Review

Clinical Cancer Research

Immunotherapy for the First-Line Treatment of Patients with Metastatic Non–Small Cell Lung Cancer

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Abstract

Immunotherapy has fundamentally changed the treatment landscape for many patients with cancer. mAbs targeting programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen-4 immune checkpoints have received regulatory approval across a wide range of tumor types, including non–small cell lung cancer (NSCLC). Indeed, treatment approaches for a majority of patients with newly diagnosed metastatic NSCLC are evolving rapidly. Only for the small proportion of patients with metastatic NSCLC and genomic-driven tumors with EGFR or anaplastic lymphoma kinase (ALK)–sensitizing mutations (5%–15%), and possibly *BRAF* mutations and *ROS* rearrangements, have initial treatment recommendations remained unchanged, with specific tyrosine kinase inhibitors as the preferred therapy. For the remaining patients, an immunotherapy-based regimen alone or in combination with chemotherapy is now the preferred option based on high-level evidence obtained from randomized controlled trials and in accordance with all available guidelines. Deciding between therapeutic options can be difficult due to the lack of direct cross-comparison studies, differences in chemotherapies and stratification factors, and differences in study populations resulting from inclusion criteria such as histology, PD-L1 expression, or tumor mutational burden (TMB). In an attempt to aid the decision-making process, we discuss and summarize the most recent data from studies using immunotherapies for the treatment of patients with previously untreated metastatic NSCLC.

Introduction

Because evidence emerged that blockade of the programmed cell death-1 (PD-1) signaling pathway could result in deep and durable antitumor responses in lung cancer, there has been a race to exploit the full potential of this new treatment modality across all stages of the disease. Initial evidence of this antitumor effect in non–small cell lung cancer (NSCLC) was reported in 2012 for nivolumab, a mAb that binds to the PD-1 receptor, and for BMS-936559, which binds to the programmed cell death ligand-1 (PD-L1), expressed on tumor cells, macrophages, and dendritic cells (1, 2). PD-1/PD-L1 immune checkpoint–blocking antibodies to treat metastatic NSCLC first entered the clinic in 2015 based on results of the CheckMate 017 trial, which demonstrated superiority of nivolumab over docetaxel in patients with squamous metastatic NSCLC who had disease progression after platinum-containing chemotherapy (3). Since then, pembrolizumab and atezolizumab have also received regulatory approval in previously treated patients with metastatic NSCLC (4, 5).

More recently, a surge of pivotal studies has assessed the role of immunotherapy in previously untreated metastatic NSCLC. This review discusses the impact of these new data on the choice of first-line therapy for the patients with metastatic NSCLC, defined by histology, biomarker status, and eligibility for platinum-based chemotherapy.

Initial Biomarker Characterization

Baseline testing for the following three independent biomarkers may help to define the most effective first-line treatment for patients with newly diagnosed metastatic NSCLC.

EGFR and anaplastic lymphoma kinase alterations

Patients with a confirmed diagnosis of nonsquamous NSCLC should be tested for *EGFR* and anaplastic lymphoma kinase (*ALK*)–sensitizing alterations before initiation of any therapy. For those patients with these specific oncogene-addicted tumors, treatment with an appropriate tyrosine kinase inhibitor (TKI) remains the most effective first-line treatment option (6, 7).

Tumor PD-L1 expression

Several IHC assays are available for evaluating PD-L1 expression levels, and specific antibodies have been used in the clinical development of different anti–PD-1/PD-L1 therapies (8). Currently, PD-L1 expression levels can impact the decision as to whether patients may be treated with first-line pembrolizumab monotherapy; the preferred method is IHC testing with the 22C3 pharmDx assay (Agilent), used in the pivotal pembrolizumab studies (9). It is approved for use in biopsy specimens and categorizes PD-L1 expression on tumor cells according to the tumor proportion score (TPS). Of note, studies comparing different IHC assays and antibodies suggest high concordance among most commercially available methods (10, 11).

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doi: 10.1158/1078-0432.CCR-18-3904

Tumor mutational burden

Tumor mutational burden (TMB) is defined as the number of nonsynonymous mutations (somatic, coding, base substitutions, and short indels) per megabase (mut/MB) of genome examined. It is assessed using formalin-fixed, paraffin-embedded tumor samples. Good concordance has been established between TMB from whole-exome sequencing and TMB from targeted next-generation sequencing, such as the FoundationOne CDx assay (12), and other assays (12, 13). In addition, although TMB has been shown to be independent of PD-L1 expression (14–16), TMB-high tumors may have a higher number of immunogenic neoantigens and thus may be more sensitive to combination immunotherapy (17). A cut-off of TMB $\geq$10 mut/MB using the FoundationOne CDx assay was defined on the basis of the phase II CheckMate 568 study (18) and subsequently used in the CheckMate 227 study investigating the combination of nivolumab plus ipilimumab (14).

Immuno-Oncology in Combination with Chemotherapy: Nonsquamous Histology

In patients with metastatic NSCLC of nonsquamous histology, three studies have shown an overall survival (OS) benefit from adding an anti–PD-1/PD-L1 antibody to standard chemotherapy: KEYNOTE-189, IMpower150, and IMpower130 (19–21).

The KEYNOTE-189 phase III trial compared a platinum plus pemetrexed doublet with either pembrolizumab 200 mg or placebo in previously untreated patients with metastatic nonsquamous NSCLC (Fig. 1; ref. 19). Patients with *EGFR*- or *ALK*-sensitizing alterations were excluded. After completing four cycles of platinum-based chemotherapy, patients continued to receive pemetrexed with pembrolizumab or placebo as maintenance therapy. The study was positive for both coprimary endpoints, that is, progression-free survival (PFS) and OS assessed by an independent central review committee. Median PFS was 8.8 versus 4.9 months [HR 0.52; 95% confidence interval (CI), 0.43–0.64; $P < 0.001$] in the pembrolizumab and placebo arms, respectively (Fig. 2). The median OS was not reached in the pembrolizumab arm compared with 11.3 months in the placebo arm (HR 0.49; 95% CI, 0.38–0.64; $P < 0.001$). Importantly, the improvement in OS with pembrolizumab was seen across all levels of PD-L1 expression (categorized by TPS), including those classified as PD-L1–negative (TPS <1%; HR 0.59; 95% CI, 0.38–0.92). Response rates were 47.6% in the pembrolizumab arm and 18.9% in the placebo arm (Fig. 3). At the time of the analysis, 50% of patients randomized to placebo had crossed over to treatment with pembrolizumab upon disease progression. The safety profile was similar for both treatment arms, although more patients discontinued treatment due to an adverse event (AE) in the pembrolizumab arm (28% vs. 15%).

Two studies investigated the combination of atezolizumab with chemotherapy in patients with nonsquamous NSCLC: IMpower150 (20) and IMpower130 (21), both of which were positive in terms of OS. The three-arm IMpower150 study (Fig. 1) compared atezolizumab plus carboplatin, paclitaxel, and bevacizumab (ACPB) and atezolizumab plus carboplatin and paclitaxel (ACP) to carboplatin, paclitaxel, and bevacizumab (CPB; ref. 20). After four or six cycles of carboplatin and paclitaxel were completed, bevacizumab and/or atezolizumab were given as maintenance. The IMpower130 study tested a similar chemotherapy

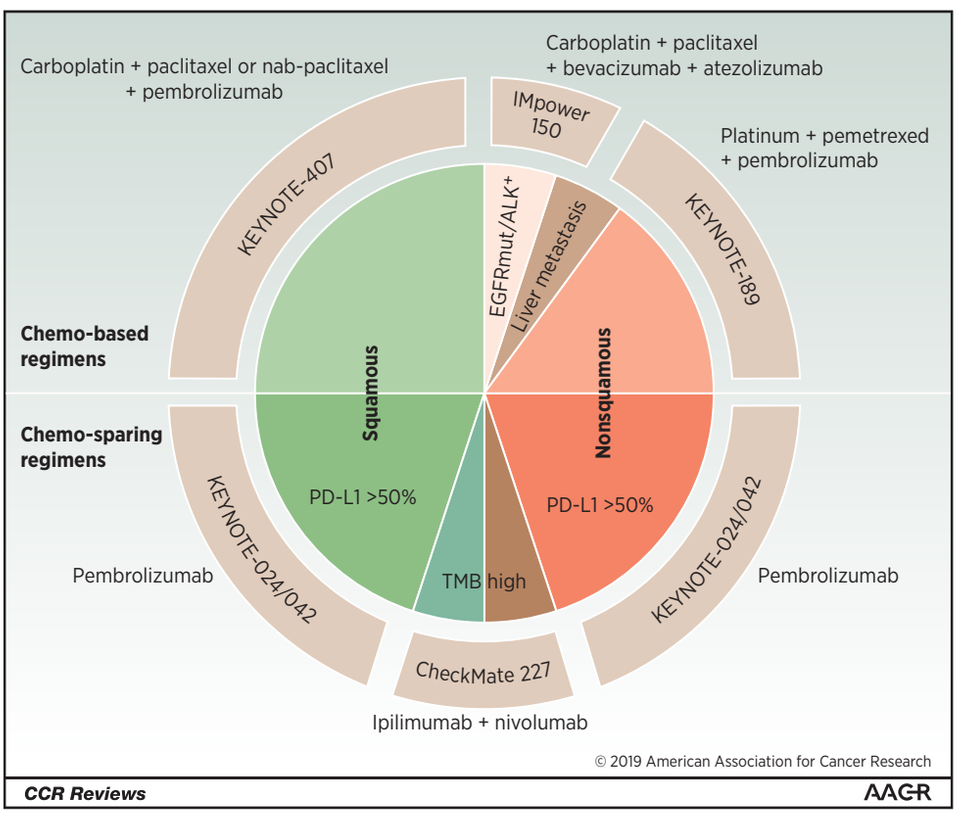

Figure 1.
Graphical representation of treatment regimens evaluated in first-line NSCLC immunotherapy studies.

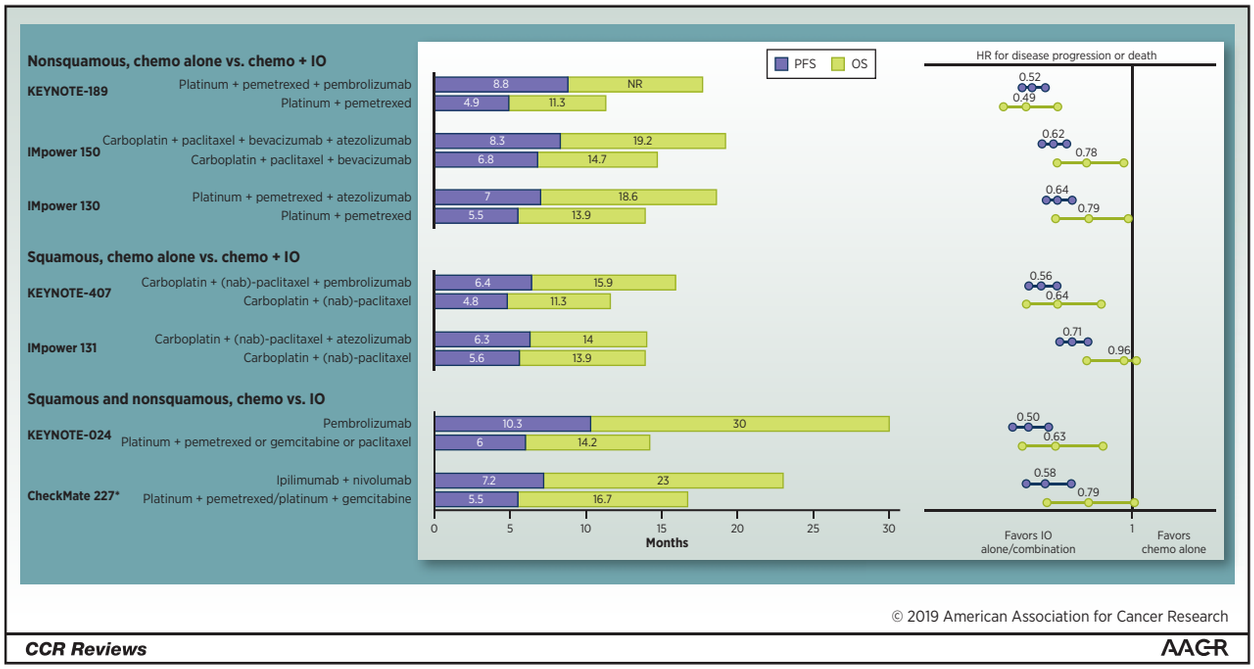

Figure 2.

PFS and OS with HRs reported in the first-line NSCLC immunotherapy studies. Chemo, chemotherapy; IO, immuno-oncology. *Results are reported for the patients with high TMB (≥10 mut/MB). HR data in blue are for PFS, and data in green represent OS data. Figure adapted from Peters S. Immunotherapy for advanced NSCLC: Biomarkers, sequence, duration. Presented at ASCO 2018.

backbone of carboplatin and nab-paclitaxel with and without atezolizumab (ACnP vs. CnP; ref. 21). Switch maintenance was permitted in the control arm of IMpower130, whereas atezolizumab maintenance was administered in the experimental arm. Patients with *EGFR* or *ALK* alterations who had exhausted their TKI therapy options were enrolled in both studies but were excluded from the primary PFS and OS analysis (intention-to-treat population with wild-type genotype; ITT-WT; refs. 20, 21). The magnitude of PFS benefit in the ITT-WT population was similar in both studies (IMpower150: 8.3 vs. 6.8 months with ACPB vs. CPB, respectively; HR 0.62; 95% CI, 0.52–0.74; $P < 0.001$; and IMpower130: 7.0 vs. 5.5 months with ACnP vs. CnP, respectively; HR 0.64; 95% CI, 0.54–0.77; $P < 0.0001$; Fig. 2). The absolute median PFS was longer and objective response rate (ORR) was greater with the bevacizumab-containing combinations in the IMpower150 study. However, median OS outcomes were very similar, being 19.2 months with ACPB and 14.7 months with CPB (HR 0.78, 95% CI, 0.64–0.96; $P = 0.02$) in the IMpower150 study (20) and 18.6 versus 13.9 months with ACnP compared with CnP, respectively (HR 0.79; 95% CI, 0.64–0.98; $P = 0.033$) in IMpower130 (Fig. 2; ref. 21). Notably, in IMpower150, the ACP arm did not show a survival benefit compared with the CPB control arm. The magnitude of PFS benefit with atezolizumab correlated well with PD-L1 expression in both studies, although the correlation was weaker for OS in that the HR 95% CIs overlapped with unity across high, low, and negative levels of PD-L1 expression.

The safety profiles of ACPB and ACnP were consistent with those of the individual regimens. The rate of grade ≥3 treatment-related AEs was slightly higher for ACPB than with CPB (58.5% vs. 50.0%, respectively) in the IMpower150 study, whereas the rate of treatment-related deaths was similar for the two regimens (2.8% vs. 2.3%, respectively; ref. 20). The rate of AEs leading to discontinuation of any study treatment was higher with ACPB (32.6% vs. 24.9%), albeit with a longer treatment duration than CPB (8.2 vs. 5.1 months; ref. 19). Similar safety trends were observed in the IMpower130 study (21).

The IMpower150 and 130 studies diverge in outcomes for the subgroup of patients with liver metastases. In IMpower150 (14% of the study population), PFS was 8.2 and 5.4 months with ACPB and CPB, respectively (HR 0.40), and OS was 13.2 versus 9.1 months (HR 0.54, ACPB versus CPB; ref. 20). However, in IMpower130, no advantage was observed for the patients not receiving bevacizumab with liver metastases (21).

For TKI-pretreated patients with EGFR- or ALK-sensitizing alterations, data from prior randomized second-line studies indicated that immunotherapies were less effective than in patients with wild-type tumors (5, 22, 23). Furthermore, patients with EGFR mutations or ALK-positive tumors showed inferior outcomes when treated with immunotherapy compared with chemotherapy regardless of PD-L1 expression levels (24, 25). In EGFR-mutant NSCLC, two meta-analyses demonstrated that PD-1/PD-L1 inhibitors are less beneficial compared with chemotherapy or EGFR-TKI therapy (26, 27). Some immunologic features may explain the lack of response observed in clinical trials with PD-1/PD-L1 inhibitors in patients with EGFR-mutant or ALK-positive NSCLC. Despite positive PD-L1 expression these tumors have a low incidence of concurrent $CD8^+$ tumor-infiltrating lymphocytes and a lower overall TMB (28–31). These findings led to the exclusion of patients with TKI-sensitive driver mutations from most first-line studies except for IMpower150 and IMpower130. In IMpower150, median PFS for the patients with

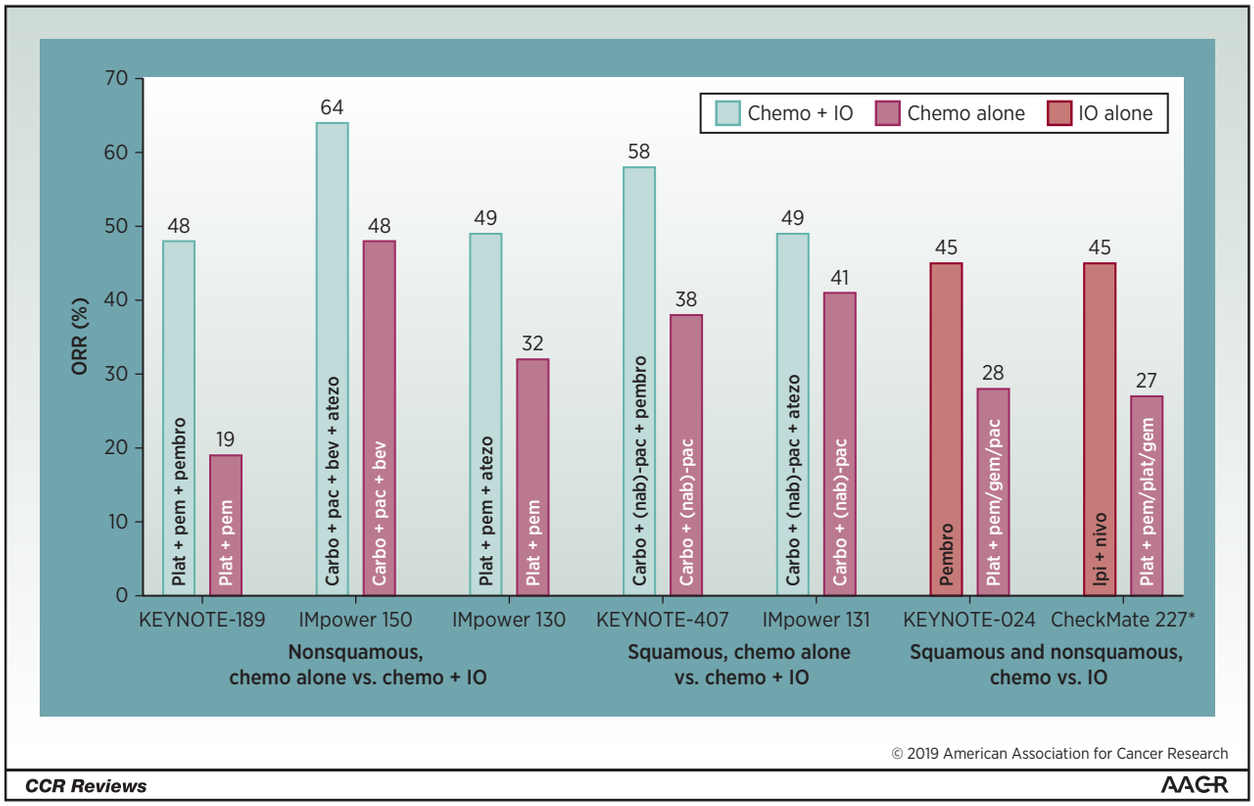

Figure 3.

ORRs reported in first-line NSCLC immunotherapy studies. Atezo, atezolizumab; bev, bevacizumab; carbo, carboplatin; chemo, chemotherapy; gem, gemcitabine; IO, immuno-oncology; ipi, ipilimumab; nivo, nivolumab; pac, paclitaxel; pembro, pembrolizumab; pem, pemetrexed; plat, platinum. *Results are reported for the patients with high TMB (≥10 mut/MB).

EGFR or ALK alterations was 9.7 versus 6.1 months with ACPB compared with CPB, respectively (HR 0.59; 95% CI, 0.37–0.94) and median OS was not reached compared with 17.5 months, respectively (HR 0.54; 95% CI: 0.29–1.03; ref. 32).

Primary outcomes for two additional first-line chemotherapy combination studies in patients with nonsquamous histology have been reported as negative and are not discussed. The randomized phase III study, IMpower132, evaluating the addition of atezolizumab to carbo- or cisplatin plus pemetrexed in the same patient population, demonstrated an improvement in PFS [7.6 vs. 5.2 months (HR 0.60; 95% CI, 0.49–0.72)], but failed to show an improvement in OS over chemotherapy alone (33).

Immuno-Oncology in Combination with Chemotherapy: Squamous

For the patients with metastatic squamous NSCLC histology, the KEYNOTE-407 study has shown that pembrolizumab added to a standard chemotherapy regimen improves survival outcomes (34). KEYNOTE-407 was a phase III study in previously untreated patients who were randomized 1:1 to receive carboplatin and physician's choice of paclitaxel or nab-paclitaxel plus pembrolizumab 200 mg or placebo for four cycles, followed by pembrolizumab or placebo maintenance (Fig. 1). Coprimary endpoints in this study were PFS and OS. Median PFS and OS were superior for the pembrolizumab-containing regimen compared with placebo [PFS: 6.4 vs. 4.8 months, respectively (HR 0.56; 95% CI, 0.45–0.70; $P < 0.001$) OS: 15.9 vs. 11.3 months (HR 0.64; 95% CI, 0.49–0.85; $P < 0.001$; Fig. 2)]. Despite the immaturity of the survival data at the time of publication (median follow-up 7.8 months), the OS benefit appeared consistent across the high, low, and negative PD-L1 expression levels. The ORR was also superior in the pembrolizumab versus placebo arm (57.9% vs. 38.4%, respectively; Fig. 3). Although the incidence of grade ≥3 AEs was similar for the two treatment arms (69% for pembrolizumab-containing therapy and 68% for the placebo group), the rate of discontinuation of any treatment due to AEs was higher for the pembrolizumab regimen (23.4% vs. 11.8%, respectively), albeit with longer duration of treatment (median 6.3 months vs. 4.7 months).

The randomized phase III IMpower131 study examined atezolizumab with a similar chemotherapy backbone of carboplatin with either paclitaxel (ACP) or nab-paclitaxel (ACnP) in separate arms against a carboplatin plus nab-paclitaxel (CnP) control (35). Although the study results were positive in terms of its coprimary endpoint of median PFS for ACnP versus CnP (6.3 vs. 5.6 months, respectively; HR 0.71; 95% CI, 0.60–0.85; $P = 0.0001$), the difference between groups in the OS coprimary endpoint was not statistically significant (14.0 vs. 13.9 months; HR 0.96; 95% CI, 0.78–1.18; Fig. 2).

Chemotherapy-Sparing Regimens

Three studies have demonstrated a survival benefit with anti–PD-1/PD-L1 monotherapy alone or in combination with a cytotoxic T-lymphocyte–associated antigen-4–blocking mAb (ipilimumab) against standard platinum-based chemotherapy in biomarker-selected patients with previously untreated NSCLC: KEYNOTE-024, KEYNOTE-042, and CheckMate 227 (refs. 14, 36–38; Fig. 1).

The KEYNOTE-024 and -042 studies compared pembrolizumab monotherapy with histology-appropriate platinum-based chemotherapy in patients whose tumors expressed PD-L1 (36–38). The phase III KEYNOTE-024 trial enrolled the patients with squamous and nonsquamous NSCLC with PD-L1 expression on at least 50% of the tumor cells and without *EGFR*- or *ALK*-sensitizing alterations (36). The study was positive in terms of its primary endpoint of PFS, which was 10.3 months in the pembrolizumab arm versus 6.0 months in the chemotherapy arm (HR 0.50; 95% CI, 0.37–068; $P < 0.001$; Fig. 2). Corresponding median OS was 30.0 months and 14.2 months (HR 0.63; 95% CI, 0.47–0.86; $P = 0.002$; ref. 38). Although PD-1 blockade can cause serious immune-related AEs, pembrolizumab monotherapy carries a substantially lower AE burden than platinum doublet chemotherapy. Indeed, the rate of treatment-related AEs of any grade and grade $\geq$3 were substantially lower in the pembrolizumab monotherapy arm than in the chemotherapy group (73.4% vs. 90% and 26.6% vs. 53.3%, respectively; ref. 36). A total of 7.1% and 10.7% of patients discontinued treatment due to treatment-related AEs in the pembrolizumab and chemotherapy arms, respectively (36). There were also differences in the type of AEs between both arms, with general symptoms such as nausea, anemia, fatigue, decreased appetite, or vomiting much more common and severe in the chemotherapy arm, and immune-mediated AEs such as hypothyroidism, pneumonitis, or skin reactions almost limited to the pembrolizumab arm (36). The KEYNOTE-024 results were first reported in 2016 and pembrolizumab has since been adopted as a chemotherapy-sparing standard of care for the patients with squamous or nonsquamous histology who have PD-L1 expression on at least 50% of their tumor cells.

The KEYNOTE-042 study assessed the potential of pembrolizumab monotherapy in patients with PD-L1 expression on at least 1% of tumor cells (37). It was a larger study than KEYNOTE-024, enrolling 1,274 untreated patients with squamous or nonsquamous NSCLC and excluding those with *EGFR*- or *ALK*-sensitizing alterations. Patients were randomized 1:1 to receive either pembrolizumab 200 mg or histology-appropriate platinum-based chemotherapy without crossover to pembrolizumab. Indeed, in contrast to the PFS primary endpoint in KEYNOTE-024, the primary endpoint of KEYNOTE-042 was OS, tested sequentially in patients with PD-L1 TPS $\geq$50%, $\geq$20%, and $\geq$1%. Pembrolizumab monotherapy significantly improved OS in all three PD-L1 expression subgroups compared with chemotherapy [(TPS $\geq$50%: 20 vs. 12.2 months, respectively; HR 0.69 (95% CI, 0.56–0.85; $P = 0.0003$); TPS $\geq$20%: 17.7 vs. 13.0 months, HR 0.77 (95% CI, 0.64–0.92; $P = 0.0020$); and TPS $\geq$1%: 16.7 vs. 12.1 months; HR 0.81 (95% CI, 0.71–0.93; $P = 0.0018$)]. However, for the PD-L1 TPS $\geq$1%–49% subpopulation, the OS benefit for pembrolizumab was not statistically significant (13.4 vs. 12.1 months; HR 0.92), indicating that patients whose tumors expressed PD-L1 TPS $\geq$50% [who made up almost half (47%) of the study population] were driving the OS benefit. Consistent with the KEYNOTE-024 study, the frequency of grade $\geq$3 drug-related AEs was substantially lower in the pembrolizumab versus chemotherapy treatment arm (17.8% vs. 41.0%, respectively).

Together, the OS benefit observed in KEYNOTE-024 and KEYNOTE-042 clearly supports the use of pembrolizumab monotherapy as first-line treatment of advanced NSCLC in patients with PD-L1 TPS $\geq$50%. However, the PFS benefit seen in the KEYNOTE-024 study was not replicated in the group of patients with PD-L1 TPS $\geq$50% in the KEYNOTE-042 study. Considerable differences between the two studies in terms of enrollment flow, patient baseline characteristics and median number of chemotherapy cycles likely contributed to differences in the efficacy outcomes (ref. 39; Table 1).

CheckMate 227 was a large study that tested multiple combinations of nivolumab, ipilimumab, and chemotherapy in patients with both squamous and nonsquamous histologies (14). On the basis of their tumor PD-L1 expression level, patients were grouped into one of two study populations, tumor PD-L1 expression $\geq$1% and <1%, and within each of these study population groups, patients were randomized 1:1:1 to nivolumab plus ipilimumab, platinum-based chemotherapy, or nivolumab monotherapy (in the PD-L1 $\geq$1% group) or nivolumab plus platinum-based chemotherapy (in the PD-L1 <1% group). Ipilimumab was administered at 1 mg/kg every 6 weeks continuously, differing from the dosage approved in melanoma in an attempt to improve tolerability. The study protocol was later modified to include a primary endpoint of PFS in the subgroup of patients classified as

Table 1. Demographic and baseline characteristics and survival outcomes in KEYNOTE-024 and KEYNOTE-042

	KEYNOTE-024		KEYNOTE-042	
	Pembrolizumab	**Chemotherapy**	**Pembrolizumab**	**Chemotherapy**
Median age (years)	64.5	66	63	63
Male sex (%)	59.7	62.9	70.6	71
East Asia (%)	13.6	12.6	29	29
ECOG 1 (%)	64.3	64.9	68.9	69.9
Never smokers (%)	3.2	12.6	22.3	22
Squamous (%)	18.8	17.9	38.1	39.1
Number of cycles (median)	10	4	9	6
Median PFS (months)				
• TPS $\geq$50%	10.3	6	7.1	6.4
• TPS $\geq$1%			5.4	6.5
Median OS (months)				
• TPS $\geq$50%	30	14.2	20	12.2
• TPS $\geq$1%			16.7	12.1

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

TMB-high, that is, ≥10 mut/MB (14). Previously, the impact of TMB on outcomes with nivolumab monotherapy in previously untreated metastatic NSCLC was suggested in an exploratory analysis of the CheckMate 026 study (40). High TMB was associated with an increased response rate and longer PFS with nivolumab compared with platinum-based chemotherapy and was independent of tumor PD-L1 expression level. A similar subgroup analysis was performed for the patients receiving nivolumab plus ipilimumab in the CheckMate 568 study (18). This analysis used the FoundationOne CDx assay for TMB assessment and established the ≥10 mut/MB cutoff (TMB-high) applied to the CheckMate 227 study. Of the 1,739 patients enrolled in CheckMate 227, 94.8% had a tumor sample available for the FoundationOne CDx assay, but only 1,004 (57.7%) patients had valid results, reflecting the demanding sample quality and quantity requirements (14). Of these patients, 44.2% were classified as TMB-high (>10 mut/MB; 24.2% of the ITT population).

For the primary endpoint analysis, all patients the allocated to nivolumab plus ipilimumab and chemotherapy arms were pooled irrespective of their tumor PD-L1 expression level (14). Of the 1,166 patients allocated to these treatment arms, 299 ($n =$ 139 receiving nivolumab plus ipilimumab; $n = 160$ receiving chemotherapy) were classified as TMB-high. In this patient population, PFS was significantly longer with nivolumab plus ipilimumab than with chemotherapy [7.2 vs. 5.5 months, HR 0.58 (97.5% CI, 0.41–0.81; $P < 0.001$)]. This PFS benefit with nivolumab plus ipilimumab was observed for all TMB-high patients regardless of the PD-L1 expression level. In the subgroup of patients with low TMB (<10 mut/MB), median PFS was numerically shorter among those receiving nivolumab plus ipilimumab compared with those treated with chemotherapy [3.2 vs. 5.5 months, respectively; HR 1.07 (95% CI, 0.84–1.35)]. The objective response rates among patients with high TMB were 45% and 27% for the nivolumab plus ipilimumab- and chemotherapy-treated groups, respectively (Fig. 3). Moreover, the preliminary median OS in this population favored nivolumab plus ipilimumab [23.0 vs. 16.4 months; HR 0.79 (95% CI, 0.56–1.10; ref. 41)]; however, this was an ad hoc analysis as the study's coprimary OS endpoint included the PD-L1–selected population and has yet to be reported. In an updated analysis, differences in OS between the treatment regimens were not statistically significant in the subgroup of patients with TMB ≥10 mut/Mb, with a HR of 0.77 (95% CI, 0.56–1.06; ref. 42). Rates of grade 3 or 4 treatment-related AEs were similar (31.2% with nivolumab plus ipilimumab and 36.1% with chemotherapy), with the rate of AEs leading to discontinuation higher with nivolumab plus ipilimumab (17.4% vs. 8.9%, respectively). However, the spectrum of AEs between both arms were less comparable, with nausea, anemia, decreased appetite, fatigue, and constipation much more common and severe in the chemotherapy arm, and with immune-mediated AEs such as rash, diarrhea, pruritus, and hypothyroidism more common in the pembrolizumab arm (42).

Discussion

Immunotherapy has changed the therapeutic strategy for the patients with metastatic NSCLC. Nowadays, one of the most common discussions among physicians and their patients are concerns about when they should receive treatment with immunotherapy, alone or in combination with chemotherapy. The only subset of patients with metastatic NSCLC for whom recommendations for first-line treatment do not include immunotherapy are those that have genomic-driven lung cancers, such as *EGFR*-mutant or *ALK*-positive NSCLC; in these patients, first-line treatment with a targeted TKI is recommended, and guidelines for genomic testing in newly diagnosed metastatic NSCLC remain unaltered.

Both the IMpower150 and the IMpower130 studies, which permitted the participation of patients with *EGFR*-mutant and *ALK*-positive tumors previously treated with an appropriate TKI, suggest that after TKIs, a combination of platinum-based chemotherapy, immunotherapy and an angiogenic agent may offer effective immunomodulation. In addition, two dedicated studies are ongoing to examine the role of immunotherapy for the treatment of *EGFR*-mutant NSCLC after progression on an EGFR TKI: the CheckMate 772 study, comparing chemotherapy alone versus chemotherapy plus nivolumab versus nivolumab plus ipilimumab; and the KEYNOTE-789 study, of chemotherapy alone or in combination with pembrolizumab. Furthermore, when transitioning from a highly potent third-generation EGFR TKI (such as osimertinib) to a PD-1/PD-L1 antibody, it is important to recommend an appropriate washout period of at least five half-lives to avoid the potential increase in risk of interstitial lung disease (43).

In newly diagnosed patients with metastatic NSCLC without TKI-sensitizing alterations, PD-L1 protein expression by IHC and TMB may help to identify the subset of patients with metastatic NSCLC for whom the use of chemotherapy can be spared. For the patients with tumor PD-L1 expression of at least 50% and for those classified as TMB-high, pembrolizumab alone and nivolumab plus ipilimumab could be considered as treatment options.

For TKI-pretreated patients with EGFR- or ALK-sensitizing alterations, data from the IMpower150 study suggested a median PFS and OS advantage for the ACPB regimen for (20), but this advantage was not seen in the IMpower130 study using ACnP without bevacizumab, suggesting an immunomodulatory role for bevacizumab. However, additional prospective evidence is needed to confirm this benefit of the ACPB regimen in this subgroup. At this time, chemotherapy remains the preferred therapy for the patients with EGFR/ALK-positive NSCLC who have exhausted their TKI options. When to add PD-1/PD-L1 inhibitors to standard chemotherapy remains an area of debate and further investigation is warranted to evaluate the immunotherapies for this population.

For the patients with nonsquamous histology, the results from three randomized studies showed that the addition of a PD-1/PD-L1 checkpoint inhibitor to standard chemotherapy is superior to standard chemotherapy alone. On this basis, three regimens, that is, platinum plus pemetrexed plus pembrolizumab (KEYNOTE-189), carboplatin plus paclitaxel plus bevacizumab plus atezolizumab (IMpower150), and carboplatin plus nab-paclitaxel plus atezolizumab (IMpower130) can be considered new standard-of-care first-line treatments for previously untreated patients with nonsquamous metastatic NSCLC. Of these, a platinum plus pemetrexed plus pembrolizumab regimen may be favored owing to its better toxicity profile and tolerability for the chemotherapy element of the regimen, together with a larger PFS and OS benefit. More controversial, and requiring prospective confirmation, is the highlighted survival benefit in patients with liver metastases in the IMpower150 study's ACPB arm. Indeed, no comparable subgroup was analyzed for pembrolizumab plus chemotherapy in KEYNOTE-189 and those differences were not found in the

IMpower130 study comparing carboplatin plus nab-paclitaxel with or without atezolizumab, or in the IMpower132 study comparing platinum plus pemetrexed with or without atezolizumab, which failed to meet its coprimary endpoint of improved OS. This again suggests that bevacizumab may be a key contributor to immunomodulation in patients with liver metastasis.

In previously untreated patients with NSCLC of squamous histology, the addition of pembrolizumab to a standard carboplatin-based doublet with paclitaxel or nab-paclitaxel should be considered the new standard of care based on the superior survival outcomes reported in the KEYNOTE-407 study. At this time, this remains the only study positive for OS in the patients with squamous histology.

For the patients with previously untreated metastatic NSCLC of any histology and PD-L1 expression $\geq$50%, treatment with pembrolizumab monotherapy provides superior results than standard chemotherapy, with a more favorable safety profile. Pembrolizumab may be an alternative for the patients with PD-L1 expression of 1%–49% who cannot receive chemotherapy, with the KEYNOTE-042 study showing comparable survival outcomes between chemotherapy and pembrolizumab monotherapy.

Nivolumab plus ipilimumab is an alternative chemotherapy-sparing regimen that may be considered for the patients with previously untreated metastatic NSCLC of any histology and high TMB, as supported by the results from CheckMate 227; however, the toxicity profile of this regimen makes it less attractive than pembrolizumab alone. Furthermore, despite the underpowered nature of the TMB-high endpoint analysis, the OS benefit was not statistically significant for this regimen with longer follow-up (42).

In summary, immunotherapy has dramatically transformed first-line treatment of metastatic NSCLC. As a new cornerstone therapy, immunotherapy with and without chemotherapy is recommended for all patients with metastatic NSCLC without TKI-sensitizing alterations. Some questions regarding the role of immunotherapy in certain subpopulations remain unanswered. For example, should patients unsuitable for chemotherapy with low PD-L1 expression levels and low TMB receive treatment with immunotherapy alone? What is the best sequential treatment after progression on an immunotherapy-containing first-line regimen?

Median OS in most of the studies discussed here approximates to 18 months, which represents an extraordinary achievement for a disease where OS had previously reached a 10- to 12-month plateau for more than two decades prior to the immunotherapy era. Long-term survival rates and ongoing immunotherapy biomarker research will help us to differentiate all current combination options and more accurately customize first-line immunotherapy strategies for metastatic NSCLC.

Disclosure of Potential Conflicts of Interest

S. Peters is a consultant/advisory board member for Abbvie, Amgen, AstraZeneca, Bayer, Biocartis, Boehringer Ingelheim, Bristol-Myers Squibb, Debiopharm, Eli Lilly, Roche, Foundation Medicine, Illumina, Janssen, MSD, Merck Serono, Novartis, PharmaMar, Pfizer, Regeneron, Sanofi, Seattle Genetics, and Takeda, and has provided satellite talks for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Roche, MSD, Novartis, Pfizer, Sanofi, and Takeda. T. Stammers holds ownership interest in AstraZeneca. J.-C. Soria is Senior Vice President of AstraZeneca, holds ownership interest in AstraZeneca and Gritstone, and is a consultant/advisory board member for Astex, Clovis, GlaxoSmithKline, Gamamabs, Lilly, MSD, Mission Therapeutics, Merus, Pfizer, PharmaMar, Pierre Fabre, Roche, Sanofi, Servier, Symphogen, and Takeda. No potential conflicts of interest were disclosed by the other author.

Acknowledgments

This study was supported by MedImmune.

Received November 30, 2018; revised December 24, 2018; accepted January 9, 2019; published first January 14, 2019.

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