LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Immunotherapy in Patients Who Have NSCLC Without *EGFR* or *ALK* Mutations

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H&O What made you and your colleagues decide to undertake the KEYNOTE-189 trial?

LG KEYNOTE-189 (Study of Pemetrexed + Platinum Chemotherapy With or Without Pembrolizumab in Participants With First Line Metastatic Nonsquamous Non-small Cell Lung Cancer) looked at adding immunotherapy to chemotherapy in the first-line treatment of patients who have advanced non–small cell lung cancer (NSCLC) without actionable mutations. We undertook this trial for 2 reasons. First, the benefits of chemotherapy alone in these patients are modest. Second, only a small subset—approximately 20%—of patients with NSCLC benefit from immunotherapy as a single agent. Given the disappointing results with chemotherapy alone and immunotherapy alone, we wanted to see if chemotherapy could make tumors more immunogenic and responsive to a programmed death 1 (PD-1) inhibitor like pembrolizumab (Keytruda, Merck). Pemetrexed (Alimta, Lilly) and platinum have been shown to decrease myeloid-derived suppressor cells (MDSCs), enhance T-cell activation, and promote the T-cell infiltration of tumors.

H&O Can you describe the design of the KEYNOTE-189 trial?

LG KEYNOTE-189 is a randomized, placebo-controlled trial that was conducted in 16 countries. The majority of the sites were in Europe. We randomly assigned 616 patients with metastatic nonsquamous NSCLC in a 2:1 ratio to receive either standard platinum/pemetrexed chemotherapy plus pembrolizumab or platinum/pemetrexed plus placebo. Patients with *EGFR* or *ALK* mutations, who are candidates for oncogene-directed therapy, were excluded from the trial. Crossover from the chemotherapy/placebo arm to the chemotherapy/pembrolizumab arm was allowed if confirmed progression occurred. The primary endpoints were overall survival (OS) and progression-free survival (PFS).

H&O What did you and your colleagues find?

LG We saw an improvement in OS with pembrolizumab vs placebo. The estimated OS rate at 12 months was 69.2% in the pembrolizumab group vs 49.4% in the placebo group (hazard ratio [HR] for death, 0.49; 95% CI, 0.38-0.64; $P<.001$). OS was longer in the pembrolizumab group than in the placebo group in patients with all levels of programmed death ligand 1 (PD-L1) expression, including those with a PD-L1 tumor proportion score of less than 1% (Table).

PFS was also better in the pembrolizumab group than in the placebo group, at 8.8 vs 4.9 months, respectively (HR for disease progression or death, 0.52; 95% CI, 0.43-0.64; $P<.001$). In addition, response rates were better in the pembrolizumab group than in the placebo group, at 47.6% vs 18.9%, respectively ($P<.001$).

The adverse events were consistent with what we expect to see during treatment with PD-1 inhibitors and with chemotherapy; no new toxicities or synergistic effects occurred. The possible exception was a slightly higher risk for nephritis and renal events with the addition of pembrolizumab. This is not surprising because platinum, pemetrexed, and pembrolizumab all can be renally toxic. The incidence of nephritis in this study was 1.7% in the pembrolizumab group, which is still low. Other studies of pembrolizumab in combination with chemotherapy have found a nephritis rate of approximately 0.4%.

Table. Subgroup Analysis of Overall Survival for PD-L1 Tumor Proportion Score

PD-L1 Tumor Proportion Score	No. of Events/ No. of Patients	Hazard Ratio for Death (95% CI)
<1%	84/190	0.59 (0.38-0.92)
≥1%	135/388	0.47 (0.34-0.66)
1%-49%	65/186	0.55 (0.34-0.90)
≥50%	70/202	0.42 (0.26-0.68)

Data from Gandhi L et al. *N Engl J Med*. 2018;378(22):2078-2092.
PD-L1, programmed death ligand 1.

H&O Were you surprised to see that pembrolizumab improved survival even among the patients who had a low PD-L1 tumor proportion score?

LG No, but the magnitude of benefit across the board was surprising. The group that had the highest level of PD-L1 expression definitely derived the greatest benefit, but the OS benefit was significant among all the groups. A trend toward improved PFS with pembrolizumab was observed in the patients who had PD-L1 expression of less than 1%, but the difference was not statistically significant. This may be attributed to the fact that this was an interim analysis, and a lot of censoring occurred. The numbers may change over time; the patients in the study will be followed for the rest of their lives.

H&O Is chemotherapy required for pembrolizumab to be effective in these patients, or could pembrolizumab be used as monotherapy?

LG Pembrolizumab monotherapy is not superior to chemotherapy in those with PD-L1 expression of less than 50%. In the KEYNOTE-042 study (Study of MK-3475 Versus Platinum-based Chemotherapy for Participants With PD-L1-positive Advanced or Metastatic Non-small Cell Lung Cancer), which Dr Gilberto Lopes recently presented at the American Society of Clinical Oncology (ASCO) annual meeting, OS was longer with pembrolizumab alone than with chemotherapy alone in patients who had metastatic NSCLC with PD-L1 expression of at least 1%, but all the benefit in this study was driven by the patients with high levels of PD-L1 expression, for whom pembrolizumab monotherapy is already standard. A cooperative group study that has just begun is addressing whether combination therapy is better than sequential therapy starting with pembrolizumab or sequential therapy starting with chemotherapy.

H&O Are the results of KEYNOTE-189 changing the way patients are treated?

LG Yes, they are. Although the US Food and Drug Administration (FDA) approved this regimen on the basis of results of the phase 2 trial, it did not become widely used. Now that we have definitive phase 3 data, we are seeing an immediate change in practice. I expect this effect to be temporary, however, because many other studies are ongoing that may eliminate the use of chemotherapy in the first-line setting for even larger groups of patients.

H&O What other studies are looking at the use of checkpoint inhibitors in patients who have metastatic NSCLC without actionable mutations?

LG Hundreds of studies are looking at that question, including many that were presented at the ASCO meeting. These studies are looking at immunotherapy combinations, such as nivolumab (Opdivo, Bristol-Myers Squibb) plus ipilimumab (Yervoy, Bristol-Myers Squibb), and at various chemotherapy regimens in combination with immunotherapy.

H&O What would you say is the next step in the research on checkpoint inhibitors in metastatic NSCLC?

LG We need to develop reliable biomarkers to let us know early on whether a particular combination is working. The better the biomarkers, the better positioned we will be to target treatment to individual patients.

Disclosure

Dr Gandhi has served as a consultant (advisory board member) for Merck, Genentech/Roche, AstraZeneca, Syndax, and Ignyta. She has received research funding from the Bristol-Myers Squibb International Immuno-Oncology Network and Merck.

Suggested Readings

Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al; KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078-2092.

Lopes G, Wu YL, Kudaba I, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. Presented at: 2018 ASCO Annual Meeting; June 1-5, 2018; Chicago, IL. LBA4.