145 NADUNOLIMAB INHIBITS IL-1α/β-INDUCED CXCR1/2 LIGAND EXPRESSION AND REDUCES SERUM LEVELS OF CXCL1 AND CXCL5 IN NSCLC AND PDAC PATIENTS

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Background Interleukin-1 receptor accessory protein (IL1RAP) is expressed on tumor cells and stromal cells in most solid tumors, including PDAC and NSCLC. IL1RAP is a co-receptor of the IL-1 receptor (IL1R1), and its dimerization with IL1R1 is required for IL-1 signaling. IL-1 is expressed in the tumor microenvironment and contribute to chemoresistance and an immune-suppressive tumor microenvironment. The chemokine receptors CXCR1 and CXCR2 and their ligands are crucial for the migration of immune-suppressive cells into the tumor and thereby influences tumor progression and metastasis. CXCR1/2 ligands can be expressed by cells in the tumor microenvironment and are downstream of IL-1 signaling. Nadunolimab is a fully humanized ADCC-enhanced monoclonal IgG1 antibody targeting IL1RAP and disrupting both IL-1α and IL-1β signaling. Currently, nadunolimab is evaluated in phase II for PDAC and NSCLC (NCT03267316) in combination with gemcitabine + Nab-paclitaxel or gemcitabine + cisplatin, respectively.

Methods Whole blood and PBMC from healthy donors as well as cancer-associated fibroblasts (CAFs) were stimulated with IL-1α or IL-1β with or without nadunolimab followed by assessment of CXCR1/2 ligands. Serum samples collected before start of treatment and after 2 weeks of treatment from 11 NSCLC patients treated with nadunolimab in combination with gemcitabine + cisplatin, and 16 PDAC patients treated with nadunolimab and gemcitabine + Nab-paclitaxel, were analyzed for the presence of CXCL1, CXCL5 and CXCL8.

Results The inhibitory effect of nadunolimab on IL-1α and IL-1β induced CXCR1/2 ligands was evaluated in different cell systems. IL-1α and IL-1β induced the secretion of the CXCR1/2 ligands CXCL1, CXCL2, CXCL5, CXCL6 and CXCL8 in CAFs. This increase was normalized with the addition of nadunolimab. In a similar fashion, nadunolimab significantly blocked the IL-1α and IL-1β induced levels of CXCL1, CXCL5 and CXCL8 from PBMC and whole blood. Therefore, CXCL1, CXCL5 and CXCL8 were evaluated as potential biomarkers in serum from patients treated with nadunolimab. Similar to the in vitro results, serum levels of CXCL1 and CXCL5 were significantly decreased in patient on treatment with nadunolimab and chemotherapy. However, levels of CXCL8 were not affected after 2 weeks of treatment.

Conclusions Nadunolimab was demonstrated to decrease the levels of CXCR1/2 ligands across different cell systems, and a reduction in CXCL1 and CXCL5 was detected in both NSCLC and PDAC patients during treatment with nadunolimab. This is in line with an effect of nadunolimab on the tumor microenvironment and indicates the potential of CXCL1 and CXCL5 as serum biomarkers for treatment with nadunolimab.

Trial Registration NCT03267316

Ethics Approval The study was approved by the Ethics committees of the concerned countries and an informed consent was obtained from all individuals included in this study. Clinical trial number NCT03267316.

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