Early pharmacodynamic changes measured by RNA sequencing in peripheral blood from patients in a phase 1 study with mitazalimab, a potent CD40 agonistic IgG1 monoclonal antibody

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Background Mitazalimab is a human FcγR crosslinking-dependent human IgG1 CD40 agonistic antibody developed for cancer immunotherapy. Mitazalimab has demonstrated a manageable safety profile when administered once every 2 weeks both with or without corticosteroid pre-treatment. Treatment with mitazalimab induces transient increases in levels of selected chemokines and activation of peripheral B cells. An ongoing phase 2 study (OPTIMIZE-1) is currently evaluating the efficacy of mitazalimab in patients with metastatic pancreatic cancer (NCT04888312).

Methods Cell-free RNA from whole blood was collected from subjects both pre- and post-treatment in a dose escalation study of mitazalimab in patients with solid tumors (NCT02829099). The whole transcriptome sequencing was conducted according to Illumina TruSeq Stranded protocol. Samples obtained pretreatment and one day after treatment from cohorts receiving 75, 200, 600 and 900 μg/kg mitazalimab without corticosteroid pretreatment (pre/post treatment; 75 μg: n=3/3, 200 μg: n=5/5, 600 μg: n=10/11 and 900 μg: n=13/14) and 600 μg/kg mitazalimab with corticosteroid pretreatment were analyzed (pre/post treatment; n=10/5). The normalized data was analyzed utilizing the edgeR limma workflow on R software. Differentially expressed genes were analyzed according to dose level and corticosteroid (yes vs no) administration. Cell phenotyping was conducted according to CIBERSORTX and Xcell cell signatures. Gene expression results were further correlated with peripheral blood concentrations of 15 cytokines 24 hours after treatment.

Results Significant mitazalimab treatment-induced transcriptional activity was identified using pre-selected gene signatures related to event associated to CD40 biology at the 600 and 900 μg/kg dose levels without corticosteroid pre-treatment. In contrast, the number of significantly expressed genes in the lower dose groups were limited. Gene signatures related to activation of B cell- and myeloid/dendritic activation were upregulated post treatment, confirming the CD40 agonistic activity of mitazalimab. Additionally, corticosteroid pre-treatment significantly reduced the magnitude of the mitazalimab treatment induced changes in gene expression in circulating immune cells in patients. This was confirmed at the protein level for circulating cytokines.

Conclusions The analysis of RNAseq data obtained from whole blood clearly demonstrated that mitazalimab induce strong CD40-mediated responses, such as activation of myeloid cells and B cells in patients. Furthermore, corticosteroid pretreatment reduced the immune stimulatory activity of mitazalimab. The presented gene expression data confirms the biological activity of mitazalimab, further strengthening the proof of mechanism.

References