LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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The Use of Biomarkers in Early-Stage NSCLC

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H&O Should patients with early-stage non–small cell lung cancer (NSCLC) get biomarker testing of their surgical specimens?

JK A few years ago, I would have said no because we were not using the information from molecular testing to drive treatment decisions in early-stage NSCLC. The only treatments we were using in these patients at that time were surgery, radiation, and platinum-based doublet chemotherapy. But over the past 3 years, we have seen a revolution in the treatment of early-stage NSCLC that has made molecular testing critical for management. As a result, we should be using biomarker testing to guide treatment to complement surgery.

That change was driven by the results of 3 major phase 3 trials: ADAURA, IMpower010, and CheckMate 816. The double-blind ADAURA trial, which appeared in the *New England Journal of Medicine* in 2020, enrolled patients with stage IB to IIIA NSCLC who had completely resected epidermal growth factor receptor (*EGFR*)-sensitizing mutations. A total of 682 patients were randomly assigned to adjuvant osimertinib (Tagrisso, AstraZeneca) or placebo. At 24 months, the disease-free survival rate was dramatically higher in the osimertinib group than in the placebo group, at 89% vs 52%, respectively. As a result, the US Food and Drug Administration (FDA) approved the use of osimertinib in December 2020 for use as adjuvant therapy in patients with NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 L858R mutations.

The open-label IMpower010 trial, which was published in the *Lancet* in 2021, enrolled patients with resected stage IB to IIIA NSCLC. A total of 1005 patients who had received adjuvant chemotherapy were randomly assigned to atezolizumab (Tecentriq, Genentech) or best supportive care. After a median follow-up of 32.2 months, disease-free survival was significantly better with atezolizumab than with best supportive care among patients with stage II to IIIA NSCLC and programmed death ligand 1 (PD-L1) expression of at least 1%, with a hazard ratio of 0.66. As a result, the FDA approved the use of adjuvant atezolizumab in October 2021 for patients with stage II to IIIA NSCLC who have PD-L1 expression of at least 1%. I am most likely to use atezolizumab for patients who have a high PD-L1 expression level, of 50% or greater.

The open-label CheckMate 816 study, which was published in the *New England Journal of Medicine* in 2022, also enrolled patients with stage IB to IIIA resectable NSCLC. A total of 358 patients were randomly assigned to neoadjuvant nivolumab (Opdivo, Bristol Myers Squibb) plus chemotherapy or chemotherapy alone. In this study, the pathological complete response was dramatically higher in the nivolumab group than in the control group, at 24.0% vs 2.2%, respectively, regardless of PD-L1 expression.

Although the only molecular markers addressed in these studies were *EGFR* mutations and PD-L1 status, the results affect the entire landscape of molecular testing because we know that patients with certain actionable

mutations are less likely to respond to immunotherapy. Data from studies of patients with stage IV NSCLC show that immunotherapy is unlikely to be effective in patients with an anaplastic lymphoma kinase (*ALK*) translocation, a *ROS1* fusion, or a *MET* mutation, for example. Extrapolating from the data on stage IV patients to those with early-stage NSCLC, it makes sense to avoid using immunotherapy in a patient with one of these mutations. In a patient with an *ALK* translocation, for example, I would continue to offer either adjuvant chemotherapy or neoadjuvant therapy using chemotherapy rather than choosing adjuvant immunotherapy or neoadjuvant chemoimmunotherapy. Even if the patient had a high PD-L1 expression, I would not recommend adjuvant immunotherapy. On the other hand, mutations in *KRAS* and *BRAF*, for example, do not affect our decision-making in NSCLC when it comes to the use of immunotherapy. PD-L1 status is the only factor that affects our decision regarding whether to use immunotherapy in that subset of patients with NSCLC.

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H&O Do you use any targeted agents off-label in patients with early-stage NSCLC who have specific mutations?

JK Except for osimertinib, which is FDA-approved for patients in the adjuvant setting who have specific *EGFR* mutations, targeted agents are not approved for patients with early-stage NSCLC. In some situations, however, we may use a targeted agent in the neoadjuvant setting to try to downstage the tumor before surgery. For example, some patients who require a pneumonectomy are very close to being eligible for a lobectomy. In that case, shrinking the tumor with systemic therapy may make a lobectomy possible and we would try to use the most active agents possible. Our choice of treatment may be driven by molecular information, meaning that we would use an ALK inhibitor in a patient with an *ALK* translocation and chemoimmunotherapy rather than chemotherapy alone in a patient who does not have any relevant alterations.

H&O Is biomarker testing especially important for certain patients, such as those who never smoked?

JK We have moved away from the era in which biomarker testing was reserved for those who never smoked. We know that people who never smoked are much more likely to have *EGFR* mutations and *ALK* translocations than those who do smoke, but those alterations are common enough in patients with a history of smoking that NSCLC patients need to be tested regardless of smoking status. From a clinical standpoint, the patients in whom testing makes the biggest difference are those on the more advanced side of early-stage NSCLC, such as those with stage IIIA NSCLC. Treatment decisions are complicated in patients with stage IIIA NSCLC, who may or may not receive surgery. Among patients who do receive surgery, another question is whether neoadjuvant chemotherapy, neoadjuvant chemoimmunotherapy, neoadjuvant chemoradiation, or adjuvant immunotherapy should be used.

H&O Which is preferred, liquid biopsy or solid tumor biopsy?

JK I recommend using both. First, we use liquid biopsy, because the turnaround time tends to be faster and we want to initiate treatment straight away in patients who have a potentially curable lung cancer. If the patient requires surgery first, we want to proceed with that as soon as possible. At the time that we order the liquid biopsy, we also order molecular testing of tumor tissue. We know that liquid biopsies are less sensitive than solid tumor biopsies, especially in patients with earlier-stage disease, because early-stage tumors shed less DNA into the blood. Liquid biopsy is far more likely to miss an *EGFR* mutation, for example, in a stage IB or IIA patient than in a stage IV patient.

Our standard for diagnosis used to be computed tomography-guided needle biopsy, but more than 90% of the patients at City of Hope now have a transbronchial biopsy with robotic-assisted bronchoscopy, typically with a fine needle. The vast majority of the time, we have enough tissue to perform molecular testing.

H&O What prognostic tests are in use for patents with early-stage NSCLC?

JK The FDA-approved prognostic test that we have available is DetermaRx from Oncocyte, which stratifies patients into low-risk and high-risk groups. Although this test is approved to determine the risk of recurrence in patients with IA or IIA NSCLC, we primarily use it in patients with stage IB disease. We generally do not

use adjuvant or neoadjuvant therapy in patients with IA disease because surgery alone is very effective in these patients. By a similar token, the risk of recurrence is high enough in patients with stage IIA disease that we would be hard pressed not to recommend neoadjuvant or adjuvant therapy. The recurrence risk after surgery is intermediate among patients with stage IB disease, although we lack clear data about the benefit these patients can expect to receive from chemotherapy or other systemic agents. Patients with stage IB NSCLC are not all the same; some have larger tumors without lymph node metastasis, whereas other patients are categorized as stage IB because their pathology shows visceral pleural invasion. Subset analyses from earlier randomized trials of adjuvant therapy tell us that patients with stage IB NSCLC based on visceral pleural invasion seem to benefit less from adjuvant chemotherapy than those with other types of stage IB disease. Another study by Woodard and colleagues showed that chemotherapy can reduce recurrence rates among patients with stage IB disease that were categorized as high-risk based on the DetermaRx test.

H&O Is there anything you would like to add?

JK The DYNAMIC study by Tie and colleagues that was published in the *New England Journal of Medicine* in 2022 found that a circulating tumor DNA–guided approach to the treatment of stage II colon cancer allowed for less use of adjuvant chemotherapy without compromising recurrence-free survival. We want to see if the same is true in lung cancer, because we are always looking for ways to avoid chemotherapy when possible.

We are also very excited about the potential for blood-based screenings to detect lung cancer early. We are fairly good at detecting lung cancer in its advanced stage, but earlier-stage tumors are less likely to shed DNA and RNA into the blood. We do not have any FDA-approved screening tests specific for lung cancer at this time, but many of these tests are currently in the clinical trial phase.

Disclosures

Dr Kim has served on the advisory board of AstraZeneca and has received research funding from Eli Lilly through the National Comprehensive Cancer Network.

Suggested Readings

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