LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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The Use of Biomarkers in Advanced, Locally Advanced, and Early-Stage Lung Cancer

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H&O How has biomarker testing evolved differently for early-stage vs advanced lung cancer?

NF We have good data regarding the use of biomarkers for neoadjuvant therapy in advanced non–small cell lung cancer (NSCLC). We are far behind, however, when it comes to biomarker testing in early-stage and metastatic disease. Biomarker testing is essential for patients with early-stage disease, and we do our patients a disservice if we start immunotherapy without biomarker testing.

The IMpower010 trial established the use of adjuvant atezolizumab (Tecentriq, Genentech) in patients with early-stage NSCLC, including those with *ALK* and *EGFR* mutations.[1] The inclusion or exclusion of patients with certain biomarkers varies among trials, ranging from including only patients with *EGFR* and *ALK* mutations to excluding patients with these same mutations, even though patients with other rearrangements (such as *RET*) also derive limited benefit from immunotherapy. For example, the KEYNOTE-671 trial[2] establishing the use of adjuvant pembrolizumab (Keytruda, Merck) and the CheckMate 77T trial[3] establishing the use of perioperative nivolumab (Opdivo, Bristol Myers Squibb) in patients with early-stage NSCLC both excluded patients with *ALK* or *EGFR* mutations. These are just 2 of the 9 mutations that have been identified in lung cancer, and some of the patients in these trials did not receive biomarker testing. Because of blanket approvals based on trials with nonspecific enrollment criteria, we are potentially putting patients on therapy that will not benefit them and carries a risk of adverse events.

Patients often arrive at large cancer centers because after they received neoadjuvant chemoimmunotherapy for early-stage NSCLC, no response was observed in the surgical specimen. Many of these patients end up having their cancer upstaged from the clinical stage at diagnosis. The problem is that in many cases, biomarker testing of the diagnostic specimen is not performed before the patients begin therapy. Testing a specimen after treatment has commenced is too late. It is far better to wait 2 weeks for the results of biomarker testing than to waste months on an ineffective treatment regimen.

H&O Could you explain the emerging role of circulating tumor DNA (ctDNA) across different stages of lung cancer?

NF We have the most data on ctDNA in metastatic *EGFR*-mutated NSCLC. The expert who has conducted the most work in this area is Dr Charu Agarwal, who has shown that ctDNA testing is a very good alternative to biopsy testing in patients with metastatic disease. ctDNA testing allows an earlier detection of biomarkers with a shorter turnaround time than is possible with tissue testing. However, validation is still evolving for the detection of fusions such as those in *ALK* and *NTRK*. We do not know if *NTRK* fusions are genuinely uncommon or whether we are missing this rearrangement because of the diagnostic challenges. Although liquid biopsy is useful

in the metastatic setting, its usefulness in the early-stage setting is more limited.

The LEADER trial is currently looking at the use of tissue and liquid biopsy to determine the proportion of patients with early-stage or locally advanced lung cancers who possess actionable oncogenic drivers, and the trial will assess the feasibility of comprehensive genomic profiling to detect actionable oncogenic drivers in patients with suspected early-stage lung cancers (NCT04712877).

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H&O Beyond the established drivers, such as *EGFR* and *ALK*, which emerging biomarkers show the most promise for clinical application in lung cancer?

NF I would say that *RET* is showing a lot of promise. A phase 3 trial called LIBRETTO-432 is looking at the use of *RET*-targeting therapy in early-stage NSCLC and has just completed enrollment (NCT04819100). The problem with studies in patients with early-stage disease is that they take 5 to 10 years to read out, whereas studies in metastatic disease can produce results in 12 to 36 months. Another important trial that is looking at *RET*-targeting therapy is the phase 2 NAUTIKA1 trial, which is continually being expanded with new arms as other arms close (NCT04302025). This design of this trial allows new arms to be added as new data become available, but the *RET* arm is small, and the results will require further validation in larger studies.

Other biomarkers that show a lot of promise in lung cancer are mutations in *ROS1* and *HER2*. Studies looking at agents to target these mutations are being designed right now.

H&O How should oncologists approach biomarker testing in patients who have insufficient tissue?

NF If the tissue sample is insufficient, the biopsy should be repeated. Even if the situation is very time-sensitive, it is always worthwhile to get the complete biomarker information. This is especially important for patients who are very likely to have a mutation, such as a 42-year-old woman with no tobacco exposure. You do not want to give her chemoimmunotherapy because the chances of a mutation are high. If an actionable mutation is present, she can simply be treated with targeted therapy, much of which is in oral form. Although lung biopsies are challenging, the benefit of finding a target mutation outweighs the risk of the procedure. Still, lung biopsies do carry a unique set of challenges, and the risk of complications is higher than it is with biopsies of other parts of the body, such as the breast.

H&O What biomarker-driven approaches to treatment are showing the potential to convert patients with locally advanced or advanced disease to surgical candidacy?

NF None at this point, although we are looking forward to data from the phase 3 NeoADAURA trial, which is comparing use of the EGFR tyrosine kinase inhibitor osimertinib (Tagrisso, AstraZeneca) as monotherapy or in combination with chemotherapy vs chemotherapy alone for the neoadjuvant treatment of patients with resectable *EGFR*-mutated NSCLC (NCT04351555). Results from this trial will be presented at the 2025 American Society of Clinical Oncology Annual Meeting.

H&O Are any specific biomarkers known that can help predict which patients with early-stage disease will benefit most from adjuvant therapy and which ones might safely avoid it?

NF The use of assays to detect measurable residual disease (MRD) is a good way to learn which patients are more likely to experience disease recurrence after therapy. Dr Tom John of the Peter MacCallum Cancer Centre in Victoria, Australia, is one of the investigators in the ADAURA trial of osimertinib as adjuvant therapy for early and locally advanced *EGFR*-mutated NSCLC. Recently published results from this trial suggest that MRD detection could possibly identify patients who might benefit from the longer use of adjuvant osimertinib.[4]

H&O What immunotherapy markers are in current use, and what immunotherapy markers are promising for the future?

NF We are currently using programmed death ligand 1 (PD-L1) expression, but this is a very limiting biomarker. Several years ago, Dr Aaron Mansfield from the Mayo Clinic showed that PD-L1 expression can be very different

in various sites in the same patient.[5] That is because PD-L1 is a dynamic, not a static, marker that is affected by the microenvironment of the tumor.

Tumor mutational burden has fallen in and out of favor a few times as an immunotherapy biomarker. What I think is the future of immunotherapy biomarkers is not a single gene, but a group of genes—the immune genomic signature. Dr Biagio Ricciuti, who is currently at the Dana-Farber Cancer Institute, has done extensive research on the immunology signature. Why base all your decisions on one marker when you could be looking at a series of markers and patient characteristics to help determine the best treatment? We should have several data points on which to base treatment decisions. It is important to get the treatment right in early-stage disease because we have just one chance of achieving a cure. If the treatment fails and the cancer progresses to stage IV, we no longer have the opportunity for a cure.

H&O How should oncologists interpret and act on serial biomarker changes during immunotherapy across different disease stages?

NF It is unknown whether the treatment plan should be changed on the basis of such changes because we do not have prospectively collected data. At this point, the main considerations that lead me to change a treatment are adverse events and the results of interval scans after the first 2 cycles of chemoimmunotherapy. Adverse events can be severe and lifelong. For example, I had a patient with a complete response to treatment who now has inflammatory joint disease that will likely last for the rest of his life. The balance between curing disease and minimizing side effects is tricky.

H&O What advancements in biomarker technology or testing methodology do you anticipate will most affect the management of lung cancer in the next 3 to 5 years?

NF We are working on an innovative study called EQUAL that recently opened to enrollment (NCT06716580). In this trial, we are using a novel blood assay to try to diagnose *EGFR*-positive lung cancer early in patients without previous tobacco use who therefore do not qualify for lung cancer screening. Feasible, cost-effective assays could represent the future for the diagnosis and monitoring of early-stage lung cancer.

Disclosures

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