139P - First-in-human (FIH), pharmacokinetic (PK) and pharmacodynamic (PD) study of IOA-244, a phosphoinositide 3-kinase delta (PI3Kd) inhibitor, in patients with advanced metastatic mesothelioma, uveal and cutaneous melanoma

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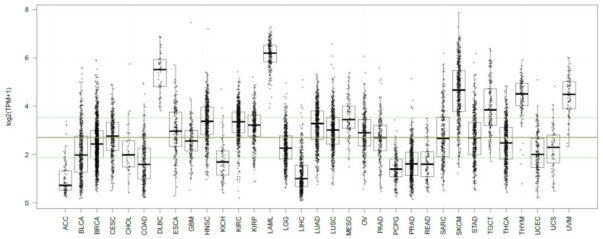
BACKGROUND

- Uveal and Cutaneous Melanoma show high *PIK3CD* gene expression (comparable to DLBCL)
- Mesothelioma, Uveal and Cutaneous Melanoma are known to have high T regulatory (T_{reg}) cells
- T_{reg} cells are highly dependent on PI3Kδ

Hypothesis:

IOA-244 will down-modulate T_{regs} and thus allow T effector (Teff) cells to be active

Figure 1



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 upregulation on basophils in relationship to exposure
- To document any antitumor activity, including ORR, DoR, PFS and OS

Exploratory:

- Changes in immune cells in pre- and post-treatment biopsies and circulating blood (only CyTOF presented here)

Figure 2

METHODS

Design:

- 3+3 cohort dose escalation: Cohort 1 (10 mg QD), Cohort 2 (20 mg QD), Cohort 3 (40 mg QD) and Cohort 4 (80 mg QD)
- By cohort re-assessment of PK and PD to inform/confirm the predictive non-clinical PK/PD model
- BED defined as the concentration of IOA-244 at which CD63 is inhibited ≥ 50% area under the effect (AUE)/24h

Patients Eligibility

- ≥ 18 years of age with the following:
- Performance status of ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale
- Histological/cytological evidence of 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 haematology and chemistry
- RECIST 1.1. based evaluation (ORR)
- Benefit/Risk for Recommended Phase 2 Dose (RP2D)

RESULTS

Cohort	10 mg	20 mg	40 mg	80 mg	Total
N	4	4	4	4	16
Age	73.5	52	70	53	57.5
Sex m/f	4/0	1/3	2/2	1/3	8/8
Cutaneous melanoma	2	1	1	1	5
Mesothelioma	1	1	0	0	2
Uveal melanoma	1	2	3	3	9

Cohort	10 mg	20 mg	40 mg	80 mg	Total
All Cause TEAEs					
Grade 1/2	7	6	4	6	23
Grade 3/4/5	1	1	1	1	4
Drug-related TEAEs					
Grade 1/2	2	1	3	0	6
Grade 3/4/5	0	0	0	0	0

Metabolite	m/z	10 mg	20 mg	40 mg	80 mg
IOA-244 (parent)	**527**	**94.03**	**94.83**	**93.70**	**93.18**
IOA-244 +O	543	1.18	0.77	0.71	1.05
IOA-244 -C_2H_2	501	1.20	0.40	0.50	0.34
IOA-244 +O +H_2	545	0.52	0.23	0.25	0.25
IOA-244 +O -H_2	541	2.60	0.78	0.57	1.06
IOA-244 +O	543	ND	0.88	0.60	1.42
IOA-244 +O +H_2	545	0.32	0.12	0.30	0.43
IOA-244 -H_2	525	1.38	2.01	3.36	2.26

- Main tumour types: 9 uveal melanoma and 5 cutaneous melanoma patients
- No dose limiting toxicities, dose reductions or interruptions, including in 4 patients treated for up to 1 year
- Low level of metabolites with no clinically relevant reactive metabolites detected

Total Uveal Melanoma	Average maximum treatment duration (median) (as of Nov'21)	Range of treatment
9 patients*	5.6 months	1.9 months - 12.7 months

*7/9 patients had radiographic PD on their last treatment prior to receiving IOA-244
*6/9 were had longer treatment periods on IOA-244 compared to their last treatment

Figure 3

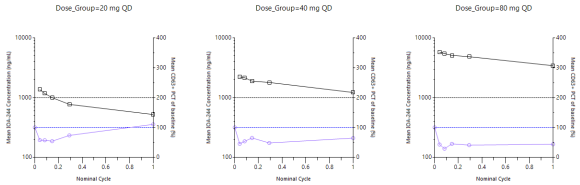


Figure 3: Above 40 mg QD, IOA-244 reaches maximum inhibition of CD63 expression at cycle 1 day 1 (Basophil Activation Test; values are mean for 4 pts).

Figure 4

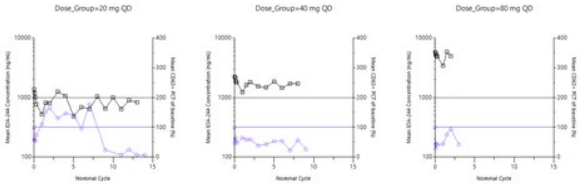


Figure 4: Rapid and sustained inhibition of CD63 expression (Basophil Activation Test; values are mean for 4 pts) observed following continuous 40 and 80 mg QD dosing.

Figure 5

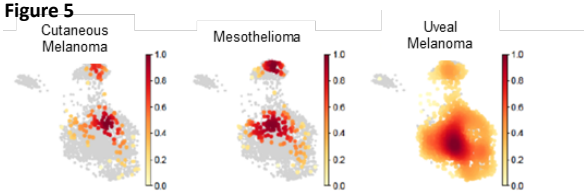


Figure 5: Uveal Melanoma Patients have more T_{reg} counts in peripheral blood (data from cohorts 10 mg and 20 mg) by cytometry by time of flight (CyTOF)

Figure 6

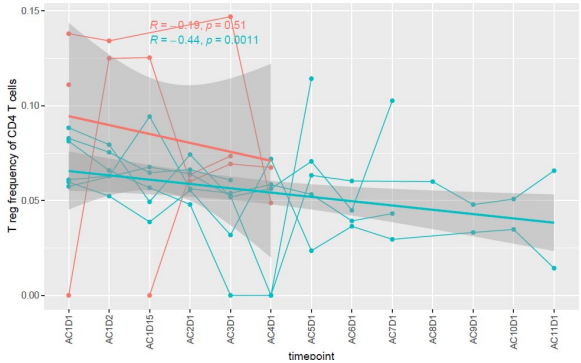


Figure 6: Uveal Melanoma patients show a reduction in T_{reg} counts in peripheral blood by CyTOF during treatment with IOA-244. Each line represents an individual patient. Colors (red and blue) show results from 2 separate runs with the respective r and p values. X-axis represents the visits: Cycle 1 has visits at Day 2 and 15 (AC1D1, AC1D2, AC1D15), and starting with Cycle 2, visits are every 28 days. Y-axis represents the units as assessed by CyTOF.

CONCLUSION

- 80 mg QD is recommended as Phase 2 dose
- No dose-limiting toxicities observed
- Low inter- and intra-patient variability in PK profile with no major metabolites
- IOA-244 administration is associated with reduction in T_{reg} counts in the peripheral blood using CyTOF

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