MAZD0171 MEDIATED LIF BLOCKADE IN COMBINATION WITH CHEMOTHERAPY AND PD-L1 INHIBITION REPOLARIZES MACROPHAGES AND INCREASES T CELL INFILTRATION VIA CX3CR1-CX3CL1 AXIS

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Background Leukemic inhibitory factor (LIF) is an IL-6 family member linked to tumor immune-suppression, maintenance of cancer initiating cells and epithelial-mesenchymal transition (EMT). AZD0171 is a monoclonal antibody that binds to LIF and prevents signalling through its receptor. We tested whether LIF blockade, using a murine surrogate (mAZD0171), sensitises tumors to T-cell checkpoint inhibitor augmented chemotherapy using multiple syngeneic mouse models of cancer.

Methods Bioinformatic analysis of patient datasets was used to explore correlations of LIF expression with other gene signatures and outcome data. mAZD0171 was tested in combination with anti-PD-L1 in CT26, MC38 and MCA205 tumor models; with follow-on studies combining this Immuno-oncology (IO) doublet with taxane and platinum-based chemotherapies.

Results Primary human NSCLC tumors produce LIF in culture and in NSCLC patients. In mouse CT26 and MCA205 tumor models, monotherapy mAZD0171 modulated tumor gene expression and induced changes in macrophage phenotype which sensitized tumors to anti-PD-L1. Combining mAZD0171 and anti-PD-L1 with chemotherapy had a marked impact on both tumor microenvironment and tumor growth; including elevated CD8+ and Granzyme B+, CX3CR1+CD8+ T cells, high expression of MHC class II on macrophages, and increased Fractalkine (CX3CL1) levels in tumor bearing mice. Antibody based neutralization of CX3CL1 in the mAZD0171+OHP+aPD-L1 treated MC38 tumor bearing mice reduced representation of CX3CR1+ effector T-cells in the tumor microenvironment. Tumor macrophage MHC class II expression levels were also diminished by neutralizing CX3CL1 in mAZD0171+OHP+aPD-L1 treated mice, further supporting the potential linkage between LIF biology and CX3CR1/CX3CL1 axis. Notably, in human NSCLC and CRC tumors, CX3CR1 is negatively correlated with LIF, and CX3CR1 expression positively associated with survival.

Conclusions LIF transcript levels are associated with inferior outcome on checkpoint inhibiting drugs in NSCLC patients, supporting a possible role in IO resistance. In preclinical models we found that adding mAZD0171 to anti-PD-L1 enhanced chemotherapy efficacy and increased the frequency of immune-supportive macrophages and effector T-cells via a mechanism involving the CX3CR1/CX3CL1 axis. Together these preclinical data support the hypothesis that AZD0171 has the potential to sensitize solid tumors to chemotherapy/IO combinations, thereby supporting clinical assessment of this combination strategy (e.g. NCT04999969).

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