Immune- and Tumor-Intrinsic Gene Expression Profiles of Response or Resistance to Tislelizumab as Monotherapy or in Combination With Chemotherapy in Non-Small Cell Lung Cancer (NSCLC)

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Background Tislelizumab, an anti-PD-1 monoclonal antibody, showed clinical benefit for patients (pts) with NSCLC alone (NCT02407990, CTR20160872) and in combination with chemotherapy (NCT03432598). Gene expression profiles (GEP) associated with response and resistance to tislelizumab in these studies were assessed.

Method The GEP of baseline tumor samples from 59 nonsquamous (NSQ) and 42 squamous (SQ) NSCLC pts treated with tislelizumab monotherapy (mono) as ≥1L treatment, and 16 NSQ and 21 SQ pts treated with tislelizumab plus chemotherapy (combo) as 1L treatment were assessed using the 1392-gene HTG GEP EdgeSeq panel. NSQ and SQ cohorts were analyzed separately due to distinct GEP features shown by PCA and t-SNE clustering.

Results Tislelizumab mono and combo showed antitumor activity in NSCLC (**Table**). In 80 biomarker-evaluable samples, inflamed tumor signatures (inflammatory GEP; antigen presentation GEP) were associated with longer overall survival (log-rank test, NSQ mono: *P*=0.04, 0.003; NSQ combo: *P*=0.05, 0.02; SQ combo: *P*=0.06, 0.06). Monotherapy non-responders (NRs) were clustered into 2 subgroups (NR1, NR2) with distinct GEPs. Compared with responders, NR1 had proliferation signatures (elevated cell cycle [CC] and DNA repair) in both NSQ (*P*=0.2, 0.02) and SQ (*P*=0.03, 0.4) cohorts, trending toward low inflamed tumor signatures. In NR pts receiving combo, CC and DNA repair signatures were not enriched, and high CC and DNA repair scores were observed in some SQ combo responders versus NRs (*P*=0.2, 0.02). NR2 had higher M2 macrophage and Treg cell signatures versus responders in both NSQ and SQ mono, despite high inflamed tumor and low proliferation signatures. NR2 also had increased expression of genes related to immune regulation and angiogenesis, including *PIK3CD*, *CCR2*, *CD244*, *IRAK3*, and *MAP4K1* (*P*<0.05) in NSQ, and *PIK3CD*, *CCR2*, *CD40*, *CD163*, *MMP12*, *VEGFC*, and *TEK* (*P*<0.05) in SQ.

Conclusions Clinical benefit in pts with NSCLC receiving tislelizumab (mono or combo) was associated with high inflamed tumor signatures, while elevated immune suppressive cell signatures may indicate resistance. High proliferation signatures were associated with resistance to monotherapy, but not to combination therapy. Both immune- and tumor-intrinsic factors may be considered for validation in future clinical trials.

	Mono NSQ	Mono SQ	Combo NSQ	Combo SQ
Median follow-up, mo	15.6	14.4	17.4	18.3
Objective response rate, %	13.6	19.5	43.8	76.2
Median OS, mo	9.9	8.6	16.6	17.1