Clinical outcomes and their correlation with gene expression in patients with advanced gastric cancer treated with pembrolizumab (MK-3475): KEYNOTE-012


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Introduction: PD-1 is a negative costimulatory receptor expressed on the surface of activated T cells. PD-1 binds to its ligands, PD-L1 and PD-L2, and inhibits effector T-cell function. Tumors, including gastric cancer, frequently overexpress PD-L1, and thereby suppress antitumor immunity. Pembrolizumab is a humanized monoclonal antibody against PD-1 that has demonstrated antitumor activity and a manageable safety profile in several advanced cancers. In the phase 1b KEYNOTE-012 study (NCT01848834), we previously showed that pembrolizumab provides robust antitumor activity and manageable toxicity in advanced gastric cancer. Here, we provide results for patients enrolled in Asia-Pacific (AP) and the rest of the world (ROW), and results from prespecified exploratory analyses of the relationship between immune-related gene expression signatures and outcomes.

Methods: Key eligibility criteria were recurrent or metastatic adenocarcinoma of the stomach or gastroesophageal junction, ECOG PS of 0-1, measurable disease per RECIST v1.1, and PD-L1 expression in ≥1% of cells in tumor nests or distinctive stromal staining using a prototype IHC assay with the 22C3 antibody. An equal number of patients from AP and ROW were to be enrolled. Patients received pembrolizumab 10 mg/kg every 2 weeks for up to 24 months or until confirmed disease progression or unacceptable toxicity. Response was assessed every 8 weeks per RECIST v1.1 by central review. The relationship between clinical outcomes and 4 prespecified RNA-based immune-related gene expression signatures that were constructed based on analyses of melanoma tumor samples and measured by the NanoString nCounter system was also assessed.

Results: Overall, 39 patients enrolled (n = 19 from AP, n = 20 from ROW). ORR was 22% (95% CI, 10-39) overall (23% [95% CI, 7-50] for AP and 21% [95% CI, 6-46] for ROW), with a median response duration of 40 weeks (range, 20+ to 48+). 6-month PFS rate was 26% in all patients (23% and 28% for AP and ROW, respectively). 6-month OS rate was 66% in all patients (63% and 70% for AP and ROW, respectively). Treatment-related grade 3-4 AEs were observed in 13% of patients and included fatigue, hypothyroidism, pneumonitis, pemphigoid, and peripheral sensory neuropathy. Relationships between the 6-gene IFN-γ, 13-gene TCR signaling, 18-gene expanded immune, and 33-gene de novo gene expression signatures and ORR and PFS were observed.

Conclusion: Pembrolizumab provided durable antitumor activity with a manageable toxicity profile in PD-L1–positive advanced gastric cancer, with similar efficacy in patients from AP and ROW. Data suggest there is an association between efficacy and immune-related gene expression signatures. The use of gene expression information may provide an additional means of identifying those patients most likely to respond to pembrolizumab.