

Keeping Pace with Immunotherapy Advances in NSCLC: Global Perspectives

Management of non-small cell lung cancer (NSCLC) has traditionally been done with systemic cytotoxic chemotherapy, and in the 40% of patients who present with metastatic disease, the goals are to prolong survival and maintain quality of life while minimizing side effects.¹ In recent years, many phase 3 clinical trials have provided evidence that supports the use of molecularly targeted therapies for first- and subsequent-line treatment in this population.² In patients newly diagnosed with metastatic NSCLC, routine testing for expression of programmed cell death ligand 1 (PD-L1) is recommended as a way to guide selection of first-line therapy, especially in combination with testing for the presence of driver mutations such as *EGFR*, *ALK*, and *BRAF* that might impact therapy choice.³⁻⁸

Tumor mutation burden (TMB) is a promising new biomarker that is being investigated.⁹ Some tumors that have a high rate of mutations, such as NSCLC, appear to respond better to immunotherapy.^{9,10} One exogenous factor associated with high TMB in lung cancer is smoking.¹¹ TMB can be assessed through whole exome sequencing or targeted next-generation sequencing (NGS).¹² While outcomes in NSCLC in relationship to TMB have been studied in several clinical trials of immunotherapies, it has not yet been validated as a biomarker for clinical use.⁹ As our understanding of the biology of lung tumors grows and more key mutations are identified, the importance of molecular testing for directing therapy for metastatic NSCLC will be increasingly supported.¹

Factors for Selection of First-Line Therapies

Immunotherapy plus chemotherapy is now the first-line treatment of choice for metastatic NSCLC, with the specific combination typically dependent on the level of PD-L1 expression in a patient's tumor and in keeping with guidelines from the American Society of Clinical Oncology (ASCO) and Ontario Health.¹³ For patients with <50% expression of PD-L1, chemotherapy plus platinum-doublet chemotherapy is standard, whereas pembrolizumab alone is standard for those whose tumors have ≥50% expression of PD-L1.¹³ If *EGFR* mutations or *ALK* or *ROSL1* translocations are present, a specific tyrosine kinase inhibitor (TKI) should be used.¹⁴ TKIs may also be appropriate for patients whose tumors carry *BRAF* mutations.

When selecting treatment, the potential for immunotherapy side effects, such as the high risk of the development of pneumonitis, and the impact of prior treatments in other settings, such as adjuvant therapies or treatment for locally advanced disease, should be taken into consideration. Determination of whether to start treatment immediately or wait for results of next-generation sequencing should be based on an assessment of the tumor's aggressiveness as reflected on imaging studies and in histologic analysis combined with consideration of the severity of the patient's symptoms.

Current and Emerging Immunotherapy Options

Based on outcomes demonstrated in several phase 3 trials in recent years, pembrolizumab has replaced cytotoxic chemotherapy as the treatment of choice in first-line therapy for patients with NSCLC whose tumors have a high expression of PD-L1. Results of the KEYNOTE-189 trial, published in 2018, showed

that in patients with previously untreated metastatic NSCLC, regardless of PD-L1 expression, adding pembrolizumab to standard chemotherapy with pemetrexed and a platinum-based drug produced significantly longer overall survival (OS) and progression-free survival (PFS) than chemotherapy alone (Table 1).¹⁵⁻¹⁷

Table 1. Overall Survival (OS) and Hazard Ratio (HR) Based on PD-L1 Status in NSCLC

KEYNOTE-189

<u>Measurement</u>	<u>Regimen</u>
	<u>Pembrolizumab + Chemotherapy vs. Placebo + Chemotherapy</u>
<u>PD-L1 status: <1%</u>	
% OS at 12 months:	61.7% 52.0% <u>HR (risk of death) = 0.59 (95% CI, 0.38-0.92)</u>
% OS at 24 months:	38.5% 15.5% <u>HR (risk of death) = 0.52 (95% CI, 0.36-0.74)</u>
<u>PD-L1 status: 1%-49%</u>	
% OS at 12 months:	71.5% 50.9% <u>HR (risk of death) = 0.55 (95% CI, 0.34-0.90)</u>
% OS at 24 months:	44.3% 33.0% <u>HR (risk of death) = 0.62 (95% CI, 0.42-0.92)</u>
<u>PD-L1 status: >50%</u>	
% OS at 12 months:	73.0% 48.1% <u>HR (risk of death) = 0.42 (95% CI, 0.26-0.68)</u>
% OS at 24 months:	51.9% 39.4% <u>HR (risk of death) = 0.59 (95% CI, 0.39-0.88)</u>
<u>Total population</u>	
% OS at 24 months:	45.5% 29.9% <u>HR (risk of death) = 0.56 (95% CI, 0.45-0.70)</u>

Data were derived from Gandhi L, et al. *N Engl J Med.* 2018;378(22):2078-2092; Gadgeel S, et al. *J Clin Oncol.* 2020;38(14):1505-1517.

Updated results from KEYNOTE-189 were presented at the ASCO conference in 2019.¹⁸ A further update was published by Gadgeel and colleagues in 2020 with a median follow-up of 24 months; these latter data are also presented in Table 1 for comparison to the 12-month OS data published in 2018.¹⁷ The ongoing OS benefit (Table 1) was reported in all PD-L1 subsets, including patients whose tumors expressed <1% PD-L1. These benefits accrued regardless of liver or brain metastases and with manageable safety and tolerability.¹⁷ For comparison to the data segmented by percent PD-L1 expression, data for OS at 24 months for the total population is also provided in Table 1.

In patients with previously untreated advanced NSCLC and PD-L1 expression of at least 50% of tumor cells in the KEYNOTE-024 trial, pembrolizumab was associated with significantly longer PFS and OS (hazard ratio [HR]=0.60; 95% CI, 0.41-0.89; $P=0.005$) and with fewer adverse events than was platinum-based chemotherapy. In KEYNOTE-042, OS was significantly longer in the pembrolizumab group than in the chemotherapy group in all three PD-L1 status populations ($\geq 50\%$; $\geq 20\%$; and $\geq 1\%$; HR=0.69; 0.77; and 0.81, respectively; $P=0.0003$; 0.0020; and 0.0018, respectively).¹⁹

Other options available for anti-PD-L1 therapy in metastatic NSCLC include combinations with atezolizumab, nivolumab, and ipilimumab.

In the phase 3 IMpower150 trial, adding atezolizumab to bevacizumab plus carboplatin plus paclitaxel (ABCP) significantly improved survival in patients with metastatic NSCLC, regardless of PD-L1 expression and *EGFR* or *ALK* status.²⁰ Median PFS was 8.3 months in the ABCP group versus 6.8 months in the group that only received BCP (HR=0.62; 95% CI, 0.52-0.74; $P<0.001$). Median OS was 19.2 months in the ABCP group versus 14.7 months in the BCP group (HR=0.78; 95% CI, 0.64-0.96; $P=0.02$).²⁰ Atezolizumab was also studied in the phase 3 IMpower130 trial, which showed a significant and clinically meaningful improvement in OS and a significant improvement in PFS with the drug in combination with carboplatin plus paclitaxel versus chemotherapy alone.²¹ In the group that received atezolizumab, median OS was 18.6 months versus 13.9 months with chemotherapy alone. Median PFS was 7.0 months with the addition of atezolizumab versus 5.5 months in the chemotherapy group ($P<0.0001$).²¹ No new safety signals were identified.

The combination of nivolumab plus ipilimumab was studied in the phase 3 CheckMate 227 trial in patients with stage IV or recurrent NSCLC and PD-L1 expression $\geq 1\%$.²² First-line treatment with the combination resulted in longer OS than chemotherapy alone (17.1 months versus 14.9 months; $P=0.007$), independent of PD-L1 expression level. At 2 years, the response rate was 49% with nivolumab plus ipilimumab versus 11% with chemotherapy.²² An analysis of patient-reported outcomes from CheckMate 227 showed improvements in symptom burden with nivolumab plus ipilimumab.²³ Symptom deterioration by week 12 was lower with the combination versus chemotherapy (22.3% versus 35.0%; absolute risk reduction: 12.7% [95% CI, 2.4-22.5]) regardless of discontinuation.²³ On May 15, 2020, the US Food and Drug Administration (FDA) approved the combination of nivolumab plus ipilimumab as first-line treatment for patients with metastatic NSCLC whose tumors express PD-L1 $\geq 1\%$, as determined by an FDA-approved test, with no *EGFR* or *ALK* or genomic tumor aberrations.²⁴

Research is ongoing on other immunotherapy combinations for first-line treatment of metastatic NSCLC. For example, the PD-L1 inhibitor durvalumab was studied in the phase 3 MYSTIC trial, which was conducted in 203 cancer treatment centers in 17 countries.²⁵ Patients with previously untreated metastatic NSCLC with no *EGFR* or *ALK* mutations received durvalumab, durvalumab plus tremelimumab, or platinum-based doublet chemotherapy. The trial did not meet its primary endpoints.

Exploratory analyses identified a blood tumor mutational burden of ≥ 20 mutations per megabase for optimal OS benefit with durvalumab plus tremelimumab.²⁵ A similar negative outcome was seen for nivolumab in the first-line treatment of stage IV or recurrent NSCLC in the phase 3 CheckMate 026 trial.²⁶ OS was similar in patients who received nivolumab and those treated with platinum-based chemotherapy, and no benefit in PFS was seen with the PD-L1 inhibitor.²⁶

Tumor Mutation Burden and Immunotherapy Efficacy

One of the most important emerging biomarkers in the armamentarium for metastatic NSCLC is TMB, or the total number of nonsynonymous mutations in a tumor.^{9,27} A study of whole-genome sequencing of NSCLC treated with pembrolizumab showed that higher TMB was associated with improved objective response, durable clinical benefit, and PFS.³ Drawbacks to clinical use of TMB as a biomarker are the need for additional tissue for testing, lengthy turnaround time for results, and the lack of standardization and validation of assays and an accepted definition of TMB.^{9,27} TMB is also not currently included in algorithms from the National Comprehensive Cancer Network.

The relationship between TMB and outcomes with immunotherapy agents for metastatic NSCLC has been investigated in several clinical trials. In CheckMate 026, nivolumab improved PFS in patients with high tumor load compared to chemotherapy.²⁶ In CheckMate 227, combining PD-L1 expression and level did not identify a subgroup with increased benefit for nivolumab plus ipilimumab versus chemotherapy alone.²² In the MYSTIC study of durvalumab plus tremelimumab, TMB ≥ 10 but not < 10 was associated with numerically longer OS in both immunotherapy groups compared to chemotherapy.²⁵

KEYNOTE-158, in which pembrolizumab was studied, demonstrated an anti-PD-L1 benefit in patients with high microsatellite instability/mismatch repair deficiency.²⁸ The FDA recently approved and expanded pembrolizumab's tumor-agnostic indication using TMB-high (TMB-H) as a biomarker to identify eligible patients with refractory solid tumors.²⁹

Conclusion

For first-line therapy in metastatic NSCLC, anti-PD-L1 therapies are the standard of care. Given the expanding evidence from clinical trials about existing agents and the ongoing development of new agents in this category, clinicians face challenges in determining how to optimize treatment for individual patients. Histology, presence or absence of driver mutations, and factors such as an individual's age and comorbidities should all be considered when determining choice of therapy for an individual. Testing for PD-L1 expression should be performed in newly diagnosed patients. Current evidence indicates that pembrolizumab is the treatment of choice for tumors with high PD-L1 expression, whereas a platinum-based chemotherapy doublet plus immunotherapy is appropriate for tumors with low or intermediate PD-L1 expression. The promise of TMB as a biomarker for response to immunotherapy has recently been validated by the FDA's approval and expansion of pembrolizumab's tumor-agnostic indication using TMB-high (TMB-H) as a biomarker to identify eligible patients with refractory solid tumors.

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