Editorial Commentary

# First-line immune-chemotherapy combination for squamous NSCLC is already a reality

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*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 Feb 28, 2020. Accepted for publication Mar 19, 2020.
doi: 10.21037/tlcr.2020.03.36
**View this article at:** http://dx.doi.org/10.21037/tlcr.2020.03.36

Immune checkpoint inhibitors (ICI) have improved the prognosis and redefined the treatment strategy of metastatic non-small cell lung cancer (NSCLC) patients. In the first-line setting, ICI have become standard of care (SoC) either as monotherapy (pembrolizumab for tumours with high programmed cell death ligand-1 (PD-L1) expression (≥50%) in Europe or with PD-L1 ≥1% in the United States of America) (1-3) regardless of histologic subtype, or in combination with chemotherapy regardless of PD-L1 expression in non-squamous (pembrolizumab/atezolizumab plus platinum-doublet chemotherapy, or atezolizumab-carboplatin-paclitaxel-bevacizumab) (4-7). In contrast to non-squamous histology where personalised treatment approaches along with ICI have improved the outcome (2,4,8), survival improvements in squamous NSCLC have been quite limited or without any meaningful clinical impact so far (9). However, based on the KEYNOTE-407 trial, the introduction of ICI in the first-line treatment of metastatic squamous NSCLC has marked a step forward in the therapeutic strategy of this patient population, improving both the outcome (1,2,10) and quality of life (11,12).

The phase III, placebo-controlled, KEYNOTE-407 trial assessed the progression free survival (PFS), assessed by independent radiological review, and overall survival (OS) benefit of adding pembrolizumab to carboplatin plus (nab)-paclitaxel in 559 treatment-naive metastatic squamous NSCLC patients. In case of no disease progression after four cycles of the combination strategy, maintenance treatment either with pembrolizumab or placebo was administered for up to 35 cycles. Stratification factors included PD-L1 expression (≥1% versus <1%), choice of taxane (paclitaxel versus nab-paclitaxel) and geographic region (East Asia *versus* rest of the world). Of note, crossover was allowed: 32% of patients in the control arm received an ICI at the time of progression, whereas for those who discontinued treatment for any reason the cross-over percentage reached 43%.

Baseline characteristics were well balanced between the two groups (median age 65 years, approximately 80% male, approximately 2/3 Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1, majority current or former smoker, approximately 2/3 PD-L1 expression ≥1%). Pembrolizumab compared to placebo significantly improved both co-primary endpoints: the OS (15.9 versus 11.3 months (HR 0.64, 95% CI: 0.49–0.85, P<0.001) and the PFS (6.4 versus 4.8 months, HR 0.56, 95% CI: 0.45–0.70, P<0.001) (10). In a secondary interim analysis, after a median follow-up of 14.3 months, the OS benefit with pembrolizumab was maintained (17.1 versus

11.6 months HR 0.71, 95% CI: 0.58–0.88), and median PFS2 was also longer in the pembrolizumab arm (13.8 versus 9.1 months) (13). Interestingly, this outcome benefit with pembrolizumab was also observed in the overall response rate (57.9% versus 38.4%). Furthermore, the addition of pembrolizumab did not increase the percentage of grade 3 adverse events (AE's) compared to chemotherapy (69.8% versus 68.2%) or deaths (8.3% versus 6.4%) and had no detrimental effect on quality of life (10,12). However, percentage of treatment discontinuations was higher in the pembrolizumab arm (23.4% versus 11.8%) (10). Based on these results, both FDA and EMA approved pembrolizumab in combination with chemotherapy in the first-line setting on October 30, 2018 and January 31, 2019, respectively.

As with most ICI trials, clinically stable patients with radiological disease progression could continue treatment till the next confirmed radiological progression. PFS and OS were co-primary endpoints thus being equally powered at both the second interim analysis and at the final analysis. Furthermore, the interim analyses were performed at a database maturity that could allow early data release. PD-L1 status, taxane choice and geographic region were stratification factors thus being balanced for the subgroup analysis across treatment arms. Of note, PD-L1 testing was performed centrally and progressive disease was confirmed by blinded independent imaging review.

As a critical note, both the allowed number of chemotherapy cycles (four) and the selection of chemotherapeutic drugs can be discussed. However, it has never been proven that six instead of four chemotherapy cycles are superior with regards to OS (14). In several countries, gemcitabine-platinum doublet is the standard of care instead of carboplatin-(nab)paclitaxel, which may limit the generalizability of the trial results. Indeed, the population enrolled may not reflect the real-life squamous NSCLC patients as they were all in good clinical conditions, with adequate organ function, relatively young, and with a low (about 8%) brain metastases rate. This potential selection of the patients enrolled into the trial can be stated by the fact that almost 30% of screened patients did not meet the in- and exclusion criteria anymore at the time of randomization.

Although the KEYNOTE 407 trial enrolled patients between August, 2016, and December, 2017, when at least four large randomized clinical trials had already reported a survival benefit with second-line ICIs, only one third of patients in the control arm received ICI at progression. Although this percentage might increase with longer follow-up, a high percentage of patients in the control arm did not receive a second line treatment potentially overestimating the survival benefit with the combination. A possible explanation could be a delayed approval for unblinding a cross-over since central confirmation of progression was mandatory, which could induce a clinical deterioration not allowing to start subsequent treatment strategies.

Based on the plethora of clinical trials assessing ICI in the first-line setting, assessment of the real role of the KEYNOTE-407 trial in this scenario merits further attention. The KEYNOTE-407 has positioned pembrolizumab in combination with (nab)-paclitaxel and carboplatin as the new SoC for metastatic squamous NSCLC (10,13). This is especially after the negative survival results of the IMpower131 trial (atezolizumab plus carboplatin and nab-paclitaxel) in the same population (15). Although differences in OS between both trials could be explained by different efficacy between anti-PD1 and anti-PD-L1 in squamous NSCLC, grade 3 AEs were similar (69% with the pembrolizumab and 66% with the atezolizumab-combination) (10,13,15). However, it should be pointed out that between the KEYNOTE-407 and IMpower131 differences in median follow-up (14.3 versus 25.5 months) exist, as well as differences in crossover rate (32% versus 43%) and in the proportion of PD-L1 positive tumors (63% versus 53%). Furthermore, PD-L1 scoring was performed differently [22C3 clone with PD-L1 TPS for pembrolizumab, SP142 clone with tumour cell (TC)/ immune cell (IC) scoring for atezolizumab]. All of these could be considered for explaining the discordant results in OS (10,13,15).

One more point merits attention. With a median follow-up of 14.3 months, pembrolizumab plus chemotherapy improved PFS regardless of PD-L1 expression, but the magnitude of OS benefit according to PD-L1 strata was less consistent, with survival improvement in tumours with PD-L1 expression between 1% to 49%, but not in PD-L1 negative tumours (HR 0.79, 95% CI: 0.56–1.11) or in tumours with high PD-L1 expression (HR 0.79, 95% CI: 0.52–1.21). However, the effects of PD-L1 expression in OS in the KEYNOTE-407 trial were only prespecified exploratory endpoints, lacking statistical power, while they were secondary endpoints in the IMpower131 (10,13). As contrary, in the IMpower131 trial, median OS was significantly improved with atezolizumab only in the subgroup with high PD-L1 expression (TC3 or IC3, HR 0.48; 95% CI: 0.29–0.81), but not in PD-L1 positive (TC1/2/3 or IC1/2/3, HR 0.86, 95% CI: 0.67–1.11) or PD-

 

L1 negative tumours (TC0 or IC0, HR 0.87; 95% CI: 0.67–1.13) (15). Therefore, is there any role of ICI-chemotherapy in PD-L1 negative squamous lung cancer? A recent pooled analysis assessed this strategy in 428 PD-L1 negative tumours enrolled in three randomized trials (KEYNOTE-021G, KEYNOTE-189 and KEYNOTE-407). The analysis reported a clinically meaningful benefit improvement in PFS (HR 0.67; 95% CI: 0.53–0.84) and OS (HR 0.56; 95% CI: 0.43–0.73) with pembrolizumab plus chemotherapy compared with chemotherapy alone, although 42% of patients in the control arm received an anti-PD(L)1 at the time of progression. The OS benefit was observed in all subgroups, including squamous NSCLC (HR 0.61; 95% CI: 0.38–0.96) (16). In the CheckMate227 trial, part 2, nivolumab plus chemotherapy did not meet its primary endpoint of significantly prolonged OS versus chemotherapy alone in treatment-naïve non-squamous NSCLC (HR 0.86, 95% CI: 0.69–1.08, P=0.186) (17). For all randomized patients in the trial as well as in the squamous group, nivolumab plus chemotherapy showed improved OS (HR 0.81; 95% CI: 0.67–0.92 and HR: 0.69; 95% CI: 0.50–0.97, respectively) compared with chemotherapy. Of note, it was a descriptive analysis and outcomes by histology according to PD-L1 expression were not reported. However, in all randomized patients, HR for OS was similar regardless of PD-L1 expression, not clearly supporting PD-L1 expression as a predictive biomarker for this combination (17).

Finally, whether ICI-ICI combination is or is not a potential strategy in squamous histology is another challenging question. CheckMate227 trial part 1 reported a significant survival improvement with nivolumab plus ipilimumab compared with chemotherapy alone in PD-L1 positive NSCLC (HR 0.79, 97.7% CI: 0.65–0.96, P=0.007) and the survival benefit occurred regardless PD-L1 expression or tumour mutational burden (TMB) cut-off. Survival benefit was also reported in squamous histological subtype (14.8 versus 9.2 months, HR 0.69, 95% CI: 0.52–0.92) (18). Of note, as patients were not stratified by PD-L1 ≥ or <50%, subgroup analyses may be impacted by imbalances and should be interpreted with caution. The role of ICI-ICI in first-line remains controversial, as the control arm in the CheckMate227 trial (platinum-based chemotherapy) is suboptimal. Moreover, the risk of early death/ progression, observed with ICI-ICI combinations based on the fact that curves crosses, seems to be averted with immune-chemotherapy combinations (10,18). Recently, two trials have not reported survival benefit with ICI-ICI combination compared with chemotherapy, the MYSTIC trial in PD-L1 ≥25% tumours (19) and the NEPTUNE trial (NCT02542293) in high blood TMB tumours, further confounding the role of ICI-ICI combinations in first-line setting. Pending data from CheckMate9LA (NCT03215706) may help to clarify the role of this strategy.

As stated above, ICI are the major improvement in this patient population in the last ten years. Since more than half of the squamous NSCLC patients still do not obtain long-term benefit from ICI treatment strategies, more data should be obtained on biomarkers as well as patient selection for ICI treatment. PD-L1 expression is a valid, although imperfect biomarker for ICI efficacy. In high PD-L1 expression tumours (≥50%), several phase III clinical trials have reported significant survival improvements with a favourable toxicity profile with anti-PD(L)1 drugs compared with platinum-based chemotherapy (2,3,20). However, the magnitude of survival benefit with monotherapy is less pronounced in squamous histology (2,20), probably due to the limited number of patients with squamous histology enrolled in these trials. However, these data do not allow rejecting monotherapy as a potential strategy in this subgroup of NSCLC patients or testing PD-L1 expression in squamous lung carcinomas. Indeed in a retrospective cohort the magnitude of benefit from pembrolizumab monotherapy increased with higher PD-L1 expression, with improved RR (60.0% versus 32.7%, P<0.001), and longer PFS [14.5 versus 4.1 months, HR 0.50 (95% CI: 0.33–0.74)], and OS (not reached versus 15.9 months, HR 0.39; 95% CI: 0.21–070) in tumours with a very high PD-L1 expression (90–100%) compared with those tumours with PD-L1 expression between 50% to 89% (21). However, for instance, no trials have compared combination therapy versus pembrolizumab monotherapy in the PD-L1 ≥50% patient population. Based on the retrospective series, future trials should probably stratify for high versus very high PD-L1 expression. Finally, the TMB has not been validated as predictive biomarker for ICI-chemotherapy combination in the KEYNOTE-407 trial (22).

Importantly, the KEYNOTE-407 included only a low percentage of (selected) patients with brain metastases (N=44, 8%). Therefore, it is unclear whether this patient population also derives benefit from pembrolizumab-chemotherapy, although a pooled analysis of three KEYNOTE trials (021, 189 and 407) suggested benefit from pembrolizumab-chemotherapy, compared with chemotherapy alone among patients with brain metastases (5).

 

A patient population that comprises approximately 25% of daily practice (23), is the performance status (PS) 2 group of patients. However, this group was excluded in all chemotherapy-ICI trials. Based on ICI monotherapy data, these patients do not derive the same benefit as those with a PS of 0-1. It is not clear whether ICI-chemotherapy combinations are safe and effective in this group.

Furthermore, new treatment strategies are needed, either in first line or upon progression. Combinations with radiotherapy are of interest because of the synergy between radiation and ICI (24). Especially in oligometastatic but also in polymetastatic NSCLC, several trials combining ICI and radiation with or without chemotherapy are ongoing [e.g., ETOP-CHESS (NCT03965468), NIRVANA-LUNG (NCT03774732), IMMUNOSABR2 (NCT03705403), NCT03391869, NCT03275597, NCT03509584)].

Last, current options in squamous NSCLC patients, progressing on chemotherapy-ICI are limited, with docetaxel monotherapy being the SoC. Treatment at progression is a challenge, and the best next line of treatment is being explored in several trials [e.g., NCT03626545, NCT03906071, NCT03705403, NCT03406468, NCT02750514 (FRACTION-lung), NCT03334617 (HUDSON)]. Results of these trials are eagerly awaited.

To conclude, the KEYNOTE-407 trial positioned pembrolizumab-chemotherapy as the new first line treatment of metastatic squamous NSCLC patients with a good PS. Future research should focus on biomarkers associated with (lack of) long-term ICI benefit, special populations such as PS2 and brain metastases, as well as new therapeutic strategies upon ICI progression.

## Acknowledgments

*Funding:* None.

## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr.2020.03.36). JR serves as the unpaid editorial board member of *Translational Lung Cancer Research* from Sep. 2019 to Sep. 2021. LELH reports other from boehringer ingelheim, other from BMS, other from Roche, other from BMS, grants from Roche, grants from Boehringer Ingelheim, other from AstraZeneca, personal fees from Quadia, grants from Astra Zeneca, other from Lilly, other from Roche, other from Pfizer, other from MSD, from Takeda, outside the submitted work; JM reports grants, personal fees and other from Boehringer-Ingelheim, grants and other from MSD, grants and other from Roche, grants and other from Astrazeneca, grants and other from Ipsen, grants and other from BMS, outside the submitted work; JR reports other from OSE Pharma, other from AstraZeneca, other from MSD, other from Pfizer, other from Roche, outside the submitted work.

*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:** Hendriks LEL, Menis J, Remon J. First-line immune-chemotherapy combination for squamous NSCLC is already a reality. Transl Lung Cancer Res 2020;9(3):819-823. doi: 10.21037/tlcr.2020.03.36

 