Management of Patients With Resectable and Metastatic Non–Small Cell Lung Cancer

Presented by Jane Yanagawa, MD, and Gregory J. Riely, MD, PhD

ABSTRACT

For patients with resectable non–small cell lung cancer (NSCLC) as well as those with metastatic disease, there have been significant recent advances in therapies. In patients with resectable disease, new evidence supports use of neoadjuvant nivolumab + chemotherapy for eligible patients with resectable stage II–IIIA NSCLC. Separate data lead to the recommendation for adjuvant atezolizumab (after adjuvant chemotherapy) for eligible patients with completely resected stage II–IIIA NSCLC and PD-L1 expression ≥1%. Adjuvant osimertinib (6 adjuvant chemotherapy) is an alternative for eligible patients with completely resected stage IB–IIIA NSCLC and EGFR mutations (exon 19 del or L858R). For patients with metastatic NSCLC, molecular testing is recommended for EGFR and BRAF mutations; MET exon skipping 14 alterations; ALK, ROS1, RET, and NTRK1/2/3 gene arrangements; and KRAS G12C mutations. First-line targeted therapies are available for many of these targets and, in the second-line setting, there are new targeted agents for KRAS G12C mutations and EGFR exon 20 insertions.

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Non–small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 84% of all lung cancer diagnoses. It is estimated that nearly 200,000 adults will be diagnosed with NSCLC in the United States in 2022. In addition to histology, classification of NSCLC by biomarkers such as mutations/gene fusions and PD-L1 expression plays an important role in treatment selection.

At the NCCN 2022 Annual Conference, Jane Yanagawa, MD, Associate Professor of Thoracic Surgery, University of California, Los Angeles (UCLA), and Director of Thoracic Surgery, UCLA–Santa Monica Hospital, discussed the management of patients with resectable NSCLC, including surgical candidacy, the role of adjuvant and neoadjuvant therapies, and the value of biomarker testing. Gregory J. Riely, MD, PhD, Vice Chair of Clinical Research, Department of Medicine, Memorial Sloan Kettering Cancer Center, and Associate Professor of Medicine, Weill Cornell Medical College, discussed targeted therapies for patients with metastatic NSCLC.

Surgical Candidacy for Early-Stage NSCLC

For patients with NSCLC, surgical candidacy depends on diagnosis and staging, as well as physiologic parameters. Diagnosis is typically made with CT-guided needle biopsy (for peripheral lesions), endobronchial biopsy (for central or peripheral lesions), or excisional biopsy.

After a diagnosis of NSCLC has been made, staging procedures include PET/CT—any abnormalities found on imaging should be confirmed via tissue. Patients with neurologic symptoms, evidence of metastases, or very large tumors should also be considered for a brain MRI as part of their staging workup, said Dr. Yanagawa.

In addition to oncologic factors, physiologic parameters play a role in determining surgical candidacy. Patients with predicted postresection forced expiratory volume in 1 second (FEV₁) and diffusing capacity of carbon monoxide (DLCO) >40% on a pulmonary function test are considered candidates for surgical resection. Conversely, those with predicted postresection FEV₁ and DLCO ≤40% are at increased risk for morbidity and mortality after surgery. Additionally, a lung ventilation/perfusion (V/Q) scan can also be used to anticipate the impact of surgical resection. For patients with risk factors for coronary artery disease, a cardiac stress test may be included in the preoperative workup.

“Much has changed in the field regarding technology for the actual surgical approach, but there are also improved perioperative factors and improvements in patient selection,” said Dr. Yanagawa.

The American Association for Thoracic Surgery recently created a consensus document that evaluated several factors for risk assessment prior to pulmonary lobectomy. After home oxygen for underlying severe lung disease, frailty was the second most important risk factor. According to Dr. Yanagawa, data showed that patients who are either frail or even prefrail are at risk for complications after thoracic operations. Ongoing research is exploring whether preoperative interventions could change the frailty phenotype to improve outcomes. One screening study of patients who underwent thoracic surgery found that 12% were considered frail and 57% were considered prefrail.
Although age has been a limiting factor for surgery in the past, elderly patients with NSCLC are increasingly undergoing treatment with improved outcomes. In the past decade, there have been improvements in local therapies, and elderly patients are increasingly being treated with either stereotactic body radiation therapy or minimally invasive surgery for stage I NSCLC,” said Dr. Yanagawa. “Enhanced recovery after surgery, or ERAS, protocols are also being prioritized to impact outcomes with improved perioperative care.”

Role for Adjuvant Systemic Therapy
For patients with stage I–IIIA resectable disease, the 5-year survival ranges from 92% for the earliest stage (IA1) to as low as 36% for stage IIIA. “Even for stage IB, the 5-year survival drops to 68%,” said Dr. Yanagawa. “This suggests there is a lot of room for improvement beyond just operating on these patients.”

The 2008 Lung Adjuvant Cisplatin Evaluation (LACE) study, a pooled analysis of >4,500 patients from 5 largest trials of adjuvant chemotherapy in resected early-stage NSCLC, showed a significant improvement in overall survival (OS). According to Dr. Yanagawa, however, the absolute benefit was “very small,” at 5.4%. There was also an increase in non-cancer-related mortality for patients who received adjuvant chemotherapy.

Targeted therapy and immunotherapy have since replaced and/or augmented therapeutic options for advanced disease, and investigators are now beginning to explore these approaches for early-stage disease. In the ADAURA trial, 682 patients with completely resected stage IB–IIIA EGFR-mutation-positive disease (exon 19 del or L858R) were randomly assigned to adjuvant osimertinib or placebo for 3 years. At 2 years, 90% of patients with stage II–IIIA disease who received adjuvant osimertinib were alive and disease-free versus 44% of those who received placebo. Among those with stage IB disease, 88% of patients randomly assigned to adjuvant osimertinib were alive and disease-free at 2 years versus 71% on placebo.

There is also an emerging role for adjuvant immunotherapy after lung resection for early-stage NSCLC. In the IMpower010 trial, 1,005 patients with completely resected stage IB–IIIA disease after adjuvant chemotherapy were randomly assigned to atezolizumab (up to 16 cycles or 1 year) or best supportive care. At 3 years, patients with stage II–IIIA NSCLC and PD-L1 expression >1% had disease-free survival rates of 60% versus 48% with best supportive care. The patients who had the most significantly improved outcomes were those with PD-L1 tumor expression >50%, said Dr. Yanagawa.

Biomarker Testing for Stage IB–IIIA Resectable NSCLC
Based on the IMpower010 and ADAURA studies, PD-L1 expression and EGFR mutations are now important biomarkers to determine whether patients would benefit from adjuvant therapy after lung resection. There are several ongoing adjuvant clinical trials exploring different combinations of targeted therapies and immunotherapies with or without chemotherapy, and additional studies are examining the role of neoadjuvant therapy. As Dr. Yanagawa explained, one benefit of the latter approach is faster results.

“Even adjuvant studies that use disease-free survival as their primary outcome take several years to determine the outcome, and OS data for the ADAURA and IMpower studies are still maturing,” said Dr. Yanagawa. “With a neoadjuvant approach, however, we can use surrogates of OS, such as pathologic response after tumor resection, to provide quicker results.”

The CheckMate 816 trial assessed neoadjuvant nivolumab with chemotherapy versus chemotherapy alone in 368 patients with resectable stage I–IIIA NSCLC (based on the 7th edition of the AJCC Cancer Staging Manual), without EGFR mutations or ALK alterations. A pathologic complete response was observed in 24% of patients in the nivolumab + chemotherapy group versus 2.2% in the chemotherapy group alone (P<.0001). Of note, there were no delays to surgery in the nivolumab + chemotherapy group, and there were no significant differences in postoperative complications. In fact, said Dr. Yanagawa, there was a shorter length of operative time in those that received nivolumab + chemotherapy compared with those who did not.

According to Dr. Yanagawa, broad mutation testing is recommended only for advanced and metastatic NSCLCs in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC and not for early-stage NSCLC (Figure 1). Molecular testing for EGFR mutations and immunohistochemistry for PD-L1 are recommended based on the previously mentioned trials for early-stage NSCLC.

Targeted Therapy for Patients With Metastatic NSCLC
As Dr. Riely explained, histology remains a critical decision point in determining how to treat patients with metastatic NSCLC. There are 3 main types of NSCLC: adenocarcinoma, squamous cell carcinoma, and other, which includes large cell neuroendocrine carcinoma and NSCLC not otherwise specified.

Beyond histology, immune and molecular biomarkers help determine treatment for patients with metastatic NSCLC: PD-L1 status, determined by immunohistochemistry, and mutations/gene fusions, determined by next-generation sequencing. Treatment options for patients with high expression of PD-L1 (≥50%) include an immune checkpoint inhibitor with or without chemotherapy. Patients with low PD-L1 scores (1%–49%) or absent...
PD-L1 typically receive chemotherapy and a checkpoint inhibitor.

Important oncogenic drivers in NSCLC include EGFR mutations, ALK gene rearrangements, KRAS mutations, ROS1 rearrangements, BRAF mutations, NTRK1/2/3 rearrangements, MET exon 14 skipping mutations, and RET rearrangements.

**EGFR Tyrosine Kinase Inhibitors**

EGFR mutations are one of the most common oncogenic drivers in NSCLC and have served as the paradigm for testing targeted therapy, according to Dr. Riely. Several EGFR tyrosine kinase inhibitors (TKIs) have demonstrated superiority over platinum-based chemotherapy, including first-generation gefitinib, showing a 5-month increase in median progression-free survival (PFS; 10.8 vs 5.4 months, respectively; hazard ratio [HR], 0.3).9

Despite this clear benefit compared with standard chemotherapy, clinical resistance to first- and second-generation EGFR TKIs develops after approximately 1 year, most commonly by emergence of a second mutation, EGFR T790M.

The discovery of **EGFR T790M** led to the development of the third-generation EGFR TKI, osimertinib. Osimertinib targets the common mutations **EGFR** L858R and EGFR exon 19 deletion, as well as **EGFR T790M**. The first- and second-generation EGFR TKIs do not target **EGFR T790M**.

“Of note, erlotinib and afatinib target wild-type **EGFR** and cause wild-type **EGFR** side effects in normal tissue,” Dr. Riely explained. “Osimertinib is much less potent against wild-type **EGFR**, and provides an opportunity for fewer toxicities compared with the first- and second-generation drugs.”

Osimertinib also demonstrated a significant improvement in PFS when compared head-to-head with gefitinib/erlotinib as first-line treatment for NSCLC.10 PFS increased from 10.2 months on a first-generation EGFR TKI to 18.9 months on osimertinib. An improvement in OS was also observed using first-line treatment with osimertinib in patients with metastatic **EGFR-mutant** NSCLC (HR, 0.8; P= .046).11

“Progress in the treatment of oncogene-addicted NSCLC is heralded by the nearly 39-month OS in the experimental arm,” said Dr. Riely. “That’s a very impressive improvement compared with median OS seen with chemotherapy alone.”

Outcomes for patients with **EGFR-mutant** NSCLC can be further improved with the addition of angiogenesis inhibition to EGFR TKIs. Erlotinib + bevacizumab showed improved PFS versus erlotinib alone (16.9 vs 13.3 months).12 Similarly, the angiogenesis inhibitor ramucirumab demonstrated a significant improvement in median PFS in combination with erlotinib versus erlotinib alone (19.4 vs 12.4 months).13

The NCCN Guidelines recommend osimertinib as a preferred first-line option for patients with **EGFR-mutant** metastatic NSCLC. Other recommended options include erlotinib, afatinib, gefitinib, dacomitinib, and erlotinib with either ramucirumab or bevacizumab.14

**Atypical EGFR Mutations and EGFR Exon 20 Insertions**

The 2 most common **EGFR** mutations, exon 19 deletion and L858R, represent 79% of patients with **EGFR-mutant** NSCLC. However, there are 2 other groups of **EGFR** mutations: 15% of patients with **EGFR-mutant** disease have atypical **EGFR** mutations such as G719, L861, and S768, and 6% have **EGFR** exon 20 insertions.15

For patients with atypical mutation-positive metastatic NSCLC the NCCN Guidelines recommend either
Afatinib or osimertinib as preferred first-line therapy options. Afatinib is approved by the FDA specifically for patients with atypical EGFR mutations, said Dr. Riely, but osimertinib is a reasonable choice. There are fewer data to support the use of erlotinib, gefitinib, or dacomitinib.

There are 2 drugs currently available to treat patients with NSCLC and EGFR exon 20 insertions: an oral TKI (mobocertinib) and an EGFR-MET–bispecific antibody (amivantamab). Mobocertinib demonstrated an overall response rate of 28%, a median PFS of 7.3 months, and a median OS of 24 months in patients with EGFR exon 20 insertions. Diarrhea was the most common severe adverse effect reported, with 91% experiencing diarrhea and >20% reporting grade 3 diarrhea.

Amivantamab demonstrated an overall response rate of 40%, with many patients having significant tumor shrinkage. Median PFS was 8.3 months, and median OS was 22.8 months. Treatment-related adverse effects included rash, paronychia, and infusion-related reactions. The current NCCN Guidelines recommend amivantamab or mobocertinib as second-line treatment options for patients with EGFR exon 20 insertion-positive metastatic NSCLC.

**ALK Gene Rearrangements**

ALK gene rearrangements occur in approximately 3% to 5% of NSCLCs, but it is an important target to identify, said Dr. Riely. Initial treatment of ALK-positive NSCLC should be with a TKI. Second- and third-generation ALK inhibitors (alectinib, brigatinib, and lorlatinib) have demonstrated improved PFS versus first-generation crizotinib as first-line treatment of ALK-positive NSCLC (Table 1).18–20

**RET and MET Exon 14**

*RET* and *MET* exon 14 are less common targets, found in approximately 2% and 3% of patients with NSCLC, respectively. First-line treatment with capmatinib demonstrated a 68% response rate in patients with *MET* exon 14 mutations and a 41% response rate in the second line. The more recently approved tepotinib was associated with a partial response in approximately half of patients with advanced NSCLC and a confirmed *MET* exon 14 skipping mutation.21

There are also 2 available agents to target *RET*: selpercatinib and pralsetinib. Treatment with selpercatinib for RET-positive NSCLC was associated with an 85% response rate in the first line and 64% in the second line. Median PFS has not been reached with selpercatinib in the first-line setting and was 17 months in the second line. The RET inhibitor pralsetinib demonstrated similar efficacy, with a 70% response rate in the first line and a 61% response rate in the second line.24

**KRAS G12C Mutations**

One of the best ways to target *KRAS* G12C mutations is with a covalent G12C-specific inhibitor. In patients with *KRAS* G12C-mutant NSCLC previously treated with platinum-based chemotherapy, sotorasib demonstrated a response rate of 37%, median PFS of 6.8 months, and median OS of 12.5 months. The most frequent adverse effects were gastrointestinal side effects, including frequent grade 1 or 2 diarrhea and nausea. There were also grade 1 to 3 changes in liver enzyme levels.

Based on these data, sotorasib received accelerated FDA approval in 2021. The current NCCN Guidelines recommend sotorasib as a second-line treatment for patients with *KRAS* G12C–mutant NSCLC.14

**Table 1. Newer ALK Inhibitors in ALK-Positive NSCLC**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>RR (vs crizotinib)</th>
<th>12-mo PFS (vs crizotinib)</th>
<th>PFS HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alectinib</td>
<td>83% vs 76%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68% vs 49%</td>
<td>0.47</td>
</tr>
<tr>
<td>Brigatinib</td>
<td>71% vs 60%</td>
<td>67% vs 43%</td>
<td>0.49</td>
</tr>
<tr>
<td>Lorlatinib</td>
<td>76% vs 58%</td>
<td>78% vs 59%</td>
<td>0.28</td>
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Abbreviations: HR, hazard ratio; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RR, response rate.

<sup>a</sup>Confirmed objective response rate not reported.

**References**


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