Targeted Therapy for Metastatic Non–Small Cell Lung Cancer
Presented by Gregory J. Riely, MD, PhD

ABSTRACT

The use of next-generation tyrosine kinase inhibitors has led to improved progression-free survival for patients with metastatic non–small cell lung cancer (NSCLC) and those with EGFR-mutant and ALK-positive tumors. Newer therapeutics can now target KRAS G12C mutations, EGFR exon 20 insertions, and ERBB2 (HER2) mutations. Patients with metastatic NSCLC should undergo molecular testing for these mutations as well as for BRAF mutations; MET exon 14 skipping alterations; and ROS1, RET, and NTRK gene rearrangements (fusions). Novel targeted therapeutics are emerging at a fast pace.

The identification of numerous oncogenic molecular alterations and the development of strategies to target these drivers have made non–small cell lung cancer (NSCLC) a complicated malignancy to manage. “NSCLC is not one disease—it’s a clinical syndrome that can be identified as multiple different diseases,” said Gregory J. Riely, MD, PhD, Attending Physician, and Vice-Chair, Clinical Research, Department of Medicine, Memorial Sloan Kettering Cancer Center. In his presentation at the NCCN 2023 Annual Conference, Dr. Riely, who is also a member of the NCCN Guidelines Panel for NSCLC, described which oncogenic molecular alterations can be targeted, and the efficacy and safety of their corresponding therapeutics according to line of treatment.

“There are multiple molecular targets with agents approved for use in the first-line setting, including EGFR, ALK, ROS1, RET, MET exon 14, and BRAF mutations. Targeted therapies are addressing targets that we’ve not been able to target before, primarily in the second-line setting,” he said, referring to fam-trastuzumab deruxtecan-nxki for ERBB2 (HER2)-mutant tumors, amivantamab-vmww and mobocertinib for tumors with EGFR exon 20 insertions, and sotorasib and adagrasib for KRAS G12C–mutant metastatic NSCLC.

Classification of NSCLC by Biomarkers
There are 2 categories of biomarkers for NSCLC: (1) PD-L1, which is expressed in approximately one-third of patients and is important in those without molecular drivers; and (2) mutations and gene rearrangements (fusions), which are the objects of targeted therapies (Figure 1). The most common molecular subtypes are EGFR-sensitizing mutations; other prominent subtypes include KRAS G12C mutations and KRAS non-G12C mutations. Other less common subtypes include MET exon 14 skipping alterations; BRAF and HER2 mutations; EGFR exon 20 insertions; and ALK, ROS1, NTRK, and RET fusions.

“Molecular analysis and staging, PD-L1 testing, and histology are critical in evaluating patients,” Dr. Riely said. “A patient with a molecular alteration should be directed toward targeted therapy as the first line of treatment. Patients without a molecular driver and who have high PD-L1 expression (≥50%) are typically started on an immune checkpoint inhibitor (ICI), alone or in combination with chemotherapy. For patients without a driver oncogene and no-to-some PD-L1 expression (<50%), we typically recommend chemotherapy plus an ICI,” he said (Figure 2).

EGFR Inhibitors
Identification of EGFR mutations in approximately 20% of patients with newly diagnosed NSCLC heralded the use of molecular markers in treating metastatic NSCLC. Multiple randomized trials showed that EGFR-targeted tyrosine kinase inhibitors (TKIs) appeared to be more effective than platinum-based doublets in these tumors. A third-generation TKI, osimertinib, is now available. Unlike the first- and second-generation TKIs (eg, gefitinib, erlotinib, and afatinib), osimertinib can target the EGFR T790M resistance mutation and avoid targeting wild-type EGFR, which reduces its off-target toxicities, such as rash. Osimertinib was shown to reduce the risk of disease progression by 54% over gefitinib and erlotinib and to reduce mortality by 20%. Median progression-free survival (PFS) of 18.9 months and median overall survival (OS) of 38.6 months with single-agent therapy were “unprecedented at the time,” Dr. Riely noted.

“However, EGFR has become more complicated,” he noted. Among patients with EGFR-mutant NSCLC, 79% have classically sensitizing EGFR mutations (exon 19...
deletion and exon 21 L858R); 15% have “atypical” EGFR mutations (S768I, L861Q, G719X); and 6% have EGFR exon 20 insertions. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC recommend afatinib and osimertinib as preferred first-line treatment options for patients with atypical EGFR mutations. There are separate recommendations for treating EGFR exon 20 insertions. EGFR exon 20 insertions are seen in 1% of patients with NSCLC and seem to be associated with better prognosis compared with tumors that lack targetable oncogenes, but a worse prognosis compared with tumors with classic EGFR mutations. First-generation EGFR TKIs are generally not active against these EGFR exon 20 tumors, yielding a 2.5% response rate and a median PFS of approximately 3 months. According to Dr. Riely, the best first-line treatment option for this subset has remained platinum-based chemotherapy, with response rates of approximately 20% and median PFS of 5.7 months.

After patients with metastatic NSCLC experience disease progression on chemotherapy, 2 new drugs are now recommended in the NCCN Guidelines as second-line therapies that target EGFR exon 20 insertions: amivantamab-vmjw, an intravenously delivered EGFR/MET-binding bispecific antibody, and mobocertinib, an oral small-molecule EGFR TKI. Clinical trial data showed that amivantamab yielded a response rate of 40%, median PFS of 8.3 months, and median OS of 22.8 months; correspondingly, these outcomes with mobocertinib were 32%, 7.3 months, and 24 months, respectively.

**ALK, MET exon 14, and RET Inhibitors**

A pivotal phase III study in patients with ALK-positive metastatic NSCLC reported a 55% reduction in disease progression with crizotinib versus cisplatin + pemetrexed. These findings were pretty remarkable at the time but really just laid the groundwork for the newer ALK inhibitors,
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including alectinib, ceritinib, brigatinib, and lorlatinib,” stated Dr. Riely. These agents are more selective for ALK (lacking much effect on MET), can inhibit mutated ALK (a mechanism for resistance), and may have greater activity in the central nervous system.10–12 Among them, lorlatinib appears to stand out in its robust effect on PFS, according to Dr. Riely, but he thinks “there is some hesitation to start with lorlatinib, because it’s a little harder to use than alectinib and brigatinib.”12

The MET exon 14 alteration is identified in approximately 4% of patients with metastatic NSCLC; patients with this genetic alteration tend to be older and have unusual histology. Capmatinib and tepotinib are 2 MET inhibitors that are preferred first-line treatment options in the NCCN Guidelines for patients with metastatic NSCLC who have MET exon 14 skipping mutations. Capmatinib produced responses in 68% of patients in the first-line setting, and in 41% in later lines.13 Similarly, the response rate with tepotinib was reported to be 46%.14 “These data show significant improvements in response rates compared with standard therapies … the data tell us that using a MET inhibitor in the first-line setting is appropriate, and the FDA has approved this,” Dr. Riely said.

Less common (1.3%) alterations include RET fusions, for which there are 2 FDA approved agents: selecratinib and pralsetinib. The response rate to selpercatinib was 85% in the first line and 64% in later lines, with median PFS not reached versus 17 months, respectively.15 With pralsetinib, the response rate was 65% overall, 61% in patients with prior platinum-based chemotherapy, and 73% in those with treatment-naive disease, with disease control rates of around 90%.16 “These drugs demonstrate clear efficacy for patients with RET-positive lung cancer (metastatic NSCLC) and provide an option for first-line therapy,” Dr. Riely said.

Approximately 2% to 3% of tumors have HER2-activating mutations, the most common of which is insertion of YVMA in exon 20, which can now be targeted with fam-trastuzumab deruxtecan-nxki. Researchers recently reported an approximately 50% response rate with this agent in patients with HER2 mutation–positive metastatic NSCLC who had been previously treated.17

“We await data to say trastuzumab deruxtecan is an effective therapy in the first line, but it’s definitely impressive therapy in the second line,” Dr. Riely observed. Ado-trastuzumab emtansine is another second-line treatment option for patients with HER2 mutations, although it is not FDA approved in this setting.18

KRAS Mutations
KRAS (or RAS) mutations occur in approximately 28% of patients with NSCLC, but targeting them has proved to be challenging. With response rates of approximately 40% in phase II trials, the oral drugs sotorasib and adagrasib received accelerated FDA approval as second-line treatment options for patients with KRAS G12C mutation–positive metastatic NSCLC.19,20 Sotorasib reduced the risk of disease progression by 44% compared with docetaxel in a phase III trial of patients with one prior line of therapy (eg, platinum-based chemotherapy plus an ICI), although the median PFS was modest at 5.6 months; there was no improvement in OS, possibly a result of crossover.21

“We look forward to seeing other trials like this, but where these drugs really shine is in their improved toxicity profile compared with docetaxel,” he said, especially with less neutropenia and alopecia. The NCCN Guidelines recommend sotorasib or adagrasib as second-line therapy options in patients with KRAS G12C mutation–positive metastatic NSCLC.4

“So, in the second-line setting, patients with EGFR exon 20 insertions, KRAS G12C mutations, and HER2 mutations have targeted therapies, but they should not receive these drugs in the first line, because we don’t have the data. Instead, these patients should receive the recommended first-line systemic therapies, which would be an ICI plus chemotherapy or a chemotherapy doublet alone,” Dr. Riely emphasized.

First-Line Checkpoint Inhibition
Dr. Riely emphasized that NSCLC tumor histology and PD-L1 status drive treatment selection. A variety of ICIs can now be given with a chemotherapy backbone for eligible patients with metastatic NSCLC. These ICIs include pembrolizumab; cemiplimab-rwlc; durvalumab + tremelimumab; ipilimumab + nivolumab (which can also be given without chemotherapy); and, for nonsquamous histology alone, atezolizumab (proven not beneficial in the squamous subtype when combined with chemotherapy). In addition, data show that ICIs can be used as neoadjuvant or adjuvant therapy for certain patients with resectable NSCLC.22–24

Disclosures: Dr. Riely has disclosed receiving grant/research support from Merck & Co., Inc., Mirati Therapeutics Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc., Roche Laboratories, Inc., and Takeda Pharmaceuticals North America, Inc.

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