

922

A NOVEL AUTOTAXIN INHIBITOR, IOA-289, MODULATES TUMOR, IMMUNE AND STROMAL CELL FUNCTION AND HAS MONOTHERAPY ACTIVITY IN FIBROTIC CANCER MODELS

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Background Autotaxin (ATX) is a secreted glycoprotein that hydrolyzes lysophosphatidylcholine (LPC) to lysophosphatidic acid (LPA). The expression of both ATX and LPA is elevated in most solid tumors and plasma. LPA signaling directly modulates tumor cell function and contributes to the development of the fibrotic tumor microenvironment, a mechanism by which tumors evade host immunity and impairs response to therapy. IOA-289 is a potent, orally available autotaxin inhibitor which is being developed as a novel treatment of solid tumours burdened with a high degree of fibrosis.

Methods Inhibition of ATX activity in human plasma was determined by measuring reduction in LPA species as quantified by LC-MS/MS. In vitro activity on biomarkers of fibrosis was assessed using the BioMAP screen and fibroblast cell cultures. T cell migration was measured using 48-well chemotaxis chambers. PK/PD studies were performed following a single oral dose of IOA-289 in mice, and plasma LPA was used as a PD biomarker. In vivo efficacy was studied in two models of breast cancer, 4T1 and E0771. Bioinformatics used TCGA and GTEX publicly available datasets.

Results IOA-289 inhibits plasma LPA18:2 with an IC₅₀ of 36nM, with similar results for other LPA species. IOA-289 inhibited fibrosis relevant factors in the BioMAP phenotypic screen, including sIL-6, MCP-1, α SMA, collagen-III, and sVEGF. In further studies, IOA-289 inhibited the secretion of PAI-1 and IL-6 by stimulated fibroblasts. LPA and cancer cell conditioned media inhibited T cell chemotaxis in vitro and the effect was overcome in the presence of IOA-289. The efficacious human dose of IOA-289 was determined following PK/PD studies using plasma LPA as a biomarker of response to ATX inhibition. In vivo studies showed that IOA-289 inhibited metastasis of 4T1 cells, enhanced the infiltration of T cells into 4T1 s.c. implanted tumors and prevented the growth of primary, orthotopically implanted E0771 tumors. Bioinformatics analysis demonstrated elevated ATX expression in pancreatic cancer (PDAC), and PDAC patient plasma showed a correlation of ATX levels with CA-19-9.

Conclusions The ATX/LPA pathway represents a novel target for anti-cancer therapy with actions on the tumor, immune cell and stromal environment. IOA-289 is a highly potent and selective inhibitor of ATX with demonstrated monotherapy activity in cancer models. Based on the mechanism of action we are investigating combinations of IOA-289 with chemotherapy, immunotherapy and novel agents in ongoing preclinical studies. An acceptable safety and PK profile support the clinical development of IOA-289 which is currently in a phase I clinical trial.

Ethics Approval The 4T1 study was approved by The University Claude Bernard Lyon 1 Ethics Board; approval number DR2014-38 (vM). The E0771 study was reviewed and approved by the Institutional Animal Care and Use Committee of the contract research organization (Covance, Ann Arbor, MI, USA), an AAALAC International accredited program.