Immunotherapy with monoclonal antibodies against programmed death-1 (PD-1) or its ligand (PD-L1) were approved for previously treated advanced non-small cell lung cancer (NSCLC) based on the results from four randomized trials showing improved survival compared to standard therapy with docetaxel (1-4). In the phase 1 study with the anti-PD-1 antibody pembrolizumab in previously treated NSCLC, the response rate and median progression-free survival (PFS) for patients with PD-L1 proportion score of ≥50% were 45.2% and 6.3 months respectively, with median PFS of 6.1 months for the 99 previously treated patients and 12.5 months for the 20 previously untreated patients (5). Therefore, the next logical step was to evaluate the role of pembrolizumab in previously untreated patients with PD-L1 score of ≥50%, where the efficacy was comparable to historical data on first-line platinum-based combination chemotherapy with or without maintenance chemotherapy (6-9).

In the Keynote-024 trial, 305 patients with previously untreated metastatic non-squamous NSCLC without sensitizing EGFR mutations or ALK translocations were randomized in a 2:1 ratio to receive platinum (carboplatin or cisplatin) plus pemetrexed and either pembrolizumab 200 mg or placebo every 3 weeks (12). The addition of pembrolizumab to the chemotherapy doublet was associated with increased response rate (47.6% vs. 18.9%, P<0.001) and median OS in the pembrolizumab and placebo arms were not reached and 11.3 months respectively (HR 0.49, P<0.001). The OS benefit from the addition of pembrolizumab was observed for all PD-L1 scores, with HR ranging from 0.59 (95% CI: 0.38–0.92) in PD-L1 less than 1% to 0.42 (95% CI: 0.26–0.68) in those with PD-L1 ≥50%. The addition of pemetrexed did not
lead to an increase in the adverse events (99.8% vs. 99%) or grade 3–5 adverse events (67.2% vs. 65.8%) compared to chemotherapy alone, with the possible exception of nephritis, which occurred in 7 patients (1.7%) treated with pembrolizumab and none of those treated with placebo. In the Keynote-407 trial, 559 patients with untreated metastatic squamous cell lung cancer were randomized to receive carboplatin plus a taxane (paclitaxel or nab-paclitaxel) and either pembrolizumab 200 mg or placebo every 3 weeks (13). The addition of pembrolizumab was associated with increased response rate (57.9% vs. 38.4%), median PFS (6.4 vs. 4.8 months, HR 0.56, P<0.001) and median OS (15.9 vs. 11.3 months, HR 0.64, P<0.001). The pembrolizumab arm was associated with a higher incidence of treatment discontinuation (23.4% vs. 11.8%) and pneumonitis (6.5% vs. 2.1%).

With the established role for first-line single agent pembrolizumab in patients with PD-L1 of ≥50% and the combination of platinum-based doublets plus pembrolizumab independent of PD-L1 score, an important remaining question was regarding the role for single agent pembrolizumab in patients with PD-L1 positive but below 50%. The Keynote-042 trial was a multicenter, open label trial where 1274 patients with previously untreated advanced NSCLC with PD-L1 score of at least 1% and no EGFR mutation or ALK translocation, were randomized to pembrolizumab 200 mg every 3 weeks or chemotherapy with carboplatin plus either paclitaxel or pemetrexed, without crossover from chemotherapy to pembrolizumab allowed as a part of the study (14). The primary endpoint was initially OS in patients with PD-L1 ≥50% and later changed to OS in patients with PD-L1 ≥50%, ≥20% and ≥1% after the enrollment had been completed. PD-L1 of ≥50% was present in 47% of patients in each of the trial arms. The OS was significantly longer in the pembrolizumab group patients (16.7 vs. 12.1 months, HR 0.81, P<0.001), for patients with PD-L1 ≥50% (20 vs. 12.2 months, HR 0.69, P=0.0003), PD-L1 ≥20% (17.7 vs. 13.0 months, HR 0.77, P=0.002), and PD-L1 ≥1% (16.7 vs. 12.1 months, HR 0.81, P=0.001). In a pre-specified exploratory analysis of patients with PD-L1 score 1–49%, the median OS was 13.4 months in the pembrolizumab group and 12.1 months in the chemotherapy group (HR 0.92, 95% CI: 0.77–1.11). The median PFS for patients with PD-L1 ≥50% treated with pembrolizumab and chemotherapy was 7.1 and 6.4 months respectively (HR 0.69, P=0.0003). For patients with PD-L1 scores of ≥20% and ≥1%, there was no improvement in the median PFS compared to chemotherapy (6.2 vs. 6.6 months and 5.4 vs. 6.5 months respectively). Only 20% of patients assigned to chemotherapy received subsequent immunotherapy.

Keynote-042 was a large study for which several observations can be made. The OS benefit was driven largely by the patients with high PD-L1 scores and the lack of crossover indicates that at least some patients that would be candidates for additional therapy with checkpoint blockers did not have access to it, representing a possible explanation for the low percentage of patients receiving subsequent immunotherapy. Among patient with PD-L1 ≥50%, the median PFS and OS for patients treated with pembrolizumab were lower than those observed in the Keynote-24 (10,11), which included a similar patient population where the PD-L1 testing was performed with the same methodology, while the outcomes for patients with chemotherapy were similar. Similarly, unlike the results from Keynote-024, the median PFS was not prolonged among patients with PD-L1 of at least 50% treated with pembrolizumab in the Keynote-042. Nevertheless, despite the caveats from the trial, pembrolizumab was found to be more effective than first-line chemotherapy in patients with PD-L1 positive and appears to be as effective in those with PD-L1 score 1–49%. Therefore, an important question is about the role of single agent pembrolizumab in previously untreated patients with PD-L1 score 1–49%. For fit and motivated patients with this range of PD-L1 score, the best first-line treatment option is a combination of chemotherapy and immunotherapy based on the results from the Keynote-189 (12), Keynote-407 (13), and IMpower-130 (15), which showed a benefit from adding the anti-PL-1 antibody atezolizumab to chemotherapy in patients with non-squamous NSCLC. Single agent pembrolizumab may be an option for patients with PD-L1 1–49% who either decline or are unfit for chemotherapy. However it should be noted that the Keynote-042 trial enrolled patients with good performance status, good organ function and life expectancy of at least 3 months.

In summary, the Keynote-042 confirmed the superiority of first-line pembrolizumab compared to chemotherapy in patients with high PD-L1 score and showed similar outcomes in those with score 1–49%, where the combination of chemotherapy and immunotherapy should be considered the standard of care for eligible patients. For patients in this PD-L1 range who are unfit for combined chemoimmunotherapy, single agent pembrolizumab may be
an option although the outcomes are expected to be inferior to the ones observed in this study where only patients eligible for carboplatin doublets were enrolled.

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None.

Footnote

Conflicts of Interest: Consultant fees: Abbvie, Bristol-Myers Squibb, PharmaMar and Takeda.

Ethical Statement: The author is 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.

References
