

Assessing the Impact of Immunotherapy on Quality of Life and Patient Outcomes in the Frontline Management of Advanced Non–Small Cell Lung Cancer

HIGHLIGHTS

- › Immunotherapy in the Frontline Management of Advanced and Metastatic NSCLC
- › The Impact of Immune Checkpoint Inhibitors on Cost and Quality of Life in the Initial Treatment of Patients With Advanced or Metastatic NSCLC
- › CE Sample Posttest

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Intended Audience:

Managed care payers, pharmacy directors, pharmacy benefit managers, specialty pharmacy directors, oncology pharmacists, and any other pharmacist and/or healthcare professional interested in scientific advances for combination therapies in the treatment of non-small cell lung cancer.

Activity Overview

While cancer treatment makes strides in improvement, lung cancer persists as a leading cause of death and cases remain high, reaching over 228,000 new cases and over 135,000 deaths in 2020. One of the major developments in the treatment paradigm of non-small cell lung cancer (NSCLC) is the advent of immune checkpoint inhibitors (ICIs). As evidence for use of ICIs in the frontline setting increases, the impact of potential toxicities, utilization of resources, and cost becomes more relevant for managed care providers. ICIs have the potential to minimize adverse effects and decrease overall cost compared with chemotherapy. Managed care professionals and pharmacists require a foundational knowledge of appropriate usage and selection of ICIs within treatment regimens for patients with NSCLC. Familiarity with currently available and emerging ICIs for treatment of NSCLC will lead to improved outcomes across patient populations. This activity will also cover biomarker analysis for candidacy of treatment with ICIs, strategies and guidelines of ICI treatment, and impact of ICI therapy on patients' quality of life.

Statement of Educational Need

Despite improvements in screening, prevention, and treatment, lung cancer remains a leading cause of death in the United States. In an effort to optimize patient outcomes, the frontline treatment for patients presenting with advanced or metastatic non-small cell lung cancer (NSCLC), who represent the vast majority of cases, is rapidly evolving into a personalized paradigm in which therapy is guided by patient- and disease-related characteristics. Recent advances in pharmacologic management with immuno-oncology agents have been associated with a decreased rate of mortality. Alongside molecularly-targeted drugs, immunotherapy in the form of immune checkpoint inhibitors (ICIs) has recently come into its own in patients with NSCLC. Comprehensive next-generation sequencing and PD-L1 testing have become part of standard treatment recommendations for advanced and metastatic disease, the latter based on the association between PD-L1 expression level and ICI

efficacy. Yet there are many challenges associated with PD-L1 testing that can impact its uptake, and even when biomarker analysis is performed, clinical decision making may deviate from recommended guidelines supported by existing data. What further complicates usage of these agents for initial treatment is biomarker testing to determine optimal treatment selection. Immuno-oncology drugs that target PD-1 and PD-L1 have been shown to be effective, but are preferred in patients who are positive for PD-L1 and/or who have no other actionable targeted therapy (eg, EGFR status). These companion tests have been studied in conjunction with specific ICIs and should not be interchanged across therapies, so it is necessary for patients to be appropriately tested to determine which type of therapy would be most appropriate for treatment. Managed care pharmacists must recognize the benefit of appropriate ICI therapy on improved health-related quality of life as well as potential decrease in healthcare resource utilization and total cost of care. Managed care providers should be aware of relevant perspectives on emerging data and best practice recommendations for use of ICIs in the frontline management of metastatic NSCLC, including clinical data that support their use, novel regimens under clinical investigation, guideline recommendations, and barriers to effective PD-L1 expression analysis. Equipped with this knowledge, managed care professionals will be well-placed to keep pace with rapid evolution of ICI therapy in metastatic NSCLC and establish strategies within their own institutions to optimize patient outcomes.

Educational Objectives

Upon completion of this activity, participants will be able to:

- Identify the clinical challenges that have the potential to impact the uptake of PD-L1 testing in non-small cell lung cancer (NSCLC).
- Employ immune checkpoint inhibitor (ICI) therapy into the frontline treatment of a patient with advanced NSCLC based on patient- and disease-related characteristics.
- Explore the potential economic impact of decreased uptake of biomarker testing.
- Analyze data demonstrating the impact of ICIs on quality of life and resource utilization in advanced NSCLC.

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OVERVIEW

Through this supplement to *The American Journal of Managed Care*[®], managed care professionals will increase their knowledge of immune checkpoint inhibitors and PD-L1 testing in the treatment landscape for non-small cell lung cancer.

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Immunotherapy in the Frontline Management of Advanced and Metastatic NSCLC

Eve M Segal, PharmD, BCOP

The Burden of Lung Cancer

Lung cancer is one of the most common types of cancer and a leading cause of cancer-related death among both sexes in the United States, with 235,760 new cases and 131,880 deaths due to lung cancer anticipated in 2021.¹ Although histologically heterogeneous, it can be broadly classified into non-small cell lung cancers (NSCLCs), which make up approximately 85% of cases, and small cell lung cancers. NSCLC is further divided into adenocarcinomas, which account for approximately 40% of cases, squamous cell carcinomas, representing 25% to 30% of cases, and large cell carcinomas comprising 5% to 10%.²

Lung cancer is more commonly diagnosed in older patients; the incidence in individuals under age 40 is low, then gradually increases to a peak between 65 and 84 years of age, with a median age at diagnosis of 71 years. In the United States, the incidence of lung cancer and associated mortality rates is highest among Black men and women compared with other racial and ethnic groups. Hispanic individuals have lower lung cancer incidence than non-Hispanics and the lowest annual incidence is observed among Asians/Pacific Islanders.²⁻⁴

The most significant risk factor for lung cancer is inhalation of carcinogens from cigarette smoking; more than 80% of lung cancer-related deaths are attributed to smoking, with an additional approximately 3% resulting from secondhand smoke exposure.^{1,5} However, nonsmoking-related lung cancer represents a significant and growing burden, particularly among women and patients younger than 55 years.^{1,6} A number of other risk factors are associated with the development of lung cancer, most notably exposure to radon.⁷

The United States Preventive Services Task Force (USPSTF) recommends annual screening with a chest low-dose computed tomography (CT) scan in high-risk individuals (30 pack-year smoking history) between the ages of 55 and 80 years, unless the individual has not smoked for 15 years or has a limited life span, as this is associated with reduced mortality.^{8,9} Owing to the implementation of screening guidelines, in addition to efforts to reduce cigarette smoking rates and advancements in treatment, the incidence of

ABSTRACT

The frontline treatment paradigm for patients with advanced or metastatic non-small cell lung cancer (NSCLC) has changed dramatically in the past decade amid efforts to tackle this leading cause of cancer-related mortality. Immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein 1 (PD-1) receptor and its ligand PD-L1 are an important therapeutic option for patients whose tumors lack genetic alterations that dictate response to molecularly targeted therapies. With a growing number of FDA-approved ICI monotherapy and combination therapy options for first-line therapy, the use of biomarkers such as PD-L1 expression has become increasingly important in guiding therapeutic decision making. Presently, PD-L1 expression remains a key biomarker in this setting, in spite of its limitations. This article will evaluate the current and evolving clinical trends in the use of ICIs in the frontline management of metastatic NSCLC, as well as the challenges associated with PD-L1 expression analysis and biomarker implementation.

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For author information and disclosures, see end of text.

lung cancer has been declining since the 1980s among men and since the later part of the 2000s among women.²

Exploiting the Antitumor Immune Response

For patients who present with early-stage lung cancer, surgical resection remains the optimal treatment. However, less than 20% of cases are diagnosed at this stage; the majority are diagnosed at an advanced stage with distant metastasis and 5-year survival is just 6%.¹⁰ Historically, the mainstay of treatment for these patients was platinum-based doublet chemotherapy; however, a greater understanding of the molecular pathogenesis of NSCLC facilitated the development of various targeted therapies that have improved survival rates for patients with certain subtypes of metastatic NSCLC.¹¹

For patients whose tumors lack mutations that respond to molecularly targeted therapies, the treatment paradigm has also changed significantly in the past decade with the development of immune checkpoint inhibitors (ICIs), which capitalizes on the potential of the immune response to restrain tumor growth.¹¹ Although cancers derive from a patient's own tissues, they are characterized by genetic abnormalities that can mark the cancer cells as nonself, triggering an antitumor immune response. A number of steps are required for the antitumor immune response to result in effective killing of cancer cells, described as the cancer-immunity cycle. The continual evolution of cancer cells, however, often allows them to develop ways of evading or actively suppressing the antitumor immune response by disrupting various points in the cancer-immunity cycle.¹²

The premise of immunotherapy is to boost or reinstate antitumor immunity. To date, the focus has been on the T cells as the major cytotoxic effectors of the immune system. T-cell activity is tightly regulated by the integration of multiple signals to ensure self-tolerance and prevent autoimmunity. Following the primary signal generated by interaction between the T-cell receptor and

the antigen-MHC complex on the surface of an antigen-presenting cell, a secondary signal is generated by the binding of inhibitory or stimulatory receptors with their corresponding ligands. These so-called immune checkpoints determine whether the T cell is switched on (stimulatory) or off (inhibitory). Programmed cell death protein 1 (PD-1) receptor is the best-known inhibitory receptor and cancer cells often exploit its immunosuppressive function by expressing one of its ligands, PD-L1, on their surface or by recruiting PD-L1-expressing immune cells to the tumor microenvironment, to downregulate T cell cytotoxic activity and prevent the host from mounting an effective antitumor immune response. ICIs, monoclonal antibodies designed to block the activity of PD-1 or its ligands, have elicited durable responses across a range of solid tumors.^{13,14}

Uptake of PD-L1 Testing

PD-L1 testing via immunohistochemical analysis has become an important tool for clinical decision making in patients with advanced or metastatic NSCLC. Several assays have been developed that differ in the specific antibodies used to detect PD-L1 expression, the detection systems employed, and the thresholds for PD-L1 positivity (Table 1¹⁵). Different ICIs were approved together with different companion diagnostics; pembrolizumab and cemiplimab were approved in conjunction with the PD-L1 IHC 22C3 pharmDx assay, while the Ventana PD-L1 (SP142) assay is approved to identify patients eligible for atezolizumab treatment.¹⁶⁻¹⁸ The 22C3 assay measures the tumor proportion score (TPS), which is defined as the total number of tumor cells demonstrating partial or complete membrane staining of any intensity. The SP142 assay reports a tumor cell and immune cell score, measuring the number of tumor cells that stain positive for PD-L1 as a proportion of the total number of tumor cells and the percentage of the total tumoral area occupied by positive immune cells, respectively.¹⁹

TABLE 1. PD-L1 Diagnostic Assays for Frontline Use of ICIs in NSCLC¹⁵

FDA-approved ICI regimen	IHC assay (manufacturer)	Cut-off	Diagnostic status
Pembrolizumab monotherapy	PD-L1 IHC 22C3 pharmDx (Agilent)	TPS ≥1%	Companion
Cemiplimab monotherapy	PD-L1 IHC 22C3 pharmDx (Agilent)	TPS ≥50%	Companion
Pembrolizumab + pemetrexed and carboplatin	N/A	N/A	Not required
Pembrolizumab + carboplatin and paclitaxel	N/A	N/A	Not required
Nivolumab + ipilimumab	PD-L1 IHC 28-8 pharmDx (Agilent)	≥1%	Companion
Nivolumab + ipilimumab + chemotherapy	N/A	N/A	Not required
Atezolizumab monotherapy	Ventana PD-L1 (SP142) assay (Ventana Medical Systems)	TC ≥50% or IC ≥10%	Companion
Atezolizumab + nab-paclitaxel and carboplatin	N/A	N/A	Not required
Atezolizumab + bevacizumab, carboplatin and paclitaxel	N/A	N/A	Not required

IC, tumor-infiltrating immune cell; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; N/A, not applicable; PD-L1, programmed cell death ligand 1; TC, tumor cells; TPS, tumor proportion score.

Although testing for PD-L1 expression is recommended as routine clinical practice prior to first-line therapy, it is not without challenges. Among the most significant is the lack of standardization among the currently available tests. Although studies evaluating assay concordance have been promising, interchangeable use of assays and cutoffs could lead to misclassification of PD-L1 status for some patients. Notably, several analyses have found that the SP142 assay consistently labels fewer tumor cells than other PD-L1 assays.^{20,21} The interpretation of PD-L1 IHC assays is challenging because of the different methods and thresholds used for determining positive results. A number of studies have demonstrated substantial levels of variation between pathologists performing the interpretation using FDA-approved PD-L1 tests.²² Additionally, PD-L1 testing does not provide the same clear binary results as other biomarker tests used in the management of lung cancer. Instead, there is significant inter- and intratumor heterogeneity in PD-L1 expression levels, as well as varying PD-L1 expression levels over time, which can also be impacted by previous and concurrent treatments. Due to this heterogeneity, a patient's PD-L1 expression status can be significantly impacted by the sampling method. Studies have demonstrated discordance in PD-L1 expression levels measured in biopsy and surgically resected specimens; however, the latter may not be available and a single biopsy is unlikely to capture heterogeneity.²³ Not all patients with PD-L1 expression respond and responses can be seen in patients who are PD-L1 negative, further highlighting the imperfect nature of PD-L1 expression as a predictive biomarker and that there are additional factors that influence ICI efficacy, which are only beginning to be elucidated.²⁴ These challenges can impact the uptake and appropriate use and interpretation of PD-L1 testing.

Alternative biomarkers, such as tumor mutational burden, defined as the number of mutations per megabase of DNA, are being explored in the setting of NSCLC; however, despite its limitations, PD-L1 IHC testing continues to be the recommended predictive biomarker at the current time.

Expanding Frontline Options

Initially approved for patients who had progressed on standard chemotherapy, a growing number of ICI options are now available for frontline management of patients with advanced or metastatic NSCLC who do not have any targetable oncogene mutations.

ICI Monotherapy

Pembrolizumab (a PD-1-targeted monoclonal antibody), atezolizumab (a PD-L1-targeted antibody), and most recently, cemiplimab (PD-1), are

each approved by the FDA as single agents for first-line treatment of patients with advanced NSCLC with high levels of PD-L1 expression (TPS $\geq 50\%$), as determined by an FDA-approved test. Pembrolizumab approval in this setting was based on the KEYNOTE-024 trial, while IMpower110 was the pivotal trial of atezolizumab monotherapy in previously untreated patients with advanced NSCLC with PD-L1 expression on at least 1% of tumor cells or immune cells within the tumoral area.²⁵⁻²⁷ In February 2021, cemiplimab became the third ICI to receive FDA approval for first-line treatment of patients with advanced NSCLC as a single agent on the basis of the EMPOWER-Lung 1 study.²⁸ In each of these studies, ICI monotherapy resulted in a statistically significant overall survival (OS) benefit compared with platinum-based chemotherapy in patients who had a PD-L1 expression $\geq 50\%$, while also yielding significant improvements in other key clinical end points (Table 2²⁶⁻³⁰).

Pembrolizumab is also approved as monotherapy for previously untreated patients with metastatic NSCLC whose tumors express lower levels of PD-L1 ($\geq 1\%$) based on the results of the KEYNOTE-042 trial, in which OS was significantly longer in patients treated with pembrolizumab compared with chemotherapy among patients with detectable PD-L1 expression in 1% or more of tumor cells (16.7 months vs 12.1 months, respectively; HR, 0.81; $P = .0018$).³¹

Combination Therapy

Despite these successes, only a fraction of patients respond to monotherapy.^{32,33} Efficacy is limited by a number of factors, including the potential for tumors to evade or suppress the resulting antitumor immune response. Combination therapies have been explored as a way to broaden the scope of ICI therapy. Chemoimmunotherapy approaches demonstrated encouraging results in clinical trials and several such combinations are now approved by the FDA for treatment of advanced NSCLC in the first-line setting, with approvals

TABLE 2. Topline Data From Immunotherapy versus Chemotherapy Frontline Trials in NSCLC²⁶⁻³⁰

Study/Treatment	Efficacy			
	mOS (months)	HR/ P value	Grade 3-5 irAEs (%)	Any grade irAEs (%)
KEYNOTE-024/ Pembrolizumab vs platinum doublet	26.3 vs 13.4	0.62/ NR	31.2 vs 53.3	34.4 vs 5.3
EMPOWER-Lung1/ Cemiplimab vs platinum doublet	NR vs 14.2	0.57/ .0002	28 vs 39	17 vs 2
IMpower110/ Atezolizumab vs platinum doublet	20.2 vs 13.1	0.59/ 0.01	33.9 vs 56.7	40.2 vs 16.7
CheckMate-227/ Nivolumab + ipilimumab vs platinum doublet	17.1 vs 14.9	0.79/ .007	33 vs 36	77 vs 82

HR, hazard ratio; irAE, immune-related adverse event; mOS, median overall survival; NR, not reached; NSCLC, non-small cell lung cancer.

based on the demonstration of improved OS for each combination regimen compared with chemotherapy alone (Table 3³⁴⁻³⁸). The molecular mechanisms underlying the synergy between chemotherapy and immunotherapy are not completely understood; however, at least in part it results from the immunomodulatory properties of chemotherapy.³⁹

The combination of pembrolizumab and pemetrexed plus platinum-based chemotherapy is approved for the first-line treatment of metastatic nonsquamous NSCLC regardless of PD-L1 expression level based on the KEYNOTE-189 trial.³⁴ The combination of pembrolizumab and a slightly different chemotherapy regimen (carboplatin plus paclitaxel or albumin-bound paclitaxel) is approved for the first-line treatment of metastatic squamous NSCLC regardless of PD-L1 expression based on data from the KEYNOTE-407 trial.³⁵

Atezolizumab is approved in combination with chemotherapy, with or without the vascular endothelial growth factor (VEGF)-targeted monoclonal antibody bevacizumab, as first-line therapy for patients with metastatic nonsquamous NSCLC following improved outcomes in the IMpower150 and IMpower130 trials.^{36,37,40} Bevacizumab and other drugs that target VEGF and its receptors are anti-angiogenic agents designed to normalize the tumor vasculature, which is structurally and functionally abnormal. The rationale for combining anti-angiogenic drugs with ICIs is that this abnormal tumor vasculature may contribute to cancer immune evasion by preventing sufficient immune cell access to the tumor and its microenvironment.^{41,42} Notably, neither atezolizumab combination is currently approved for the treatment of squamous NSCLC. In the IMpower131 study, the combination of nab-paclitaxel, carboplatin, and atezolizumab improved progression-free survival (PFS) but not OS in this NSCLC subtype.⁴³

In May 2020, the FDA approved the combination of nivolumab and ipilimumab for the treatment of metastatic squamous or

nonsquamous NSCLC in the first-line setting for patients with PD-L1 expression levels of 1% or more. Ipilimumab and nivolumab have complementary mechanisms of action, with ipilimumab blocking the activity of a different immune checkpoint receptor, cytotoxic T-lymphocyte antigen 4 (CTLA-4). In the pivotal CheckMate 227 trial, 29% of patients treated with combination therapy were still alive and more than one-third remained in response after 4 years of follow-up.⁴⁴ Based on the phase 3 CheckMate 9LA study, the combination of nivolumab and ipilimumab plus 2 cycles of platinum-doublet chemotherapy is another frontline treatment option for patients with advanced NSCLC regardless of PD-L1 expression levels and histology.^{38,45}

Recommended Treatment Paradigm

With the growing number of competing FDA-approved ICIs for the frontline management of advanced NSCLC, optimal treatment selection depends increasingly on patient-specific factors. The National Comprehensive Cancer Network (NCCN) has developed evidence-based guidelines to help guide treatment selection (Figure 1¹¹). Testing for actionable biomarkers, including PD-L1 expression, is recommended before first-line treatment in patients with metastatic NSCLC, if clinically feasible. Patients with actionable molecular variants in driver oncogenes (eg, epidermal growth factor receptor and anaplastic lymphoma kinase) should receive first-line targeted therapy for that oncogene, independent of PD-L1 expression levels. For patients without these targetable alterations, the choice of therapy is guided by PD-L1 expression level and histology.¹¹

PD-L1 greater than or equal to 50%

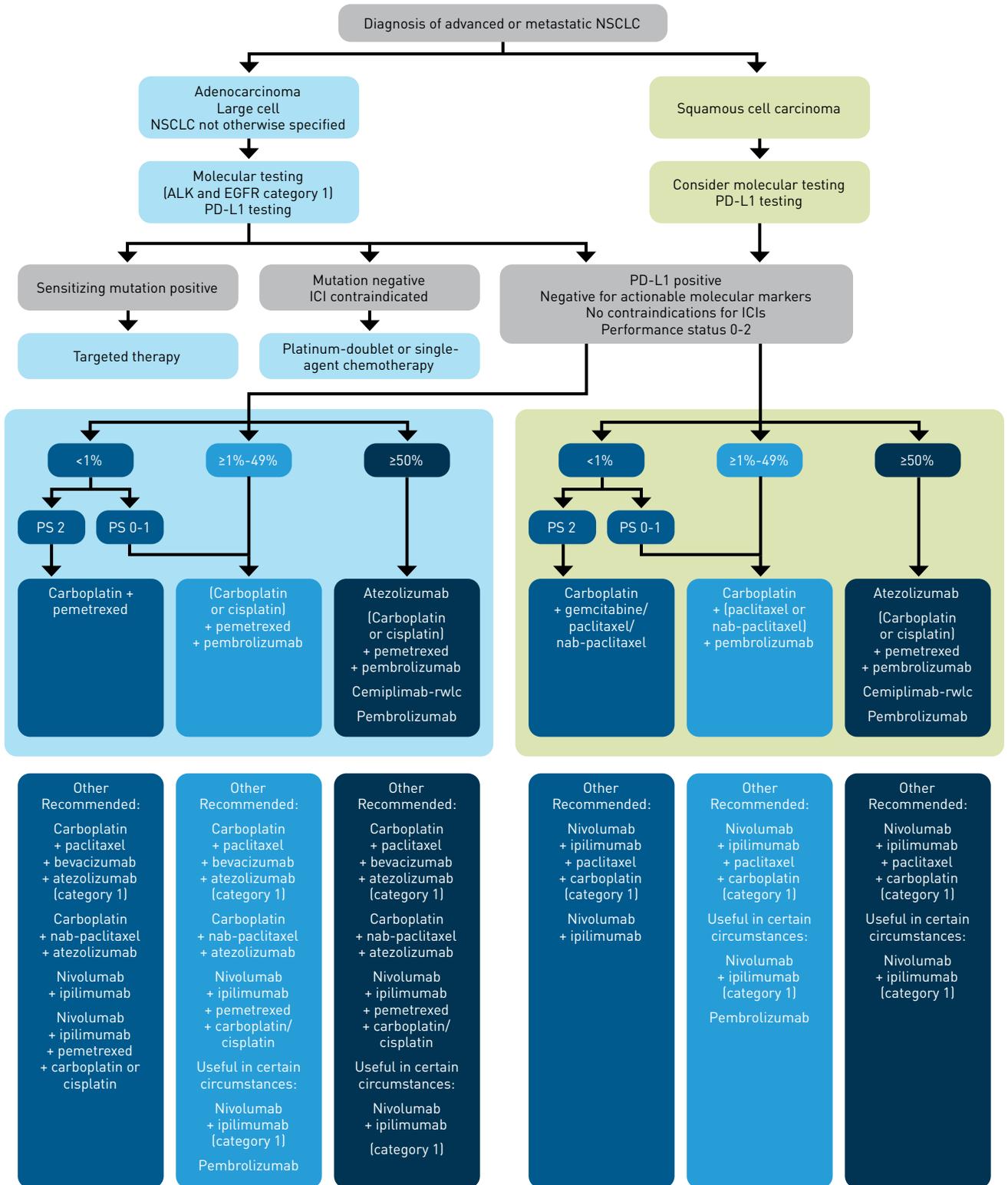
Regardless of histology, single-agent therapy with pembrolizumab, atezolizumab, or cemiplimab are preferred treatment options for patients with metastatic NSCLC with no contraindications to ICIs,

TABLE 3. Topline Data From Chemoimmunotherapy versus Chemotherapy Trials in NSCLC³⁴⁻³⁸

Study/Treatment	Efficacy			
	mOS (mo)	HR/ P value	Grade 3-5 irAEs (%)	Any grade irAEs (%)
KEYNOTE-189/ Pembrolizumab + platinum doublet vs platinum doublet (nonsquamous)	22 vs 10.6	0.56/ NR	72.1 vs 66.8	27.2 vs 12.9
KEYNOTE-407/ Pembrolizumab + platinum doublet vs platinum doublet (squamous)	17.1 vs 11.6	0.71/ NR	74.1 vs 69.6	35.3 vs 8.9
IMpower150/ Atezolizumab + bevacizumab + platinum doublet vs bevacizumab + platinum doublet	19.2 vs 14.7	0.78/ .02	58.5 vs 50	NR
IMpower130/ Atezolizumab + platinum doublet vs platinum doublet	18.6 vs 13.9	0.79/ .033	75 vs 61	45 vs NR
CheckMate-9LA/ Nivolumab + ipilimumab + platinum doublet vs platinum doublet	15.8 vs 11	0.73/ NR	48 vs 38	NR

HR, hazard ratio; irAE, immune-related adverse event; mOS, median overall survival; NR, not reached; NSCLC, non-small cell lung cancer.

FIGURE 1. Guideline-Recommended Frontline Treatment Paradigm for Advanced NSCLC¹¹



ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PS, performance status.

negative test results for actionable molecular alterations, and a performance status (PS) of 0-2.¹¹

PD-L1 greater than or equal to 1% to 49%

For patients with lower levels of PD-L1 expression, pembrolizumab and chemotherapy combination therapy is preferred over monotherapy, based on currently available clinical data. For patients with nonsquamous NSCLC, the preferred chemotherapeutic combination is pemetrexed and either carboplatin or cisplatin, while for squamous NSCLC, a regimen of carboplatin and either paclitaxel or albumin-bound paclitaxel is preferred.

The NCCN also recommends single-agent pembrolizumab as a category 2A treatment option that may be useful in certain circumstances for patients with lower PD-L1 expression levels, for example, in patients who cannot tolerate platinum-based chemotherapy.¹¹

Independent of PD-L1 Status

The combination of pembrolizumab and chemotherapy is a preferred frontline treatment option regardless of PD-L1 expression level and offers an equally effective treatment option to monotherapy in patients with high levels of PD-L1 expression. It may offer an advantage in patients with certain clinical factors, such as rapidly progressing or very extensive disease.

The combination of atezolizumab, bevacizumab, and paclitaxel is a category 1 “other recommended” option for the frontline treatment of patients with metastatic nonsquamous NSCLC, regardless of PD-L1 expression levels, but is not currently approved for patients with squamous NSCLC. Likewise, atezolizumab in combination with albumin-bound paclitaxel, without the addition of bevacizumab, is also an “other recommended” option in this setting, but is a category 2A recommendation.

Irrespective of histology and PD-L1 expression level, nivolumab plus ipilimumab in combination with chemotherapy is a category 1 other recommended treatment option, with choice of chemotherapy determined by histology. The dual nivolumab and ipilimumab offers a chemotherapy-sparing alternative regimen, which may be useful in certain circumstances.¹¹

PD-L1 less than 1%

For patients with PD-L1 expression levels less than 1%, the recommended treatment options depend on their PS. Chemotherapy remains the standard for patients with a PS of 2, while for patients with PS 0-1 the recommended treatment paradigm is the same as for patients with PD-L1 expression levels of greater than or equal to 1% to 49%, with pembrolizumab in combination with chemotherapy the preferred choice, while atezolizumab plus chemotherapy, with or without bevacizumab (with bevacizumab is a category 1 recommendation), and nivolumab plus ipilimumab with or without chemotherapy (the latter being the category 1 recommendation) are other recommended options.¹¹

Emerging Options

In addition to approved immunotherapy options, there are a number of emerging investigational strategies for frontline management of advanced NSCLC.

ICI plus Chemotherapy

In the phase 3 EMPOWER-Lung 3 trial, the combination of cemiplimab and platinum-based chemotherapy was evaluated as first-line treatment of advanced/metastatic NSCLC. The trial was halted early due to a statistically significant improvement in OS in the combination arm at the interim analysis (mOS: 22 months vs 13 months; HR, 0.71; $P = .014$). No new safety signals were reported.⁴⁶

Tislelizumab is a novel PD-1-targeted antibody designed to have reduced binding to Fc-gamma receptors, in an effort to overcome a potential mechanism of resistance to PD-1 inhibitor antibody therapy.^{47,48} Several ongoing phase 3 clinical trials are evaluating the efficacy and safety of tislelizumab in combination with chemotherapy. In the RATIONALE-304 trial, the combination of tislelizumab plus pemetrexed and platinum-based chemotherapy is being evaluated in patients with advanced nonsquamous NSCLC, while the RATIONALE-307 trial is testing the addition of tislelizumab to paclitaxel or nab-paclitaxel plus carboplatin in advanced squamous NSCLC. In both trials, the addition of tislelizumab to chemotherapy significantly improved PFS, ORR, and duration of response compared with chemotherapy alone.^{49,50} The combination is approved in China for squamous NSCLC and is under review for nonsquamous NSCLC.^{51,52}

ICI + Targeted Therapy

ICIs also are being explored in combination with targeted therapies in a number of phase 3 clinical trials, based on preclinical studies that suggest potential synergistic activity. Notably, the LEAP clinical program is evaluating the combination of pembrolizumab and the multikinase inhibitor lenvatinib across a range of solid tumor types. In the LEAP-006 trial, the combination of pembrolizumab, platinum-based chemotherapy, and lenvatinib demonstrated impressive response rates and acceptable safety and tolerability in the first part of this study in patients with advanced nonsquamous NSCLC.⁵³ The phase 3 LEAP-007 trial is evaluating the combination of pembrolizumab and lenvatinib without chemotherapy in patients with metastatic NSCLC. Several ongoing studies are also assessing ICIs in combination with poly (ADP-ribose) polymerase inhibitor therapy in the frontline setting.

Dual Immunotherapy Combinations

Among other notable emerging treatment options are several dual immunotherapy combinations. In the phase 2 CITYSCAPE trial, the combination of atezolizumab and tiragolumab (an inhibitor of an alternative inhibitory checkpoint protein TIGIT, which is expressed on multiple immune cells, including T cells) demonstrated clinically

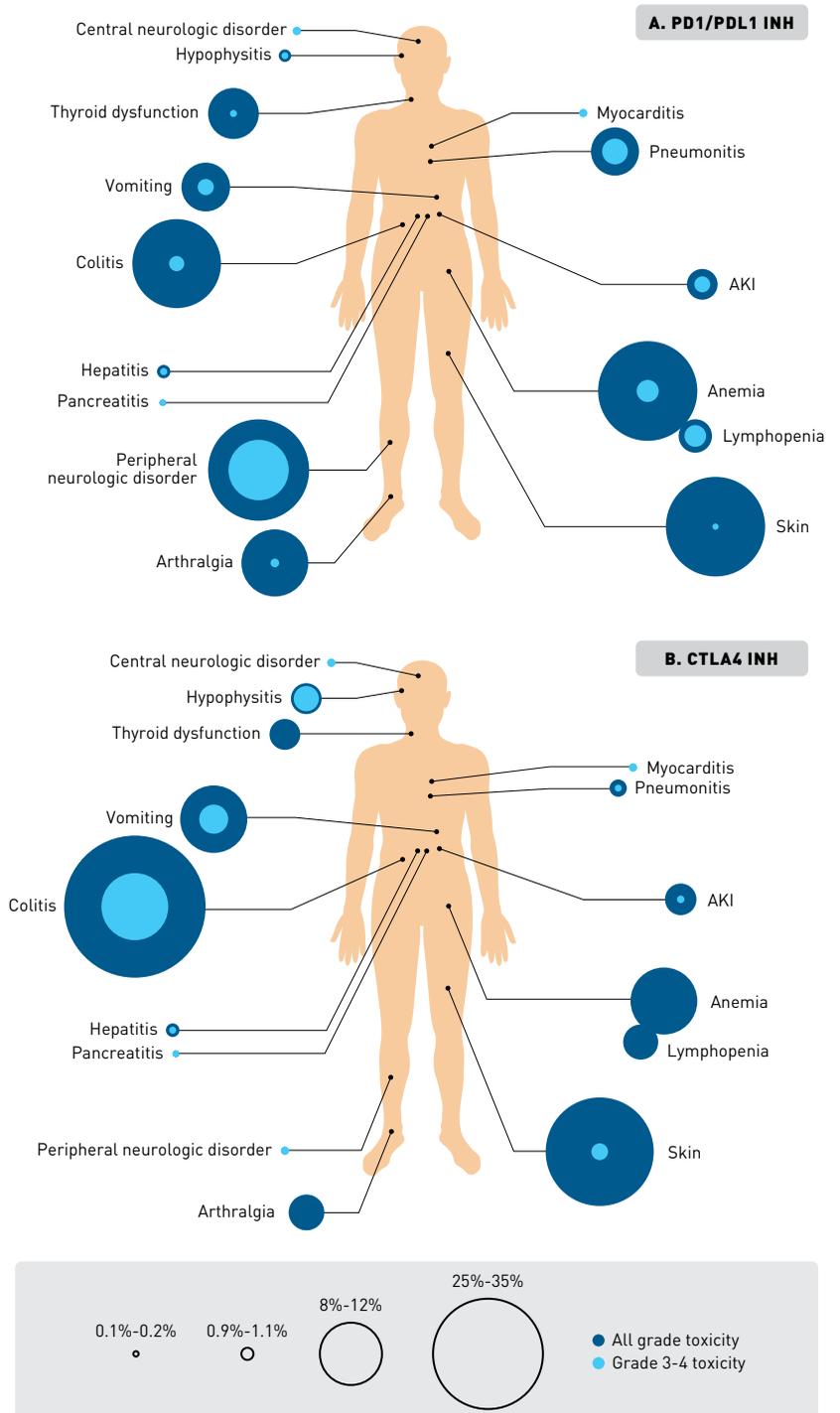
meaningful improvements in ORR and PFS over a median follow-up of 10.9 months.⁵⁴ The combination was granted breakthrough therapy designation in January 2021 and the phase 3 SKYSCRAPER-01 trial of this combination is ongoing.⁵⁵ Meanwhile, in the POSEIDON trial, the combination of durvalumab (PD-1 inhibitor), tremelimumab (CTLA-4 inhibitor), and chemotherapy demonstrated a statistically significant OS benefit compared with chemotherapy alone.⁵⁶

Immune-related Adverse Events (irAEs)

Immune checkpoint blockade results in activation of T cells against tumor cells, which underlies their antitumor efficacy but can also result in unique irAEs. irAEs can impact virtually any organ, with varying frequency and severity across patients and according to the specific ICI (Figure 2⁵⁷). CTLA-4 inhibitors are associated with more frequent and severe irAEs than PD-1 and PD-L1 inhibitors, while PD-1 inhibitors tend to elicit a higher rate of irAEs compared with PD-L1 inhibitors. A patient's overall health, the presence of comorbidities, or receipt of prior ICI therapy can impact the risk of irAEs.⁵⁸⁻⁶⁰

In general, irAEs are mild or moderate in severity and are reversible with appropriate timely management, but some can become severe or fatal if not promptly diagnosed and appropriately managed. Common high-grade AEs include diarrhea and severe skin reactions, while cardiac, hematologic, and neurologic irAEs are rarer causes of potentially severe toxicity. A notable exception to the reversibility of irAEs are those that affect the endocrine system. The pituitary, thyroid, and adrenal glands are the most commonly affected endocrine organs, but inflammation of individual glands also leads to dysfunction in downstream target organs, resulting in a diverse range of symptoms that can be relatively nonspecific, making diagnosis challenging.^{59,60} An irAE of particular relevance to patients with lung cancer is pneumonitis, which although uncommon is potentially life-threatening and has been shown to occur more frequently and with an earlier onset in patients with NSCLC than those with other cancer types. The incidence of

FIGURE 2. Spectrum of irAEs⁵⁷



AKI, acute kidney injury; INH, inhibitor; CTLA4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.
 Frequency of immune-related adverse events. *Toxicity related to anti-PD-1/PD-L1; †toxicity related to CTLA-4i. The size of the circles reflects the incidence of toxicity: dark blue, toxicity of any grade; light blue, grade III/IV toxicity. None of the circles describe toxicity related to CTLA-4i associated with PD-1/PD-L1 inhibitors [the incidence of combined treatments is higher than the toxicity of each inhibitor].

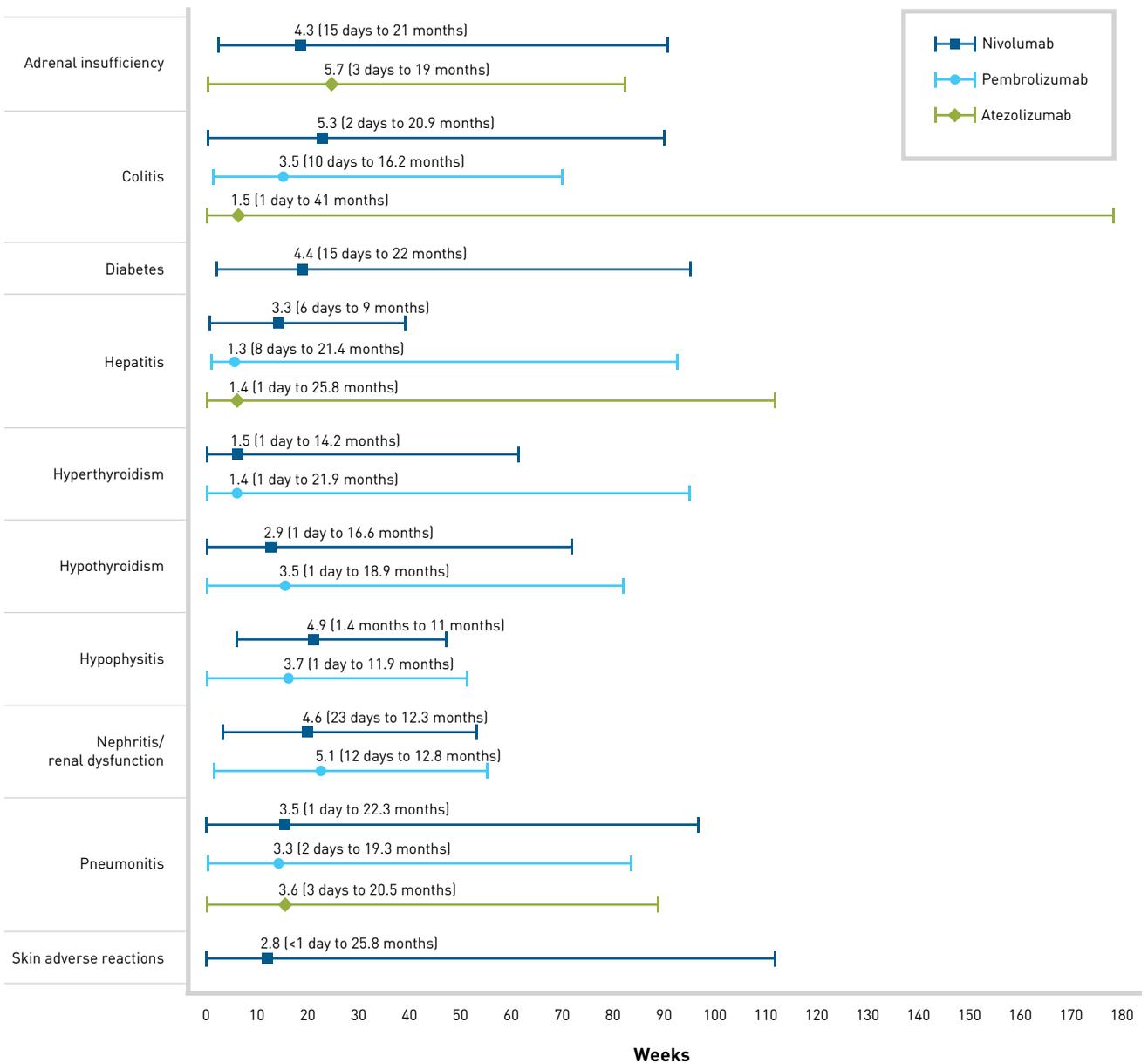
pneumonitis is higher in former or current smokers and in patients treated with combination therapy.⁶¹⁻⁶³

The greater efficacy of combination therapy comes at the expense of increased toxicity. In particular, dual ICI combinations can lead to more frequent or severe irAEs. The combination of ICIs with chemotherapy or targeted therapies typically has less impact on the frequency and severity of irAEs because the toxicity profiles of the drugs are largely non-overlapping. However, these combinations

can present a challenge in distinguishing irAEs from toxicities caused by the partner drug, which can have distinct underlying causes that may necessitate different management strategies.^{59,60}

A distinguishing factor of irAEs is their time of onset (typically 3-6 months after treatment initiation) and longer duration compared with targeted therapies (Figure 3⁶⁴). In some cases, irAEs may develop months or even years after ICI treatment discontinuation.^{33,65} irAEs from CTLA-4 inhibitors tend to present sooner than

FIGURE 3. Timing of Onset of irAEs With PD-1/PD-L1 Inhibitors Across FDA-Approved Tumor Types⁶⁴



irAE, immune-related adverse event; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

those from PD-1 or PD-L1 inhibitors, and irAEs from combination therapies present sooner than those from monotherapies.⁶⁰

There is some evidence that patients who experience certain irAEs may experience better treatment outcomes. While further investigation is still needed, this could have implications for retreatment with ICIs after discontinuation due to irAEs.^{63,66,67} Furthermore, it could impact adherence if patients become concerned that they are not responding in the absence of irAEs.

Management of irAEs varies depending on the grade and type of irAE.³³ Some can be managed with over-the-counter treatments and mild irAEs may not necessitate discontinuation while supportive care is administered. Immunosuppressants, predominantly corticosteroids, are the primary treatment used in higher-grade irAEs, and short-term use of corticosteroids does not appear to reduce anti-tumor efficacy of ICIs. irAEs that do not respond to corticosteroids may require additional treatment with other immunomodulatory drugs.⁶⁷ For moderate/severe irAEs, temporary or permanent discontinuation of therapy is recommended. Re-administration of PD-1 or PD-L1 inhibitors after high-grade irAEs has been shown to be well tolerated; the risk of recurrence must be weighed against the potential benefits of reinitiating therapy. Irreversible endocrinopathies are often managed with endocrine-directed therapies and ICIs can be resumed in stable patients.^{59,60} Given the broad spectrum of irAEs and their unique nature, their effective management requires a coordinated multidisciplinary team of specialists.⁶⁸

Conclusions

Immunotherapy has shaped a new standard of care for patients with advanced or metastatic NSCLC who lack targetable molecular alterations. The preferred treatment paradigm continues to evolve as new ICI-based regimens are approved and with growing appreciation of the importance of PD-L1 expression status in guiding frontline therapeutic choices. With a number of ongoing studies reporting promising data for ICI-chemotherapy, ICI-targeted therapy, and dual immunotherapy combinations, the stage is set for the treatment of metastatic NSCLC to further evolve over the next few years. Although PD-L1 expression is an established predictive biomarker, it is not without limitations that may drive the implementation of alternative biomarkers that further help to shape frontline treatment to ensure optimal outcomes for patients with a tumor type that remains a leading cause of cancer-related mortality. ■

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The Impact of Immune Checkpoint Inhibitors on Cost and Quality of Life in the Initial Treatment of Patients With Advanced or Metastatic NSCLC

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Introduction

Lung cancer is the second most common type of cancer among men and women in the United States, accounting for approximately 12.4% of all new cancer cases. There are an estimated 235,760 new cases of lung cancer in 2021, along with an estimated 131,880 deaths (21.7% of all cancer deaths).¹ Patients with non-small cell lung cancer (NSCLC) can present with either adenocarcinoma, squamous cell, or large cell carcinoma. Research has shown that NSCLC is a heterogeneous disease at the cellular and histologic level. These differences have a significant impact on pathogenesis, diagnosis, and selection of a targeted treatment regimen.²

A retrospective analysis of data from the Surveillance, Epidemiology, and End Results (SEER) database showed that mortality from NSCLC decreased at a faster rate than the incidence from 2013 to 2016. This decrease in mortality correlated to the approval of targeted therapy, which has been shown to significantly improve overall survival (OS) in this population. For men, the mortality rate for NSCLC declined by 3.2% annually from 2006 to 2013, and declined by a faster rate of 6.3% annually from 2013 to 2016. During this time, incidence decreased at an annual rate of 3.1% from 2008 to 2016. A similar increase in survival was seen in the female population as well. This study also noted that in the same timeframe, mortality in the small cell lung cancer population only decreased as a result of decreased incidence.³

The most recent advances in the initial treatment of advanced and metastatic NSCLC are immune checkpoint inhibitors (ICIs), a form of targeted immuno-oncology (IO). At this time there are 2 major targets for ICIs: cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) and its receptor PD-L1.⁴ Ipilimumab is a monoclonal antibody that binds to CTLA-4 and inhibits the negative regulator effect that it has on T-cell activity. This in turn has been shown to increase T-cell (eg, tumor infiltrating T-effector cells) activation and proliferation as well as decrease T-regulatory cell function. While effective, ipilimumab is not recommended as a preferred first-line agent for advanced or metastatic NSCLC.⁵

Another ICI target is PD-1 and its ligand PD-L1. The PD-1 checkpoint protein is found on T cells, and serves as an off switch to

ABSTRACT

Immune checkpoint inhibitors (ICIs) represent a significant benefit for the initial treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC). Beyond clinical benefit of increased overall survival, it represents a class of medications with a favorable adverse effect profile compared with chemotherapy. Drugs that target programmed cell death protein 1 (PD-1) receptor and its ligand PD-L1 are ICIs that work by taking the brakes off the immune system and promote T-cell-mediated cancer cell destruction. Current NCCN guidelines recommend that all patients with advanced or metastatic NSCLC have their PD-L1 status (amount of PD-L1 on cancer cells) assessed to guide treatment selection. However, this recommendation is not always followed and may lead to inappropriate treatment selection and potential increased cost. Through appropriate biomarker testing, subsequent appropriate utilization of ICIs may help to drive down other costs and improve health-related quality of life. Managed care pharmacists should continue to focus on promotion of guideline concordant care that includes appropriate biomarker testing and selection of an evidence-based preferred treatment option.

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For author information and disclosures, see end of text.

prevent cells from attacking each other. When PD-1 binds to its receptor PD-L1, it signals to the T cell to not attack. The problem arises when cancer cells exhibit PD-L1, and therefore escape T cell-mediated destruction. As of August 2021, the FDA had approved several therapies that target and bind to either PD-1, PD-L1, or CTLA-4 (pembrolizumab, nivolumab plus ipilimumab, cemiplimab, atezolizumab) for the first-line treatment of advanced or metastatic NSCLC. In general, selection of an agent is guided by the presence of a targeted treatment (eg, epidermal growth factor receptor status) identified through molecular testing. However, in patients who are PD-L1 positive with no other actionable molecular markers, regimens that include PD-1 and PD-L1 inhibitors are the preferred first-line agents for advanced or metastatic NSCLC.^{4,6} These recommendations are summarized in **Table 1**.⁶

Determination of which agent to select is determined on the PD-L1 status.⁷ As summarized in Table 1,⁶ treatment of patients who express PD-L1 is segregated into 3 categories: (1) PD-L1 less than 1%, (2) PD-L1 greater than or equal to 1% to 49%, and (3) PD-L1 greater than or equal to 50%. Clinical trials have demonstrated OS benefit of regimens specifically in these PD-L1 ranges. It is recommended to test all patients with newly diagnosed advanced or metastatic NSCLC for PD-L1 status to select a treatment regimen with optimal OS benefit. However, there is not one standard assay for PD-L1 status and each ICI has a specific FDA-approved companion diagnostic immunohistochemistry assay. **Table 2**⁸ summarizes the current ICIs recommended in first-line regimens for advanced or metastatic NSCLC and companion diagnostic immunohistochemistry assays.

Not all patients with advanced or metastatic NSCLC present with the same level of PD-L1 expression. In a worldwide, retrospective study of real-world evidence of 2617 adult patients (aged ≥ 18 years) with histologically confirmed (stage IIIB/IV NSCLC) found that 2368 (90%) of patients had PD-L1 data evaluated with PD-L1 IHC 22C3 pharmDx. Of this evaluable population, a majority had PD-L1 less than 1% ($n = 1136$, 48%), followed by PD-L1 greater than or equal to 1% to 49% ($n = 702$, 30%) and PD-L1 greater than or equal to 50% ($n = 530$, 22%).⁹

Economic Impact of Insufficient Biomarker Testing

Clinical trials have supported the OS benefit of biomarker testing to guide treatment selection based on PD-L1 status. This benefit is reflected in NCCN guidelines as a recommendation to test all patients with newly diagnosed advanced or metastatic NSCLC for PD-L1 status. However, real-world concordance with these recommendations is not always adhered to. While these tests all measure PD-L1 status, they use different antibody clones, staining platform, and scoring system (eg, tumor proportion score, tumor cell, tumor infiltrating immune cells). Therefore, specific tests need to accompany specific ICIs. Efforts have been taken to determine if these tests can be interchanged. In the Blueprint Phase 2 Project, study investigators suggested interchangeability between PD-L1 IHC 22C3 pharmDx, PD-L1 IHC 28-8 pharmDx, and VENTANA PD-L1(SP263) Assay, but not VENTANA PD-L1(SP142) Assay.^{10,11} However, use

TABLE 1. ICIs for First-line Treatment of Advanced or Metastatic NSCLC⁶

Testing results	Targeted therapy
PD-L1 $\geq 1\%$ -49% and negative for other actionable molecular markers	<ul style="list-style-type: none"> • Pembrolizumab • (Carboplatin or cisplatin) / pemetrexed / pembrolizumab (nonsquamous)^a • Carboplatin / paclitaxel / bevacizumab / atezolizumab (nonsquamous) • Carboplatin / (paclitaxel or albumin-bound paclitaxel) / pembrolizumab (squamous)^a • Carboplatin / albumin-bound paclitaxel / atezolizumab (nonsquamous) • Nivolumab/ipilimumab • Nivolumab / ipilimumab / pemetrexed / (carboplatin or cisplatin) (nonsquamous) • Nivolumab / ipilimumab / paclitaxel / carboplatin (squamous)
PD-L1 $\geq 50\%$ and negative for other actionable molecular markers	<p>All regimens listed for PD-L1 $\geq 1\%$-49% are also considered appropriate. Additionally, the following recommendations are specifically different for PD-L1 $\geq 50\%$</p> <ul style="list-style-type: none"> • Atezolizumab^a • Cemiplimab-rwlc^a • Pembrolizumab^a • Carboplatin / (paclitaxel or albumin-bound paclitaxel) / pembrolizumab (squamous) <p>For those with a good PS (0-2), IO systemic therapy can be initiated. However, IO not preferred in PS 2.</p>
PD-L1 $< 1\%$ and negative for other actionable molecular markers	<ul style="list-style-type: none"> • Preferred treatment for adenocarcinoma (PS 0-1): <ul style="list-style-type: none"> › Pembrolizumab / carboplatin / pemetrexed › Pembrolizumab / cisplatin / pemetrexed • Preferred treatment for squamous cell carcinoma (PS 0-1): <ul style="list-style-type: none"> › Pembrolizumab / carboplatin / pemetrexed › Pembrolizumab / carboplatin / albumin-bound paclitaxel

ICI, immune checkpoint inhibitor; IO, immuno-oncology; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death protein ligand 1; PS, performance status.

^aPreferred first-line agents.

of an unapproved companion diagnostic test may lead to the inappropriate identification of a treatment eligible, or ineligible, patient.

One of the drawbacks of utilizing ICIs for the treatment of NSCLC is the limitation on testing for biomarkers. Insufficient or improper usage of biomarker testing may lead to underutilization of effective treatments, increased risk of inappropriate care, and increased unnecessary costs. In a retrospective observational claims study of the IBM Watson Health MarketScan Commercial and Medicare Supplemental Claims and Encounters databases from October 2012 to September 2017, a total of 3095 patients with advanced or metastatic NSCLC treated with an ICI were propensity matched to a population of 3095 patients with NSCLC who were eligible for ICI therapy but were treated with another regimen. Study investigators found that the overall utilization of PD-L1 testing was moderate at 0.6 and 0.7 tests per patient in the ICI treated and non-ICI treated group. This represents a significant discordance with current guidance to test all patients for PD-L1 status. Those in the ICI group incurred significantly higher total costs per patient than the non-ICI treated group in the 6 months post-treatment initiation (\$141,537 vs \$75,429; $P < .0001$). This study suggested that some patients who received ICI therapy did not have PD-L1 testing before treatment.¹² This in turn could lead to inappropriate additional costs. For example, if a patient had a PD-L1 greater than or equal to 50% and negative for other actionable molecular markers, monotherapy with either atezolizumab, cemiplimab-rwlc, or pembrolizumab are preferred regimens for initial treatment. Inappropriate usage of treatment regimens may have incurred unnecessary direct costs from combination ICI plus chemotherapy treatment regimens and other costs such as treating chemotherapy-related adverse effects (AEs) versus immune-related adverse events (irAEs).¹³

AEs associated with chemotherapy are clinically and economically burdensome. In general, IOs (eg, ICIs) are considered safer as they are not directly cytotoxic. irAEs are associated with IO and can necessitate hospitalization, if severe. In a single center study, the cost associated with treating patients on ICI therapy from February 2011 to June 2017 was collected and summarized. While the annual cumulative costs due to irAEs increased from \$218,700 to \$1.3 million, the average cost per day of irAE hospitalization was significantly less than non-irAE oncology-related hospitalizations (\$3142/day vs \$8257/day; $P = 10^{-10}$). Study investigators noted that this decrease in cost per day was possibly associated with irAEs being more readily intervenable.¹³

A systematic review of studies conducted between 2009 and 2019 evaluated the cost-effectiveness of biomarker tests for targeted therapy (including ICIs) compared with nonguided therapy or chemotherapy. Thirty-seven studies (conducted in multiple countries) were identified, with 64 different scenarios. Of those 64 scenarios, 34 scenarios (53%) were cost-effective, 28 (44%) were not cost-effective, and 2 were neither.¹⁴ Cost-effectiveness was dependent

on an individual country's willingness to pay threshold, which is usually set at 3 times that country's gross domestic product per capita.¹⁵ When study authors compared biomarker-guided treatment selection to therapy for all patients approach, all scenarios were cost-effective. A limitation of this study was that a majority of studies (81%) were inappropriately designed for cost-effectiveness. However, all of the remaining 7 studies (19%) demonstrated cost-effectiveness of biomarker testing.¹⁴

Impact of ICIs on Quality of Life and Resource Utilization in the Initial Treatment of Advanced or Metastatic NSCLC

Atezolizumab

No studies were identified regarding the health-related quality of life (HRQOL) of atezolizumab monotherapy as initial treatment of advanced or metastatic NSCLC. However, a study that compared combination atezolizumab, bevacizumab, carboplatin, and paclitaxel to bevacizumab, carboplatin, and paclitaxel or atezolizumab, carboplatin, and paclitaxel had secondary end points that evaluated HRQOL on the Quality-of-Life Questionnaire Core 30 items (QLQ-C30) and Quality-of-Life Questionnaire Lung Cancer 13 items (QLQ-LC13) scales. No significant differences were observed between treatment groups regarding HRQOL measures.¹⁶

Pembrolizumab

One study evaluated the HRQOL of pembrolizumab monotherapy for the initial treatment of advanced PD-L1-positive NSCLC. The KEYNOTE-024 trial was a pivotal open-label phase 3, randomized trial that compared pembrolizumab to chemotherapy in patients with PD-L1 greater than or equal to 50%. The key prespecified exploratory end points were baseline-to-week-15 change in the QLQ-C30 (100-point scale) global health status (GHS)/quality-of-life (QOL) score, and the time to deterioration of the composite of cough, chest pain, and dyspnea in the QLQ-LC13. Pembrolizumab monotherapy showed a significantly better (lower) QLQ-C30 score at 15 weeks compared with chemotherapy with a difference of 7.8 (95% CI, 2.9-12.8; $P = .0020$). Additionally, time to deterioration was

TABLE 2. FDA-Approved Companion Diagnostic IHC Assay of ICIs Recommended in First-Line Regimens for Treating Advanced or Metastatic NSCLC⁸

Select ICIs	Companion diagnostic immunohistochemistry assay
Atezolizumab	VENTANA PD-L1 (SP142) Assay
Cemiplimab-rwlc	PD-L1 IHC 22C3 pharmDx
Nivolumab	PD-L1 IHC 28-8 pharmDx
Pembrolizumab	PD-L1 IHC 22C3 pharmDx

ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death protein ligand 1.

also longer in the pembrolizumab group compared with chemotherapy with a hazard ratio of 0.66 (95% CI, 0.44-0.97; $P = .029$). This study suggests that for patients with advanced or metastatic NSCLC and a PD-L1 greater than or equal to 50%, first-line treatment with pembrolizumab provides an HRQOL benefit over chemotherapy.¹⁷

This benefit in HRQOL of pembrolizumab was also demonstrated in combination with chemotherapy compared with chemotherapy alone in patients with nonsquamous metastatic NSCLC. In the KEYNOTE-189 study, pembrolizumab plus pemetrexed-platinum had better maintained GHS/QOL at week 21 compared with placebo plus pemetrexed-platinum with a between-group difference of 5.3 points (95% CI, 1.1-9.5); $P = .014$). Additionally, there was no significant difference in the time to deterioration between groups.¹⁸ Patients in this study had presented with varied PD-L1 status of PD-L1 less than 1% (31%), PD-L1 greater than or equal to 1% to 49% (31.2%), and a PD-L1 greater than or equal to 50% (32.2%).¹⁹ These findings further support the HRQOL benefit of pembrolizumab added to pemetrexed-platinum for patients of varied PD-L1 status. An argument can also be made that a more pronounced benefit may have been observed if the PD-L1 status was limited to greater than or equal to 50%.¹⁸

Nivolumab

The CheckMate 227 study was an open-label trial that evaluated nivolumab plus ipilimumab compared with chemotherapy for the initial treatment of advanced NSCLC with a high tumor burden. Beyond efficacy and safety, one of the exploratory end points was Lung Cancer Symptom Scale LCSS 3-item global index (LCSS 3-IGI), which was on a 300-point scale (higher number, better HRQOL). In this study, a minimally important difference was noted as a change in score of 30 or more. At week 6, there were noted improvements in HRQOL in the nivolumab plus ipilimumab arm compared with the chemotherapy arm that reached a minimally important difference at 12 weeks that was maintained through the rest of the study.²⁰

Cemiplimab

The EMPOWER-Lung 1 trial was a randomized, open-label, multicenter, phase 3 study that evaluated cemiplimab dosed 350 mg intravenously every 3 weeks (up to 108 weeks) or 4 to 6 cycles of provider's choice platinum-doublet therapy for initial treatment of advanced NSCLC with PD-L1 greater than or equal to 50%. The median follow-up time in this study was about 10.8 months in both groups. In regard to efficacy, median overall survival was not reached in the cemiplimab group ($n = 283$), and was 14.2 months in the chemotherapy group ($n = 280$). This translated to a significantly reduced risk for those in the cemiplimab group compared with chemotherapy with a hazard ratio of 0.57 (95% CI, 11.2-17.5; $P = .0002$). Median progression-free survival was also significantly higher in the cemiplimab group (8.2 months) compared with the chemotherapy group (5.7 months), with a hazard ratio for disease

progression of 0.54 (95% CI, 0.43-0.68; $P < .001$). Utilizing the intention-to-treat population, which included some patients with lower PD-L1 expression, fewer patients in the cemiplimab group ($n = 356$) versus the chemotherapy group ($n = 354$) had grade 3-4 treatment-emergent AEs (28% vs 39%, respectively). QOL was also assessed as a secondary outcome in the intention-to-treat population, and a meaningful change in QLQ-C30 from baseline throughout the trial was observed in only patients on cemiplimab, not chemotherapy. While not definitive, this may have been attributed to the favorable benefit and AE profile of cemiplimab compared with chemotherapy and/or the open-label design of the study.²¹

Other QOL Considerations

A real-world patient-reported outcome study of patients who received IO or chemotherapy plus IO for metastatic NSCLC was evaluated to determine if clinical practice differed significantly from clinical trials. From 2017 to 2018, patients at a single academic medical center completed the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) and the National Cancer Institute Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). A total of 60 patients participated, of which 57% received a single-agent IO. Results of this study showed a mean EORTC-QLQ-C30 global health score of 62.6, which was similar to second-line single-agent IO (65-67), but worse than first-line IO with pembrolizumab alone (71). Of note, insomnia and financial concerns were meaningfully worse than what was observed in previous trials. The most common concerns noted also included dermatologic symptoms, cough, arthralgia, and myalgia. Study investigators note that a limitation of this study may be that the sampled population may have been at a lower socioeconomic status or had more noncancer comorbidities. Results suggest that healthcare providers should expect similar QOL and symptom burden as seen in clinical trials, but real-world factors may adversely affect these values.²²

With the increased OS seen in patients on IO-based treatment regimens, some patients are living beyond their initial life expectancy. In one international study of 24 survivors who received IO for stage IV NSCLC, qualitative interviews and other assessments were performed by study investigators who spent a total of 2 days at their homes and health-related outings. Investigators noted that long-term survivors of patients who were on IO experienced their journey in 2 phases. The first phase was when their cancer diagnosis took over all aspects of their life. The second phase occurred when cancer only took a small part of everyday living. Those patients who lived beyond the initial prognosis of a terminal disease lived in what was described as a limbo period, where life returned almost to normal besides having a terminal diagnosis. This limbo period impacted various aspects of the survivor's life that included life

priorities, decision making, how they experienced patient support, and how they sought health information. All of these changes were noted to impact QOL in a way that may not be well understood by healthcare providers, the cancer community, or by current QOL assessment tools that were designed before IO treatment options were available. What investigators recommended was increased awareness of healthcare providers on how increased life expectancy may change a patient's view on QOL and how to best direct resources to the patient.²³

Resource Utilization

The treatment of advanced and metastatic NSCLC continues to be a high economic burden. High costs of care are driven by inpatient, outpatient, and medication costs associated with treatment. While varying studies have supported the cost-effectiveness of ICIs in the initial treatment of advanced or metastatic NSCLC, treatment can be expensive due to high direct costs of care.²⁴ Previous studies have evaluated the total cost of care and resource usage. However, many have not accounted for the added mortality benefit, improved safety profile, and other considerations of ICI treatment. There still remain limited studies that have evaluated the resource utilization of ICIs in the initial treatment of advanced and metastatic NSCLC.²⁵

Previously discussed was the potential for decreased usage of hospital resources for managing treatment-emergent AEs or irAEs. One real-world claims-based study found that AEs were least common in patients treated with IO compared with either chemotherapy or IO plus chemotherapy with an incident rate ratio of 1.4 for both. This can be interpreted as a 40% higher relative rate of AEs in the chemotherapy or IO plus chemotherapy group compared with IO alone. This translated to a significantly lower per-member per-month cost of AEs in the IO cohort (\$4259) compared with either chemotherapy (\$6323; $P < .001$) or IO plus chemotherapy (\$6269; $P = .020$).²⁶

A single-center retrospective chart review of STANford medicine Research data Repository (STARR) data indicated that 97 patients with NSCLC treated with either a tyrosine kinase inhibitor (TKI), ICI-based regimen, or chemotherapy visited the emergency department (ED) in 2018 a total of 173 times. Therapy-related encounters were a significantly smaller portion of ED visits in the TKI group (2%), ICI group (12%), and chemotherapy group (21%). This real-world evidence supports the potential for decreased healthcare resource utilization associated with ICIs compared with chemotherapy.²⁷ For patients receiving ICIs, providers should closely monitor for AEs that are expected to be immune related to prevent additional healthcare costs.

A retrospective claims review of Medicare Part D patients in the Optum Research Database from March 1, 2014, through April 30, 2019, evaluated the healthcare resource utilization, cost, and mortality of those who received a PD-1- or PD-L1-targeted ICI. Results showed

that patients who had an AE associated with ICI therapy were at a 2-fold greater risk of an inpatient hospital stay with a hazard ratio of 2.2 (95% CI, 1.9-2.5) and a higher risk of an emergency visit with a hazard ratio of 1.8 (95% CI, 1.6-2.1) than patients who did not experience an AE. This translated to a significantly higher adjusted 6-month cost of \$24,301 (95% CI, \$18,828-\$29,774; $P < .001$). The main driver for this increased cost was associated with inpatient visits that accounted for 89% of the total. Mortality was noted as similar between groups that had or did not have an AE.²⁸

To better understand the impact of IO on the total cost of care associated with the initial treatment of advanced NSCLC, one study was conducted that assessed the direct costs between a pre-immuno-oncology (pre-IO) period from March 2013 to March 2014 to a post-immuno-oncology (post-IO) period from March 2015 to December 2016. Patients were identified through the Medical Outcomes Research for Effectiveness and Economics Registry Research database, which is composed of multiple payer data. A total of 5741 patient records were included, and were propensity score matched to include 1550 in each cohort. Results from the study show that in the matched cohorts, there were significantly fewer hospitalizations (61% vs 46%; $P < .001$), any ED visit (77% vs 66%; $P < .001$), mean number of ED visits (3.3 vs 2.9; $P < .002$), total cost of care (\$129,977 vs \$113,117; $P < .001$), and mean per-patient per-month total cost of care (\$12,681 vs \$10,758; $P < .001$). These results are summarized in [Table 3](#).²⁹

Compared with second-line or third-line treatment, only the first-line treatment mean total cost of care was only significantly higher in the pre-IO group compared with the post-IO group (\$87,890 vs \$80,206; $P = .011$). Additionally, when taking a look at predictors of a higher total cost in the post-IO group, the variables that stand out include use of IO in any line of treatment, first-line combination therapy, and biomarker testing. A limitation of this study was that a characterization of what chemotherapy or IO was not provided in the pre-IO and post-IO periods. A breakdown of these variables is illustrated in the [Figure](#).²⁹

Conclusions

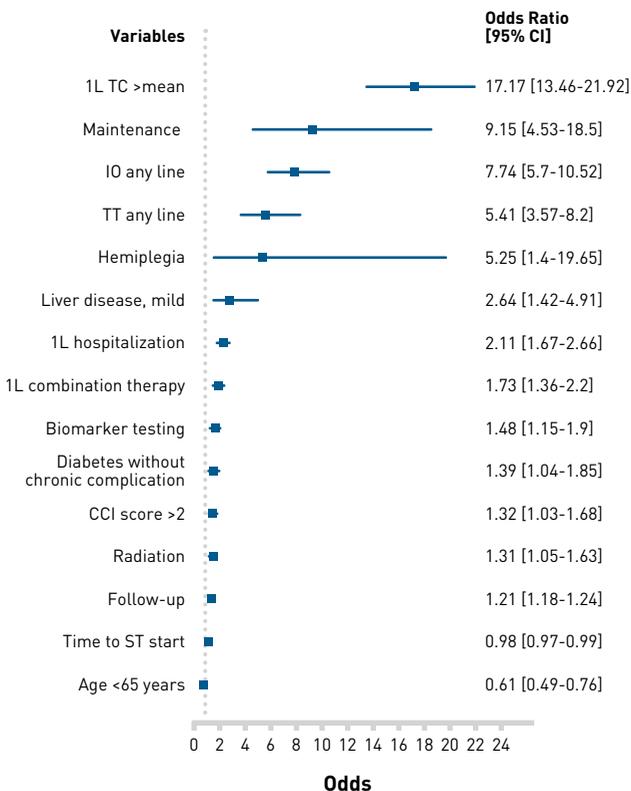
The initial management of advanced or metastatic NSCLC has evolved with the incorporation of ICIs into the treatment paradigm. These therapies have not only demonstrated a significant increase in OS, but have also provided a treatment option with potentially fewer AEs. One limitation regarding the utility of ICIs for treatment is the need for specific biomarker companion assays to help determine appropriate treatment selection. At this time, these assays are not interchangeable, and companion tests have to be used with their corresponding companion ICI. Current NCCN guidelines recommend that all patients with advanced or metastatic NSCLC have PD-L1 status assessed with an FDA-approved test to determine status. However, real-world concordance with this recommendation

TABLE 3. Healthcare Resource Utilization and Cost Comparison for the Entire Follow-up Period Between Pre-IO and Post-IO²⁹

	Unmatched Cohorts			Matched Cohorts		
	Cohort 1 Pre-IO n = 2744	Cohort 2 Post IO n = 2997	P	Cohort 1 Pre-IO n = 1550	Cohort 2 Post IO n = 1550	P
Any hospitalization (n, %)	1678 (61)	1353 (45)	<.001	946 (61)	713 (46)	<.001
Hospitalizations (mean, SD)	2.5 (2.1)	2.0 (1.5)	<.001	2.3 (1.6)	2.1 (1.7)	.006
LOS (mean, SD)	1.9 (4.3)	2.2 (9.5)	.159	1.7 (2.7)	2.1 (8.4)	.155
Any ED visit (n, %)	2145 (78)	1896 (63)	<.001	1194 (77)	1016 (66)	<.001
ED visits, mean (SD)	3.7 (4.4)	2.7 (2.5)	<.001	3.3 (3.0)	2.9 (2.6)	.002
Total cost of care (mean, SD)	\$165,548 (\$153,049)	\$95,715 (\$90,337)	<.001	\$129,977 (\$112,479)	\$113,117 (\$96,557)	<.001
ED visit cost	\$40,281 (\$61,000)	\$22,764 (\$31,091)	<.001	\$36,639 (\$50,541)	\$23,331 (\$27,065)	<.001
Hospitalization cost	\$29,924, (\$84,072)	\$17,459 (\$51,412)	<.001	\$24,876, (\$61,778)	\$17,680 (\$56,115)	<.013
ST cost	\$31,487 (\$62,644)	\$21,599 (\$39,940)	<.001	\$21,025 (\$38,531)	\$27,928 (\$48,566)	<.001
Per patient per month total cost of care (mean, SD)	\$11,522 (\$9580)	\$11,977 (\$8763)	.060	\$12,681 (\$10,371)	\$10,758 (\$7221)	<.001

ED, emergency department; IO, immuno-oncology, LOS, length of stay; SD, standard duration; ST, systemic antineoplastic therapy.

FIGURE. Predictors of Total Cost Above the Mean in Post-IO²⁹



1L, first-line; 2L, second-line; CCI, Charlson Comorbidity Index; ED, emergency department; IO, immuno-oncology; ST, systemic antineoplastic therapy; TC, total cost; TT, targeted therapy.

is not 100%. Patients with PD-L1 greater than or equal to 50% are able to start monotherapy with an ICI that includes atezolizumab, cemiplimab-rwlc, or pembrolizumab. Real-world evidence has shown that use of IO may result in lower healthcare resource utilization, fewer ED visits, and potentially lower costs. Additionally, IOs may offer a more favorable benefit/risk profile compared with chemotherapy that may be associated with decreased AEs and cost. The use of ICIs for initial treatment of advanced or metastatic NSCLC is also supported through increased HRQOL, especially in the PD-L1 greater than or equal to 50% population treated with pembrolizumab. As patients continue to live beyond the initial prognosis, it is important for healthcare providers to assess and discuss with their patients what is important to them now and how their healthcare should be prioritized. Managed care pharmacists should prioritize guideline concordance to biomarker testing and utilization of preferred treatment options that can increase HRQOL while controlling costs. Clinical treatment pathways may be considered to help guide optimal treatment selection guided by preferred ICI-based treatment regimens. ■

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Assessing the Impact of Immunotherapy on Quality of Life and Patient Outcomes in the Frontline Management of Advanced Non-Small Cell Lung Cancer

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Sample of Online Posttest

Choose the best answer for each of the following:

1. According to the current National Comprehensive Cancer Network guidelines for non-small cell lung cancer (NSCLC), what is the preferred frontline option for patients with metastatic disease with a programmed cell death ligand 1 (PD-L1) expression level of $\geq 1\%$ -49%?
 - A. Pembrolizumab monotherapy
 - B. Atezolizumab plus chemotherapy and bevacizumab
 - C. Pembrolizumab plus chemotherapy
 - D. Cemiplimab monotherapy
2. When using the PD-L1 immunohistochemistry (IHC) 22C3 pharmDx assay as a companion diagnostic, what cutoff of PD-L1 positivity is required for treatment with cemiplimab monotherapy in metastatic NSCLC?
 - A. $\geq 50\%$
 - B. $\geq 1\%$
 - C. $>10\%$
 - D. This is not an appropriate companion diagnostic for use with cemiplimab monotherapy.
3. AN is a 65-year-old man who presents with newly diagnosed metastatic NSCLC. Next-generation sequencing (NGS) testing identified no actionable biomarkers. His performance status is 1 and he has no contraindications for immune checkpoint inhibitors (ICIs). He has not undergone PD-L1 testing. Which statement is correct?
 - A. The patient should be enrolled in a clinical trial.
 - B. The patient should be treated with pembrolizumab monotherapy.
 - C. The patient should be treated with targeted therapy.
 - D. The patient should undergo PD-L1 testing to help determine the appropriate therapeutic option.
4. Patient AN undergoes PD-L1 testing and subsequently receives pembrolizumab monotherapy as his tumor expressed levels of PD-L1 exceeding 50%. Which statement is true?
 - A. Pembrolizumab is safer than chemotherapy so the patient is unlikely to experience any adverse effects.
 - B. The safety profile of pembrolizumab is very similar to chemotherapy.
 - C. The patient should be closely monitored for the development of immune-related adverse events (irAEs), which can affect any organ.
 - D. If the patient has not experienced any irAEs 2 weeks after treatment initiation, then he is unlikely to experience an irAE.
5. Which statement is incorrect regarding the currently available PD-L1 IHC assays?
 - A. They can be used interchangeably to determine PD-L1 status in patients with NSCLC.
 - B. They are associated with many clinical challenges.
 - C. Different assays are approved for use with different ICIs.
 - D. They use different thresholds for PD-L1 positivity.
6. Can the companion diagnostic immunohistochemistry assay PD-L1 IHC 28-8 pharmDx be used to assess PD-L1 before treatment selection of atezolizumab, cemiplimab-rwlc, nivolumab, and/or pembrolizumab?
 - A. The PD-L1 IHC 28-8 pharmDx can be used to assess the PD-L1 before treating with any ICI.
 - B. The PD-L1 IHC 28-8 pharmDx can only be used to assess the PD-L1 before treating with nivolumab.
 - C. The PD-L1 IHC 28-8 pharmDx can only be used to assess the PD-L1 before treating with pembrolizumab.
 - D. No PD-L1 testing is required before initiation of atezolizumab, cemiplimab-rwlc, nivolumab, or pembrolizumab.

- 7. Treatment guidelines for patients with NSCLC segregate recommendations based on PD-L1 expression into which categories?**
- A. Initial treatment of advanced or metastatic NSCLC is not guided by PD-L1 status.
 - B. PD-L1-positive tumors are all treated with the same preferred treatment regimens.
 - C. PD-L1 <1%, PD-L1 \geq 1%-49%, and PD-L1 \geq 50%.
 - D. PD-L1 <1%, PD-L1 \geq 50%, and PD-L1 \geq 75%.
- 8. A colleague asks you if ICIs for the initial treatment of advanced or metastatic NSCLC have improved health-related quality of life (HRQOL) for patients. What is the most appropriate response?**
- A. There is no evidence to support improved HRQOL in patients on ICIs compared with other standard-of-care treatment.
 - B. All ICIs have been shown definitively to provide a markedly improved HRQOL.
 - C. Only atezolizumab has been shown to provide improved HRQOL.
 - D. Limited evidence supports that all ICIs did not worsen HRQOL when compared with other treatments such as chemotherapy. Pembrolizumab also demonstrated a statistically significant improvement in HRQOL compared with chemotherapy.
- 9. Which statement is true regarding real-world evidence on adverse reactions of ICI therapy and chemotherapy?**
- A. In general, chemotherapy has a more favorable adverse effect profile than ICIs.
 - B. Utilization of ICIs has been attributed to more frequent usage of emergency department services when compared with chemotherapy.
 - C. Retrospective claim review studies support that ICIs may have a more favorable adverse effect profile compared with chemotherapy and are associated with decreased emergency department services.
 - D. There are no studies that evaluated real-world evidence regarding adverse reactions of ICI therapy and chemotherapy.
- 10. Why should healthcare providers be alert for patients who experience an adverse reaction while on an ICI?**
- A. One study noted more than a 2-fold increased risk of hospitalization in patients who experienced an adverse reaction versus no adverse reaction while on an ICI.
 - B. One study noted no significant difference in total cost of care associated with adverse reactions.
 - C. One study noted a 5-fold increased risk of emergency department visits in patients who experienced an adverse reaction versus no adverse reaction while on an ICI.
 - D. Healthcare providers do not have to be concerned about adverse reactions while a patient is on an ICI.

POSTTEST

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