CD8 T cells and macrophage abundances associated with clinical benefit of tislelizumab in various tumor types

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Abstract:

Background

Functionally activated immune cells (ICs) in the tumor microenvironment (TME) are critical to antitumor efficacy. Here, we report association between ICs and the clinical efficacy of tislelizumab (TIS), an anti-programmed cell death protein 1 monoclonal antibody, by examining tumor tissues from various tumor types in three pooled Phase 1/2 studies (NCT02407990, NCT04068519, NCT04004221).

Methods

Available baseline tumor tissues from patients (pts) with advanced solid tumors who received TIS were tested with either multiplex-immunohistochemistry(m-IHC) (n=67, Opal automation Multiplex IHC kit) or gene expression profile (n=629, HTG EdgeSeq Precision Immuno-Oncology Panel). High/low cell density/signature scores were defined per median score, respectively. Median overall survival (OS) was estimated by the Kaplan-Meier method and log rank test was used to compare survival curves between pts with different biomarker levels.

Results

Pts with a high CD68 density ($CD68^{Hi}$) (n=34) had a longer OS compared with pts who had a low CD68 density (n=33), with a median OS of 15.0 vs 10.4 months, p=0.11. A weak association was observed between survival and CD8 cell density. When the two cell types were combined as a composite biomarker, pts with high CD8 ($CD8^{Hi}$) and $CD68^{Hi}$ showed the longest OS (**Table**). A consistent finding was confirmed in the gene expression population (**Table**). Further TME analysis revealed that pts with $CD8^{Hi}$ and $CD68^{Hi}$ signature showed most elevated CD8 T cell cytotoxicity (*CD8A, GNLY, GZMA, GZMB*), T cell trafficking (*CXCL9, CXCL10, CCL4, CCL5*), MHCI antigen presentation (*TAP1, TAP2, HLA.A/B/C*) signatures/genes, and enriched expression of pro-inflammatory macrophage polarization pathway (*STAT1, SLAMF7/8, ISG15*).

Conclusion

Co-enrichment of CD8 T cells and macrophages were associated with survival benefit and an immune-activated TME in pts with various tumor types treated with TIS. This observation warrants further investigation.

Table. Association between ICs and the clinical efficacy of TIS

m-IHC analysis	**CD8^{Hi}/CD68^{Hi} (n=24)**	**CD8^{Hi}/CD68^{Lo} (n=10)**	**CD8^{Lo}/CD68^{Hi} (n=10)**	**CD8^{Lo}/CD68^{Lo} (n=23)**
Median OS, months (95% CI)	15.7 (8.5, NA)	5.1 (0.8, 10.8)	6.3 (1.8, NA)	11.2 (4.0, 17.6)
Gene expression analysis	**CD8^{Hi}/CD68^{Hi} (n=202)**	**CD8^{Hi}/CD68^{Lo} (n=113)**	**CD8^{Lo}/CD68^{Hi} (n=113)**	**CD8^{Lo}/CD68^{Lo} (n=201)**
Median OS, months (95% CI)	14.9 (11.2, 19.2)	11.1 (7.1, 13.5)	7.7 (5.6, 11.4)	9.8 (7.4, 11.6)
p value*	0.00033			

**p value obtained from log-rank test*
CI, confidence interval; ^{Hi}, high density; IC, immune cell; m-IHC, multiplex immunohistochemistry; ^{Lo}, low density; NA, not available; OS, overall survival; TIS, tislelizumab