Editorial Commentary

Building on success: key takeaways from the 5-year update of the KEYNOTE-407 study

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Over the past decade, the treatment landscape of metastatic non-oncogene addicted non-small cell lung cancer (NSCLC) has undergone a revolutionary transformation with the emergence of immune checkpoint inhibitors (ICIs), particularly those targeting the programmed death-1 (PD-1) axis. This advancement has significantly changed the therapeutic approach for NSCLC patients, providing new and more effective options for disease management.

In 2015, the Food and Drug Administration approved the first ICI, nivolumab, for patients with NSCLC whose disease had progressed after platinum-based chemotherapy. This approval was based on the results of a phase III clinical trial that demonstrated the superiority of nivolumab compared to docetaxel in this setting (1). Subsequently, atezolizumab and pembrolizumab were also shown to be more effective than docetaxel, leading to their approval for NSCLC treatment (2,3).

The next milestone was the introduction of these drugs as first-line treatment options. Initially, pembrolizumab was compared to platinum-based chemotherapy in patients with high (≥50%) PD-L1 expression, showing longer progression-free survival (PFS) and overall survival (OS) (4). However, ICI monotherapy did not demonstrate significant benefits in patients with PD-L1 expression levels below 50% (5). Given these findings, several phase III trials were designed to compare chemotherapy plus ICI versus chemotherapy alone as first-line treatment for patients with metastatic NSCLC. As the choice of chemotherapy regimen may vary based on histology, some trials were specifically tailored to evaluate these combinations in either squamous or non-squamous advanced NSCLC.

KEYNOTE-407 was a phase III, randomized, global clinical trial comparing chemotherapy alone versus chemotherapy combined with pembrolizumab in patients with advanced squamous NSCLC. The patient population was stratified based on PD-L1 tumour proportion score (TPS) of either less than 1% or greater than or equal to 1%, as determined by immunohistochemistry (IHC, Dako 22C3 antibody). The chemotherapy regimen used in the trial was a combination of carboplatin and a taxane, either paclitaxel or nab-paclitaxel. Patients received four cycles of the combination treatment, followed by a total of up to 35 cycles of pembrolizumab or placebo, provided there was no disease progression, death, or unacceptable toxicity. It should be noted that this trial excluded patients with symptomatic brain metastases or an ECOG of 2 or higher, which could limit its applicability to the real-world population.

The initial results of the KEYNOTE-407 trial were published in 2018, demonstrating a longer overall survival

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(OS) and progression-free survival (PFS) in patients treated with the platinum doublet plus pembrolizumab (6). In 2020, Paz-Ares *et al.* published the final analysis specified by the trial protocol, further confirming the significant benefit in terms of prolonging both OS and PFS (7). Additionally, the final analysis provided the results of PFS after the second line of treatment (PFS-2), defined as time from randomisation to progressive disease after next line of treatment or death. This endpoint also favoured the pembrolizumab arm (7).

A further update of the trial results is essential to provide a more comprehensive understanding of the long-term efficacy and toxicity associated with the combination of pembrolizumab and chemotherapy. Long-term results are crucial for evaluating the durability of treatment responses and the sustained impact on OS and PFS. Moreover, immunotherapy is known for its potential late-onset toxicities, which may not be apparent in earlier assessments. This comprehensive evaluation of long-term outcomes will ultimately contribute to optimizing therapeutic strategies for this patient population.

In February 2023, Novello *et al.* published an update of the KEYNOTE-407 trial with a median follow-up of approximately 5 years (median time from random assignment to database cut-off of 56.9 months) (8). The updated results demonstrated a sustained benefit in the pembrolizumab arm, with longer PFS and OS. The 5-year OS rates were 18.7% in the pembrolizumab arm compared to 9.7% in the placebo arm, while the historical, pre-immunotherapy era data, shows a 5-year OS consistently under 10% (9). Notably, among the 55 patients who completed the 35 cycles of pembrolizumab, the 5-year OS rate was an impressive 69.1%.

The remarkable OS benefit is even more noteworthy considering the high rate of patients in the placebo arm who received immunotherapy as later line of treatment. Per the trial protocol, pembrolizumab was administered to 117 patients, while an additional 26 patients received subsequent anti-PD-(L)1 treatment outside the trial, resulting in an effective crossover rate of 50.9%. Despite this high crossover rate, PFS-2 was significantly higher in the experimental arm [hazard ratio (HR) 0.60; 95% CI: 0.50 to 0.72], underscoring the advantages of administering ICI as part of the first-line treatment for advanced squamous NSCLC patients.

Even though the benefits of pembrolizumab in terms of PFS and OS were observed across all pre-specified PD-L1 subgroups, some differences warrant further discussion. For patients whose tumours had negative PD-L1 expression, approximately a third of the study population, the benefit of this strategy was less evident. Despite a significantly longer PFS (HR 0.70; 95% CI: 0.52 to 0.95), the median PFS was 6.1 *vs.* 5.7 for the pembrolizumab arm and the placebo arm, respectively. Additionally, there was no significant difference in OS (HR 0.83, 95% CI: 0.61 to 1.13). Despite the lower benefit in this subgroup, administering ICI should not be disregarded. In fact, a pooled analysis of several trials administering ICI plus chemotherapy in PD-L1 negative patients showed consistent benefits in OS and PFS (10).

On the other hand, patients with high (>50%) PD-L1 expression undoubtedly benefit the most from ICI, with higher ORR and longer OS. The challenge in clinical practice lies in selecting the appropriate regimen (ICI monotherapy *vs.* combination treatment) for each individual patient, as no randomized studies have compared these alternatives in the subgroup of patients with high PD-L1 expression. Some retrospective studies have suggested that the benefit in this subgroup is mainly driven by those with a very high expression (PD-L1 >90%) (11,12), so the level of PD-L1 expression could be helpful for selecting the appropriate regimen. Other retrospective series have identified clinical characteristics that predict a higher probability of ICI benefit. Among them, one of the most consistent findings is that never smokers could have a shorter OS when treated with ICI monotherapy (13). Other possible clinical predictive biomarkers of response to single agent ICI include having an ECOG <2, a BMI ≥25 and being a male (14).

Adding to the complexity of treatment selection in the last years, the CheckMate 9LA trial introduced a new chemo-immunotherapy regimen that consists of two cycles of chemotherapy plus nivolumab and ipilimumab followed by nivolumab and ipilimumab (15). This regimen was compared with histology-specific chemotherapy alone in a phase III, randomized, open-label study that included patients with both non-squamous and squamous NSCLC. After three years of follow-up, the trial showed a prolonged median OS of 15.8 months in the experimental arm versus 11.0 months in the control arm (HR 0.74; 95% CI: 0.62–0.87), and this benefit was also observed in the subgroup of patients with squamous NSCLC (HR 0.64; 95% CI: 0.48–0.86) (16). The study allowed the inclusion of patients with treated, stable brain metastases, who obtained a significant benefit in terms of OS and PFS. Interestingly, the prespecified group of patients without PD-L1 expression also achieved a statistically significant OS

benefit (HR 0.67; 95% CI: 0.51–0.88) (16). These results could favour choosing this regimen in these subgroups, but it should be noted that no direct comparison has been made so far, so no definite conclusions can be currently drawn. Updated safety data showed that treatment-related grade 3–5 adverse events (AEs) were reported in 57.2% of patients in the experimental arm and 55.7% in the control arm. However, treatment discontinuation due to AEs occurred in 20.9% of patients in the pembrolizumab arm, compared to 7.5% in the placebo arm. This difference may be attributed to immune-related AEs in the experimental arm, but the available information is not sufficient to confirm this hypothesis definitively.

Understanding the adverse event profile of the treatment is crucial for evaluating the risk-benefit balance and guiding clinical decision-making. The higher rate of treatment discontinuation in the experimental arm underscores the importance of ongoing research to clarify the specific causes of toxicity and develop strategies to manage and mitigate these side effects. By gaining a more comprehensive understanding of the safety profile, clinicians can optimize the use of pembrolizumab and chemotherapy combinations, ensuring that patients receive the most effective and tolerable treatment for their advanced squamous NSCLC.

In conclusion, the updated results of KEYNOTE-407 reinforce the importance of administering pembrolizumab in combination with chemotherapy as part of the first-line treatment for advanced squamous NSCLC, providing sustained benefits across different patient subgroups. However, the varying degrees of benefit observed across PD-L1 subgroups emphasize the need for further research to optimize treatment selection based on individual patient characteristics, such as PD-L1 expression levels and smoking status.

Despite the demonstrated advantages of pembrolizumab and chemotherapy combinations, the 5-year overall survival rate remains below 20%, underlining the pressing need to improve current treatment strategies and continue the pursuit of more effective therapeutic approaches for patients with advanced squamous NSCLC.

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