Development of immune checkpoint inhibitors (ICIs) has changed our daily care practices for patients with lung cancer. First-line ICIs have been a part of the standard of care for advanced NSCLC without a targetable driver mutation. In the KEYNOTE-189 trial (NCT02578680) for advanced nonsquamous lung cancer, after a median follow-up of 31.0 months, the median overall survival (OS) in the pembrolizumab plus pembrolizumab and platinum doublet arm was 22.0 months, whereas that in the pembrolizumab and platinum doublet arm was 10.6 months (hazard ratio [HR] = 0.56, 95% confidence interval [CI]: 0.46–0.69).1 In the final analysis of the KEYNOTE-407 trial (NCT02775435) for advanced squamous lung cancer, after a median follow-up of 14.3 months, the median OS in the pembrolizumab plus carboptatin and paclitaxel or nab-paclitaxel arm was 17.1 months, whereas that in the carboptatin and paclitaxel or nab-paclitaxel arm was 11.6 months (HR = 0.71, 95% CI: 0.58–0.88).2 In the IMpower150 trial (NCT02366143) for advanced nonsquamous lung cancer, after a median follow-up of approximately 40 months, the median OS in the atezolizumab plus bevacizumab, paclitaxel, and carboplatin arm was 19.5 months, whereas that in the bevacizumab, paclitaxel, and carboplatin was 14.7 months (HR = 0.80, 95% CI: 0.67–0.95).3 The survival benefits regardless of programmed death-ligand 1 (PD-L1) status in the KEYNOTE-189, KEYNOTE-407, and IMpower150 trials were sustainable after years of follow-up. Although KEYNOTE-189 excluded patients with EGFR mutations or ALK fusion, these patients could have been included in the IMpower150 trial. Adding an ICI to traditional chemotherapy as first-line therapy prolongs survival in a patient with advanced NSCLC.

Nivolumab is a fully human immunoglobulin G4 programmed cell death protein-1 receptor-blocking monoclonal antibody. It is the first approved anti-programmed cell death protein-1 agent in the world (in July 2014, for metastatic melanoma in Japan).4 In the CheckMate 017 (NCT01642004)5 and CheckMate 057 (NCT01673867)6 trials, nivolumab was better than docetaxel as second-line treatment for advanced squamous and nonsquamous lung cancer. The U.S. Food and Drug Administration approved its use as a second-line treatment for advanced NSCLC in 2015. Nevertheless, its first-line use in patients with advanced NSCLC is struggling. CheckMate 227, a phase 3, open-label, randomized controlled trial, recruited treatment-naive patients with stage IV or recurrent NSCLC without sensitizing EGFR mutations or ALK rearrangement. In part 1a of the study, 1189 patients with PD-L1 expression level greater than or equal to 1% were randomized 1:1:1 to receive nivolumab plus ipilimumab, nivolumab alone, or standard platinum doublet chemotherapy. In part 1b of the study, 550 patients with PD-L1 expression level less than 1% were randomized 1:1:1 to receive nivolumab plus ipilimumab, nivolumab plus platinum doublet chemotherapy, or standard platinum doublet chemotherapy alone. The primary end points after multiple protocol amendments were (1) progression-free survival (PFS) in the nivolumab plus ipilimumab arm
compared with that in the chemotherapy arm in patients with high tumor mutation burden (≥10 mutations per megabase) and (2) OS in the nivolumab plus ipilimumab arm compared with that in the chemotherapy arm in patients with PD-L1 expression level greater than or equal to 1%. First-line monotherapy with nivolumab or nivolumab combined with chemotherapy was not the primary objective in the final analysis. In part 2 of the study, 755 patients, regardless of their PD-L1 status, were randomized 1:1 to receive nivolumab plus platinum doublet chemotherapy or standard platinum doublet chemotherapy alone. The primary end point was OS with nivolumab plus chemotherapy compared with that with chemotherapy alone in patients with nonsquamous NSCLC. In the European Society for Medical Oncology 2019, the final analysis of part 2 of CheckMate 227 was reported. Nivolumab plus platinum doublet chemotherapy did not meet the primary end point (HR = 0.86, 95.62% CI: 0.69–1.08, p = 0.1859) in patients with nonsquamous NSCLC, although nivolumab plus platinum doublet chemotherapy might be better than chemotherapy alone in patients with squamous lung cancer (HR = 0.69, 95% CI: 0.50–0.97). Thus, nivolumab plus chemotherapy has not been approved as first-line therapy for NSCLC.

The PFS result of part 1 of CheckMate 227 was released in 2018. For patients with high tumor mutation burden, detected using FoundationOne Cdx, the PFS in the nivolumab plus ipilimumab arm was longer than that in the chemotherapy arm (HR = 0.58, 97.5% CI: 0.41–0.81, p < 0.001). In 2019, after a minimum follow-up of 29.3 months, nivolumab plus ipilimumab met the OS coprimary end point in patients with PD-L1 expression level greater than or equal to 1%. The median OS was 17.1 months with nivolumab plus ipilimumab and 14.9 months with chemotherapy (p = 0.007). The HR for death was 0.79 (97.72% CI: 0.65–0.96). Finally, part 1 of CheckMate 227 met its two coprimary end points. The U.S. Food and Drug Administration approved nivolumab plus ipilimumab as first-line treatment for advanced NSCLC with PD-L1 expression level greater than or equal to 1% in May 2020. For patients with PD-L1 expression level less than 1%, the median OS with nivolumab plus ipilimumab (17.2 mo; 95% CI: 12.8–22.0) was also longer than with chemotherapy (12.2 mo; 95% CI: 9.2–14.3), with an HR for death of 0.62 (95% CI: 0.48–0.78) in part 1 of CheckMate 227.

In this issue of the Journal of Thoracic Oncology, Luis G. Paz-Ares et al. reported the updated results of OS for part 1 of CheckMate 227. After a median follow-up of 54.8 months, all patients were off nivolumab plus ipilimumab treatment for at least 2 years. OS remained longer with nivolumab plus ipilimumab than with chemotherapy in patients with PD-L1 expression level greater than or equal to 1% (median OS = 17.1 mo versus 14.9 mo, HR = 0.76, 95% CI: 0.65–0.90) and PD-L1 expression level less than 1% (median OS = 17.2 mo versus 12.2 mo, HR = 0.64, 95% CI: 0.51–0.81). OS benefits were found in both nonsquamous histology and squamous histology and across most patient subgroups. The incidence of any-grade and grade 3 to 4 treatment-related adverse effects (TRAEs), serious TRAEs, and TRAEs leading to treatment discontinuation in all arms was similar to previous reports. It is worth to emphasize that most TRAEs in the nivolumab plus ipilimumab arm leading to treatment discontinuation were immune-related adverse events (irAEs) as the patients did not receive any chemotherapy in the trial. For patients who discontinued treatment because of TRAEs in the nivolumab plus ipilimumab arm (n = 97), the median OS was 41.5 months, with a response rate of 51.5%, almost double than that of the whole treatment group. These patients only received nivolumab plus ipilimumab for a median duration of 3.68 months. Although the authors did not disclose the OS in patients who did not discontinue treatment because of TRAEs in the nivolumab plus ipilimumab arm, the very long OS suggested a positive effect of irAEs in the group. For years, investigators have been keen to know the prognostic factors for ICI therapy other than PD-L1. Furthermore, irAEs have been suspected to be associated with better immunotherapy outcomes, but most data are from retrospective or small prospective studies. This is the first large prospective randomized controlled trial to report the association between TRAEs (mostly irAEs in the nivolumab plus ipilimumab arm) and prolonged OS. It would be interesting if the authors further analyzed the types and severity of TRAEs in terms of patient survival. In contrast, in KEYNOTE-598 (NCT03302234), which has a similar design with pembrolizumab plus ipilimumab, it was not reported whether TRAE-related discontinuation is associated with OS benefits.

For advanced NSCLC with PD-L1 expression level greater than or equal to 50%, pembrolizumab, atezolizumab, and cemiplimab are approved as first-line monotherapy. In this final analysis, nivolumab plus ipilimumab had an HR of 0.66 (95% CI: 0.52–0.84) compared with chemotherapy. In the final analysis of KEYNOTE-189, pembrolizumab plus chemotherapy had an HR of 0.59 (95% CI: 0.40–0.86) compared with chemotherapy. In KEYNOTE-598, the addition of ipilimumab to pembrolizumab did not reveal survival benefits (HR = 1.08, 95% CI: 0.85–1.37). Therefore, it is unclear whether nivolumab plus ipilimumab is superior to pembrolizumab monotherapy for the treatment of NSCLC with PD-L1 expression level greater than or equal to 50%.

The publication of results of the final OS analysis of CheckMate 227 part 1 reinforces the strength of...
nivolumab plus ipilimumab therapy as a first-line treatment for advanced NSCLC without targetable driver mutations. During such a long follow-up period, the dual ICI combination revealed a durable response. Recently, the 2-year follow-up results of CheckMate 9LA have been published. Adding two cycles of chemotherapy to nivolumab plus ipilimumab continued to reveal survival benefits compared with chemotherapy alone (median OS = 15.8 mo versus 11.0 mo, HR = 0.72, 95% CI: 0.61–0.86). Nevertheless, further investigations are needed to clarify whether adding two cycles of chemotherapy has more survival benefit. For most nontargetable advanced NSCLC (i.e., PD-L1 expression level < 50%), first-line ICI and chemotherapy combination, dual ICIs, and dual ICIs plus two cycles of chemotherapy are better than ICI monotherapy or chemotherapy alone. Two heads are better than one. Nevertheless, on the basis of the current evidence, partners do matter. Pembrolizumab requires platinum doublets, atezolizumab requires bevacizumab and platinum doublets, and nivolumab requires ipilimumab.

CRediT Authorship Contribution

Yen-Ting Lin: Conceptualization, Methodology, Investigation, Data curation, Writing—original draft, Writing—review and editing.

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References


