JAMA | Review

Systemic Therapy for Locally Advanced and Metastatic Non–Small Cell Lung Cancer
A Review

Kathryn C. Arbour, MD; Gregory J. Riely, MD, PhD

IMPORTANCE Non–small cell lung cancer remains the leading cause of cancer death in the United States. Until the last decade, the 5-year overall survival rate for patients with metastatic non–small cell lung cancer was less than 5%. Improved understanding of the biology of lung cancer has resulted in the development of new biomarker–targeted therapies and led to improvements in overall survival for patients with advanced or metastatic disease.

OBSERVATIONS Systemic therapy for metastatic non–small cell lung cancer is selected according to the presence of specific biomarkers. Therefore, all patients with metastatic non–small cell lung cancer should undergo molecular testing for relevant mutations and expression of the protein PD-L1 (programmed death ligand 1). Molecular alterations that predict response to treatment (eg, *EGFR* mutations, *ALK* rearrangements, *ROS1* rearrangements, and *BRAF* V600E mutations) are present in approximately 30% of patients with non–small cell lung cancer. Targeted therapy for these alterations improves progression-free survival compared with cytotoxic chemotherapy. For example, somatic activating mutations in the *EGFR* gene are present in approximately 20% of patients with advanced non–small cell lung cancer. Tyrosine kinase inhibitors such as gefitinib, erlotinib, and afatinib improve progression-free survival in patients with susceptible *EGFR* mutations. In patients with overexpression of ALK protein, the response rate was significantly better with crizotinib (a tyrosine kinase inhibitor) than with the combination of pemetrexed and either cisplatin or carboplatin (platinum-based chemotherapy) (74% vs 45%, respectively; $P < .001$) and progression-free survival (median, 10.9 months vs 7.0 months; $P < .001$). Subsequent generations of tyrosine kinase inhibitors have improved these agents. For patients without biomarkers indicating susceptibility to specific targeted treatments, immune checkpoint inhibitor–containing regimens either as monotherapy or in combination with chemotherapy are superior vs chemotherapy alone. These advances in biomarker-directed therapy have led to improvements in overall survival. For example, the 5-year overall survival rate currently exceeds 25% among patients whose tumors have high PD-L1 expression (tumor proportion score of ≥50%) and 40% among patients with *ALK*-positive tumors.

CONCLUSIONS AND RELEVANCE Improved understanding of the biology and molecular subtypes of non–small cell lung cancer have led to more biomarker-directed therapies for patients with metastatic disease. These biomarker-directed therapies and newer empirical treatment regimens have improved overall survival for patients with metastatic non–small cell lung cancer.

CME Quiz at jamanetwork.com/learning

Author Affiliations: Thoracic Oncology Service, Division of Solid Tumor, Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, New York.

Corresponding Author: Gregory J. Riely, MD, PhD, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065 (rielyg@mskcc.org).

Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

JAMA. 2019;322(8):764-774. doi:10.1001/jama.2019.11058

Lung cancer is the leading cause of cancer-related deaths in the United States, and will account for an estimated 142 670 deaths in 2019. Among the common subtypes of lung cancer, non–small cell lung cancer (NSCLC) represents 85% of lung cancer cases.[1] Advances in treatment of NSCLC have been facilitated by an improved understanding of pathogenic genomic alterations of NSCLC, the development of new drugs,[2] and the use of biomarkers to identify patients most likely to respond to immune checkpoint blockade therapy. Cytotoxic chemotherapy remains an important component of systemic therapy for most patients, but regimens that forgo chemotherapy in favor of molecularly targeted therapies or immunotherapy are standard first-line therapies for about 50% of patients with advanced NSCLC.

This review provides an overview of the pathological evaluation of NSCLC and describes current evidence-based approaches to systemic therapy for patients with locally advanced or metastatic NSCLC. Because there have been few recent advances for NSCLC stage I or II, this review focuses on advances in NSCLC stages III and IV.

Methods

A PubMed search for English-language articles describing clinical trials of medical therapies for NSCLC was conducted from January 1, 2013, to May 1, 2019. We prioritized data from randomized trials that have influenced current standards of care for patients with NSCLC. Nonrandomized studies that led to changes in standard treatments or regulatory approval of new therapies for patients with NSCLC also were evaluated for inclusion. Articles agreed on by both authors (K.C.A. and G.J.R.) that define current clinical practice were included. The guidelines from major professional societies also were reviewed.

Clinical Presentation and Epidemiology of NSCLC

Approximately 228 000 people in the United States will be diagnosed with lung cancer in 2019, and lung cancer accounts for 40% of cancer-related deaths.[3] Smoking is the most common risk factor for the development of NSCLC. However, 15% of patients diagnosed with NSCLC never smoked cigarettes.[4] Recent evidence has shown that low-dose computed tomography screening can reduce lung cancer–specific mortality by 62 events per 100 000 person-years and is recommended by the US Preventive Services Task Force (grade B) for patients aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years.[5]

Widespread screening has the potential to diagnose earlier-stage cancers; however, more than half of newly diagnosed patients with lung cancer have metastatic disease at the time of initial diagnosis.[6] Patients diagnosed with NSCLC often present with respiratory symptoms such as cough or dyspnea, but may also present with symptoms related to the most common sites of metastatic disease: lung, brain, adrenal glands, bone, and liver.[7]

Pathological Classification and Characterization of NSCLC

Histological Classification

Histological analysis is necessary to diagnose NSCLC and allows subtyping and molecular analysis of lung tumors. The 2 most common histological subtypes are adenocarcinoma (60%) and squamous cell carcinoma (15%); mixed histology tumors and large cell carcinoma are uncommon variants.[8] The safety and efficacy of some therapeutic agents vary by tumor histology. Bevacizumab, an antibody to the vascular endothelial growth factor, is contraindicated in patients with squamous cell carcinoma because clinical trials have demonstrated a higher risk of fatal or life-threatening hemoptysis.[9]

Histological classification is also relevant with the use of pemetrexed, which is a cytotoxic chemotherapy commonly used in patients with adenocarcinomas. The combination of pemetrexed and cisplatin led to poorer overall survival compared with gemcitabine and cisplatin in patients with squamous cell NSCLC (median overall survival, 9.4 months vs 10.8 months, respectively; hazard ratio [HR], 1.23 [95% CI, 1.00-1.51]; $P = .05$).[10]

Molecular Characterization

Molecular testing is now performed at the time of metastatic NSCLC diagnosis to guide therapy. Molecular testing determines the presence of gene mutations or rearrangements for which the US Food and Drug Administration (FDA) has approved therapies. These molecular alterations include epidermal growth factor receptor (*EGFR*) gene mutations, anaplastic lymphoma kinase (*ALK*) gene rearrangements, ROS proto-oncogene receptor tyrosine kinase 1 (*ROS1*) rearrangements, *BRAF* V600E mutations, and neurotrophic receptor tyrosine kinase (*NTRK*) gene fusions.[11,12] Testing, such as hybridization capture-based next-generation sequencing platforms,[2] allows oncologists to obtain comprehensive molecular test results with 1 assay. These approaches may be more cost-effective and reduce waiting time for patients compared with single-gene assays.[13]

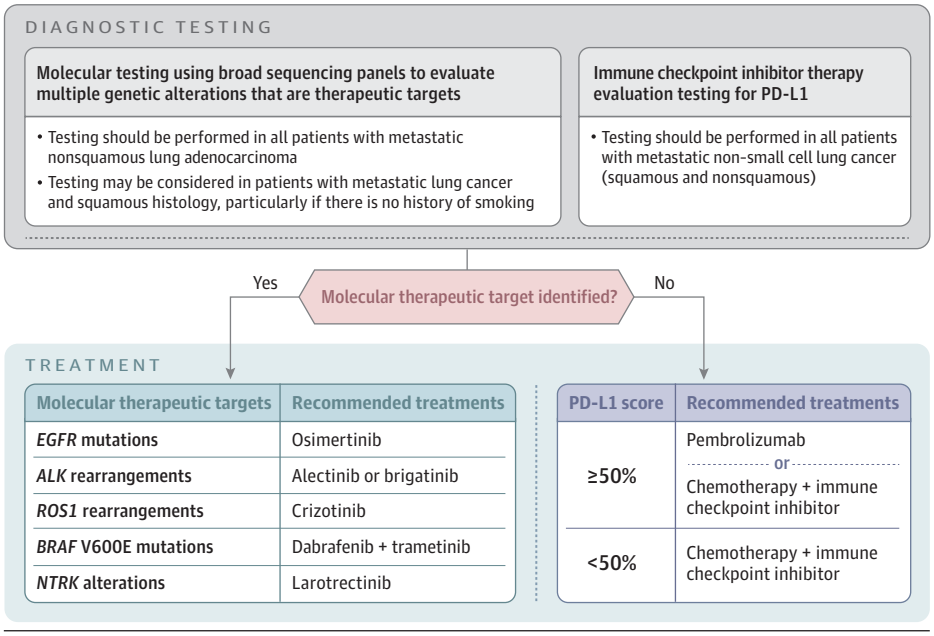
The importance of identifying molecular alterations in patients for whom insufficient tissue is available for molecular testing has led to the study of plasma circulating tumor DNA (ctDNA).[14] This method isolates and detects small amounts of tumor DNA that exist within the plasma of most patients with metastatic NSCLC. With some platforms, plasma ctDNA testing has a detection rate greater than 75% (ie, can identify >75% of mutations identified in tissue), a concordance rate greater than 95% (ie, the mutations detected in plasma are the same as seen in tissue in >95% of patients), and achieves a faster time to results.[15]

When mutations that predict responsiveness to a specific drug therapy are detected with ctDNA, another biopsy is not needed (initial biopsy was used to make the diagnosis).[16] However, 20% of patients with negative ctDNA testing have molecular alterations responsive to drug treatment in tumor samples.[16] A combination of plasma testing and tissue testing may provide the greatest sensitivity for identifying molecular alterations responsive to treatment.[17] Although plasma testing has demonstrated unique value in patients for whom tumor tissue is not available, the standard of care consists of testing tumor tissue and this should be performed for all patients with metastatic NSCLC when feasible.

Biomarkers for Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are a standard treatment for patients with NSCLC and biomarkers can identify patients who are more likely to respond to single-agent immune checkpoint inhibitors. Clinical trials of antibodies targeting the programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1) pathway have shown that PD-L1 tumor proportion score (measured by the

Figure. Approach to Choosing Systematic Therapy for Patients With Metastatic Non–Small Cell Lung Cancer



Nonsquamous non–small cell lung cancer includes adenocarcinoma, poorly differentiated carcinomas, and large cell carcinoma. Chemotherapy regimen and immune checkpoint inhibitor therapy are chosen based on tumor histology and available evidence (additional information appears in Table 2). The programmed death ligand 1 (PD-L1) score is the tumor proportion score (measured by a PD-L1 immunohistochemical assay). *ALK* indicates anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; *NTRK*, neurotrophic receptor tyrosine kinase; *ROS1*, ROS proto-oncogene receptor tyrosine kinase 1.

PD-L1 immunohistochemical assay) can identify patients more likely to respond to immune checkpoint inhibitors, making tissue testing for PD-L1 tumor proportion score necessary for all patients with metastatic NSCLC.

In some studies, a greater number of nonsynonymous tumor mutations (those that lead to changes in the amino acids of proteins) has been associated with improved clinical outcomes following PD-1 inhibition, and the association of tumor mutational burden with clinical outcomes has been studied for patients receiving PD-1 and PD-L1 antibodies.[18] With large-panel next-generation sequencing testing, it is possible to accurately estimate tumor mutational burden from clinical assays. Tumor mutational burden may identify patients who have a durable response to PD-1 and PD-L1 blockade despite a low PD-L1 tumor proportion score.[19] However, tumor mutational burden is not yet a standard biomarker for therapy selection.

Overview of Treatment for Metastatic NSCLC

The primary goal of systemic therapy in patients with metastatic NSCLC is to reduce symptom burden from cancer and improve survival, with a concurrent goal of improving quality of life. Combination platinum-based chemotherapy regimens (such as carboplatin and paclitaxel or carboplatin and pemetrexed) have been shown to improve survival compared with single-agent chemotherapy.[20] Cytotoxic chemotherapy can also benefit patients with limited performance status (Eastern Cooperative Oncology Group performance status of 2).

Although many cytotoxic chemotherapy regimens are associated with significant toxic effects (eg, alopecia, nausea, myelosuppression, and fatigue), many platinum-based treatments have lower rates of these toxic effects. Some patients have only mild to moderate toxic effects and are able to continue routine activities, including employment during treatment. In some patients, surgery, radiation, or both may be indicated to treat disease-related symptoms. The role of surgery and radiation in prolonging disease-free survival is being investigated in patients with a smaller burden of metastatic disease, described as oligo metastatic disease (defined as disease with a limited number of disease sites; ranging from 3-5 sites).

Over the past decade, investigation has focused on identifying targets for drugs that are essential for tumor cell viability or for immune evasion (**Figure**). Once a target is identified, therapy is directed at the characteristics of a patient's tumor. The clinical efficacy and common toxic effects of therapies using this approach appear in **Table 1** and **Table 2**.

Molecularly Targeted Therapies

EGFR-Mutant NSCLC

Somatic activating mutations in *EGFR* have been found in approximately 20% of patients with advanced NSCLC.[32] The 2 most common mutations are *EGFR* L858R and *EGFR* exon 19 deletion. Patients with these *EGFR* tumor mutations are treated with *EGFR* tyrosine kinase inhibitors (EGFR-TKIs), including gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib. Use of molecularly targeted therapy has led to longer progression-free survival compared with platinum-based chemotherapy.[33-35] More recently, a phase 3 randomized trial (N = 452) showed that dacomitinib, a TKI that targets both *EGFR* and *HER2*, was superior vs initial treatment with gefitinib among patients with *EGFR*-mutant NSCLC (median overall survival, 34.1 months vs 26.8 months, respectively; $P = .04$).[36]

However, among patients treated with first-generation EGFR-TKIs (erlotinib or gefitinib) or second-generation EGFR-TKIs (afatinib or dacomitinib), emergence of the *EGFR* T790M mutation has been associated with treatment resistance in 60% of patients.[37-40] Treatment with the third-generation EGFR-TKI, osimertinib, has been shown to overcome this resistance mutation and

Table 1. First-Line Regimens for Patients With Metastatic Non-Small Cell Lung Cancer With Targetable Molecular Alteration

		Clinical Efficacy			Toxic Effects			
Molecular Marker	Treatment Regimen	Response Rate, %[a]	Progression-Free Survival	Overall Survival	Common (Any Grade)	%	Uncommon Serious	%
EGFR	Osimertinib[21]	80	Median: 19 mo	NR	Dry skin	36	Pneumonitis	3
					Diarrhea	42	Cardiomyopathy	1
					Lymphopenia	63		
					Thrombocytopenia	54		
ALK	Alectinib[22,23]	83	Median: 35 mo	12 mo: 84%	Hyperbilirubinemia	54	Pneumonitis	1
					Increased AST	50	Renal impairment (grade 3-4)	2
					Increased ALT	40		
					Anemia	62		
					Constipation	34		
	Brigatinib[24]	71	12 mo: 67%	12 mo: 85%	Nausea	33	Pneumonitis	4
					Increased AST	38	Bradycardia	7
					Increased ALT	34	Visual disturbances	7
					Creatine kinase elevation	27		
					Lipase elevation	21		
ROS1	Crizotinib[25]	72	Median: 19.2 mo	12 mo: 85%	Diarrhea	61	Pneumonitis	1
					Edema	49		
					Visual disturbance	71		
					Increased AST	79		
					Increased ALT	66		
					Asymptomatic bradycardia	14		
BRAF V600E mutation	Dabrafenib and trametinib[26]	64	Median: 10.9 mo	Median: 24.6 mo	Fever	28	Cardiomyopathy	6
					Rash	17	Uveitis	2
					Hyperglycemia	50	Cutaneous squamous cell cancers	7
					Hypophosphatemia	37		

Abbreviations: *ALK*, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; *EGFR*, epidermal growth factor receptor; NR, not reported; *ROS1*, ROS proto-oncogene receptor tyrosine kinase 1.

[a] Defined by Response Evaluation Criteria in Solid Tumor and requires indicator lesions to have a greater than 30% reduction in tumor diameter that is confirmed on a second scan 4 weeks later.

Table 2. First-Line Regimens for Patients With Metastatic Non-Small Cell Lung Cancer Without Identified Molecular Alterations

Histological Classification	Treatment Regimen	Clinical Efficacy of Regimen vs Control Regimen (Without Anti–PD-1 or PD-L1 Antibody Therapy)		Toxic Effects			
		Response Rate, %[a]	Median Survival, mo	Common (Any Grade)	%	Uncommon Serious	%
Nonsquamous[b]	Platinum-based chemotherapy[c] pemetrexed and pembrolizumab[27,d]	48 vs 19	NR vs 11.3[e]	Nausea	56	Pneumonitis	4
				Anemia	46	Colitis	2
				Fatigue	41	Rash	2
	Carboplatin, pacliaxel,[f] atezolizumab,[d] and bevacizumab[28]	64 vs 48	19.2 vs 14.7	Neuropathy	36	Febrile neutropenia	9
				Nausea	30	Pneumonitis	3
				Fatigue	22	Hepatitis	2
				Hypertension	19		
Squamous	Carboplatin and paclitaxel,[f] pembrolizumab[29,d]	58 vs 38	15.9 vs 11.3	Anemia	53	Pneumonitis	6
				Neutropenia	46	Colitis	3
				Nausea	35	Hepatitis	2
				Neuropathy	20		
PD-L1 tumor proportion score ≥50%	Pembrolizumab[d] (single agent vs combination chemotherapy)[30,31]	45 vs 28	30.0 vs 14.2	Diarrhea	14	Pneumonitis	6
				Fatigue	10	Colitis	2
				Hypothyroidism	9		

Abbreviations: NR, not reached; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1.

[a] Defined by Response Evaluation Criteria in Solid Tumor and requires indicator lesions to have a greater than 30% reduction in tumor diameter.

[b] Includes adenocarcinoma, large cell carcinoma, and poorly differentiated non-small cell lung cancer.

[c] Cisplatin or carboplatin can be used.

[d] Anti–PD-1 and PD-L1 therapy.

[e] The 12-month survival rate was 69% vs 74%, respectively.

[f] Nab-paclitaxel can be substituted.

tumor responses have been demonstrated in patients with resistance to first- or second-generation EGFR-TKIs mediated by the *EGFR* T790M mutation.[41]

Based on the efficacy of osimertinib after resistance to first- or second-generation EGFR-TKIs among patients with *EGFR*-mutant NSCLC, osimertinib was tested as a first-line treatment to evaluate whether a mutation-specific EGFR-TKI could prolong disease control and improve survival. In a randomized trial (N = 556), patients with *EGFR* mutations who were treated with osimertinib as initial therapy had improved progression-free survival vs those treated initially with first-generation EGFR-TKIs gefitinib or erlotinib (progression-free survival, 18.9 months vs 10.2 months, respectively; HR, 0.46 [95% CI, 0.37-0.57]; $P < .001$).[21,42] There was evidence of central nervous system (CNS) penetration of osimertinib, with similar benefit for progression-free survival in both patients with CNS metastases and in those without CNS metastases. In that trial,[21,42] severe adverse events (≥grade 3) were less frequent with osimertinib vs erlotinib or gefitinib (34% vs 45%, respectively). The most common adverse event with all EGFR-TKIs has been rash, likely due to the effect of the drug on nonmutated *EGFR* in the skin. Among erlotinib- or gefitinib-treated patients, 78% had any rash and 38% had moderate or severe rash. Among patients treated with osimertinib, 58% of patients had any rash and 10% had moderate or severe rash. Osimertinib was approved by the FDA for the initial treatment of patients with *EGFR*-mutant NSCLC. Current investigation focuses on understanding the mechanisms of resistance to third-generation EGFR-TKIs.[43,44]

ALK-Positive NSCLC

Gene fusions that lead to overexpression of ALK protein have been found to occur in approximately 5% of people with metastatic NSCLC. Crizotinib, a TKI that targets both *MET* and *ALK* receptor tyrosine kinases, was the first drug to achieve tumor responses in patients with *ALK*-positive NSCLC,[45] confirming that targeting this alteration has a biological benefit. Subsequent data demonstrated the superiority of crizotinib vs the combination of pemetrexed and either cisplatin or carboplatin as first-line treatment (response rate of 74% [128/172] vs 45% [77/171], respectively; $P < .001$ and median progression-free survival, 10.9 months vs 7.0 months; $P < .001$),[46] resulting in adoption of ALK-TKIs as initial therapy and underscoring the importance of routine molecular testing at the time of metastatic NSCLC diagnosis.

Newer ALK-TKIs (alectinib, ceritinib, and brigatinib) have a more potent and specific kinase inhibition effect and can be effective in patients with resistance to crizotinib. Among patients previously treated with crizotinib, early-phase trials demonstrated treatment responses for all 3 second-generation ALK-TKIs, with radiographic responses observed among patients with a variety of *ALK* mutations resistant to crizotinib and among those for whom no resistance mutation was identified.[47-49]

For initial treatment of patients with *ALK*-positive NSCLC, the next-generation ALK-TKIs brigatinib and alectinib have been shown to be superior vs crizotinib. In a phase 3 randomized trial (N = 303), patients with *ALK*-positive lung cancer were randomized to receive either alectinib or crizotinib as initial treatment of metastatic disease.[22] Alectinib improved progression-free survival compared with crizotinib therapy (median progression-free survival, 34.8 months vs 10.9 months, respectively; HR, 0.47 [95% CI, 0.34-0.65]; $P < .001$). Improvements in disease control were observed in the CNS, a common site of metastasis in patients with *ALK*-positive NSCLC. Similarly, patients receiving treatment with brigatinib had improved efficacy vs crizotinib (N = 275; 12-month Kaplan-Meier progression-free survival rate, 69% vs 40%, respectively; $P < .001$), with fewer episodes of progressive disease in the CNS.[24] Both brigatinib and alectinib were approved by the FDA as initial therapy for patients with *ALK*-positive NSCLC. The most common toxic effects of individual therapies appear in Table 1. For example, elevated liver function test results are commonly found during treatment with both alectinib and brigatinib (though more common with alectinib). Treatment with brigatinib was associated with a risk of pneumonitis in 4% of patients.[24]

Despite a median period of disease control lasting more than 2 years with alectinib and brigatinib, drug resistance remains a challenge. In 2018, based on a multiple-cohort phase 2 trial, lorlatinib,[50] a third-generation *ALK* inhibitor, was approved for the treatment of patients with *ALK*-positive NSCLC and progressive disease following treatment with 2 prior ALK-TKIs. With the introduction of more potent and specific ALK-TKIs, median survival was nearly 5 years among patients with *ALK*-positive NSCLC treated with crizotinib followed by a second-generation TKI after development of resistance,[51] highlighting the effects of routine testing for *ALK* and selection of drug therapy based on the natural history of NSCLC.

ROS1-Rearranged NSCLC

Chromosomal rearrangements of the gene encoding *ROS1* have been found in approximately 1% of patients with NSCLC.[52] The kinase domains of *ALK* and *ROS1* share substantial homology[53]; therefore, some ALK-TKIs have been shown to be effective in patients with *ROS1* rearrangement. Among 50 patients with NSCLC and *ROS1* rearrangement, crizotinib treatment yielded a response rate of 72% and a median progression-free survival of 19 months.[25] Not all ALK-TKIs have been proven effective for patients with *ROS1* rearrangements. Crizotinib is currently the only agent with FDA approval for NSCLC; however, other agents have shown tumor responses.[54-56]

BRAF-Mutant NSCLC

Somatic activating *BRAF* V600E mutations have been found in 1% to 2% of patients with lung adenocarcinoma. Treatment with the single-agent *BRAF* inhibitors dabrafenib or vemurafenib has yielded relatively short-lived responses.[57,58] A subsequent phase 2 trial (N = 59) studied combined pathway blockade using a *BRAF* inhibitor (dabrafenib) and a *MEK* inhibitor (trametinib) in patients with metastatic *BRAF* V600E-mutant NSCLC. The response rate was 64% with a median progression-free survival of 11 months.[26] These data support a molecularly targeted approach to treating patients with *BRAF*-mutant lung cancer.

Additional Targetable Molecular Alterations in NSCLC

The routine use of molecular testing for hundreds of genetic mutations, and the development of drugs targeting these alterations has increased the identification of molecular aberrations in small subsets of patients with NSCLC. Some clinical trials aim to assess newly identified alterations using drugs that are already approved by the FDA for other diseases. For example, in patients with *MET* exon 14 skipping mutations (occurring in approximately 4% of patients with NSCLC), preliminary evidence suggested that crizotinib (both a MET-TKI and ALK-TKI) decreased tumor size with a radiographic

response rate of 32% in a relatively small study of 69 participants.[59,60] There are no FDA-approved drugs for the treatment of *MET* exon 14–altered NSCLC, but newer drugs are in development, and crizotinib was recommended in guidelines from the National Comprehensive Cancer Network.

Similarly, *HER2* mutations have been found in approximately 2% of patients with lung cancers. Among these patients, the *HER2*-targeted antibody-drug conjugate, trastuzumab emtansine, has achieved tumor responses (N = 18; response rate of 44% and median progression-free survival of 5 months),[61] suggesting that, in patients with NSCLC, *HER2* mutation status may be a better biomarker for *HER2*-directed therapies than protein overexpression, and that *HER2* mutations are yet another molecular alteration that can be used to select lung cancer therapy.

NTRK gene alterations have been identified in less than 1% of NSCLC tumors. Larotrectinib, a treatment for *NTRK* alteration, was developed using a clinical trial that enrolled patients with *NTRK* gene rearrangements regardless of cancer type (N = 55) and demonstrated a tumor response rate of 75%, a 12-month progression-free survival rate of 55%, and led to FDA approval of larotrectinib for *NTRK*-altered cancers regardless of primary site. In the case series leading to FDA approval, 4 patients with lung cancer were included and the remainder of patients had a variety of tumor types, including soft tissue sarcoma, salivary gland tumors, and others.[62]

Rearrangements in the *RET* (rearranged during transfection) gene can promote tumor growth and occur in 1% to 2% of patients with NSCLC.[63] Multiple available TKIs that target *RET* have demonstrated modest clinical efficacy in patients whose tumors have *RET* rearrangements, including cabozatinib[64] (tumor response rate of 28% and median progression-free survival of 5.5 months) and vendatinib[65] (response rate of 18% and median progression-free survival of 4.5 months). Other more specific *RET* inhibitors are currently under development.[66,67]

Immunotherapy in NSCLC

The recent development of treatments that disrupt the PD-1 and PD-L1 pathway, commonly referred to as immune checkpoint inhibitors, have fundamentally changed how patients with metastatic NSCLC are treated. These treatments are thought to stimulate cell-mediated immunity to recognize and destroy cancer cells and act by modulating T-cell function and targeting relevant mechanisms of immune resistance, such as immune inhibitory molecules in the tumor microenvironment.[68] One such inhibitory ligand is PD-L1 and it is frequently expressed in NSCLC.[69]

Single-Agent PD-1 and PD-L1 Inhibitor

After the approval of PD-1 and PD-L1 therapy for use after initial treatment with platinum-based chemotherapy, investigators evaluated therapy for PD-1 and PD-L1 in the first-line setting.[30,70,71] The best support for single-agent therapy for PD-1 and PD-L1 as initial treatment has emerged from trials of pembrolizumab, an anti–PD-1 antibody. In a phase 3 randomized trial (N = 305), patients with a PD-L1 score of 50% or greater who did not have *EGFR* mutations or *ALK* gene rearrangements were randomized to receive pembrolizumab or platinum-based chemotherapy.[30] Patients treated with pembrolizumab had an improved radiographic response rate vs patients who received chemotherapy (45% [69/154] vs 28% [42/151], respectively), an improved progression-free survival (median, 10.3 months vs 6.0 months; HR, 0.50 [95% CI, 0.37-0.68]; $P < .001$), and an improved overall survival (median, 30.0 months vs 14.2 months; HR, 0.63 [95% CI, 0.47-0.86]; 1-sided nominal $P = .002$). Pembrolizumab treatment was associated with a lower frequency of severe adverse events (27% vs 53% of patients who had grade ≥3 treatment-related adverse events).

In another trial, 1274 patients with metastatic NSCLC and a PD-L1 tumor proportion score of 1% or greater were randomized to receive pembrolizumab or platinum-based chemotherapy.[72] Although overall survival improved, the benefits were greatest among patients with a PD-L1 tumor proportion score of 50% or greater. In a post hoc subgroup analysis of patients with a PD-L1 tumor proportion score of 1% to 49%, there was no difference in overall survival vs platinum doublet chemotherapy (13.4 months vs 12.1 months, respectively; HR, 0.92 [95% CI, 0.77-1.11]).[72] Among patients with a PD-L1 tumor proportion score of 50% or greater, pembrolizumab has been found to be superior vs chemotherapy as an initial treatment; however, among patients with lower PD-L1 tumor proportion scores, the treatment role of single-agent pembrolizumab remains less certain. With these data, the FDA has expanded the approval of pembrolizumab to include first-line treatment of patients with metastatic NSCLC whose tumors had PD-L1 expression of either 1% or greater or 50% or greater of tumor cells. These FDA approvals have led to routine testing for PD-L1 at the time of metastatic NSCLC diagnosis. In contrast to the trial results observed with pembrolizumab, first-line trials using nivolumab (another PD-1 inhibitor) and durvalumab (an antibody to PD-L1) have failed to demonstrate superiority vs platinum-based chemotherapy among patients with advanced NSCLC.[71,73]

The immune-related adverse events from pembrolizumab monotherapy that can occur during or after treatment with any immune checkpoint inhibitor include pneumonitis, colitis, and thyroiditis.[74] These commonly develop during the initial weeks to months of therapy, but can develop at any time or even after completion of therapy.[75] Any grade immune-related adverse events have occurred in approximately 25% to 30% of patients and the rate of grade 3-5 toxicity has been low (8%-10% of patients).[30,72,76] Treatment of immune-related adverse events includes discontinuation of therapy and administration of corticosteroids, which typically lead to rapid improvement in symptoms.[77] For patients with steroid refractory immune-related adverse events, other immunosuppressive agents (such as anti–tumor necrosis factor monoclonal antibodies, mycophenolate mofetil, or cyclosporine) can be considered.

Recommendations for the management of immune-related adverse events are currently based on consensus guidelines rather than prospective clinical trials evaluating different approaches to management.[78] The use of immunosuppressive medications for the treatment of immune-related adverse events does not appear to diminish the efficacy of these agents and response to therapy can continue even in the setting of permanent discontinuation of therapy for PD-1 and PD-L1 due to toxic effects.[79]

Combination Chemotherapy and Inhibition of PD-1 and PD-L1

For patients with a PD-L1 tumor proportion score of less than 50%, combination therapy with chemotherapy and immune checkpoint

inhibitors has been found to be the most effective treatment. Some evidence suggests that the antitumor effect of chemotherapy is mediated through both a cytotoxic effect and immunological effects, including reducing the regulatory T-cell effect and enhancing cross-presentation of tumor antigens.[80] Chemotherapy has been shown to induce changes in PD-L1 tumor proportion score, providing additional support for combining chemotherapy and inhibition of PD-1 and PD-L1.[81] In addition to the potential synergy, combining first- and second-line therapy may be beneficial because many patients with NSCLC only receive 1 line of therapy due to rapid progression of cancer with functional decline.

The benefits of combining chemotherapy and immune checkpoint inhibitors were first observed in a small phase 2 randomized trial that evaluated the combination of carboplatin, pemetrexed, and pembrolizumab in patients with metastatic nonsquamous NSCLC (a term encompassing lung adenocarcinoma, poorly differentiated carcinomas, and large cell lung cancers).[82] These findings were confirmed in a phase 3 randomized trial (N = 616) in which pembrolizumab plus chemotherapy (pemetrexed plus cisplatin or carboplatin) was compared with chemotherapy alone in patients with nonsquamous NSCLC.[27] The combination of chemotherapy and pembrolizumab showed an improved radiographic response rate vs chemotherapy alone (48% vs 19%, respectively; $P < .001$), progression-free survival (median, 8.8 months vs 4.9 months; $P < .001$), and overall survival rate (Kaplan-Meier probabilities for proportion of patients alive at 12 months, 69% vs 49%; HR, 0.49 [95% CI, 0.38-0.64]; $P < .001$). Benefits occurred regardless of PD-L1 tumor proportion score. A similar benefit was seen in a separate phase 3 clinical trial in patients with squamous NSCLC (N = 559) among patients receiving a combination of carboplatin, pembrolizumab, and either paclitaxel or albumin-bound paclitaxel vs chemotherapy alone (median overall survival, 15.9 months vs 11.3 months, respectively; HR, 0.64 [95% CI, 0.49-0.85]; $P = .001$).[29]

Atezolizumab, an anti–PD-L1 antibody, has also demonstrated benefit in combination with chemotherapy as a first-line treatment. Patients with advanced, nonsquamous NSCLC treated with quadruplet therapy (atezolizumab, paclitaxel, carboplatin, and the antivascular endothelial growth factor antibody, bevacizumab)[28] were compared with patients receiving the same regimen without atezolizumab (triplet therapy) (N = 692). Patients receiving quadruplet therapy had improved median progression-free survival vs patients receiving triplet therapy (8.3 months vs 6.8 months, respectively; HR, 0.62 [95% CI, 0.52-0.74]; $P < .001$) as well as improved overall survival (19.2 months vs 14.7 months; HR, 0.78 [95% CI, 0.64-0.96]; $P = .02$). The benefits of progression-free survival were irrespective of tumor PD-L1 proportion score.

The results of these large randomized studies have resulted in incorporation of immunotherapy into the first-line setting for all patients except those with molecular alterations that respond to drug therapy. For patients without these molecular alterations, PD-L1 testing determines available treatment options. Patients with PD-L1 tumor proportion scores of less than 50% typically receive combination chemotherapy and PD-L1 blockade. Among patients with PD-L1 tumor proportion scores of 50% or greater, standard treatment typically includes administration of either single-agent pembrolizumab or chemotherapy combined with an inhibitor for PD-1 and PD-L1. Clinical decisions are often made based on individualized considerations such as symptom burden or treatment toxicity.

Treatment Advances in the Nonmetastatic Setting

In stage III NSCLC in which the disease is localized to the lung and regional lymph nodes, it is potentially curable with multimodality therapy (induction chemotherapy followed by surgery or combined chemotherapy and radiation), but cure rates are low (generally <20%).[83] There has been interest in incorporating immune checkpoint inhibitors to improve the cure rate for patients with stage III NSCLC. Multiple trials are currently exploring the role of adjuvant immunotherapy following surgical resection and potentially as neoadjuvant therapy prior to surgical resection.[84]

Among patients without metastatic disease, the role of checkpoint inhibitors has been established best for patients who have completed curative-intent concurrent chemoradiation for treating unresectable stage III NSCLC. A phase 3 randomized trial (N = 713) compared the outcomes of patients who received placebo or durvalumab for 1 year following chemoradiation.[85] In this trial, there were improvements in the tumor response rate, progression-free survival, and overall survival. Patients who received durvalumab had improved overall survival compared with placebo (HR for death, 0.68 [99.73% CI, 0.47-0.997]; $P = .003$). The improvement in outcomes for patients treated with durvalumab as consolidation therapy was observed across all prespecified subgroups, but a post hoc exploratory analysis suggested that the benefit may be less clear in patients with PD-L1–negative cancers. Therefore, the utility of treatment with durvalumab as consolidation therapy in patients with PD-L1–negative tumors must be specifically addressed in future clinical trials. Regarding the toxicity of durvalumab following chemoradiation, the risk of severe or life-threatening adverse events was higher in those patients who received durvalumab vs those who did not (30.5% vs 26.0%, respectively), including a higher rate of pneumonitis in patients treated with durvalumab (12.6% vs 7.7% for all cancer grades).

Future Directions

Treatment for patients with NSCLC has greatly improved during recent years. Newer TKIs for patients with *EGFR* and *ALK* alterations have replaced earlier targeted therapies. Treatment goals have evolved to preventing the development of resistance to targeted therapy. Since the introduction of inhibitors of PD-1 and PD-L1 in 2015, virtually all patients without molecular alterations that are susceptible to current therapies now receive treatment with one of these agents in the first-line setting. These advances are substantial, but long-term durable responses remain uncommon for most patients. These insights into treating metastatic disease have informed the design of trials for new treatment strategies among patients with early-stage disease. The goal of NSCLC research is to understand and address mechanisms of resistant and refractory disease in patients with advanced disease and, ultimately, to increase cure rates.

Conclusions

Improved understanding of the biology and molecular subtypes of non–small cell lung cancer have led to more biomarker-directed

therapies for patients with metastatic disease. These biomarker-directed therapies and newer empirical treatment regimens have improved overall survival for patients with metastatic non–small cell lung cancer.

ARTICLE INFORMATION

Accepted for Publication: July 29, 2019.

Author Contributions: Both authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Both authors.
Acquisition, analysis, or interpretation of data: Riely.
Drafting of the manuscript: Both authors.
Critical revision of the manuscript for important intellectual content: Both authors.
Administrative, technical, or material support: Riely.
Supervision: Riely.

Conflict of Interest Disclosures: Dr Arbour reported serving as a consultant to AstraZeneca; and receiving nonfinancial research support from Novartis and Takeda. Dr Riely reported receiving grants and nonfinancial support from Pfizer, Roche/Genentech/Chugai, Novartis, Merck, and Takeda; having US patent 20170273982A1 pending for an alternate dosing of erlotinib for which he has no right to royalties; and being paid by the National Comprehensive Cancer Network to participate in a committee that oversaw solicitation and selection of grants to be awarded by AstraZeneca.

Funding/Support: This work was partially supported by grant P30 CA008748 from the National Cancer Institute awarded to Memorial Sloan Kettering Cancer Center.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank Clare Wilhelm, MD, PhD (Memorial Sloan Kettering Cancer Center), for providing editorial support. Dr Wilhelm was not paid for his contribution.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

1. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the Surveillance, Epidemiologic, and End Results database. *J Clin Oncol*. 2006;24(28):4539-4544. doi:10.1200/JCO.2005.04.4859

2. Jordan EJ, Kim HR, Arcila ME, et al. Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. *Cancer Discov*. 2017;7(6):596-609. doi:10.1158/2159-8290.CD-16-1337

3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69(1):7-34. doi:10.3322/caac.21551

4. Couraud S, Zalcman G, Milleron B, Morin F, Souquet P-J. Lung cancer in never smokers—a review. *Eur J Cancer*. 2012;48(9):1299-1311. doi:10.1016/j.ejca.2012.03.007

5. Moyer VA; US Preventive Services Task Force. Screening for lung cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(5):330-338. doi:10.7326/M13-2771

6. Chen VW, Ruiz BA, Hsieh M-C, Wu X-C, Ries LAG, Lewis DR. Analysis of stage and clinical/prognostic factors for lung cancer from SEER registries: AJCC staging and collaborative stage data collection system. *Cancer*. 2014;120(suppl 23):3781-3792. doi:10.1002/cncr.29045

7. Spiro SG, Gould MK, Colice GL; American College of Chest Physicians. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest*. 2007;132(3 supp):149S-160S. doi:10.1378/chest.07-1358

8. National Cancer Institute. Surveillance, Epidemiology, and End Results Program: cancer of the lung and bronchus: cancer stat facts. https://seer.cancer.gov/statfacts/html/lungb.html. Accessed July 27, 2019.

9. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*. 2004;22(11):2184-2191. doi:10.1200/JCO.2004.11.022

10. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol*. 2008;26(21):3543-3551. doi:10.1200/JCO.2007.15.0375

11. Travis WD, Brambilla E, Riely GJ. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. *J Clin Oncol*. 2013;31(8):992-1001. doi:10.1200/JCO.2012.46.9270

12. Travis WD, Brambilla E, Nicholson AG, et al; WHO Panel. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol*. 2015;10(9):1243-1260. doi:10.1097/JTO.0000000000000630

13. Pennell NA, Mutebi A, Zhou Z-Y, et al. Economic impact of next-generation sequencing versus single-gene testing to detect genomic alterations in metastatic non–small-cell lung cancer using a decision analytic model [published online May 16, 2019]. *JCO Precis Oncol*. doi:10.1200/PO.18.00356

14. Husain H, Velculescu VE. Cancer DNA in the circulation: the liquid biopsy. *JAMA*. 2017;318(13):1272-1274. doi:10.1001/jama.2017.12131

15. Sabari JK, Offin M, Stephens D, et al. A prospective study of circulating tumor DNA to guide matched targeted therapy in lung cancers. *J Natl Cancer Inst*. 2018;111(6):575-583. doi:10.1093/jnci/djy156

16. Aggarwal C, Thompson JC, Black TA, et al. Clinical Implications of plasma-based genotyping with the delivery of personalized therapy in metastatic non–small cell lung cancer. *JAMA Oncol*. 2018;5(2):173-180. doi:10.1001/jamaoncol.2018.4305

17. Leighl NB, Page RD, Raymond VM, et al. Clinical utility of comprehensive cell-free DNA analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non–small cell lung cancer. *Clin Cancer Res*. 2019. doi:10.1158/1078-0432.CCR-19-0624

18. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology: mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348(6230):124-128. doi:10.1126/science.aaa1348

19. Hellmann MD, Ciuleanu T-E, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*. 2018;378(22):2093-2104. doi:10.1056/NEJMoa1801946

20. Zukin M, Barrios CH, Pereira JR, et al. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. *J Clin Oncol*. 2013;31(23):2849-2853. doi:10.1200/JCO.2012.48.1911

21. Soria J-C, Ohe Y, Vansteenkiste J, et al; FLAURA Investigators. Osimertinib in untreated *EGFR*-mutated advanced non–small-cell lung cancer. *N Engl J Med*. 2018;378(2):113-125. doi:10.1056/NEJMoa1713137

22. Peters S, Camidge DR, Shaw AT, et al; ALEX Trial Investigators. Alectinib versus crizotinib in untreated *ALK*-positive non–small-cell lung cancer. *N Engl J Med*. 2017;377(9):829-838. doi:10.1056/NEJMoa1704795

23. Camidge DR, Peters S, Mok T, et al. Updated efficacy and safety data from the global phase III ALEX study of alectinib (ALC) vs crizotinib (CZ) in untreated advanced *ALK*+ NSCLC. *J Clin Oncol*. 2018;36(15)(suppl):9043-9043. doi:10.1200/JCO.2018.36.15_suppl.9043

24. Camidge DR, Kim HR, Ahn M-J, et al. Brigatinib versus crizotinib in *ALK*-positive non–small-cell lung cancer. *N Engl J Med*. 2018;379(21):2027-2039. doi:10.1056/NEJMoa1810171

25. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in *ROS1*-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371(21):1963-1971. doi:10.1056/NEJMoa1406766

26. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol*. 2016;17(7):984-993. doi:10.1016/S1470-2045(16)30146-2

27. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al; KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078-2092. doi:10.1056/NEJMoa1801005

28. Socinski MA, Jotte RM, Cappuzzo F, et al; IMpower150 Study Group. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378(24):2288-2301. doi:10.1056/NEJMoa1716948

29. Paz-Ares L, Luft A, Vicente D, et al; KEYNOTE-407 Investigators. Pembrolizumab plus

chemotherapy for squamous non–small-cell lung cancer. *N Engl J Med*. 2018;379(21):2040-2051. doi:10.1056/NEJMoa1810865

30. Reck M, Rodríguez-Abreu D, Robinson AG, et al; KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *N Engl J Med*. 2016;375(19):1823-1833. doi:10.1056/NEJMoa1606774

31. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non–small-cell lung cancer with PD-L1 tumor proportion score of 50% or greater. *J Clin Oncol*. 2019;37(7):537-546. doi:10.1200/JCO.18.00149

32. Dogan S, Shen R, Ang DC, et al. Molecular epidemiology of *EGFR* and *KRAS* mutations in 3,026 lung adenocarcinomas: higher susceptibility of women to smoking-related *KRAS*-mutant cancers. *Clin Cancer Res*. 2012;18(22):6169-6177. doi:10.1158/1078-0432.CCR-11-3265

33. Sequist LV, Yang JC-H, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with *EGFR* mutations. *J Clin Oncol*. 2013;31(27):3327-3334. doi:10.1200/JCO.2012.44.2806

34. Mitsudomi T, Morita S, Yatabe Y, et al; West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11(2):121-128. doi:10.1016/S1470-2045(09)70364-X

35. Rosell R, Carcereny E, Gervais R, et al; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13(3):239-246. doi:10.1016/S1470-2045(11)70393-X

36. Mok TS, Cheng Y, Zhou X, et al. Improvement in overall survival in a randomized study that compared dacomitinib with gefitinib in patients with advanced non–small-cell lung cancer and *EGFR*-activating mutations. *J Clin Oncol*. 2018;36(22):2244-2250. doi:10.1200/JCO.2018.78.7994

37. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the *EGFR* kinase domain. *PLoS Med*. 2005;2(3):e73. doi:10.1371/journal.pmed.0020073

38. Kobayashi S, Boggon TJ, Dayaram T, et al. *EGFR* mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2005;352(8):786-792. doi:10.1056/NEJMoa044238

39. Oxnard GR, Arcila ME, Sima CS, et al. Acquired resistance to *EGFR* tyrosine kinase inhibitors in *EGFR*-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res*. 2011;17(6):1616-1622. doi:10.1158/1078-0432.CCR-10-2692

40. Yu H, Arcila ME, Rekhtman N, et al. Analysis of mechanisms of acquired resistance to *EGFR* TKI therapy in 155 patients with *EGFR*-mutant lung cancers. *Clin Cancer Res*. 2013;19(8):2240-2247. doi:10.1158/1078-0432.CCR-12-2246

41. Mok TS, Wu Y-L, Ahn M-J, et al; AURA3 Investigators. Osimertinib or platinum–pemetrexed in *EGFR* T790M–positive lung cancer. *N Engl J Med*. 2017;376(7):629-640. doi:10.1056/NEJMoa1612674

42. Ramalingam SS, Yang JC-H, Lee CK, et al. Osimertinib as first-line treatment of *EGFR* mutation–positive advanced non–small-cell lung cancer. *J Clin Oncol*. 2018;36(9):841-849. doi:10.1200/JCO.2017.74.7576

43. Oxnard GR, Hu Y, Mileham KF, et al. Assessment of resistance mechanisms and clinical implications in patients with *EGFR* T790M–positive lung cancer and acquired resistance to osimertinib. *JAMA Oncol*. 2018;4(11):1527-1534. doi:10.1001/jamaoncol.2018.2969

44. Yu HA, Tian SK, Drilon AE, et al. Acquired resistance of *EGFR*-mutant lung cancer to a T790M-specific EGFR inhibitor: emergence of a third mutation (C797S) in the *EGFR* tyrosine kinase domain. *JAMA Oncol*. 2015;1(7):982-984. doi:10.1001/jamaoncol.2015.1066

45. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring *ALK* gene rearrangement: a retrospective analysis. *Lancet Oncol*. 2011;12(11):1004-1012. doi:10.1016/S1470-2045(11)70232-7

46. Shaw AT, Kim D-W, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced *ALK*-positive lung cancer. *N Engl J Med*. 2013;368(25):2385-2394. doi:10.1056/NEJMoa1214886

47. Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *Lancet Oncol*. 2016;17(2):234-242. doi:10.1016/S1470-2045(15)00488-X

48. Gettinger SN, Bazhenova L, Salgia R, et al. Brigatinib (AP26113) efficacy and safety in *ALK* plus NSCLC: phase 1/2 trial results. *J Thorac Oncol*. 2015;10(9):S238-S239.

49. Shaw AT, Kim TM, Crinò L, et al. Ceritinib versus chemotherapy in patients with *ALK*-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(7):874-886. doi:10.1016/S1470-2045(17)30339-X

50. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with *ALK*-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol*. 2018;19(12):1654-1667. doi:10.1016/S1470-2045(18)30649-1

51. Solomon BJ, Kim D-W, Wu Y-L, et al. Final overall survival analysis from a study comparing first-line crizotinib versus chemotherapy in *ALK*-mutation-positive non-small-cell lung cancer. *J Clin Oncol*. 2018;36(22):2251-2258. doi:10.1200/JCO.2017.77.4794

52. Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: *ROS1* and *RET* fusions. *Oncologist*. 2013;18(7):865-875. doi:10.1634/theoncologist.2013-0095

53. Huber KVM, Salah E, Radic B, et al. Stereospecific targeting of MTH1 by (S)-crizotinib as an anticancer strategy. *Nature*. 2014;508(7495):222-227. doi:10.1038/nature13194

54. Drilon A, Ou SI, Cho BC, et al. Repotrectinib (TPX-0005) is a next-generation *ROS1/TRK/ALK* inhibitor that potently inhibits *ROS1/TRK/ALK* solvent-front mutations. *Cancer Discov*. 2018;8(10):1227-1236. doi:10.1158/2159-8290.CD-18-0484

55. Lim SM, Kim HR, Lee J-S, et al. Open-label, multicenter, phase II study of ceritinib in patients with non–small-cell lung cancer harboring *ROS1* rearrangement. *J Clin Oncol*. 2017;35(23):2613-2618. doi:10.1200/JCO.2016.71.3701

56. Shaw AT, Felip E, Bauer TM, et al. Lorlatinib in non-small-cell lung cancer with *ALK* or *ROS1* rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol*. 2017;18(12):1590-1599. doi:10.1016/S1470-2045(17)30680-0

57. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with *BRAF* V600 mutations. *N Engl J Med*. 2015;373(8):726-736. doi:10.1056/NEJMoa1502309

58. Planchard D, Kim TM, Mazieres J, et al. Dabrafenib in patients with *BRAF*(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(5):642-650. doi:10.1016/S1470-2045(16)00077-2

59. Paik PK, Drilon A, Fan P-D, et al. Response to *MET* inhibitors in patients with stage IV lung adenocarcinomas harboring *MET* mutations causing exon 14 skipping. *Cancer Discov*. 2015;5(8):842-849. doi:10.1158/2159-8290.CD-14-1467

60. Drilon A, Clark J, Weiss J, et al. OA12.02 updated antitumor activity of crizotinib in patients with MET exon 14-altered advanced non-small cell lung cancer. *J Thorac Oncol*. 2018;13(10):S348. doi:10.1016/j.jtho.2018.08.300

61. Li BT, Shen R, Buonocore D, et al. Ado-trastuzumab emtansine for patients with *HER2*-mutant lung cancers: results from a phase II basket trial. *J Clin Oncol*. 2018;36(24):2532-2537. doi:10.1200/JCO.2018.77.9777

62. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in *TRK* fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378(8):731-739. doi:10.1056/NEJMoa1714448

63. Gautschi O, Milia J, Filleron T, et al. Targeting *RET* in patients with *RET*-rearranged lung cancers: results from the global, multicenter *RET* registry. *J Clin Oncol*. 2017;35(13):1403-1410. doi:10.1200/JCO.2016.70.9352

64. Drilon A, Rekhtman N, Arcila M, et al. Cabozantinib in patients with advanced *RET*-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. *Lancet Oncol*. 2016;17(12):1653-1660. doi:10.1016/S1470-2045(16)30562-9

65. Lee S-H, Lee J-K, Ahn M-J, et al. Vandetanib in pretreated patients with advanced non-small cell lung cancer-harboring *RET* rearrangement: a phase II clinical trial. *Ann Oncol*. 2017;28(2):292-297.

66. Drilon A, Fu S, Patel MR, et al. A phase I/Ib trial of the *VEGFR*-sparing multikinase *RET* inhibitor RXDX-105. *Cancer Discov*. 2019;9(3):384-395. doi:10.1158/2159-8290.CD-18-0839

67. Drilon AE, Subbiah V, Oxnard GR, et al. A phase 1 study of LOXO-292, a potent and highly selective *RET* inhibitor, in patients with *RET*-altered cancers. *J Clin Oncol*. 2018;36(15)(suppl):102-102. doi:10.1200/JCO.2018.36.15_suppl.102

68. Davar D, Kirkwood JM. PD-1 immune checkpoint inhibitors and immune-related adverse events: understanding the upside of the downside

of checkpoint blockade. *JAMA Oncol*. 2019;5(7):942-943. doi:10.1001/jamaoncol.2019.0413

69. Brahmer JR, Pardoll DM. Immune checkpoint inhibitors: making immunotherapy a reality for the treatment of lung cancer. *Cancer Immunol Res*. 2013;1(2):85-91. doi:10.1158/2326-6066.CIR-13-0078

70. Lopes G, Wu Y-L, Kudaba I, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: open-label, phase 3 KEYNOTE-042 study. *J Clin Oncol*. 2018;36(18)(suppl):LBA4-LBA4. doi:10.1200/JCO.2018.36.18_suppl.LBA4

71. Carbone DP, Reck M, Paz-Ares L, et al; CheckMate 026 Investigators. First-line nivolumab in stage IV or recurrent non–small-cell lung cancer. *N Engl J Med*. 2017;376(25):2415-2426. doi:10.1056/NEJMoa1613493

72. Mok TSK, Wu Y-L, Kudaba I, et al; KEYNOTE-042 Investigators. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):1819-1830. doi:10.1016/S0140-6736(18)32409-7

73. Rizvi NA, Chul Cho B, Reinmuth N, et al. LBA6: durvalumab with or without tremelimumab vs platinum-based chemotherapy as first-line treatment for metastatic non-small cell lung cancer: MYSTIC. *Ann Oncol*. 2018;29(suppl 10):mdy511.005. doi:10.1093/annonc/mdy511.005

74. Johnson DB, Chandra S, Sosman JA. Immune checkpoint inhibitor toxicity in 2018. *JAMA*. 2018;320(16):1702-1703. doi:10.1001/jama.2018.13995

75. Naidoo J, Wang X, Woo KM, et al. Pneumonitis in patients treated with anti–programmed death-1/programmed death ligand 1 therapy. *J Clin Oncol*. 2017;35(7):709-717. doi:10.1200/JCO.2016.68.2005

76. Wang Y, Zhou S, Yang F, et al. Treatment-related adverse events of PD-1 and PD-L1 inhibitors in clinical trials: a systematic review and meta-analysis. *JAMA Oncol*. 2019;5(7):1008-1019. doi:10.1001/jamaoncol.2019.0393

77. Johnson DB, Chandra S, Sosman JA. Immune checkpoint inhibitor toxicity in 2018. *JAMA*. 2018;320(16):1702-1703. doi:10.1001/jama.2018.13995

78. Thompson JA, Schneider BJ, Brahmer J, et al. Management of immunotherapy-related toxicities, version 1.2019. *J Natl Compr Canc Netw*. 2019;17(3):255-289. doi:10.6004/jnccn.2019.0013

79. Santini FC, Rizvi H, Plodkowski AJ, et al. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. *Cancer Immunol Res*. 2018;6(9):1093-1099. doi:10.1158/2326-6066.CIR-17-0755

80. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. *Cancer Cell*. 2015;28(6):690-714. doi:10.1016/j.ccell.2015.10.012

81. Peng J, Hamanishi J, Matsumura N, et al. Chemotherapy induces programmed cell death-ligand 1 overexpression via the nuclear factor-κb to foster an immunosuppressive tumor microenvironment in ovarian cancer. *Cancer Res*. 2015;75(23):5034-5045. doi:10.1158/0008-5472.CAN-14-3098

82. Langer CJ, Gadgeel SM, Borghaei H, et al; KEYNOTE-021 investigators. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17(11):1497-1508. doi:10.1016/S1470-2045(16)30498-3

83. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs concurrent chemoradiation for stage III non–small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst*. 2011;103(19):1452-1460. doi:10.1093/jnci/djr325

84. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med*. 2018;378(21):1976-1986. doi:10.1056/NEJMoa1716078

85. Antonia SJ, Villegas A, Daniel D, et al; PACIFIC Investigators. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-2350. doi:10.1056/NEJMoa1809697