Updating the Targeted Therapy Paradigm for Patients With Metastatic NSCLC

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

The treatment paradigm for metastatic non–small cell lung cancer has changed significantly since the advent of targeted therapy. During JADPRO Live 2022, presenters focused on important updates to clinical practice guidelines, data from recent clinical trials of biomarkers and their respective targeted therapies, and best practices for monitoring and managing side effects associated with targeted therapies for metastatic non–small cell lung cancer.

The targeted therapy paradigm for patients with metastatic non–small cell lung cancer (NSCLC) has revolutionized treatment options, offering new hope for patients with previously limited options. During JADPRO Live 2022, Narjust Florez (Duma), MD, of Dana-Farber Cancer Institute and Harvard Medical School, and Stephanie McDonald, NP, of Dana-Farber Cancer Institute, explained the evidence base underlying recent FDA drug approvals and important updates to clinical practice guidelines leading to new molecular targeted therapies for patients with metastatic NSCLC. The presenters also described relevant data from recent clinical trials of emerging biomarkers and their matching targeted therapies for patients with metastatic NSCLC.

BIOMARKER TESTING

Biomarker testing has become an essential part of the diagnosis and treatment of metastatic NSCLC. Therapeutic advances in lung cancer have allowed for a more personalized approach to care, said Ms. McDonald, who noted that approximately 52% of patients with advanced nonsquamous NSCLC have an actionable driver mutation that is targetable by an FDA-approved agent.

The most common actionable driver mutations are *KRAS* (25%), *EGFR* (17%), and *ALK* (5%; Nassar et al., 2021). Ms. McDonald also mentioned that approximately 31% of patients still have an unknown oncogenic driver detected, but she notes that "research is progressing quickly in identifying these."

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Dr. Florez also underscored how important molecular testing has become for patients with NSCLC and how it has changed the targeted therapy paradigm. For example, PD-L1 testing can be used to determine eligibility for certain treatments, but it should not be relied upon in cases where a target mutation is present, as this could lead to inaccurate results.

"We're trying to find the key to a lock," Dr. Florez said, demonstrating how she explains it to her patients. "The lock is the cancer, and the key is the biomarker testing. I cannot open your lock unless I have the right key, and the right key is the right biomarker."

Liquid biopsy, which is the detection of circulating tumor DNA, can be a useful alternative to tissue biopsy in cases where tissue is not available or not enough is present.

"Liquid biopsy results are often quicker, with a turnaround time of 5 to 7 business days," said Dr. Florez, who noted that liquid biopsies are more successful in patients with liver metastasis. "However, liquid biopsies have a high positive predictive value but a low negative predictive value, which means that if the liquid biopsy is negative, tissue biopsy is still necessary to confirm the results."

Dr. Florez also discussed the importance of biomarker testing in guiding treatment for lung cancer in neoadjuvant, adjuvant, and metastatic settings.

"With new approvals for immunotherapy in the neoadjuvant setting, testing is crucial to determine which patients will respond to this type of treatment," she said. "Biomarker testing is important even for early-stage lung cancer."

The National Comprehensive Cancer Network (NCCN) Guidelines for biomarker testing in lung cancer patients indicate that patients with stage IB to IIIA nonsquamous lung cancer should be tested for *EGFR* and *ALK*, patients with stage III nonsquamous lung cancer should be tested for EGFR, and all nonsquamous patients should be tested (Figure 1).

For squamous cell, next-generation sequencing should be done in young patients, patients who are non-smokers, and patients who have a small sample or adenosquamous histology, said Dr. Florez.

EGFR MUTATIONS IN NSCLC: FIRST-LINE TREATMENT

Dr. Florez highlighted the importance of identifying specific *EGFR* mutations, such as exon 19 deletions and *L858R* mutations in exon 21, which are common in women. Dr. Florez also noted that there are unclassical or atypical mutations, such as G719X, L861Q, or S7681, which are treated differently (Remon et al., 2020).

For patients with *EGFR* mutations, results of the FLAURA trial demonstrated longer progres-

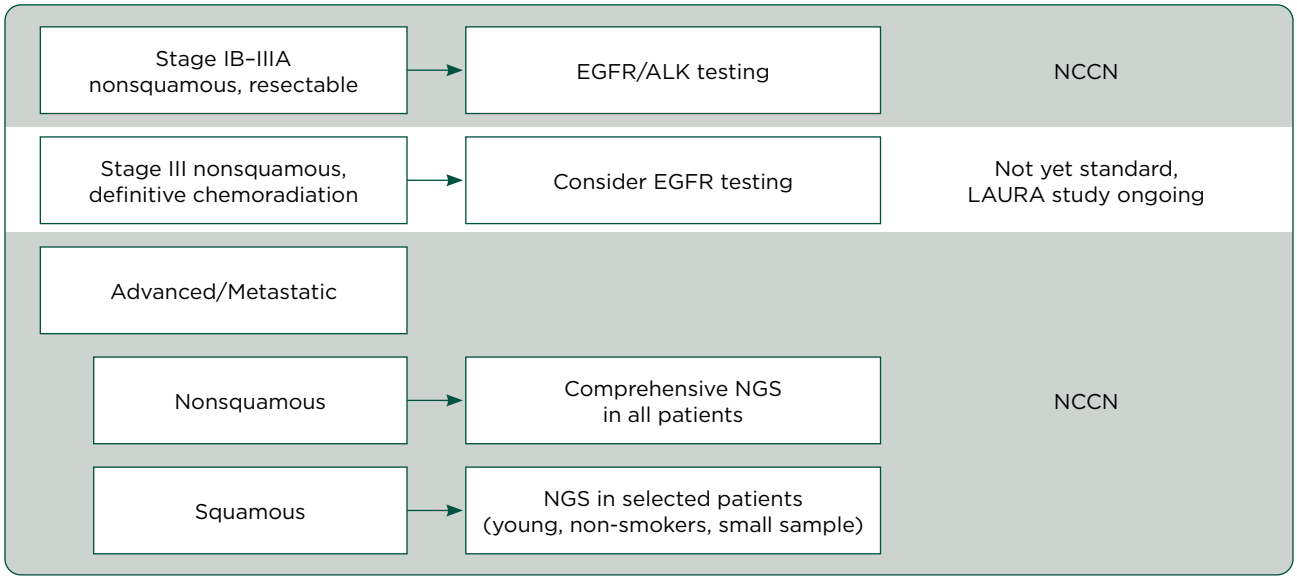

Figure 1. Which patients require biomarker testing in 2022? NGS = next-generation sequencing. Information from NCCN (2022); Li et al. (2021).

sion-free survival and overall survival as well as better quality of life with osimertinib (Tagrisso) compared with standard EGFR tyrosine kinase inhibitors (TKI; Ramalingam et al., 2020). Osimertinib has also been shown to be effective in treating patients with central nervous system (CNS) metastases, who have higher morbidity and comorbidities.

Common side effects of osimertinib include diarrhea, neutropenia, fatigue, and rashes. According to Ms. McDonald, these side effects can start as soon as 2 weeks after initiating therapy, which underscores the importance of early management of these symptoms.

"Starting antidiarrheal medication early is important," said Ms. McDonald. "Monitoring electrolytes and renal function is also necessary due to the risk of dehydration."

Rashes can be managed with a good skin care program, clindamycin gel, and oral antibiotics like minocycline or doxycycline, while fatigue can be managed with an exercise program, a well-balanced diet, and proper hydration, Ms. McDonald recommended.

Ms. McDonald also highlighted the risk of interstitial lung disease and pneumonitis, which are typically found incidentally on scans. Additionally, the risk of osimertinib-induced cardiomyopathy is 3%, and risk for QT prolongation is less than 1%. Patients with cardiac risk factors should receive baseline echoes and electrocardiograms, and be monitored periodically, said Ms. McDonald.

TREATMENT OPTIONS AFTER FIRST-LINE EGFR TKI THERAPY

For patients without a *T790M* mutation who progress after osimertinib treatment, histology-driven, platinum-based chemotherapy is the standard of care. Dr. Florez recommended a clinical trial, if possible, or continuing osimertinib past progression in combination with chemotherapy, especially in patients with brain metastases.

Amivantamab (Rybrevant) and mobocertinib (Exkivity) are both approved therapies for *EGFR* exon 20 mutations. The US Food and Drug Administration (FDA) granted accelerated approval for amivantamab, a bispecific EGFR-directed and MET receptor–directed antibody in May 2021. The approval was based on the results of the CHRYSALIS trial, which evaluated the safety and efficacy of amivantamab in patients with metastatic NSCLC whose disease had progressed after platinum-based chemotherapy (Shu et al., 2022).

The trial demonstrated an overall response rate of 40% in this patient population, with a median duration of response of 11 months. Amivantamab is administered intravenously, with a dosing regimen of once weekly for 4 weeks, followed by every 2 weeks thereafter. The first week of treatment must be given through a peripheral IV due to the high risk of infusion reactions. The dosing is weight based, with a dosage of 1,050 mg for patients less than 80 kg and 1,400 mg for patients greater than 80 kg.

The most common side effects associated with amivantamab are infusion reactions, rash, paronychia, stomatitis, and pruritus. Infusion reactions are most common on the first day of treatment, said Ms. McDonald, who noted that 67% of patients experience some form of reaction. To minimize this risk, both an antihistamine and an antipyretic are administered prior to all infusions. The risk of infusion reaction drops to 3% on the second day of treatment and is less than 1% for each infusion thereafter.

Another targeted therapy, mobocertinib, was approved by the FDA in September 2021 for the treatment of patients with metastatic NSCLC whose disease has progressed after platinum-based chemotherapy (Riely et al., 2021). The overall response rate for this therapy was 28%, with a median duration of response of 17.5 months. Mobocertinib is an irreversible EGFR TKI that targets the *EGFR* exon 20 insertion mutation. The recommended dose is 160 mg once a day, and it is taken orally.

According to Ms. McDonald, diarrhea is the most troublesome side effect, but if managed early, patients can stay on therapy and do well. Other side effects of mobocertinib include rash, paronychia, stomatitis, and pruritus. There is also a box warning for QT prolongation and torsades de pointes.

"It is important to follow your institution's protocol or algorithm for managing hypersensitivity reactions and to closely monitor patients for any complications to ensure the best possible outcomes," said Ms. McDonald.

Special Considerations

Of note, immune checkpoint inhibition has shown a lack of efficacy in patients with *EGFR* mutation-positive NSCLC. In fact, one phase II study of pembrolizumab (Keytruda) found zero response to immunotherapy, and the trial was closed early as a result (Lisberg et al., 2018). It is therefore crucial to test for *EGFR* mutations and to use osimertinib before immunotherapy, said Dr. Florez, as using immunotherapy first can lead to a high risk of pneumonitis.

ALK REARRANGEMENTS

ALK rearrangements are found in approximately 5% of patients with NSCLC and tend to occur in younger, light or never-smokers, and males (Shaw et al., 2009). According to Dr. Florez, however, smoking history should not be an exclusion criterion for biomarker testing. Dr. Florez also noted that patients with an *EGFR* mutation are unlikely to have an *ALK* mutation.

Biomarker-directed therapy is a focus of treatment for *ALK*-positive NSCLC, with two drugs being particularly effective. Alectinib (Alecensa) is used in first-line therapy and has been shown to extend patients' lives for up to 35 months. Lorlatinib (Lorbrena) is also an effective drug, particularly for CNS penetration and for patients with brain lesions (Gainor et al., 2017).

"Brigatinib (Alunbrig) and ceritinib (Zykadia) are also approved in first-line therapy, but alectinib is my drug of choice due to its better tolerance and effectiveness," said Dr. Florez.

There are several important side effects associated with alectinib, including hepatic toxicity, interstitial lung disease, pneumonitis, and myalgia (Table 1).

"It is crucial to monitor for hepatic toxicity and bring patients in every 1 to 2 weeks for the first 3 months due to this risk," said Ms. McDonald. "Any patients who report chest pain, shortness of breath, or respiratory complaints should be brought in and monitored for signs of pneumonitis. Myalgias should be checked by measuring creatine phosphokinase every 2 weeks for the first month, and as indicated thereafter."

Lorlatinib is typically less well tolerated than alectinib and has three key side effects to be aware of: hepatic toxicity, cognitive effects, and hyperlipidemia. As with alectinib, patients should be brought in every 2 weeks for the first month to monitor for hepatic toxicity.

Table 1. ALK Inhibitors: Dosing and Side Effects

Drug	Dosage and administration	Frequent side effects	Grade ≥ 3 side effects (≥ 2%)
Crizotinib	250 mg twice daily; dose adjust for renal impairment	≥ 25%: Vision disorders, nausea, diarrhea, vomiting, edema, constipation, elevated transaminases, fatigue, decreased appetite, URI, dizziness, neuropathy	QT prolongation (2%), diarrhea (2%), vomiting (2%), constipation (2%), esophagitis (2%)
Ceritinib	450 mg once daily with food	≥ 25%: Diarrhea, nausea, abdominal pain, vomiting, fatigue	Fatigue (7%), vomiting (5%), diarrhea (4.8%), stomach pain (3.7%), weight loss (3.7%), nausea (2.6%), QT prolongation (2.6%)
Alectinib	600 mg twice daily with food	≥ 20%: Fatigue, constipation, edema, myalgia, anemia	Renal impairment (3.9%), including 2 grade 5
Brigatinib	90 mg once daily × 7 days, then 180 mg once daily with or without food	≥ 25%: Diarrhea, fatigue, nausea, rash, cough, myalgia, headache, hypertension, vomiting, dyspnea	Hypertension (13%), pneumonia (5.1%), rash (2.9%), dyspnea (2.9%), pneumonitis (2.9%), diarrhea (2.2%), nausea (2.2%), pulmonary embolism (2.2%), headache (2.2%)
Lorlatinib	100 mg once daily	≥ 20%: Edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, diarrhea	Dyspnea (5.7%), weight gain (4.4%), edema (3.1%), peripheral neuropathy (2.7%), cognitive effects (2.0%)

Note. Information from Pfizer Inc. (2019, 2020); Novartis Pharmaceuticals Corporation (2019); Genentech, Inc. (2018); Takeda Pharmaceuticals (2020); Camidge et al. (2020); Mok et al. (2020).

"Cognitive effects can be mild but also scary for patients, so it is important to rule out other causes and do a thorough workup," Ms. McDonald added. "Hyperlipidemia is common with lorlatinib, and approximately 83% of patients will require lipid-lowering agents, typically rosuvastatin."

Lorlatinib has been found to have better penetration into the CNS, making it a suitable option for patients with more brain metastases.

TARGETED THERAPY TRADE-OFFS

As Dr. Florez explained, every cancer therapy has trade-offs between response and toxicity, so it's important for patients to have realistic expectations and be prepared for potential side effects before they start treatment.

ROS1 rearrangements are present in 1% to 2% of NSCLC cases, particularly among younger women who are light or never-smokers (Almquist & Ernani, 2021). Crizotinib (Xalkori) and entrectinib (Rozlytrek) are approved therapies for ROS1, but entrectinib can cause significant edema, which may result in a weight gain of 20 to 40 pounds in some cases. This is a different side effect than what is typically seen with ALK-targeted chemotherapy, which often causes hair loss and weight loss, said Dr. Florez.

MET exon 14 rearrangements are seen in around 3% to 4% of nonsquamous NSCLC and sarcomatoid subtypes of lung cancer. Capmatinib (Tabrecta) and tepotinib (Tepmetko) are approved drugs for *MET* exon 14, with similar tolerability and response rates around 44% and a median duration of response of 10 to 11 months. These patients also may experience weight gain and edema, which requires monitoring in the clinic.

"Capmatinib and tepotinib are often difficult to manage and have a negative effect on patient quality of life," said Ms. McDonald. "To help mitigate the bothersome side effects, patients should be encouraged to elevate their legs and wear compression stockings regularly. In addition, referral to a lymphedema clinic or physical therapy for fitted sleeves or wraps may be beneficial."

BRAF V600E MUTATIONS

BRAF V600E mutations account for approximately 1% to 2% of all NSCLC cases and are found most commonly in adenocarcinoma patients, both those with a smoking history and never-smokers. Treatment for *BRAF* V600E-positive NSCLC typically consists of dabrafenib (Tafinlar; 150 mg twice a day on an empty stomach) and trametinib (Mekinist; 2 mg once a day on an empty stomach; Planchard et al., 2016).

Clinicians should be especially aware of pyrexia, which can cause high fevers—up to 104 degrees—especially within the first 4 weeks of receiving therapy.

"It is important to monitor patients closely, provide antipyretics and hydration if needed, and hold therapy if they are experiencing high fevers," said Ms. McDonald.

Additionally, patients should be monitored for signs of deep vein thrombosis or pulmonary embolism, as these are rare but more common side effects that can be easily managed. Patients should also be educated about the risk cardiomyopathy and uveitis associated with these drugs; any chest pain or shortness of breath should prompt urgent medical evaluation, as well as any acute vision changes or eye pain.

RET MUTATIONS

Currently, two RET inhibitors are available, selpercatinib (Retevmo) and pralsetinib (Gavreto), that have been found to provide a long-term response of 28 months in those receiving directed therapy. Common side effects of RET inhibitors include rash, diarrhea, fatigue, and hypertension. Patients may also have an increased risk of hemorrhagic events and QTc prolongation.

According to Dr. Florez, it is important to have a good blood pressure regimen in place before starting treatment if the patient does not already have hypertension.

HER2 ALTERATIONS

HER2 alterations in NSCLC are mostly exon 20 in-frame insertions, which occur primarily in never-smokers. However, as Dr. Florez pointed out, smoking status should not be an exclusion criterion for biomarker testing since there have been cases of smokers with *HER2* mutations.

HER2 alterations can take three different forms: mutations, gene amplification, and protein over-expression; however only 2% of these are from mutations, and gene amplification is associated with *ALK* and *EGFR* resistance mutations

found by fluorescence in situ hybridization testing. If a report comes back as *ERBB2*, it is actually an indication of *HER2* mutation, said Dr. Florez.

Trastuzumab deruxtecan (Enhertu) was approved in August 2022 based on the DESTINY-Lung02 trial, which showed a progression-free survival of 8.2 months, overall survival of 17.8 months, and a response rate of 55% (Li et al., 2022). Trastuzumab deruxtecan is used only in patients with a *HER2* mutation who have failed first-line treatment with platinum-based chemotherapy or immunotherapy but not those who have protein overexpression or gene amplification due to their different treatment needs.

The most common side effects to be aware of include interstitial lung disease (26% occurrence rate) and cardiotoxicity (ejection fraction monitoring is recommended).

"I used to think it was similar, but HER2-directed therapy can be more toxic in patients with lung cancer than breast cancer," advised Dr. Florez.

KRAS MUTATIONS

The most common oncogenic driver, *KRAS* mutations are present in 37% of nonsquamous NSCLC and 4% of squamous NSCLC. *KRAS* G12C is the most common variant and comprises 40% of *KRAS* mutations overall.

Sotorasib (Lumakras), the only targeted therapy approved for *KRAS*-positive, metastatic NSCLC, is approved for adults with locally advanced or metastatic *KRAS* G12C–mutated NSCLC who received at least one prior systemic treatment. According to Dr. Florez, however, patients do not tend to respond as well to sotorasib in comparison to other therapies.

"Typically, patients experience a maximum of 12 months' benefit from sotorasib after progressing from chemotherapy and immunotherapy," said Dr. Florez.

The dosing for sotorasib is 960 mg daily, eight pills once a day, which can be quite large and may cause diarrhea or lead to an elevation in liver function tests," said Ms. McDonald. It's important to monitor patients closely with liver functions tests every 2 to 3 weeks for at least the first 3 months of treatment. Dose reductions may be needed if diarrhea cannot be managed or if liver function tests remain elevated. ●

Disclosure

Dr. Florez has served as an advisor/consultant for AstraZeneca, BMS, DSI, Janssen, Merck, Mirati, Neogenomics, and Pfizer. Ms. McDonald has no relevant financial relationships to disclose.

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