Editorial Commentary

KEYNOTE-407: an effective and safe first-line treatment option for metastatic squamous non-small cell lung cancer

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We read with interest the article by Novello *et al.* titled "Pembrolizumab plus chemotherapy in squamous non-small-cell lung cancer: 5-year update of the Phase III KEYNOTE-407 Study" published in the *Journal of Clinical Oncology* (1). The study reported the 5-year follow-up results of the KEYNOTE-407 trial, which enrolled 559 patients with previously untreated metastatic squamous non-small cell lung cancer (NSCLC) and randomized them 1:1 to receive either pembrolizumab plus carboplatin and paclitaxel/nab-paclitaxel or placebo plus carboplatin and paclitaxel/nab-paclitaxel. After induction treatment of 4 cycles, a pembrolizumab/placebo was prescribed total up to 35 cycles. Crossover to pembrolizumab monotherapy in case of treatment failure in the placebo group was allowed. Patients were eligible to receive second-course pembrolizumab monotherapy for 17 cycles (approximately 1 year) on PD after either completing 35 cycles of pembrolizumab with a best overall response of stable disease (SD) or better or achieving a confirmed complete response (CR) per investigator assessment after receiving eight or more cycles of pembrolizumab and having received two or more cycles beyond the initial CR assessment.

The study showed that the combination therapy resulted in significant improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) compared to chemotherapy alone. After a median follow-up of 56.9 months (range, 49.9–66.2), the median OS was 17.2 months [95% confidence interval (CI): 13.8 to 23.4) in the combination therapy group compared to 11.6 months (95% CI: 6.5 to 13.7) in the chemotherapy alone group. The 5-year OS rate was 18.4% (95% CI: 13.8% to 23.4%) in the combination therapy group versus 9.7% (95% CI: 6.5% to 13.7%) in the placebo plus chemotherapy group. The combination therapy group also had a longer median PFS of 8.0 months (95% CI: 6.3 to 8.5) compared to 5.1 months (95% CI: 4.3 to 6.0) in the chemotherapy alone group. The ORR was 62.2% (95% CI: 56.2% to 68.0%) and 38.8% (95% CI: 33.1% to 44.8%) with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. Toxicity was consistent with prior reports from KEYNOTE-407 and KEYNOTE-189 (2,3).

In the pembrolizumab plus chemotherapy group, 55 patients completed 2 years of pembrolizumab treatment, and 38 (69%) of those patients were still alive at the data cut off. In the placebo plus chemotherapy group, a flattening of the Kaplan-Meier curve was observed, which was not seen in historical chemotherapy trials before the introduction of immune checkpoint inhibitors (ICIs). One possible explanation for this is that 50.9% (n=143) of the patients from placebo with chemotherapy arm received subsequent

anti-PD(L)1 therapy, with 117 patients crossing over to receive pembrolizumab and 26 patients receiving treatment outside of the study.

ICIs have brought about a revolution in the treatment of NSCLC, especially for patients with advanced stages of the disease. In addition to KEYNOTE 407, various clinical trials, such as IMPOWER131, Checkmate 227, and Checkmate 9LA (4-6), have also demonstrated the effectiveness of ICIs as the first line chemotherapy in treating advanced stage of NSCLC. The IMPower131 study also showed results for atezolizumab plus chemotherapy in the treatment of advanced squamous NSCLC, which enrolled 1,021 patients with previously untreated advanced squamous NSCLC and randomly assigned them 1:1:1 to receive atezolizumab plus carboplatin plus paclitaxel, atezolizumab plus carboplatin plus nab-paclitaxel (referred to as the A + CnP group), or carboplatin plus nab-paclitaxel (referred to as the CnP group). After a median follow-up of 18.1 months in the A + CnP group and 16.1 months in the CnP group, the study found that the A + CnP therapy resulted in a longer median PFS of 6.3 months (95% CI: 5.7 to 7.1) compared to 5.6 months (95% CI: 5.5 to 5.7) in the CnP group. However, after a median follow up of 26.8 months in the A + CnP group and 24.8 months in the CnP group, there was no significant difference in OS between the two groups, with a median OS of 14.2 months (95% CI: 12.3 to 16.8) in the A + CnP group and 13.5 months (95% CI: 12.2 to 15.1) in the CnP group (4).

The two studies, KEYNOTE-407 and IMPower131, have shown different outcomes in terms of their primary endpoints when comparing their results. The KEYNOTE-407 study demonstrated a significant improvement in both OS and PFS with A + CnP compared to CnP alone. On the other hand, the IMPower131 study showed a significant improvement in PFS but no significant difference in OS with atezolizumab plus chemotherapy compared to chemotherapy alone. One possible explanation for this difference is that pembrolizumab and atezolizumab have different mechanisms of action. Pembrolizumab targets PD-1, while atezolizumab targets PD-L1. Additionally, the chemotherapy regimens combined in the two studies were also different. KEYNOTE-407 used either paclitaxel or nab-paclitaxel, while IMPower131 only used nab-paclitaxel in the analysis.

The CheckMate 227 trial highlights the significance of ICIs in treating metastatic NSCLC. The study enrolled patients with non-squamous and squamous NSCLC, who did not have EGFR mutations or ALK translocations and allocated them in a 1:1:1 ratio to receive nivolumab plus ipilimumab, nivolumab alone, or chemotherapy as first-line treatment. PFS and OS were reported as two independent primary end points by previous studies (7,8). According to the CheckMate 227 trial, after a minimum follow-up of 61.3 months, the combination of nivolumab and ipilimumab displayed a superior overall survival rate compared to chemotherapy for patients with NSCLC (5). The median OS was 17.1 months (95% CI: 15.0 to 20.2) for patients receiving nivolumab plus ipilimumab compared to 14.9 months (95% CI: 12.7 to 16.7) for those receiving chemotherapy in patients with tumor PD-L1 expression ≥1%. The CheckMate 227 trial revealed that the median OS was 17.4 months (95% CI: 13.2 to 22.0) for patients with PD-L1 expression <1% receiving nivolumab and ipilimumab, compared to 12.2 months (95% CI: 9.2 to 14.3) for those receiving chemotherapy. The 5-year OS rates were 24% for nivolumab plus ipilimumab versus 14% for chemotherapy (PD-L1 ≥1%), and 19% versus 7% for PD-L1 <1% (8).

The CheckMate 227 trial showed that nivolumab and ipilimumab were superior to chemotherapy in terms of OS and PFS, regardless of PD-L1 expression. After a median follow-up of 54.8 months, the median OS was 14.8 months (95% CI: 12.1 to 18.7) for squamous NSCLC patients with PD-L1 ≥1% who received nivolumab and ipilimumab treatment, compared to 9.2 months (95% CI: 7.6 to 13.9) for those who received chemotherapy. For squamous NSCLC patients with PD-L1 <1%, the OS was 15.9 months (95% CI: 9.0 to 33.9) for those treated with nivolumab and ipilimumab, compared to 8.8 months (95% CI: 6.4 to 13.0) for those who received chemotherapy (9). Conversely, the KEYNOTE 407 trial demonstrated that pembrolizumab plus chemotherapy was superior to chemotherapy alone. PD-L1 expression is a useful biomarker, but it is not the sole determinant for the decision to use pembrolizumab. Although some patients with tumors that have low or no PD-L1 expression may still benefit from pembrolizumab in combination with chemotherapy treatment, the KEYNOTE 407 trials did not demonstrate any improvement for patients with PD-L1 <1%. Although the KEYNOTE 407 trial specifically enrolled squamous NSCLC patients, both studies investigated the use of immunotherapy as a first-line treatment for patients with NSCLC. These studies provide valuable insights into the use of immunotherapy in NSCLC.

Another important clinical trial aimed to investigate the safety and efficacy of a different combination of ICI

and chemotherapy is ChekMate 9LA. The CheckMate 9LA trial compared first-line treatment with nivolumab plus ipilimumab and two cycles of chemotherapy to chemotherapy alone (four cycles) in patients with advanced NSCLC, including 227 cases of squamous NSCLC and 493 cases of non-squamous NSCLC. The trial included patients with stage IV or recurrent NSCLC without EGFR mutation or ALK translocations, and patients were randomly assigned to receive either treatment. After a median follow-up of 30.7 months, the trial showed that the combination therapy led to a significant improvement in OS compared to chemotherapy alone. The median OS was 15.8 months (95% CI: 13.9–19.7) in the combination group compared to 11 months (95% CI: 9.5–12.7) in the chemotherapy group, and the 2-year OS rate was 38%in the combination group compared to 26% in the chemotherapy group (6).

The CheckMate 9LA and KEYNOTE 407 trials both demonstrated the benefit of platinum-doublet chemotherapy combined with immunotherapy as the first-line treatment for patients with advanced NSCLC. The CheckMate 9LA trial showed that nivolumab plus ipilimumab and chemotherapy significantly improved OS compared to chemotherapy alone, with a manageable safety profile. The KEYNOTE 407 trial demonstrated that pembrolizumab plus chemotherapy significantly improved OS compared to placebo plus chemotherapy, with a similar safety profile. The two trials differ in terms of the number of cycles of chemotherapy used. The KEYNOTE-407 trial used four cycles of chemotherapy, while the CheckMate 9LA trial used only two cycles of chemotherapy in combination with immunotherapy. Both trials have demonstrated that the inclusion of immunotherapy along with chemotherapy leads to a significant improvement in OS, irrespective of PD-L1 expression.

The trend for ICIs in the treatment of NSCLC is moving towards personalized treatment through combination therapy. The POSEIDON study, which enrolled metastatic NSCLC patients with EGFR/ALK wild-type status, has shown that a combination of durvalumab with or without tremelimumab in combination with chemotherapy has significantly improved PFS. The PFS were 6.2 months (95% CI: 5.0 to 6.5), 5.5 months (95% CI: 4.7 to 6.5), and 4.8 months (95% CI: 4.6 to 5.8) for the tremelimumab plus durvalumab and chemotherapy group, durvalumab plus chemotherapy group, and chemotherapy alone group, respectively (10). Biomarkers such as PD-L1 expression, tumor mutational burden (TMB), and microsatellite instability (MSI) are being utilized to personalize treatment with ICIs in NSCLC. The field of immuno-oncology is continuously progressing, and new ICIs such as tislelizumab, sintilimab and so on (11,12) will likely continue to be developed and tested in NSCLC and other tumor types. In NSCLC clinical trials, the latest ICIs being researched target other immune checkpoints like TIM-3 and LAG-3 (13,14). These agents may provide additional treatment options for patients who do not respond to current ICI therapies.

In conclusion, a 5-year follow-up analysis of the KEYNOTE-407 trial investigated the long-term efficacy and safety of pembrolizumab in combination with chemotherapy as a first-line treatment for metastatic squamous NSCLC. The study showed that the combination therapy continued to provide significant improvement in OS and PFS compared to chemotherapy alone, with durable responses observed in a subset of patients. The combination therapy also maintained a manageable safety profile over the long term. These findings suggest that pembrolizumab in combination with chemotherapy was an effective and safe first-line treatment option for metastatic squamous NSCLC.

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