

LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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The Use of Immunotherapy in the First-Line Treatment of Lung Cancer



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H&O How does immunotherapy in lung cancer work?

NR There has been tremendous recent progress in the understanding of how immunotherapy works in lung cancer. The immune system should recognize alterations in the genetic code within tumor cells as foreign, and eradicate these abnormal cells through immune surveillance. However, chronic exposure to tobacco carcinogens and accumulation of mutations over time eventually can lead to T-cell exhaustion and trigger T cells to turn off. This is manifested through the upregulation of programmed death ligand 1 (PD-L1) on tumor cells, which can inhibit T-cell function by binding to programmed death 1 (PD-1) on T cells.

Expression of PD-L1 and the mutational load both correlate with the likelihood of response to immune checkpoint blockade. Immune checkpoint inhibitors restore the ability of T cells to recognize mutations by blocking the interaction between PD-L1 on tumor cells and PD-1 on T cells. T cells are then able to activate, recognize the cancer cells as foreign, and destroy them.

H&O Which immunotherapeutic agents are used in lung cancer?

NR Nivolumab (Opdivo, Bristol-Myers Squibb), a PD-1 antibody, is approved in the second-line setting after platinum-based doublet chemotherapy in non-small cell lung cancer (NSCLC), both squamous and nonsquamous. Pembrolizumab (Keytruda, Merck), another PD-1 anti-

body, is approved in the second-line setting for tumors that express at least 1% PD-L1, which represents approximately 75% of patients with lung cancer.

In October 2016, pembrolizumab was approved in the first-line setting, for patients with NSCLC who have more than 50% PD-L1 expression. These patients represent approximately 30% of cases. Approval in the first-line setting was based on the KEYNOTE-024 trial (Study of Pembrolizumab [MK-3475] Compared to

Our research has shown that the mutational landscape, in particular the mutational burden and signature associated with tobacco smoking, can dictate a response to PD-1 therapy.

Platinum-Based Chemotherapies in Participants With Metastatic Non-Small Cell Lung Cancer), which showed very positive data for pembrolizumab as compared with platinum-based doublet chemotherapy. The response rate was 45% with pembrolizumab vs 28% with chemotherapy. Progression-free survival was 10 months with

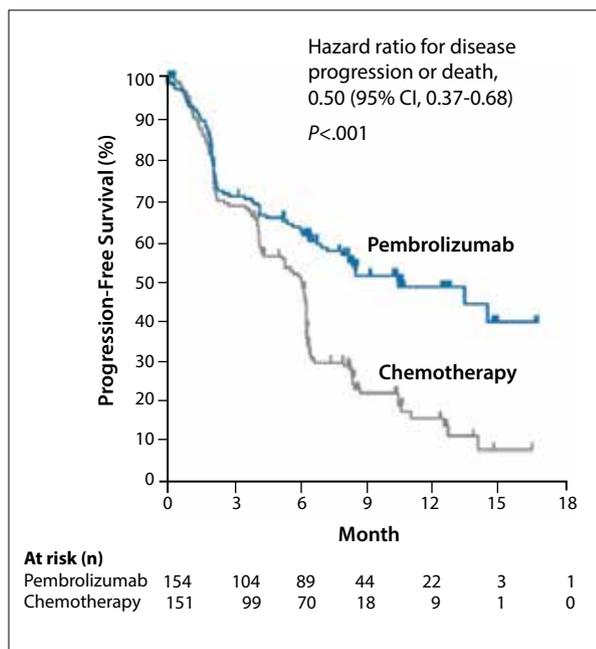


Figure 1. Progression-free survival in the phase 3 KEYNOTE-024 trial, which compared pembrolizumab vs investigator's choice of platinum-based chemotherapy in patients with non-small cell lung cancer positive for programmed death ligand 1. KEYNOTE-024, Study of Pembrolizumab [MK-3475] Compared to Platinum-Based Chemotherapies in Participants With Metastatic Non-Small Cell Lung Cancer.

Adapted from Reck M et al. *N Engl J Med.* 2016;375(19):1823-1833.

pembrolizumab vs 6 months with chemotherapy (Figure 1). Overall survival was also significantly improved with pembrolizumab vs chemotherapy.

Atezolizumab (Tecentriq, Genentech), another PD-L1 antibody, was approved in October 2016 for patients with NSCLC who were previously treated with platinum-doublet chemotherapy.

H&O How do immunotherapies compare with chemotherapies?

NR A major difference between immunotherapy and chemotherapy is in long-term survival. The longest follow-up is with nivolumab, which shows a 3-year survival of approximately 20%. In contrast, long-term survival is negligible with chemotherapy.

Toxicity profiles are also different. The traditional adverse events seen with chemotherapy include myelosuppression, neuropathy, alopecia, gastrointestinal fatigue, nausea, and vomiting. Immunotherapy is associated

with immune-related adverse events, such as rash, diarrhea, gastrointestinal toxicity, and pulmonary toxicity. In general, there are far fewer toxicities with immunotherapy than with chemotherapy. In clinical trials, there were significantly fewer grade 3 and 4 toxicities with immunotherapy than chemotherapy.

H&O Does immunotherapy work differently in the first-line and subsequent settings?

NR We do not yet know whether these agents work more favorably in the first-line or second-line settings. In general, the first-line data show very high response rates with single-agent PD-1 antibodies (eg, pembrolizumab), as well as with immunotherapy combinations (eg, ipilimumab [Yervoy, Bristol-Myers Squibb] plus nivolumab) and chemotherapy combined with pembrolizumab. Intriguingly, in the KEYNOTE-024 trial, the complete response rate with first-line pembrolizumab (in tumors $\geq 50\%$ PD-L1) was approximately 10%. In contrast, in the second- or third-line settings, complete responses are infrequently seen with immune checkpoint blockade in NSCLC.

H&O Is there a potential for synergy with combination therapy?

NR The most mature data are for PD-1/PD-L1 inhibitors in combination with cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, such as ipilimumab. In patients with melanoma, the combination of ipilimumab and nivolumab has been shown to be superior to either ipilimumab or nivolumab alone. In lung cancer, the preliminary evidence, particularly with nivolumab and ipilimumab, showed higher response rates with the combination regimen. PD-1/PD-L1 inhibitors and CTLA-4 inhibitors have different mechanisms of action. PD-1 functions more within the tumor microenvironment, and CTLA-4 functions more in the nodal compartments. There is the potential for synergy between these 2 therapies.

H&O What is your clinical experience with immunotherapy in lung cancer?

NR The first evidence that immunotherapy could be effective in lung cancer was seen in 2008. I started to participate in phase 1 trials with nivolumab in 2009. We were excited to see any activity with immunotherapy agents in lung cancer because the previous immunotherapeutic approaches, such as vaccines, had not shown benefit. Since then, there has been rapid approval of multiple agents in a very short time, which speaks to the activity of these agents.

H&O Are the immunotherapies used in lung cancer associated with heart damage?

NR Immunotherapies can lead to activation of the immune system against any organ in the body, and toxicities can occur anywhere. In general, however, the percentage of patients who experience a serious immune-related adverse event is very low.

H&O What has your research into the genomic determinants of response to this therapy shown?

NR Our research has shown that the mutational landscape, in particular the mutational burden and signature associated with tobacco smoking, can dictate a response to PD-1 therapy. Efforts now are trying to characterize this association further, and to determine whether there are certain characteristics to those mutations. These tumors may be more clonal in nature, as was demonstrated in a recent study published in *Science*. At this point, we are expanding our efforts to test more patients' tumors for mutational burden. The mutational signature is likely to be a complement of mutational burden, PD-L1 expression, and other potential immune signatures that could

be used in concert to more clearly define the kinds of patients who might benefit from PD-1 therapy.

Disclosure

Dr Rizvi is a consultant for Roche, AstraZeneca, Pfizer, Lilly, Merck, Novartis, and BMS. He is a cofounder and shareholder of Gritstone Oncology.

Suggested Readings

Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *Lancet Oncol.* 2017;18(1):31-41.

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