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.

J Natl Compr Canc Netw 2021;19(5.5):610–613
doi: 10.6004/jnccn.2021.5020

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 al[5] 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.[6]

"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.[7] "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

Table 1. Treatment Options for Patients Without Driver Oncogenes

PD-L1 Expression	Treatment Options[a]
High (≥50%, TC_3/IC_3)	Pembrolizumab Atezolizumab
Low (TPS >1%)	Pembrolizumab (category 2B)
Any (squamous)	Carboplatin, paclitaxel, pembrolizumab Ipilimumab/Nivolumab Carboplatin, paclitaxel, ipilimumab/nivolumab
Any (nonsquamous)	Carboplatin, pemetrexed, pembrolizumab Carboplatin, paclitaxel, bevacizumab, atezolizumab Carboplatin, nab-paclitaxel, atezolizumab Ipilimumab/Nivolumab Carboplatin, pemetrexed, ipilimumab/nivolumab

Abbreviations: IC, immune cells; TC, tumor cells; TPS, tumor propensity score.
[a]See the NCCN Guidelines for detailed recommendations, including other treatment options.

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.[8] Stable brain metastases were permitted. Median PFS was 18.9 months with osimertinib versus 10.2 months with standard EGFR TKI ($P<.001$), 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 ($P=.046$).[9] "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.[10] 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.[11]

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 ADAURA trial evaluated adjuvant osimertinib versus placebo in patients with completely resected stage IB–III NSCLC, with a planned treatment duration of 3 years.[4] 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 ADAURA 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 ($P<.001$).[12] 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 ($P<.001$).[13] A separate study found that brigatinib improved PFS versus crizotinib.[14] A third trial found similar results for lorlatinib versus crizotinib.[15]

The data from these 3 trials[13–15] 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%.[16] In addition, 2 new drugs—capmatinib and tepotinib—have been found useful in *MET* exon 14–positive NSCLC.

A study of capmatinib in stage IIIB–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).[17] 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.[18]

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[19] and pralsetinib.[20] The updated Guidelines list both these agents as "preferred" (category 2A) for patients with *RET*-positive 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.[21] 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.

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, 12705 East Montview Boulevard, Suite 400, Aurora, CO 80045. Email: dara.aisner@cuanschutz.edu; and
Gregory J. Riely, MD, PhD, Memorial Sloan Kettering Cancer Center, 530 East 74th Street, New York, NY 10021. Email: rielyg@mskcc.org

References

1. Cheung AH, Tong JH, Chung LY, et al. EGFR mutation exists in squamous cell lung carcinoma. Pathology 2020;52:323–328.
2. Ho HL, Kao HL, Yeh YC, Chou TY. The importance of EGFR mutation testing in squamous cell carcinoma or non-small cell carcinoma favor squamous cell carcinoma diagnosed from small lung biopsies. Diagn Pathol 2019;14:59.
3. Lu S, Lu C, Xiao Y, et al. Comparison of EML4-ALK fusion gene positive rate in different detection methods and samples of non-small cell lung cancer. J Cancer 2020;11:1525–1531.
4. Wu YL, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med 2020;383:1711–1723.
5. Benayed R, Offin M, Mullaney K, et al. High yield of RNA sequencing for targetable kinase fusions in lung adenocarcinoma with no mitogenic driver alterations detected by DNA sequencing and low tumor burden. Clin Cancer Res 2019;25:4712–4722.
6. Hong DS, Fakih MG, Strickler JH, et al. KRAS G12C inhibition with sotorasib in advanced solid tumors. N Engl J Med 2020;383:1207–1217.
7. Aggarwal C, Rolfo CD, Oxnard GR, et al. Strategies for successful implementation of plasma-based NSCLC genotyping in clinical practice. Nat Rev Clin Oncol 2021;18:56–62.
8. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113–125.
9. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. N Engl J Med 2019;382:41–50.
10. Saito H, FukiharaT, Furuya N, et al. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small cell lung cancer: interim analysis of an open-label randomized, multicenter, phase 3 trial. Lancet Oncol 2019;20:625–635.
11. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated EGFR-mutated, advanced non-small cell lung cancer (RELAY): a randomized, double-blind, placebo-controlled phase 3 trial. Lancet Oncology 2019;20:1655–1669.
12. Solomon BJ, Mok T. First-line crizotinib in ALK-positive lung cancer. N Engl J Med 2015;372:782.
13. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 2017;377:829–838.
14. Camidge DR, Kim HR, Ahn MY, et al. Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N Engl J Med 2018;379:2027–2039.
15. Shaw AT, Bauer TM, de Marinis F, et al. First-line lorlatinib or crizotinib for ALK-positive lung cancer. N Engl J Med 2020;383:2018–2029.
16. Drilon A, Clark JW, Weiss J, et al. Antitumor activity of crizotinib in lung cancers harboring a MET exon 14 alteration. Nat Med 2020;26:47–51.
17. Wolf J, Seto T, Han JY, et al. Capmatinib (INC280) in MET exon-14 mutated advanced non-small cell lung cancer (NSCLC): efficacy data from the phase II GEOMETRY mon-1 study [abstract]. J Clin Oncol 2019;37(Suppl):Abstract 9004.
18. Paik PH, Felip E, Veillon R, et al. Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. N Engl J Med 2020;383:931–943.
19. Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med 2020;383:813–824.
20. Gainor J, Curigliano G, Kim DW, et al. Registration dataset from the phase I/II ARROW trial of pralsetinib (BLU-667) in patients with advanced RET fusion+ non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2020;38(Suppl):Abstract 9515.
21. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomized, open-label, phase 3 trial. Lancet Oncol 2021;22:198–211.