Abstract #42362: First-in-human (FIH) phase I dose escalation study (Part A) of the first oral allosteric modulator of phosphoinositide 3-kinase inhibitor delta (PI3Kδ) roginolisib in patients with advanced cancer and dose confirmation in Uveal Melanoma (Part B)

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BACKGROUND
Roginolisib (formerly I0A-244) has a unique mechanism of action as an allosteric modulator and a highly selective PI3Kδ inhibitor

OBJECTIVES
Primary: Safety and tolerability of escalating doses of I0A-244 to the predicted biological effective dose (BED)

Secondary: To assess the pharmacokinetic (PK) profile

Characterize pharmacodynamic (PD) effect as determined by inhibition of CD63 expression on basophils in response to I0A-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)

Methods
Design: 3×3 cohort dose escalation

Patients Eligibility
Patients with histologically or cytologically confirmed diagnosis of advanced cancer including melanoma, cutaneous and uveal melanoma or non-Hodgkin lymphoma follicular lymphoma (NHL-FL) are eligible for treatment. A performance status of ≤2 on the ECOG scale and an estimated life expectancy of ≥ 3 months are required. Patients must have a diagnosis of cancer that is advanced and/or metastatic disease for which no curative treatment is available. Patients must have had previous therapy for their malignancy and all patients must have had an adequate recovery from previous therapy

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) – exploratory studies with radiomics were conducted, including assessment of changes in spleen volume
Benefit/Risk for Recommended Phase 2 Dose (RP2D)

Results

Safety and tolerability of escalating doses of I0A-244 to the predicted biological effective dose (BED)

Primary:

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)

Characterize pharmacodynamic (PD) effect as determined by inhibition of CD63 expression on basophils in response to I0A-244

Secondary:

To assess the pharmacokinetic (PK) profile

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)

Table 2: Safety (All Cause and Drug-related)

Figure 1: Burden of Therapy/Toxicity (BOTH) for all cause TEAEs

Figure 2: Spider plots for usual melanoma patients

Figure 3: Time on roginolisib for UM patients - >50% treated beyond 6 months

Figure 4: Proteomic analysis of plasma cytokine/chemokine

Figure 5: Changes in spleen volume using Radiomics assessment in UM patients

Figure 6: Survival Rate (% of UM patients at landmark time points [6, 12 and 18 months]

Figure 7: Kaplan-Meier (KM) Plots for uveal melanoma patients (OS data still evolving)

Figure 8: Evolving survival curves based on numbers of prior lines of treatment (TN) and OS data still evolving

CONCLUSIONS
Roginolisib, given as an oral monotherapy, has a favourable toxicity profile compared to 1st generation PI3Kδ Inhibitors (especially in patients treated >6 months)

Roginolisib increases plasma IL-15, INFγ while reducing CCL22

Patients treated with roginolisib have extended time on treatment (ToTx) beyond progression, due to the favourable toxicity profile

Long term administration of roginolisib (>6 months) translates to encouraging Overall Survival (>20 months)

References