A novel, highly selective PI3Kδ inhibitor for the treatment of solid malignancies that express high levels of target protein as assessed by immunohistochemistry

AACR Poster # 666

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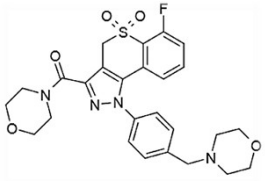
Background

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, most notably in uveal and cutaneous melanoma. We are conducting a First-in-Human study to test whether inhibition of PI3Kδ may modulate tumour growth and development via intrinsic as well as immune driven effects.

IOA-244

Figure 1

IOA-244 chemical structure



IOA-244 properties

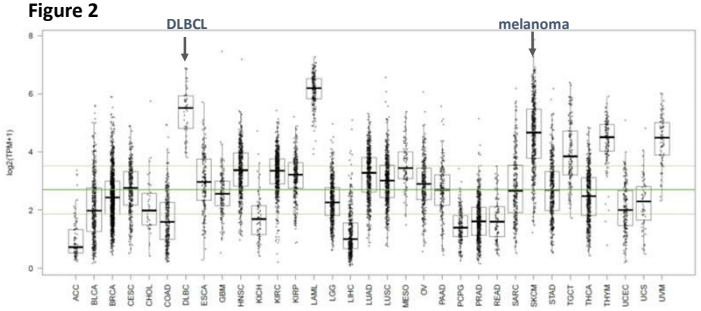
Parameter	IOA-244
IC_{50} PI3Kδ	142 nM
ATP competitive	no
IC_{50} PI3Kα (ratio)	130
IC_{50} PI3Kβ (ratio)	20
IC_{50} PI3Kγ (ratio)	>1,000
IC_{50} CD63 (hWB)	~ 1 µM

IOA-244 KEY FEATURES

- Unique chemical structure
- Excellent selectivity
- Non-ATP competitive activity
- Excellent PK properties
- Favourable safety profile

PIK3CD expression in solid tumours (TCGA)

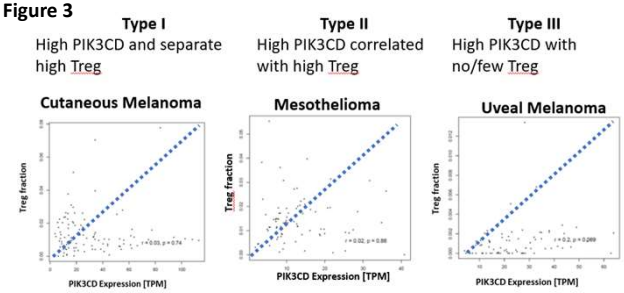
Figure 2



- The data used for the analysis was downloaded from The Cancer Genome Atlas (TCGA) database (http://firebrowse.org).
- Expression analysis was conducted on normalized data in TPM (transcript per million) units.
- Cutaneous Melanoma is notably high in PIK3CD expression

PIK3CD / Treg: Three sub-types in patients

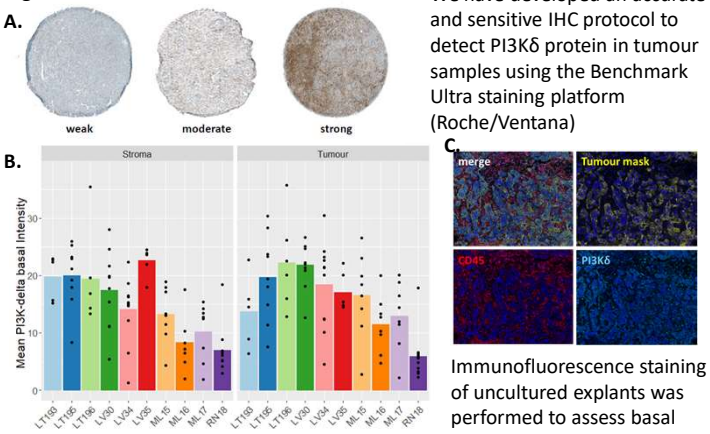
Figure 3



- Based on TCGA data, we postulate that the relationship between PIK3CD expression and the presence of Treg can be separated into three sub-types
- Based on MoA of IOA-244 we expect activity in all three sub-types

Development of an IHC test for PI3Kδ

Figure 4



We have developed an accurate and sensitive IHC protocol to detect PI3Kδ protein in tumour samples using the Benchmark Ultra staining platform (Roche/Ventana)

Immunofluorescence staining of uncultured explants was performed to assess basal level of PI3K-delta signal in tumour and stroma areas.

LT=lung; LV=colorectal liver mets; ML=melanoma; RN=renal

D.

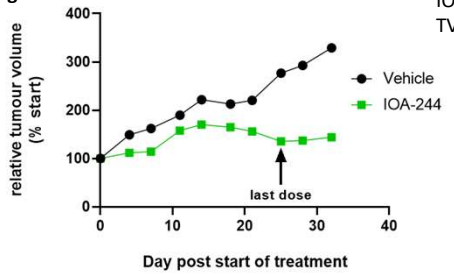
Stage – Clinical Stage (I-IV)	I	II	III	IV	No stage all Lymph node (stage IV)	No stage - skin
Number of Tissue Samples evaluated (note: duplicates from same patient)	4	10	1	1	14	1
Samples with any positive staining for PI3Kδ	4/4	10/10	1/1	1/1	13/14	1/1
H-score* of ≥50 of positive staining for PI3Kδ	0/4 (0%)	0/10 (0%)	1/1 (100%)	1/1 (100%)	1/13 (8%)	0/1 (0%)
H-score of ≥100 of positive staining for PI3Kδ	3/4 (75%)	6/10 (60%)	0/1 (0%)	0/1 (0%)	7/13 (54%)	0/1 (0%)

*H-score: Combination of staining intensity and number of positive stained tumour cells

By H-score classification of cytoplasmic anti-PI3K delta staining of tumour cells from melanoma patients, 28 (100 %) cores were classified as PI3K delta-positive, 18 (64.3 %) cores were classified as weakly positive, nine (32.1 %) cores were classified as moderately positive and one (3.6 %) core was classified as strongly positive

IOA-244 inhibits melanoma in a PDX model

Figure 5



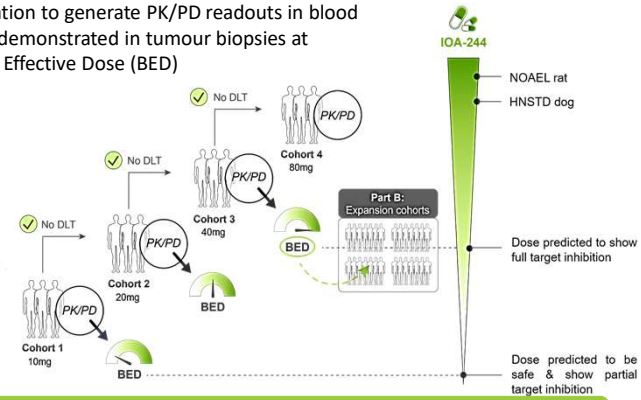
IOA-244 dosed 30 mg/kg BID
TV at start of therapy ~100 mm^3

- MEXF 2104 is a patient derived xenograft (PDX) derived from primary skin melanoma in Nude mice
- PIK3CD expression is high (8.9) and similar to that of a PDX from DLBCL (8.7)

Phase Ia study design

Figure 6

- 28 day cycle, once daily dosing, **indications selected with expected 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
- We have previously shown that IOA-244 selectively modulates Treg cell proliferation and function with no effect on CD8+ cytotoxic T cells
- Targeting tumours with a high intrinsic PI3Kδ expression can stimulate an anti-tumour response in the absence of T cells
- IOA-244 is in a First-in-Human study in Europe (NCT04328844)
- Levels of PI3Kδ in tumour biopsies pre and post dosing will be evaluated from patients enrolled in the study

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AACR 2020|Virtual Annual Meeting II| June 22-24 2020

Conflict of Interest Statement: K Niewola, L Van der Veen, M Lahn and Z Johnson are all employees and shareholders of iOnctura. P Shah has no conflicts to declare