LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Advances in Immune Checkpoint Inhibition for Patients With Lung Cancer

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H&O What are the newest indications for checkpoint inhibitors in lung cancer?

HB The newest indication in the neoadjuvant setting is the use of nivolumab (Opdivo, Bristol Myers Squibb) plus platinum-doublet chemotherapy for resectable non–small cell lung cancer (NSCLC), based on the results of CheckMate 816. CheckMate 816 showed that neoadjuvant nivolumab plus chemotherapy resulted in significantly longer event-free survival and more pathological complete responses than chemotherapy alone. This new indication, which was granted in March 2022, represents the first approval for neoadjuvant therapy in early-stage NSCLC.

The newest indication in the adjuvant setting is the use of atezolizumab (Tecentriq, Genentech) with or without chemotherapy in locally advanced programmed death ligand 1 (PD-L1)–positive NSCLC. This indication was granted in November 2021 based on the results of IMpower010. IMpower010 showed that adjuvant atezolizumab led to longer disease-free survival vs best supportive care in patients with resected stage II to IIIA NSCLC. The benefit was pronounced in the subgroup of patients whose tumors expressed PD-L1 on 1% or more of tumor cells.

These approvals represent an overall shift in the use of checkpoint inhibitors in lung cancer. We previously used them only as adjuvant therapy in the metastatic setting, whereas now we can use them as adjuvant therapy in the locally advanced setting and as neoadjuvant therapy in early-stage disease. The fact that we saw such good clinical efficacy with these agents in metastatic disease, combined with a largely manageable side effect profile, is what led to our explorations of checkpoint inhibition in earlier-stage disease. The results of CheckMate 816 and IMpower010 suggest that at least some patients benefit from this approach, and we hope to see cure rates improve as a result. We may also see approvals for additional checkpoint inhibitors and new indications for existing checkpoint inhibitors as data from ongoing studies mature.

H&O How do the results of these 2 studies inform the decision to provide neoadjuvant vs adjuvant therapy?

HB The pros and cons of the neoadjuvant vs the adjuvant approach have been debated in the world of lung cancer for many years. For example, neoadjuvant treatment has the advantage of being shorter, lasting for just 3 cycles or so. It also provides much earlier information about tumor response to a specific regimen. On the other hand, 76% of patients who had surgery after chemotherapy plus nivolumab in CheckMate 816 still had residual tumor, which supports the use of adjuvant therapy. We still do not have the definitive answer as to which approach is best, and the publication of these studies has reignited interest in answering that question. We need more studies to address this issue.

H&O What ongoing trials are you involved with that are looking at the use of checkpoint inhibition in lung cancer?

HB I am the co–principal investigator with Dr Anne Chiang at the Yale Cancer Center of a phase 3 study called INSIGNIA that has National Cancer Institute (NCI) sponsorship and is being conducted by the ECOG-ACRIN Cancer Research Group. For this study, we are randomly assigning patients with metastatic NSCLC to 1 of 3 different arms: (1) first-line pembrolizumab (Keytruda, Merck), followed by pemetrexed/carboplatin in the case of disease progression; (2) first-line pembrolizumab, with the addition of standard chemotherapy to pembrolizumab in the case of disease progression; and (3) first-line pembrolizumab/pemetrexed/carboplatin as per the KEYNOTE-189 study by Gandhi and colleagues. We want to answer a couple of questions. First, what happens if we begin with a checkpoint inhibitor and add chemotherapy at the time of progression? Second, is it better to sequence treatment as immunotherapy followed by chemotherapy, or as chemotherapy followed by immunotherapy? Our goal is to enroll 846 patients, and we are approximately halfway there.

In addition, I am involved in the Lung-MAP study that is looking at multiple targeted and immunotherapy-based agents for use as second-line therapy for patients with recurrent, metastatic NSCLC who were previously treated with a checkpoint inhibitor with or without chemotherapy. As an example of a successful study conducted through Lung-MAP, Dr Karen Reckamp reported data at the 2022 annual meeting of the American Society of Clinical Oncology (simultaneously published online in the *Journal of Clinical Oncology*) showing improved overall survival with the vascular endothelial growth factor (VEGF) inhibitor ramucirumab (Cyramza, Lilly) plus pembrolizumab vs standard of care in a subset of 136 patients who were ineligible for other targeted agents based on biomarkers. This study is also being sponsored by the NCI, along with the SWOG Cancer Research Network.

H&O Are there any other studies of special interest in checkpoint inhibition that you would like to mention?

HB Regarding nivolumab, the phase 3 ANVIL study—which is part of the broader ALCHEMIST protocol—is looking at the use of nivolumab after surgical resection and adjuvant chemotherapy in stage IB to IIIA NSCLC (NCT02595944). Now that ANVIL has completed accrual, we are looking forward to future presentations of data.

Another study of interest is PEARLS, which is also known as KEYNOTE-091 (NCT02504372). This phase 3 study randomly assigned 1177 patients with early-stage NSCLC (IB through IIIA) to receive either pembrolizumab or placebo after surgery, with or without adjuvant chemotherapy. In results that Dr Luis Paz-Ares presented at the March European Society for Medical Oncology (ESMO) Virtual Plenary, disease-free survival at a median of 36 months was significantly better in the pembrolizumab group than in the placebo group, at a median of 53.6 vs 42.0 months (hazard ratio, 0.76; 95% CI, 0.63-0.91; P=.0014). A subgroup analysis revealed that pembrolizumab was beneficial in most subgroups but did not improve outcomes among patients who did not receive adjuvant chemotherapy and those with squamous histology. I was surprised to see that pembrolizumab did not lead to a more pronounced improvement in outcomes among patients with a PD-L1 tumor proportion score of 50% or higher; we will need to see longer-term data in order to know how to interpret that finding.

H&O What makes checkpoint inhibitors more effective in NSCLC than in SCLC?

HB It is true that although checkpoint inhibitors are used frequently in SCLC, the magnitude of benefit is less than in the setting of NSCLC. At this time, we believe that 4 or 5 different subtypes of SCLC exist and that only 1 of these subtypes is sensitive to checkpoint inhibitors. These patients will truly benefit from checkpoint inhibition, whereas other patients need different treatment strategies.

H&O What are the limitations of checkpoint inhibition in lung cancer?

HB We are not helping everybody who receives these drugs. Although the addition of checkpoint inhibition to chemotherapy has been shown to improve PFS, and we have 5-year survival data regarding the use of pembrolizumab monotherapy compared with chemotherapy in patients with high PD-L1 expression, we still need to make more progress. We need to be able to identify the patients who will benefit from checkpoint inhibition, and develop new second-line options for patients who are not benefiting from the currently available checkpoint inhibitors, whether they are used in combination with chemotherapy or with other checkpoint inhibitors.

The side effect profile of checkpoint inhibitors is relatively good. Although side effects are less common with checkpoint inhibitors than with chemotherapy, patients who receive these drugs can experience troubling side effects that have a lasting impact. For example, patients who develop thyroid dysfunction or adrenal dysfunction from checkpoint inhibition may need to take medication for these conditions for the rest of their life. Other patients will require hospitalization. We need to learn how to limit these side effects by developing agents that are better able to activate the immune system against the tumor without affecting the normal organs.

H&O What changes do you see occurring over the next couple of years when it comes to the use of checkpoint inhibition in lung cancer?

HB I hope to see more novel checkpoint inhibitors or other immunotherapy-based options being used in combination with the currently available checkpoint inhibitors, and I hope to see proof of improved overall survival in the metastatic setting. If we can achieve that, we should see studies of new checkpoint inhibitor regimens being used as frontline treatment in locally advanced lung cancer. We would like to build upon the results we have seen in CheckMate 816 and IMpower010 to further improve outcomes.

In addition to novel checkpoint inhibitors, the other immunotherapy options that are being investigated include vaccines and tumor-infiltrating lymphocytes (TILs). TILs are being investigated to alter the tumor microenvironment in patients who have evidence of disease progression during checkpoint inhibition. The goal is to improve outcomes without greatly increasing the risk or severity of side effects. We often need to balance clinical efficacy against risk, bearing in mind the patient's quality of life.

H&O Are there any specific studies on vaccines or TILs that you would like to mention?

HB There are many worthwhile studies of vaccines and TILs in lung cancer. Vaccines may be custom-made or off-the-shelf, and several studies with oncolytic viruses are ongoing. Regarding TILs, a phase 1 study by Dr Ben Creelan and colleagues at the Moffitt Cancer Center that was published in 2021 looked at the use of TILs plus nivolumab in 20 patients with metastatic NSCLC following initial progression on nivolumab monotherapy. Among 13 evaluable patients, 3 had a confirmed response and 11 had a reduction in tumor burden. Two patients had complete responses that persisted 1.5 years later. As promising as these results are, they underscore that this approach will not work in all our patients. Our task is to try to identify which patients can benefit from these treatments. This is much harder than it sounds because the science of doing biomarker research and identifying patients ahead of time who will benefit from a specific treatment usually lags behind development of the treatment. There are multiple approaches that are interesting and worth pursuing, but it will take several years before we have good data to tell us which approach to use for a certain patient.

One factor that has caused delays in research is COVID, because many of the centers had fewer patients available to screen for studies. Although some staffing challenges remain across the country, most clinical trials are once again running at their original speed, or close to it. Participating in a clinical trial is not an easy decision for patients and caregivers, but many of our patients realize that what we use now as a standard of care was once experimental. Although the past couple of years have been exceptionally difficult, I encourage my colleagues to get back into the mindset of enrolling patients in clinical studies. We are all in this together.

Disclosure

Dr Borghaei has received research support from BMS/Lilly and Amgen; has served on the advisory board of or as a consultant for BMS, Lilly, Genentech, Pfizer, Merck, EMD Serono, Boehringer Ingelheim, AstraZeneca, Novartis, Genmab, Regeneron, BioNTech, Amgen, Axiom, PharmaMar, Takeda, Mirati, Daiichi Sankyo, Guardant, Natera, Oncocyte, BeiGene, iTeos Therapeutics, Jazz Pharmaceuticals, Janssen, and Da Volterra; has served on the data and safety monitoring board of the University of Pennsylvania's CAR T-cell program, Takeda, Incyte, and Novartis; has served on the scientific advisory board of and received stock options from Sonnet BioTherapeutics, Inspirna (formerly Rgenix), and Nucleai; has received honoraria from Amgen, Pfizer, and Daiichi Sankyo; and has received travel reimbursement from Amgen, BMS, Merck, Lilly, EMD Serono, and Genentech.

Suggested Readings

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