REVIEW ARTICLE

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Precision Diagnosis and Treatment for Advanced Non–Small-Cell Lung Cancer

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Lung cancer remains one of the most frequent and most deadly tumor entities, with 1.6 million tumor-related deaths annually worldwide.[1] The correlation between smoking status and mortality from lung cancer has been confirmed, and a decrease in mortality after cessation of tobacco use has been observed in the United States since the early 1990s for men and since the 2000s for women.[2]

Although direct or environmental exposure to tobacco smoke is the predominant risk factor, inhalation of carcinogens through marijuana or hookah use also contributes to the risk of lung cancer. Additional risk factors include exposures to radon, asbestos, diesel exhaust, and ionizing radiation. Increasing evidence suggests a correlation between lung cancer and chronic obstructive lung disease that is independent of tobacco use and is probably mediated by genetic susceptibility.[3] Lung cancer in patients who have never smoked, accounting for approximately one quarter of all cases of lung cancer in the United States, has attracted growing interest because of treatable oncogenic alterations and the opportunity for individualized treatment.[4]

Pathological Features

A pathological diagnosis should be established in accordance with the 2015 World Health Organization classification, since major treatment options are determined on the basis of histologic features.[5] Lung cancer comprises small-cell lung cancer (SCLC; approximately 15% of all lung cancers) and non–small-cell lung cancer (NSCLC; approximately 85%). When tissue samples of lung cancer (obtained by means of bronchoscopy or surgical biopsy) or cytologic samples (effusion, aspirates, or brushings) show clear morphologic features of adenocarcinoma or squamous-cell carcinoma, the diagnosis can be firmly established, and in these cases, immunocytochemical or immunohistochemical analysis is not routinely needed. If morphologic evaluation reveals neuroendocrine features, the tumor may be classified as SCLC or NSCLC (probably large-cell neuroendocrine carcinoma). If there is no clear morphologic evidence of adenocarcinoma or squamous-cell carcinoma, the tumor is classified as NSCLC, not otherwise specified (NOS).[6]

The category of tumors classified as NSCLC NOS can be further subdivided according to immunocytochemical or immunohistochemical analysis, mucin staining, or molecular data. NSCLC NOS that is positive for cytokeratin 7 and thyroid transcription factor 1, with negative markers for squamous-cell cancer, is classified as NSCLC favoring adenocarcinoma. A tumor that is positive for one or more markers of squamous-cell cancer, such as p63, cytokeratin 5, or cytokeratin 6, with negative adenocarcinoma markers, is classified as NSCLC favoring squamous-cell

carcinoma. If all markers are negative, the tumor is classified as NSCLC NOS.

The discovery of treatable oncogenic alterations led to the recommendation to include molecular testing in the standard approach in order to further classify NSCLC. This includes testing for mutations in the gene encoding epidermal growth factor receptor (*EGFR*) and in *BRAF* V600E, searching for translocations in the genes encoding anaplastic lymphoma kinase (*ALK*) and rat osteosarcoma (*ROS1*), and more recently, assessing expression of programmed death ligand 1 (PD-L1). Currently, most of these molecular tests can be performed in small biopsy samples and in cytologic specimens[6-9] (Figs. 1 and 2). It is likely that as the science advances, this list will expand. According to a recent report on whole-exome sequencing of 100 NSCLC tumor samples, not only clonal driver mutations but also genetic heterogeneity associated with several processes, such as chromosomal instability, genome duplications, and additional subclonal mutations, have a substantial effect on prognosis.[10] These findings are of clinical interest because they may guide the development of novel treatment strategies targeting neoantigens — for example, peptide vaccines or adoptive cell therapy.[10]

STAGING OF LUNG CANCER

The eighth edition of the lung cancer stage classification[11] reemphasizes the need for a correct tumor–node–metastasis (TNM)–based staging of lung cancer, given the large differences in survival in relation to tumor stage (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Furthermore, the emergence of personalized therapies for NSCLC underscores the need for cytologic or tissue verification of lung cancer.[12] Computed tomography (CT) remains a powerful tool for the staging of lung cancer. Advances in other imaging methods — specifically, positron-emission tomography with CT (PET-CT) and magnetic resonance imaging (MRI) — can improve the accuracy of baseline staging, as compared with CT alone, and can allow a more rapid and accurate assessment of the response to treatment.[13] Although the results are statistically equivalent, each test has particular advantages over the other. MRI is better than PET-CT for visualizing brain and liver metastases, and PET-CT is better than MRI for evaluating lymph nodes and other soft tissues.[14] However, even though noninvasive imaging is extremely useful, tissue diagnosis remains the standard essential element for staging lung cancer and monitoring the treatment response.

If imaging studies strongly suggest mediastinal or hilar lymph-node involvement,[13] endosonography (endobronchial or esophageal ultrasonography or the two combined) with needle aspiration is recommended over surgical staging as the best initial means of validation[15-17] (Fig. 1). Although tumor seeding is theoretically possible with the use of these procedures, there are no reports of tumor seeding in the staging of lung cancer. On the contrary, endobronchial ultrasound staging appears to be associated with improved survival among patients with NSCLC.[16]

For diagnostic purposes, endosonography is suggested in patients with a centrally located lung tumor that is not visible on conventional bronchoscopy, provided the tumor is immediately adjacent to the larger airways (endobronchial ultrasonography) or esophagus (esophageal ultrasonography). For mediastinal nodal staging in patients with suspected or proven NSCLC and abnormal mediastinal or hilar nodes on CT or PET-CT, endosonography is recommended over surgical staging as the initial procedure. The combination of endobronchial ultrasonography with real-time, guided transbronchial needle aspiration and endoscopic esophageal ultrasonography is preferred over either test alone. If the clinical suspicion of mediastinal-node involvement remains high after a negative result with the use of a needle technique, surgical staging is recommended.[12]

CURRENT LANDSCAPE OF TREATMENT

In patients who have advanced NSCLC without treatable oncogenic alterations, platinum-based chemotherapy remains the cornerstone of treatment. The rate of response, defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) as a tumor reduction of at least 30%,[18]

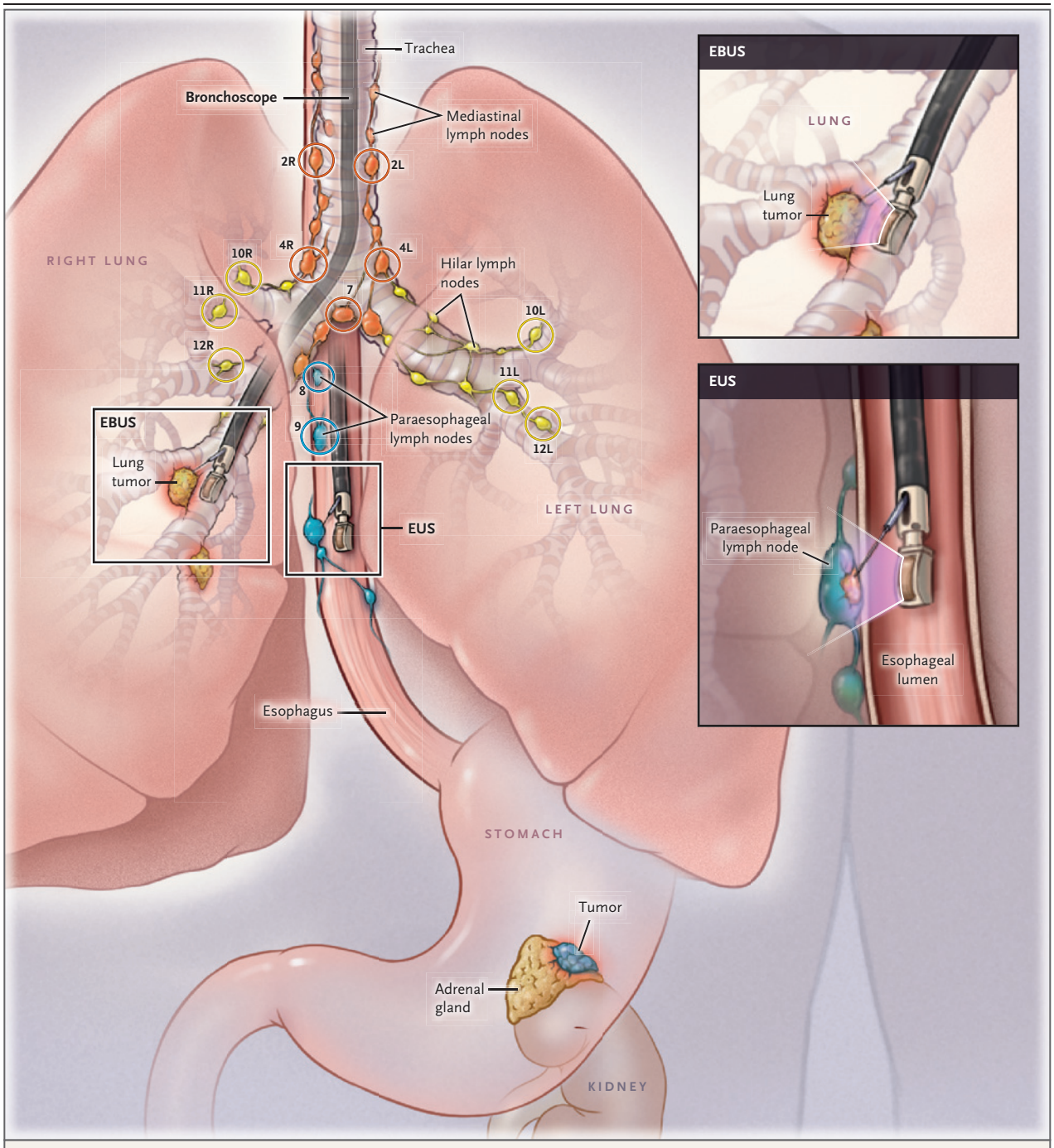

Figure 1. Endoscopic Diagnosis of Lung Cancer.

Endoscopic bronchial ultrasonography (EBUS) and endoscopic esophageal ultrasonography (EUS) are endoscopic approaches for the diagnosis of lung cancer, lymph-node metastases, and adrenal metastases. The lymph nodes shown in orange can be accessed by either technique, those shown in yellow can be accessed primarily by means of EBUS, and those shown in blue can be accessed primarily by means of EUS. Nodes that are clinically relevant and are often decision makers are encircled. L denotes left, and R right.

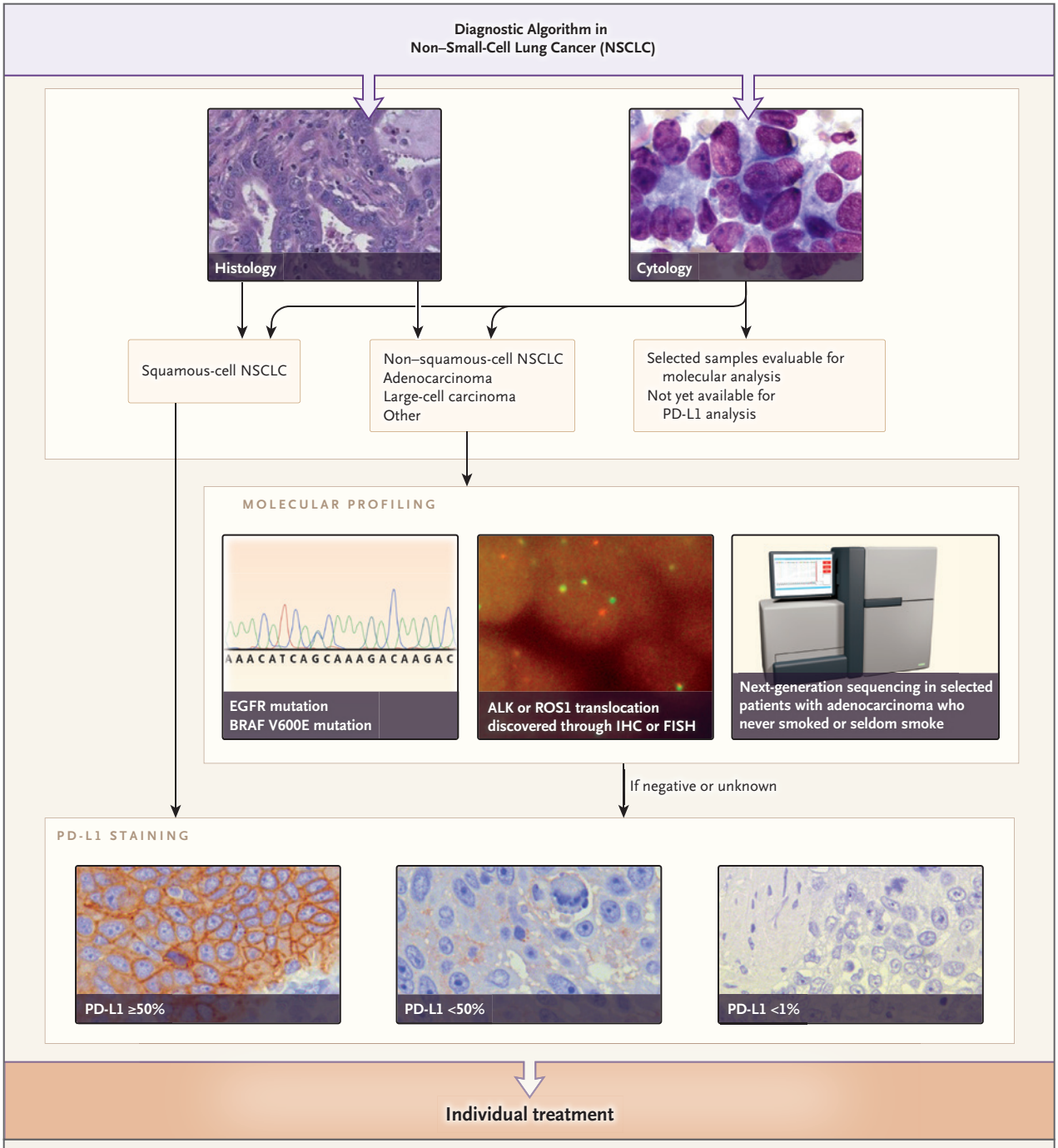

Figure 2. Diagnostic Algorithm for Non–Small-Cell Lung Cancer (NSCLC).

The upper portion of the algorithm shows the morphologic classification of NSCLC based on histologic (hematoxylin and eosin) and cytologic (Giemsa) evaluation. The middle portion of the algorithm shows the molecular analysis for the key treatable oncogenic alterations: *EGFR* and *BRAF* V600E mutations and *ALK* and *ROS1* translocations, as well as additional molecular analyses in selected patients. The lower portion of the algorithm shows the assessment of programmed death ligand 1 (PD-L1) expression by means of immunohistochemical staining. FISH denotes fluorescence in situ hybridization, and IHC immunohistochemical analysis.

is 25 to 35%, the median survival is 8 to 12 months, and the 1-year survival rate is 30 to 40%.[19,20] In addition to first-line chemotherapy, strategies such as maintenance therapy and second-line chemotherapies have further improved outcomes in patients with advanced NSCLC.

In clinical practice, pemetrexed maintenance therapy often follows first-line treatment with platinum-based chemotherapy in patients with non–squamous-cell NSCLC. With the introduction of novel immune and antiangiogenic therapies, however, accepted practices with respect to second and subsequent lines of therapy have changed substantially.[19,20]

Local treatment approaches, and radiotherapy in particular, play an important role in pain and symptom management in the palliative setting. Stereotactic radiation therapy of brain metastases has been shown to have similar efficacy and reduced toxicity, as compared with conventional whole-brain radiation therapy.[21] Furthermore, specific surgical techniques such as video-assisted thoracoscopy can be helpful for the management of pleural effusions or local complications.[19,20]

ANTIANGIOGENIC THERAPIES AND TREATMENT BASED ON HISTOLOGIC FEATURES

Besides pemetrexed,[22] the anti–vascular endothelial growth factor (VEGF) antibody bevacizumab, administered in combination with platinum-based chemotherapy, has been shown to improve the response rate and progression-free survival, as compared with chemotherapy alone, in eligible patients with non–squamous-cell NSCLC.[23,24] However, the frequency of adverse events — in particular, hypertension, proteinuria, and thromboembolic and bleeding events — was increased with combination therapy. Necitumumab, an EGFR antibody, has shown a modest improvement in efficacy when administered in combination with cisplatin and gemcitabine, as compared with chemotherapy alone, in patients with EGFR-expressing squamous-cell NSCLC (median overall survival, 11.7 vs. 10.0 months; hazard ratio for death, 0.79; 95% confidence interval [CI], 0.69 to 0.92; P=0.002).[25]

Two recent trials investigated the combination of the anti–VEGF receptor 2 antibody ramucirumab with docetaxel as compared with docetaxel alone (REVEL trial) or the combination of the antiangiogenic tyrosine kinase inhibitor nintedanib with docetaxel as compared with docetaxel alone (LUME–Lung 1 trial) in previously treated patients with advanced NSCLC.[26,27] In both studies, improved outcomes were noted with the experimental combination. In the REVEL trial, median progression-free survival and overall survival were significantly prolonged for patients with any histologic findings (progression-free survival, 4.5 vs. 3.0 months; hazard ratio for progression or death, 0.76; 95% CI, 0.68 to 0.86; P<0.001; overall survival, 10.5 vs. 9.1 months; hazard ratio for death, 0.86; 95% CI, 0.75 to 0.98; P=0.02). The LUME–Lung 1 trial showed significant improvements in median progression-free and overall survival among patients with adenocarcinoma (progression-free survival, 3.4 vs. 2.7 months; hazard ratio for progression or death, 0.79; 95% CI, 0.68 to 0.92; P=0.002; overall survival, 12.6 vs. 10.3 months; hazard ratio for death, 0.83; 95% CI, 0.70 to 0.99; P=0.04). The magnitude of these gains is quite small. It appeared that the efficacy of nintedanib and of ramucirumab was greater in patients with rapidly progressing tumors and the efficacy of nintedanib was also greater in patients with refractory tumors that progressed directly after first-line chemotherapy, suggesting that this aggressive type of lung cancer might be more dependent on proangiogenic pathways (Fig. 3). The results of the French ULTIMATE trial, which compared the combination of bevacizumab and paclitaxel with paclitaxel alone, were consistent with this hypothesis: the combined treatment prolonged progression-free survival in previously treated patients (median, 5.4 months vs. 3.9 months; hazard ratio for progression or death, 0.6; 95% CI, 0.44 to 0.86; P=0.005).[28]

In patients with previously treated squamous-cell lung cancer, the LUX–Lung 8 trial showed the superiority of the EGFR tyrosine kinase inhibitor afatinib as compared with erlotinib (median overall survival, 7.9 months vs. 6.8 months; hazard ratio for death, 0.81; 95% CI, 0.69 to 0.95; P=0.008).[29] However, the interpretation of these

Histology	Molecular Pathology	PD-L1 Status (TPS)	First-Line Therapy	Maintenance Therapy	Second-Line Therapy
Squamous-cell NSCLC	NA	<50%	Platinum-based chemotherapy Gemcitabine and cisplatin+ necitumumab (EMA)	Necitumumab	Immunotherapy Chemotherapy Docetaxel+ramucirumab Afatinib
	NA	≥50%	Pembrolizumab	Pembrolizumab	Platinum-based chemotherapy
Non–squamous-cell NSCLC	Positive for EGFR mutation	NA	Erlotinib+bevacizumab Erlotinib Afatinib Gefitinib	Erlotinib+bevacizumab Erlotinib Afatinib Gefitinib	Osimertinib Platinum-based chemotherapy
	ALK	NA	Crizotinib (also for ROS1-positive patients) Ceritinib (FDA and EMA)	Crizotinib (also for ROS1-positive patients) Ceritinib (FDA and EMA)	Ceritinib Alectinib (after failure of crizotinib) Platinum-based chemotherapy
	Wild type	<50%	Platinum-based chemotherapy (bevacizumab optional in eligible patients)	Pemetrexed (continuation or switch maintenance) Bevacizumab (continuation maintenance)	Immunotherapy Chemotherapy Docetaxel+ramucirumab Docetaxel+nintedanib (adenocarcinoma, EMA) Erlotinib (EMA)
	Wild type	≥50%	Pembrolizumab	Pembrolizumab	Platinum-based chemotherapy

Figure 3. Individualized Treatment Algorithm for NSCLC.

The tumor proportion score (TPS) was assessed with the use of 22C3 anti–PD-L1 antibody (Dako). First-line therapy with a combination of necitumumab (approved by the European Medicines Agency [EMA]) and gemcitabine or cisplatin is approved only in patients with epidermal growth factor receptor (EGFR)–expressing squamous-cell NSCLC. Second-line therapy with immunotherapy involves nivolumab (approved by the EMA and the Food and Drug Administration [FDA]), pembrolizumab (for PD-L1–positive NSCLC) (EMA and FDA), and atezolizumab (FDA). Second-line therapy with osimertinib has been approved in patients with an EGFR mutation after treatment with an EGFR tyrosine kinase inhibitor and proven occurrence of an EGFR T790M mutation. Second-line therapy with erlotinib is for patients in whom chemotherapy is associated with unacceptable side effects. NA denotes not applicable.

results is constrained by the continuing debate over the appropriateness of erlotinib as a control treatment.

TREATMENT BASED ON TARGETABLE ONCOGENIC ALTERATIONS

An exploratory analysis involving 1007 patients with advanced adenocarcinoma, conducted by the Lung Cancer Mutation Consortium, showed longer overall survival among patients with oncogenic driver mutations who received targeted therapies than among either patients with driver mutations who did not receive targeted therapies or patients without driver mutations (median survival, 3.5 years vs. 2.4 years and 2.1 years, respectively).[30] Therefore, appropriate testing for treatable oncogenic alterations should be implemented in the routine diagnostic evaluation of patients with advanced non–squamous-cell NSCLC.[19,20]

MUTATIONS IN *EGFR*

The identification of activating mutations in *EGFR*, mostly seen in exon 19 (deletion) or in exon 21 (L858R point mutation), together with an increased sensitivity to EGFR tyrosine kinase inhibitors, has been the first and most important step toward molecular-guided precision therapy of lung cancer.[31,32] Whereas EGFR mutations are seen in 10 to 20% of white patients, higher incidence rates have been observed among patients of East Asian origin (approximately 48%).[33] The incidence of these mutations also correlates with the histologic finding of adenocarcinoma, no previous or current smoking, younger age, and female sex.[34] In a meta-analysis, randomized trials of the EGFR tyrosine kinase inhibitors gefitinib, erlotinib, and afatinib showed significant improvements in the response rate and progression-free survival, as compared with first-line chemotherapy (median progression-free survival, 9.6 to 13.1 months vs. 4.6 to 6.9 months; hazard ratio for progression or death, 0.37; 95% CI, 0.32 to 0.41; P<0.001), among patients with activating *EGFR* mutations, as well as lower rates of adverse events and better symptom control.[35] Higher activity of EGFR tyrosine kinase inhibitors was seen in patients with exon 19 *EGFR* mutations

(hazard ratio for progression or death, 0.24; P<0.001) than in patients who had exon 21 *EGFR* mutations (hazard ratio for progression or death, 0.48; P<0.001).[35] None of the trials showed significant differences in overall survival, although a pooled exploratory analysis of the LUX–Lung 3 and LUX–Lung 6 trials suggested that afatinib was associated with an improvement in overall survival for patients with exon 19 mutations (median, 27.3 months vs. 24.3 months; P=0.04).[36]

Despite impressive responses to an EGFR tyrosine kinase inhibitor, the disease progresses in most patients after 9 to 12 months of treatment. The occurrence of a secondary exon 20 T790M missense mutation is the most frequent alteration, occurring in 40 to 60% of patients, and from a clinical perspective, the most important.[37,38] Osimertinib, a third-generation, irreversible EGFR tyrosine kinase inhibitor that targets the T790M mutation and the primary activating *EGFR* mutations, has been reported to have a response rate of 61%, with a median progression-free survival of 9.6 months, in patients with T790M mutations whose disease progressed during treatment with an EGFR tyrosine kinase inhibitor.[39] Recently, the efficacy of osimertinib was investigated in a randomized, phase 3 trial (AURA3), which compared osimertinib with platinum-based chemotherapy in 419 previously treated patients with a confirmed T790M mutation after failure of an EGFR tyrosine kinase inhibitor. Osimertinib led to a prolongation of median progression-free survival from 4.4 to 10.1 months (hazard ratio for progression or death, 0.30; P<0.001) and an increase in the response rate from 31 to 71% (odds ratio for an objective response, 5.39; P<0.001) (Table 1).[40] More treatment options to overcome resistance are under clinical investigation.[41]

ALK and *ROS1* Translocations

Translocations of *ALK* have been identified in 2 to 7% of patients with NSCLC,[42] and translocations of *ROS1* in 1 to 2% of patients with NSCLC[43]; these translocations lead to novel fusion genes with transforming activity. Crizotinib, a tyrosine kinase inhibitor originally developed as a c-MET kinase inhibitor, has shown significant activity in patients with *ALK* and *ROS1* translocations. In two randomized phase 3 trials involving patients with NSCLC and *ALK* alterations, crizotinib had superior efficacy, as compared with chemotherapy, in previously treated patients (median progression-free survival, 7.7 months vs. 3.0 months), as well as in previously untreated patients (median progression-free survival, 10.9 months vs. 7.0 months).[44,45] Patients with *ALK* translocations acquire resistance to crizotinib during treatment, but the mechanisms of resistance appear to be complex, with several secondary mutations and escape mechanisms.[46] However, with second-generation ALK tyrosine kinase inhibitors such as ceritinib or alectinib, the response rates have been 38 to 56%, with a median progression-free survival of 5.7 to 8.0 months, when given to patients with *ALK* translocations after the failure of crizotinib therapy. Furthermore, these drugs show efficacy in patients with brain metastases (brain response rate, 33 to 57%), which is of clinical importance for this group of patients. In untreated patients with *ALK* alterations, ceritinib proved superior to chemotherapy in the ASCEND-4 trial (median progression-free survival, 16.6 months vs. 8.1 months; hazard ratio for progression or death, 0.55; 95% CI, 0.42 to 0.73; P<0.001).[47] Alectinib was superior to crizotinib in the Japanese J-ALEX trial (progression-free survival not reached vs. 10.2 months; hazard ratio for progression or death, 0.34; 95% CI, 0.17 to 0.70; P<0.001)[48] and in the ALEX trial (progression-free survival not reached vs. 11.1 months; hazard ratio for progression or death, 0.47; 95% CI, 0.34 to 0.65; P<0.001) (see the study by Peters et al., published in this issue of the *Journal*[49]). Second-generation ALK tyrosine kinase inhibitors in clinical development for the treatment of crizotinib-refractory NSCLC include brigatinib, lorlatinib, and ensartinib.[46]

For patients with *ROS1* translocation, clinical efficacy has been reported with crizotinib (response rate, 72%; median progression-free survival, 19.2 months).[50] Additional agents are under evaluation (Table 1).

Other Targetable Alterations

So far, all clinical efforts to target *KRAS*, which is the most frequent driver mutation, seen in 25% of patients with adenocarcinoma,[51] have been disappointing. Recently, the addition of the MEK (MAPK–ERK kinase) inhibitor selumetinib to docetaxel failed to improve the outcome, as compared with docetaxel alone,[52] but more clinical data on the efficacy of various approaches to

Table 1. Targeted Therapies for Non–Small-Cell Lung Cancer (NSCLC).*

Drug	Target	Dose	Indication (Source)
Erlotinib	EGFR	150 mg/day orally; dose modification: 100 mg/day, followed by 50 mg/day	EGFR-mutated metastatic NSCLC; refractory NSCLC after previous chemotherapy (EMA); EGFR-mutated NSCLC (FDA)
Gefitinib	EGFR	250 mg/day orally	EGFR-mutated metastatic NSCLC (EMA, FDA)
Afatinib	EGFR, HER2, HER3, HER4	40 mg/day orally; dose modification: 30 mg/day, followed by 20 mg/day	EGFR-mutated metastatic NSCLC; refractory metastatic squamous-cell NSCLC after previous chemotherapy (EMA, FDA)
Osimertinib	EGFR, T790M mutation	80 mg/day orally; dose modification: 40 mg/day	EGFR-mutated NSCLC with T790M mutation (EMA, FDA)
Crizotinib	ALK, ROS1	250 mg orally twice a day; dose modification: 200 mg twice a day, followed by 250 mg/day	ALK-positive or ROS1-positive metastatic NSCLC (EMA, FDA)
Ceritinib	ALK	750 mg/day orally; dose modification: 600 mg/day, followed by 450 mg/day, and then 300 mg/day (FDA, EMA)	First-line treatment in adults with ALK-positive advanced NSCLC or ALK-positive NSCLC previously treated with crizotinib (EMA); patients with metastatic ALK-positive NSCLC (FDA)
Alectinib	ALK	600 mg orally twice a day; dose modification: 450 mg twice a day, followed by 300 mg twice a day	ALK-positive metastatic NSCLC previously treated with crizotinib (EMA); ALK-positive metastatic NSCLC after progression with or unacceptable adverse effects of crizotinib (FDA)
Trametinib and dabrafenib	BRAF V600E	Trametinib 2 mg/day orally; dose modification: 1.5 mg/day, followed by 1 mg/day; and dabrafenib 150 mg orally twice a day; dose modification: 100 mg twice a day, followed by 75 mg twice a day, and then 50 mg twice a day	Patients with advanced NSCLC with a *BRAF* V600E mutation (EMA, FDA)
Nintedanib	VEGFR, PDGFR, FGFR	200 mg orally twice a day; dose modification: 150 mg twice a day, followed by 100 mg twice a day (EMA)	Metastatic or locally recurrent NSCLC; adenocarcinoma, given after first-line chemotherapy in combination with docetaxel (EMA)
Ramucirumab	VEGFR2	10 mg/kg of body weight IV every 3 wk before docetaxel infusion; for East Asian patients, consider a reduced docetaxel starting dose of 60 mg/m^2 of body-surface area (EMA)	Locally advanced or metastatic NSCLC, in patients with progression during or after platinum-based chemotherapy in combination with docetaxel (EMA); metastatic NSCLC, in patients with progression during or after platinum-based chemotherapy in combination with docetaxel (FDA)
Bevacizumab	VEGF	7.5 mg/kg or 15 mg/kg IV every 3 wk; with erlotinib, 15 mg/kg IV every 3 wk (EMA); with carboplatin and paclitaxel, 15 mg/kg IV every 3 wk (FDA)	Unresectable advanced, recurrent, and metastatic NSCLC with predominantly non–squamous-cell NSCLC, given in combination with platinum-based chemotherapy as first-line therapy (EMA); unresectable advanced, recurrent, and metastatic NSCLC with EGFR-activating mutations, given in combination with erlotinib as first-line therapy (EMA); unresectable, locally advanced, recurrent, or metastatic non–squamous-cell NSCLC in combination with carboplatin and paclitaxel as first-line therapy (FDA)
Necitumumab	EGFR	800 mg IV on days 1 and 8 every 3 wk (EMA, FDA)	Locally advanced or metastatic EGFR-expressing, squamous-cell NSCLC, given in combination with gemcitabine and cisplatin as first-line therapy (EMA); metastatic squamous-cell NSCLC, given in combination with gemcitabine and cisplatin as first-line therapy (FDA)

Pembrolizumab	PD-1 receptor	2 mg/kg IV every 3 wk (in pretreated patients); 200 mg IV every 3 wk as first-line treatment (EMA); 200 mg IV every 3 wk as first- or second-line treatment (FDA)	Metastatic PD-L1–positive NSCLC (TPS ≥1%) and at least one prior chemotherapeutic regimen (EMA); metastatic NSCLC with high PD-L1 expression (TPS ≥50%) and no EGFR mutation or ALK translocation, given as first-line therapy (FDA); metastatic PD-L1–positive NSCLC (TPS ≥1%) with progression during or after platinum-based chemotherapy (FDA); metastatic NSCLC with high PD-L1 expression (TPS ≥50%) and no EGFR mutation or ALK translocation, given as first-line therapy (FDA)
Nivolumab	PD-1	3 mg/kg IV every 2 wk (EMA); 240 mg IV every 2 wk (FDA)	Locally advanced or metastatic NSCLC, given after chemotherapy (EMA); metastatic NSCLC with progression during or after platinum-based chemotherapy (FDA)
Atezolizumab	PD-L1	1200 mg IV every 3 wk	Metastatic NSCLC with progression during or after platinum-based chemotherapy (FDA)

* ALK denotes anaplastic lymphoma kinase; EGFR epidermal growth factor receptor; EMA European Medicines Agency; FDA Food and Drug Administration; FGFR fibroblast growth factor receptor; HER2, HER3, and HER4 human epidermal growth factor receptor 2, 3, and 4, respectively; IV intravenously; PDGFR platelet-derived growth factor receptor; PD-1 programmed death 1; PD-L1 programmed death ligand 1; TPS tumor proportion score; VEGFR vascular endothelial growth factor receptor; and VEGFR2 vascular endothelial growth factor receptor 2.

inhibiting *KRAS*-driven pathways are expected soon. *BRAF* mutations have been identified in 2% of patients with NSCLC, half of whom have a *BRAF* V600E mutation. With the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib, the response rate was 63.2%, and the median progression-free survival was 9.7 months.[53] A response rate of 42% and a median progression-free survival of 7.3 months were reported after treatment with vemurafenib, another BRAF inhibitor.[54] Additional molecular targets of clinical interest include *RET* translocations, *HER2* mutations, *MET* alterations, and *NTRK1* translocations.

THE PROBLEM OF TARGETED THERAPIES IN SQUAMOUS-CELL NSCLC

Squamous-cell lung carcinoma has a distinct oncogenic profile, exhibiting frequent molecular alterations of the gene encoding fibroblast growth factor 1 (with amplification in 25% of patients) and phosphoinositide 3–kinase pathway modifications (in 30 to 50% of patients), as well as mutations in the gene encoding discoidin domain receptor 2 (*DDR2*; in 3 to 4% of patients) and *ErB2* amplification (in 4% of patients). Unfortunately, so far no efficacy has been shown for agents targeting these alterations, a failure that is probably related to the lack of a clear, prominent driver mutation of squamous-cell lung cancer.[55]

IMMUNOTHERAPIES FOR NSCLC

Tumor-induced suppression of specific T-cell activation, mediated by predominantly inhibitory pathways, so-called immune checkpoints, represents one of the major mechanisms by which tumors avoid recognition and rejection by the immune system. Specific antibodies interacting either with cytotoxic T-lymphocyte–associated antigen 4 or with programmed death 1 (PD-1) or PD-L1 have shown clinical activity and have opened a completely new treatment option.[56,57]

In five randomized, phase 2–3 trials involving previously treated patients with advanced NSCLC, monotherapies with antibodies against PD-1 or PD-L1, as compared with chemotherapy, were associated with a significant improvement in overall survival (9.2 to 13.8 months vs. 6.0 to 9.7 months), corresponding to a hazard ratio for death of 0.59 to 0.73, regardless of histologic

features, together with an improved safety and side-effect profile.[58-62] However, specific adverse events, probably related to activation of the immune system, were observed in approximately 30% of patients, including gastrointestinal, hepatic, endocrine, pulmonary, and dermatologic events. Such inflammatory events require close monitoring and early treatment with immunosuppressive medication.[56]

PD-L1 EXPRESSION AS A PREDICTIVE MARKER

Identification of patients who might benefit most from immunotherapies should involve immunohistochemical assessment of PD-L1 expression on tumor cells and immune cells. Although in general, a correlation between PD-L1 expression and the efficacy of antibodies against PD-1 or PD-L1 has been reported in several trials, activity has also been described in patients with PD-L1–negative tumors. Variations in the techniques and antibodies used to measure PD-L1 expression make it difficult to compare trial results and have generated confusion.[63]

In an attempt to harmonize PD-L1 testing in lung cancer, a joint initiative of manufacturers and academic societies, as well as a multi-institutional assessment by several pathologists revealed similar results for PD-L1 staining in tumor cells for most of the diagnostic antibodies, and additional studies with larger samples are planned.[64,65] According to the Food and Drug Administration (FDA) and European Medicines Agency labels, a confirmation of high PD-L1 expression (tumor proportion score ≥50%) is required for initial treatment with pembrolizumab, whereas previously treated patients, even those with PD-L1–negative tumors, may receive immunotherapies such as nivolumab or atezolizumab but not pembrolizumab, which requires the presence of a PD-L1–positive tumor. However, in patients with PD-L1–negative tumors, additional characteristics such as tumor burden, tumor growth rate, and performance status may be taken into account for the selection of treatment.

FIRST-LINE MONOTHERAPY AND FUTURE TRIALS

Results of anti–PD-1 antibodies in selected, untreated patients have prompted several phase 3 trials. In the KEYNOTE-024 trial, untreated patients with advanced NSCLC and a high level of PD-L1 expression on tumor cells (tumor proportion score ≥50%) were randomly assigned to receive the anti–PD-1 antibody pembrolizumab or platinum-based chemotherapy, with the opportunity of crossover to pembrolizumab at the time of disease progression. Significant improvements were observed with pembrolizumab, including prolongation of progression-free survival (median, 10.3 months vs. 6.0 months; $P<0.001$), as well as overall survival (hazard ratio for death, 0.60; $P=0.005$), a higher response rate (44.8% vs. 27.8%), and a lower rate of treatment-related grade 3 or 4 adverse events (26.6% vs. 53.3%).[66] In contrast, among untreated patients with a lower level of PD-L1 expression (tumor proportion score ≥5%), the anti–PD-1 antibody nivolumab was not associated with superior progression-free survival, as compared with chemotherapy (median progression-free survival, 4.2 months vs. 5.9 months; $P=0.25$).[67]

Ongoing clinical trials are addressing the efficacy and safety of combined checkpoint inhibitors or checkpoint inhibitors in combination with cytotoxic agents (ClinicalTrials.gov numbers, NCT02453282, NCT02477826, NCT02578680, NCT02366143, and NCT02367794).[68] Recently, a randomized, phase 2 study showed improved efficacy with the combination of pembrolizumab and chemotherapy as compared with chemotherapy alone (response rate, 55% vs. 29%; $P=0.002$).[69]

Besides the approach involving identification of the most appropriate efficacy end point for the unique mode of action of immunotherapies, there is a strong focus on identifying novel predictive markers, with the exploration of genetic markers such as mutation burden, tissue-based markers such as PD-L2 (programmed death ligand 2) expression, and correlative inflammatory markers such as the interferon-gamma signature.[63]

SUMMARY

An individualized approach to the treatment of patients with NSCLC starts with an accurate pathological diagnosis and staging according to the eighth edition of the TNM classification for lung cancer[70] and with the comprehensive use of appropriate imaging methods, as well as endoscopic techniques for tissue sampling. In addition to a precise description of histologic fea-

tures, rational use of immunohistochemical markers is recommended. Patients with non–squamous-cell NSCLC should be screened for treatable oncogenic alterations, including *EGFR* mutations, *BRAF* V600E mutations, and *ALK* or *ROS1* translocations. Further molecular screening for rare treatable alterations is recommended in patients with adenocarcinoma who do not have a history of smoking. PD-L1 expression should be assessed in patients without known oncogenic alterations, regardless of the histologic findings (Figs. 1 and 2). A panel of appropriate specialists should oversee these evaluations to ensure that the diagnosis and staging are correct and that adequate tissue samples are obtained for molecular testing.

The choice of first-line treatment, based on the initial molecular pattern, includes chemotherapies, targeted therapies, and the new treatment option with pembrolizumab in patients with high levels of PD-L1 expression. Subsequent treatment options include chemotherapy combinations and immunotherapies in patients without oncogenic alterations, as well as targeted therapies for patients with refractory, molecular-driven tumors. Adequate tumor-biopsy samples obtained at the time of progression are crucial for the determination of the specific resistance mechanism[19,20] (Fig. 3 and Table 1). The next step in precision diagnosis and treatment of lung cancer will be the identification of novel molecular markers, particularly those characterizing the likely response to immunotherapies.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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