Advancing Care for Patients With Resectable NSCLC

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Abstract

Advances in immunotherapy, targeted therapy, and biomarker-driven treatment strategies are transforming the management of resectable non–small cell lung cancer (NSCLC). During JADPRO Live 2024, presenters discussed the latest advancements in perioperative and adjuvant therapies, biomarker testing, and future directions in NSCLC treatment.

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non–small cell lung cancer (NSCLC) accounting for 80% to 85% of cases. While surgical resection offers the best chance for cure, recurrence rates remain high, highlighting the need for more effective treatment strategies for early-stage NSCLC. At JADPRO Live 2024, Sarah Anderson, MSN, APRN, AGNP-C, AOCNP, and Danielle Fournier, DNP, APRN, AGPCNP-BC, AOCNP, both of The University of Texas MD Anderson Cancer Center, provided an overview of neoadjuvant and adjuvant treatments, strategies for managing adverse events, biomarker testing, and future directions in managing resectable NSCLC.

ROLE OF SURGERY AND SYSTEMIC THERAPY

Surgical resection is the primary curative option for patients with early-stage NSCLC. Unfortunately, only about 30% of patients are diagnosed at an early enough stage that they are amenable to resection. In addition, recurrence rates after surgery remain high. Since 2004, adjuvant platinum-based chemotherapy has been the standard of care, offering a modest survival benefit. However, with advances in DNA sequencing over the past 20 years, researchers have gained a better understanding of the genomic landscape of NSCLC.

"Immunotherapy and targeted therapy have transformed the treatment for lung cancer and led to the greatest improvements in overall survival in this patient population," Dr. Fournier commented. "So it makes sense that we're now starting to explore the effectiveness of some of these drugs in the early stage setting."

There are currently FDA approvals for neoadjuvant immuno-

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therapy given prior to resection, perioperative immunotherapy regimens given prior to surgery and following surgery, and in the adjuvant space, approvals for both targeted therapy and immunotherapy administered after the patient has undergone resection.

BIOMARKER TESTING IN EARLY-STAGE NSCLC

Biomarker testing identifies oncogenic genomic driver variants for which targeted therapies are approved. These can include somatic gene mutations or gene fusions.

For patients with advanced and metastatic disease, it is standard to perform comprehensive biomarker testing to identify any oncogenic driver mutations that impact treatment selection (Table 1). Currently, there are 10 actionable biomarkers that are recommended to be tested for patients with advanced and metastatic disease.

Testing for *EGFR* alterations is important, as patients with *EGFR* mutations derive minimal benefit from immunotherapy and may benefit from treatment with adjuvant osimertinib (Tagrisso). Similar to EGFR, anaplastic lymphoma kinase (*ALK*)-rearranged tumors do not respond well to immunotherapy. Alectinib (Alecensa) is the preferred adjuvant targeted therapy for these patients. Programmed cell death ligand 1 (PD-L1) expression is assessed using immunohistochemistry (IHC) and determines eligibility for immune checkpoint inhibitors such as adjuvant atezolizumab (Tecentriq).

Liquid biopsy has shown promise in early detection and treatment monitoring. However, it tissue-based testing in still the gold standard in early-stage NSCLC.

NEOADJUVANT SYSTEMIC THERAPY

Until recently, neoadjuvant therapy options for NSCLC were largely limited to chemotherapy-based treatments. The preferred chemotherapy regimens depend on tumor histology and patient characteristics. For nonsquamous NSCLC, cisplatin plus pemetrexed is commonly used, while carboplatin serves as an alternative for patients with contraindications to cisplatin. In squamous NSCLC, cisplatin with either gemcitabine or docetaxel is the standard. Carboplatin plus paclitaxel is an option for mixed histologies or cases where the histology is unclear.

With the advent of immunotherapy, neoadjuvant treatment has seen significant improvements

Table 1. Immunotherapy and Targeted Therapy Options for NSCLC Based on Treatment Setting and Biomarker Status

Treatment setting	Medication	Indications for therapy	Biomarker testing considerations
Neoadjuvant	Nivolumab	Tumors ≥ 4 cm or node positive	No known EGFR or ALK rearrangements[a]
Perioperative	Pembrolizumab	Tumors ≥ 4 cm or node positive	No known EGFR or ALK rearrangements[a]
	Durvalumab	Tumors ≥ 4 cm or node positive	No known EGFR or ALK rearrangements[b]
	Nivolumab	Tumors ≥ 4 cm or node positive	No known EGFR or ALK rearrangements[b]
Adjuvant	Osimertinib	Stage IB, II, or IIIA NSCLC	EGFR exon 19 del positive[b] or EGFR exon 21 L858R positive[b]
	Alectinib	Stage IB, II, or IIIA NSCLC	ALK rearrangement positive[b]
	Atezolizumab	Stage II to IIIA NSCLC	PD-L1 ≥ 1%[b] No known EGFR or ALK rearrangements[b]
	Pembrolizumab	Stage IB, II, or IIIA NSCLC	No known EGFR or ALK rearrangements[a]

Note. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer, Version 11.2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
[a]NCCN recommended criteria
[b]FDA-approved criteria.

in outcomes. The CheckMate 816 trial demonstrated improved event-free survival and pathologic complete response rates with nivolumab plus chemotherapy compared to chemotherapy alone.

PERIOPERATIVE THERAPY: THE "SANDWICH" APPROACH

Perioperative therapy, which is surgery that is sandwiched by upfront chemotherapy and immunotherapy followed by post-operative immunotherapy, is an area of current research interest.

The KEYNOTE-671 trial investigated pembrolizumab (Keytruda) plus chemotherapy for four cycles before surgery, followed by 1 year of adjuvant pembrolizumab. It showed significant improvement in survival outcomes for patients with resectable NSCLC. The AEGEAN trial examined durvalumab (Imfinzi) plus chemotherapy, followed by 1 year of adjuvant durvalumab. It showed a higher rate of complete pathologic response in patients who received durvalumab as compared to those in the placebo group.

One of the most recent approvals, based on data from the CheckMate 77T trial, has introduced perioperative nivolumab combined with platinum doublet chemotherapy, followed by surgery and single-agent nivolumab as adjuvant therapy. This approval, granted in October, expands the available treatment options for patients with resectable NSCLC.

ADJUVANT SYSTEMIC THERAPY

For patients who undergo surgery, adjuvant therapy plays a role in reducing recurrence risk, particularly for those with specific biomarkers. The ADAURA trial demonstrated the effectiveness of osimertinib (Tagrisso) for patients with *EGFR*-mutant NSCLC. At 5 years, 88% of patients were still living as compared to 78% in the placebo group. This improvement in survival has made osimertinib the standard adjuvant treatment for *EGFR*-positive cases. The ALINA trial established alectinib (Alecensa) as a superior option for *ALK*-positive NSCLC. At 2 years, 93% of patients were disease-free in the alectinib group, whereas only 63% of patients in the chemotherapy-only group were disease-free.

Immunotherapy has also demonstrated efficacy in the adjuvant setting. The IMpower010 trial led to the approval of atezolizumab (Tecentriq) for PD-L1-positive NSCLC. The PEARLS/KEYNOTE-091 trial evaluated pembrolizumab (Keytruda) in resected NSCLC and showed notable benefits. Looking at the high PD-L1 expressing patients, 66% of patients were disease-free at 3 years as compared to 58% in the placebo group.

Treatment decisions and timing depend on tumor size, nodal involvement, biomarker testing, comorbidities, and performance status. Immunotherapy regimens are available in the perioperative setting, with ongoing research needed to determine the optimal drug choice and timing.

"If there is even a chance that one of your patients may be resectable, they should be undergoing multidisciplinary evaluation to see if there are systemic therapy options," Ms. Anderson concluded.

THERAPY TOXICITIES

Systemic therapies for NSCLC come with various side effects that require careful monitoring and management. "One thing that will ring true for all of the therapies is that each patient should have a baseline history and physical, and this should be repeated periodically while they are on treatment," Ms. Anderson stated.

Chemotherapy agents such as cisplatin are associated with hypersensitivity reactions, nephrotoxicity, ototoxicity, and cytopenias. Patients receiving cisplatin require regular renal function tests, audiology exams, and neurological assessments to mitigate toxicity. Taxane-based therapies, including paclitaxel and docetaxel, present risks such as peripheral neuropathy, cytopenias, dermatologic reactions, and fluid retention. Pemetrexed, a key agent in nonsquamous NSCLC, requires folic acid and vitamin B12 supplementation to prevent severe toxicity. Patients should avoid NSAIDs due to the increased risk of nephrotoxicity.

Immune checkpoint inhibitors such as pembrolizumab, nivolumab, and atezolizumab carry risks of immune-related adverse events, including pneumonitis, colitis, and endocrinopathies. Hypothyroidism is common.

"If patients develop diarrhea, make sure you are paying attention to the grade or severity of their diarrhea and how persistent is it, because there is a risk of colitis with immunotherapy," Ms. Anderson noted.

Targeted therapies, such as osimertinib and alectinib, have their own distinct toxicities, including QT prolongation, hepatotoxicity, and interstitial lung disease. Patients receiving these treatments should undergo regular cardiac monitoring and liver function tests to detect potential complications early.

FUTURE DIRECTIONS

Identifying patients who will benefit from specific therapies requires early and comprehensive biomarker testing, which can also facilitate enrollment in clinical trials.

"With the larger treatment arsenal comes the need for broader biomarker testing," Dr. Fournier said.

The LMC Leader Neoadjuvant Screening Trial is investigating the feasibility of broad-panel biomarker testing in resectable NSCLC (Lee et al., 2023). This trial aims to determine how frequently oncogenic driver mutations appear in early-stage NSCLC patients. As enrollment continues, findings from this trial could influence the standard approach to biomarker testing in early-stage NSCLC.

Several phase II and III clinical trials are currently exploring targeted therapies and immunotherapies in the neoadjuvant, perioperative, and adjuvant settings.

Several ongoing trials are investigating additional neoadjuvant strategies. The NeoADAURA trial is a phase III study comparing neoadjuvant osimertinib with or without chemotherapy vs. chemotherapy alone for patients with resectable, *EGFR*-positive NSCLC. The IMpower030 trial examines neoadjuvant atezolizumab plus chemotherapy followed by surgery and adjuvant atezolizumab, compared to a placebo with chemotherapy.

In the adjuvant setting, ADAURA2 is extending the use of adjuvant osimertinib to patients with earlier-stage *EGFR*-positive NSCLC. The ANVIL study assesses adjuvant nivolumab for 1 year post-surgery in patients with resected NSCLC, while BR31 examines durvalumab as an adjuvant therapy following chemotherapy. The results of these trials will help refine the role of systemic therapy in improving long-term survival after surgical resection.

While immune checkpoint inhibitors have improved NSCLC treatment, not all patients respond equally. Research into additional biomarkers like microsatellite instability (MSI) and tumor mutational burden (TMB) is ongoing to better predict treatment responses. Factors such as the tumor microenvironment and gut microbiota are also being studied to enhance precision immunotherapy and optimize patient outcomes.

Radiomics uses advanced imaging analysis to predict disease recurrence, differentiate tumor types, and assess treatment responses. Meanwhile, liquid biopsy, though not yet standard in early-stage NSCLC, shows promise in detecting minimal residual disease (MRD) and identifying patients at higher risk for recurrence. Recent studies highlight that circulating tumor DNA (ctDNA) can predict recurrence up to 28 weeks before imaging detects it, underscoring its potential role in treatment monitoring.

CONCLUSION

The management of resectable NSCLC has evolved, incorporating targeted therapy and immunotherapy to improve patient outcomes. Biomarker testing is integral to guiding therapy selection, and both neoadjuvant and adjuvant treatment strategies play a role in reducing recurrence and extending survival. As research progresses, the integration of personalized medicine, innovative diagnostic tools, and emerging therapies will continue to refine treatment paradigms and improve the treatment of patients with resectable NSCLC. ●

Disclosure

The presenters have no relevant financial relationships to disclose.

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