Molecular Markers and Targeted Therapies in the Management of Non-Small Cell Lung Cancer

Viola W. Zhu, MD, PhD, and Sai-Hong Ignatius Ou, MD, PhD

INTRODUCTION

Lung cancer is the second most common type of cancer in the United States, with 222,500 estimated new cases in 2017, according to the American Cancer Society. However, it is by far the number one cause of death due to cancer, with an estimated 155,870 lung cancer–related deaths occurring in 2017, which is higher than the number of deaths due to breast cancer, prostate cancer, and colorectal cancer combined. Despite slightly decreasing incidence and mortality over the past decade, largely due to smoking cessation, the 5-year survival rate of lung cancer remains dismal at approximately 18%.

Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancer cases. Traditionally, it is further divided based on histology: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and not otherwise specified. Chemotherapy had been the cornerstone of treatment for stage IV NSCLC. It is not target-specific and is most effective against rapidly growing cells. Common adverse effects include alopecia, nausea/vomiting, myelosuppression, cardiotoxicity, neuropathy, and nephrotoxicity. However, this paradigm has shifted following the discovery of mutations of the epidermal growth factor receptor (EGFR) gene as an oncogenic driver that confers sensitivity to small molecule tyrosine kinase inhibitors (TKIs) targeting EGFR. The EGFR inhibitors are given orally and have a spectrum of toxicities (eg, such as rash, diarrhea, and elevated transaminases) different from that of systemic chemotherapy, which is often administered intravenously. Following the discovery of EGFR mutations, rearrangements of the anaplastic lymphoma kinase (ALK) gene and ROS1 gene were identified as targetable driver mutations in NSCLC. The frequency of both rearrangements is lower than that of EGFR mutations. Additionally, BRAF V600E mutation has been identified in NSCLC. This activation mutation is commonly seen in melanoma. Agents that have already been approved for the treatment of melanoma with the BRAF V600E mutation are being tested in NSCLC patients with this mutation.

Given the effectiveness and tolerability of targeted therapy, identifying this distinct molecular subset of NSCLC patients is critical in treatment. Currently, molecular testing is mandatory in all stage IV patients with non-squamous cell carcinoma, as a preponderance of patients with driver mutations have this histology subtype. For patients with squamous cell carcinoma, molecular testing should be considered if the biopsy specimen is small, there is mixed histology, or the patient is a nonsmoker. Several techniques are commonly utilized in detecting these genetic alterations. EGFR mutation can be detected by polymerase chain reaction (PCR), ALK or ROS1 rearrangement can be detected by fluorescence in-situ hybridization (FISH), and immunohistochemistry (IHC) can also be used to detect ALK rearrangement.
The current guideline is to use comprehensive genomic profiling to capture all the potential molecular targets simultaneously instead of running stepwise tests just for EGFR, ALK, and ROS1.\textsuperscript{5} BRAF V600E mutation,\textsuperscript{13-16} MET exon 14 skipping mutation,\textsuperscript{21-24} RET rearrangements,\textsuperscript{25-27} and HER2 mutations\textsuperscript{28-30} are among the emergent genetic alterations with various responses to targeted therapy.\textsuperscript{31} Some of these targeted agents have been approved for other types of malignancy, and others are still in the development phase.

Several initiatives worldwide have reported better outcomes of patients with driver mutations treated with targeted therapy. For instance, the Lung Cancer Mutation Consortium in the United States demonstrated that the median survival of patients without driver mutations, with drivers mutations but not treated with targeted therapy, and with driver mutations and treated with targeted therapy was 2.08 years, 2.38 years, and 3.49 years, respectively.\textsuperscript{32} The French Cooperative Thoracic Intergroup-French National Cancer Institute demonstrated that the median survival for patients with driver mutations versus those without driver mutations was 16.5 months versus 11.8 months.\textsuperscript{33} The Spanish Lung Cancer Group demonstrated that the overall survival (OS) for patients with EGFR mutations treated with erlotinib was 27 months.\textsuperscript{34} The mutations in lung cancer, their frequencies, and the downstream signaling pathways are depicted in the Figure.\textsuperscript{35}

In this review article, we discuss targeted therapy for patients with EGFR mutations, ALK rearrangements, ROS1 rearrangements, and BRAF V600E mutation. We also discuss the management of patients with EGFR mutations who develop a secondary mutation after TKI therapy. Almost all of the targeted agents discussed herein have been approved by the US Food and Drug Administration (FDA), so they are considered standard of care. All available phase 3 trials pertinent to these targeted therapies are included in the discussion.

### EGFR Mutations

#### CASE PRESENTATION I

A 54-year-old Caucasian man who is a former smoker with a 10 pack-year history and past medical history of hypertension and dyslipidemia presents with progressive dyspnea for several weeks. A chest x-ray shows moderate pleural effusion on the left side with possible mass-like opacity on the left upper lung field. An ultrasound-guided thoracentesis is performed and cytology is positive for adenocarcinoma of likely pulmonary origin. Staging workup including positron emission tomography (PET)/computed tomography (CT) and magnetic resonance imaging of the brain with and without contrast is done. PET/CT shows a 5.5-cm mass in the left upper lobe of the lung with high fluoro(deoxyglucose (FDG) uptake, several 1 to 2 cm mediastinal lymph nodes with moderate FDG uptake, and small pleural effusion on both sides with moderate FDG uptake. MRI-brain is negative for malignancy. The patient subsequently undergoes a CT-guided biopsy of the lung mass, which shows moderately differentiated adenocarcinoma. Comprehensive molecular profiling reveals \textit{EGFR} L858R mutation only. The patient now presents for the initial consultation. Of note, his Eastern Cooperative Oncology Group performance status is 1.

- **What is the next step in the management of this patient?**

#### FIRST-LINE TKI FOR SENSITIZING EGFR MUTATIONS

The 2 most common \textit{EGFR} mutations are deletions in exon 19 and substitution of arginine for leucine in exon 21 (L858R). These mutations are found in approximately 45% and 40% of patients with \textit{EGFR} mutations, respectively.\textsuperscript{36} Both mutations are sensitive to EGFR TKIs. The benefit may be greater in patients with exon 19 deletions as compared to exon 21 L858R substitution,\textsuperscript{37,38} but this has not been demonstrated consistently in clinical trials.\textsuperscript{39-43} In the United States, \textit{EGFR} mutations are found in approximately 10% of patients
with NSCLC, while the incidence can be as high as 50% in Asia. Even though the cobas EGFR mutation test is the companion diagnostic approved by the US FDA, a positive test result from any laboratory with the Clinical Laboratory Improvement Amendments (CLIA) certificate should prompt the use of an EGFR TKI as the initial treatment.

Three EGFR TKIs that have been approved as first-line therapy in the United States are available: erlotinib, afatinib, and gefitinib. Both erlotinib and gefitinib are considered first-generation TKIs. They have higher binding affinity for the 2 common EGFR mutations than wild-type EGFR. In addition, they reversibly bind to the intracellular tyrosine kinase domain, resulting in inhibition of autophosphorylation of the tyrosine residues. Afatinib, a second-generation and irreversible TKI, targets EGFR (HER1) as well as HER2 and HER4.

The superior efficacy of the EGFR TKIs over platinum doublet chemotherapy in treatment-naive patients with EGFR mutations has been demonstrated in 7 randomized trials to date (Table). Erlotinib was the TKI arm for the OPTIMAL, EURTAC, and ENSURE trials; afatinib was the TKI arm for LUX-LUNG 3 and 6; gefitinib was the TKI arm for NEJ002 and WJTOG3405. A meta-analysis of these 7 trials

![Genetic mutations and signaling pathways in lung cancer. (Adapted with permission from Rosell R, Karachaliou N. Large-scale screening for somatic mutations in lung cancer. Lancet 2016;387:1355.)](image-url)
by Lee et al showed that progression-free survival (PFS) was significantly prolonged by EGFR TKIs (hazard ratio [HR] 0.37 [95% confidence interval [CI] 0.32 to 0.42]). For instance, in the EURTAC trial, median PFS was 9.7 months for patients treated with erlotinib as compared to 5.2 months for patients treated with platinum/gemcitabine or platinum/docetaxel. In this meta-analysis, prespecified subgroups included age, sex, ethnicity, smoking status, performance status, tumor histology, and EGFR mutation subtype. The superior outcome with TKIs was observed in all subgroups. Furthermore, patients with exon 19 deletions, nonsmokers, and women had even better outcomes.

Erlotinib is the most commonly used TKI in the United States largely because gefitinib was off the market for some time until it was re-approved by the FDA in 2015. Interestingly, this “re-approval” was not based on either 1 of the 2 prospective trials (NEJ002 and WJTOG3405), but rather was based on an exploratory analysis of the IPASS trial as well as a prospective phase 4, single-arm trial in Europe (IFUM). The superior efficacy of gefitinib over carboplatin/paclitaxel among patients with EGFR mutations in the IPASS trial was confirmed by blind independent central review, with longer PFS (HR 0.54 [95% CI 0.38 to 0.79] \( P = 0.0012 \)) and higher objective response rate (ORR; odds ratio 3 [95% CI 1.63 to 5.54], \( P = 0.0004 \)).

### CASE 1 CONTINUED

Based on the EGFR L858R mutation status, the patient is started on erlotinib. He is quite happy that he does not need intravenous chemotherapy but wants to know what toxicities he might potentially have with erlotinib.

- **What are the common adverse effects (AEs) of EGFR TKIs? How are AEs of TKIs managed?**

#### Safety Profile

The important toxicities associated with EGFR TKIs are rash, gastrointestinal toxicity, hepatic toxicity, and pulmonary toxicity. Rash is an AE specific to all agents blocking the EGFR pathway, including small molecules and monoclonal antibodies such as cetuximab. The epidermis has a high level of expression of EGFR, which contributes to this toxicity. Rash usually presents as dry skin or acneiform eruption. Prophylactic treatment with oral tetracyclines and topical corticosteroids is generally recommended upon initiation of TKI therapy. Diarrhea is the most prevalent gastrointestinal toxicity. All patients starting treatment should be given prescriptions

---

**Table.** Randomized Trials Comparing EGFR Tyrosine Kinase Inhibitors to Chemotherapy

<table>
<thead>
<tr>
<th>TKI</th>
<th>Trial Name</th>
<th>Origin</th>
<th>Comparison Arm</th>
<th>N</th>
<th>Median PFS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>OPTIMAL41</td>
<td>China</td>
<td>Carboplatin/gemcitabine</td>
<td>154</td>
<td>13.1 vs 4.6</td>
</tr>
<tr>
<td></td>
<td>EURTAC42</td>
<td>France, Italy, Spain</td>
<td>Cisplatin or carboplatin + docetaxel or gemcitabine</td>
<td>173</td>
<td>9.7 vs 5.2</td>
</tr>
<tr>
<td></td>
<td>ENSURE48</td>
<td>China, Malaysia, The Philippines</td>
<td>Cisplatin/gemcitabine</td>
<td>217</td>
<td>11 vs 5.5</td>
</tr>
<tr>
<td>Afatinib</td>
<td>LUX-LUNG 3</td>
<td>Global</td>
<td>Cisplatin/pemetrexed</td>
<td>345</td>
<td>11.1 vs 6.9</td>
</tr>
<tr>
<td></td>
<td>LUX-LUNG 6</td>
<td>China, Thailand, South Korea</td>
<td>Cisplatin/gemcitabine</td>
<td>364</td>
<td>11 vs 5.6</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>NEJ00249</td>
<td>Japan</td>
<td>Carboplatin/paclitaxel</td>
<td>224</td>
<td>10.8 vs 5.4</td>
</tr>
<tr>
<td></td>
<td>WJTOG34050</td>
<td>Japan</td>
<td>Cisplatin/docetaxel</td>
<td>172</td>
<td>9.2 vs 6.3</td>
</tr>
</tbody>
</table>

CI = confidence interval; EGFR = epidermal growth factor receptor; HR = hazard ratio; PFS = progression-free survival; TKI = tyrosine kinase inhibitor.
to manage diarrhea such as loperamide and be advised to call when it occurs. Hepatic toxicity is often manifested as elevated transaminases or bilirubin. Interstitial lung disease (ILD) is a rare but potentially fatal pulmonary toxicity.

Rash of any grade was reported in 49.2% of patients treated with erlotinib in clinical trials, while grade 3 rash occurred in 6% of patients and no grade 4 was reported. Diarrhea of any grade was reported in 20.3% of patients, grade 3 diarrhea occurred in 1.8%, and no grade 4 was reported. Grade 2 and 3 alanine aminotransferase (ALT) elevations were seen in 2% and 1% of patients, respectively. Grade 2 and 3 bilirubin elevations were seen in 4% and less than 1% of patients, respectively. The incidence of serious ILD-like events was less than 1%.52

Afatinib is associated with higher incidences of rash and diarrhea. Specifically, diarrhea and rash of all grades were reported in 96% and 90% of patients treated with afatinib, respectively. Paronychia of all grades occurred in 58% of patients. Elevated ALT of all grades was seen in 11% of patients. Approximately 1.5% of patients treated with afatinib across clinical trials had ILD or ILD-like AEs.53

Gefitinib, the most commonly used TKI outside United States, has a toxicity profile similar to erlotinib, except for hepatic toxicity. For instance, rash of all grades occurred in 47% of patients, diarrhea of all grades occurred in 29% of patients, and ILD or ILD-like AEs occurred in 1.3% of patients across clinical trials. In comparison, elevated ALT and aspartate aminotransferase (AST) of all grades was seen in 38% and 40% of patients, respectively.54 Therefore, close monitoring of liver function is clinically warranted. In particular, patients need to be advised to avoid concomitant use of herbal supplements, a common practice in Asian countries.

CASE 1 CONTINUED

The patient does well while on erlotinib at 150 mg orally once daily for about 8 months, until he develops increasing abdominal pain. A CT scan of the abdomen and pelvis with contrast shows a new 8-cm right adrenal mass. Additionally, a repeat CT scan of the chest with contrast shows a stable lung mass but enlarging mediastinal lymphadenopathy.

- How would you manage the patient at this point?

MANAGEMENT OF T790M MUTATION AFTER PROGRESSION ON FIRST-LINE EGFR TKIS

As mentioned above, the median PFS of patients with EGFR mutations treated with any 1 of the 3 TKIs is around 9 to 13 months.46 Of the various resistance mechanisms that have been described, the T790M mutation is found in approximately 60% of patients who progress after treatment with first-line TKIs.55,56 Other mechanisms, such as HER2 amplification, MET amplification, or rarely small cell transformation, have been reported.56 The first- and second-generation EGFR TKIs function by binding to the ATP-binding domain of mutated EGFR, leading to inhibition of the downstream signaling pathways (Figure, part B) and ultimately cell death.35 The T790M mutation hinders the interaction between the ATP-binding domain of EGFR kinase and TKIs, resulting in treatment resistance and disease progression.57,58

Osimertinib is a third-generation irreversible EGFR TKI with activity against both sensitizing EGFR and resistant T790M mutations. It has low affinity for wide-type EGFR as well as insulin receptor and insulin-like growth factor receptor.50 Osimertinib has been fully approved for NSCLC patients with EGFR mutations who have progressed on first-line EGFR TKIs with the development of T790M mutation. An international phase 3 trial (AURA3) randomly assigned 419 patients in a 2:1 ratio to either osimertinib or platinum/pemetrexed. Eligible patients all had the documented EGFR mutations and disease progression after first-line EGFR TKIs. Central confirmation of the T790M mutation was required. Median PFS by investigator assessment, the trial’s primary end point, was
10.1 months for osimertinib versus 4.4 months for chemotherapy (HR 0.3 [95% CI 0.23 to 0.41]; P < 0.001). ORR was 71% for osimertinib versus 31% for chemotherapy (HR 5.39 [95% CI 3.47 to 8.48], P < 0.001). A total of 144 patients with stable and asymptomatic brain metastases were also eligible. Median PFS for this subset of patients treated with osimertinib and chemotherapy was 8.5 months and 4.2 months, respectively (HR 0.32 [95% CI 0.21 to 0.49]). In the AURA3 trial, osimertinib was better tolerated than chemotherapy, with 23% of patients treated with osimertinib experiencing grade 3 or 4 AEs as compared to 47% of chemotherapy-treated patients. The most common AEs of any grade were diarrhea (41%), rash (34%), dry skin (23%), and paronychia (22%).

For the case patient, a reasonable approach would be to obtain a tissue biopsy of the adrenal mass and more importantly to check for the T790M mutation. Similar to the companion diagnostic for EGFR mutations, the cobas EGFR mutation test v2 is the FDA-approved test for T790M. However, if this resistance mutation is detected by any CLIA-certified laboratories, osimertinib should be the recommended treatment option. If tissue biopsy is not feasible, plasma-based testing should be considered. A blood-based companion diagnostic has also been approved by the FDA.

**ALK REARRANGEMENTS**

**CASE 2 PRESENTATION**

A 42-year-old Korean woman who is a non-smoker with no significant past medical history presents with fatigue, unintentional weight loss of 20 lb in the past 4 months, and vague abdominal pain. A CT can of the abdomen and pelvis without contrast shows multiple foci in the liver and an indeterminate nodule in the right lung base. She subsequently undergoes PET/CT, which confirms multiple liver nodules/masses ranging from 1 to 3 cm with moderate FDG uptake. In addition, there is a 3.5-cm pleura-based lung mass on the right side with moderate FDG uptake. MRI-brain with and without contrast is negative for malignancy. A CT-guided biopsy of 1 of the liver masses is ordered and pathology returns positive for poorly differentiated adenocarcinoma consistent with lung primary. Molecular analysis reveals an echinoderm microtubule-associated protein-like 4 (EML4)-ALK rearrangement. She is placed on crizotinib by an outside oncologist and after about 3 weeks of therapy is doing well. She is now in your clinic for a second opinion. She says that some of her friends told her about another medication called ceritinib and was wondering if she would need to switch her cancer treatment.

- How would you respond to this patient’s inquiry?

**FIRST-LINE TKIS FOR ALK REARRANGEMENTS**

ALK rearrangements are found in approximately 2% to 7% of NSCLC, with EML4-ALK being the most prevalent fusion variant. The inversion of chromosome 2p leads to the fusion of the EML4 gene and the ALK gene, which causes the constitutive activation of the fusion protein and ultimately increased transformation and tumorigenicity. Patients harboring ALK rearrangements tend to be non-smokers. Adenocarcinoma, especially signet ring cell subtype, is the predominant histology. Compared to EGFR mutations, patients with ALK mutations are significantly younger and more likely to be men. ALK rearrangements can be detected by either FISH or IHC, and most next-generation sequencing (NGS) panels have the ability to identify this driver mutation.

Crizotinib is the first approved ALK inhibitor for the treatment of NSCLC in this molecular subset of patients. PROFILE 1014 is a phase 3 randomized trial that compared crizotinib with chemotherapy containing platinum/pemetrexed for up to 6 cycles. Crossover to crizotinib was allowed for patients with disease progression on chemotherapy. The primary
end point was PFS by independent radiologic review. The crizotinib arm demonstrated superior PFS (10.9 months versus 7 months; HR 0.45 [95% CI 0.35 to 0.6], \( P < 0.001 \) ) and ORR (74% versus 45%, \( P < 0.001 \) ). Median survival was not reached in either arm (HR 0.82 [95% CI 0.54 to 1.26], \( P = 0.36 \) ). Based on this international trial, crizotinib is considered standard of care in the United States for treatment-naïve patients with advanced NSCLC harboring ALK rearrangements. The current recommended dose is 250 mg orally twice daily. Common treatment-related AEs of all grades include vision disorder (62%), nausea (53%), diarrhea (43%), vomiting (40%), edema (28%), and constipation (27%). PROFILE 1007 compared crizotinib with pemetrexed or docetaxel in ALK-rearranged NSCLC patients with prior exposure to 1 platinum-based chemotherapy. The median PFS was 7.7 months for crizotinib as compared to 3 months for chemotherapy (HR 0.49 [95% CI 0.37 to 0.64], \( P < 0.001 \) ). The response rates were 65% and 20% for crizotinib and chemotherapy, respectively (\( P < 0.001 \) ). In other countries, crizotinib following 1 prior platinum-based regimen may be considered standard of care based on this trial.

Ceritinib is an oral second-generation ALK inhibitor that is 20 times more potent than crizotinib based on enzymatic assays. It also targets \( \text{ROS1} \) and insulin-like growth factor 1 receptor but not c-MET. It was first approved by the FDA in April 2014 for metastatic ALK-rearranged NSCLC patients with prior exposure to 1 platinum-based chemotherapy. The median PFS was 7.7 months for crizotinib as compared to 3 months for chemotherapy (HR 0.49 [95% CI 0.37 to 0.64], \( P < 0.001 \) ). The response rates were 65% and 20% for crizotinib and chemotherapy, respectively (\( P < 0.001 \) ). In other countries, crizotinib following 1 prior platinum-based regimen may be considered standard of care based on this trial.

Alectinib is another oral second-generation ALK inhibitor that was approved by the FDA in December 2015 for the treatment of NSCLC patients with ALK rearrangements who have progressed on or are intolerant to crizotinib. Its indication will soon be broadened to the first-line setting based on the ALEX trial. Alectinib is a potent and highly selective TKI of ALK with activity against known resistant mutations to crizotinib. It also inhibits RET but not ROS1 or c-MET. ALEX, a randomized phase 3 study, compared alectinib with crizotinib in treatment-naïve patients with NSCLC harboring ALK rearrangements. The trial enrolled 303 patients and the median follow-up was approximately 18 months. The alectinib arm (600 mg twice daily) demonstrated significantly higher PFS by investigator-assessment, the trial’s primary end point. The 12-month event-free survival was 68.4% (95% CI 61% to 75.9%) versus 48.7% (95% CI 40.4% to 56.9%) for alectinib and crizotinib, respectively (HR 0.47 [95% CI 0.34 to 0.65], \( P < 0.001 \) ). The median PFS was not reached in the alectinib arm (95% CI 17.7 months to not estimable) as compared to 11.1 months in the crizotinib arm (95% CI 9.1 to 13.1 months). Alectinib is generally well tolerated. Common AEs of all grades include fatigue (41%), constipation (34%), edema (30%), and
myalgia (29%). As alectinib can cause anemia, lymphopenia, hepatic toxicity, increased creatine phosphokinase, hyperglycemia, electrolyte abnormalities, and increased creatinine, periodic monitoring of these laboratory values is important, although most of these abnormalities are grade 1 or 2.77

Brigatinib, another oral second-generation ALK inhibitor, was granted accelerated approval by the FDA in April 2017 for ALK-rearranged and crizotinib-resistant NSCLC based on the ALTA trial. This randomized phase 2 study of brigatinib showed an ORR by investigator assessment of 54% (97.5% CI 43% to 65%) in the 180 mg once daily arm with lead-in of 90 mg once daily for 7 days. Median PFS was 12.9 months (95% CI 11.1 months to not reached [NR]).78 Currently, a phase 3 study of brigatinib versus crizotinib in ALK inhibitor–naïve patients is recruiting participants (ALTA-1L). It will be interesting to see if brigatinib can achieve a front-line indication.

Starting the case patient on crizotinib is well within the treatment guidelines. One may consider ceritinib or alectinib in the first-line setting, but both TKIs can be reserved upon disease progression. We would recommend a repeat biopsy at that point to look for resistant mechanisms, as certain secondary ALK mutations may be rescued by certain next-generation ALK inhibitors. For instance, the F1174V mutation has been reported to confer resistance to ceritinib but sensitivity to alectinib, while the opposite is true for I1171T. The G1202R mutation is resistant to ceritinib, alectinib, and brigatinib, but lorlatinib, a third-generation ALK inhibitor, has shown activity against this mutation.79 Furthermore, brain metastasis represents a treatment challenge for patients with ALK rearrangements. It is also an efficacy measure of next-generation ALK inhibitors, all of which have demonstrated better central nervous system activity than crizotinib.69,78,80 If the case patient were found to have brain metastasis at the initial diagnosis, either ceritinib or alectinib would be a reasonable choice given crizotinib has limited penetration of blood-brain barrier.81

**ROS1 REARRANGEMENTS**

**CASE PRESENTATION 3**

A 66-year-old Chinese woman who is a non-smoker with a past medical history of hypertension and hypothyroidism presents to the emergency department for worsening lower back pain. Initial workup includes x-ray of the lumbar spine followed by MRI with contrast, which shows a soft tissue mass at L3-4 without cord compression. CT of the chest, abdomen, and pelvis with contrast shows a 7-cm right hilar mass, bilateral small lung nodules, mediastinal lymphadenopathy, and multiple lytic lesions in ribs, lumbar spine, and pelvis. MRI-brain with and without contrast is negative for malignancy. She undergoes endo-bronchial ultrasound and biopsy of the right hilar mass, which shows poorly differentiated adenocarcinoma. While waiting for the result of the molecular analysis, the patient undergoes palliative radiation therapy to L2-5 with good pain relief. She is discharged from the hospital and presents to your clinic for follow up. Molecular analysis now reveals ROS1 rearrangement with CD74-ROS1 fusion.

- What treatment plan should be put in place for this patient?

**FIRST-LINE THERAPY FOR ROS1 REARRANGEMENTS**

Approximately 2.4% of lung adenocarcinomas harbor ROS1 rearrangements.82 This distinct genetic alteration occurs more frequently in NSCLC patients who are younger, female, and never-smokers, and who have adenocarcinomas.8 It has been shown that ROS1 rearrangements rarely overlap with other genetic alterations including KRAS mutations, EGFR mutations, and ALK rearrangements.83 As a receptor tyrosine kinase, ROS1 is similar to ALK and insulin receptor family members.84 Crizotinib, which targets ALK, ROS1, and c-MET, was approved by the FDA on March 11, 2016, for the treatment of metastatic ROS1-rearranged NSCLC.85 The approval was based on a phase 2 expansion
Management of Non-Small Cell Lung Cancer

cohort of the original phase 1 study. Among 50 US patients enrolled in this expansion cohort, 3 had complete responses and 33 had partial responses with ORR of 72% (95% CI 58% to 84%). Median PFS was 19.2 months (95% CI 14.4 months to NR) and median duration of response (DOR) was 17.6 months (95% CI 14.5 months to NR). During longer follow-up, independent radiology review confirmed high ORR of 66% and median DOR of 18.3 months.

Interestingly, no companion diagnostic assay has been approved for the detection of ROS1 rearrangements with the approval of crizotinib. In the United States, break apart FISH is the most common detection method. In fact, in the above mentioned phase 2 study, ROS1 rearrangements were detected in 49 out of 50 patients by this method. FISH can be technically challenging when dealing with high volume and multiple targets. Reverse transcriptase-PCR is another detection method, but it requires knowledge of the fusion partners. To date, at least 14 ROS1 fusion partners have been reported, with CD74 being the most common. NGS with appropriate design and validation can also be used to detect ROS1 rearrangements.

For the case patient, the recommendation would be to start her on crizotinib at 250 mg twice daily. Monitoring for vision disturbance, gastrointestinal complaints, and edema is warranted. Because the estimated onset of response is around 7.9 weeks, plans should be made to repeat her scans in approximately 2 months.

**BRAF V600E MUTATIONS**

**CASE PRESENTATION 4**

A 71-year-old Caucasian man with a past medical history of hypertension, dyslipidemia, and ischemic cerebrovascular accident without residual deficits was diagnosed with stage IV adenocarcinoma of the lung about 8 months ago. He has a 40 pack-year smoking history and quit smoking when he was diagnosed with lung cancer. His disease burden involved a large mediastinal mass, scattered pleural nodules, multiple lymphadenopathy, and several soft tissue masses. His outside oncologist started him on chemotherapy containing carboplatin and pemetrexed for 6 cycles followed by maintenance pemetrexed. The most recent restaging scans show disease progression with enlarging soft tissue masses and several new lytic bone lesions. MRI-brain with and without contrast shows 2 subcentimeter enhancing lesions. He transferred care to you approximately 4 weeks ago. You ordered a repeat biopsy of 1 of the enlarging soft tissue masses. Molecular analysis revealed BRAF V600E mutation. In the interim, he underwent stereotactic radiosurgery for the 2 brain lesions without any complications. The patient is now in your clinic for follow up.

- **What would be your recommended systemic treatment?**

**TARGETED THERAPIES FOR BRAF V600E MUTATION**

BRAF mutations were first recognized as activating mutations in advanced melanomas, with BRAF V600E, resulting from the substitution of glutamic acid for valine at amino acid 600, being the most common. BRAF plays an important role in the mitogen-activated protein kinase (MAPK) signaling pathway. Briefly, the activation of MAPK pathway occurs upon ligand binding of receptor tyrosine kinases, which then involves RAS/BRAF/MEK/ERK in a stepwise manner, ultimately leading to cell survival. BRAF mutations have been increasingly recognized also as driver mutations in NSCLC. BRAF mutations have been described by various groups. For instance, 1 case series showed that the incidence was 2.2% among patients with advanced lung adenocarcinoma; 50% of mutations were V600E, while G469A and D594G accounted for the remaining 39% and 11% of patients, respectively. All patients were either current or former smokers. The median OS of
patients with *BRAF* mutations in this case series was NR, while it was 37 months for patients with *EGFR* mutations (*P* = 0.73) and NR for patients with *ALK* rearrangements (*P* = 0.64). For patients with *BRAF* V600E–mutant NSCLC who have progressed on platinum-based chemotherapy, the combination of dabrafenib (*BRAF* inhibitor) and trametinib (MEK inhibitor) may represent a new treatment paradigm. This was illustrated in a phase 2, nonrandomized, open-label study. A total of 57 patients were enrolled and 36 patients (63.2% [95% CI 49.3% to 75.6%]) achieved an overall response by investigator assessment, the trial’s primary end point. Disease control rate was 78.9% (95% CI 66.1% to 88.6%), with 4% complete response, 60% partial response, and 16% stable disease. PFS was 9.7 months (95% CI [6.9 to 19.6 months]). The safety profile was comparable to what had been observed in patients with melanoma treated with this regimen. More specifically, 56% of patients on this trial reported serious AEs, including pyrexia (16%), anemia (5%), confusional state (4%), decreased appetite (4%), hemoptysis (4%), hypercalcemia (4%), nausea (4%), and cutaneous squamous cell carcinoma (4%). In addition, neutropenia (9%) and hyponatremia (7%) were the most common grade 3–4 AEs. The case patient has experienced disease progression after 1 line of platinum-based chemotherapy, so the combination of dabrafenib and trametinib would be a robust systemic treatment option. Dabrafenib as a single agent has also been studied in *BRAF* V600E–mutant NSCLC in a phase 2 trial. The overall response by investigator assessment among 84 patients was 33% (95% CI 23% to 45%). Vemurafenib, another oral *BRAF* TKI, has demonstrated efficacy for NSCLC patients harboring *BRAF* V600E mutation. In the cohort of 20 patients with NSCLC, the response rate was 42% (95% CI 20% to 67%) and median PFS was 7.3 months (95% CI 3.5 to 10.8 months). Patients with non-V600E mutations have shown variable responses to targeted therapies. MEK TKIs may be considered in this setting; however, the details of this discussion are beyond the scope of this review.

**CONCLUSION**

The management of advanced NSCLC with driver mutations has seen revolutionary changes over the past decade. Tremendous research has been done in order to first understand the molecular pathogenesis of NSCLC and then discover driver mutations that would lead to development of targeted therapies with clinically significant efficacy as well as tolerability. More recently, increasing efforts have focused on how to conquer acquired resistance in patients with disease progression after first-line TKIs. The field of *EGFR*-mutant NSCLC has set a successful example, but the work is nowhere near finished. The goals are to search for more driver mutations and to design agents that could potentially block cell survival signals once and for all.

**REFERENCES**


76. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase positive non-small-cell...


