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ADVANCES IN ONCOLOGY

Optimal Front-Line Therapy for Non-Oncogene-Driven Non-Small Cell Lung Cancer

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KEY POINTS

- Immunotherapy has significantly improved survival outcomes in patients with metastatic non-small cell lung cancer (NSCLC) over the last decade.
- Although imperfect, programmed death-ligand 1 (PD-L1) expression remains the best biomarker for prediction of response to immunotherapy.
- Although treatment decisions for metastatic NSCLC can be made based on PD-L1 expression, there are no head-to-head comparisons of immune checkpoint inhibitor (ICI) regimens to definitively demonstrate superiority of one regimen over another.
- ICIs generally cause adverse events by overstimulating the immune system to act on nonmalignant cells. These toxicities are generally treated with immunotherapy cessation and immune suppression.
- Retrospective studies highlight KRAS mutations, STK11 mutations, and KRAS/STK11 co-mutations as both prognostic and predictive biomarkers of benefit from immunotherapy in NSCLC.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death in the United States and worldwide [1,2]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer (85%) as opposed to small cell lung cancer (15%), and adenocarcinoma is the most common NSCLC histology [3]. Identification of oncogenic driver mutations, particularly in adenocarcinoma, and treatment with targeted therapies significantly improved outcomes for NSCLC for patients whose tumors have mutations. Until 2016, most treatments for NSCLC without mutations included cytotoxic chemotherapy, resulting in a median overall survival (OS) of 7.9 months [4]. Some advances, such as targeting vascular endothelial growth factor and including maintenance chemotherapy, pushed OS beyond 1 year for adenocarcinoma histology [5,6]. In addition to the discovery of more mutations and development of targeted therapies, there have been breakthroughs in the understanding of lung cancer biology, and this has shifted the treatment paradigm toward immunotherapy.

The discovery of how tumors evade the immune system has changed cancer treatment significantly [7]. T cells play a primary role in the elimination of malignant cells. To activate a T cell, a second signal in addition to the T-cell receptor engaging with the antigen is needed.

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Inhibitory checkpoints, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), and the programmed cell death protein 1 (PD-1) axis are known to play a role in NSCLC. CD4-positive and CD8-positive T lymphocytes typically express CTLA-4, whereas PD-1 is expressed on natural killer cells, B cells, and T cells. CTLA-4 acts as an early inhibitor of T-cell activation, whereas PD-1 helps regulate immune tolerance [8]. PD-1 is most upregulated on T cells overwhelmed by antigen. Programmed death-ligand 1 (PD-L1) is the ligand for PD-1, and the interaction between PD-L1 and PD-1 leads to the inactivation of T cells [9]. When T cells are overwhelmed by cancer, they upregulate the expression of PD-1 and CTLA-4 and T-cell activity becomes suppressed. Therapy directed against PD-1, PD-L1, and CTLA-4 is expected to boost T cells back into action so they can rid the body of tumor cells (TCs) [10].

In the setting of metastatic NSCLC, many immune checkpoint inhibitors (ICIs) have been approved for treatment based on demonstrated improvements in survival. The Food and Drug Administration (FDA) has approved PD-1 inhibitors pembrolizumab, nivolumab, and cemiplimab, PD-L1 inhibitors atezolizumab and durvalumab, and CTLA-4 inhibitors ipilimumab and tremelimumab as monotherapy, in combination with chemotherapy or in combination with each other in the treatment of NSCLC (Tables 1 and 2).

PROGRAMMED DEATH-LIGAND 1 ASSAYS

PD-L1 is expressed on both TCs and immune cells (ICs) that infiltrate the tumor [7]. Measuring PD-L1 expression can serve as a predictor for response to immunotherapy. The FDA has approved three different types of assays for testing PD-L1 expression via immunohistochemistry (IHC). These assays are approved as companion diagnostics which make them essential for the proper use of a corresponding immunotherapy drug. The Dako 22C3 assay is approved for use with pembrolizumab, the Ventana SP142 assay is approved for use with atezolizumab, and the Dako 28-8 assay is approved for use with ipilimumab and nivolumab, all in NSCLC (other solid cancers as well) [7]. Complementary diagnostics are helpful in deciding to use a certain drug but are not required to give the drug. In patients with metastatic NSCLC, the Ventana SP263 and 28-8 assays are complementary diagnostics for the use of nivolumab [7]. The Blueprint PD-L1 Comparability Project evaluated five PD-L1 assays and concluded that 22C3, 28-8, and SP263 were comparable sensitivity for detecting PD-L1 on TCs and it is likely that these can be used interchangeably [11]. SP142 had lower sensitivity.

PD-L1 assays can be reported as tumor proportion score (TPS) or combined positive score (CPS). TPS is calculated by dividing the number of viable TCs with at least partial expression of PD-L1 by all viable TCs and then multiplying that fraction by 100%. CPS is determined by dividing the number of viable tumor and ICs with at least partial PD-L1 expression by the total quantity of viable TCs and then multiplying that fraction by 100. TC is the equivalent of TPS. All studies mentioned in this review used TPS scores with the exception of the atezolizumab studies which used TC and IC.

TUMOR MUTATIONAL BURDEN

Tumor mutational burden (TMB) may serve as another potential biomarker to predict response to immunotherapy. TMB is calculated by dividing the number of non-synonymous missense mutations by megabases in the tumor genome as determined by the next-generation sequencing [12]. It is thought that TMB is proportional to the number of tumor antigens and therefore would increase presentation of cancer cells and subsequent elimination. Clinical trial survival data are inconsistent regarding the benefits of TMB, and therefore, TMB is not currently used as a biomarker for selecting immunotherapy treatments.

APPROACH TO ADVANCED NON-SMALL CELL LUNG CANCER

Biomarker testing has become essential for patients diagnosed with metastatic NSCLC to personalize treatments for the best outcomes based on biomarkers identified. Required testing includes driver mutations and PD-L1. FDA-approved targeted therapy treatment is often indicated in the first-line setting when a driver mutation is identified, depending on the specific mutation. Many targeted therapy treatments have been shown to be more effective than chemotherapy or immunotherapy. Mutations where first-line targeted therapy is indicated include *EGFR* mutations, *ALK* rearrangements, *ROS1* rearrangements, the *BRAF V600*E mutation, *NTRK* 1/2/3 gene fusions, the *METex14* skipping mutations, and *RET* rearrangements [8]. Most clinical trials that have led to the approval immunotherapy in the treatment of NSCLC have excluded patients with *EGFR* and *ALK* mutations. Retrospective and some prospective studies show that the use of immunotherapy for NSCLC with targetable mutations has limited efficacy and increased toxicity when combined with tyrosine kinase inhibitors [13–15]. One notable exception is *KRAS*, the most common mutation occurring in lung adenocarcinoma,

TABLE 1
Landmark Clinical Trials Regarding Immune Checkpoint Inhibitors in the Treatment of Metastatic Non-small Cell Lung Cancer

Trial	Date Published	Histology	PD-L1 Inclusion Criteria	PD-L1 Assay	Experimental Arm	Control Arm	Median PFS (Months, Experimental vs Control)	Median OS (Months, Experimental vs Control)	Adverse Events (Experimental vs Control)
Single-Agent Immunotherapy									
KEYNOTE-024 [30]	November 2016	All	≥50%	PD-L1 IHC 22C3 pharmDx assay	Pembrolizumab	Platinum-based chemotherapy	10.3 vs 6	30 vs 14.2	Any: 73.4% vs 90%
CheckMate 026 [28]	June 2017	All	≥1%	Anti-PD-L1 antibody (28–8 antibody)	Nivolumab	Platinum-based chemotherapy	4.2 vs 5.8[a] (all) 5.4 vs 5.8[a] (PD-L1≥50%) 4.2 vs 5.9[a] (PD-L1≥5%)	13.7 vs 13.8[a] 15.9 vs 13.9[a] (PD-L1≥50%) 14.4 vs 13.2[a] (PD-L1≥5%)	Any: 71% vs 92%
KEYNOTE-042 [32]	May 2019	All	≥1%	PD-L1 IHC 22C3 pharmDx assay	Pembrolizumab	Platinum-based chemotherapy	7.1 vs 6.4 (PD-L1≥50%) 6.2 vs 6.6 (PD-L1≥20%) 5.4 vs 6.5 (PD -L1≥1%)	20 vs 12.2 (PD-L1≥50%) 17.7 vs 13 (PD-L1≥20%) 16.7 vs 12.1 (PD-L1≥1%)	Any: 63% vs 90%
IMpower110 [26]	October 2020	All	≥1%	SP142 IHC assay	Atezolizumab	Platinum-based chemotherapy	8.1 vs 5 (PD-L1≥50%) 7.2 vs 5.5 (PD-L1≥5%) Not listed (PD-L1≥1%)	20.2 vs 13.1 (PD-L1≥50%) 18.2 vs 14.9 (PD-L1≥5%) 17.5 vs 14.1[a] (PD-L1≥1%)	Any: 90.2% vs 94.7%
EMPOWER-Lung 1 [27]	February 2021	All	≥50%	PD-L1 IHC 22C3 pharmDx assay	Cemiplimab	Platinum-based chemotherapy	8.2 vs 5.7	Not reached vs 14.2	Grade 3 & 4: 28% vs 39%
Single-Agent Immunotherapy with Chemotherapy									
KEYNOTE-189 [16,17]	May 2018	Non-squamous	Any	PD-L1 IHC 22C3 pharmDx assay	Pemetrexed + platinum-based chemotherapy + pembrolizumab	Pemetrexed + platinum-based chemotherapy + placebo	9 vs 4.1 (all) 11.3 vs 4.8 (PD-L1≥50%) 9.4 vs 4.9 (PD-L1 1%–49%) 6.2 vs 5.1 (PD-L1<1%)	22 vs 10.6 mo (all) 27.7 vs 10.1 (PD-L1≥50%) 21.8 vs 12.1 (PD-L1 1%–49%) 17.2 vs 10.2 (PD-L1<1%)	Any: 99.8 vs 99%

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TABLE 1
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Trial	Date Published	Histology	PD-L1 Inclusion Criteria	PD-L1 Assay	Experimental Arm	Control Arm	Median PFS (Months, Experimental vs Control)	Median OS (Months, Experimental vs Control)	Adverse Events (Experimental vs Control)
KEYNOTE-407 [18,29]	November 2018	Squamous	Any	PD-L1 IHC 22C3 pharmDx assay	Carboplatin + paclitaxel/ nab-paclitaxel + pembrolizumab	Carboplatin + paclitaxel/ nab-paclitaxel + placebo	8 vs 5.1 (all) 8.3 vs 4.2 (PD-L1≥50%) 8.2 vs 6 (PD-L1 1%–49%) 6.3 vs 5.9 (PD-L1<1%)	17.2 vs 11.6 (all) 19.9 vs 11.5 (PD-L1≥50%) −18 vs 13.1 (PD-L1 1%–49%) −15 vs 11[a] (PD-L1<1%)	Any: 98.2% vs 97.9%
IMpower150[b] [19,20]	June 2018	Non-squamous	Any	SP142 IHC assay	Atezolizumab + bevacizumab + carboplatin + paclitaxel	Bevacizumab + carboplatin + paclitaxel	8.3 vs 6.8 (WT) 12.6 vs 6.8 (TC3 or IC3) 11 vs 6.8 (TC1/2/3 or IC 1/2/3) 8.3 vs 6.6 (TC1/2 or IC1/2) 8 vs 6.8 (TC0/1/2 or IC0/1/2) 7.1 vs 6.9 (TC0 and IC0)	19.5 vs 14.7 (WT) 30 vs 15[a] (TC3 or IC3) 22.5 vs 16 (TC1/2/3 or IC 1/2/3) 16.9 vs 14.1[a] (TC0 and IC0)	Any: 98.2% vs 99%
IMpower130 [21]	July 2019	Non-squamous	Any	SP142 IHC assay	Atezolizumab + carboplatin + nab-paclitaxel followed by atezolizumab maintenance	Carboplatin + nab-paclitaxel followed by pemetrexed maintenance or best supportive care	7 vs 5.5 (WT) 6.4 vs 4.6 (TC3 or IC3) 8.3 vs 6 (TC1/2 or IC1/2) 6.2 vs 4.7 (TC0 and IC0)	18.6 vs 13.9 (WT) 17.4 vs 16.9[a] (TC3 or IC3) 23.7 vs 15.9[a] (TC1/2 or IC1/2) 15.2 vs 12[a] (TC0 and IC0)	Any: 99.6% vs 99.1%
IMpower131[b] [48]	August 2020	Squamous	Any	SP142 IHC assay	Atezolizumab + carboplatin + nab-paclitaxel followed by atezolizumab maintenance	Carboplatin + nab-paclitaxel	6.3 vs 5.6 (all) 10.1 vs 5.1 (TC3 or IC3) 8.4 vs 5.6 (TC2/3 or IC2/3) 7.1 vs 5.6 (TC1/2/3 or IC 1/2/3) 6.5 vs 5.6 (TC1/2 or IC1/2) 5.7 vs 5.6[a] (TC0 and IC0)	14.2 vs 13.5 (all) 23.4 vs 10.2 (TC3 or IC3) 20.4 vs 14.5[a] (TC2/3 or IC2/3) 14.8 vs 15[a] (TC1/2/3 or IC 1/2/3) 12.8 vs 15.5[a] (TC1/2 or IC1/2) 14 vs 12.5[a] (TC0 and IC0)	Any: 99.4% vs 97%

Impower132 [49]	April 2021	Non-squamous	Any	SP142 IHC assay	Atezolizumab + platinum-based chemotherapy + pemetrexed	Platinum-based chemotherapy + pemetrexed	7.6 vs 5.2 (all) 10.8 vs 6.5 (TC3 or IC3) 6.2 vs 5.7[a] (TC1/2 or IC1/2) 8.5 vs 4.9 (TC0 and IC0)	17.5 vs 13.6[a] (all) NR vs 26.9[a] (TC3 or IC3) 12.7 vs 16.2[a] (TC1/2 or IC1/2) 15.9 vs 10.5 (TC0 and IC0)	Any: 98.6% vs 97.1%
EMPOWER-Lung 3 [22,50]	August 2022	Any	Any		Cemiplimab + platinum-based chemotherapy	Placebo + platinum-based chemotherapy	8.2 vs 5 10.8 vs 5.5 (PD-L1≥50%) 8.2 vs 6.1 (PD-L1 1%–49%) 6.2 vs 4.4[a] (PD-L1<1%)	21.9 vs 12.9 23.5 vs 14.4 (PD-L1≥50%) 23.2 vs 12 (PD-L1 1%–49%) 12.8 vs 14.2[a] (PD-L1<1%)	Any: 95.8% 94.1%
Combined Immunotherapy									
CheckMate 227 [51] Part 1a	November 2019	Any	≥1%	Anti-PD-L1 antibody (28–8 antibody)	(Cohort A) Nivolumab + ipilimumab (Cohort B) Nivolumab + platinum-based chemotherapy	(Cohort C) Platinum-based chemotherapy	5.1 (A) vs 4.2 (B) vs 5.6 (C) (PD-L1≥1%) 6.7 (A) vs 5.6 (B) vs 5.6 (C) (PD-L1≥50%)	17.1 (A) vs 15.7 (B) vs 14.9 (C) (PD-L1≥1%) 21.2 (A) vs 18.1 (B) vs 14 (C) (PD-L1≥50%)	77% (A) vs 65.5% (B) vs 84% (C)
CheckMate 227 [38,51] Part 1b	November 2019	Any	<1%	Anti-PD-L1 antibody (28–8 antibody)	(Cohort D) Nivolumab + ipilimumab (Cohort E) Nivolumab + platinum-based chemotherapy	(Cohort F) Platinum-based chemotherapy	5.1 (D) vs 5.6 (E) vs 4.7 (F)	17.4 (D) vs 15.2 (E) vs 12.2 (F)	76% (D) vs 92% (E) vs 78% (F)
KEYNOTE-598 [31]	July 2021	Any	≥50%	PD-L1 IHC 22C3 pharmDx assay	Ipilimumab + pembrolizumab	Placebo + pembrolizumab	8.2 vs 8.4[a]	21.4 vs 21.9[a]	Any: 96.5% vs 93.6%
Combined Immunotherapy with Chemotherapy									
CheckMate 9LA [23,34]	January 2021	Any	Any	Anti-PD-L1 antibody (28–8 antibody)	Nivolumab + ipilimumab + platinum-based chemotherapy	Platinum-based chemotherapy	6.4 vs 5.3 6.9 vs 4.7 (PD-L1≥1%) 5.8 vs 5 (PD-L1<1%)	15.8 vs 11 18.9 vs 12. 9[a] (PD-L1≥50%) 15.2 vs 10.4 (PD-L1 1%–49%) 15.8 vs 10.9 (PD-L1≥1%) 17.7 vs 9.8 (PD-L1<1%)	92% vs 88%

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TABLE 1
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Trial	Date Published	Histology	PD-L1 Inclusion Criteria	PD-L1 Assay	Experimental Arm	Control Arm	Median PFS (Months, Experimental vs Control)	Median OS (Months, Experimental vs Control)	Adverse Events (Experimental vs Control)
POSEIDON [24]	November 2022	Any	Any	SP263 IHC assay	(Cohort A) Tremelimumab + durvalumab + chemotherapy (Cohort B) Durvalumab + chemotherapy	(Cohort C) Chemotherapy	6.2 (A) vs 5.5 (B) vs 4.8 (C)	14 (A) vs 13.3 (B) vs 11.7 (C) B vs C[a] A vs C: HR 0.65 (0.47–0.89) (PD-L1≥50%) HR 0.94 (0.77–1.14)[a] (PD-L1<50%) HR 0.79 (0.64–0.98) (PD-L1≥1%) HR 0.99 (0.76–1.30)[a] (PD-L1<1%)	Any: 92.7% (A) vs 88.6% (B) vs 89.5% (C)

Unless otherwise indicated, the HR CI upper limit is less than 1. WT = wild type, EGFR negative and ALK negative. TC3 or IC3 = PD-L1 expression on at least 50% of tumor cells or at least 10% of tumor-infiltrating immune cells (PD-L1 high).

TC 1/2/3 or IC 1/2/3 = PD-L1 expression on at least 1% of tumor cells or tumor-infiltrating immune cells (PD-L1 positive).

TC 2/3 or IC 2/3 = PD-L1 expression on greater than or equal to 5% of tumor cells or tumor-infiltrating tumor cells.

TC1/2 or IC1/2 = PD-L1 expression on at least 1% of tumor cells or tumor-infiltrating immune cells and less than 50% of tumor cells or less than 10% of tumor-infiltrating immune cells (low PD-L1 expression).

TC0/1/2 or IC0/1/2 = PD-L1 expression on less than 50% of tumor cells and less than 10% of tumor-infiltrating immune cells (low or negative PD-L1 expression).

TC0 and IC0 = PD-L1 expression on less than 1% of tumor cells and tumor-infiltrating immune cells (PD-L1 negative).

[a] HR CI crosses 1.

[b] Had a third arm of patients that received atezolizumab + carboplatin + paclitaxel but results not reported in original analysis.

TABLE 2
List of Clinical Trials that Led to Food and Drug Administration Approval of Immune Checkpoint Inhibitors in the Treatment of Metastatic Non-small Cell Lung Cancer

Trial that Led to FDA Approval [8]	PD-L1	Histology	Agents	Date of Approval
KEYNOTE-024	PD-L1 ≥50%	Any	Pembrolizumab	October 2016
IMPower110	PD-L1 ≥50%	Any	Atezolizumab	May 2020
EMPOWER-Lung 1	PD-L1 ≥50%	Any	Cemiplimab	February 2021
KEYNOTE-042	PD-L1 ≥1%	Any	Pembrolizumab	April 2019
CheckMate 227	PD-L1 ≥1%	Any	Ipilimumab + nivolumab	May 2020
KEYNOTE-189	Any	Non-squamous	Pembrolizumab + pemetrexed + platinum-based therapy	August 2018
KEYNOTE-407	Any	Squamous	Pembrolizumab + paclitaxel/ nab-paclitaxel + platinum-based therapy	October 2018
IMPower 150	Any	Non-squamous	Atezolizumab + bevacizumab + paclitaxel + platinum-based therapy	December 2018
IMPower 130	Any	Non-squamous	Atezolizumab + nab-paclitaxel + carboplatin	December 2019
CheckMate 9LA	Any	Any	Ipilimumab + nivolumab + platinum-based therapy	May 2020
EMPOWER-Lung 3	Any	Any	Cemiplimab + platinum-based chemotherapy	November 2022
POSEIDON	Any	Any	Tremelimumab + durvalumab + platinum-based chemotherapy	November 2022

which tends to occur in patients with tobacco exposure and increases likelihood of response to immunotherapy. After ruling out presence actionable mutations with lower likelihood of benefit from immunotherapy (specifically *EGFR* and *ALK* mutations as studied), PD-L1 expression can help guide appropriate immunotherapy or chemoimmunotherapy. Some trial enrollment criteria and subsequent FDA approvals are based on PD-L1 cutoffs, whereas others, particularly those evaluating chemotherapy plus immunotherapy, enrolled and treated patients regardless of PD-L1 expression. Thinking about treatment options based on PD-L1 cutoffs is a useful approach for comparing available options.

TREATMENT FOR NON-ONCOGENE-DRIVEN NON-SMALL CELL LUNG CANCER

Any Programmed Death-Ligand 1

Multiple clinical trials have evaluated the use of immunotherapy in combination with chemotherapy regardless of PD-L1 expression. In KEYNOTE-189, patients with previously untreated metastatic non-squamous NSCLC without *EGFR* or *ALK* alterations were randomized to receive pemetrexed, platinum-based chemotherapy, and pembrolizumab or pemetrexed, platinum-based chemotherapy, and placebo. In the overall analysis of patients, regardless of PD-L1 expression, those who received chemotherapy and pembrolizumab had improved OS.

The median OS was not reached (NR) in the chemotherapy and pembrolizumab cohort versus 11.3 months (95% CI, 8.7–15.1) in the chemotherapy and placebo cohort (hazard ratio [HR] 0.49, 95% CI, 0.38–0.64) [16]. After 5 years of follow-up, the OS in the pembrolizumab arm was 22 months (95% CI, 19.5–24.5) [17]. In KEYNOTE-407, patients with previously untreated metastatic squamous NSCLC were randomized to receive carboplatin, paclitaxel or nab-paclitaxel, plus pembrolizumab or carboplatin, paclitaxel or nab-paclitaxel, plus placebo. Patients who received chemotherapy and pembrolizumab had improved OS with a median of 17.2 months (95% CI, 14.4–19.7) versus 11.6 months (95% CI, 10.1–13.7) in the chemotherapy and placebo arm (HR 0.71; 95% CI, 0.59–0.85) [18]. In IMpower150, patients with metastatic non-squamous NSCLC who previously did not receive chemotherapy were randomized to receive atezolizumab, carboplatin, plus paclitaxel, or bevacizumab, carboplatin, plus paclitaxel (BCP), or atezolizumab, BCP (ABCP). Regardless of PD-L1 expression, patients in the ABCP arm had improved OS [19]. The median OS was 19.5 months (95% CI, 17–23.8) versus 14.7 months (95% CI, 13.6–16.9) in the BCP arm (HR 0.78, 95% CI, 0.64–0.96) in the updated OS analysis [20]. In IMpower130, patients with metastatic non-squamous NSCLC without previous chemotherapy were randomized to receive atezolizumab plus carboplatin plus nab-paclitaxel followed by atezolizumab maintenance or carboplatin plus nab-paclitaxel followed by pemetrexed maintenance or best supportive care. Patients with any PD-L1 expression in the atezolizumab plus chemotherapy arm had OS of 18.6 months (95% CI, 16–21.2) versus 13.9 (95% CI, 12–18.7) months in the chemotherapy-alone group (HR 0.79, 95% CI, 0.64–0.98) [21]. In EMPOWER-Lung 3, patients with any histology were randomized to receive either cemiplimab and chemotherapy or placebo and chemotherapy. The median OS in the cemiplimab group was 21.1 months (95% CI, 15.9–23.5) versus 12.9 months (95% CI, 10.6–15.7) in the chemotherapy group (HR 0.65, 95% CI, 0.51–0.82) in the 2-year updated analysis [22].

In CheckMate 9LA, patients who were treatment-naïve with advanced NSCLC of any histology were randomized to receive either nivolumab, ipilimumab, plus chemotherapy or platinum-based chemotherapy alone. In the 3-year follow-up, the immunotherapy and chemotherapy cohort had a median OS of 15.8 months (95% CI, 13.9–19.7) versus 11 months (95% CI, 9.5–12.7) in the patients who received chemotherapy alone (HR 0.74, 95% CI, 0.62–0.87) [23]. In POSEIDON, patients with advanced NSCLC of any histology were randomized to receive either tremelimumab plus durvalumab plus chemotherapy (cohort A) or durvalumab plus chemotherapy (cohort B) or chemotherapy alone (cohort C). Irrespective of PD-L1 expression, the median OS was 14 months (95% CI, 11.7–16.1) in cohort A versus 11.7 months (95% CI, 10.5–13.1) in cohort C (HR 0.77, 95% CI, 0.65–0.92) [24].

All the above-mentioned trials led to FDA approval of immunotherapy plus chemotherapy regimens (see Tables 1 and 2) and are available for use for patients whose tumors have any level of PD-L1 expression. Despite these approvals of multiple regimens regardless of PD-L1 expression, it is useful to consider PD-L1 subgroups for consideration of the available treatment options, as discussed as follows.

Programmed Death-Ligand 1 ≥50%

Single-agent immunotherapy

There are three trials that evaluated single-agent immunotherapy and have led to FDA approval of pembrolizumab, atezolizumab, and cemiplimab for NSCLC with PD-L1 expression ≥50%. The first, KEYNOTE-024, was a landmark phase III trial that led to FDA approval of pembrolizumab as monotherapy for advanced NSCLC. KEYNOTE-024 only included patients with a PD-L1 expression of ≥50%. Patients of all histology types were incorporated in this trial. The median OS in the pembrolizumab group was 30 months (95% CI, 18.3 months to NR) versus 14.2 months in the platinum-based chemotherapy group (95% CI, 9.8–19 months) with an HR of 0.63 (95% CI 0.47–0.86) in the updated analysis [25]. The FDA approved the use of pembrolizumab as monotherapy for the treatment of advanced NSCLC in patients with PD-L1 ≥50% in October 2016.

IMPower110 enrolled advanced NSCLC patients with PD-L1 ≥1% and randomized them to receive atezolizumab or platinum-based chemotherapy. There was a significant survival benefit in the PD-L1 ≥50% group: 20.2 months versus 13.1 months (HR 0.59, P=.01) [26]. The cohort with PD-L1 ≥5% who received atezolizumab had an OS of 18.2 months versus 14.9 months in the group that received chemotherapy (HR 0.72, 95% CI, 0.52–0.99, P=.04). Because the PD-L1 ≥5% did not cross the prespecified alpha boundary, the OS was not formally tested for the PD-L1 ≥1% group. The median OS benefit was not statistically significant in the PD-L1 ≥1% group: 17.5 months versus 14.1 months (HR 0.83, 95% CI, 0.65–1.07) [26]. IMPower110 led to the FDA approval of single-agent atezolizumab in the treatment of advanced NSCLC patients with a PD-L1 ≥50% in May 2020.

EMPOWER-Lung 1 enrolled patients with PD-L1 ≥50% and randomized them to receive cemiplimab versus platinum-based chemotherapy. The median PFS in the cemiplimab group was 8.2 months (95% CI, 6.1–8.8) as compared with 5.7 months (95% CI, 4.5–6.2) in the chemotherapy group. The median OS in the cemiplimab group was NR (95% CI, 17.9 to NR) compared with 14.2 months (95% CI, 11.2–17.5) in the chemotherapy group (HR 0.57, 95% CI 0.42–0.77) [27]. EMPOWER-Lung 1 led to the FDA approval of single-agent cemiplimab in the treatment of advanced NSCLC in February 2021.

Of note, CheckMate 026, a phase III study comparing nivolumab to platinum-based chemotherapy, enrolled patients with PD-L1 ≥1% with a primary end point of PFS among patients with PD-L1 ≥5%. Unlike other single-agent PD-1 and PD-L1 trials, there was no significant PFS or OS benefit of nivolumab over chemotherapy [28]. An exploratory analysis of the subgroup of patients with PD-L1 ≥50% did not identify PFS or OS improvement, but there were imbalances in treatment allocation and sex distribution as PD-L1 ≥50% was not a stratification factor. Owing to small numbers of patients in this PD-L1 ≥50% subgroup, it was likely underpowered to detect any differences.

Single-agent immunotherapy with chemotherapy

Although single-agent immunotherapy and chemotherapy is approved in patients with any PD-L1 expression, it is important to note the subgroup analyses. In the KEYNOTE-189 5-year update, patients with a PD-L1 ≥50% had a median OS of 27.7 months (95% CI, 20.4–38.2) in the pembrolizumab plus chemotherapy arm versus 10.1 months (95% CI, 7.5–22) in the chemotherapy only group (HR 0.68, 95% CI, 0.49–0.96) [17]. In the KEYNOTE-407 5-year update, patients with a PD-L1 ≥50% had an OS of 19.9 months (95% CI, 12.2–25.2) in the pembrolizumab plus chemotherapy arm versus 11.5 months (95% CI, 7.5–17.1) in the chemotherapy group (HR 0.68, 95% CI, 0.47–0.97) [29]. These results are similar to those seen with single-agent pembrolizumab in KEYNOTE-024, although there is notably lower median survival for patients with squamous histology, which is consistent across numerous NSCLC studies regardless of treatment. There was a difference in objective response rate (ORR) between KEYNOTE-024 and the PD-L1 greater than 50% group in KEYNOTE-189. In KEYNOTE-024, patients in the pembrolizumab arm had an ORR of 44.8% (95% CI, 36.8–53), whereas patients in the chemotherapy arm had an ORR of 27.8% (95% CI, 20.8–35.7) [30]. In KEYNOTE-189, patients with PD-L1 greater than 50% who received pembrolizumab plus chemotherapy had an ORR 61.4% (95% CI, 52.5–69.7) versus 22.9% (95% CI, 13.7–34.4) in the chemotherapy-alone group. Without direct head-to-head comparison, it is difficult to conclude whether single-agent pembrolizumab or chemotherapy with pembrolizumab is superior. The ongoing INSIGNA phase III trial (NCT03793179) may provide the best direct comparison of these regimens.

Other phase III trials have shown similar results with chemotherapy immunotherapy combinations in the high PD-L1 subgroup. In the IMpower150 updated OS analysis, patients in the ABCP arm had an OS of 30 months (95% CI, 21.8 to NR) versus 15 months (95% CI, 9.8–26) in BCP arm (HR 0.7, 95% CI, 0.46–1.08) [20]. In IMpower130, patients with a PD-L1 ≥50% had a median OS of 17.4 months (95% CI, 14.78 to NR) in the atezolizumab plus chemotherapy arm versus 16.9 months (95% CI, 10.94 to NR) in the chemotherapy group alone (HR 0.84, 95% CI, 0.51–1.39) [21]. The HRs for death cross 1 in both IMpower150 and IMpower130. In both trials, the PD-L1 ≥50% made up less than 20% of the total population. In the 2-year update of EMPOWER-Lung 3, patients with a PD-L1 ≥50% in the cemiplimab plus chemotherapy arm had an OS of 23.5 months (95% CI, 17.9 to NR) versus 14.4 months (95% CI, 9.3–19.5) in the chemotherapy arm (HR 0.56, 95% CI, 0.36–0.86) [22].

Combined immunotherapy

CheckMate 227 split patients into part 1a and 1b depending on if their PD-L1 expression was ≥1% or less than 1%, respectively. There were three different treatment cohorts: one that received nivolumab and ipilimumab, one that received platinum-based chemotherapy alone, and one that received nivolumab alone (if PD-L1 >1%) or chemotherapy plus nivolumab (if PD-L1 <1%). In the PD-L1 ≥50% subgroup, nivolumab and ipilimumab had a significant survival benefit over chemotherapy alone: 21.2 months versus 14 months (HR 0.70, 95% CI, 0.55–0.90). In a separate study, the addition of ipilimumab increased toxicity but did not increase the efficacy of pembrolizumab in patients with advanced NSCLC with any histology and a PD-L1 ≥50% in KEYNOTE-598 [31].

Combined immunotherapy with chemotherapy

CheckMate 227 showed that initially patients seemed to do better on chemotherapy versus combination immunotherapy until the OS curves crossed around 6 months after starting treatment. This observation informed the

study design for CheckMate 9LA which added two cycles of chemotherapy to combination immunotherapy.

In the CheckMate 9LA 3-year follow-up, there was a nonsignificant increase in median OS (18.9 months with the combination vs 12.9 months with chemotherapy; HR 0.75 [95% CI, 0.53–1.07]) in the PD-L1 ≥50% subgroup [23]. In POSEIDON, there was a statistically significant benefit of tremelimumab, durvalumab, and chemotherapy over chemotherapy alone along with durvalumab and chemotherapy over chemotherapy alone in the PDL1 ≥50% subgroup (HR 0.63, 95% CI, 0.45–0.88; HR 0.65, 95% CI, 0.47–0.89, respectively). It is unclear whether the addition of anti-CLTA-4 agents provides any additional benefit over single-agent PD-1 or PD-L1 agents in the setting of high PD-L1 expression.

Programmed Death-Ligand 1 ≥1% to 49%

Single-agent immunotherapy

The FDA expanded single-agent pembrolizumab approval to encompass patients with a PD-L1 ≥1% in April 2019 based on results from KEYNOTE-042 that demonstrated a significant survival benefit over platinum-based chemotherapy. The primary outcome of OS was achieved in the total population with PD-L1 ≥1% and key subgroups of ≥20% and ≥50%. However, the cohort with PD-L1 ≥ 20% consisted of a majority of patients with PD-L1 ≥50%. As randomization was stratified by PD-L1 1% to 49% and PD-L1 ≥50%, nearly half the patients in the trial had PD-L1 ≥50% [32]. In an unplanned post hoc analysis of the PD-L1 1% to 49% subgroup, there was no significant improvement in OS (HR 0.92, 95% CI, 0.77–1.11).

IMpower110, the phase III study of single-agent atezolizumab versus chemotherapy, showed improvement in OS in the PD-L1 ≥50% and ≥5% subgroups as discussed above, but there was no significant survival benefit in the analysis of all patients with PD-L1 ≥1%. The FDA did not expand approval of single-agent atezolizumab therapy for patients with PD-L1 ≥1% or ≥5%.

Single-agent immunotherapy with chemotherapy

KEYNOTE-189 and KEYNOTE-407 showed a significant benefit of pembrolizumab and chemotherapy over chemotherapy alone in the subgroup analysis that included patients with PD-L1 of 1% to 49%. In the KEYNOTE-189 5-year update, OS in this PD-L1 1% to 49% subgroup was 21.8 months (95% CI, 17.7–25.6) in the pembrolizumab and chemotherapy arm versus 12.1 months (95% CI, 8.7–19.4) in the chemotherapy-alone group (HR 0.65, 95% CI, 0.46–0.9) [17]. KEYNOTE-407 demonstrated an OS of 18 months (95% CI, 13.6–22.8) in the pembrolizumab and chemotherapy arm versus 13.1 months (95% CI, 9.1–15.2) in the chemotherapy only arm (HR 0.61, 95% CI 0.45–0.83) in the 5-year update [29]. IMpower150, 130, and 131 all showed a significant PFS benefit of atezolizumab and chemotherapy compared with chemotherapy alone in the positive or low PD-L1 expression groups (see Table 1). IMpower132 did not show a PFS benefit in this group. IMpower150 showed an OS benefit of atezolizumab and chemotherapy compared with chemotherapy alone in the positive or low PD-L1 expression groups but IMpower130 and 131 did not show (see Table 1). EMPOWER-Lung 3 demonstrated a significant OS and PFS benefit for cemiplimab and platinum-based chemotherapy over platinum-based chemotherapy alone in the patients that had a PD-L1 of 1% to 49%.

Combined immunotherapy

CheckMate 227 led the FDA to approve ipilimumab and nivolumab in the treatment of advanced NSCLC in patients with PD-L1 ≥1% and any histology. The median OS in patients with PD-L1 ≥1% was 17.1 months (95% CI, 15–20.1) in the ipilimumab and nivolumab group, 14.9 months (95% CI, 12.7–16.7) in the chemotherapy group (P=.007). For the PD-L1 1% to 49% subgroup, the OS HR was 0.90, 95% CI 0.72 to 1.12, although this was likely underpowered to detect a difference in this subgroup [33].

Combined immunotherapy with chemotherapy

CheckMate 9LA showed a PFS and OS benefit in patients with PD-L1 ≥1% that received nivolumab, ipilimumab, and platinum-based chemotherapy compared with those that received platinum-based chemotherapy alone [34]. With 3-year follow-up, the PD-L1 1% to 49% group maintained significant OS benefit with median 15.2 months in the ipilimumab and nivolumab plus chemotherapy arm compared with 10.4 months with chemotherapy alone (HR 0.70, 95% CI 0.53–0.93) [23]. POSEIDON demonstrated the efficacy of tremelimumab, durvalumab, and chemotherapy to chemotherapy alone in the PD-L1 ≥1% population (OS: HR 0.79, 95% CI, 0.64–0.98), but did not provide results specifically for the PD-L1 1% to 49% group.

Programmed Death-Ligand 1 less than 1%

Single-agent immunotherapy

Multiple agents are approved for use as single agent in the second-line setting after progression on platinum-doublet chemotherapy based on previous phase III

trials comparing PD-1 and PD-L1 agents to docetaxel chemotherapy. The Checkmate 057 and Checkmate 017 trials demonstrated improved OS with nivolumab for non-squamous and squamous NSCLC, respectively [35,36]. The OAK achieved OS with atezolizumab over docetaxel, regardless of PD-L1 expression [37]. One notable finding from these second-line trials was that higher PD-L1 expression correlated with improved likelihood of benefit. Based on PD-L1 enrichment for response and OS, there are no single-agent immunotherapies approved by the FDA for the treatment of advanced NSCLC in patients with PD-L1 less than 1% of any histology in the first-line setting as strategies in first-line trials focused on PD-L1 positive tumors or combination strategies for the PD-L1 less than 1% group.

Single-agent immunotherapy with chemotherapy

Not all clinical trials showed a significant benefit of single-agent immunotherapy with chemotherapy over chemotherapy alone in patients whose tumors had no PD-L1 expression. In the 5-year updated analysis, KEYNOTE-189 demonstrated a significant OS benefit of pembrolizumab and chemotherapy over chemotherapy alone in patients with no PD-L1 expression (17.2 vs 10.2 months, HR 0.55, 95% CI, 0.39–0.76) [17]. The 5-year updated analysis of KEYNOTE-407 showed a nonsignificant OS benefit of pembrolizumab and chemotherapy over chemotherapy alone in patients negative for PD-L1 expression (15 vs 11 months, HR 0.83, 95% CI, 0.61–1.13) [29]. IMpower150, 130, and 131 all showed no significant OS benefit of atezolizumab and chemotherapy over chemotherapy alone but IMpower132 did show a significant OS benefit in the PD-L1 less than 1% group (15.9 vs 10.5, HR 0.67, 95% CI 0.46–0.96). EMPOWER-Lung 3 showed no PFS or OS benefit in this PD-L1 subset.

Combined immunotherapy

There is no combination of immunotherapies without chemotherapy approved by the FDA for advanced NSCLC with PD-L1 less than 1%. However, CheckMate 227 subgroups that explored nivolumab and ipilimumab in patients with PD-L1 less than 1% demonstrated significant OS benefit compared with chemotherapy alone in the 5-year update [38]. Because OS in the PD-L1 less than 1% population was not a primary endpoint of the study, it is not FDA-approved for use. However, nivolumab and ipilimumab are included as category 2A recommendation as option in the NCCN guidelines for PD-L1 less than 1%, which may be useful for patients in this group who are not able or choose not to receive chemotherapy.

Combined immunotherapy with chemotherapy

CheckMate 9LA showed both a significant PFS and OS benefit of nivolumab, ipilimumab, plus platinum-based chemotherapy over platinum-based chemotherapy alone in patients with no PD-L1 expression. The 3-year updated analysis demonstrated a PFS of 5.8 (95% CI, 4.4–7.7) versus 5 months (95% CI, 4.2–5.8), respectively. The median OS was 17.7 months (95% CI, 13.7–20.3) versus 9.8 months (95% CI, 7.7–13.5) in patients with PD-L1 less than 1% (HR 0.67, 9% CI, 0.51–0.88) [23]. POSEIDON did not demonstrate an OS benefit in this group (see Table 1).

GENERAL APPROACH TO TREATMENT

Given the landmark trials above, there are many available choices for first-line treatment of metastatic NSCLC without genomic driver mutations. Although imperfect, PD-L1 remains the best biomarker to predict response to immunotherapy. Beyond PD-L1, other clinical factors such as burden of disease, symptoms, performance status, and comorbidity that preclude chemotherapy and/or immunotherapy are important to consider when selecting a treatment regimen. In general, single-agent immunotherapy is appropriate for patients with advanced NSCLC who have PD-L1 expression $\geq$50%. Platinum-doublet chemotherapy can be added to single-agent immunotherapy if the patient has a large burden of disease and symptoms given the higher response rate seen in trials using combination chemotherapy and immunotherapy. When patient tumors have a PD-L1 expression of 1% to 49%, the preferred treatment is single-agent immunotherapy with chemotherapy. If the patient is not a candidate for chemotherapy, single-agent pembrolizumab or combined ipilimumab and nivolumab would also be appropriate. If PD-L1 is less than 1%, it would be reasonable to consider single-agent immunotherapy with chemotherapy or combined ipilimumab and nivolumab with chemotherapy. It is unclear without head-to-head comparisons if one of these strategies has superior OS over the other. For patients with contraindications to chemotherapy and PD-L1 $\leq$1%, it would be appropriate to consider combined ipilimumab and nivolumab alone. Long-term follow-up on these trials may show differences in durability of survival benefit, but cross-trial comparisons are difficult given small numbers of patients, particularly in different PD-L1 subgroups.

DURATION OF TREATMENT

Although the exact optimal duration of treatment with immunotherapy is not known, the trials listed in this review continued immunotherapy for 2 years and that is generally the recommendation in practice. Patients enrolled in the immunotherapy arms of KEYNOTE-189 (13.9%) and KEYNOTE-407 (19.8%) received 2 years of immunotherapy in total. One recently published retrospective analysis showed no statistically significant OS benefit of indefinite immunotherapy over 2 years of immunotherapy [39]. In addition, one meta-analysis demonstrated the benefit of rechallenging with immunotherapy in patients that completed a set amount of cycles of initial immunotherapy and later progressed [40].

TOXICITIES

ICIs generally cause adverse events by overstimulating the immune system to act on nonmalignant cells. These can lead to numerous toxicities including dermatitis, pneumonitis, colitis, and thyroiditis, among other processes. For the most part, these toxicities are treated with ICI cessation and immune suppression with corticosteroids [8]. There is controversial evidence about how steroids impact the efficacy of immunotherapy [41,42]. In general, the toxicities of immunotherapy do not overlap with chemotherapy, although managing multiple adverse events at once can be challenging, especially for patients with lower performance status. Kidney injury is one toxicity that has some overlap, and rates of acute kidney injury have been noted to be higher in approaches that combine chemotherapy and immunotherapy. For patients who may not be able to tolerate chemotherapy, immunotherapy-alone regimens may be preferred. Dual immunotherapy regimens do have challenges of increasing risk of immune-related adverse events that need to be taken into consideration.

SPECIAL CONSIDERATIONS

In addition to PD-L1 expression and TMB, there have been many retrospective studies that highlight *KRAS* mutations, *STK11* mutations, and *KRAS/STK11* co-mutations (also called the KL co-mutations) as both prognostic and predictive biomarkers of benefit from immunotherapy in NSCLC [43]. Overall, the presence of a KRAS mutation is a poor prognostic factor in NSCLC. *STK11* is a tumor suppressor gene and somatic mutations in this gene promote cellular growth and tumorigenesis. *STK11* mutations also lead to a depletion of CD8+ T lymphocytes and an increase in pro-inflammatory cytokines in the tumor microenvironment, making that microenvironment more immunosuppressive. The KL co-mutations (occurring in up to 20%–32% of metastatic NSCLC) give rise to a unique phenotype of NSCLC that is more aggressive and has an immunosuppressive or "cold" tumor microenvironment.

One pooled analysis of 23 studies showed that *KRAS* mutant tumors in comparison to *KRAS* wild-type tumors were more likely to express PD-L1 and have a higher TMB, showing that the presence of *KRAS* mutations can also serve as a predictive biomarker for response to ICIs in NSCLC [44]. On the other hand, one univariate analysis demonstrated no survival benefit in patients with *KRAS* mutations versus wild type, who all had PD-L1 expression greater than 50% [45].

In general, most studies have concluded that *STK11* mutations serve as prognostic but not predictive biomarkers in NSCLC [43]. The KL co-mutation also has mixed data on its role as a prognostic or predictive biomarker in NSCLC. In one retrospective study, KL mutations were shown to be a genomic driver of resistance to therapy along the PD-1 axis in *KRAS*-mutant NSCLC and therefore a negative predictive biomarker for immunotherapy [46].

An exploratory analysis of POSEIDON showed that patients with a *STK11* mutation and non-squamous histology had an OS benefit with tremelimumab, durvalumab, and chemotherapy compared with chemotherapy alone that was clinically significant but not statistically significant (15 vs 10.7 months, HR of 0.56, 95% CI, 0.3–1.03) [47–51]. Given the mixed results, more prospective studies should be conducted to determine the relevance of the above mutations as predictive biomarkers in NSCLC.

SUMMARY

ICIs have significantly changed the landscape of outcomes for patients with metastatic NSCLC in the last decade, allowing patients to live considerably longer with this disease. There are ongoing studies about predictive biomarkers for ICIs in the treatment of NSCLC which will further help elucidate the best population to receive ICIs. There are many available regimens using single-agent ICIs, chemotherapy plus ICI, and dual-ICIs incorporating CTLA-4 inhibition. Treatment choices can be made based on PD-L1 expression level, but head-to-head comparisons of different ICI treatment regimens are not available to definitively demonstrate superiority of one regimen over another. There are several clinical

trials exploring other targets in the immune pathway for treatment of NSCLC as well. Immunotherapy will likely continue to help improve outcomes in NSCLC in the near and distant future.

CLINICS CARE POINTS

- Immune checkpoint inhibitors have have improved median overall survival for the first line treatment of metastatic NSCLC without actionable genomic driver mutations.
- Although many patients benefit a modest amount, a minority have substantial and durable responses to these treatments that may last for years.
- Multiple immune checkpoint inhibitors, either alone, or in combination with chemotherapy are currently available for use.

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