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

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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 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) 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 nanoparticle 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/m² or NAB-PACLITAXEL 100 mg/m² 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%).

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 event-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 IPIVIMUMAB 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 questioning**

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 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.

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Footnote

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