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

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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

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

PIK3CD / Treg: Three sub-types in patients

- 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

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.

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

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