Novel Systemic Therapies for Advanced Non–Small-Cell Lung Cancer

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BACKGROUND: Several novel drugs have been approved by the US Food and Drug Administration (FDA) in the past 5 years for the treatment of patients with non–small-cell lung cancer (NSCLC). Despite new treatments, lung cancer remains a major cause of cancer-related death in the United States.

OBJECTIVE: To review the treatment of patients with advanced NSCLC, with a focus on drugs that were recently approved by the FDA for this patient population.

DISCUSSION: Platinum-based regimens remain the first-line treatment for patients with advanced NSCLC that is not associated with driver mutations. The recent drugs approved by the FDA in the past 5 years for NSCLC include afatinib, alectinib, ceritinib, crizotinib, erlotinib, gefitinib, nivolumab, osimertinib, pembrolizumab, and ramucirumab. Several of these agents have been found to increase overall survival in the first- and second-line settings. These medications also have different toxicity profiles compared with the traditional cytotoxic drugs used in the treatment of NSCLC. This article highlights the outcomes associated with these novel therapies in the treatment of patients with NSCLC.

CONCLUSION: The novel therapies introduced into the market in the past 5 years have significantly improved outcomes for patients with advanced NSCLC.

Lung cancer is the leading cause of cancer-related death in men and women in the United States. It has been estimated that in 2016, approximately 224,000 new lung cancer cases would be diagnosed (approximately 13.3% of all new cases of cancer), and 158,000 deaths would occur in the United States. Lung cancer is subdivided into small-cell lung cancer and non–small-cell lung cancer (NSCLC), with the latter accounting for 85% of all cases. Approximately 40% of NSCLC cases are adenocarcinomas, and approximately 25% are of squamous-cell histology. Adenosquamous and large-cell carcinoma are the least common types. In 2012, the 5-year relative survival rates were 54.8% for localized, 27.4% for regional, 4.2% for distant, and 7.5% for unstaged disease. However, these data include small-cell lung cancer, which has a poorer prognosis.

Most cases of NSCLC are locally advanced or metastatic at the time of diagnosis, and, if left untreated, the median survival is approximately 7 months. In addition to the extent of disease, other clinical factors play a role in the prognosis of patients with lung cancer, including poor performance status, medical comorbidities, and smoking status. African Americans with lung cancer have poorer performance status and more weight loss (than other populations), which has been associated with reduced survival. Although lymphatic invasion worsens overall survival, intense lymphocytic infiltration is associated with a better prognosis.

The diagnosis of lung cancer involves performing a tissue biopsy to determine the histology of the disease. Tissue testing is recommended as initial workup for patients with relapsed disease, and may result in the discovery of activating mutations, including epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), ROS1, and KRAS. The Figure outlines the frequency of common activating mutations in lung cancer.

Many other mutations have been identified in lung cancer, but their clinical significance requires further research. Adenocarcinoma is the most common subtype of NSCLC (approximately 40% of all cases), and approximately 15% of patients with adenocarcinoma harbor activating EGFR mutations.

In unselected patients with NSCLC, ALK mutations occurred in approximately 5% of cases in the United States. ALK mutations are also more common in adenocarcinoma than in other types of NSCLC and in those who are nonsmokers or light smokers, and is independent of the effect of EGFR or KRAS mutations.
Activating KRAS mutations are observed in approximately 20% to 25% of lung adenocarcinomas in the United States, and are generally associated with a history of smoking.\textsuperscript{15,16} Further research is needed to determine whether patients with KRAS mutations have a worse prognosis than those with wild-type KRAS tumors.\textsuperscript{17}

Based on the presence or absence of a genetic mutation, a targeted drug may cause regression of the tumor or be ineffective. According to the National Comprehensive Cancer Network (NCCN), only patients with advanced lung cancer should have multiplex genotyping to determine the presence of a genetic mutation, because it may provide the opportunity to receive an effective targeted therapy.\textsuperscript{18}

The purpose of this article is to review the treatment of patients with advanced NSCLC, with a focus on novel, targeted therapies.

**Treatment of Advanced NSCLC**

Despite improvement in outcomes with the use of chemoradiotherapy and targeted systemic therapy in treating advanced lung cancer, the overall survival remains poor.\textsuperscript{9} The intent of treatment for patients with advanced lung cancer favors a palliative approach, with the goals of prolonging good quality of life and minimizing side effects. Platinum combinations remain the standard of care for treatment of early and advanced stages of NSCLC.\textsuperscript{18}

Age may be an important determinant in treatment decisions. For nonelderly patients with good performance status, initial systemic therapy is usually personalized and is based on the tumor histology and molecular profile.\textsuperscript{18,19} Other factors that may affect the choice of therapy include the extent of disease, presence or absence of symptoms, and whether a driver mutation receptor is present.

For elderly patients and those with poor performance status, host factors such as age, comorbidities, toxicities, and drug metabolism often play a larger role in therapeutic decisions.

**Systemic Treatment for Patients without Driver Mutations**

According to the NCCN guidelines, the recommended first-line therapy in this setting is platinum-based chemotherapy for 4 to 6 cycles.\textsuperscript{18} Most regimens contain cisplatin in combination with other drugs, including vinorelbine, gemcitabine, docetaxel, or pemetrexed. A 2004 meta-analysis with more than 13,000 patients from 65 randomized trials showed that a 2-drug, platinum-based regimen produced a response rate of approximately 26%, with 35% of patients surviving 1 year.\textsuperscript{20} Three-drug combinations increase the response rate, but not overall survival. Several studies have looked at the substitution of carboplatin for cisplatin because of its better toxicity profile. It is particularly preferred for elderly patients and those with poor performance status or multiple comorbidities. Although substitution with carboplatin produces a lower response rate, the difference in overall survival is not significant.\textsuperscript{21} A weekly lower-dose regimen of paclitaxel and carboplatin produces a similar response rate to regimens given every 3 to 4 weeks but has significantly less neurotoxicity.\textsuperscript{22}

NSCLC has traditionally been managed as one disease, but this is no longer the case because histology is playing a major role in tumor response and drug toxicity. One example is that pemetrexed is effective in

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**Figure**

Incidence of Oncogenic Drivers in NSCLC Adenocarcinoma

<table>
<thead>
<tr>
<th>Mutation Target</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>EGFR</td>
<td>15%</td>
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<tr>
<td>KRAS</td>
<td>25%</td>
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<tr>
<td>ALK</td>
<td>4%</td>
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<tr>
<td>ROS1</td>
<td>1%</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>3%</td>
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<tr>
<td>Nondrivers</td>
<td>52%</td>
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</table>

Mutation targets in NSCLC for which drugs are currently indicated for initial therapy include EGFR (drugs: erlotinib, gefitinib, afatinib, osimertinib), ALK (drug: crizotinib), ROS1 (drug: crizotinib), BRAF V600E (drugs: vemurafenib, dabrafenib), and MET exon 14 skipping mutations (drugs: crizotinib, caboazatinib).\textsuperscript{12} Inhibitors for other mutations may be available in a clinical trial setting.\textsuperscript{1}

ALK indicates anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non–small-cell lung cancer.


nonsquamous NSCLC but ineffective in squamous NSCLC. Furthermore, bevacizumab in combination with chemotherapy is active in nonsquamous NSCLC but is contraindicated in squamous NSCLC because of pulmonary toxicity.

Maintenance refers to continuation of therapy after patients have received 4 to 6 cycles of first-line chemotherapy and may involve continuation or switch maintenance therapy. "Continuation maintenance therapy" means that ≥1 drugs from the first-line therapy regimen are continued. "Switch maintenance" means that the therapy was switched to another drug that was not included in the first-line therapy. Drug selection is based on several factors, including performance status, tumor histology, and biomarker analysis. In patients with advanced nonsquamous NSCLC whose disease responded to first-line chemotherapy, the NCCN recommends continuation maintenance therapy with bevacizumab, pemetrexed, or gemcitabine. In patients with asymptomatic EGFR mutation, maintenance therapy with erlotinib, gefitinib, or afatinib is recommended, even in those with acquired resistance.

**Targeted Therapies for Advanced NSCLC**

The discovery of predictive biomarkers has revolutionized the treatment of patients with NSCLC and allowed the clinician to be more selective in choosing therapeutic drugs. Patients with specific mutations are candidates for targeted therapies, which may improve treatment outcomes and may also have better side-effect profiles compared with the standard chemotherapy. The NCCN has incorporated biomarker testing into their clinical practice guidelines, and recommends EGFR and ALK testing in high-risk or late-stage patients with adenocarcinoma, large-cell NSCLC, or NSCLC not otherwise specified. In addition, the NCCN suggests testing patients with squamous NSCLC, especially never smokers, for EGFR and ALK mutations.

**EGFR Inhibitors**

Because studies have shown the superiority of EGFR tyrosine kinase inhibitors (TKIs) in terms of progression-free survival (PFS) compared with standard platinum-based chemotherapy, these drugs are now well-established as first-line therapy in patients who have EGFR mutations. Erlotinib, gefitinib, afatinib, and osimertinib provide several options for effective strategies resulting in extended PFS and increased quality of life. These drugs are less effective in those without EGFR mutations. Although these TKIs improve PFS, they have not shown a benefit in overall survival because of the emergence of rapid resistance of driver mutations and crossover to variable therapeutic regimens when the disease progresses.

Approximately 50% of the cases of acquired resistance result from mutations in exon 20 of the EGFR gene, especially T790M. Osimertinib is an effective agent that increases PFS in patients with resistant T790M NSCLC and is discussed below.

In patients without a driver mutation and a lack of programmed death ligand 1 (PD-L1) tumor expression, platinum-based doublet chemotherapy is recommended.

Drugs that block EGFR-mediated pathways produce a unique set of adverse reactions that differ substantially from traditional cytotoxic drugs. Skin reactions are common, because skin and adnexal tissues express abundant amounts of cutaneous EGFRs. The most common side effects associated with EGFR TKIs include rash and acne. Diarrhea can usually be managed with loperamide, whereas normal acne is generally treated with standard acne therapy plus emollients. Lacouture and Balagula have written an excellent review on the management of skin reactions. EGFR TKIs are discussed in detail below. The Table (page 38) provides important drug and food interactions for the drugs discussed in this article.

**Erlotinib.** Erlotinib (Tarceva) was approved by the US Food and Drug Administration (FDA) in 2004 as second-line treatment for NSCLC. In 2013, erlotinib was approved for the first-line treatment of patients with metastatic NSCLC associated with EGFR exon 19 deletions or exon 21 (L858R) substitutions. Many randomized trials have studied the efficacy of erlotinib versus the combination of carboplatin or cisplatin with gemcitabine.

In the ENSURE trial, 217 eligible patients at 30 centers across China, Malaysia, and the Philippines were randomized to receive erlotinib or gemcitabine plus cisplatin. The investigator-assessed median PFS for erlotinib versus gemcitabine plus cisplatin was 11.0 months versus 5.5 months, respectively (hazard ratio [HR] 0.34; 95% confidence interval [CI], 0.22-0.51; log-rank P = .0001). The PFS was significantly prolonged in Asian patients with an EGFR mutation treated with first-line erlotinib versus chemotherapy, but overall survival remained the same. This may have been the result of allowing patients from the gemcitabine/cisplatin group to cross over to the erlotinib group at disease progression. Two other large trials (EURTAC and OPTIMAL) showed improved PFS and response rates when compared with chemotherapy, but no difference in overall survival. The addition of erlotinib should be considered a standard first-line treatment regimen for this population.

The NCCN now recommends that patients with tumors found to have EGFR mutations after the start of chemotherapy may be switched to erlotinib alone.
The most common adverse effect reported with the use of erlotinib is rash.\textsuperscript{27} Severe adverse effects of interstitial lung disease, gastrointestinal perforation, and hepatotoxicity (including hepatorenal syndrome) were rare, but, in some cases, fatal.\textsuperscript{25} Extra caution should be used in those with an elevated serum bilirubin. Patients should be monitored for signs and symptoms of these severe toxicities, and erlotinib should be discontinued permanently if they occur.

Erlotinib is a minor substrate of cytochrome (CY) P1A2, and a major substrate of CYP3A4; therefore, patients should be screened for drug interactions.\textsuperscript{28} Erlotinib has increased bioavailability when taken with food, and should be taken 1 hour before or 2 hours after a meal. Patients should avoid grapefruit or grapefruit juice while taking erlotinib.\textsuperscript{28}

\textbf{Gefitinib.} Gefitinib (Iressa) initially received accelerated FDA approval in 2003 under subpart H as monotherapy for the treatment of patients with advanced NSCLC that progressed with platinum-based and docetaxel therapies.\textsuperscript{26} In 2015, the FDA approved gefitinib for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions.\textsuperscript{26} The most extensive data for the recent approval came from the Iressa Pan-Asia Study that compared the efficacy of gefitinib with the combination of carboplatin plus paclitaxel.\textsuperscript{29}

For the entire cohort, PFS was significantly better with gefitinib compared with chemotherapy (12-month PFS rate, 25% vs 7%; HR, 0.74). The difference in overall survival was not significant (median, 18.8 months vs 17.4 months; HR, 0.90; 95% CI, 0.79-1.02).\textsuperscript{12} The primary end point was overall survival, which was not significantly different between the 2 groups. However, the overall response rate was significantly higher (58.9% vs 44.8%) in patients with high EGFR gene copy and EGFR mutation.\textsuperscript{29}

For patients without EGFR mutation, the PFS was significantly shorter compared with the carboplatin plus paclitaxel group. There have been reports of severe interstitial lung disease with gefitinib that resulted in death.\textsuperscript{30}

Gefitinib is a major substrate of CYP2D6 and CYP3A4, which gives it the potential for many drug interactions. It is recommended that concomitant use of gefitinib and grapefruit juice be avoided, because it may increase the serum concentration of gefitinib. Gefitinib is also a weak inhibitor of CYP2C19 and CYP2D6 and significantly affects drugs metabolized by these enzymes.\textsuperscript{28}

\textbf{Afatinib.} Afatinib (Gilotrif) is an irreversible EGFR TKI, and was approved by the FDA in 2013, for the treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions.\textsuperscript{26} The LUX-Lung 3 trial compared afatinib with cisplatin plus pemetrexed, showing that in a subset of patients with EGFR mutations and exon 19 deletion or L858R substitution, the PFS was improved from 11.1 months to 13.8 months compared with 6.9 months with afatinib and cisplatin plus pemetrexed ($P = .0014$).\textsuperscript{31,32}

The median overall survival with afatinib was 27.3 months versus 24.3 months with chemotherapy (HR, 0.81; 95% CI, 0.66-0.99). In patients with exon 19 deletions, the overall survival was extended to 33.3 months (HR, 0.54; 95% CI, 0.36-0.79). Diarrhea, rash, acne, nail effects, and stomatitis were among the most frequently reported adverse events in the afatinib group.\textsuperscript{31}

Moderately severe acne and rash are common and may manifest as blistering, exfoliative lesions. Very severe reactions include Stevens Johnson syndrome and toxic epidermal necrolysis and require discontinuation of therapy. It is important for patients to avoid sun exposure while taking afatinib. Taking afatinib with a fatty meal decreases its bioavailability. It is recommended to take afatinib 1 hour before, or 2 hours after, a meal.\textsuperscript{26,28,33}

\textbf{Osimertinib.} For patients with disease resistant to first-line EGFR TKIs, osimertinib (Tagrisso) may be an option. The most common mechanism of acquired resistance to EGFR TKIs is the presence of T790M mutation, which has been shown to occur in more than 50% of NSCLC tumors that are rebiopsied.\textsuperscript{26} Osimertinib was granted a breakthrough therapy designation in April 2014, followed by an accelerated approval in November 2015, for the treatment of patients with metastatic EGFR T790M mutation–positive NSCLC whose disease progressed during or after receiving an FDA-approved EGFR TKI.\textsuperscript{27}

These approvals were based on phase 1 and 2 clinical trials showing that osimertinib produced a significantly higher response rate and PFS in metastatic EGFR T790M mutation–positive NSCLC compared with NSCLC without mutations (61% vs 21% and 9.6 months vs 2.8 months, respectively).\textsuperscript{35} Common side effects were rash, diarrhea, nausea, and decreased appetite, but at the FDA-approved dose of 80 mg daily, only 1% of patients had grade $\geq 3$ adverse events.\textsuperscript{35}

Osimertinib is a major substrate of CYP3A4, and has the potential for many drug interactions.\textsuperscript{28} Therapy should be monitored accordingly to prevent adverse events related to interactions and drug toxicities. Osimertinib can be taken with or without food.\textsuperscript{28}

\textbf{Necitumumab.} In November 2015, the FDA approved necitumumab (Portrazza) in combination with gemcitabine and cisplatin for the first-line treatment of patients with metastatic squamous NSCLC.\textsuperscript{26} It is the first biologic monoclonal antibody EGFR inhibitor approved for the treatment of lung cancer. Necitumumab
<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral dose for NSCLC</th>
<th>CYP/P-gp food interactions</th>
<th>Management</th>
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<tbody>
<tr>
<td>Afatinib</td>
<td>40 mg once daily</td>
<td><strong>Effect of P-gp inhibitors:</strong> oral administration of a P-gp inhibitor (ritonavir, 200 mg twice daily) 1 hour before administration of afatinib increased systemic exposure to afatinib by 48% and 39% in C\text{max}. No change in afatinib exposure when ritonavir was administered simultaneously with or 6 hours after afatinib. No CYP interactions. <strong>Food interactions:</strong> taken with a high-fat meal decreases the C\text{max} by 50% and AUC by 39% compared with the fasted state.</td>
<td>Avoid concurrent P-gp inhibitors, including (but not limited to) ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, neflavanir, saquinavir, amiodarone. If given with ritonavir, separate the dosing by at least 6 hours.</td>
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<td>Ceritinib</td>
<td>750 mg once daily</td>
<td><strong>Strong CYP3A4 inducers:</strong> coadministration of a single 750-mg ceritinib dose with rifampin (a strong CYP3A4 inducer) 600 mg daily for 14 days decreased ceritinib AUC (90% CI) by 70% (61%, 77%) and C\text{max} (90% CI) by 44% (24%-59%) in 19 healthy patients. <strong>Strong CYP3A4 inhibitors:</strong> a strong CYP3A4/P-gp inhibitor (ketoconazole) increased systemic exposure of ceritinib; average ceritinib AUC was increased by 2.9-fold in 19 healthy volunteers who had received a strong CYP3A4 inhibitor, ketoconazole (200 mg twice daily for 14 days). <strong>Food interactions:</strong> a meal high in fat increases AUC by 73% and C\text{max} by 41%; a low-fat meal increases AUC by 58% and C\text{max} by 43%; a ≥600-mg ceritinib dose taken with a fatty meal is expected to have systemic exposure exceeding a 750-mg dose taken while fasting. Grapefruit and grapefruit juice may inhibit ceritinib metabolism and increase its systemic exposure.</td>
<td>Avoid strong CYP3A4 inducers, including carbamaepine, eralalatamide, fosphenytoin, lumacaftor, mitotane, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentine, and St. John’s wort. Avoid concurrent use of strong CYP3A inhibitors with ceritinib, including certain antivirals (eg, ritonavir), macrolide antibiotics (eg, telithromycin), antifungals (eg, ketoconazole), and nefazodone; if unavoidable, reduce ceritinib dose by approximately 33%, rounded to the nearest multiple of the 150-mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume ceritinib dose taken before initiating a strong CYP3A4 inhibitor. Use on an empty stomach, ≥2 hours before or after a meal. Avoid grapefruit and grapefruit juice.</td>
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<tr>
<td>Crizotinib</td>
<td>250 mg twice daily</td>
<td><strong>Strong CYP3A4 inducers:</strong> in 14 healthy volunteers who received 1 dose of crizotinib (250 mg) on day 9 of rifampin administration (600 mg daily for 14 days), rifampin decreased crizotinib’s AUC by an average of 82% and the C\text{max} by 69%. <strong>Strong CYP3A4 inhibitors:</strong> may increase blood levels of crizotinib; ketoconazole increased crizotinib’s AUC by 3.2-fold. <strong>Food interactions:</strong> grapefruit, grapefruit juice may increase serum crizotinib levels.</td>
<td>Avoid concomitant use of strong CYP3A inducers, including (but not limited to) carbamaepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John’s wort. Avoid concomitant use of strong CYP3A inhibitors, including (but not limited to) atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, neflavanir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole; use caution with concomitant use of moderate CYP3A inhibitors. Avoid grapefruit, grapefruit juice.</td>
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<tr>
<td>Drug</td>
<td>Oral dose for NSCLC</td>
<td>CYP/P-gp food interactions</td>
<td>Management</td>
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<td>Erlotinib&lt;sup&gt;f&lt;/sup&gt; (Tarceva)</td>
<td>150 mg once daily</td>
<td><strong>Strong CYP3A4 inducers:</strong> pretreatment with the CYP3A4 inducer rifampin for 7 days before erlotinib decreased erlotinib's AUC by approximately 66%-80%, equivalent to approximately 30-50 mg in patients with NSCLC; treatment with rifampin for 11 days coadministered with a single 450-mg dose of erlotinib on day 8 resulted in a mean erlotinib exposure (AUC) 57.6% of that seen with a single 150-mg dose of erlotinib without rifampin</td>
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<td><strong>Strong CYP3A4 inhibitors:</strong> erlotinib is metabolized predominantly by CYP3A4, and CYP3A4 inhibitors are expected to increase exposure; concomitant administration of the potent CYP3A4 inhibitor ketoconazole increases erlotinib AUC by approximately 66% When erlotinib was coadministered with ciprofloxacin, an inhibitor of CYP3A4 and CYP1A2, the AUC increased by 39% and C&lt;sub&gt;max&lt;/sub&gt; by 17%</td>
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<td><strong>Food interactions:</strong> grapefruit and grapefruit juice are strong CYP3A4 inhibitors</td>
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<td><strong>Management:</strong> Avoid concomitant use of strong CYP3A inducers, including (but not limited to) carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John’s wort</td>
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<td>If a strong inducer is used concurrently, increase erlotinib dose by 50 mg/day at 2-week intervals as tolerated, to a maximum of 450 mg daily</td>
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<td>**Use caution when taking erlotinib with ketoconazole and other strong CYP3A4 inhibitors, such as (but not limited to) atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole</td>
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<td><strong>Avoid grapefruit and grapefruit juice</strong></td>
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<td>Gefitinib&lt;sup&gt;g&lt;/sup&gt; (Iressa)</td>
<td>250 mg once daily</td>
<td><strong>Strong CYP3A4 inducers:</strong> concomitant administration of rifampin, 600 mg daily for 16 days, with gefitinib, single 500-mg dose on day 10 of gefitinib administration, reduced mean gefitinib AUC by 83%</td>
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<td><strong>Strong CYP2D6 inhibitors:</strong> gluoxetine, paroxetine, quinidine, and tipranavir reduced gefitinib AUC by approximately 47%</td>
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<td><strong>Strong CYP3A4 inhibitors:</strong> concomitant administration of itraconazole, 200 mg daily for 12 days, increased mean AUC of gefitinib by 80%</td>
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<td></td>
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<td><strong>Food interactions:</strong> grapefruit juice may increase serum gefitinib concentrations</td>
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<td><strong>Management:</strong> Avoid concomitant use of strong CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John’s wort</td>
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<td>Avoid strong CYP2D6 inducers, including gluoxetine, paroxetine, quinidine, and tipranavir</td>
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<td>Monitor adverse events when administering strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole) with gefitinib</td>
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<td>Avoid grapefruit and grapefruit juice</td>
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<tr>
<td>Osimertinib&lt;sup&gt;h&lt;/sup&gt; (Tagrisso)</td>
<td>80 mg once daily</td>
<td><strong>Strong CYP3A4 inducers:</strong> clinical studies evaluating osimertinib with strong CYP3A4 inducers have not been conducted</td>
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<td><strong>Strong CYP3A4 inhibitors:</strong> clinical studies evaluating osimertinib with strong CYP3A4 inhibitors have not been conducted</td>
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<td><strong>Management:</strong> Use caution with concomitant administration of osimertinib and strong CYP3A4 inducers (eg, phenytoin, rifampin, carbamazepine, St. John’s wort)</td>
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<td>Use caution with concomitant administration of osimertinib and strong CYP3A3 inhibitors, including macrolide antibiotics (eg, telithromycin), antifungals (eg, itraconazole), antivirals (eg, ritonavir), and nefazodone</td>
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AUC indicates area under the curve; CI, confidence interval; C<sub>max</sub>, maximum serum concentration; CY, cytochrome; NSCLC, non–small-cell lung cancer; P-gp, P-glycoprotein.

<sup>a</sup>Gilotrif (afatinib) tablets prescribing information. October 2016.
<sup>b</sup>Zykadia (ceritinib) capsules prescribing information. September 2016.
<sup>d</sup>Tarceva (erlotinib) tablets prescribing information. October 2016.
<sup>e</sup>Iressa (gefitinib) tablets prescribing information. July 2015.
<sup>f</sup>Tagrisso (osimertinib) tablets prescribing information. August 2016.
binds specifically to the extracellular domain of EGFR, preventing ligand binding and activation of EGFR.\(^2\) This results in a decrease in cancer-cell proliferation.

In the SQUIRE trial, necitumumab in combination with gemcitabine and cisplatin was compared with gemcitabine and cisplatin alone, with overall survival a primary end point.\(^3\) Preliminary results, based on a 25-month follow-up, indicated that the combination significantly increased overall survival with necitumumab in combination with gemcitabine and cisplatin compared with gemcitabine plus cisplatin alone (median 11.5 months vs 9.9 months; HR, 0.84; 95% CI, 0.74-0.96; \(P = .01\)).\(^4\) More patients in the necitumumab group had \(\geq 1\) grade 3 or worse adverse events than those in the gemcitabine plus cisplatin cohort (72% vs 62%, respectively), and had more serious adverse events (48% vs 38%, respectively). Overall, 9% of patients in the necitumumab group had grade 3 or 4 hypomagnesemia, and grade 3 rash occurred in 20% of these patients.\(^4\)

Although other monoclonal antibodies (ie, cetuximab and panitumumab) have been studied in advanced NSCLC, they do not improve overall survival significantly when combined with chemotherapy, and are not FDA approved in this setting. Necitumumab is not indicated for the treatment of nonsquamous NSCLC.\(^5\)

**ALK Inhibitors**

Patients with an ALK mutation may be effectively managed with ALK inhibitors. Three agents are currently approved in this setting, including crizotinib, ceritinib, and alectinib.

**Crizotinib.** Crizotinib (Xalkori) is a first-generation ALK inhibitor approved for the treatment of ALK-positive NSCLC.\(^2\) Crizotinib initially received accelerated FDA approval for this indication in August 2011 based on the results of 2 studies.\(^5\)

Study A included 136 patients with locally advanced or metastatic ALK-positive NSCLC. The median treatment duration was 22 weeks, with 1 complete remission and 67 partial remissions, for an objective response rate of 50%. Seventy-nine percent of objective responses were achieved during the first 8 weeks of treatment. The median response duration was 41.9 weeks. Study B included 119 patients with locally advanced or metastatic ALK-positive NSCLC. There were 2 complete and 69 partial responses, for an objective response rate of 61%. Fifty-five percent of objective tumor responses were reached in the first 8 weeks of therapy. The median response duration was 48.1 weeks.\(^5\)

Crizotinib received full approval in November 2013 for the treatment of patients with metastatic NSCLC whose tumors are ALK positive based on the follow-up PROFILE studies.\(^2\) In the PROFILE studies 1007 and 1014, crizotinib was superior to platinum-based chemotherapy in patients with relapsed disease and treatment-naïve patients in PFS (7.7-10.9 months vs 3-7 months, respectively), response rates (65%-74% vs 20%-45%, respectively), and quality of life.\(^3,\)\(^4\)

The most common adverse events associated with crizotinib were vision disorders, diarrhea, nausea, and edema.\(^3\) Crizotinib was rarely associated with severe toxicities, which included erythema multiforme, acute interstitial lung disease, renal polycytosis, contact eosinophilic, reduced glomerular filtration rates, and hypersensitivity reactions.\(^3\) Patients should be monitored and the drug discontinued in cases of severe toxicity. Crizotinib is a major substrate and moderate inhibitor of CYP3A4, and thus, the potential for drug interactions is high. Grapefruit and grapefruit juice should be avoided while taking crizotinib.\(^2\)

**Ceritinib.** Ceritinib (Zykadia) is a second-generation ALK inhibitor that was granted accelerated approval by the FDA in April 2014 for the treatment of patients with ALK mutation–positive metastatic NSCLC that has progressed with crizotinib or is intolerant to crizotinib.\(^5\) The basis for the FDA approval was a phase 1 trial that demonstrated a response rate of 56% and a median PFS of 7 months in patients who previously received crizotinib.\(^3,\)\(^4\)

The most common dose-related adverse effects were diarrhea, vomiting, nausea, dehydration, elevated alanine aminotransferase, and hypophosphatemia.\(^3\) Ceritinib is a major substrate and strong inhibitor of CYP3A4 with a high potential for drug interactions; it is also a moderate inhibitor of CYP2C9. Grapefruit or grapefruit juice may decrease ceritinib metabolism and should be avoided.\(^2\) Ceritinib should be taken on an empty stomach, because a fatty meal significantly increases its area under the curve and potential for toxicity.

**Alectinib.** Alectinib (Alecensa) received FDA approval in December 2015 for the treatment of patients with metastatic NSCLC and ALK mutation, and whose disease progressed with crizotinib or who could not tolerate crizotinib.\(^5\) Alectinib has shown activity against the Leu1196Met ALK mutation, which is associated with crizotinib resistance.\(^3,\)\(^4\) Phase 1/2 studies have demonstrated overall response rates of 93% in patients who were ALK inhibitor naïve.\(^4\)

Phase 2 studies have also reported an objective response rate of approximately 50% and median PFS of 8.9 months in patients intolerant to, or whose disease had progressed with, crizotinib.\(^3,\)\(^4\) These studies also demonstrated that alectinib was particularly effective in patients with central nervous system disease. The major dose-limiting toxicities were grade 3 neutropenia and headache. Other adverse effects included elevated creat-
inine phosphokinase, dyspnea, and abdominal pain. Alectinib is a minor substrate of CYP3A4, with minimal-to-moderate potential for interactions.48

**Anti-Angiogenesis Agents**

**Ramucirumab.** Ramucirumab (Cyramza Injection) is a VEGFR2 antagonist that received FDA approval in December 2014 for use in combination with docetaxel for the treatment of patients with metastatic squamous and nonsquamous NSCLC whose disease progressed during or after receiving platinum-based chemotherapy.26 Its approval was based on the results of the phase 3 REVEL trial comparing the combination of ramucirumab plus docetaxel to docetaxel alone.44

The end points of PFS and overall survival were modestly improved with the ramucirumab combination. Median PFS was significantly better in the ramucirumab group compared with the control group (4.5 months vs 3.0 months; \( P = .0001 \)). The median overall survival was also significantly improved in the combination group compared with the control group (10.5 months vs 9.1 months; \( P = .023 \)).44

Common adverse events were slightly more frequent in the combination group, and consisted of neutropenia (49%), febrile neutropenia (16%), fatigue (14%), and hypertension (6%). Grade 3 neutropenia and febrile neutropenia occurred in 49% and 16% of patients, respectively. Bleeding and hemorrhagic events were more common in the combination group than in the control group (29% vs 15%). Three of 627 patients died from grade 4 adverse events in the combination group, and 1 patient had a grade 4 intracranial bleeding episode. Dose reductions were frequently necessary to control toxicities in the ramucirumab arm.44

**PD-1 and PD-L1 Inhibitors: Immunotherapies for Advanced NSCLC**

Inhibitors of PD-1 are now the standard of care for refractory NSCLC. The NCCN recently updated its NSCLC guidelines to include PD-L1 inhibitors.45 Although PD-L1 is expressed on activated T-cells, testing for this biomarker is not required for prescribing nivolumab.46 Patients with PD-L1 expressed in ≥5% of tumor cells respond better to nivolumab and pembrolizumab than those without PD-L1 expression.47 However, the role of PD-L1 as a prognostic and predictive marker is controversial and is not established.47

**Nivolumab.** In October 2015, the FDA approved nivolumab (Opdivo) for the treatment of patients with metastatic nonsquamous NSCLC that is EGFR- or ALK-mutation–positive and whose disease has progressed during or after platinum-based chemotherapy.26 The expanded FDA approval now includes squamous types, which was based on the results of the CheckMate-057 phase 3 clinical trial that compared nivolumab with docetaxel.48,49 PD-L1 expression was balanced in both groups. The median overall survival was significantly better for nivolumab than for docetaxel (12.2 months vs 9.4 months). The 1-year overall survival rate was 51% for nivolumab versus 39% for docetaxel. The PFS favored docetaxel (4.2 months vs 2.3 months with nivolumab).48,49

These outcomes were further improved in patients expressing PD-L1 in ≥1% of the tumor. The overall survival was greater with higher PD-L1 expression: the HR was 0.59 (\( P = .06 \)) for 1%, the HR was 0.43 (\( P = .0004 \)) for 5%, and for 10%, the HR was 0.40 (\( P = .0002 \)).48,49 The rate of PFS at 1 year was greater with nivolumab versus docetaxel (19% vs 8%). The partial response rate was significantly higher (18% vs 12%), and duration of response consistently longer, for nivolumab compared with docetaxel. The most common side effects (>5%) associated with nivolumab were fatigue, nausea, asthenia, pruritus, diarrhea, and hypothyroidism. The incidence of grade 3 or 4 adverse effects associated with nivolumab was much lower than with docetaxel (10% vs 54%, respectively).48

**Pembrolizumab.** Pembrolizumab (Keytruda) received accelerated approval in October 2015 for the treatment of patients with advanced NSCLC expressing PD-L1 whose disease progressed during or after platinum-containing chemotherapy, or, if appropriate, targeted therapy against ALK or EGFR mutation.26 Pembrolizumab was approved for use with a companion diagnostic, the PD-L1 IHC 22C3 pharmDx, which is the first test approved to detect PD-L1 expression in NSCLC tumors. The FDA granted pembrolizumab breakthrough therapy designation for this indication, because it was shown to produce substantial improvement over available therapies. The approval was based on the results of the KEYNOTE-001 trial.49

This phase 1 study evaluated patients who received pembrolizumab 2 mg or 10 mg per kg of body weight every 3 weeks, or 10 mg per kg every 2 weeks. The results were impressive, with a 45.2% response rate and a median PFS of 6.3 months in all patients with ≥50% expression of PD-L1 and median overall survival has not been reached.50

A follow-up study has confirmed the results of KEYNOTE-001. This study, the KEYNOTE-010 trial, was a 3-arm trial of pembrolizumab 2 mg/kg and 10 mg/kg compared with docetaxel 75 mg/m² every 3 weeks.51 No significant difference was seen in the median PFS for both doses of pembrolizumab versus docetaxel. However, the median overall survival was significantly longer in the 2-mg/kg (14.9 months) and 10-mg/kg (17.3 months)
The most common adverse events were decreased appetite, fatigue, nausea, and rash. Grade 3 to 5 adverse events occurred in 13% and 16% of patients with pembrolizumab 2 mg/kg and 10 mg/kg, respectively, compared with 35% with docetaxel. Grade 3 to 5 toxicities occurring in ≥1% of patients were pneumonitis and severe skin reactions. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions, including pneumonitis, nephritis, colitis, hepatitis, and hypophysitis. Therapy with pembrolizumab may have to be discontinued based on the severity of the reaction, and corticosteroids should be administered if pembrolizumab therapy is resumed or continued in patients who have these severe reactions.

Conclusion
This review highlights the features of novel therapies used in the treatment of patients with advanced or metastatic NSCLC. Before 2011, few active drugs were available for this disease, and most were classified as cytotoxic chemotherapy agents. With the advent of personalized therapy, the number of new and more effective targeted drugs has expanded rapidly. The toxicity profile of these targeted agents is substantially different from that of cytotoxic chemotherapy and has necessitated alternative preventive measures to manage their associated adverse effects. It is likely that the treatment paradigm for NSCLC will continue to evolve as targeted therapy is moved forward as a strategy for the treatment of earlier stages of this disease.

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