LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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What's Next for Immunotherapy in Locally Advanced NSCLC?

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H&O Which immunotherapy agents have been approved for use in locally advanced non–small cell lung cancer?

NR Durvalumab (Imfinzi, AstraZeneca) is the only agent to have received approval so far in locally advanced non–small cell lung cancer (NSCLC). Approval was based on the improvements in both progression-free survival (PFS) and overall survival (OS), with a relatively minimal increase in toxicity, demonstrated in the landmark PACIFIC trial. The results of this trial established standard chemoradiotherapy followed by durvalumab maintenance for 1 year as the new standard of care in unresectable stage III NSCLC. One of the concerns with immunotherapy is inflammation, which is why PACIFIC excluded patients who had an autoimmune disease or uncontrolled medical condition. Fortunately, the use of immunotherapy following radiation to the lung did not cause excessive lung toxicity, and the therapeutic index clearly favors the use of durvalumab in locally advanced NSCLC.

PACIFIC came after 20 years of attempts to improve on results with the standard chemoradiotherapy backbone. Approaches such as giving chemotherapy either before or after chemoradiotherapy and boosting the dose of radiation were all without success, so this trial was clearly a step forward.

H&O What other important trials are looking at the use of immunotherapy following chemoradiation in locally advanced NSCLC?

NR A whole family of trials is looking to build on the results of PACIFIC by studying the addition of other agents to immunotherapy and chemoradiation in locally advanced NSCLC. For example, the phase 3 KEYLYNK-012 trial from Merck is examining the use of pembrolizumab (Keytruda, Merck) at the time of radiation and chemotherapy, followed by additional pembrolizumab with or without the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib (Lynparza, AstraZeneca). Similar trials are looking at the use of nivolumab (Opdivo, Bristol Myers Squibb), atezolizumab (Tecentriq, Genentech), and other agents in the same manner.

H&O Which trials are looking at concurrent immunotherapy and chemoradiation?

NR The phase 3 PACIFIC-2 trial is examining the concurrent administration of durvalumab with the standard chemoradiotherapy backbone (NCT03519971), and similar phase 3 trials are being carried out with pembrolizumab, nivolumab, and atezolizumab.

The results with immunotherapy alone in locally advanced NSCLC are dramatic and have a tremendous potential to teach us about the mechanisms of immune sensitivity and immune resistance, but the approach that will probably change the standard of care for patients with potentially resectable stage III lung cancer is chemotherapy plus adjuvant or neoadjuvant immunotherapy.

H&O Can you discuss the trials looking at immunotherapy as neoadjuvant therapy in locally advanced NSCLC?

NR In a phase 2 study that appeared in the *New England*

Journal of Medicine in 2018, Forde and colleagues found a high response rate when 2 doses of nivolumab were given before surgery. We were surprised to see a major pathologic response to treatment in many of the tumors. Here at Duke, we conducted a trial in which neoadjuvant pembrolizumab was used, and I presented the results at the IASLC 2019 World Conference on Lung Cancer.

In another phase 2 trial, called NEOSTAR, Cascone and colleagues at MD Anderson found a higher response rate with the combination of ipilimumab (Yervoy, Bristol Myers Squibb) and nivolumab than with nivolumab alone in 44 patients who had operable NSCLC. The LCMC3, PRINCEPS, and AFT-16 trials all examined neoadjuvant atezolizumab, and the IONESCO trial examined neoadjuvant durvalumab (NCT03030131).

In all of the neoadjuvant trials that I have just mentioned, we saw reductions of at least 90% in the amount of viable tumor in a significant number of patients. Some patients had complete pathologic responses after only a few weeks of immune therapy, which is absolutely amazing.

Finally, we have 4 large randomized trials ongoing, with 360 to 800 patients enrolled in each, that are looking at the addition of immunotherapy to chemotherapy before surgery. The results of these trials will affect the standard of care for patients with locally advanced NSCLC who potentially could go to surgery. CheckMate 816 is studying chemotherapy with or without nivolumab, KEYNOTE-671 chemotherapy with or without pembrolizumab, IMpower030 chemotherapy with or without atezolizumab, and AEGEAN chemotherapy with or without durvalumab. So far, the response rates to chemotherapy plus immunotherapy are truly impressive. In results from CheckMate 816, which Forde presented at the 2021 American Association for Cancer Research Annual Meeting, the pathologic complete response rate increased from 2.2% with chemotherapy alone to 24.0% with the addition of nivolumab. We were expecting to see excellent results on the basis of phase 2 trials, such as the nonrandomized study by Shu and colleagues that appeared in *Lancet Oncology* in 2020 and showed a major pathologic response rate of 57% and a pathologic complete response rate of 33%. The results of CheckMate 816 are even better than we were expecting, however.

H&O Can immunotherapy be used in place of chemotherapy?

NR Not at this point. In the future, we may become good enough at evaluating predictors of a response to immunotherapy that we will be able to identify patients who do not need chemotherapy added to their treatment for locally advanced lung cancer, but we are not there yet. In the meantime, the use of immunotherapy alone, as either neoadjuvant or adjuvant therapy, should be reserved for clinical trials.

> The approach that will probably change the standard of care for patients with potentially resectable stage III lung cancer is chemotherapy plus adjuvant or neoadjuvant immunotherapy.

H&O How do factors such as programmed death ligand 1 (PD-L1) expression and *EGFR* mutations affect response to immunotherapy?

NR We know that tumors with *EGFR* mutations may respond to EGFR-targeting therapies, such as osimertinib (Tagrisso, AstraZeneca), erlotinib, gefitinib (Iressa, AstraZeneca), and afatinib (Gilotrif, Boehringer Ingelheim), whereas tumors without these mutations do not respond at all. Tumors with *EGFR* mutations are much less likely than those without them to respond to immunotherapy, however. This is consistent with the fact that people who have *EGFR*-mutated lung cancers are more likely to be nonsmokers, and nonsmokers are less likely to respond to immunotherapy. Patients with *EGFR*-mutated lung cancers also are much more likely to have low-level or nonexistent PD-L1 expression, which decreases the likelihood of a response to immunotherapy. A lack of PD-L1 expression does not preclude a response to immunotherapy, however. We have all had patients with PD-L1 expression of less than 1%, yet their tumors melted during immune checkpoint therapy. Conversely, some patients with PD-L1 expression of 90% or higher do not respond to immunotherapy.

H&O What are some of the disadvantages and challenges of using immunotherapy?

NR We know that immunotherapy can cause immune-related toxicities that are similar to autoimmune diseases, such as lupus, psoriasis, colitis, rheumatoid arthritis, and

interstitial pulmonary disease. Immunotherapy may also affect the thyroid gland, causing a boost followed by a reduction in thyroid function. Even though the toxicity of immunotherapy in lung cancer is significantly less than that of chemotherapy, a severe toxicity will develop in approximately 1 of 10 patients, making it necessary to halt treatment and use corticosteroids to calm down the immune system. Approximately 1% or 2% of patients will have a life-threatening toxicity, and a few patients will die of complications of the immunotherapy. Another consideration is "financial toxicity"; immunotherapy is extraordinarily expensive, and even a co-pay may be thousands and thousands of dollars.

H&O To sum up, what would you say is the future role of immunotherapy in the treatment of locally advanced NSCLC?

NR Now that we have established maintenance durvalumab as an exciting new standard of care after chemoradiotherapy, numerous trials are looking to build on that by adding immunotherapy to chemoradiotherapy, and by adding agents to immunotherapy after chemoradiotherapy.

For patients who have locally advanced NSCLC that is potentially surgically resectable, the standard of care at this time is either preoperative or postoperative chemotherapy. The initial results of phase 2 trials that include PD-1 checkpoint immune therapy have shown dramatic improvements in tumor pathologic response rates in comparison with historical chemotherapy controls. We do not yet know whether these exciting, dramatic results, with major pathologic responses in a majority of patients and many complete responses, will translate into improved OS. Will this approach eradicate microscopic cancer, or just suppress it for a while? We do not know, which is why we need to do the trials. Fortunately, we have good reason to be optimistic that the results of phase 3 trials will be positive, and that our next standard of care will be chemotherapy with immune therapy.

Disclosure

Dr Ready has served as a paid advisor for AstraZeneca, BMS, Merck, Novartis, G1 Therapeutics, EMD Serono, Tesaro, Roche, and Genentech; has received research funding from BMS and Merck; and has served as an unbranded speaker for BMS.

Suggested Readings

Antonia SJ, Villegas A, Daniel D, et al; PACIFIC Investigators. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377(20):1919-1929.

Antonia SJ, Villegas A, Daniel D, et al; PACIFIC Investigators. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379(24):2342-2350.

Besse B, Adam J, Cozic N, et al. Neoadjuvant atezolizumab (A) for resectable non-small cell lung cancer (NSCLC): results from the phase II PRINCEPS trial [ESMO abstract 1215O]. 2020;31(5)(suppl).

Cascone T, William WN Jr, Weissferdt A, et al. Neoadjuvant nivolumab or nivolumab plus ipilimumab in operable non-small cell lung cancer: the phase 2 randomized NEOSTAR trial. *Nat Med*. 2021;27(3):504-514.

Fernando HC, Yang J, Ferraro GL, et al. Randomized, double-blind phase 3 study evaluating neoadjuvant platinum-based chemotherapy with perioperative pembrolizumab or placebo in resectable stage IIB or IIIA NSCLC: KEYNOTE-671. *J Clin Oncol*. 2018;36(15)(suppl).

Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. *N Engl J Med*. 2018;378(21):1976-1986.

Forde PM, Spicer J, Lu S, et al. Nivolumab + platinum-doublet chemotherapy vs chemotherapy as neoadjuvant treatment for resectable (Ib-IIIa) non-small cell lung cancer in the phase III CheckMate 816 trial. Presented at: American Association for Cancer Research Annual Meeting; April 10-15; Virtual. Abstract CT003.

Heymach J, Taube J, Mitsudomi T, et al. The AEGEAN phase 3 trial of neoadjuvant/adjuvant durvalumab in patients with resectable stage II/III NSCLC [IASLC abstract P1.18-02]. *J Thorac Oncol*. 2019;14(10)(suppl).

Lee JM, Chaft J, Nicholas A, et al. Surgical and clinical outcomes with neoadjuvant atezolizumab in resectable stage IB–IIIB NSCLC: LCMC3 trial primary analysis. Presented at: World Conference on Lung Cancer; January 28-31, 2021; Virtual. Abstract PS02.05.

Peters S, Kim AW, Solomon B, et al. IMpower030: Phase III study evaluating neoadjuvant treatment of resectable stage II-IIIB non-small cell lung cancer (NSCLC) with atezolizumab (atezo) + chemotherapy [ESMO abstract 82TIP]. *Ann Oncol*. 2019;30(2)(suppl).

Ready N, Tong B, Clarke J, et al. Neoadjuvant pembrolizumab in early stage non-small cell lung cancer: toxicity, efficacy, and surgical outcomes. Poster presented at: World Conference on Lung Cancer; September 7-9, 2019; Barcelona, Spain. Abstract P2.04-89.

Ross HJ, Kozono DE, Urbanic JJ, et al. AFT-16: phase II trial of atezolizumab before and after definitive chemoradiation (CRT) for unresectable stage III non-small cell lung cancer (NSCLC) [ASCO abstract 9045]. *J Clin Oncol*. 2020;38(15)(suppl).

Shu CA, Gainor JF, Awad MM, et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2020;21(6):786-795.

Wislez M, Mazieres J, Lavole A, et al. Neoadjuvant durvalumab in resectable non-small cell lung cancer (NSCLC): preliminary results from a multicenter study (IFCT-1601 IONESCO) [ESMO abstract 1214O]. *Ann Oncol*. 2020;31(4)(suppl).