IDENTIFICATION OF MICROENVIRONMENT FEATURES ASSOCIATED WITH PRIMARY RESISTANCE TO ANTI-PD-1/PD-L1 + ANTIANGIOGENESIS IN GASTRIC CANCER: A JOINT ANALYSIS OF THE REGOMUNE AND REGONIVO STUDIES

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Background The REGOMUNE and REGONIVO studies showed promising antitumor activity when anti-PD-1/PD-L1 antibodies were paired with the multitarget inhibitor regorafenib in the treatment of Advanced Gastric Cancer (AGC). 1, 2 This study aims to uncover the factors that contribute to primary resistance against this therapeutic strategy.

Methods Tumor samples were collected from patients with AGC enrolled in the REGOMUNE (NCT03475953) and REGONIVO (NCT03406871) studies. We spatially profiled the expression of >18,000 protein-coding genes across six tumors (three responders and three progressors) using the GeoMx whole-transcriptome atlas (WTA) assay. ROIs were drawn to analyze the expression of the WTA gene panel within the tumor region. Each tumor ROI was further segmented in 3 AOs (to analyze the ‘Tumor’ (PanCK+ CD45+), ‘Immune’ (CD45+) and ‘Stroma’ (PanCK-) compartments. To visualize the differences in immune cell abundances between responders and non-responders, we developed two multiplex IHC panels that enabled simultaneous detection of CD8+ T cells, monocytes, activated dendritic cells M2 macrophages, S100A10, AnxA2, and tumor cells in all the patients with available tumor material from the REGOMUNE and from the REGONIVO studies (n=45). To detect potential peripheral biomarkers associated with resistance to regorafenib plus ICI, we implemented a proteomics analysis of plasma samples by using the Olink Multiplex platform as previously described. 3

Results Comparative spatial transcriptomic analysis of the tumor compartment revealed a strong upregulation of S100A10, a member of the S100 protein family, alongside its ligand, Annexin A2, in non-responding patients. Notably, these two elements form a heterotetrameric complex playing a key role in regulating tumor cell proliferation, angiogenesis and macrophage infiltration. The tumor compartment of non-responders was significantly enriched in several oncogenic hallmark pathways, including TGFb signaling. Deconvolution analysis of the Immune cell compartment revealed a significant enrichment in macrophages in the non-responder group. By using multiplex IF, we confirmed that M2 macrophages defined as CD68+ HLA-DR- was the immune cell population most differentially represented between responders and non-responders (median PFS and OS 1.8 and 4.3 months versus 4.26 and 13.4 months respectively; P = 0.006 and P = 0.004). Higher S100A10-expressing tumor cells correlated with worse PFS and OS. Plasma studies showed cytokines like CSF-1, IL-4, and TWEAK, linked with macrophage infiltration, were prevalent in patients with unfavorable outcomes.

Conclusions This in-depth exploratory analysis of blood and tumor samples indicates that elimination and reprogramming of tumor-associated macrophages may be a breakthrough to efficiently induce potent anti-tumor immunity in patient with ADG.

REFERENCES

2. Cousin et al. REGOMUNE: a phase II study of regorafenib plus avelumab in solid tumors—Results of the oesophageal or gastric carcinoma (OGC) cohort. Journal of Clinical Oncology 40, no. 16 suppl (June 01, 2022) 4060–4060.

Ethics Approval Both REGOMUNE and REGONIVO studies get ethics approval [1,2]. All participants gave informed consent before taking part.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1521