Editorial Commentary

Chemotherapy and immune checkpoint inhibitor combination, a new standard in squamous non-small cell lung cancer?

Camille Travert, Pascale Tomasini, Fabrice Barlesi

Multidisciplinar Oncology & Therapeutic Innovations Department, Aix Marseille University, CNRS, INSERM, CRCM, APHM, Marseille, France
Correspondence to: Camille Travert. Multidisciplinar Oncology & Therapeutic Innovations Department, Aix Marseille University, CNRS, INSERM, CRCM, APHM, Marseille, France. Email: travertcam@gmail.com.

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

Comment on: Paz-Ares L, Luft A, Vicente D, *et al.* Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51.

Submitted Jan 22, 2020. Accepted for publication Feb 07, 2020.
doi: 10.21037/tlcr.2020.02.08
View this article at: http://dx.doi.org/10.21037/tlcr.2020.02.08

Squamous non-small cell lung cancer (sqNSCLC), recent improvements and immunotherapy

SqNSCLC accounts for a third of NSCLC, but did not benefit from notable improvements in the last decades, compared to non-squamous NSCLC. Indeed, actionable mutations are much less frequent in this subtype and the place of targeted therapies is limited. This is the reason why standard first-line treatment remained conventional chemotherapy.

Some improvements have been made a few years ago with the combination of chemotherapy to new molecules as CETUXIMAB or NECITUMUMAB, epidermal growth factor receptor (EGFR) antibodies, but without consequent changes in overall survival (OS). Herbst *et al*. reported a non-significant difference in OS with the combination of CETUXIMAB to chemotherapy by CARBOPLATIN/PACLITAXEL {median OS 9.6 months [95% confidence interval (CI): 8.2–11.5] *vs.* 8 months (7.1–8.8) hazard ratio (HR) 0.85 (95% CI: 0.67–1.07) P=0.17)}. In a sub-group analysis, they showed that a benefit can be reached for EGFR FISH-positive subpopulation [OS 11.8 (95% CI: 8.6–13.5) *vs.* 6.1 months (95% CI: 4.2–8.7) HR for death 0.58 (95% CI: 0.39–0.86) P=0.0071] (1). Thatcher *et al*. reported a higher OS in patients treated by the addition of NECITUMUMAB to CISPLATIN/GEMCITABINE [median OS 11.5 months (95% CI: 10.4–12.6) *vs.* 9.9 months (8.9–11.1) HR 0.84 (95% CI: 0.74–0.96) P=0.01] (2). But this study presented a lack of power and clinical benefit was not enough consequent to lead to the approval of this combination.

The development of immunotherapy opened a new area of promising results in sqNSCLC. First, the anti-CTLA4 antibody IPILIMUMAB was assessed in the study reported by Lynch *et al*. For the "phased group" treated by two cycles of CARBOPLATIN-PACLITAXEL followed by four cycles with the combination of IPILIMUMAB or PLACEBO to chemotherapy, an improved OS was reached (median OS 12.2 *vs.* 8.3 months) (3). Then, PD-L1 inhibitors were developed, first in second line. Indeed, previous publications validated in second line for sqNSCLC the place of Immune Checkpoint Inhibitor (ICI) of the PD-1/PD-L1 axis irrespectively of the PD-L1 status. These are NIVOLUMAB, an anti-PD-1 antibody [OS 9.2 months (95% CI: 7.3–13.3) versus 6.0 months (95% CI: 5.1–7.3) HR 0.59 (95% CI: 0.44–0.79) P<0.001] (4); or ATEZOLIZUMAB, an anti-PD-L1 antibody [OS 13.8 months (95% CI: 11.8–15.7) *vs.* 9.6 months (95% CI: 8.6–11.2) HR 0.73 (CI: 0.62–0.87) P=0.0003] (5,6). For sqNSCLC with a PD-L1 expression ≥1%, PEMBROLIZUMAB, an anti-PD-1 antibody, showed significant benefit in OS in second line for patients [OS 12.7 *vs.* 8.5 months HR 0.61 (95% CI: 0.49–0.75) P<0.0001] (7).

Moreover, PEMBROLIZUMAB single agent is now the standard in first line in stage IV squamous and non-squamous NSCLC with a PD-L1 expression ≥50% [median progression-free survival (PFS) 10.3 months (95% CI: 6.7 to not reached (NR) *vs.* 6.0 months (95% CI: 4.2–6.2)

© Translational lung cancer research. All rights reserved.

HR 0.50 (95% CI: 0.37–0.68) P<0.001] (8). These results were confirmed in a similar trial using ATEZOLIZUMAB in first line in NSCLC presented at the 2019 ESMO congress. In an interim analysis ATEZOLIZUMAB single agent significantly improved OS compared to platinum-based chemotherapy in first line in NSCLC with a PD-L1 expression ≥50% on tumor cells or ≥10% on tumor-infiltrating lymphocytes [median OS 20.2 months (95% CI: 16.5–NR) *vs.* 13.1 months (95% CI: 7.4–16.5) HR 0.59 (95% CI: 0.40–0.89) P=0.0106].

But for sqNSCLC with a PD-L1 expression <50%, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) still recommended until recently the platinum-based doublet chemotherapy regimen in first line (9). Indeed, NIVOLUMAB monotherapy in first line failed to demonstrate a benefit for stage IV sqNSCLC with PD-L1 positive tumors but with an expression ≥5% [median OS 14.4 *vs.* 13.2 months HR 1.02 (95% CI: 0.80–1.30)] (10).

We might hypothesize that the combination of PEMBROLIZUMAB to platinum-based chemotherapy lead to improved response rate (RR) and OS by sensitizing tumor with PD-L1 expression <50% to immunotherapy.

Combination of ICI and chemotherapy showed relevant benefit in OS in non-squamous NSCLC: PEMBROLIZUMAB + platinum-based drug and PEMETREXED in the KEYNOTE-189 [OS at 12 months was 69.2% (95% CI: 64.1–73.8) *vs.* 49.4% (95% CI: 42.1–56.2) HR 0.49 (95% CI: 0.38–0.64) P<0.001] (11), ATEZOLIZUMAB in the IMpower 150 study (association to CARBOPLATIN, PACLITAXEL and BEVACIZUMAB) [median OS 19.2 *vs.* 14.7 months HR 0.78 (95% CI: 0.64–0.96 P=0.02] (12) and IMpower 130 study (combination to CARBOPLATIN and NAB-PACLITAXEL) [median OS 18.6 months (95% CI: 16.0–21.2) *vs.* 13.9 months (12.0–18.7) HR 0.79 (95% CI: 0.64–0.98) P=0.033] (13).

The KEYNOTE-407 trial

KEYNOTE-407 study was conducted at the same time of these studies, and assessed the association of platinum-based chemotherapy and PEMBROLIZUMAB in squamous NSCLC. This study (14) is a prospective double-blind multicentric randomized placebo controlled trial and assessed the addition of PEMBROLIZUMAB to chemotherapy with CARBOPLATIN and either PACLITAXEL or nanoparticule albumin-bound (nab)-PACLITAXEL in the first-line setting for stage IV sqNSCLC. It is the first phase 3 trial evaluating in first line the association of PEMBROLIZUMAB to the standard chemotherapy regimen in stage 4 sqNSCLC.

Eligibility criteria were common ICI clinical trials criteria. Randomization was stratified according to PD-L1 status (assessed by IHC 22C3 pharmDx assay) (63.1% of patients), taxane choice (60.1% of PACLITAXEL), and geographic region (19% of East Asia). Response was assessed by blinded independent central radiologists. Patients were randomly assigned to receive either PEMBROLIZUMAB 200 mg or saline placebo every 3 weeks up to 35 cycles. For the first 4 cycles, they all also received chemotherapy by CARBOPLATIN AUC 6 (Area Under the concentration-time Curve of 6 mg) and either PACLITAXEL 200 mg/m^2 or NAB-PACLITAXEL 100 mg/m^2 on days 1, 8 and 15.

Paz-Ares *et al.* reported the results of the prespecified second interim analysis (14). 559 patients were included in 125 sites, 278 were assigned to PEMBROLIZUMAB group and 281 to placebo group.

This trial met its co-primary endpoints. Median OS was 15.9 months (95% CI: 13.2–NR) in PEMBROLIZUMAB group versus 11.3 (95% CI: 9.5–14.8) [HR 0.64 (95% CI: 0.49–0.85) P<0.001]. This result persisted in PD-L1 subgroup analysis with an estimated 1-year survival rate of 64.2%, 65.9% and 63.4% in respectively PD-L1 <1%, 1–49% and >50% groups, versus 43.3%, 50% and 51% (HR 0.61, 0.57 and 0.64). The benefit persisted regardless of other stratification factors (geographic region and taxane choice).

Median progression-free survival (PFS) was also significantly higher in the PEMBROLIZUMAB group: 6.4 (95% CI: 6.2–8.3) *vs.* 4.8 months (95% CI: 4.3–5.7) [HR 0.56 (95% CI: 0.45–0.70) P<0.001]. But interestingly, on the opposite for OS, PEMBROLIZUMAB effect on response increased incrementally with PD-L1 expression (HR 0.68 *vs.* 0.49 for PD-L1 <1% *vs.* >1%; and HR 0.56 *vs.* 0.37 for PD-L1 1–49% *vs.* >50%).

Tolerance profile was the same as expected for a combination therapy with anti PD-1 and chemotherapy. There was the same rate of grade 3 or higher events between the 2 groups (69.8% and 68.2%). But there were more grade 5 events in the PEMBROLIZUMAB group (23 patients 8.3% versus 18 6.4%) even it was not significant. Discontinuation of any or both treatments were twice more frequent in PEMBROLIZUMAB group than in placebo one (24.4% *vs.* 11.8% and 13.3% *vs.* 6.4%).

© Translational lung cancer research. All rights reserved.

This trial is an important step in sqNSCLC treatment strategy. This is the first time in decades that an outstanding benefit in OS is reached in first line. These results were accordingly followed by the approval of this combination by United States Food and Drug Administration (FDA) and European Medical Agency (EMA).

The strengths of this study are: the design, the number of patients included, and the well balanced representative population which is perfectly comparable to control groups in the previous clinical trials cited above (1,2). Findings are consistent with those found in KEYNOTE-189 study (11) in non-squamous NSCLC. Nevertheless, the OS in KEYNOTE-189 was better as the median OS was not reached at 21 months, partly explained by a better OS in PD-L1 >50% in non-squamous versus squamous NSCLC.

However, this study presents some limits. The median duration of follow up was very short [7.8 months (0.1–19.1 months)] because this second-interim analysis was events-driven. It may partly explain the absence of incremental benefit with PD-L1 expression in OS versus PFS.

Moreover, only 4 cycles of chemotherapy were administered. Proportion of patients who received the entire 4 cycles was more important in the PEMBROLIZUMAB group even it was not statistically significant (78.8% *vs.* 73.2% for CARBOPLATIN, 78.7% versus 71.3% for PACLITAXEL, and 22.9% *vs.* 21.2% for NAB-PACLITAXEL). However, benefit from two more cycles is controversial, as Rossi *et al* reported in a meta-analysis [median OS 9.54 months (95% CI: 8.98–10.69) *vs.* 8.68 months (8.03–9.54)] between patients assigned to six cycles *vs.* four cycles [HR 0.94 (95% CI: 0.83–1.07) P=0.33] (15).

Cross over of second line treatment by any ICI of the PD-1/PD-L1 axis in the placebo group occurred only for 89 patients (31.7%) which corresponds to 42.8% in treatment discontinued population. The reasons are not well explained and data about specific reasons for not receiving a subsequent ICI were not collected. This rate is low and may be a limit of this study if patients were fit enough to receive an ICI in second line but did not. On the opposite, if patients were not any more eligible to second line treatment because of a low performance status or because there were dead, this is one more argument in favor of the combination of chemotherapy and ICI in first line. During long-term follow up, the rate of cross-over may increase.

Perspectives

KEYNOTE-407 succeeded where IMpower 131 did not prove any benefit yet. Indeed, IMpower 131 is assessing the adjunction of ATEZOLIZUMAB to chemotherapy by CARBOPLATIN and NAB-PACLITAXEL in sqNSCLC regardless PD-L1 status. OS results were presented to the *WCLC 2019* (World Conference on Lung Cancer) in September 2019 and there was no statistically significant difference between the two groups [median OS 14.2 *vs.* 13.5 months HR 0.88 (95% CI: 0.73–1.05) P=0.16], although subgroup analysis found a significant difference in high PD-L1 subgroup (median OS 23.4 *vs.* 10.2 months). This study is still ongoing and further results may change. Another study evaluated the combination of IPILIMUMAB and chemotherapy in sqNSCLC, also failing in finding a significant difference in OS [13.4 *vs.* 12.4 months HR 0.91 (95% CI: 0.77–1.07) P=0.25] (16).

Interestingly, median OS in the placebo group (11.3 months), although comparable with results reached in SQUIRE trial (2), is lower than the placebo groups in IMpower131 and Govindan study (16). The reasons are not well determined but this difference reinforces the efficacy of pembrolizumab chemotherapy combination.

The survival gain in PEMBROLIZUMAB group could also be only a matter of a maintenance therapeutic strategy. But this type of strategy has been evaluated in several trials in sqNSCLC, especially with GEMCITABINE, and never led to significant benefit [GEMCITABINE maintenance reported by Pérol *et al*. HR 0.89 (95% CI: 0.69–1.15) P=0.3867, and by Brodowicz *et al*. 13.0 months (95% CI: 11.0–16.7) *vs.* 11 months (95% CI: 9.7–13.5) P=0.195] (17,18).

Recently, Mazieres *et al.* (19) published data on quality of life of patients included in the KEYNOTE-407 trial. The combination with PEMBROLIZUMAB maintained and improved Health-related quality of life measurements versus chemotherapy alone. The cost of such a therapeutic could be a matter of concern, but a recently published study found out that the Incremental Cost Effectiveness Ratio (ICER) was inferior to $100,000/QALY (Quality Adjusted Life Year), which makes it acceptable (20).

Further questionings

A recurrent question without any response yet regarding these combinations of chemotherapy and ICI is the right strategy for patients with PD-L1 expression ≥50%: is the combination better than PEMBROLIZUMAB?

Moreover, even in this study, only a subset of patients had durable response. PD-L1 expression does not seem to

© Translational lung cancer research. All rights reserved.

be predictive of response, but benefit in PFS increased with the level of expression, even if it was not the case for OS [HR for progression or death for: PD-L1 <1% 0.68 (0.47–0.98); PD-L1 1–49% 0.56 (0.39–0.80); PD-L1 ≥50% 0.37 (0.24–0.58)]. Now the challenge may be to find predictive biomarkers of response: may tumor mutational burden help to select more specifically the patients (21)?

The best chemotherapy regimen also has to be found: sub-group analysis revealed a tendency in favor of nab-paclitaxel over paclitaxel in PFS (HR for progression or death 0.52 (0.40–0.68) *vs.* 0.65 (0.45–0.94). The absence of premedication by corticoids may be responsible for this difference. However it seems that corticosteroid treatment ≥10 mg negatively impacts PFS and OS only in a use for palliative indications (22). What would be the results if another regimen had been selected (i.e., GEMCITABINE)?

Another questioning is the place of ICI combination compared to ICI plus chemotherapy in the first line setting, taking into account the last results published by Hellmann *et al*. of NIVOLUMAB and IPILUMAB combination in first line for all NSCLC [median OS 17.1 months (95% CI: 15.0–20.1) *vs.* 14.9 months (12.7–16.7) P=0.007] (23).

In conclusion, the combination of PEMBROLIZUMAB with chemotherapy by CARBOPLATIN + (NAB) PACLITAXEL in first line for sqNSCLC is an effective and a safe option and should be recommended and financially supported everywhere.

Acknowledgments

To the editorial team of *TLCR* for their invitation to the writing of this manuscript
Funding: None.

Footnote

Conflict of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr.2020.02.08). PT reports grants from Roche, grants from Astra Zenecca, grants from BMS, grants from BI, grants from Takeda, outside the submitted work; FB reports personal fees from Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer–Ingelheim, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, MSD, Pierre Fabre, Pfizer and Takeda, outside the submitted work. CT 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.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Herbst RS, Redman MW, Kim ES, et al. Cetuximab plus carboplatin and paclitaxel with or without bevacizumab versus carboplatin and paclitaxel with or without bevacizumab in advanced NSCLC (SWOG S0819): a randomised, phase 3 study. Lancet Oncol 2018;19:101-14.
2. Thatcher N, Hirsch FR, Luft AV, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. Lancet Oncol 2015;16:763-74.
3. Lynch TJ, Bondarenko I, Luft A, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. J Clin Oncol 2012;30:2046-54.
4. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
5. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837-46.
6. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017;389:255-65.
7. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a

© Translational lung cancer research. All rights reserved.

randomised controlled trial. Lancet 2016;387:1540-50.
8. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med 2017;376:2415-26.
9. Socinski MA, Obasaju C, Gandara D, et al. Current and Emergent Therapy Options for Advanced Squamous Cell Lung Cancer. J Thorac Oncol 2018;13:165-83.
10. Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med 2017;376:2415-26.
11. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med 2018;378:2078-92.
12. 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.
13. 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 multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:924-37.
14. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2040-51.
15. Rossi A, Chiodini P, Sun JM, et al. Six versus fewer planned cycles of first-line platinum-based chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data. Lancet Oncol 2014;15:1254-62.
16. Govindan R, Szczesna A, Ahn MJ, et al. Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non-Small-Cell Lung Cancer. J Clin Oncol 2017;35:3449-57.
17. Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2012;30:3516-24.
18. Brodowicz T, Krzakowski M, Zwitter M, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer 2006;52:155-63.
19. Mazieres J, Kowalski D, Luft A, et al. Health-Related Quality of Life With Carboplatin-Paclitaxel or nab-Paclitaxel With or Without Pembrolizumab in Patients With Metastatic Squamous Non-Small-Cell Lung Cancer. J Clin Oncol 2020;38:271-80.
20. Insinga RP, Vanness DJ, Feliciano JL, et al. Cost-effectiveness of pembrolizumab in combination with chemotherapy versus chemotherapy and pembrolizumab monotherapy in the first-line treatment of squamous non-small-cell lung cancer in the US. Curr Med Res Opin 2019;35:1241-56.
21. Greillier L, Tomasini P, Barlesi F. The clinical utility of tumor mutational burden in non-small cell lung cancer. Transl Lung Cancer Res 2018;7:639-46.
22. Ricciuti B, Dahlberg SE, Adeni A, et al. Immune Checkpoint Inhibitor Outcomes for Patients With Non-Small-Cell Lung Cancer Receiving Baseline Corticosteroids for Palliative Versus Nonpalliative Indications. J Clin Oncol 2019;37:1927-34.
23. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med 2019;381:2020-31.

Cite this article as: Travert C, Tomasini P, Barlesi F. Chemotherapy and immune checkpoint inhibitor combination, a new standard in squamous non-small cell lung cancer? Transl Lung Cancer Res 2020;9(2):401-405. doi: 10.21037/tlcr.2020.02.08

© Translational lung cancer research. All rights reserved.