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

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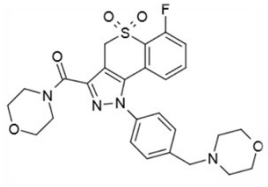
Background

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 PIK3CD / 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.

IOA-244

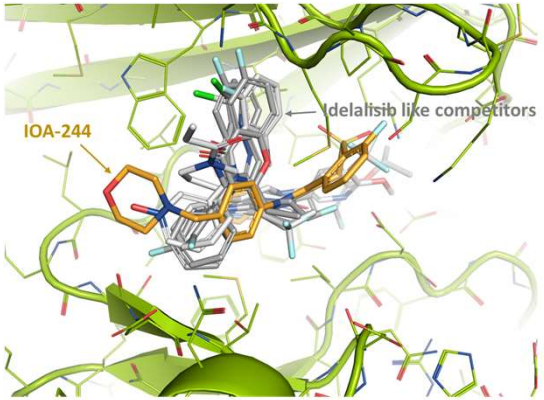
IOA-244 chemical structure



IOA-244 properties

Parameter	IOA-244
IC_{50} PI3Kδ	142 nM
ATP competitive	no
IC_{50} PI3Kα (ratio)	130
IC_{50} PI3Kβ (ratio)	20
IC_{50} PI3Kγ (ratio)	>1,000
IC_{50} CD63 (hWB)	~ 1 µM

IOA-244 binding overlaid with other PI3Kδ inhibitors



Methods

Human T cells were isolated using MACS from 3 donors. *In vitro* proliferation of primary human T cells was measured following anti-CD3/anti-CD28 stimulation with or without compound. *In vivo* immune mediated effects of IOA-244 were tested using the CT26/Balb/c s.c. mouse model. At termination tumours were harvested and analysed by flow cytometry for phenotypic profiling of immune cell components. *In vivo* intrinsic activity of IOA-244 was tested using high PI3Kδ expressing MDA-MB-231 cells as well as a patient derived melanoma model with high PIK3CD profile, inoculated s.c. in nude mice.

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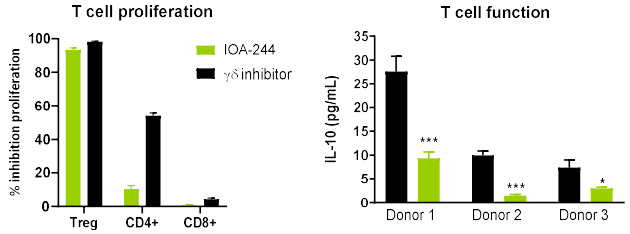
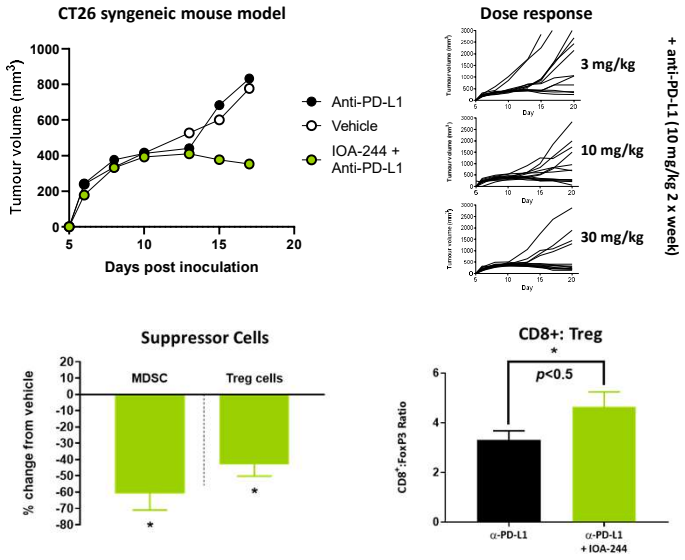
In vitro human T cell assays



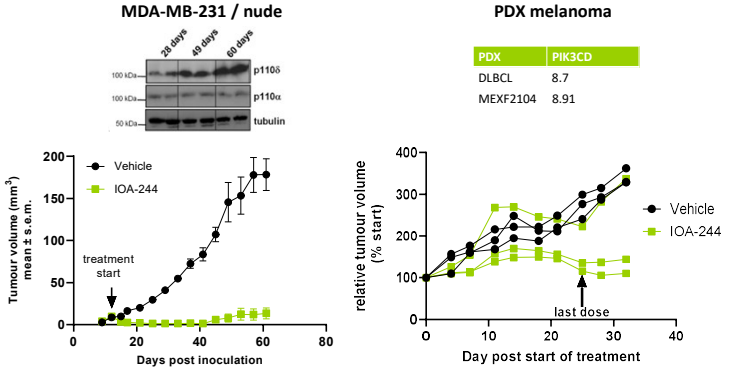
Selective inhibition of PI3Kδ profoundly inhibits the proliferation of Treg cells whilst having no effect on CD8+ T cell proliferation. Dual inhibition of PI3Kδ and PI3Kγ also inhibits the proliferation of CD4+ T cells. Addition of IOA-244 to Treg cell cultures *in vitro* reduces the secretion of IL-10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

Immune mediated effects



IOA-244 was dosed BID at 3, 10 or 30 mg/kg (p.o.) in the CT26 s.c. syngeneic mouse model with anti-PD-L1 at 10 mg/kg (i.p.). Dosing started when TV reached 250 mm^3. Anti-PD-L1 combined with IOA-244 at 30 mg/kg resulted in an inhibition and regression of tumour growth in most animals. The effect of IOA-244 was dose dependent, with a loss of effect at 3 mg/kg (results similar to anti-PD-L1 treatment alone). *Ex vivo* analysis of the tumours by flow cytometric analysis showed that IOA-244 treatment at 30 mg/kg increased the total CD45+ cell infiltrate of the tumours, with a corresponding increase in CD8+ T cell infiltration (data not shown). Furthermore, the Treg and MDSC suppressor cell populations were significantly reduced in IOA-244 treated animals compared with anti-PD-L1 treatment alone. Overall the combination of IOA-244 at 30 mg/kg with anti-PD-L1 significantly altered the ratio of CD8+ : FoxP3+ cells.

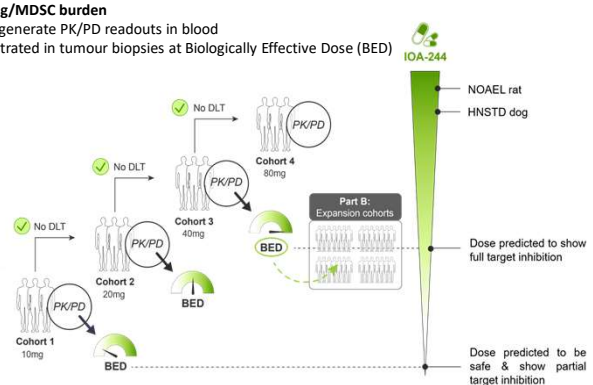
Intrinsic effects



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 Ia study design

- 28 day cycle, once daily dosing, **two indications selected with high PI3Kδ expression and Treg/MDSC 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

Conflict of Interest Statement: E Papakonstanti and A Tsapara received funding from iOnctura. L Van der Veen, M Lahn and Z Johnson are all employees and shareholders of iOnctura. P Shah has no conflicts to declare