Advancing Precision-Targeted Treatment for Patients With Metastatic Non–Small Cell Lung Cancer

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Abstract

At JADPRO Live 2023, presenters discussed the implications of biomarker testing, pivotal clinical trials leading to recent FDA approvals, and evidence-based best practices for monitoring and managing adverse events associated with molecular targeted and combination therapies for patients with metastatic non–small cell lung cancer.

Advances in the past two decades in targeted therapy and immunotherapy have significantly improved the treatment of patients with metastatic non–small cell lung cancer (NSCLC). At JADPRO Live 2023, Tajuana Bradley, MSN, APRN-BC, a nurse practitioner at Georgia Cancer Specialists affiliated with the Northside Hospital Cancer Institute, and Beth Sandy, MSN, CRNP, FAPO, a nurse practitioner in thoracic oncology at Abramson Cancer Center at the Hospital of University of Pennsylvania, examined these trends along with what advanced practitioners (APs) need to know about these novel agents.

BIOMARKER TESTING

Studies have shown that patients who receive chemotherapy as opposed to targeted therapy if a driver mutation is present experience worse outcomes. In one study, the overall survival for patients receiving a targeted therapy for a driver mutation was 18.6 months, as opposed to 11.4 months on standard chemotherapy when patients had a driver mutation (Singal et al., 2019).

It is also important to wait for results before prescribing immunotherapy, since data indicate that if patients receive immunotherapy in the presence of an *EGFR* mutation, and treatment then switches to an EGFR tyrosine kinase inhibitor (TKI) in the following several months, patients experience high rates of immune-related adverse events, particularly pneumonitis and hepatitis (Schoenfeld et al., 2019).

Biomarker testing is recommended for all patients diagnosed with NSCLC. There are both predictive and prognostic biomarkers. A

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predictive biomarker is indicative of therapeutic effect due to the interaction between the biomarker and the therapy outcome.

"For example, if a person has an *EGFR* mutation and receives EGFR-targeted therapy, predictively speaking, these patients will have better outcomes based on getting that targeted therapy," explained Ms. Bradley.

A prognostic biomarker is indicative of patient survival that is independent of the treatment that is being received, since the biomarker is an indicator of the innate tumor behavior. In the context of NSCLC, *EGFR* and PD-L1 expression are predictive while *KRAS*, *TP53*, *STK11*, and *KEAP1* are prognostic biomarkers.

Figure 1 shows the frequency of these aberrations in adenocarcinoma of the lung. About a quarter of patients will have a *KRAS* mutation, 27% with unknown aberrations, 19% with *EGFR*, followed by biomarkers such as *HER2, BRAF, RET*, and *MET*, ranging anywhere from 1% to 9% of cases.

National Comprehensive Cancer Network (NCCN) Guidelines recommend performing a broad panel-based molecular test, typically next-generation sequencing (NGS) testing. If no biomarkers are identified, clinicians should consider performing an RNA sequencing panel if not already done to detect RNA fusions. The NCCN NSCLC Panel recommends molecular testing and strongly advises broad molecular profiling to identify any rare driver mutations for which targeted therapies may be available. Testing should also be considered in patients with squamous histology and should also be done in the perioperative setting.

EGFR

A large proportion of patients with NSCLC have sensitizing mutations in exon 19 or 21. Osimertinib is the preferred first-line treatment per NCCN guidelines for *EGFR*-positive NSCLC. Gefitinib, erlotinib, afatinib, and dacomitinib are also US Food and Drug Administration (FDA) approved. In addition, there is the option of erlotinib in combination with bevacizumab or ramucirumab.

There are *EGFR* uncommon mutations, which are typically resistant to classic EGFR inhibitors.

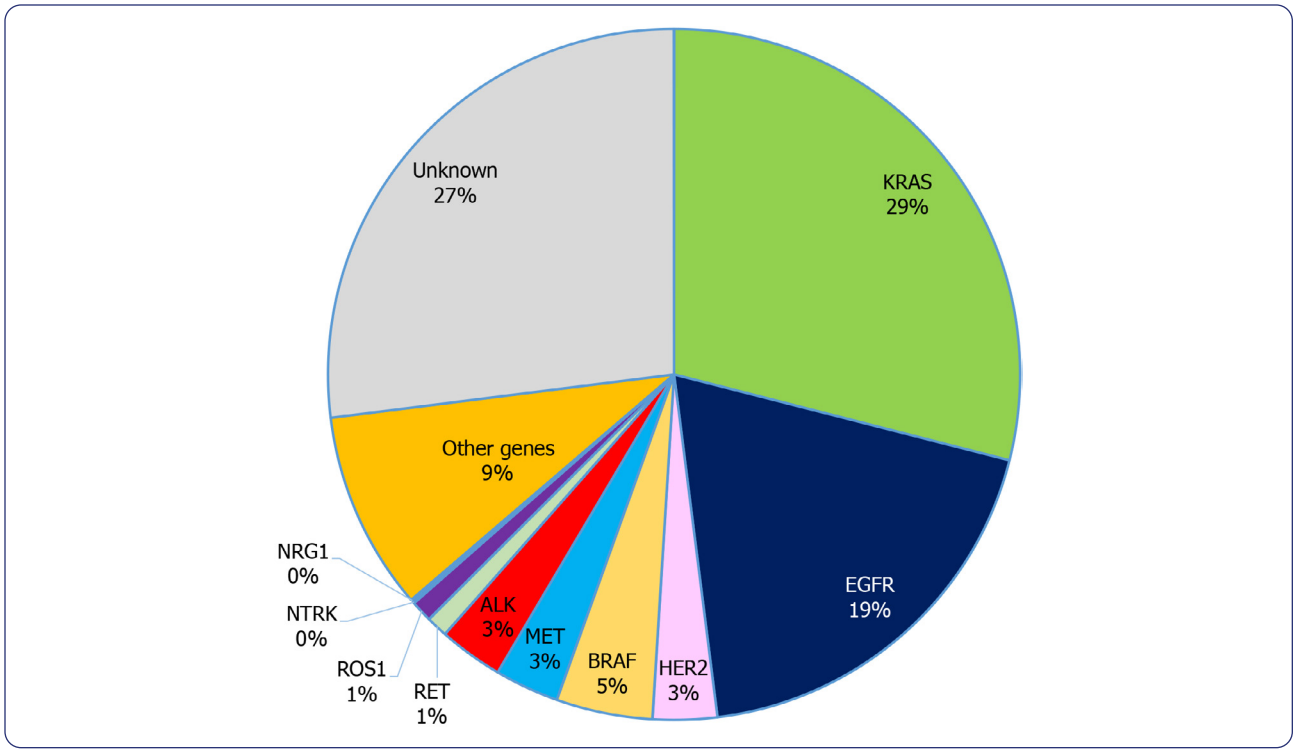

Figure 1. Incidence of oncogenic drivers in adenocarcinoma, NSCLC. KRAS = Kirsten rat sarcoma; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; HER2 = human epidermal growth factor receptor 2; ROS1 = c-ROS oncogene 1; NTRK = neurotrophic tropomyosin tyrosine kinase; RET = rearranged during transfection; NRG1 = neuregulin-1.

Examples include *G719X, L861Q,* and *S768I*. Afatinib is the only FDA-approved agent for these patients. Osimertinib is NCCN recommended but not FDA approved.

For *EGFR* exon 20 insertion mutations, there are a few drugs that were approved post progression on first-line therapy. The monoclonal antibody amivantamab is approved in this setting. Notable adverse events include infusion reactions and rash. Infusion reactions can occur with first treatment but are commonly grade 1 or 2, and the drug can be rechallenged. It is administered weekly for 4 weeks, with the initial dose as a split infusion in week 1 on day 1 and day 2, then administered every 2 weeks thereafter, starting at week 5, until disease progression or unacceptable toxicity. Mobocertinib was an oral tyrosine kinase inhibitor that was voluntarily removed from the US market in 2023. In October 2023, the FDA granted Breakthrough Therapy designation to furmonertinib for NSCLC *EGFR* exon 20 insertion mutations.

At the recent ASCO meeting, 5-year data from ADAURA trial were presented that examined the use of adjuvant osimertinib for resected *EGFR* mutations in NSCLC. The 5-year overall survival rates were 88% with osimertinib and 78% with placebo. Patients took osimertinib for 3 years after surgery and adjuvant chemotherapy. Adverse reactions that occurred in the trial included cytopenias, diarrhea, anemia, rash, musculoskeletal pain, nail toxicities, cough, and fatigue.

One particular safety consideration with osimertinib is interstitial lung disease (ILD).

"Be mindful that with patients who have lung cancer, it's important to decipher if it's disease progression or if it's toxicity and work these patients up," noted Ms. Sandy.

Other less common safety considerations include QT prolongation, cardiomyopathy, keratitis, Stevens-Johnson syndrome, as well as aplastic anemia.

A major toxicity for EGFR inhibitors is rash. Patients should be given topical antibiotics or topical steroid preparations, as well as oral antibiotics if needed. For diarrhea, there are over-the-counter options or prescription antidiarrheals. For nail toxicities, it is important to avoid friction and extreme temperature, and recommend moisturizers and to keep their hands clean. If needed, patients can be referred to dermatology or podiatry for nail avulsion.

ALK

ALK mutations occur in about 4% to 6% of adenocarcinoma NSCLC cases. It is most common in never-smokers or distant minimal smokers, and in younger patients. Approved agents are alectinib, brigatinib, and lorlatinib (preferred first-line therapies per NCCN Guidelines). Lorlatinib is also approved in the second- or third-line setting. Crizotinib and ceritinib were the first ALK inhibitors to be approved, but are not currently used as frequently due to the inferiority of crizotinib to the other three preferred ALK inhibitors and the higher toxicity profile associated with ceritinib.

When comparing the ALK inhibitors alectinib, brigatinib, and lorlatinib, Ms. Bradley commented, "It depends on your patient: What other health issues they are having, and whether they prefer twice-a-day dosing or once-a-day dosing."

Concerning adverse events include creatine phosphokinase elevation with alectinib and brigatinib, ILD with brigatinib, and hyperlipidemia with lorlatinib.

ROS1

The *ROS1* gene is altered in about 1% to 2% of patients with lung cancer and generally appears in adenocarcinoma NSCLC. Patients who are *ROS1*-positive are almost exclusively never-smokers and tend to be younger than the average age of patients with NSCLC. It tends to spread locally and less commonly with distant metastases. The three drugs approved are crizotinib, entrectinib, and repotrectinib. Crizotinib has very good long-term survival data. Edema, bradycardia, and gastrointestinal are side effects that can be common. Entrectinib has better central nervous system penetration if there are brain metastases. Treatment with repotrectinib was also shown to shrink tumors that had spread to the brain.

KRAS

KRAS is the most common oncogenic driver in NSCLC, found in up to 30% of NSCLC cases. There are several variants, but the only currently actionable variant is *KRAS* G12C, making up 40%

of all *KRAS* mutations and around 13% of adenocarcinoma NSCLC. It is more common in patients who have smoked.

Sotorasib and adagrasib are KRAS inhibitors approved for patients harboring the *KRAS* G12C mutation. Sotorasib, the first approved KRAS inhibitor, is indicated for locally advanced or metastatic NSCLC with *KRAS* G12C mutation after at least one prior systemic therapy.

The other drug approved for *KRAS* G12C is adagrasib, also in the second-line setting. The duration of the responses was long and the disease control rate 80%. Diarrhea is of concern with adagrasib, in addition to QT interval prolongation and ILD.

When comparing the two, one consideration is drug-drug interactions that sotorasib has with proton pump inhibitors (PPIs).

"A lot of our patients are on PPIs, and this is something that can significantly decrease the uptake of sotorasib. Do I want to use that in a patient who absolutely has to be on one of their PPIs, like omeprazole?" posed Ms. Sandy.

On the other hand, QT interval prolongation was a noted adverse event in the study with adagrasib. Clinicians must take into consideration the individual patient and the study data to select therapy.

MET

A *MET* exon 14 skipping mutation is present in approximately 1% to 3% of adenocarcinoma patients and can be found on RNA fusion panel.

The two drugs approved are capmatinib and tepotinib. Patients did slightly better when they received treatment in the frontline compared with the second line. Edema is a major side effect, and common laboratory abnormalities are decreased albumin and increased creatinine.

RET

RET fusions are found in 1% to 2% of patients with NSCLC. This is a gene fusion that is often found on an RNA fusion panel but can be detected on a routine NGS panel. It is often associated with younger age and non-smokers. Brain metastases are also common with *RET* fusions.

Selpercatinib and pralsetinib are approved for *RET* fusion–positive advanced NSCLC. Both produced response rates of around 60%. Patients with *RET* fusions can respond to chemotherapy and immunotherapy.

Edema is a common concern with both MET and RET inhibitors. When edema becomes severe, it can interfere significantly with patients' quality of life, which is when dose reductions must be taken into consideration. It is also important to rule out deep vein thrombosis and cellulitis. Elevation and compression stockings can be recommended, with diuretics used sparingly.

Hypertension is also common with the RET inhibitors, with all-grade rates at 35%. A grade 3 hypertension calls for holding therapy and likely dose reducing.

"The interesting thing about this is that hypertension grade 3 per CTCAE grading criteria is 160 over 100. That's really high in my world. That also makes grade 2 a 155 over 98, which is still high. I think these have to be taken case by case, and when you feel comfortable with continuing," commented Ms. Bradley.

Hepatotoxicity is common with these oral therapies. Patients' hepatic function should be monitored at baseline then every 2 weeks for 3 months, then monthly or as indicated. Finally, QT interval prolongation is seen with RET inhibitors. Clinicians should assess QT interval, electrolytes, and thyroid stimulating hormone at baseline and periodically. Therapy should be held at grade 3 and discontinued at grade 4.

HER2

HER2 or *ERBB2* mutation is found in 1% to 2% of patients with NSCLC. The antibody-drug conjugate trastuzumab deruxtecan (T-DXd) is approved in this setting, with response rates observed of around 50%. Most responses were partial responses.

As it has a chemotherapy payload, patients can experience chemotherapy side effects. Interstitial lung disease was seen in around 13% of patients, and it was seen more commonly in patients who had received prior immunotherapy, although this is not a contraindication. Unlike with immunotherapies, where if a patient has symptomatic ILD, clinicians would manage it with steroids and rechallenge, this is not typically the case for ADCs. Grade 2 or higher ILD indicates a permanent discontinuation. At grade 1, it can be rechallenged; however, a grade 1 ILD is radiographic findings only with no symptoms.

BRAF V600E

BRAF V600E mutations are found in 1% to 3% of NSCLC cases. It is more commonly found in smokers and can respond well to chemotherapy and immunotherapy in first- or second-line settings.

The combination drug regimens approved in this setting are dabrafenib/trametinib and encorafinib/binimetinib. One notable adverse event is pyrexia, which is often treated with acetaminophen. If it is refractory, APs can consider prednisone and holding the drug, then rechallenging at the same dose or at a dose reduction.

NTRK

Neurotrophic tropomyosin receptor kinase (*NTRK*) fusions are rare and found in approximately 0.24% of patients. They have a higher prevalence in pediatric patients. They are best found on a fusion panel. The first-generation TRK inhibitors larotrectinib and entrectinib are recommended as the first-line treatment for locally advanced or metastatic NSCLC patients with positive *NTRK* fusion. These have been found to produce high response rates of around 70%.

ORAL ADHERENCE

Best practices for oral adherence include patient monitoring and feedback (asking patients how and if they are taking their medication) and having a follow-up appointment at the 2-week mark after starting therapy. Tools such as calendars, interactive voice response, text messages, and cellphone alarms can be helpful, along with patient and caregiver education and counseling by the AP.

The decision to dose reduce or hold a drug before a dose reduction is often something that APs must determine.

"Personally, I think there's a lot of art to this, and knowing the comorbidities of your patient," commented Ms. Sandy. "I also take into account quality of life."

Clinical pharmacists can be an extremely helpful resource on information within the package insert and studies on how long to hold a drug, as well as colleagues to consult with about drug-drug interactions. ●

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