

Lung cancer is the most common cancer in the US with an estimated 221,200 new cases in 2015. An estimated 158,040 patients will die of the disease this year. The overall 5-year survival rate for all stages of lung cancer is 17%, and for advanced disease, 4%. Lung cancer will account for approximately 27% of all cancer deaths in the US in 2015; these statistics underscore the need for effective therapeutic agents in this patient population.

Histologically, the majority (85%) of lung cancers are classified as non-small cell lung cancers (NSCLCs), comprising squamous cell carcinoma (25–30% of all lung cancers), adenocarcinoma (~40%), and large-cell carcinoma (10–15%). Advances in the past decade now allow for treatment of NSCLC based on molecular subtype versus solely by histologic subtype of the tumor. Genetic alterations that contribute to the pathogenesis of NSCLC and are reasonable targets for pharmacotherapies have been identified, including epidermal growth factor receptor (EGFR)-activating gene mutations and anaplastic lymphoma kinase (ALK) gene rearrangements. Other emerging targets involving genetic alteration include ROS1 rearrangements, BRAF V600E mutation, mesenchymal epithelial transition factor (MET) amplification, human epidermal growth factor 2 (HER2) mutations, and rearranged during transfection (RET) rearrangements.

The prevalence of EGFR (EGFRm) mutations (EGFRm) in NSCLC ranges from 7–14% in Western populations and 30–50% in Asian populations. Among patients with NSCLC, EGFRm is more commonly seen in women (42%) versus men (14%); in never smokers (51%) versus smokers (10%); and in adenocarcinoma histology (40%) versus nonadenocarcinomas (3%). EGFRm drive tumor growth and progression by activating cell survival and proliferation signal transduction cascades. A subset of these activating EGFRm are commonly referred to as sensitizing mutations because their presence is predictive of response to EGFR tyrosine kinase inhibitors (TKIs). The most common sensitizing EGFR gene mutations are deletions in exon 19 (ex19del; 45–49%) and point mutations in exon 21 (L858R; 40%).

Abstract

Treatment for advanced non-small cell lung cancer (aNSCLC) is no longer based solely on histologic subtype. Recent discoveries have led to treatments tailored to the molecular drivers associated with each tumor (e.g., epidermal growth factor receptor [EGFR]-activating mutations). In the US, there are now three approved EGFR tyrosine kinase inhibitors (TKIs): gefitinib, erlotinib, and afatinib for first-line therapy in EGFR mutation-positive metastatic NSCLC. These agents have comparable efficacy, however, their tolerability profiles differ. Therefore, multiple factors should be considered before initiation of therapy. NSCLC tumors eventually develop resistance to EGFR TKIs; the most prevalent resistance mechanism is the EGFR T790M mutation, which occurs in 51–68% of EGFR TKI-resistant aNSCLC. Two agents, osimertinib (AZD9291) and rociletinib (CO-1686), are currently in late-stage development. They target the T790M mutation and are expected to provide an important option for patients with acquired resistance to EGFR TKIs. Identification of the T790M mutation or other resistance mechanisms will allow for a personalized treatment approach for patients with EGFR TKI-resistant aNSCLC. This review discusses the current and future treatment options for patients with activating mutations in EGFR and the importance of biopsy and molecular testing at disease progression.

Keywords

Epidermal growth factor receptor, tyrosine kinase inhibitors, non-small cell lung cancer, gefitinib, afatinib, erlotinib, AZD9291, osimertinib, rociletinib

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The prevalence of EGFR (EGFRm) mutations (EGFRm) in NSCLC ranges from 7–14% in Western populations and 30–50% in Asian populations. Among patients with NSCLC, EGFRm is more commonly seen in women (42%) versus men (14%); in never smokers (51%) versus smokers (10%); and in adenocarcinoma histology (40%) versus nonadenocarcinomas (3%). EGFRm drive tumor growth and progression by activating cell survival and proliferation signal transduction cascades. A subset of these activating EGFRm are commonly referred to as sensitizing mutations because their presence is predictive of response to EGFR tyrosine kinase inhibitors (TKIs).

The most common sensitizing EGFR gene mutations are deletions in exon 19 (ex19del; 45–49%) and point mutations in exon 21 (L858R; 40%).
Similarly, ALK-rearranged patients treated with ALK inhibitors such as crizotinib have demonstrated high overall response rates. Therefore, guidelines from the National Comprehensive Cancer Network (NCCN), National Cancer Center, American Society of Clinical Oncology, College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology all recommend routine EGFR and ALK testing and strongly recommend molecular profiling to identify rare actionable alterations that already have effective agents or are being studied in clinical trials for patients with nonsquamous adenocarcinoma NSCLC.

This review examines the clinical evidence supporting three EGFR TKIs currently available for first-line treatment of EGFRm-positive metastatic NSCLC in the US. It also discusses resistance mechanisms acquired by tumors after treatment with EGFR TKIs and how to identify the mutations at disease progression. Lastly, current and future therapies for treatment of EGFR TKI-resistant NSCLC are reviewed.

### EGFR Tyrosine Kinase Inhibitors

The current NCCN guidelines treatment paradigm recommends EGFR inhibitors as a first-line treatment for patients with EGFRm-positive advanced or metastatic NSCLC. The available TKIs for first-line treatment of metastatic NSCLC are gefitinib (IRESSA®; AstraZeneca, Wilmington, DE), erlotinib (Tarceva®; OSI Pharmaceuticals, LLC, Farmingdale, NY), and afatinib (GILOTRIF®; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT) with response rates ranging from 56 to 84 % and a median progression-free survival (PFS) in the range of 8–14 months. Gefitinib is a first-in-class EGFR TKI that was initially introduced in 2002 in Japan and other parts of the world. Gefitinib was introduced to the US market in 2003, however, in 2005 its use was restricted based on lack of survival benefit in an unselected patient population in a phase III trial. Following the discovery of EGFRm, gefitinib became available in the EU in 2009. More recently, gefitinib was reintroduced in the US for the first-line treatment of EGFRm-positive metastatic NSCLC, based on the results of two clinical trials. IRESSA® Follow-Up Measure (IFUM) was an open-label, single-arm, phase IV, bridging study of first-line gefitinib conducted in Caucasian patients with EGFRm-positive advanced NSCLC (n=106). Gefitinib-treated patients experienced an objective response rate (ORR) of 70 % (95 % confidence interval [CI], 61–78), median PFS of 9.7 months, and median overall survival (OS) of 19 months. Supporting these results was a subset analysis of the Iressa Pan-Asia Study (IPASS). The IPASS trial was a phase III, randomized, open-label, multicenter, parallel-group study in an Asian population that compared first-line gefitinib with carboplatin + paclitaxel chemotherapy in a subset of patients with EGFRm-positive aNSCLC. For patients with EGFRm-positive tumors the median PFS (as assessed by blinded independent central review) was 10.9 months for gefitinib compared with 7.4 months for chemotherapy (hazard ratio [HR] 0.54; 95 % CI 0.38–0.79). Although median OS did not differ between treatment groups in a phase III trial, gefitinib (21.6 months versus chemotherapy, 21.9 months; HR 1.0; 95 % CI 0.76–1.33) and the ORR was greater for gefitinib-treated patients (67 %; 95 % CI 56–77 %) compared with patients treated with chemotherapy (41 %; 95 % CI 31–51 %). The ORR and PFS in this Asian patient population were similar to those observed in the IFUM Caucasian population and confirm the consistent efficacy of gefitinib in patients of different ethnicities with EGFRm-positive aNSCLC.

### Erlotinib

Erlotinib was approved in the US in 2004 for treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. It was subsequently approved in 2010 as maintenance treatment for patients without disease progression after four cycles of platinum-based, first-line chemotherapy. After the discovery of EGFRm, erlotinib received approval in 2013 as first-line treatment in patients with EGFRm-positive metastatic NSCLC, based on the results of an open-label, randomized, phase III study (the European Tarceva versus Chemotherapy [EURTAC] trial). Caucasian patients with EGFRm-positive aNSCLC treated with erlotinib experienced significant improvement in median PFS (10.4 months) compared with those who received a standard-of-care platinum-based doublet chemotherapy (5.2 months; HR 0.34; 95 % CI 0.23–0.49; p<0.0001). Whereas there was no difference in median OS between erlotinib-treated and chemotherapy-treated patients (22.9 months versus 19.5 months, respectively; 95 % CI 0.64–1.35; p=0.93) the ORR was higher for erlotinib versus chemotherapy (65 %; 95 % CI 54.1–75.1 % versus 16 %; 95 % CI 9.0–25.3 %, respectively). Although not included in the US label, the OPTIMAL (CTONG-0802) trial was an open-label, randomized, phase III trial of first-line erlotinib versus chemotherapy in Asian patients with EGFRm-positive aNSCLC. The median PFS was 13.1 months (95 % CI 10.58–16.53) for erlotinib-treated patients compared with 4.6 months (95 % CI 4.21–5.42) for those treated with chemotherapy (HR 0.16; 95 % CI 0.10–0.26; p<0.0001). Similar to gefitinib, the erlotinib trials demonstrated efficacy in both Asian and Caucasian patients with EGFRm-positive aNSCLC.

### Afatinib

Afatinib was approved in the US in 2013 as first-line treatment of EGFRm-positive metastatic NSCLC, based on the results of the LUX-Lung 3 trial. Patients with EGFRm-positive aNSCLC who were treated with afatinib experienced PFS of 11.1 months compared with 6.9 months in patients treated with pemetrexed/cisplatin (HR 0.58; 95 % CI 0.43–0.78; p<0.001), with an ORR of 50.4 % versus 19.1 %, respectively.

Similar to the results seen with other EGFR TKIs, data from both the LUX-Lung 3 and LUX-Lung 6 (a second open-label, randomized, phase III trial) demonstrated no difference in OS with afatinib compared with chemotherapy (LUX-Lung 3: HR 0.88; 95 % CI 0.66–1.17; p=0.39; LUX-Lung 6: HR 0.93; 95 % CI 0.72–1.22; p=0.61). However, a preplanned analysis of these two trials revealed a significant improvement in OS with afatinib compared with chemotherapy for patients with an EGFRex19del mutation (LUX-Lung 3: HR 0.54; 95 % CI 0.36–0.79; p=0.0015; LUX-Lung 6: HR 0.64; 95 % CI 0.44–0.94; p=0.023), but not for patients with the L858R mutation (LUX-Lung 3: HR 1.3; 95 % CI 0.80–2.11; p=0.29; LUX-Lung 6: HR 1.22; 95 % CI 0.81–1.83; p=0.34). The reason for such a difference by EGFR subtype is not fully understood. However, other studies, including a recent meta-analysis, support improved outcomes in patients treated with gefitinib, erlotinib, or afatinib who harbor an EGFRex19del mutation compared with L858R mutation-positive tumors. Data from other EGFR TKI studies support these observations. In the EURTAC trial, patients in the ex19del subgroup treated with erlotinib had significant improvements in median PFS compared with chemotherapy (HR 0.30; 95 % CI 0.18–0.50; p<0.0001) but improvement in PFS for patients with L858R mutations was
not statistically significant (HR 0.55; 95 % CI 0.29–1.02; p=0.0539). In the IPASS trial, when compared with chemotherapy, gefitinib-treated patients in both mutational subgroups had statistically significant improvements in median PFS (ex19del: HR 0.38; 95 % CI 0.26–0.56; L858R: HR 0.55; 95 % CI 0.35–0.87); however, the ex19del subgroup had a slightly greater advantage. These data suggest different EGFR gene mutations may carry different prognoses.

**EGFR Tyrosine Kinase Inhibitor Resistance Mechanisms**

Inevitably, acquired resistance to first-line EGFR TKIs occurs in most patients with a median PFS of approximately 12 months (range, 8–14 months) after treatment initiation. Clinical progression after EGFR TKI therapy can be broadly categorized into three subtypes, each requiring a different treatment approach. The first subtype is oligo-progressive disease, defined as progression at new sites or a limited number of areas with regrowth. The second, central nervous system (CNS) sanctuary progressive disease, refers to isolated CNS failure (e.g., brain metastasis) without systemic progression. In this case, progression in the CNS may be the result of poor penetration of the blood–brain barrier by TKIs. For oligo-progressive disease and CNS sanctuary progressive disease, it is reasonable to institute local therapy with radiation while continuing TKI therapy. The last subtype, systemic progressive disease, is defined as multisite progression with possible new metastatic sites and regrowth in previously responsive areas. There are multiple approaches to treating systemic progressive disease after EGFR TKI resistance, including continuing on the same TKI, switching to chemotherapy, or adding on a therapy—such as chemotherapy or another targeted agent—to the TKI regimen. It is important to note that these approaches have limited efficacy in progressive disease after EGFR TKI therapy. In the ASPIRATION study, continuation with erlotinib therapy post progression demonstrated a median PFS of only 3.7 months. Furthermore, the recent IMPRESS trial demonstrated no statistically significant PFS improvement by continuing gefitinib with the chemotherapy after progression on gefitinib. The molecular mechanisms that generate EGFR TKI resistance are many and are distinct from the original tumor, thus they need to be managed differently. Among them, the most common resistance mechanism is the gatekeeper mutation in the EGFR kinase domain (EGFR T790M), followed by HER2 gene amplification, MET gene amplification, transformation to small-cell carcinoma, and phosphatidylinositol 3-kinase-CA (PIK3A) gene mutation. As more mechanisms of resistance are discovered it becomes increasingly important to not only identify them at disease progression, but also to understand which of these mechanisms can be targeted with currently available agents (see Table 2).
Therapies Targeting EGFR-Activating Mutations in Non-small Cell Lung Cancer

EGFR T790M

A substitution of methionine for threonine at the 790 position of exon 20 (T790M) in the EGFR kinase domain is the most common EGFRm, with a reported incidence ranging from 51 to 68 % in patients whose disease has progressed on erlotinib and gefitinib.\(^{39-50}\) As afatinib is the newest of the TKIs, there are limited data reporting the incidence of T790M resistance with afatinib disease progression. However, an in vitro model of acquired resistance to first-line afatinib demonstrated that T790M mutations may occur.\(^{51}\) Though afatinib appears to have some activity in patients who progressed on other EGFR TKIs (LUX-Lung 1 study),\(^{22}\) a more recent study showed no response in patients with a T790M-acquired mutation.\(^{52}\) In a phase Ib trial, the combination of afatinib plus cetuximab in pretreated patients with EGFRm-positive acquired resistance to gefitinib/erlotinib demonstrated a median PFS of 4.7 months (95 % CI 4.3–6.4).\(^{53}\) However, larger-scale studies are needed to determine its efficacy and toxicities in comparison with EGFR TKIs that specifically target T790M. Perhaps the combination may be useful in resistant tumors that do not harbor T790M.

The T790M mutation is thought to be resistant to EGFR TKIs through several mechanisms, including steric hindrance from the introduction of a bulkier amino acid (reduced binding of reversible TKIs), increased binding affinity of ATP, and increased phosphorylation levels, leading to reduced potency of TKIs.\(^{54,55}\) Multiple novel agents are in clinical development that target the T790M mutation, including osimertinib (AZD9291; AstraZeneca, Wilmington, DE), ASP8273 (Astellas Pharma US, Inc., Northbrook, IL), rociletinib (CO-1686; Clovis Oncology, San Francisco, CA), and HM61713 (Hanmi Pharmaceutical Co, Seoul, Korea). Osimertinib and rociletinib are designed to target both the T790M mutation and mutant EGFR with low activity against wtEGFR, the insulin receptor (IR), and the insulin-like growth factor receptor type 1 (IGF-1R).\(^{58-60}\) An interim analysis of a phase I/II study demonstrated that patients with T790M mutation-positive aNSCLC (n=59) in the osimertinib 80 mg once-daily arm experienced an ORR of 59 % (95 % CI 41–76 %) with a median PFS of 13.5 months (95 % CI 8.3–not calculable) and a median PFS of 10.9 months (95 % CI 8.3–not calculable) and a median PFS of 8.2 months (35 % data maturity).\(^{61}\) In this safety population, rates of treatment-related AEs were generally mild. Although there were no 119 patients treated with all formulations of rociletinib 500 mg reported 8.0 months (35 % data maturity) in T790M mutation-positive patients treated with 500 g or 625 mg of rociletinib (n=270). Safety analysis for the 119 patients treated with all formulations of rociletinib 500 mg reported that treatment-related AEs were generally mild. Although there were no reports of rash, diarrhea was reported in 33 % of patients. Hyperglycemia was reported in 35 % of patients, of which 17 % were classified as grade 3/4.\(^{55}\) The hyperglycemia associated with rociletinib has been linked to the inhibition of the IGF-1R.\(^{53,54}\)

In 2014, the US Food and Drug Administration granted breakthrough therapy designation for rociletinib and osimertinib. Both therapies appear to have similar efficacy; however, their tolerability profiles differ, possibly reflecting their different affinities for wtEGFR and other receptors such as HER2-1R. Updated data from the ongoing clinical trials for both therapies are expected. The approval of these agents in the US is eagerly anticipated and will provide a much needed option for patients with T790M mutation-positive aNSCLC.

Table 2: Reported Acquired Mechanisms of EGFR Tyrosine Kinase Inhibitor Treatment Resistance in Advanced Non-small Cell Lung Cancer and Potential Investigative Therapies

<table>
<thead>
<tr>
<th>Resistance Mechanism</th>
<th>Reported Prevalence Range</th>
<th>Investigational Studies in Pretreated aNSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR T790M</strong></td>
<td>51–68 %(^{45-51})</td>
<td>• Osimertinib (phase II, NCT02094261; phase III, NCT02151981)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rociletinib (phase II, NCT02147990; phase III, NCT02322821)</td>
</tr>
<tr>
<td><strong>HER2 amplification</strong></td>
<td>13 %(^{61})</td>
<td>• Intermittent, high-dose afatinib (phase II, NCT01647711)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Neratinib + temsirolimus(^{64})</td>
</tr>
<tr>
<td><strong>MET amplification</strong></td>
<td>5–11 %(^{41,49})</td>
<td>• Cabozantinib + erlotinib (phase II, NCT01866410)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• LY2875358 +/- erlotinib (phase II, NCT01900652)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• INC280 + gefitinib (phase Ib/2, NCT01610336)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Savolitinib (MET inhibitor; HIPM-504, volitinib, AZD6094) + osimertinib (phase II, NCT02143466)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Savolitinib + gefitinib (phase I, NCT02374645)</td>
</tr>
<tr>
<td><strong>Transformation</strong></td>
<td>3–14 %(^{41,49})</td>
<td>• Platinum-etoposide-based chemotherapy(^{44})</td>
</tr>
<tr>
<td>to SCLC</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PI3KCA mutation</strong></td>
<td>0–5 %(^{29,49})</td>
<td>• Buparlisib (BKM120) + erlotinib (phase II, NCT01487265)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Buparlisib (BKM120) + gefitinib (phase II, NCT01570296)</td>
</tr>
</tbody>
</table>

aNSCLC = advanced non-small cell lung cancer; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor 2; MET = mesenchymal epithelial transition factor; PI3KCA = phosphatidylinositide 3-kinase-CA; SCLC = small-cell lung cancer. 8.0 months (35 % data maturity) in T790M mutation-positive patients treated with 500 g or 625 mg of rociletinib (n=270). Safety analysis for the 119 patients treated with all formulations of rociletinib 500 mg reported that treatment-related AEs were generally mild. Although there were no reports of rash, diarrhea was reported in 33 % of patients. Hyperglycemia was reported in 35 % of patients, of which 17 % were classified as grade 3/4.\(^{55}\) The hyperglycemia associated with rociletinib has been linked to the inhibition of the IGF-1R.\(^{53,54}\)
Table 3: Important Biomarkers and Recommended Diagnostic Tests with Potential Treatment Options in Advanced Non-small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Tests</th>
<th>Timing</th>
<th>Methods</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR sensitizing mutations (EGFRm)</td>
<td>Diagnosis</td>
<td>RT-PCR, Sequencing, NGS, ctDNA*</td>
<td>Erlotinib†, Gefitinib†, Afatinib†</td>
</tr>
<tr>
<td>EGFR T790M</td>
<td>Disease progression</td>
<td>RT-PCR, Sequencing, NGS, ctDNA*</td>
<td>Osimertinib†, Rociletinib†</td>
</tr>
<tr>
<td>ALK rearrangement</td>
<td>Diagnosis</td>
<td>FISH, IHC</td>
<td>Crizotinib†, Ceritinib†</td>
</tr>
<tr>
<td>ROS1 rearrangements</td>
<td>Diagnosis</td>
<td>FISH, IHC</td>
<td>Crizotinib†</td>
</tr>
<tr>
<td>RET rearrangement</td>
<td>Diagnosis</td>
<td>FISH</td>
<td>Cabozantinib†</td>
</tr>
<tr>
<td>HER2 mutation or amplification</td>
<td>Diagnosis and disease progression</td>
<td>ISH, IHC</td>
<td>Trastuzumab†, Afatinib†</td>
</tr>
<tr>
<td>BRAF V600E mutation</td>
<td>Diagnosis and disease progression</td>
<td>RT-PCR, Sequencing, NGS, IHC</td>
<td>Vemurafenib†, Dabrafenib†</td>
</tr>
<tr>
<td>MET amplification</td>
<td>Diagnosis and disease progression, ISH,ISH</td>
<td>No recommended agents</td>
<td></td>
</tr>
</tbody>
</table>

*Soon to be available in the US, currently only available in the EU; †Per National Comprehensive Cancer Network guidelines; ‡Anticipated US Food and Drug Administration approval in late 2015 based on phase II data: NCT02094261 and NCT02147990. ALK = anaplastic lymphoma kinase; ctDNA = circulating tumor DNA; EGFR = epidermal growth factor receptor; EGFRm = epidermal growth factor receptor mutation; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor 2; IHC = immunohistochemistry; ISH = in situ hybridization; MET = mesenchymal epithelial transition factor; NGS = next-generation sequencing; RT = rearranged during transfection; RT-PCR = reverse transcription polymerase chain reaction.

Transformation to Small-cell Lung Cancer

Two studies found that histologic transformation of aNSCLC to small-cell lung cancer (SCLC) occurs in approximately 3–14 % of patients with EGFR TKI-acquired resistance.65,66 An alternative theory suggests that this may not be transformation, but rather that an SCLC clone is associated with NSCLC and as the adenocarcinoma is treated with TKI therapy, the SCLC is able to grow.71 In Sequist et al., four patients who had SCLC were treated with the classic SCLC treatment, platinum-etoposide-based chemotherapy, and a 60 % response rate was observed.69

PI3KCA Mutations (PI3Kinase)

Studies have also found that mutations in the PI3KCA gene range from 0–5 % of patients with EGFR TKI-acquired resistance.7,65,69 The PI3K cell growth and survival pathway is downstream of EGFR and therefore targeting the PI3K pathway could potentially have a synergistic effect when used with an EGFR inhibitor.44 Two clinical trials are currently investigating the pan-class I PI3K inhibitor buparlisib (BKM120) in combination with erlotinib (phase II, NCT01487265) or gefitinib (phase II, NCT01570296) in EGR TKI-resistant aNSCLC.

Biopsy and Molecular Testing at Disease Progression

According to the NCCN, reevaluation with biopsy upon disease progression is reasonable for the identification of patients with actionable mutations or those who may have SCLC histology.7 However, a recent NCCN survey indicates that only ~27 % of clinicians generally conduct a biopsy at disease progression.70 This low percentage may be explained by perceived barriers associated with biopsy at disease progression (e.g., patient unwillingness, AEs associated with the biopsy procedures, insufficient tissue acquisition).70 Additionally, physicians may be less willing to test without having approved targeted therapies available. According to one prospective multicenter study (GFPC study 12-01) that assessed the feasibility and clinical utility of biopsy upon disease progression in aNSCLC, >90 % of the time patients are willing to undergo biopsy.71 Of the 82 % of patients with a biopsy upon progression, 94 % and 74.4 % of tumors can be histologically and molecularly analyzed, respectively.72 Two separate studies reported low (<5 %) biopsy-related AEs at progression.73,74 Based on these findings it is critical that the mechanisms of resistance are identified at the point of disease progression in order to guide subsequent therapeutic choices.

Tissue biopsy at progression requires collaboration among oncologists, interventional radiologists, and/or pulmonologists and pathologists.74 The types of testing will vary by institution and practice, but may include commercially available kits (eg, cobas® EGFR Mutation Test, Roche Diagnostics, Indianapolis, IN; and FoundationOne® testing, Foundation Medicine, Inc., Cambridge, MA) or laboratory-developed tests. Other molecular tests include immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and next-generation sequencing (NGS).75 Table 3 lists the types of tests that are routinely ordered for aNSCLC molecular testing and includes tests for both biopsy at initial diagnosis and biopsy at disease progression.

Recent advances in noninvasive approaches such as plasma testing, or “liquid” biopsy, provide an exciting alternative to molecular testing.66 Due to the moderate sensitivity of current circulating tumor DNA (ctDNA) assays (range, 46–81 %), it is important to note that if a test result is negative,
a tissue biopsy may still be required to rule out a false-negative.13,14 However, improvements to ctDNA testing are underway that enhance detection, including more sensitive reverse transcription polymerase chain reaction (RT-PCR) and the development of newer methods, such as digital PCR.15,16
cDNA testing is available in Europe as an assessment for £GFRm status and it may be used where no tumor sample is available, or as a means to monitor disease progression. This test is highly predictive of £GFRm tumors.17,18,19,20 ctDNA testing can also identify the £GFR T790M resistance mutation.21 Albeit preliminary, new developments such as £GFR mutational analysis from urine samples are on the horizon.22,23

Conclusions
Choice of first-line therapy for £GFRm-positive aNSCLCs should be based on multiple factors, including efficacy (e.g., £GFRm ex19del, L858R, and rare mutations), tolerability profiles, and costs. Unfortunately, most patients’ disease will progress on £GFR TKI therapy, highlighting the need to test for mechanisms of resistance and to develop targeted agents. Multiple mechanisms of resistance have been identified, with the most common being the £GFR T790M mutation. Targeted therapies for £GFRm, such as osimertinib and rociletinib, will provide crucial options for these patients. Based on the clinical trial data to date, efficacy seems similar for the two agents. However their tolerability profiles differ with different rates of rash and diarrhea, and high rates of hyperglycemia observed with rociletinib. Therefore, choosing which option to use will depend on the ease of administration, dosing schedule, compliance factors, tolerability profile, and cost.

Before osimertinib and rociletinib, chemotherapy was also an important option when choosing a therapy at the time of progression after first-line £GFR TKI treatment, due to its benefits to response rate and PFS. However, patients who have T790M-positive aNSCLCs may potentially be treated with third-generation £GFR TKIs, such as osimertinib or rociletinib. Therefore, biopsy at progression on £GFR TKI is strongly recommended to evaluate the mechanism of resistance and guide the selection of targeted therapies. In addition to traditional biopsy methods, “liquid” biopsy or plasma ctDNA could potentially help identify these resistance mechanisms in some patients. This is an exciting time for personalized treatments for aNSCLCs, as more research is dedicated to understanding each of these mechanisms of progression and the novel ways to detect and treat them.
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