Non–Small Cell Lung Cancer: Epidemiology, Screening, Diagnosis, and Treatment

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Learning Objectives: On completion of this article, you should be able to (1) identify risk factors for non–small cell lung cancer (NSCLC); (2) compare epidermal growth factor receptor inhibitors as first- and second-line therapy and their commonly seen adverse events in patients with NSCLC; (3) recognize the benefits and risks of immune checkpoint inhibitors in the treatment of advanced NSCLC; (4) assess special considerations for patients with brain metastasis and autoimmune disorders before receiving immune checkpoint inhibitors for the treatment of advanced/metastatic NSCLC; and (5) summarize systemic therapies available for patients with metastatic NSCLC.

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Abstract

Lung cancer remains the leading cause of cancer deaths in the United States. In the past decade, significant advances have been made in the science of non–small cell lung cancer (NSCLC). Screening has been introduced with the goal of early detection. The National Lung Screening Trial found a lung cancer mortality benefit of 20% and a 6.7% decrease in all-cause mortality with the use of low-dose chest computed tomography in high-risk individuals. The treatment of lung cancer has also evolved with the introduction of several lines of tyrosine kinase inhibitors in patients with *EGFR, ALK, ROS1,* and *NTRK* mutations. Similarly, immune checkpoint inhibitors (ICIs) have dramatically changed the landscape of NSCLC treatment. Furthermore, the results of new trials continue to help us understand the role of these novel agents and which patients are more likely to benefit; ICIs are now part of the first-line NSCLC treatment armamentarium as monotherapy, combined with chemotherapy, or after definite chemoradiotherapy in patients with stage III unresectable NSCLC. Expression of programmed cell death protein-ligand 1 in malignant cells has been studied as a potential biomarker for response to ICIs. However, important drawbacks exist that limit its discriminatory potential. Identification of accurate

predictive biomarkers beyond programmed cell death protein-ligand 1 expression remains essential to select the most appropriate candidates for ICI therapy. Many questions remain unanswered regarding the proper sequence and combinations of these new agents; however, the field is moving rapidly, and the overall direction is optimistic.

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Lung cancer is the leading cause of cancer-related mortality in the United States for both men and women.[1] For 2018, it is expected that 154,050 Americans will die of lung cancer, a rate that exceeds the combined 3 next most common cancers (colon, breast, and prostate cancers).[2] The 60-month overall survival rate for non–small cell lung cancer (NSCLC) remains poor, from 68% in patients with stage IB disease to 0% to 10% in patients with stage IVA-IVB disease.[3]

Some environmental and lifestyle factors have been associated with the subsequent development of lung cancer, of which cigarette smoking is the most important. This is estimated to account for 85% to 90% of lung cancers.[4] The risk of developing cancer is associated with the extent of smoking and exposure to other carcinogenic factors, such as asbestos.

Other factors associated with increased lung cancer risk include ionizing radiation, as found in patients with a history of Hodgkin lymphoma[5] or breast cancer[6]; environmental toxins, such as secondhand smoke, radon, and metals (arsenic, chromium, and nickel); and polycyclic aromatic hydrocarbons.[4] History of pulmonary fibrosis, human immunodeficiency virus infection, and alcohol consumption have also been defined as risk factors for lung cancer.[7,8]

EPIDEMIOLOGY

Lung cancer incidence and mortality rates are highest in the developed countries. In contrast, lung cancer rates in underdeveloped geographic areas, including Central/South America and most of Africa, are estimated to be lower. However, many developing countries lack a centralized reporting system, and it is stipulated that many cases of lung cancer go unreported, obscuring the real incidence of the disease.[9] The World Health Organization (WHO) estimates that lung cancer death rates worldwide will continue to rise, mainly as a result of an increase in global tobacco use, particularly in Asia.[10]

In the United States, the incidence and death rates from lung cancer have been decreasing for men, and these numbers were initially rising for women until approximately 2000 and have since been leveling off.[2] Because of the changes in lung cancer incidence in women, lung cancer death rates decreased in women more than a decade after they decreased in men.[11] The incidence of lung cancer, although declining for both white and black men, is approximately 20% higher for black men.[12] On the contrary, the lowest incidence and mortality rates are seen in Asian Americans, Pacific Islanders, and Hispanic women.[2] Race-related differences are the result of complex interactions between socioeconomic status, occupational exposures, and lifestyle.

The incidence of lung cancer remains low in patients younger than 40 years.[13] It then slowly begins to rise and peaks between ages 65 and 84 years. In the United States, the median age at diagnosis of lung cancer is 71 years, with approximately 90% of diagnoses and deaths occurring in patients older than 55 years.[11]

Current trends in smoking behavior will continue to be a significant predictor of future trends in lung cancer incidence. Nevertheless, 19% of cases in women and 9% in men in the United States are seen in never-smokers,[14] with a rising incidence in young women.[15]

CLASSIFICATION

There are 2 main forms of lung cancer: NSCLC (85% of patients) and small cell lung cancer (SCLC) (15%). The WHO has classified NSCLC into 3 main types: adenocarcinoma, squamous cell carcinoma, and large cell.[16,17] There are also several variants and combinations of clinical subtypes.

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Adenocarcinoma is the most common type of NSCLC and accounts for approximately 40% of lung cancers.[17] Adenocarcinoma arises from alveolar cells located in the smaller airway epithelium and tends to express immunohistochemical markers such as TTF-1 and napsin A. The WHO classification of lung cancer also recognizes early stages of lung cancer as adenocarcinoma in situ (pre-invasive lesion), minimally invasive adenocarcinoma, or invasive adenocarcinoma based on the extent of invasiveness.[16] Adenocarcinoma in situ is defined as an adenocarcinoma comprising a lepidic pattern with a diameter of less than 3 cm. Minimally invasive adenocarcinoma is defined as adenocarcinoma with a diameter of more than 3 cm; exclusion factors include an invasion size of more than 5 mm even if the tumor size and invasion size comply with the definition of minimally invasive adenocarcinoma and the presence of lymphovascular invasion, perineural invasion, or tumor necrosis.

Squamous cell carcinomas represent 25% to 30% of lung cancers; they tend to arise from cells located in the airway epithelium. Immunohistochemical markers such as CK5, CK6, p40, and desmoglein-3 are usually present.[18]

Large cell cancers account for approximately 5% to 10% of all lung cancers, and the incidence is declining due to newer immunophenotyping techniques, allowing better classification of more poorly differentiated squamous cell carcinomas and adenocarcinomas. These tumors are typically poorly differentiated and composed of large cells with abundant cytoplasm and large nucleoli.

SCREENING

Clinical outcome for NSCLC is directly related to stage at the time of diagnosis, bringing importance to a screening modality that would allow detection. Screening for lung cancer using chest radiographs or sputum cytologic analysis failed to provide a mortality benefit in several clinical trials.[19,20] The National Lung Screening Trial tested computed tomography (CT) vs radiography in 53,454 patients at high risk and found a lung cancer mortality benefit of 20% and a 6.7% decrease in all-cause mortality ($P<.02$).[21,22] The US Preventive Services Task Force recommends annual screening with chest low-dose CT in high-risk individuals (30 pack-year smoking history) from age 55 to 80 years, with discontinuation of screening once the individual has not smoked for 15 years or has a limited life expectancy.[23] Furthermore, the NELSON trial, a randomized low-dose CT—based lung cancer screening trial, included 15,822 current or former smokers in the Netherlands and Belgium and compared low-dose CT at increasing screening intervals (1, 2, and 2.5 years) with no screening. The study found a 26% reduction in lung cancer deaths in high-risk men at 10-year follow-up.[24-26]

Despite these results, the adoption of lung cancer screening practices remains poor owing to many challenges, including insurance coverage and secondary costs, high rates of false-positive results, fear of radiation exposure, added patient distress due to the need for prolonged follow-up, and the risk of overdiagnosis in a population at increased risk for other potentially life-threating comorbidities, as in the case of smokers.[27] Controversy also exists regarding the role of lung cancer screening in individuals with an extensive smoking history who quit for more than 15 years as well as the management of false-positive test results; these are relevant topics for future studies.

DIAGNOSIS

Often, NSCLC is not diagnosed until advanced-stage disease is present.[2,28] Cough, seen in 50% to 75% of patients, is the most common symptom, followed by hemoptysis, chest pain, and dyspnea.[28] Other less common symptoms include laboratory abnormalities or paraneoplastic syndromes. Diagnosis requires biopsy for histologic confirmation.

Diagnosis also requires determination of the extent of the tumor to define the TNM stage, which will ultimately guide cancer treatment options. A Danish randomized study compared staging with positron emission tomography (PET) combined with CT vs the traditional invasive staging alone (mediastinoscopy and mediastinal lymph node biopsy with echoendoscopy), their findings reported a better

classification of N stage diagnosis with PET-CT.[29,30] Any positive node on PET-CT must be sampled, as confirmed by the analysis of a secondary objective from another randomized study.[31] Computed tomography or magnetic resonance imaging of the head is recommended for patients to be treated with curative intent or for those with signs or symptoms suggestive of brain metastasis.

According to the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society multidisciplinary classification of lung cancer,[3,32] obtaining sufficient tissue material is necessary. The potential for mutation identification and tailored treatment has implications at the initial evaluation of all suspected lung cancers.

TREATMENT

Treatment of NSCLC is stage specific. Patients with stage I or II should be treated with complete surgical resection when not contraindicated. Nonsurgical patients should be considered for conventional or stereotactic radiotherapy. Percutaneous thermal ablation procedures such as cryoablation, microwave, and radiofrequency ablation have been found to be useful treatment options in the setting of salvage therapy after surgery, radiotherapy, or chemotherapy or for palliation in advanced NSCLC.

Surgery

Lobectomy, the surgical resection of a single lobe, is generally accepted as the optimal procedure for early-stage NSCLC. Data regarding lobectomy vs sublobar resection are mixed but generally favor lobectomy. The best evidence comes from the Lung Cancer Study Group trial 801, which reported a 3-fold increase in the rate of local recurrence in patients undergoing sublobar resections.[33] However, note that this trial is older than 25 years and precedes the introduction of PET. Furthermore, retrospective analyses have also found that survival generally seems to be lower with limited resection than with lobectomy.[34,35]

However, several prospective, small, nonrandomized studies have reported favorable long-term survival after wedge resection or segmentectomy in patients with peripheral N0 lung cancers measuring 2 cm or less,[36,37] particularly those with bronchioloalveolar carcinoma on histologic examination.[38] Ongoing clinical trials, including the Cancer and Leukemia Group B trial 140503 and the Japan Clinical Oncology Group 0802/WJOG 4607L trial, have completed accrual, and we hope that they will help address this question. Today, the surgical approach to early-stage NSCLC remains complex and unique to each patient.

Neoadjuvant Chemotherapy

The potential advantages of neoadjuvant chemotherapy include early treatment of micrometastases; downstaging of the tumor, which may allow complete resection; and improved tolerability compared with the adjuvant approach. A large French study comparing preoperative chemotherapy with mitomycin, ifosfamide, and cisplatin plus surgery vs surgery alone did not report a benefit with neoadjuvant therapy, but a subset analysis suggested a survival advantage for N0 and N1 disease but not for N2 disease.[39] Another randomized study compared surgery alone for stage IB/IIIA with induction chemotherapy with cisplatin and gemcitabine followed by surgery[39] but was stopped early due to lack of recruitment. Nevertheless, the authors observed a statistically significant improvement in survival in stage IIB/IIIA by induction chemotherapy. Today, the role of neoadjuvant therapy is not clear, and no studies have reported a survival benefit for preoperative therapy.[40,41]

Adjuvant Chemotherapy

The rationale for adjuvant chemotherapy for patients with early-stage lung cancer is based on the observations that distant metastases are the most common site of failure after potentially curative surgery. Adjuvant therapy consists of cisplatin-based combination regimens and is indicated in patients with stage II and IIIA disease after surgical resection. In a pooled analysis of the 5 trials studying adjuvant therapy, there was a 5.4% absolute survival benefit at 5 years.[42] Other studies have also reported survival benefits

for adjuvant therapy, especially for patients with large tumors (>4 cm), for those with stage II disease, and after complete resection in patients with stage IIIA disease.[42]

There is growing interest in the incorporation of molecularly targeted agents and immunotherapy in the treatment of early-stage NSCLC. However, this approach is not recommended outside of clinical trials. Several studies that include *EGFR* and anaplastic lymphoma kinase (*ALK*) inhibitors did not report significant improvement in progression-free survival (PFS) and overall survival (OS) after surgical resection.[43,44]

Immunotherapy Use in Unresectable Stage III NSCLC

Management of stage III NSCLC is accordingly complex and subject to much debate. For the past 10 years, concurrent chemoradiation therapy has been the preferred treatment for unresectable stage III NSCLC in an effort to treat both locoregional and distant micrometastatic disease. Unfortunately, the stage III NSCLC prognosis remains poor, with only 15% of patients being alive at 5 years.[45] The PACIFIC trial[46] reported a PFS benefit in patients treated with durvalumab, a programmed cell death protein-ligand 1 (PD-L1) inhibitor, vs the placebo arm (16.8 vs 5.6 months; $P<.001$) and a higher response rate (RR) (28.4% vs 16%; $P<.001$).

In addition, an OS benefit was observed (hazard ratio [HR] of death, 0.68; 95% CI, 0.54-0.86).[47] The tolerability of durvalumab was similar to that in previous studies. These findings led to the Food and Drug Administration (FDA) approval of durvalumab for unresectable stage III NSCLC.

OLIGOMETASTATIC DISEASE

Oligometastatic NSCLC implies limited metastatic lesions affecting 1 or 2 organ systems that can be treated with local therapy (surgery or radiation) in conjunction with the primary tumor. The treatment options depend on the organ systems affected. Solitary brain metastases are usually treated with surgical resection or stereotactic radiosurgery. In the case of adrenal lesions, these can be resected in patients responding to systemic therapy or receiving local therapy for the primary tumor. In a US retrospective study with 37 cases, 5-year survival of 34% was reported with adrenalectomy in the case of a single secondary lesion.[48] Many organ systems can be affected by metastatic NSCLC. In a systematic review that included patients with NSCLC receiving treatment for a solitary metastasis, 5-year survival was reported to be 50% for the entire cohort (62 patients).[49] This therapeutic approach, although it can rarely be offered, should not be forgotten.

Recent data have strengthened the role of radiation in the treatment of oligometastatic NSCLC. Patients with fewer than 3 metastatic lesions and at least stable disease with systemic therapy had improved PFS and OS (41.2 and 17.0 months) with consolidative radiation to the metastatic sites compared with maintenance systemic therapy alone.[50,51]

METASTATIC NSCLC

Chemotherapy for Advanced Disease

Patients who present with metastatic disease require systemic treatment (Table 1). Before the era of immunotherapy, the standard treatment was a platinum doublet with either carboplatin or cisplatin with gemcitabine, vinorelbine, or taxanes (paclitaxel or docetaxel). Several studies have concluded that in patients with NSCLC these doublets have comparable efficacy, with differences in their toxicity profile. Pemetrexed, a multitargeted antifolate, was studied in combination with cisplatin and compared with cisplatin and gemcitabine in patients with all NSCLC. In a prespecified analysis for survival concerning histologic type (squamous vs nonsquamous), a significant survival difference in favor of cisplatin/pemetrexed occurred in patients with nonsquamous histologic type (median OS, 11.8 vs 10.4 months; HR, 0.81; 95% CI, 0.74-0.94). The pemetrexed combination was also found to be better tolerated and, therefore, became the standard of care in patients with nonsquamous histologic type. In all histologic types, treatment with a platinum doublet is limited to 4 to 6 cycles because several trials have suggested a lack of improvement in OS on continuing until progression. In patients

with nonsquamous histologic findings who have no evidence of progression after the initial 4 cycles of doublet chemotherapy, the continuation of pemetrexed alone has been associated with an improvement in survival compared with placebo.

The introduction of chemoimmunotherapy has significantly changed the treatment landscape of NSCLC and is discussed further in the Immunotherapy section.

TARGETED THERAPY

Epidermal Growth Factor Receptor Inhibitors

Epidermal growth factor receptor (*EGFR*) mutations are present in 15% of patients with NSCLC in the United States, with a higher frequency in Asian patients.[52,53] These occur more frequently in women and nonsmokers. There are 2 main approaches to targeting *EGFR*: tyrosine kinase inhibitors (TKIs) and monoclonal antibodies.

The *EGFR* TKIs are composed of first-generation erlotinib and gefitinib, second-generation afatinib and dacomitinib, and third-generation osimertinib (Table 2).[54-62] The *EGFR* TKIs significantly prolonged PFS in patients with advanced NSCLC that contains an activating mutation in *EGFR* compared with platinum-based chemotherapy. However, these agents have had little or no effect on OS in large clinical trials, in part because these agents were studied in second-line therapy after disease progression on chemotherapy, and a high proportion of crossover was allowed in the studies. A meta-analysis by Lee et al[63,64] summarizes 13 phase 3 trials in which an *EGFR* TKI was compared with platinum-based chemotherapy; PFS was significant prolonged (HR, 0.43; 95% CI, 0.38-0.49), whereas no effect on OS was observed (HR, 1.01; 95% CI, 0.87-1.18). Lower rates of adverse effects and better symptom control were also reported in favor of the *EGFR* TKIs (Table 2).[63,64]

The landscape in the treatment of *EGFR*-mutant NSCLC has changed dramatically in the past few years, with newer data reporting improved PFS outcomes with frontline osimertinib compared with gefitinib or erlotinib and moving osimertinib to frontline therapy. Osimertinib is now approved by the FDA for the first-line treatment of patients with metastatic

TABLE 1. Summary of Systemic Therapy for Metastatic Non–Small Cell Lung Cancer

Line of therapy	Nonsquamous, driver mutation (PS 0-3)	Nonsquamous, no driver (PS 0-2)	Squamous and nonsquamous, PD-L1 >50% (PS 0-2)	Squamous, PD-L1 <50% (PS 0-2)
First line	*EGFR*+: osimertinib *ALK/ROS1*+: alectinib, crizotinib *BRAF*+: debrafenib/trametinib *NTRK*+: larotrectinib *RET, MET, HER-2:* specific TKI	Platinum/pemetrexed plus pembrolizumab or platinum doublet (carboplatin + taxane), atezolizumab plus bevacizumab	Pembrolizumab	Platinum with paclitaxel or nab-paclitaxel plus pembrolizumab
Maintenance	Continue TKI	Pembrolizumab ± pemetrexed, atezolizumab ± bevacizumab, erlotinib, or none	Clinical trial if available, otherwise continue pembrolizumab until progression or unacceptable toxicity.	Pembrolizumab
Second and third line	Second- or third-generation TKI if not used in the first-line setting (alectinib, osimertinib) Lorlatinib (*ALK*+) followed by chemotherapy	Clinical trial if available, docetaxel ± ramucirumab. Single-agent: gemcitabine or necitumumab	Clinical trial if available, docetaxel ± ramucirumab. Single-agent: gemcitabine, erlotinib, or necitumumab	Clinical trial if available, docetaxel ± ramucirumab. Single-agent: gemcitabine, erlotinib, or necitumumab

ALK = anaplastic lymphoma kinase, *EGFR* = epidermal growth factor receptor, *HER-2* = human epidermal growth factor receptor 2, *NTRK* = neurotrophic receptor tyrosine kinase, PD-L1 = programmed cell death protein-ligand 1, PS = Performance Status, TKI = tyrosine kinase inhibitor.

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TABLE 2. Selected Phase 3 trials of *EGFR* Inhibitors for Non–Small Cell Lung Cancer

Trial	Drug (TKI)	Line of therapy	Dose (mg/d)	Population	Treatment	Primary outcome	Toxicity
OPTIMAL[54]	Erlotinib	First-line metastatic	150	Stage IIIB/IV with *EGFR* mutations in China	Erlotinib vs gemcitabine/carboplatin	PFS: 13.1 mo (erlotinib) vs 4.6 mo (gemcitabine/carboplatin) ($P<.001$)	Increased ALT (4%), rash (2%), diarrhea (1%), and stomatitis (1%)
EURTAC[55]	Erlotinib	First-line metastatic	150	Stage IV *EGFR* mutation positive in Europe	Erlotinib vs carboplatin/docetaxel or carboplatin/gemcitabine	PFS: 9.7 vs 5.2 mo ($P<.001$)	Rash (13%), fatigue (6%), diarrhea (5%), and increased ALT (2%)
WJTOG3405[56]	Gefitinib	First-line metastatic	250	Stage IIIB/IV *EGFR* mutations in Japan	Gefitinib vs cisplatin/docetaxel	PFS: 9.2 mo (gefitinib) vs 6.3 mo (cisplatin/docetaxel) ($P<.001$)	Increased ALT (27%), increased AST (16%), rash (2.3%), and fatigue (2.3%)
NEJ002[57]	Gefitinib	First-line metastatic	250	Stage IIIB/IV with *EGFR* mutations in Japan	Gefitinib vs carboplatin/paclitaxel	PFS: 10.4 mo (gefitinib) vs 5.5 mo (carboplatin/paclitaxel) ($P<.001$)	Increased LFTs (26.3%), anorexia (5.3%), rash (5.3%), and fatigue (2.6%)
LUX-Lung 3[58]	Afatinib	First-line metastatic	40	Stage IV, *EGFR* mutation positive	Afatinib vs cisplatin/pemetrexed	PFS: 13.6 vs 6.9 mo ($P<.001$)	Rash/acne (16.2%), diarrhea (14.4%), paronychia (11.4%), and stomatitis/mucositis (8.7%)
LUX-Lung 6[59]	Afatinib	First-line metastatic	40	Stage IV, *EGFR* mutation positive	Afatinib vs cisplatin/gemcitabine	PFS: 11.0 vs 5.6 mo ($P<.001$)	Rash (14.2%), diarrhea (5.4%), stomatitis/mucositis (5.4%), and anorexia (1.3%)
AURA 3[60]	Osimertinib	Second-line metastatic	80	T790M positive after progression on other EFGR TKI	Osimertinib vs platinum-based chemotherapy (pemetrexed)	PFS: 10.1 vs 4.4 mo ($P<.001$) ORR: 71% vs 31%	Diarrhea (1%), rash (1%), anorexia (1%), and fatigue (1%)
FLAURA[61]	Osimertinib	First-line metastatic	80	Advanced NSCLC, *EGFR* mutation positive	Osimertinib vs gefitinib or erlotinib	PFS: 18.9 vs 10.2 mo ($P<.001$) OS: HR, 0.63 (pending, only 25% of cases reported)	Anorexia (3%), diarrhea (2%), prolonged QT interval on ECG (2%), and rash/acne (1%)
ARCHER 1050[62]	Dacomitinib	NA	NA	Advanced NSCLC, *EGFR* mutation positive	Dacomitinib vs gefitinib	PFS: 14.7 vs 9.2 mo OS: 34 vs 27 mo	Dermatitis (14%), grade 3/4 diarrhea (9%)

ALT = alanine aminotransaminase; AST = aspartate aminotransferase; ECG = electrocardiogram; *EGFR* = epidermal growth factor receptor; HR = hazard ratio; LFT = liver function test; NA = not available; NSCLC = non–small cell lung cancer; ORR = overall response rate, OS = overall survival; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.

NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 L858R mutations. In the interim analysis of the phase 3 FLAURA trial,[61] where patients with *EGFR*-mutated advanced NSCLC were randomly assigned to receive osimertinib vs first-generation *EGFR* TKIs. Osimertinib demonstrated improvement in PFS (18.9 vs 10.2 months) and a longer duration of response (17.2 vs 8.5 months) compared with first-generation TKIs. The PFS benefit was consistent across all subgroups, including patients with or without brain metastases, suggesting greater intracranial efficacy. However, OS results are immature, with only 25% of events collected.

Also, dacomitinib has been approved in the United States for the frontline treatment of *EGFR*-mutated advanced NSCLC. In a multinational phase 3 trial, dacomitinib demonstrated improved PFS compared with gefitinib (14.7 vs 9.2 months) as well as improved OS (34 vs 27 months).[62,65] However, grade 3 to 4 dermatitis was more frequent with dacomitinib (14% vs 0%), as was grade 3 to 4 diarrhea (9% vs 1%).

Resistance to *EGFR* TKIs

Despite the high RRs achieved with *EGFR* TKIs, the disease progresses in most patients after 6 to 12 months of treatment and develops "resistance" to the original agent. Although all the mechanisms of resistance are not fully understood, a secondary exon 20 *T790M* missense mutation develops in 40% to 60% of patients, for which treatment is switched to osimertinib. Osimertinib targets the *T790M* mutation and the primary activating *EGFR* mutations. The initial phase 2 trial of osimertinib after progression on *EGFR* TKIs reported an RR of 61% and median PFS of 10 months (Table 2).[66]

In addition, cases of secondary resistance seem to be caused by amplification of the *MET* oncogene in 5% to 20% of patients during treatment with erlotinib or gefitinib[67,68] and potentially as high as 30% in patients with acquired resistance to osimertinib.[69] Mutations in *PIK3CA* and human epidermal growth factor receptor 2 (*HER-2*) amplifications among other bypass tracts have also been implicated as resistance mechanisms. In a small group of patients, transformation to SCLC has also been reported as a mechanism of resistance to *EGFR* TKIs.[70,71] These patients are usually switched to SCLC first-line treatment with platinum-based regimens.

For patients who do not have a *T790M* mutation or who progress on osimertinib, systemic chemotherapy is the current standard of care when no clinical trials are available.

Anti-*EGFR* Monoclonal Antibodies

The effects of these agents do not seem to be associated with the presence of activating *EGFR* mutations. Two phase 3 clinical trials incorporating anti-*EGFR* monoclonal antibodies have been conducted, with both reporting modest improvement in OS for cetuximab (HR, 0.87; $P<.04$) or necitumumab (HR, 0.84; $P<.01$) when added to systemic cytotoxic therapy.[72,73]

ALK and *ROS1* Translocations

Approximately 5% of patients with NSCLC have tumors containing a translocation in the *ALK* gene, and 1% to 2% of patients have *ROS1* translocations.[74] Crizotinib, a TKI, was initially developed as a c-*MET* inhibitor and later found to have activity in patients with *ALK* and *ROS1* translocations. The efficacy of crizotinib was first seen in an expanded cohort of a multicenter phase 1 study[74] reporting a radiographic response of 57% and stable disease in 33% of patients. The PROFILE 10007 phase 3 trial confirmed that crizotinib had a higher RR and better PFS compared with investigators' choice of docetaxel or pemetrexed for patients with *ALK*-positive tumors who progressed on first-line chemotherapy (overall RR [ORR], 65% vs 20%; median PFS, 7.7 vs 3 months; $P<.001$).[75]

Ceritinib, a second-generation *ALK* TKI, has shown improved efficacy over combination chemotherapy in the first-line setting in the ASCEND-4 trial, with an improvement of PFS in the ceritinib arm of 16.6 months vs 8.1 months in the chemotherapy arm (HR, 0.55; 95% CI, 0.42-0.73; $P<.001$) and a longer duration of response (23.9 vs 11.1 months).[76]

Alectinib, a second-generation *ALK* TKI, is now FDA approved for first-line treatment of *ALK*-positive NSCLC and those who have

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progressed on crizotinib. In the J-ALEX trial, alectinib had superior efficacy compared with crizotinib; at a planned interim analysis, an improved PFS was observed with alectinib (not reached vs 10.2 months in the crizotinib arm; HR, 0.34; 95% CI, 0.17-0.70; $P<.001$).[77] In the ALEX trial, a global study, alectinib showed similar results compared with crizotinib, with median PFS of 34.8 months vs 10.9 months for those receiving crizotinib.[78,79] However, preliminary OS data showed an HR of death of 0.76 (95% CI, 0.50-1.15). A secondary benefit from the use of alectinib was the time to central nervous system progression (a common feature in *ALK*-positive NSCLC); in the overall population, this was improved with alectinib (HR, 0.16; 95% CI, 0.10-0.28). In both clinical trials, alectinib was better tolerated compared with crizotinib.

Based on the available data, alectinib is the preferred agent for first-line therapy in *ALK*-positive NSCLC.

Lorlatinib is a new-generation *ALK* inhibitor with activity against all the known *ALK* inhibitor resistance mutations, and it is our preferred agent in the setting of resistance to alectinib.[80,81] Lorlatinib was granted FDA approval for *ALK*-positive NSCLC with progression on crizotinib and at least 1 other *ALK* inhibitor, as well as for those who have progressed on either alectinib or ceritinib as frontline therapy. The FDA approval was based on a phase 2 study that included a subgroup of 198 patients with *ALK*-positive metastatic NSCLC previously treated with 1 or more *ALK* inhibitors. The ORR with lorlatinib in these patients was 47%.[82]

In the case of patients with *ROS1*-positive NSCLC, crizotinib has become the preferred initial therapy based on the results from an expansion cohort of the crizotinib phase 1 study, where 50 patients with *ROS1*-NSCLC were enrolled. The ORR was 72%, with 3 complete responses and 33 partial responses and median PFS of 19.2 months. The safety profile of crizotinib was similar to that seen in patients with *ALK*-rearranged NSCLC.[83]

Other second-generation agents are being studied, including ceritinib and cabozantinib in patients with progression on first-line crizotinib.[84,85]

Vascular Endothelial Growth Factor Receptor Inhibitors

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor receptor A, was approved for the treatment of nonsquamous cell carcinoma combined with chemotherapy. Based on the results of the Eastern Cooperative Oncology Group (ECOG) 4599 phase 3 trial,[86] the bevacizumab arm showed improved median survival of 12.3 months vs 10.3 months in the chemotherapy alone arm (HR, 0.79; $P<.003$). Due to bleeding adverse effects reported in the phase 2 trial, this trial was restricted to patients with nonsquamous cell lung cancer. Despite these restrictions, significant bleeding was reported in the bevacizumab arm (4.4% vs 0.9%; $P<.001$). Benefits and risks about the use of bevacizumab should be delineated to patients with advanced NSCLC due to the associated risk of bleeding and thromboembolic events.

Other agents targeting vascular endothelial growth factor include ramucirumab and aflibercept. Ramucirumab plus docetaxel showed improved OS vs docetaxel alone (10.5 vs 9.7 months). Improved PFS was also reported (4.5 vs 3.0 months), with an overall incidence of grade 3 or 4 toxicity of 79% vs 72% in the combination arm.[87]

Other Targetable Alterations

BRAF mutations have been identified in 2% of patients with NSCLC, half of whom have a *BRAF V600* mutation.[88] Vemurafenib, an oral small-molecule TKI, was studied in a small phase 2 trial; responses were seen in 42% of the patients, with median PFS of 7.3 months.[89] In patients with *BRAF V600E* mutations that progressed on chemotherapy, the combination of dabrafenib plus trametinib is now FDA approved, based on the results of the phase 2 trial of dabrafenib plus trametinib, which reported RR of 63.2% and median PFS of 9.7 months.[90]

Fusions involving 1 of 3 tropomyosin receptor kinases are l% prevalent in NSCLC.[91] The oral tropomyosin receptor kinase inhibitor larotrectinib is FDA approved for advanced tumors that harbor a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion, lack a known

acquired resistance mutation, and have no satisfactory alternative treatments available.[92] In the case of *NTRK*-positive NSCLC, we suggest larotrectinib after progression on previous chemotherapy or immunotherapy.

KRAS mutations are observed in 20% to 25% of NSCLC.[93] Numerous agents are under investigation, but some studies have not found any survival or therapeutic benefit.[94] Similar outcomes were seen with addition of the MAPK/ERK kinase inhibitor selumetinib to docetaxel.[95]

Other possible molecular targets include *HER-2* mutations, *MET* abnormalities, and *RET* translocations.

IMMUNOTHERAPY

Immunotherapy has dramatically changed the landscape of treatment of NSCLC. Because of the rapidly changing landscape, this review is directed to the practicing oncologist, and it focuses on recent clinical developments that have led to the approval of immune checkpoint inhibitors (ICIs) for the treatment of NSCLC. As a premise, an essential role of the immune system is to recognize and destroy neoplastic cells before they become clinically meaningful.[96] To limit damage to healthy cells, this process is highly regulated by an equilibrium of activating and inhibitory pathways.[97] By altering this equilibrium, malignancies can escape immune surveillance and thrive. One of these pathways is the programmed cell death protein 1 (PD-1)/ /PD-L1 axis. The PD-1 is a transmembrane receptor that is expressed in a variety of tissues.[98] Its ligand, PD-L1, is expressed in T cells,[99] and this interaction leads to the inactivation of T cells. Malignancies can overexpress PD-L1 as a mechanism of defense against the host's immune system. This interaction can be blocked with antibodies directed against PD-1 or its ligand. This strategy has been proved to be an effective therapeutic option for many malignancies, including NSCLC.[98] One of the most attractive features of these types of treatment is that a subset of patients seems to have long-lasting benefits, with a subgroup of patients being alive 5 years after diagnosis, something that was unthinkable a decade ago.[100]

IMMUNOTHERAPY AS FIRST-LINE TREATMENT

Immunotherapy Monotherapy

A phase 3 clinical study, KEYNOTE-024, randomized 305 patients with NSCLC who had PD-L1 expression of more than 50% of cells (30% of screened samples) to receive the investigator's choice of chemotherapy or pembrolizumab.[101] Treatment with pembrolizumab increased the RR (45% vs 28%), PFS (10.3 vs 6 months; HR, 0.50; 95% CI, 0.37-0.68; $P<.001$), and OS (30 vs 14.2 months), establishing pembrolizumab as the standard of care for this subset of patients.[101] In contrast, nivolumab was studied in a phase 3 trial, CheckMate 026, in patients with all the histologic findings of NSCLC.[102] Here, patients were eligible if their tumors had more than 1% expression of PD-L1 and were randomized to receive nivolumab alone vs the investigator's choice of platinum doublet chemotherapy. In the primary efficacy analysis (423 patients with >5% PD-L1 expression) there was no advantage of treatment with nivolumab in RR (26% vs 33%), PFS (4.2 vs 5.9 months; HR, 1.15; 95% CI, 0.91-1.45; $P=.25$), or OS (14.4 vs 13.2 months; HR, 1.02; 95% CI, 0.80-1.30). In an exploratory analysis, the subset of patients with more than 50% expression of PD-L1 had similar results (HR for disease progression, 1.07; 95% CI, 0.77-1.49; and HR for death, 0.90; 95% CI, 0.63-1.29).

It is unknown, and an area of active investigation, why there are discrepant results between nivolumab and pembrolizumab. Possible explanations include differences in trial design (including crossover to the experimental arm), biomarker requirements (KEYNOTE-024 allowed only patients with >50% PD-L1 expression), or heterogeneity between the different compounds.

Combination Chemoimmunotherapy

The combination of a platinum doublet and pembrolizumab has proved to improve the efficacy of treatment compared with chemotherapy alone for patients with metastatic NSCLC with both nonsquamous and squamous histologic findings, irrespective of PD-L1 expression

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(Table 1).[103-105] Patients treated with chemoimmunotherapy had improved OS, PFS, and ORR, making these regimens the current standard of care. Despite some initial concerns of an increase in adverse events (AEs), phase 2 studies established that the addition of pembrolizumab was not associated with an increase in the rate of grade 3 or 4 AEs compared with chemotherapy alone.[104] However, patients treated with pembrolizumab had a higher percentage of treatment discontinuation compared with patients treated with chemotherapy alone (13.8% vs 7.9% in nonsquamous histologic type and 12.2% vs 6.4% in squamous histologic type). As was seen with single-agent pembrolizumab, immune-mediated AEs occurred in 22.7% and 28.8% of patients with nonsquamous and squamous NSCLC, respectively; most were manageable. Note that in these studies, as well as those with pembrolizumab alone, eligibility was restricted to patients with an ECOG Performance Status (PS) of 0 or 1; therefore, caution extrapolating these results to patients who have an ECOG PS of 2 or greater, which constitutes a significant number of patients with NSCLC, is strongly advised.

The benefit of using pembrolizumab and chemotherapy was seen across subgroups of PD-L1 expression but were more impressive in patients who were high expressors of PD-L1.[103] As stated previously herein, these subgroups of patients also respond better to pembrolizumab alone compared with chemotherapy, and it is currently unknown whether instituting triple therapy in these patients would be associated with an improved benefit over pembrolizumab alone, which is likely to be better tolerated.

Regarding PD-L1 antibodies, atezolizumab was studied in a phase 3 trial in which 1202 patients with nonsquamous NSCLC were randomized to the control arm of carboplatin, paclitaxel, and bevacizumab or carboplatin, paclitaxel, and atezolizumab or the same chemoimmunotherapy plus bevacizumab. The study used a hierarchical analysis, and the initial report compared the chemoimmunotherapy plus bevacizumab arm with the control arm of chemotherapy plus bevacizumab.[106] The results were similar to the above chemoimmunotherapy trials in that it improved OS, PFS, and ORR compared with chemotherapy alone, with no safety signals encountered. Interestingly, this study enrolled a subset of patients with *EGFR* and *ALK* abnormalities into a subgroup analysis; these patients seem to have a similar benefit compared with patients with wild-type *EGFR* and *ALK* NSCLC, although the small number of post hoc analyses makes it hard to draw a conclusive answer, and prospective trials in this population are needed. Atezolizumab is now FDA approved in the first-line setting in combination with carboplatin, paclitaxel, and bevacizumab for patients with metastatic nonsquamous NSCLC with no *EGFR* or *ALK* genomic tumor aberrations.

Combination Immunotherapy

Cytotoxic T-lymphocyte—associated protein 4 (CTLA-4) is another ICI that is expressed in T cells; when activated, it sends an inhibitory signal that modulates effector T-cell activation, proliferation, and function.[107] The combination of an anti—PD-1 antibody and a CTLA-4 inhibitor improves antitumor immunity in patients with malignant melanoma and is currently being studied in patients with lung cancer.

The phase 1 CheckMate 012 trial enrolled 78 patients with chemotherapy-naive NSCLC with different schedules and doses of nivolumab and the anti—CTLA-4 antibody ipilimumab.[108] The activity of this regimen varied across subgroups of patients categorized based on their PD-L1 expression. In patients with less than 1% PD-L1, the ORR was 21%, 57% in patients with at least 1% PD-L1, and 92% in patients with at least 50% PD-L1.[108]

Improvements in PFS favored the combination over nivolumab alone: 8 vs 3.6 months with less than 1% PD-L1 and 12.7 vs 3.5 months with at least 1% PD-L1; for patients with at least 50% PD-L1, the median had not been reached compared with 8.3 months with monotherapy alone. The combination therapy showed a higher incidence of grade 3/4 AEs, 19% with nivolumab monotherapy, 42% with the combination therapy, and 31% with the more-frequent combination therapy. CheckMate 227 trial is a phase 3 study that

randomized 1189 patients with chemotherapy-naive NSCLC with more than 1% of PD-L1 expression to receive nivolumab alone vs nivolumab at a dose of 3 mg/kg every 2 weeks and ipilimumab at 1 mg/kg every 6 weeks vs the control arm of platinum doublet chemotherapy.[109] A second cohort of 550 patients with PD-L1 expression of less than 1% was randomized to similar arms except that there was no nivolumab alone arm; instead, this subgroup was replaced by a platinum doublet and nivolumab. The results of this trial are difficult to interpret because the study was amended early on to use tumor mutation burden (TMB) as a primary end point, as this seemed to be an important predictive factor independent of PD-L1 staining. Analysis of TMB was limited to 139 patients in the combination immunotherapy arm and 160 in the standard chemotherapy arm. A high TMB was defined as 10 or more mutations per megabases and was present in 86 patients (29%) with PD-L1 expression of less than 1%. Patients with a high TMB had improved PFS (median, 7.2 vs 5.5 months; HR, 0.58; 95% CI, 0.41-0.81; $P<.001$). Adverse events were reported in all patients who received treatment; the combination immunotherapy had more AEs than treatment with nivolumab alone, with 31.2% of patients having grade 3/4 AEs. Seven patients (1.2%) treated with nivolumab plus ipilimumab died secondary to treatment, with 3 of these being secondary to pneumonitis. Further studies are needed before TMB can be used for clinical decision making.

In a similar strategy, the PD-L1 inhibitor durvalumab was used in combination with a CTLA-4 inhibitor, tremelimumab, in a phase 1 study using different doses and schedules. The combination showed increased toxicity compared with either agent alone, with an incidence of grade 3 or 4 AEs of 46% and high rates of pneumonitis. Although most cases of toxicities were manageable, there were 3 treatment-related deaths.[110] Early reports from the phase 3 study (ARCTIC trial) revealed no statistically significant OS or PFS benefit in patients with low PD-L1 expression receiving durvalumab and tremelimumab, although final results from this study are pending.[111,112]

Immunotherapy for Progressive Disease After Chemotherapy

In NSCLC, these therapeutic tools were first tested in patients who had progressed through platinum-based chemotherapy, and the comparator arm was docetaxel, the standard therapy at the time. With slight differences in trial design, the anti—PD-1 antibodies nivolumab[113,114] and pembrolizumab,[115] as well as the anti—PD-L1 antibody atezolizumab,[116] demonstrated superior OS rates and have now become the standard of care in the second-line setting for patients who are immunotherapy naive. Remarkably, PFS across these 3 studies was not different than that in the docetaxel arm. One potential explanation could be that the traditional way of measuring responsive disease by the response evaluation criteria in solid tumors (RECIST) does not apply well to immunotherapy.[117] This was evident in a study of 160 patients who received nivolumab or pembrolizumab; patients were assessed by serial CT as part of their clinical care.[118] Although pseudoprogression, a phenomenon by which the tumor appears larger during the initial reevaluation scan before regressing, was rare (0.6%), 16% of patients (n=26) experienced tumor growth fluctuations that would qualify them as having progressive disease by the RECIST criteria at some point during their treatment and yet had benefited from ongoing therapy.

The AE profile of PD-1/PD-L1 ICIs differs drastically from that of chemotherapy, but, in general, PD-1/PD-L1 ICIs are better tolerated. The incidence rates of grade 3 to 5 AEs were 35% to 55% with docetaxel compared with 7% to 15% with ICIs.[119] The most common AEs are grade 1 to 2 fatigue and anorexia, which are present in 14% to 24% of patients.[120] Severe toxicities, such as pneumonitis or colitis, are infrequent and can be managed in most cases by the discontinuation of therapy and prompt initiation of corticosteroids or other anti-immunotherapy when corticosteroids are not effective.[121]

By interfering exclusively with the PD-L1 receptor, the PD-L1 inhibitors leave the PD-1/PD-L2 pathway intact, which theoretically could be more specific for tumor immunology

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with decreased immune-mediated toxicities. At the moment, we lack head-to-head comparisons, but differences have been observed in the first-line setting, where nivolumab was not associated with significantly longer PFS than was chemotherapy.[102]

Biomarkers of Activity

Immunotherapy is an essential tool in the armamentarium against NSCLC; however, in reality, most patients do not benefit from this type of treatment. Expression of PD-L1 in malignant cells has been studied as a potential biomarker; PD-L1 expression by immunohistochemical analysis correlates with benefit from ICIs.[122] However, important drawbacks exist that limit its discriminatory potential,[123] including the lack of consensus as to the level of PD-L1 expression that constitutes positive vs negative results (ranging from 1%-50% expression) and the fact that there is significant intratumor heterogeneity for PD-L1 expression, and a biopsy may not be representative of the entire tumor mass.[124] Also, diagnostic PD-L1 immunohistochemistry assays vary, with each pharmaceutical company using its own test, potentially leading to discordant results. Other biomarkers, such as gene expression signatures, TMB, and T-cell receptor sequencing, are currently being evaluated as potential markers of response.[125]

For most patients who respond to ICIs, this is unfortunately transitory. The mechanisms of resistance are currently poorly understood and an area of active investigation. A minority of patients achieve a durable response that might lead to long-term survival.[126] Identifying the characteristics of these patients is also of paramount importance because it challenges a very important dogma in this field wherein patients with metastatic disease are currently treated with palliative intent with the goal of improving the quality and length of life. If long-term survival is a possibility, patients and providers might be willing to endure more toxic therapy to achieve this goal.

Patients With Genetic Driver Abnormalities

Whether immunotherapy is active in patients with NSCLC who have an activating genetic abnormality such as *EGFR* mutation or *ALK* translocation is a matter of debate. In a meta-analysis of patients with *EGFR* mutations enrolled in the CheckMate 057, KEYNOTE-010, and POPLAR studies, in which nivolumab, pembrolizumab, and atezolizumab, respectively, were compared with docetaxel, 186 patients with an *EGFR* mutation did not seem to benefit from immunotherapy (HR, 1.05; 95% CI, 0.70-1.55; $P=.81$). This is in stark contrast to the 1362 *EGFR* wild-type patients (HR, 0.66; 95% CI, 0.58-0.76; $P<.001$).[127] Patients with genetic drivers such as *EGFR* mutations have a significantly lower TMB compared with wild-type patients.[128] It has been hypothesized that an increase in TMB leads to an increased number of mutated proteins, or neoantigens, on the surface of tumor cells capable of eliciting an immune response.[129] The low TMB might explain the apparent lack of efficacy for this subset of patients. In our clinical practice, we reserve the use of immunotherapy for patients with genetic driver abnormalities only after they have exhausted the available targeted therapies and possibly cytotoxic therapy, including platinum doublets.

Brain Metastasis

At diagnosis, 10% of patients have metastatic brain disease, and 30% of patients develop this during their illness. Patients with untreated and asymptomatic brain metastasis are typically excluded from clinical trials but are frequently encountered in clinical practice.[130] In a phase 2 study, 36 patients with new or progressive brain metastasis (5-20 mm in diameter and not requiring corticosteroid treatment) received treatment with pembrolizumab (monotherapy). Half of the patients had NSCLC, and the other half had melanoma. All the patients with NSCLC had to have greater than 1% PD-L1 staining.[131] Brain metastasis response was observed in 6 of 18 patients with NSCLC.

All the patients with brain metastatic responsive disease also had a systemic response. Adverse events were consistent with previous studies. Transient grade 3 cognitive dysfunction or grade 1 or 2 seizures were observed in 3 patients with melanoma (17%), despite mandated antiepileptic therapy in the protocol. These results suggest that immunotherapy can be safe and effective in patients with asymptomatic central nervous system disease. Further studies are necessary before final recommendations can be made.

Patients With Preexisting Autoimmune Conditions

Patients with previous autoimmune conditions were excluded in all immunotherapy clinical trials. However, this group of patients is frequently encountered by general oncologists and represents a treating dilemma. Therapy with ICI blockade carries the risk of activating the immune phenomena. Guidance comes from retrospective reviews in which patients with melanoma and autoimmune disorders, including psoriasis, inflammatory bowel disease, multiple sclerosis, and others, were treated with CTLA-4[132] and PD-1 inhibitors.[133,134] Of the patients treated with ipilimumab, 27% experienced exacerbations of their autoimmune disease and 33% experienced immune-related AEs requiring treatment. The results were similar in patients treated with PD-1 inhibitors: 30% experienced an autoimmune flare and 29% experienced an immune-related AE. In both studies, both disease flares and AEs responded to standard treatment algorithms, and a single patient with a history of psoriasis died of ipilimumab-associated colitis. These data are limited given their retrospective nature and potential selection bias. Clinically, we have detailed discussions with our patients regarding benefits, risks, and alternatives to immune-based treatment. A multidisciplinary approach, including rheumatology, is crucial for the initial evaluation and monitoring of these patients.

Palliative Care and End of Life

In the United States, a randomized study showed that most patients with metastatic lung cancer had a poor perception of their prognosis, and the early introduction of palliative care enhanced their understanding of their situation and, thus, their decisions about their future.[135]

In many European countries, palliative care is managed by general practitioners. In Belgium and the Netherlands,[136] most patients spend their last years or months of life at home, where many die. Most patients with NSCLC will encounter physical and psychological distress during their lifetime, and early referral to palliative care services is recommended and associated with better pain control and emotional support and less associated caregiver fatigue.[137,138]

SURVIVORSHIP

The risk of developing secondary lung cancers is high (approximately 2%-3% annually) for patients with resected stage I and II NSCLC. Vitamin A and selenium have been found to be ineffective as chemoprevention therapy and deleterious in current smokers.[139-141] The National Comprehensive Cancer Network guidelines help physicians determine the appropriate surveillance plans based on lung cancer stage. Smoking, radiation therapy, and systemic cytotoxic therapy are known risk factors for secondary primary malignancies. Regular follow-up with primary care physicians is recommended for these patients after completing their initial surveillance plan.

CONCLUSION

The use of targeted therapy and ICI has dramatically changed the treatment of patients with NSCLC. In the case of immunotherapy, it has become the standard first-line treatment as monotherapy or combined with chemotherapy. Many questions remain regarding the sequence and combination of these new agents but, thankfully the field is moving at a very aggressive pace as the results of clinical trials and other investigations percolate at a rate not seen previously in NSCLC.

Abbreviations and Acronyms: **AE** = adverse event; ***ALK*** = anaplastic lymphoma kinase; **ALT** = alanine aminotransaminase; **AST** = aspartate aminotransferase; **CT** = computed tomography; **CTLA-4** = cytotoxic T-lymphocyte–associated protein 4; **ECG** = electrocardiogram; **ECOG** = Eastern Cooperative Oncology Group; ***EGFR*** = epidermal growth factor receptor; **FDA** = Food and Drug Administration; ***HER-2*** = human epidermal growth factor receptor 2; **HR** = hazard ratio; **ICI** = immune checkpoint inhibitor; **LFT** = liver function test; **NSCLC** = non–small cell lung cancer; ***NTRK*** = neurotrophic receptor tyrosine kinase; **ORR** = overall response rate; **OS** = overall survival; **PD-1** = programmed cell death protein 1; **PD-L1** = programmed cell death protein-ligand 1; **PET** = positron emission tomography; **PFS** = progression-free survival; **RECIST** = response evaluation criteria in solid tumors; **RR** = response rate; **SCLC** = small cell lung cancer; **TKI** = tyrosine kinase inhibitor; **TMB** = tumor mutation burden; **WHO** = World Health Organization

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The Thematic Review Series on Neoplastic Hematology and Medical Oncology will continue in an upcoming issue.

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