Association Between Immune and Tumor Gene Signatures with Response or Resistance to Tislelizumab Monotherapy or in Combination with Chemotherapy in Gastroesophageal Adenocarcinoma

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Background Tislelizumab, an anti-PD-1 monoclonal antibody, has demonstrated clinical benefit as a single agent and in combination with chemotherapy for patients (pts) with gastroesophageal adenocarcinoma (GEA), including gastric, gastroesophageal junction (G/GEJ), and esophageal adenocarcinoma (EAC). Immune- and tumor-transcriptomic features of response and resistance to tislelizumab were assessed from data collected in two monotherapy studies (NCT02407990, CTR20160872) and one tislelizumab plus chemotherapy study (NCT03469557).

Method Gene expression profiling (GEP), using the 1392-gene HTG EdgeSeq panel, was performed on baseline tumor samples from 103 pts with GEA receiving monotherapy and 13 receiving combination therapy. Signature scores were calculated using the Gene Set Variation Analysis package with publicly available gene signatures (GS). Differential gene signature (DEG) analysis was performed between responders and nonresponders (NRs) using Wilcoxon rank-sum test; GS associated with survival were evaluated using Cox proportional hazards model.

Results Of the 76 pts with available GEP data, 64 (n=51 G/GEJ; n=13 EAC) had evaluable responses. Across these pts with GEA, tislelizumab demonstrated antitumor activity (**Table**). In pts treated with monotherapy, DEG showed IFNγ GS (*IFNG*, *CXCL9*, *CXCL10*, *HLA-DRA*, *IDO1*, *STAT1*) scores were positively correlated with response (*P*=0.03) as well as progression-free (HR=0.5, 95% CI: 0.27–0.93) and overall survival (HR=0.44, 95% CI: 0.21–0.89). Monotherapy NRs could be clustered into distinct GEP subgroups. Compared with responders, two NR subgroups had lower IFNγ GS (*P*=0.002, 0.047) along with either higher epithelial-mesenchymal transition (EMT; *P*=0.027), and angiogenesis (*P*=0.002) or cell cycle (CC; *P*=0.097) GS expression. A third NR subgroup showed higher CC GS scores compared with responders (*P*=0.015), despite high IFNγ GS levels. Unlike tislelizumab monotherapy, responders to combination therapy showed higher CC GS expression versus NRs (*P*=0.089).

Conclusion While higher IFNγ GS was associated with clinical benefit with monotherapy, elevated EMT/angiogenesis and CC GS levels may indicate resistance. The effects of these signatures in pts treated with combination therapy may vary. Both immune- and tumor-intrinsic factors may be considered for validation in a phase 3 study (NCT03777657).

	Monotherapy (n=53)	Combination (n=11)
Median follow-up, mo	14.3	16.3
ORR, %	13.2	54.5