Non–Small Cell Lung Cancer: Recommendations for Biomarker Testing and Treatment

Presented by Dara L. Aisner, MD, PhD, and Gregory J. Riely, MD, PhD

ABSTRACT

Updates to the NCCN Guidelines for Non–Small Cell Lung Cancer (NSCLC) for 2021 include recommendations for biomarker testing in all appropriate patients with newly diagnosed advanced lung cancer, including squamous cell lung cancer. When a targetable genetic alteration is detected, the NCCN Guidelines recommend treatment with a first-line therapy targeted to that alteration. The guidelines contain new information on use of adjuvant treatment with osimertinib for resected early-stage EGFR-mutated NSCLC. New targeted agents are now recommended for the treatment of ALK rearrangements, RET alterations, MET exon 14 skipping mutations in patients with advanced NSCLC; and new immunotherapy agents are recommended for advanced NSCLC without a driver oncogene.

Biomarker testing is now recommended in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non–Small Cell Lung Cancer (NSCLC) for all appropriate patients with newly diagnosed stage IV disease, and can be considered for those with squamous histology, explained Dara L. Aisner, MD, PhD, Associate Professor, University of Colorado Cancer Center, and Gregory J. Riely, MD, PhD, Vice Chair, Clinical Research, Memorial Sloan Kettering Cancer Center, at the NCCN 2021 Virtual Annual Conference. This is because numerous lines of evidence show that patients with stage IV NSCLC and a targetable mutation typically have improved overall survival (OS) when treated with a targeted therapy.

“A relatively new addition to the NCCN Guidelines for NSCLC is dedicated to biomarker selection. For newly diagnosed stage IV NSCLC, there is always a tension between the need to start therapy versus waiting for molecular results. This is because if a recommended targeted option is identified, it is the optimal first-line therapy,” explained Dr. Aisner. “Targeted therapy cannot be given to everyone. Different biomarkers predict response to different agents. This has been well illustrated and it makes testing critically important for patients with NSCLC,” she continued.

“We believe that all patients with NSCLC should be tested, and that molecular testing should be considered for squamous cell lung cancer. The 2021 guidelines include broader language [than the 2020 NCCN Guidelines] related to testing,” she noted. The guidelines recommend considering testing in stage IV squamous cell lung cancer as quickly as possible upon diagnosis, because it is not possible to exclude an adenocarcinoma component in a biopsy, and studies show that approximately 5% to 10% of tumors with squamous cell histology harbor targetable mutations when considered across all targetable alterations.1–3

Another change in the guidelines is a strong push toward testing in resectable stage IB–IIIA NSCLC. The ADAURA trial found that the third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib improved 3-year disease-free survival in stage IB–III, EGFR-positive NSCLC.4 “This study galvanized the push for earlier testing in NSCLC," Dr. Aisner stated.

The 2021 NCCN Guidelines now list osimertinib as an option for adjuvant therapy in patients with resectable stage IIB–IIIA or high-risk stage IB–IIA NSCLC harboring EGFR mutations who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.

Which Biomarkers to Test?

Broad, panel-based testing is strongly advised in appropriate patients with stage IV NSCLC, because it is more efficient than testing for one biomarker at a time. Testing is recommended for the most commonly observed biomarkers, including EGFR, ALK, ROS1, BRAF, and PD-L1 immunohistochemistry, all of which have approved targeted therapies or immunotherapies. EGFR mutations occur in 10% to 20% of all adenocarcinomas, ALK rearrangements in 5% to 7%, ROS1 rearrangements in 1% to 3%, and BRAF mutations in 2% to 5%.
“The best therapeutic outcome is seen if therapy is targeted to the first 3 mutations—EGFR, ALK, and ROS1. It is critically important to perform testing for these mutations before starting therapy. The jury is still out on BRAF,” Dr. Aisner said. Among all BRAF mutations, BRAF V600E is the most common, accounting for approximately 50% of all BRAF mutations in NSCLC. These mutations respond to treatment with the dabrafenib and trametinib regimen. A spectrum of other BRAF mutations are currently under study. For ALK and ROS1 rearrangements, testing looks for a fusion event that leads to aberrant expression and signaling.

Biomarker testing is also recommended for other less commonly observed mutations, such as RET, MET exon 14 skipping, and NTRK1/2/3, all of which have approved targeted therapies for NSCLC with excellent outcomes. Individually, each of these mutations accounts for approximately 1% to 2% of all adenocarcinoma, but in the aggregate, from 3% to 6%. Dr. Aisner noted that there are some challenges in testing for these rare mutations.

Furthermore, “as panel testing becomes more common, rare mutations may be identified that may not have targetable alterations,” she added. Testing is also recommended for emerging biomarkers, such as MET amplification and ERBB2 (HER2) mutations, for which targeted therapies are available but have not been approved for NSCLC. In the future, targeted agents may be approved for treating patients with NSCLC who have MET amplification, ERBB2 (HER2) mutations, or KRAS mutations; these biomarkers will then move into the established list of biomarkers, such as EGFR and ALK.

**PD-L1 Immunohistochemistry**

“PD-L1 immunohistochemistry is a MUST test, because it can help with first-line therapy decision-making,” Dr. Aisner stated. “There are good data to show that tumors with the highest levels of PD-L1 expression drive the benefit, but increasingly we understand there is heterogeneity. PD-L1 immunohistochemistry results will always come back before mutational analysis.” But, she cautioned to “avoid starting a patient on first-line immunotherapy before knowing the results of mutational testing [if clinically feasible].”

In the current NCCN Guidelines, all patients with stage IV NSCLC, but without actionable mutations, now have a pathway to immunotherapy agents. Certain immunotherapy agents are recommended as first-line therapy options for patients with PD-L1 expression levels of ≥50%; combination immunotherapy/chemotherapy is also a recommended option in this setting. Certain first-line combination immunotherapy/chemotherapy regimens are recommended options for patients with PD-L1 expression levels of ≥1% to 49%; a specific single-agent immunotherapy is also an option in this setting based on performance status or other contraindications to chemotherapy. Those with PD-L1 levels <1% have the option for first-line immunotherapy/chemotherapy combinations or chemotherapy alone and the option for immunotherapy or chemotherapy at disease progression.

**Testing Methodology**

“The methodology of testing affects detection. Next-generation sequencing [NGS] is a platform that can cover testing of 3 described alterations, including RET gene fusions, MET exon 14 skipping, and NTRK1/2/3 gene fusions. Many tests deploy DNA-based NGS, but RNA-based techniques overcome the limitations of DNA-based techniques for detecting gene fusions and MET exon 14 skipping. However, RNA-based techniques require a high-quality sample,” she explained. “Complex genomic events do not lend themselves easily for DNA-based testing.”

A recent paper by Benayed et al5 demonstrated the high yield of RNA-based NGS. Among all cases that were negative on DNA testing, 15.5% were positive with RNA technology. The results of this study led to a change in the NCCN Guidelines, which now recommend a broad, panel-based approach and to consider RNA-based testing in patients with no identified driver. “The primary value of KRAS [mutation] testing has been that if it is positive, it is unlikely that there is another driver mutation. But, there are new KRAS agents coming down the pike, and that therapy implication is likely to change,” she said.

“Liquid biopsy” (also known as plasma) with cell-free DNA testing is another strategy for genotyping if tumor tissue is unavailable or the sample is inadequate. “If the initial biopsy is insufficient, [and] rebiopsy is not feasible,” she said.

**Targeted Therapies and Immunotherapies**

The 2021 NCCN Guidelines have become broader in advocating for biomarker testing. “The expanded figure shows us how biomarker recommendations have changed,” said Gregory J. Riely, MD, PhD, Memorial Sloan-Kettering Cancer Center. If a targetable oncogenic driver is detected, then targeted therapy is typically the best option. For patients without targetable driver mutations and with PD-L1 levels <50%, chemotherapy ± anti–PD-1/PD-L1 is the best option; for those with PD-L1 levels >50%, single-agent immunotherapy or combination treatment with anti–PD-1/PD-L1 + chemotherapy is recommended.

**Targetable Mutations**

“The paradigmatic oncogenic driver mutation is EGFR. With first-generation EGFR TKIs, median progression-free survival [PFS] was approximately 9 to 11 months; for patients with the T790M mutation, the third-generation EGFR TKI osimertinib provides another 10 months of PFS...
versus another 4 months when we use chemotherapy,” Dr. Riely continued. “Now we have a better way to start treatment for newly diagnosed EGFR-positive NSCLC.”

A randomized trial of osimertinib versus gefitinib or erlotinib enrolled 556 patients with newly diagnosed metastatic NSCLC. Stable brain metastases were permitted. Median PFS was 18.9 months with osimertinib versus 10.2 months with standard EGFR TKI (P < 0.001), reducing the risk of progression or death by 54%. Median OS was improved from 31.8 months with standard EGFR TKI versus 38.6 months with osimertinib (P =.046). “A median OS in metastatic NSCLC of 3 years reminds us how far we have come, but there is still a long way to go,” Dr. Riely noted. “At 4 years, a significant proportion of patients have died, so we still need new therapies.”

The addition of VEGF inhibitors to EGFR TKIs is a strategy that can improve outcomes. In a phase III study, combination erlotinib + bevacizumab improved PFS by 3.6 months compared with erlotinib alone. A different phase III trial of ramucirumab + erlotinib versus erlotinib alone showed a 7-month improvement in PFS with the addition of the anti-VEGF inhibitor.

The newest version of NCCN Guidelines for patients with stage IV EGFR-mutated NSCLC recommends first-line osimertinib (preferred, category 1); erlotinib, afatinib, gefitinib, and dacomitinib are also category 1 recommendations. Erlotinib + bevacizumab or erlotinib + ramucirumab are category 2A recommendations.

**Earlier Stages?**

“Patients with stage IB disease have a 5-year survival rate of 69%, so we still have a long way to go,” Dr. Riely stated. The randomized phase III ADJURA trial evaluated adjuvant osimertinib versus placebo in patients with completely resected stage IB–IIIA NSCLC, with a planned treatment duration of 3 years. Results favored osimertinib. Patients had significant improvement in disease-free survival, and the vast majority are still on osimertinib. “We don’t know if it adds to the cure rate, but osimertinib clearly improves disease-free survival in stage IB–IIIA disease,” Dr. Riely stated. “Time will tell if it improves OS,” he added. Adverse events associated with osimertinib include diarrhea, paronychia, dry skin, pruritis, cough, and stomatitis. The rates of grades 3 and 4 adverse events are “relatively low,” he said.

Based on the ADJURA study, adjuvant therapy with osimertinib is now recommended for resected early-stage NSCLC in the updated version of the NCCN Guidelines.

**ALK Rearrangements**

The first ALK inhibitor to be approved as first-line therapy for ALK rearrangement–positive advanced NSCLC was crizotinib, based on a phase III trial showing improved PFS over chemotherapy (P < 0.001). Now there are 4 additional approved next-generation ALK inhibitors: alectinib, ceritinib, brigatinib, and lorlatinib. These agents are more selective for ALK than crizotinib and may have the advantage of improved activity in the central nervous system. Furthermore, next-generation ALK inhibitors improve PFS, so the question has been whether to initiate treatment with next-generation drugs. Numerous randomized trials have been conducted with crizotinib as the comparator arm. One study found that alectinib significantly improved PFS compared with crizotinib (P < 0.001). A separate study found that brigatinib improved PFS versus crizotinib. A third trial found similar results for lorlatinib versus crizotinib.

The data from these 3 trials have been incorporated into the latest version of the NCCN Guidelines for ALK-positive advanced NSCLC, with alectinib, brigatinib, and lorlatinib as preferred (category 1) recommendations, and ceritinib and crizotinib (both category 1) recommended in certain circumstances. “Oncologists can look at the efficacy and toxicity of each of these agents in clinical trials to optimize the treatment choice,” he explained.

**MET Exon 14 Skipping Mutations**

Crizotinib (both an ALK and MET inhibitor) has shown activity in MET exon 14 skipping mutation–positive advanced NSCLC, with a response rate of 34%. In addition, 2 new drugs—capmatinib and tepotinib—have been found useful in MET exon 14–positive NSCLC.

A study of capmatinib in stage IIB–IV MET exon 14–positive NSCLC demonstrated good results in cohort 4 (69 pretreated patients; 41% overall response rate) and cohort 5b (28 treatment-naïve patients; 68% overall response rate). Tepotinib also showed good activity in patients with MET exon 14–positive NSCLC: 60 patients were selected by tissue biopsy, 66 by liquid biopsy, and 96 with a combined biopsy.

**Table 1. Treatment Options for Patients Without Driver Oncogenes**

<table>
<thead>
<tr>
<th>PD-L1 Expression</th>
<th>Treatment Options*</th>
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<tbody>
<tr>
<td>High (≥50%, TC2/IC2)</td>
<td>Pembrolizumab, Atezolizumab</td>
</tr>
<tr>
<td>Low (TPS &gt;1%)</td>
<td>Pembrolizumab (category 2B)</td>
</tr>
<tr>
<td>Any (squamous)</td>
<td>Carboplatin, paclitaxel, pembrolizumab, Ipilimumab/Nivolumab</td>
</tr>
<tr>
<td>Any (nonsquamous)</td>
<td>Carboplatin, pemetrexed, pembrolizumab, Carboplatin, nab-paclitaxel, bevacizumab, atezolizumab, Ipilimumab/Nivolumab</td>
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Abbreviations: IC, immune cells; TC, tumor cells; TPS, tumor propensity score.

*See the NCCN Guidelines for detailed recommendations, including other treatment options.
The updated NCCN Guidelines include a new page with capmatinib and tepotinib as preferred (category 2A) first-line options for patients with MET exon 14–positive advanced NSCLC. Crizotinib remains a reasonable choice in certain circumstances.

**RET Rearrangements**

There are 2 new targeted therapy options for RET rearrangement–positive advanced NSCLC: selpercatinib\(^1^{9}\) and pralsetinib.\(^2^{0}\) The updated Guidelines list both these agents as “preferred” (category 2A) for patients with RET-negative advanced NSCLC. Cabozantinib and vandetanib (category 2B) are useful in certain circumstances.

**NSCLC Without a Driver Mutation**

An option for patients with stage IV or recurrent NSCLC without a driver mutation is chemotherapy + anti-PD-1 (nivolumab) + CTLA-4 (ipilimumab) for 2 cycles.\(^2^{1}\) A randomized study of 719 patients found that chemotherapy + 2 cycles of nivolumab/ipilimumab improved OS regardless of PD-L1 status: median OS was 14 versus 10.7 months with 4 cycles of chemotherapy (\(P\)=.00065). Examining OS by PD-L1 status, the triplet regimen was superior in both the PD-L1–negative and PD-L1–positive groups.

Current immunotherapy ± chemotherapy options for patients with advanced or recurrent NSCLC and without driver oncogenes are listed in Table 1.

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**References**


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**Disclosures:** Dr. Aisner has disclosed receiving honoraria from Blueprint Medicines and grant/research support from Genentech, Inc. 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.

**Correspondence:** Dara L. Aisner, MD, PhD, University of Colorado Cancer Center, 2705 East Montview Boulevard, Suite 400, Aurora, CO 80045. Email: dara.aisner@cuanschutz.edu; and Gregory J. Riely, MD, PhD, Memorial Sloan Kettering Cancer Center, 330 East 74th Street, New York, NY 10021. Email: rielyg@mskcc.org