Background OCI is a humanized monoclonal antibody (mAb) against T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) with high affinity and specificity, enabling Fc-mediated effector functions that induce antibody-dependent cellular cytotoxicity. The Phase 1/1b open-label AdvanTIG-105 trial was designed to assess the safety and efficacy of OCI plus TIS (an anti-programmed cell death protein 1 mAb) in patients with advanced solid tumors (NCT04047862). In the dose-escalation part, the combination was well tolerated, and preliminary antitumor responses were observed. Here, we report PD biomarker data from peripheral blood.

Methods Eligible patients had locally advanced/metastatic, unresectable solid tumors previously treated with standard systemic therapy or for which treatment was not available/tolerated, ECOG PS ≤1 and had received no prior anti-TIGIT therapy. Patients received five escalating doses of OCI (50–1800mg) intravenously (IV) on Cycle (C) 1 Day (D) 1 and TIS 200mg IV was initiated on C1D8. If tolerated, patients received OCI (50–1800mg) plus TIS 200mg on D29 (C2D1) and every three weeks thereafter until discontinuation. Peripheral blood samples were collected to monitor changes in total and TIGIT-expressing immune cell subsets pre- and post-treatment. Meso Scale Discovery V-plex panels were used to assess cytokine/chemokine release in plasma samples. Wilcoxon signed-rank test compared pre- and post-treatment cytokine/chemokine levels; p values are descriptive.

Results At data cutoff (09/01/2021), 32 patients had received ≥1 dose of OCI plus TIS. Total peripheral regulatory T cells (Tregs) decreased following OCI monotherapy (at C1D2 and C1D8) with doses of 900mg and 1800mg (not dose proportional), but not 450mg; the decrease was maintained with subsequent combination with TIS (at C1D15 and C2D1). CD4+ and CD8+ T-cell populations were not impacted at any OCI dose. TIGIT downregulation was observed on Tregs, CD4+, and CD8+ T cells at C1D8 with multiple OCI doses (not dose proportional); the reduction was sustained after combination with TIS. Plasma IL12/23p40 (p<0.001), CCL4 (p<0.05), and CXCL10 (p<0.05) were notably induced post-OCI (C1D8), and further elevated following combination with TIS (p<0.001, p<0.001, and p<0.0001, respectively) at C2D1. Plasma IFNγ and TNFα increased post-OCI at C1D8 and were dramatically induced post-combination at C2D1 (p<0.0001 and p<0.001, respectively).

Conclusions OCI, with or without TIS, led to Treg reduction at higher doses, TIGIT downregulation, and proinflammatory cytokine/chemokine release, reflecting the potential mechanism of action of OCI as an Fc-competent anti-TIGIT mAb.

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