disease is still an area of debate.[15]

Besides the differences relating to the tumour itself, a trial population might also be heterogeneous regarding the factors inherent to the host. There is a growing research field investigating the impact of body mass index, body composition and gut microbiome on the response to immune checkpoint inhibitors and all these factors are yet to be explored in patients with metastatic TNBC.

Different taxanes and the role of steroids

This is not the first time that a different clinical activity between nab-paclitaxel and paclitaxel has been suggested. For example, in early breast cancer, the GeparSepto trial indicated a superiority of nab-paclitaxel compared with paclitaxel in combination anthracycline based chemotherapy in terms of improvement of pathological complete response and invasive disease-free survival.[16 17] Of note, the nab-paclitaxel dose used in this trial was higher than that used in IMpassion130 (150 mg/m^2 vs 100 mg/m^2).

Besides its immunosuppressive effects, chemotherapy agents can enhance the host immune response through different mechanisms. Taxanes are able to reprogramme tumour-associated macrophages and increase the levels of TILs;[18 19] therefore, the concomitant use of steroids associated with paclitaxel could perhaps diminish this effect as well as the efficacy of immunotherapy itself and is an important point to be considered when analysing the results of IMpassion131.

On the other hand, an initial presentation of the Keynote 355 trial, which investigated the combination of pembrolizumab or placebo with different regimens of chemotherapy (nab-paclitaxel, paclitaxel and gemcitabine/carboplatin) demonstrated a statistically significant improvement in progression-free survival with the addition of immunotherapy in the PD-L1 positive population.[20] The presumed use of steroids in the Keynote 355 trial challenges the real share of blame of this concomitant medication for the negative results of the IMpassion131 trial. However, it is important to mention that the Keynote 355 trial was not designed to detect differences in efficacy within the chemotherapy regimens and therefore these data were not reported.

Additional remarks

The knowledge of the proportion of patients with residual disease after prior neoadjuvant chemotherapy is also relevant as these patients may present tumours more resistant to subsequent treatment with immunotherapy and this information was neither reported in IMpassion130 nor IMpassion131 trials. In addition, concomitant use of antibiotics can also interfere with the response to immunotherapy and would deserve ad-hoc investigation as well. Mature follow-up of the Impassion131 trial might bring important information, and overall survival results interpretation should also take into account subsequent treatments. At this moment, it is unknown which treatment was given after disease progression with paclitaxel and atezolizumab or placebo.

What then should be the main message from IMpassion131? Although its results are negative, this trial offers us a tremendous opportunity to learn more and refine our knowledge in order to identify who are the patients with metastatic TNBC who truly benefit from immunotherapy and how can we optimise the use of immunotherapy in this breast cancer subtype. In the meantime, the recent FDA statement that in clinical practice oncologists should pair atezolizumab with nab-paclitaxel in patients with inoperable, locally advanced or metastatic PD-L1 positive TNBC remains valid (atezolizumab must not be combined with other chemotherapy partner at this moment unless in the context of a clinical trial). However, this recommendation poses two important challenges: (1) nab-paclitaxel use in countries where it is not approved and (2) extra financial burden in countries where this drug is approved (much costly than weekly paclitaxel). In addition, oncologists should be aware that this is a rapidly evolving field, and the treatment of the metastatic disease will also soon be impacted by the shift of the use of immunotherapeutic agents into the early setting, which will further challenge the first-line therapy.

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