

Best Practices in Treating Early-Stage NSCLC

THE TREATMENT LANDSCAPE OF early-stage non-small cell lung cancer (NSCLC) is rapidly evolving. Presently, it includes use of platinum-based chemotherapy, radiotherapy, and immunotherapy with checkpoint inhibitors or targeted therapy. Molecular testing has become increasingly important, and it determines the choice of therapy. Treatment recommendations for stage I to IIIB NSCLC are changing. Adjuvant targeted therapy and immunotherapy are important options for resectable NSCLC, whereas treatment approaches for unresectable stage III NSCLC are less well defined.

This article presents best practices in managing early-stage NSCLC from an *OncLive* Scientific Interchange and Workshop. The meeting, moderated by **Benjamin Philip Levy, MD**, included **Neel P. Chudgar, MD**; **Daniel Gomez, MD, MBA**; **Corey J. Langer, MD, FACP**; **Ticiana Leal, MD**; **Tarek Mekhail, MD, MSc, FRCSI, FRCSEd**; **Bruna Pellini, MD**; **Samuel Rosner, MD**; and **Eric Vallieres, MD, FRCSC**.

The Role of Molecular Testing

Many biomarkers have been recognized as oncogenic drivers in NSCLC; 62% of them represent actionable therapeutic targets. *KRAS* mutations are seen in 29% of NSCLC tumors, followed by *EGFR* mutations in 19%; several other genetic alterations are present in a smaller proportion of tumors.¹ The degree of expression of PD-L1 also has important implications.²

The American Association for Thoracic Surgery 2023 Expert Consensus recommends testing with molecular sequencing and other biomarker analysis in patients with early-stage NSCLC, and the National Cancer Center Network (NCCN) provides a list of mutations that should be included in the assessment.^{3,4} NSCLC with *KRAS* mutations is frequently resistant to other targeted drugs such as EGFR inhibitors, and the *EGFR* T790M sequence variation is linked to acquired resistance to EGFR tyrosine kinase inhibitors (TKIs).⁵ Current testing rates of patients with NSCLC vary from 74% to 80%, and they have increased over time.^{6,7} Using targeted therapy based on driver mutation analyses and the degree of PD-L1 expression results in improved outcomes.^{3,8}

Commonly used tests are real-time polymerase chain reaction, Sanger sequencing, or simultaneous evaluation for multiple mutations (at a minimum, for *EGFR*, *ALK*, and *ROS*) with next-generation sequencing and immunohistochemistry for PD-L1.^{4,9} Many organizations use reflex testing to evaluate the specimen for a multitude of driver mutations without the need for individual orders. A multidisciplinary approach may help to avoid the problem of insufficient tissue quantity in a biopsy and ensure optimal planning for targeted therapy.

Early-Stage Resectable NSCLC Neoadjuvant/Perioperative Strategies

Neoadjuvant and perioperative strategies in early-stage resectable NSCLC have been the topic of several recent studies. In the CheckMate 816 trial (NCT02998528), patients with stage IB to IIIA resectable NSCLC were randomly assigned to receive resection after treatment with neoadjuvant nivolumab plus platinum-based chemotherapy or platinum-based chemotherapy alone.¹⁰ Adding nivolumab to chemotherapy resulted in an improved median event-free survival (EFS) of 31.6 months vs 20.8 months with chemotherapy alone, and the percentage of patients achieving a pathological complete response (pCR) was 24.0% vs 2.2%, respectively. The 3-year EFS was 57% when nivolumab was combined with chemotherapy compared to 43% with chemotherapy alone, regardless of PD-L1 status.^{11,12}

In subsequent studies, an adjuvant continuation phase was added after neoadjuvant therapy and surgery. In the CheckMate-77T study (NCT04025879), patients with stage IIA to IIIB NSCLC were randomly assigned to receive neoadjuvant nivolumab plus chemotherapy or placebo plus chemotherapy; this was followed by surgery and adjuvant nivolumab or placebo.¹³ Neoadjuvant nivolumab improved EFS and pCR without significant differences in the rates of definitive surgeries.

In the KEYNOTE-671 study (NCT03425643), investigators evaluated neoadjuvant pembrolizumab or placebo plus chemotherapy followed by resection and adjuvant pembrolizumab or placebo in participants with resectable stage II, IIIA, and »

resectable IIIB (T3-4N2) NSCLC.¹⁴ After 24 months, the EFS was 62.4% in the pembrolizumab group vs 40.6% in the placebo group; the pCR was 18.1% vs 4.0%, respectively. The rate of treatment-related adverse events was similar in both groups. Notably, the benefit of pembrolizumab was similar in patients with squamous or nonsquamous histology.

Toripalimab was investigated in the neoadjuvant setting and followed by surgery and adjuvant therapy in the Neotorch study (NCT04158440) in patients with stage II to IIIA resectable NSCLC.¹⁵ At 24 months, the median length of EFS was not estimable in the toripalimab group vs 15.1 months in the placebo group. The pCR rate was 24.8% vs 1.0%, respectively.

In the AEGEAN study (NCT03800134), investigators compared neoadjuvant use of durvalumab vs chemotherapy alone, which was followed by adjuvant durvalumab vs placebo after surgery; randomization was stratified by disease stage (IIA-III B) and PD-L1 expression ($\geq 1\%$ or $< 1\%$).¹⁶ Treatment with the PD-L1 inhibitor resulted in superior EFS and pCR outcomes regardless of stage of disease or PD-L1 expression, although the benefit was more pronounced in patients with PD-L1 expression of 50% or greater.

In summary, neoadjuvant immunotherapy combined with chemotherapy was more beneficial than was use of chemotherapy alone. The ability to perform surgery was not negatively impacted by the addition of immunotherapy in these trials; approximately 80% of patients underwent definitive surgery.^{13,14,16,17}

Faculty agreed that postponing surgery for a few weeks to allow the patient to recover from neoadjuvant therapy would not have a significant negative effect. They said the decision to perform surgical resection following neoadjuvant therapy is based upon disease spread and bulk. They emphasized the importance of a multidisciplinary assessment of the patient before starting any treatment, since neoadjuvant therapy would not be started unless the surgeon and the interdisciplinary team agree that the patient is medically operable and that the disease is resectable.

It is less clear whether adjuvant chemotherapy after neoadjuvant immunotherapy and chemotherapy is always needed after surgery, especially in patients who achieved a pCR. The panelists agreed that more data are needed to clarify the role of adjuvant immunotherapy in this setting. The current NCCN guidelines recommend that all patients be evaluated for preoperative therapy and that oncologists strongly consider combining nivolumab or pembrolizumab with chemotherapy as a single regimen without a change in immunotherapy.⁴

Adjuvant Therapy for Resectable NSCLC

Adjuvant therapy may benefit patients whose tumors have an *EGFR* mutation, who have undergone surgery, and who do not tolerate a platinum-based chemotherapy regimen. In the ADAURA trial (NCT02511106), patients with completely resected, *EGFR*-mutated NSCLC were randomly assigned to receive osimertinib or a placebo for 3 years. At 24 months, 90% of patients in the osimertinib group vs 44% of those in the placebo group were alive and free of disease.¹⁸ The 5-year overall survival (OS) rate in patients with stage II to IIIA disease was 85% in the osimertinib group and 73% in the placebo group.¹⁹

On April 18, 2024, the FDA approved alectinib for use as adjuvant treatment following tumor resection in patients with *ALK*-positive NSCLC whose tumors are at least 4cm or node positive, as detected by an FDA-approved test.²⁰ The approval was based on the ALINA trial (NCT03456076) that evaluated alectinib vs platinum-based chemotherapy in patients with completely resected, stage IB to IIIA, *ALK*-positive NSCLC. A subgroup of patients with stage II to IIIA disease were randomly assigned to receive oral alectinib for up to 24 months or up to four 21-day cycles of platinum-based chemotherapy.²¹ Median disease-free survival (DFS) was not reached in the alectinib arm vs 44.4 months in the chemotherapy arm.

In the IMpower010 trial (NCT02486718) involving patients with completely resected stage IB to IIIA NSCLC, researchers compared use of adjuvant atezolizumab with standard of care (1-4 cycles of platinum-based chemotherapy followed by best supportive care).²² Atezolizumab treatment improved the 3-year DFS in patients with stage II to IIIA disease whose tumors expressed PD-L1 of 1% or more (atezolizumab group, 60%; best supportive care group, 48%) and in all patients with stage II to IIIA disease (56% vs 49%, respectively). Longer-term follow-up indicated a survival advantage for the stage II to IIIA subgroup with tumors having a PD-L1 expression above 50%.²³

The PEARLS/KEYNOTE-091 trial (NCT02504372) evaluated adjuvant pembrolizumab versus placebo given for about 1 year in patients with completely resected, stage II to IIIA NSCLC.²⁴ The results showed a DFS of 53.6 months vs 42 months for the pembrolizumab vs placebo arms, respectively.

The faculty had varying opinions regarding targeted adjuvant therapy. They noted that many factors (eg, the right agent for each molecular subtype, the treatment duration) remain unclear. They concurred that for stage IB to IIIA disease with a PD-L1 of 50% or greater, chemotherapy combined with atezolizumab seems to be the best option for adjuvant therapy.

Unresectable Stage III NSCLC

Approximately one-third of patients with NSCLC have stage III, locally advanced disease at diagnosis.²⁵ The definition of *unresectable* stage III NSCLC varies among surgeons, oncologists/pulmonologists, and radiotherapists, with surgeons generally being more optimistic about potential resectability.^{26,27}

Today, the standard of care for inoperable patients is platinum-based chemotherapy with concurrent radiotherapy followed by consolidation with durvalumab.⁴ Before the addition of durvalumab, patients achieved a median PFS of 8 to 10 months, and the 5-year survival rate was 15% to 25%.²⁵ In the PACIFIC trial (NCT02125461), use of the PD-L1 inhibitor durvalumab was compared with placebo as consolidation therapy after radiochemotherapy in patients with stage III unresectable NSCLC.²⁸ At 12 months, the PFS was 55.9% with durvalumab vs 35.3% with placebo. The 5-year median OS was 47.5 vs 29.1 months, respectively. Similar results were achieved in the real-world PACIFIC-R study (NCT03798535), especially among patients with higher PD-L1 expression.²⁹

In the PACIFIC-2 trial (NCT03519971), concurrent durvalumab and chemoradiotherapy for patients with stage III unresectable NSCLC did not improve outcomes.³⁰ The molecular profile of the tumor will impact results. When comparing consolidation therapy with durvalumab or osimertinib, patients with *EGFR*-mutated tumors did better with osimertinib.³¹ In the phase 3 LAURA study (NCT03521154), investigators are evaluating osimertinib as consolidation after chemoradiation in such patients. The workshop faculty said they expected this would show positive results for a subset of patients.³² Durvalumab plus other immunomodulators in this patient subgroup is being studied in the phase 3 PACIFIC-9 trial (NCT05221840).³³

Future Needs

Over the past decade, significant progress in treating early-stage NSCLC has been made, especially when the molecular profile of the tumor indicates that targeted therapy may be used. However, unmet needs persist. Further data are needed about the utility of surgery following neoadjuvant treatment in patients with multinodal involvement. More options and guidelines for perioperative treatment in resectable disease are needed, especially when there is no evidence of residual tumor. The faculty also emphasized that regular meetings of the multidisciplinary team are essential to ensure optimal patient care—especially for patients with stage II or stage III NSCLC—and that molecular testing should be done for patients diagnosed with any stage of NSCLC. ■

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