Immunotherapeutic Advances in the Treatment of Metastatic Non-Small Cell Lung Cancer

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Abstract

Lung cancer remains the leading cause of cancer-related mortality in the United States. Most patients are diagnosed with advanced disease, and while progress has been made in targeted therapy, very few changes in the platinum backbone have been made for those patients without actionable mutations or PD-L1 positivity. The utilization of immunotherapy in advanced non–small cell lung cancer (NSCLC) has completely altered the approach to treating this disease. Within less than two years, multiple agents have been FDA approved for the treatment of second-line therapy in metastatic NSCLC. Even more recently, a PD-1 antibody was approved for the first-line treatment of metastatic NSCLC in patients whose tumors have ≥50% PD-L1 expression. Multiple immunotherapeutics are being evaluated in combinations, sequences, and various stages in the treatment of all lung cancer. These immunotherapeutic advances have shifted a long-term paradigm in lung cancer treatment.

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Background

Lung cancer is the leading cause of cancer-related mortality in the United States[1]. Most patients with newly diagnosed non–small cell lung cancer (NSCLC) have incurable disease. For decades, standard first-line treatment for metastatic NSCLC (mNSCLC) has been platinum-doublet chemotherapy with anticipated response rates (RR) of about 30% and median overall survivals (mOS) of 10 to 12 months.[2] Second-line chemotherapy with single-agent docetaxel has anticipated RR around 5% to 10% with mOS of 7 months.[3] The identification of driver mutations such as *EGFR*, *ALK* and *ROS1* has led to the approval of multiple agents targeting these specific tumor alterations, resulting in improved RR and even mOS with fewer toxicities when compared with chemotherapy. Acquired resistance limits next-line treatment options. Additionally, the frequency of these mutations is low and broader applications of novel interventions for all NSCLC has been prioritized.

The capacity of the host immune system to disrupt tumors is not a new concept. However, prior immunological approaches to the treatment of lung cancer were not successful. With the introduction of checkpoint inhibitors, immunotherapy re-emerged as a potential intervention in lung cancer.

Programmed cell death 1 (PD-1) is a type I transmembrane protein expressed on the surface of activated T cells. When PD-1 binds to one of its ligands (PD-L1 or PD-L2), T-cell activity is downregulated. Tumor cells can express PD-L1, and interaction with PD-1 on T cells can enable tumor growth via immune evasion. New immunotherapies block the binding of PD-1 and PD-L1, allowing ongoing activation of T cells.

Within 18 months, three different checkpoint inhibitors were FDA-approved with multiple indications in mNSCLC (**Table 1**). These unprecedented advances have led to a completely different approach to mNSCLC treatment.

First-line Treatment

Although different immunotherapies had already proven similar benefits in the second-line setting, phase 3 data on two agents in the first-line treatment of mNSCLC yielded very different results.

KEYNOTE-024 is the pivotal trial that led to the first FDA approval of immunotherapy in first-line treatment of patients with mNSCLC.[4] Of 1934 patients screened, 305 with previously untreated mNSCLC with ≥50% PD-L1 expression on tumor cells by immunohistochemistry (IHC) and without *EGFR* mutation or *ALK* rearrangement were randomized to pembrolizumab (Keytruda) 200 mg every 3 weeks versus investigator-choice platinum-based doublet chemotherapy.

Patients in control arm could cross over to pembrolizumab at progression. Progression free survival (PFS), the primary endpoint, was 10.3 months with pembrolizumab versus 6 months with chemotherapy, including 43.7% of patients who crossed over to pembrolizumab (HR, 0.50; P <.001). Six-month OS was 80.2% with pembrolizumab compared with 72.4% with chemotherapy (HR, 0.60; P <.005). Overall RR was also higher with pembrolizumab (45% versus 28%), and median duration of response (DoR) was longer with pembrolizumab (not reached versus 6.3 months). Pembrolizumab was better tolerated with 27%

of patients experiencing grade 3 to 5 treatment-related toxicities compared with 53% of patients receiving chemotherapy. Based on these results, the FDA approved pembrolizumab in October 2016 as first-line treatment in patients with mNSCLC whose tumors have ≥50% PD-L1 expression and no *EGFR* or *ALK* genomic tumor aberrations. These significant results changed the multi-decade-old treatment paradigm in first-line mNSCLC, offering an effective and tolerable treatment for approximately 30% of the patients with high PD-L1 expressing tumors.

Nivolumab, an IgG4 anti–PD-1 monoclonal antibody, failed to meet expectations in the same setting. CheckMate 026 randomized 541 patients for first-line treatment of mNSCLC with PD-L1-positive tumors (≥ 5% expression by IHC) to nivolumab 3 mg/kg every 2 weeks versus investigator-choice platinum-based doublet chemotherapy.[5] The study did not meet its primary endpoint of PFS (4.2 months with nivolumab versus 5.9 months with chemotherapy; HR, 1.15; P = .25), including 60% of patients who crossed over to nivolumab. One-year PFS was 23.6% versus 23.2%, respectively. In patients with PD-L1 tumor expression >5%, OS was 14.4 months with nivolumab versus 13.2 months

TABLE. Important Immunotherapy Clinical Trials in mNSCLC

Trial	Agent	Study Design	# of Patients	ORR (%)	mPFS (mos)	mOS (mos)	G 3-4 Tox (%)
First line							
KEYNOTE-024		Phase 3, mNSCLC with PD-L1 ≥50%	305				
	Pembrolizumab 200 mg		154	45	10.3	NR	27
	Platinum-doublet chemo		151	28	6	NR	53
Second line							
CheckMate 017		Phase 3, squamous mNSCLC, platinum refractory	272				
	Nivolumab 3 mg/m^2		135	20	3.5	9.2	7
	Docetaxel 75 mg/m^2		137	9	2.8	6	55
CheckMate 057		Phase 3, non-squamous mNSCLC, platinum refractory	582				
	Nivolumab 3 mg/kg		292		2.3	12.2	10
	Docetaxel 75 mg/m^2		290		4.2	9.4	54
KEYNOTE-001	Pembrolizumab	Phase 1, mNSCLC	495	19.4		12	
KEYNOTE-010		Phase 2/3, mNSCLC	1034				
	Pembrolizumab 2 mg/kg		345		3.9	10.4	13
	Pembrolizumab 10 mg/kg		346		4	12.7	16
	Docetaxel 75 mg/m^2		343		4	8.5	35
POPLAR		Phase 2, mNSCLC, platinum refractory	287				
	Atezolizumab 1200 mg		144			12.6	11
	Docetaxel 75 mg/m^2		143			9.7	39
OAK		Phase 3, mNSCLC, platinum refractory	1225 (850 analyzed)				
	Atezolizumab 1200 mg			13.6	2.8	13.8	15
	Docetaxel 75 mg/m^2			13.4	4	9.6	43

Chemo indicates chemotherapy; G, grade; mNSCLC, metastatic non-small cell lung cancer; mOS, median overall survival; mos, months; mPFS, media progression-free survival; NR, not reached; ORR, overall response rate; Tox, toxicity.

with chemotherapy. Overall RR was not higher with nivolumab (26% versus 34%), although those who did respond, median DoR was longer with nivolumab (12.1 versus 5.7 months). Nivolumab was well tolerated with 18% grade 3/4 treatment-related toxicities compared with 51% with chemotherapy. Interestingly and quite surprisingly, subgroup analysis of those patients with PD-L1 tumor expression ≥50% did not show significantly improved PFS or OS.

Other immunotherapeutics including anti-PD-L1 antibodies atezolizumab and durvalumab are being evaluated in first-line treatment for mNSCLC.

Second-line Treatment

Immune checkpoint inhibitors were first approved in mNSCLC in the second-line setting. Currently two PD-1 inhibitors and one PD-L1 inhibitor are FDA-approved as second-line treatment with varied indications in mNSCLC.

Two large phase 3 randomized trials were conducted comparing nivolumab 3 mg/kg every 2 weeks to docetaxel 75 mg/m^2 every 3 weeks in mNSCLC, one in squamous histology (CheckMate 017)[6] and another in non-squamous histology (CheckMate 057).[7] CheckMate-017 randomized 272 patients with squamous mNSCLC with disease progression on platinum-based doublet chemotherapy to either nivolumab or docetaxel. Primary endpoint OS was improved with nivolumab (9.2 versus 6 months; HR, 0.59; 95% CI 0.44-0.79). RR was higher with nivolumab, 20% versus 9%. Eighty-three percent of patients had quantifiable PD-L1 expression on archived tumor tissue. Expression of PD-L1 was neither prognostic nor predictive of efficacy in patients with squamous NSCLC. Nivolumab was well tolerated with 7% grade 3/4 toxicities compared with 55% in docetaxel group. Based on these results, in March 2015, FDA approved nivolumab for squamous mNSCLC with disease progression after first-line chemotherapy.

CheckMate-057 randomized 582 patients with non-squamous mNSCLC whose disease failed platinum-based doublet chemotherapy to nivolumab or docetaxel. Median OS, primary endpoint, was prolonged with nivolumab compared with docetaxel (12.2 versus 9.4 months; HR, 0.73; 95% CI 0.59-0.89).

Nivolumab demonstrated superior 1-year and 18-month survival rates (51% versus 39% and 39% versus 23%, respectively). PD-L1 expression was measured on archived samples in 78% of patients; unlike the squamous trial, PD-L1 expression was predictive of response to nivolumab with trend toward higher RR as PD-L1 expression level increased. Nivolumab was well tolerated with 10% grade 3/4 toxicities compared with 54% with docetaxel. In October 2015, nivolumab received FDA approval for all patients with non-squamous mNSCLC whose disease progressed after first-line platinum-based chemotherapy.

KEYNOTE-001 is a phase 1 study of 495 evaluable patients with mNSCLC to determine safety, side-effect profile, and antitumor activity of pembrolizumab.[8] Unlike the CheckMate trials, patients were required to have biopsy-proven PD-L1 expression and previously untreated patients were also allowed to enroll. Overall RR was 19.4%, including RR of 18% in 394 previously treated patients and 24.8% in 101 previously untreated patients. Additionally, in 61 previously treated patients with ≥ 50% PD-L1 tumor expression, RR was 41%. In addition to the frontline, FDA granted accelerated approval to pembrolizumab for the treatment of patients with mNSCLC whose tumors express PD-L1 on ≥50% of all cells with disease progression after platinum-containing chemotherapy.

KEYNOTE-010 is a phase 2/3 study of 1034 patients with mNSCLC who received either pembrolizumab 2 mg/kg or 10 mg/kg or docetaxel 75 mg/m^2 every 3 weeks.[9] Primary endpoints were OS and PFS, both in the total population and in patients with ≥50% PD-L1 tumor expression. Median OS was significantly longer with pembrolizumab 2 mg/kg at 10.4 months (HR, 0.71; 95% CI, 0.58-0.88; P = .0008) and with pembrolizumab 10 mg/kg at 12.7 months (HR, 0.61; 95% CI, 0.49-0.75; P <.0001) compared with 8.5 months with docetaxel. Median PFS was not significantly different with either pembrolizumab 2 mg/kg (3.9 months) or pembrolizumab 10 mg/kg (4 months) compared with docetaxel (4 months). Among patients with ≥50% PD-L1 tumor expression, mOS was significantly longer with pembrolizumab 2 mg/kg at 14.9 months (HR, 0.54; 95% CI, 0.38-0.77; P = .0002) and pembrolizumab 10 mg/kg at 17.3 months (HR 0.50; 95% CI 0.36-0.70; P <.0001) compared with 8.2 months with docetaxel. PFS was significantly longer with both pembrolizumab dosing groups (5 and 5.2 months) versus docetaxel (4.1 months). The researchers reported that pembrolizumab was well tolerated with 13% to 16% grade 3/4 treatment-related toxicities compared with 35% in the docetaxel group.

POPLAR[10] is an open-label, phase 2 trial of 287 patients with mNSCLC who failed platinum-based chemotherapy randomized to atezolizumab 1200 mg or docetaxel 75 mg/m^2 every 3 weeks. Primary endpoint was met with OS of 12.6 months with atezolizumab versus 9.7 months with docetaxel (HR, 0.73; 95% CI, 0.53–0.99; P = .04). Patients were stratified based on percentage of PD-L1-expressing tumor cells (TC) by IHC to TC3 ≥50%, TC2 ≥5% and <50%, TC1 ≥1% and <5%, and TC0 <1% and percentage of tumor-infiltrating immune cells (IC) to IC3 ≥10%, IC2 ≥5% and <10%, IC1 ≥1% and <5%, and IC0 <1%. Increasing improvement in OS was associated with increasing PD-L1 expression. Atezoluzumab was well tolerated with 11% treatment-related grade 3/4 toxicities compared with 39% patients in the docetaxel group.

OAK,[11] a randomized phase 3 study comparing atezolizumab with docetaxel in previously treated mNSCLC, confirmed the efficacy of atezolizumab seen in POPLAR. In the trial, 1225 patients stratified by PD-L1 status, prior chemotherapy regimens, and histology were randomized to atezolizumab 1200 mg every 3 weeks or docetaxel 75 mg/m^2 every 3 weeks. Co-primary

endpoints were OS in the entire study population and in a PD-L1-defined subgroup. Secondary endpoints included PFS, ORR, DoR and safety. Within 850 evaluable patients, mOS was 13.8 months with atezolizumab versus 9.6 months with docetaxel (HR, 0.74; 95% CI, 0.62-0.87; *P* = .0003). Survival was improved regardless of PD-L1 expression levels, including in patients with no PD-L1 expression (TC0 and IC0) (HR, 0.82; 95% CI, 0.68– 0.98). However, there was pronounced benefit in patients with high PD-L1 expression (TC3 or IC3; HR, 0.41; 95% CI, 0.27– 0.64). The benefit was consistent across histologic subgroups, smoking status, or baseline brain metastasis status. PFS was 2.8 versus 4.0 months, ORR was 13.6% versus 13.4%, and DoR was 16.3 versus 6.2 months for atezoluzumab versus docetaxel, respectively. Atezolizumab was well tolerated with 15% grade 3/4 toxicities compared with 43% in docetaxel group. Atezolizumab was approved by the FDA in October 2016 for treatment of mNSCLC progressing after platinum-containing chemotherapy irrespective of PD-L1 status.

Combination Treatment

Combination of immunotherapies such as PD-1/PD-L1 inhibitors with anti–CTLA-4 antibodies is being evaluated in both first- and next-line mNSCLC treatment. CheckMate-227 is an open-label randomized phase 3 trial investigating nivolumab or nivolumab plus ipilumumab versus platinum-doublet chemotherapy in patients with chemotherapy-naïve mNSCLC.[12] MYSTIC is a phase 3 trial evaluating durvalumab or durvalumab plus tremelimumab versus chemotherapy as first-line therapy for mNSCLC.[13] ARCTIC is a phase 3
trial evaluating durvalumab or tremelimumab alone or durvalumab plus tremelimumab versus chemotherapy in PD–L1–negative patients after at least 2 lines of chemotherapy.[14]

Another active area of research is combining immunotherapy with chemotherapy. Multiple ongoing trials are combining PD-1/PD-L1 inhibitors or anti–CTLA-4 antibodies with chemotherapy. KEYNOTE-021 is a phase 2 multi-cohort study of pembrolizumab combination therapies in mNSCLC.[15] One cohort included treatment with four cycles of carboplatin-pemetrexed-pembrolizumab followed by 24 months of pembrolizumab and indefinite pemetrexed maintenance or four cycles of carboplatin-pemetrexed followed by pemetrexed maintenance. RR was 55% with pembrolizumab combination compared with 29% with chemotherapy alone. RR was 57% in patients with <1% PD-L1 expression while RR was 80% in patients with ≥50% PD-L1 expression. This treatment combination may be effective and tolerable and is being evaluated in a phase 2 study. Multiple phase 3, multicenter, randomized open-label studies are evaluating atezolizumab in combination with platinum-based chemotherapy or chemotherapy plus bevacizumab.[16]

Patient Selection

As indicated by the variability in results with different agents and different PD-L1 tumor expression levels, appropriate identification of those patients most likely to garner responses to those agents has been challenging. Regardless of assay or treating agent, high expression of PD-L1 is associated with better response. However, PD-L1 may be an imperfect surrogate marker, as levels may be affected by intra-tumoral heterogeneity, dynamic expression, and assay variability. Interestingly, some patients with no PD-L1 expression benefit from immunotherapy, suggesting another mechanism for response. Current evidence supports use of PD-L1 assay to guide management until a better biomarker is identified. Higher somatic nonsynonymous mutation burden in tumors was associated with better response to PD-L1 therapy than total mutation burden, indicating that neoantigens likely associated with smoking might play an important role in response to therapy.[17] Higher RRs were observed in patients with history of smoking across multiple studies[1,6] with response rates up to 30% in patients with ≥5 pack-year tobacco history compared with no response in patients with <5 pack-year tobacco history.[18] This continues to be an area of active research and debate.

Conclusion

The field of immunotherapy in lung cancer treatment is evolving rapidly. Although lung cancer was previously thought to be non-immunogenic, immunotherapy has shown durable responses with fewer side effects compared with traditional chemotherapy in treatment of mNSCLC. Although PD-L1 expression has been associated with better response to therapy, other biomarkers such as mutational load need further investigation for improved patient selection. Additional studies are underway evaluating combinations and sequences of checkpoint inhibitors with chemotherapy and other immunotherapies that will continue to evolve the treatment landscape of lung cancer.

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