Frontline Pembrolizumab with Chemotherapy Improves Survival in Phase III Non Squamous NSCLC Trial

Jason M. Broderick @jasoncology

Published: Tuesday, Jan 16, 2018

Roger M. Perlmutter, MD, PhD

Combining pembrolizumab (Keytruda) with chemotherapy in the frontline setting improved survival in patients with nonsquamous non–small cell lung cancer (NSCLC), according to findings from the phase III KEYNOTE-189 trial.

In KEYNOTE-189, patients received frontline pembrolizumab or placebo in combination with pemetrexed (Alimta) and either cisplatin or carboplatin. The study met the coprimary endpoints of improved overall survival (OS) and progression-free survival (PFS). Merck, the manufacturer of pembrolizumab reported in a press release that the data from the trial will be shared at an upcoming medical meeting.

The KEYNOTE-189 study is a confirmatory trial for the accelerated approval of pembrolizumab in this setting. In May 2017, the FDA granted an accelerated approval to pembrolizumab (Keytruda) for use in combination with pemetrexed plus carboplatin as a frontline treatment for patients with metastatic or advanced nonsquamous NSCLC, regardless of PD-L1 expression.

“KEYNOTE-189 showed significant improvement in overall survival and progression-

free survival for patients receiving Keytruda in the first-line setting in combination with traditional chemotherapy, compared with those receiving chemotherapy alone," **Roger M. Perlmutter, MD, PhD, president, Merck Research Laboratories**, said in a statement. "We are deeply grateful to the KEYNOTE-189 patients and investigators for their important contributions to this landmark study, and we look forward to presenting the data in the near future."

The double-blind phase III KEYNOTE-189 study accrued 614 patients with advanced or metastatic nonsquamous NSCLC, regardless of PD-L1 expression. Patients were not EGFR- or ALK-positive, and had received systemic therapy for advanced disease. The trial randomization was 2:1 in favor of the pembrolizumab arm.

In the experimental arm, patients received pembrolizumab at a 200 mg fixed dose every 3 weeks plus 500 mg/m2 of pemetrexed plus either 75 mg/m2 of cisplatin or carboplatin (AUC 5) on day 1 every 3 weeks for 4 cycles, followed by 200 mg of pembrolizumab plus 500 mg/m2 of pemetrexed every 3 weeks. The regimen administered to the control group was identical, except that pembrolizumab was replaced with placebo.

Treatment was administered until disease progression, unacceptable toxicity, physician decision, or consent withdrawal. Patients in the control arm with disease progression were allowed to cross over to receive pembrolizumab. Beyond the primary OS and PFS endpoints, secondary endpoints included overall response rate (ORR) and duration of response. There were no new safety signals reported for pembrolizumab beyond outcomes previously reported for the PD-1 inhibitor.

The accelerated approval for the frontline pembrolizumab regimen in NSCLC was based on part 2 of cohort G in the KEYNOTE-021 trial, in which the pembrolizumab triplet elicited an ORR of 55% compared with 29% with the chemotherapy agents alone (*P* = .0032). The median PFS was 13.0 months with the addition of pembrolizumab versus 8.9 months for chemotherapy alone (HR, 0.53; 95% CI, 0.31-0.91; *P* = .0205).

In the open-label phase II KEYNOTE-021 cohort study, 123 patients were randomized to receive pemetrexed and carboplatin alone (n = 63) or in combination with pembrolizumab (n = 60). In both groups, carboplatin was given at AUC 5 mg/mL per min and pemetrexed was given at 500 mg/m2 every 3 weeks for 4 cycles followed by indefinite pemetrexed maintenance. In the investigational arm, pembrolizumab was continued for 24 months.

The baseline characteristics were balanced between the 2 arms. The average age of

participants was 62.5 years in the pembrolizumab group versus 63.2 years for the control arm. The ECOG performance status was 0 (40% vs 46%) and 1 (58% and 54%) for those in the pembrolizumab and control arms, respectively. Eighteen percent of those in the pembrolizumab arm were of non-white ethnic origin compared with 8% in the control arm. Additionally, 25% of those in the pembrolizumab arm were never smokers versus 14% in the control group.

After 10.6 months of follow-up, 88% of those in the pembrolizumab arm remained alive and progression free compared with 78% for the chemotherapy agents alone. The median time to response was 1.5 months with pembrolizumab compared with 2.7 months for the chemotherapy agents alone. Overall, a response of at least 6 months was seen for 92% of patients in the pembrolizumab group compared with 81% of those in the control arm.

The 6-month PFS rate was 77% with pembrolizumab (95% CI, 64-86) compared with 63% for chemotherapy alone (95% CI, 49-74). At the time of the analysis, 78% of patients remained alive in each arm, with no discernible differences in survival between the two groups (HR, 0.90; 95% CI, 0.42-1.91; $P = .39$). The 6-month OS was 92% in both arms. However, this analysis was likely confounded by crossover, since 74% of patients in the chemotherapy alone arm went on to receive a subsequent PD-1 or PD-L1 inhibitor compared with none in the pembrolizumab arm.

In assessments of PD-L1 staining, those with expression of less than 1% had an ORR of 57% with the pembrolizumab combination (12 of 21) compared with 13% in the chemotherapy arm (3 of 23). In those with expression on greater than 1% of cells, the ORR was 54% with pembrolizumab and chemotherapy (21 of 39) compared with 38% in the chemotherapy-alone arm. The ORRs were 80% and 35% in those with ≥50% expression for the pembrolizumab (16 of 20) and chemotherapy arms (6 of 17), respectively.

Frequently observed all-grade treatment-related adverse events (AEs) in the pembrolizumab and chemotherapy arms, respectively, included fatigue (71% vs 50%), nausea (68% vs 56%), constipation (51% vs 37%), rash (42% vs 21%), vomiting (39% vs 27%), dyspnea (39% vs 21%), diarrhea (37% vs 23%), and decreased appetite (31% vs 23%). AEs led to treatment discontinuations for 10% of those in the pembrolizumab arm versus 13% in the control group.

The most common grade ≥3 treatment-related AEs were decreased lymphocytes (23% with pembrolizumab vs 28% with chemotherapy alone), hemoglobin decreased (17% vs 19%), decreased neutrophil count (14% vs 8%), and platelets decreased (9% vs 10%).