

# 192-P Safety and Clinical Activity of IOA-244, a Highly Selective Phosphoinositide 3-kinase Inhibitor delta (PI3Kδ), in a Phase I First in Human (FIH) Study (Study Part A)

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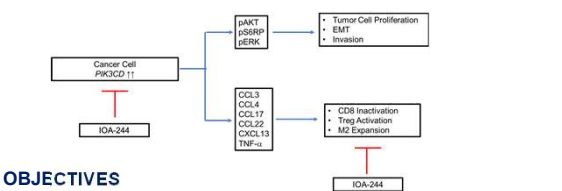
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**BACKGROUND**

- High *PIK3CD* gene expression is observed in a wide range of cancers, including haematologic malignancies, and solid tumours, such as Uveal and Cutaneous Melanoma
- PIK3CD* expression is correlated with immune suppressive immune cells, such as T<sub>reg</sub> cells

**Hypothesis:**  
IOA-244 will

- down-modulate T regulatory (T<sub>regs</sub>) and thus allow T effector (T<sub>eff</sub>) cells to be active
- Block *PIK3CD*-associated tumour growth



**OBJECTIVES**

**Primary:**  
Safety and tolerability of escalating doses of IOA-244 to the predicted biological effective dose (BED)

**Secondary:**  
To assess the pharmacokinetic (PK) profile  
Characterize PD effect as determined by inhibition of CD63 expression on basophils in response to IOA-244  
To document antitumor activity, including overall response rate (ORR), duration of response (DoR), progression free survival (PFS) and overall survival (OS)

**Exploratory:**  
Changes in immune cell numbers within pre- and post-treatment biopsies and in the circulating blood (multiplex IHC and Cytometry by Time of Flight, CyTOF/Mass Cytometry, MS)

**METHODS**

**Design:** 3+3 cohort dose escalation

**Patients Eligibility**  
≥18 years of age with the following:

- A performance status of ≤2 on the ECOG scale
- Historical or cytological evidence of a diagnosis of cancer that is advanced and/or metastatic disease for mesothelioma, cutaneous, and uveal melanoma
- Adequate organ functioning

**Assessments:**

- Toxicities graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
- Standard laboratory hematology and chemistry
- RECIST 1.1, based evaluation (ORR)
- Benefit/Risk for Recommended Phase 2 Dose (RP2D)

**RESULTS**

**Demography and Baseline Characteristics**

Cohort	10 mg	20 mg	40 mg	80 mg	Overall
N	4	8	4	8	24
Age (median)	73.5	54.5	70.0	61.5	65.0
Sex (m/f)	4/0	3/5	2/2	2/6	11/13

Primary Diagnosis	10 mg	20 mg	40 mg	80 mg	Overall
Uveal Melanoma	1	2	3	3	9
Mesothelioma	1	1	0	0	2
Melanoma	2	1	1	1	5
Follicular Lymphoma	0	4	0	4	8

Median prior Tx	10 mg	20 mg	40 mg	80 mg	Overall
	2 (1-3)	3 (1-7)	2 (1-3)	2 (1-5)	2 (1-7)

**Safety**

	10 mg	20 mg	40 mg	80 mg	Overall
<b>All Causality TEAEs</b>					
<b>Any Grade</b>	4 (100%)	7 (87%)	4 (100%)	6 (75%)	21 (87%)
<b>Grade 1</b>	4 (100%)	7 (87%)	2 (50%)	6 (75%)	6 (75%)
<b>Grade 2</b>	3 (75%)	3 (37%)	2 (50%)	5 (62%)	5 (62%)
<b>Grade 3</b>	0	1 (13%)	0	4 (50%)	0
<b>Grade 4</b>	0	0	0	0	0
<b>Grade 5*</b>	1 (25%)	1 (13%)	1 (25%)	0	3 (12%)
<b>Drug-related TEAEs</b>	2 (50%)	4 (50%)	2 (50%)	1 (13%)	9 (38%)
<b>All TEAEs related to IOA 244</b>	2 (50%)	4 (50%)	1 (25%)	0	8 (33%)
<b>Grade 1</b>	2 (50%)	4 (50%)	1 (25%)	0	2 (8%)
<b>Grade 2</b>	0	1 (25%)	1 (25%)	0	2 (8%)
<b>Grade 3†</b>	0	1 (25%)	0	1 (25%)	2 (8%)
<b>Grade 4</b>	0	0	0	0	0
<b>Grade 5</b>	0	0	0	0	0

\*The CTCAE Grade 5 toxicities observed were associated with tumour progression and NOT considered related to treatment. †The Grade 3 related TEAEs resolved whilst continuing on treatment. 20 mg FL – Platelet Count decrease, 80 mg FL – Neutrophil decrease

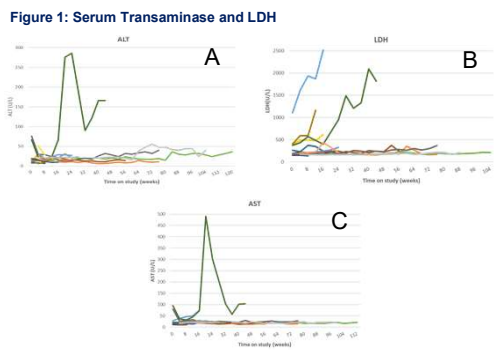


Figure 1 Panel A-D: IOA-244 was given without dose modifications in patients treated for more than 4 months. ALT (A), LDH (B), and AST (C) remain unchanged during treatment unless where progression is observed in the liver.

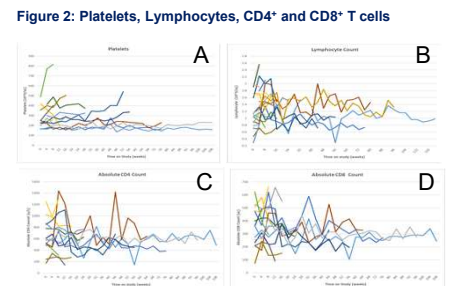


Figure 2 Panel A-D – Haematology and Flow Cytometry (FC): No changes in platelet counts, total lymphocytes, including total CD4+ and CD8+ T cells with long-term treatment with IOA-244

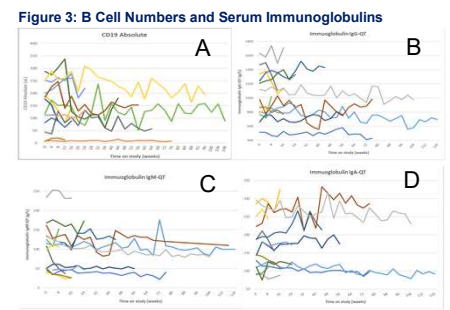


Figure 3 Panel A-D: FC and Serum Analyses: Long-term treatment with IOA-244 does not reduce B cell counts (CD19+) (A) or immunoglobulin titres (IgG, IgA, IgM) (B-D)

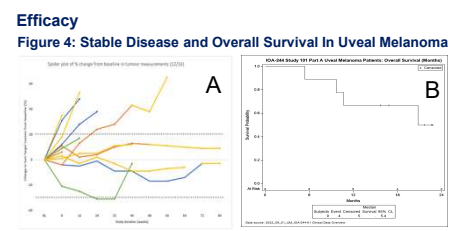


Figure 4 Panel A/B: Long-term treatment with IOA-244 is associated with long-term Stable Disease (SD) (A) and associated with long survival (OS >12 months) (B)

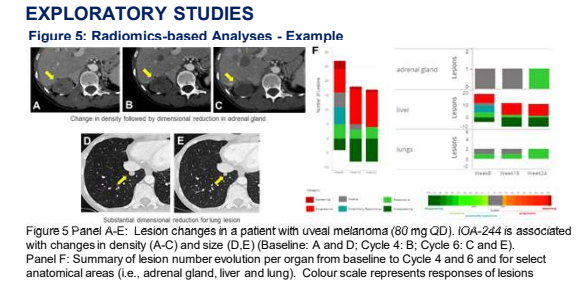


Figure 5 Panel A-E: Lesion changes in a patient with uveal melanoma (80 mg QD). IOA-244 is associated with changes in density (A-C) and size (D,E) (Baseline: A and D; Cycle 4: B; Cycle 6: C and E). Panel F: Summary of lesion number evolution per organ from baseline to Cycle 4 and 6 for selected anatomical areas (i.e., adrenal gland, liver and lung). Colour scale represents responses of lesions

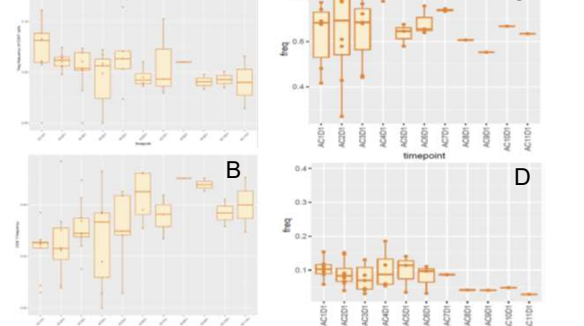


Figure 6 Panel A-D: Mass Cytometry (MC; CyTOF) Analyses: Initial Studies indicated Treg reduction (A) and increase in CD8 population (B) in peripheral blood. Among the CD8 population, cluster analyses (Leiden) indicate that CD8+CD28+ (=activated CD8) increase or remain stable (C), while CD8+CD39+ (=exhausted CD8) diminish over during treatment.

**CONCLUSION**

- IOA-244 monotherapy has a Grade 1/2 CTCAE profile:
  - No increased toxicity for pts treated >6 months
  - Similar toxicity profile for Pts with NHL (FL)
  - Grade 3 toxicities (n=2) in NHL (FL) were transient (<24 hrs)
- Uveal Melanoma patients with long treatments (>4 months)
  - SD (some pts with mixed responses)
  - OS >12 months
- IOA-244
  - Down-modulates Tregs and exhausted CD8+ T cells
  - Increases activated CD8+ cells