



Carboplatin, nab-paclitaxel plus atezolizumab in IMpower 130 trial: new weapons beyond controversies

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Comment on: West H, McCleod M, Hussein M, *et al.* Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicenter, randomized, open-label, phase 3 trial. *Lancet Oncol* 2019;20:924-37.

Submitted Dec 05, 2019. Accepted for publication Dec 19, 2019.

doi: 10.21037/tcr.2019.12.69

View this article at: <http://dx.doi.org/10.21037/tcr.2019.12.69>

Introduction

In the last decade, the management of advanced non-small cell lung cancer (NSCLC) has radically changed. The standard chemotherapy treatment based on histology constituted for 25 years the cornerstone of anticancer treatment, but was finally put aside when molecular diagnosis and precision medicine have modified the therapeutic algorithm.

In the contest of non-oncogene addicted disease, the development of monoclonal antibodies directed against the immune checkpoint (ICI) opened the way to unexpected improvements of survival with a low percentage of stunning durable responses.

Firstly, several studies demonstrated that monotherapy of anti PD-(L)1 in pretreated patients, both in squamous and non-squamous histology, was superior to chemotherapy in terms of survival and safety profile (1-5).

Therefore, researchers raised the bar up testing the anti-PD1 Pembrolizumab in treatment naïve patients (6) and showing the superiority of pembrolizumab respect to a standard platinum-based doublet for high PD-L1 ($\geq 50\%$) expressors, gaining quickly the approval of international regulatory agencies.

Notwithstanding, in all the studies the amount of responders regardless of the PD-L1 status ranges from 20% to 30% suggesting an urgent need for both more affordable biomarkers and new therapeutic strategies to extend the benefit to an higher proportion of patients.

In fact, the predictive role of PD-L1 tumor proportion score (TPS) is not clear and depends on several factors such as the site of sample collecting, the methodology of staining, and the presence of biological cofactors insisting dynamically on the tumor microenvironment (7).

Furthermore, patients potentially eligible for the PD-L1 status but with deteriorating clinical conditions due to a high burden disease may not have 'enough time' to respond to a single agent immune checkpoint blockade. Finally, the 'grey' zone of patients expressing from 1% to 49% of PD-L1 TPS did not experience significant benefits when treated with single-agent immunotherapy as upfront strategy and the standard of care until recently was platinum-based chemotherapy.

Increasing evidences suggest that the combination of immunotherapy and chemotherapy produces a synergistic effect to the immune system, ranging from the enhancing of adaptive/innate immunity to the modification of intracellular pathways and tumor microenvironment (8).

In the light of these data, multiple trials explored the efficacy of a combination between chemotherapy and immunotherapy in first line for advanced NSCLC (9-14) (*Table 1*).

Study presentation

West *et al.* published in July 2019 on *Lancet Oncology* results of a multicenter, randomized, open-label, and

Table 1 Immunotherapy plus chemotherapy combination in 1st line advanced NSCLC

| Study | Histology | Investigational drugs | Primary endpoint | Pts | PFS (m) | HR | OS (m) | HR | ORR (%) |
|------------------|-----------|---|---------------------|--------|---------|------------------|--------|------------------|---------|
| IMpower130 (9) | NSq | Atezolizumab + CBDCA + Nab-Paclitaxel | PFS and OS in ITTwt | 451 wt | 7.0 | 0.64 (0.54-0.77) | 18.6 | 0.79 (0.64-0.98) | 49.2 |
| Keynote189 (10) | NSq | CBDCA + Nab-Paclitaxel | | 228 wt | 5.5 | | 13.9 | | 31.9 |
| | | Pembrolizumab + CDDP/CBDCA + Pemetrexed | PFS and OS | 410 | 8.8 | 0.52 (0.43-0.64) | 22.0 | 0.56 (0.45-0.70) | 47.6 |
| IMpower 132 (11) | NSq | CDDP/CBDCA + Pemetrexed | | 206 | 4.9 | | 10.7 | | 18.9 |
| | | Atezolizumab + CDDP/CBDCA + Pemetrexed | PFS and OS | 292 | 7.6 | 0.60 (0.42-0.79) | 18.1 | 0.81 (0.64-1.05) | 47 |
| IMpower 150 (12) | NSq | CDDP/CBDCA + Pemetrexed | | 286 | 5.2 | | 13.6 | | 32 |
| | | Atezolizumab + CBDCA + Paclitaxel + Bevacizumab | PFS and OS in ITTwt | 353wt | 8.3 | 0.62 (0.52-0.74) | 19.2 | 0.78 (0.64-0.96) | 63.5 |
| Keynote 407 (13) | Sq | CBDCA + Paclitaxel + Bevacizumab | | 331wt | 6.8 | | 14.7 | | 48 |
| | | Pembrolizumab + CBDCA + Paclitaxel/Nab-Paclitaxel | PFS and OS | 278 | 6.4 | 0.56 (0.45-0.70) | 15.9 | 0.64 (0.49-0.85) | 57.9 |
| IMpower 131 (14) | Sq | CBDCA + Paclitaxel/Nab-Paclitaxel | | 281 | 4.8 | | 11.3 | | 38.4 |
| | | Atezolizumab + CBDCA + Nab-Paclitaxel (Arm B) | PFS and OS | 343 | 6.5 | 0.74 (0.62-0.87) | 14.6 | 0.92 (0.76-1.12) | 49.4 |
| | | CBDCA + Nab-Paclitaxel (Arm C) | | 340 | 5.6 | | 14.3 | | 41.3 |

PFS, progression-free survival; OS, overall survival; ITT, intention to treat; wt, wild type; Pts, patients; HR, hazard ratio; ORR, overall response rate, m, months; Sq, squamous NSCLC; NSq, non squamous NSCLC.

phase 3 study named IMpower130. The 724 patients were randomized to receive carboplatin plus nab-paclitaxel chemotherapy with or without atezolizumab (2:1) as first line therapy for metastatic non-squamous NSCLC (NSq-NSLCL). The induction cycles (from 4 to 6) were followed by a maintenance therapy of atezolizumab for the combination group and a switch to pemetrexed or best supportive care for control group until progression or unacceptable toxicity. Cross-over to atezolizumab, at progression in the chemotherapy group, was initially allowed. Thereafter, in order to minimize a possible confounding factor on co-primary outcomes the protocol was amended to remove cross-over.

Inclusion criteria were age ≥ 18 years, cytologically or histologically confirmed stage IV, ECOG PS 0–1 and no previous treatment. Patients with sensing mutation in EGFR gene or ALK fusion oncogene must have progressed during or after treatment with at least one TKI to be included. Patients with CNS involvement were also eligible if metastasis were treated and asymptomatic. Patients were stratified for sex, baseline liver metastases and PD-L1 tumor expression. Co-primary endpoints were investigator-assessed progression-free survival (PFS) and overall survival (OS) in the intention-to-treat (ITT) wild type (EGFR^{wt} and ALK^{wt}) population. Secondary endpoints were intention to treat (ITT) investigator assessed PFS and OS, ITT wild type (ITTwt) and ITT investigator-assessed PFS and OS according to PD-L1 status, ITTwt objective response (OR) and duration of response (DOR), time to deterioration based on EORTC scales for lung cancer symptoms and change from baseline based on Symptoms in Lung Cancer scales.

Considering the ITT population, they included 483 patients (451 ITTwt) in the atezolizumab plus chemotherapy group and 240 patients (228 ITTwt) in the chemotherapy group in the ITT population. The two arms resulted well balanced.

In the ITTwt population median PFS was 7.0 months in the experimental arm (95% CI, 6.2–7.3) *vs.* 5.5 months in the control arm (95% CI, 4.4–5.9) respectively [HR 0.64 (95% CI, 0.64–0.77), $P < 0.0001$].

Median OS was 18.6 months in the atezolizumab plus chemotherapy group (95% CI 16.0–21.2) and 13.9 months (95% CI, 12.0–18.7) in the chemotherapy group [HR 0.79 (95% CI, 0.64–0.98), $P = 0.033$].

The subgroup analysis showed consistent PFS and OS benefit across all the subgroups, excluding patients with liver metastasis at the baseline (HR for OS 0.93; 95% CI, 0.59–1.47) and patients with EGFR and ALK mutations (HR

for OS 0.98; 95% CI, 0.41–2.31). The outcome analysis according the PD-L1 expression showed similar benefits across all the subgroups both in the ITT and ITTwt population.

With regard to safety profile, grade 3–4 adverse events were 81% in the atezolizumab plus chemotherapy group and 71% in the chemotherapy group. Most common grade 3 or worse treatment-related adverse events were neutropenia (32% in the atezolizumab plus chemotherapy group *vs.* 28% in the chemotherapy group), anaemia (29% *vs.* 20%), and decreased neutrophil count (12% *vs.* 8%). Grade 5 events occurred in eight (2%) of 473 patients in the experimental arm and one (<1%) of 232 patients in the control group.

Discussion

This study provided the rationale to include platinum based chemotherapy in combination with atezolizumab among the treatment options in untreated non squamous NSCLC.

The original protocol design permitted crossover before the study amendment and allowed the 60% of chemotherapy treated patient to receive at least one cycle of immunotherapy. That notwithstanding, the combination resulted in longer OS and this confirms the superiority of the combination over the sequence, considering moreover that the OS of the chemotherapy arm was aligned with literature.

No difference in terms of overall-survival was found across the different PD-L1 subgroups. Nevertheless, a recent meta-analysis including 14,395 patients treated with immunotherapy for advanced NSCLC identified a growing benefit related to PD-L1 expression and pembrolizumab combination with platinum-based chemotherapy as the best first-line strategy. Intriguingly, they found that tumors with tumor-cell score (TC) 2/3 or immune cell score (IC) 2/3 had greater benefit with a single ICI, whereas the TC 1 or IC1 tumors responded better to the combination of chemotherapy and immunotherapy (15).

Another point to discuss is the specific regimen of chemotherapy chosen by investigators, namely carboplatin plus nab-paclitaxel.

In a randomized phase III trial this regimen showed improved overall response rate compared to carboplatin plus paclitaxel in chemotherapy naïve NSCLC patients (33% *vs.* 25%, $P = 0.005$) but no advantage in PFS (6.3 *vs.* 5.8 months, $P = 0.214$) and OS (12.1 *vs.* 11.2 months, $P = 0.271$) (16).

Thus, this regimen falls between the approved first lines

for advanced NSCLC, even if it is not widely used excepted to squamous histology.

This is the first trial of chemo-immuno combination using a regimen containing carboplatin plus nab-paclitaxel in non-squamous NSCLC, while Keynote 407 (13) and IMpower 131 (14) addressed this issue in squamous histology. The first showed the superiority of the combination of pembrolizumab and carboplatin with either paclitaxel or nab-paclitaxel over chemotherapy alone. The superiority was confirmed for both nab paclitaxel and paclitaxel and, despite no formal interaction test was performed, the inspection of the forest plot for subgroup analysis suggest that there is no difference between carboplatin paclitaxel and atezolizumab or carboplatin nab-paclitaxel and atezolizumab. The latter did not achieve a significant improvement in OS for the combination of platinum doublet with atezolizumab *vs.* chemotherapy alone.

The investigators favored nab-paclitaxel over paclitaxel in order to avoid the use of corticosteroids, needed with paclitaxel and pemetrexed regimens, because they are supposed to reduce the efficacy of immunotherapy.

Notably, the IMpower130 protocol stated that atezolizumab should be withheld until steroids were tapered to a dose of prednisone equivalents less or equal to 10 mg. Of note, there was no difference in terms of corticosteroids introduction among the arms.

The debate around the impact of corticosteroids on immunotherapy is controversial and still opened.

Several retrospective studies showed that the introduction of a corticosteroid therapy at baseline or early had a negative prognostic role during immunotherapy (17,18). These retrospective analysis share that the steroid-treated patients fell into worst prognosis subgroups because they are more likely to have PS ECOG ≥ 2 , brain metastasis or a number of metastatic sites > 2 .

Moreover corticosteroids used to treat immune-related adverse events seem not to affect the outcome after resumption of therapy (19).

Finally, a retrospective paper evaluating outcomes of ICI treated patients dividing steroid use according to the clinical indication (palliative *vs.* non-palliative) at baseline found no negative impact of corticosteroids introduced for cancer unrelated symptoms (e.g., COPD exacerbation, symptomatic brain metastasis) thus suggesting that the steroid therapy should not be avoided or tapered without a proven-same-efficacy alternative (20).

The third theme to highlight is the absence of benefit for

patients with liver metastasis or oncogene addiction treated with the chemo-immuno-combination.

With regard to liver metastasis, the IMpower130 trial suggests that the presence of liver metastasis at baseline retains predictive as well as prognostic value in patients treated with ICI.

Transversal experiences confirmed these findings (21) and probably liver metastasis induce immune tolerance and lack of response to immunotherapy not related to the primary. A liver metastatic involvement was associated with a higher level of Eotaxin-2 and IP-10, which are cytokines with a systemic immunosuppressive state both in colon and melanoma models (22,23).

Back to Lung cancer, the updated analysis of CheckMate 017 and CheckMate 057 trials (24) showed a poorer 3-year survival for patients with liver involvement respect to the whole population (8% *vs.* 17%) and these data were also confirmed in real-life setting experiences (25,26). A subgroup analysis of the IMpower150 study showed for the first time a 48% reduction in risk for death for patient with liver metastasis at baseline and treated with the four-drug-combination (bevacizumab, atezolizumab, carboplatin, paclitaxel) compared with the three-drug-combination without atezolizumab (HR, 0.52; 95% CI, 0.33–0.82). The same paper addressed the issue of oncogene addicted NSCLC (EGFR and ALK), suggesting that these patients could benefit from the chemo immune combination plus bevacizumab (12).

A meta-analysis including three trials of immunotherapy in pretreated patients (CheckMate 057, Keynote 010, and POPLAR) suggested anyway that the presence of EGFR mutation increased risk of death for IO-treated patients respect to the docetaxel arm (HR 1.11; 95% CI: 0.80–1.53, $P=0.54$, interaction $P=0.005$) (27). EGFR mutation was also associated with an increased risk of hyper-progressive disease (28) and the inclusion of EGFR mutated patients in immunotherapy trials should be carefully monitored.

Few data are available for ALK-addicted patients, evidencing poor outcomes among this population.

As previously reported, the single-agent immunotherapy should be avoided or proposed at the end of the therapeutic algorithm, while a strategy of combination with targeted therapy or with chemotherapy may be an alternative for pretreated patients with oncogene addiction (29).

Conclusions

The IMpower130 trial confirmed that a combination of anti PD-1 plus chemotherapy could be an appropriate

strategy for patients affected by advanced NSCLC, without oncogenic drivers, regardless of the PD-L1 status. We claim the need for further prospective studies aimed to identify patients more likely to benefit from a combination strategy including both chemotherapy and immunotherapy.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Editorial Office, *Translational Cancer Research*. This article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2019.12.69>). 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: De Giglio A, Nuvola G, Dall'Olio FG. Carboplatin, nab-paclitaxel plus atezolizumab in IMpower 130 trial: new weapons beyond controversies. *Transl Cancer Res* 2019;8(8):E18-E23. doi: 10.21037/tcr.2019.12.69