Preclinical development of a novel, highly selective PI3Kδ inhibitor, IOA-244 for the treatment of solid malignancies

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Background

Inhibiting PI3Kδ preferentially targets regulatory T cells and myeloid derived suppressor cells, breaking tumour-induced immune tolerance and restoring anti-tumour immunity. Bioinformatics and protein expression studies have shown that PI3KCD / PI3Kδ is highly expressed in certain solid malignancies, and therefore inhibition of PI3Kδ may modulate tumour growth and development via intrinsic as well as immune driven effects.

Methods

In vitro human T cell assays

Selective inhibition of PI3Kδ profoundly inhibits the proliferation of Treg cells whilst having no effect on CD8+ T cell proliferation. Dual inhibition of PI3Kδ and PI3Kγ also inhibits the proliferation of CD4+ T cells. Addition of IOA-244 to Treg cell cultures in vitro reduces the secretion of IL-10 compared with vehicle treated controls (grey bars). Compounds tested at 1 µM.

Immune mediated effects

CT26 syngeneic mouse model

Dose response

Expression of PI3Kδ by tumour cells is shown by western blot (MDA-MB-231) or RNAseq data (MEXF2104, a melanoma PDX cell line compared with a DLBCL PDX). Treatment of high PI3Kδ expressing tumours in s.c. implanted nude mice with IOA-244 reduces tumour growth in vivo.

Phase la study design

• 28-day cycle, once daily dosing, two indications selected with high PI3Kδ expression and Treg/MSC burden
• Dose escalation to generate PK/PD readouts in blood
• MOA to be demonstrated in tumour biopsies at Biologically Effective Dose (BED)

Summary

• IOA-244 is a novel, highly selective, PI3Kδ inhibitor with unique chemical properties, and demonstrates excellent PK and a good safety profile in non-clinical studies
• IOA-244 selectively modulates Treg cell proliferation and function with no effect on CD8+ cytotoxic T cells
• Thus IOA-244 modulates the balance of immune cells in the TME (tumour microenvironment) and stimulates an anti-cancer response
• Furthermore, targeting tumours with a high intrinsic PI3Kδ expression can stimulate an anti-tumour response in the absence of T cells
• IOA-244 has received approval to start First-in-Human studies in Europe and MOA will be further investigated using pre and post treatment biopsies and circulating biomarker analysis