Background Tislelizumab, an anti-PD-1 monoclonal antibody, demonstrated efficacy as monotherapy in patients with previously treated PD-L1+ urothelial carcinoma (UC) during a phase 2 study (NCT04004221). Here, gene expression profiles correlating with response and resistance to tislelizumab treatment are reported.

Methods Gene expression profiling (GEP) was conducted on baseline tumor samples from 100 Chinese patients with UC enrolled in the phase 2 tislelizumab study using a 1,392-gene panel by HTG EdgeSeq. Gene Signature (GS) scores were calculated using the Gene Set Variation Analysis package. Differential gene expression (DEG) analysis was performed between responders and non-responders using the Wilcoxon test; survival was evaluated using the Cox proportional hazards model and the odds of tumor response for subgroup analysis was estimated by logistic regression.

Results Of patients with available confirmed response results (n=85), DEG analysis found that responders had significantly higher T-cell GS (CD3D, CD3E, CD3G, CD6, SH2D1A, TRAT1) (P=0.04) and MHC I GS (HLA-A, TAP1) (P=0.05), respectively. Using median GS scores as a cutoff, improvement in overall survival (OS) was observed in T-cell–high versus T-cell–low groups (P=0.01) and a trend of longer OS was seen between MHC I–high versus MHC I–low groups. Patients in T-cell and MHC I–double-high subgroups showed further improvement in clinical efficacy (40% objective response rate [ORR], 5.26 month median progression-free survival [PFS], and 15.2 month median OS) than other subgroups (table 1). In addition to immune-related genes in the microenvironment, DEG analysis also revealed that tumor-related genes were highly expressed in non-responders, such as intrinsic genes related to angiogenesis (VEGFA [P=0.07], KDR [P=0.07]), the mTOR pathway (MTOR [P=0.015]), and DNA damage repair (REV3L [P=0.007]). MTOR and REV3L were associated with shorter PFS (P=0.02; P=0.003) and OS (P=0.03; P=0.008), respectively.

Conclusions By using GEP, T-cell and MHC I GS were identified as potentially predictive biomarkers of response to tislelizumab monotherapy in PD-L1+ UC in this retrospective analysis. By combining these two GS scores, patients with optimal efficacy responses could be identified. Conversely, high expression of tumor intrinsic genes related to angiogenesis and the mTOR pathway may indicate resistance and suggest potential future drug combinations for these patients. Both findings warrant further validation in a phase 3 study (NCT03967977).

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