Abstract #422362: 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

- *PIK3CD* expression is correlated with immune suppressive immune cells, such as T_{reg} cells
- Highly selective PI3Kd inhibition results in blocking tumour-cell intrinsic and extrinsic pathways
- Roginolisib (formerly IOA-244) has a unique mechanism of action as an allosteric modulator and a highly selective PI3Kd inhibitor

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 pharmacodynamic (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)

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
- Histological or cytological evidence of a diagnosis of cancer that is advanced and/or metastatic disease for mesothelioma, cutaneous, and uveal melanoma or non-Hodgkin lymphoma follicular lymphoma (NHL-FL)
- 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) – exploratory studies with radiomics were conducted, including assessing changes in spleen volume
- Benefit/Risk for Recommended Phase 2 Dose (RP2D)

BOTh – Burden of Therapy (Toxicity)

BOTh ™ is a highly sensitive, novel methodology that utilises patient-level data to derive a quantitative estimate for the "Burden of Therapy/Toxicity" (BOTh) that pts experience on each day of a clinical study .

Reference for BOTh: Abdul-ahad et al. Contemporary Clinical Trials Communications 4 (2016) 186e191

RESULTS

Table 1. Demography and Baseline Characteristics

Cohort	Part A 10 mg	Part A 20 mg	Part A 40 mg	Part A 80 mg	Part B 80 mg	Overall
N	4	8	4	8	20	44
Median Age (range)	74 (52-76)	55 (47 -74)	70 (66-82)	62 (44-75)	56 (26-73)	59 (26-82)
Sex (m/f)	4/0	3/5	2/2	2/6	10/10	21/23
Primary Diagnosis						
Uveal Melanoma	1	2	3	3	20	29
Mesothelioma	1	1	0	0	0	2
Melanoma	2	1	1	1	0	5
Follicular Lymphoma	0	4	0	4	0	8
Stage at Screening						
IIIc	0	2	0	3	0	5
IV	4	6	4	5	19	39
Median prior Tx	2 (1-3)	3 (1-7)	3 (1-4)	2 (1-8)	2 (0-8)	2 (0-8)
1st Line Tx						
Pembrolizumab	0	0	2	2	8	12
Nivolumab	1	1	1	1	6	10
Nivolumab/Ipilimumab	1	1	1	0	2	6
Ipilimumab	0	1	0	0	0	1
Tebentafusp	1	0	0	0	1	2
Other	1	1	0	1	0	3
R-CHOP/R-Bendamustine	0	4	0	4	0	8
None	0	0	0	0	2	2

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

	ST 10 mg n=4	ST 20 mg n=8	NHL 20 mg n=4	ST 40 mg n=4	ST 80 mg n=8	NHL 80 mg n=4	UM Part B n=20	Overall n=44
All Causality TEAEs								
Any Grade n patients (%)	4 (100%)	3 (75%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)	15 (79%)	38 (88%)
Grade 1	4 (100%)	3 (75%)	4 (100%)	2 (50%)	4 (100%)	4 (100%)	15 (79%)	36 (84%)
Grade 2	3 (75%)	2 (50%)	1 (25%)	2 (50%)	4 (100%)	3 (75%)	12 (63%)	27 (63%)
Grade 3	0	0	1 (25%)	0	3 (75%)	1 (25%)	3 (16%)	8 (19%)
Grade 4	0	0	0	0	0	0	2 (11%)	2 (5%)
Grade 5*	1 (25%)	1 (25%)	0	1 (25%)	0	0	0	3 (7%)
Drug-related TEAEs								
All TEAEs related to IOA 244 n patients (%)	2 (50%)	1 (25%)	3 (75%)	2 (50%)	0 (0%)	1 (25%)	7 (37%)	16 (37%)
Grade 1	2 (50%)	1 (25%)	3 (75%)	2 (50%)	0	0	7 (37%)	15 (35%)
Grade 2	0	0	1 (25%)	1 (25%)	0	0	3 (16%)	5 (12%)
Grade 3*	0	0	1 (25%) ¥	0	0	1 (25%) ¥	1 (5%)	3 (7%)
Grade 4	0	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0	0

ST: solid tumour, NHL: non-Hodgkin lymphoma, UM: uveal melanoma

*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 – Platelet Count decrease, 80 mg - neutrophil decrease, lipase increase)

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

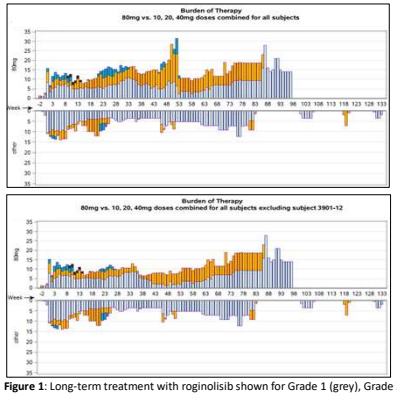

Figure 1: Long-term treatment with roginolisib shown for Grade 1 (grey), Grade 2 (orange), Grade 3 (blue) all-cause toxicity for patients receiving 80 mg (n= 28) vs all other dose levels (n=16). Panel A: all patients. Panel B: one patient with uveal melanoma had an initial increase and reduction in ALT coinciding with viral infection. Excluding this patient identifies this patient as the main driver for Grade 3 toxicity evaluation in uveal melanoma.

Anti-tumour activity

Figure 2: Spider plots for uveal melanoma patients

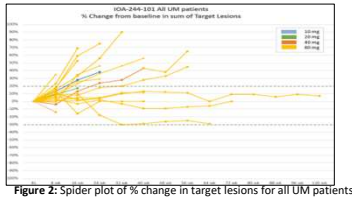

Figure 2: Spider plot of % change in target lesions for all UM patients with measurable disease as per RECIST 1.1 by dose level.

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

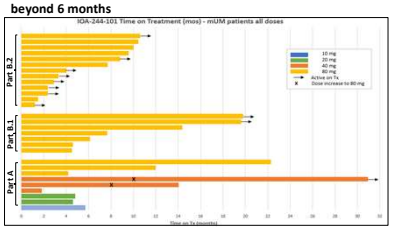

Figure 3: Bar chart for patients with uveal melanoma (n=29) (11/29 pts (45%) continue on roginolisib

Figure 4: Proteomic analysis of plasma cytokine/chemokine

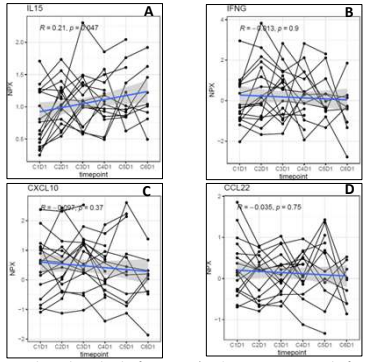

Figure 4: Panel A-D Plasma levels of IL15, IFNG (IFNγ), CXCL10 increase in the first 28 days for all patients with uveal melanoma (blue line=median). Panel A: IL15 level remain stable over the treatment period; Panel B and C: IFNγ, CXCL10 appear to be stable or slightly reduced over the treatment period. The Treg inducing chemokine CCL22 is reduced and continues a trend of reduction over time

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

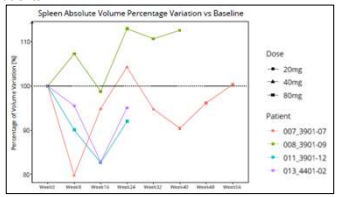

Figure 5: A treatment-related reduction of spleen volume is observed in all 4 patients analysed

Figure 6: Survival Rate (%) of UM patients at landmark time points (6, 9 and 12 months)

% Survival (95% CI)	Roginolisib (ongoing) Part A (n=9)	Part B.1 (n=7)	Part B.2 (n=13)	Overall (n=29)	Rantala After CPI (n=318)
6 months	88.9% (43.3%, 98.4%)	100% (-)	75.0% (29.8%, 93.4%)	87.4% (65.8%, 95.8%)	58.1% (32.3%, 63.5%)
9 months	88.9% (43.3%, 98.4%)	71.4% (25.8%, 92.0%)	75.0% (29.8%, 93.4%)	78.7% (56.0%, 90.5%)	42.4% (36.6%, 48.1%)
12 months	66.7% (28.2%, 87.8%)	71.4% (25.8%, 92.0%)	-	67.3% (42.7%, 83.2%)	34.2% (28.6, 39.9%)

Figure 6: UM patients treated with roginolisib (n=29) compared to patients treated with different drugs after progression on prior checkpoint inhibitor (CPI) (n=318) (Historic external control Rantala et al 2019)

Ref: Rantala et al Melanoma Research 2019, 29:561–568

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

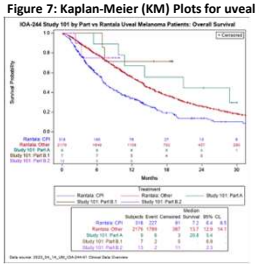

Figure 7: Patients treated with roginolisib have extended time on treatment (ToTx), beyond progression, due to the favourable toxicity profile.

This translates to long OS for patients treated in the dose escalation part (Part A), initial expansion cohort (part B.1) and final expansion cohort (Part B.2).

The median OS is only available for Part A (20.8 mo) The median has not been reached for Parts B.1 and B.2.

Figure 8: KM Plots for uveal melanoma patients by number of prior lines of treatment (Tx) (OS data still evolving)

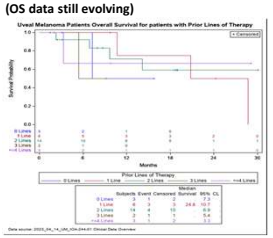

Figure 8: Evolving survival curves based on numbers of prior lines of treatment with 88% of patients with prior Tx received at least one CPI (Part A, B.1 and B.2):

Blue: no prior Tx: 3
Red: 1 prior Tx 6
Green: 2 prior Tx 14
Brown: 3 prior Tx 2
Purple: ≥4 prior Tx 3

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, IFNγ while reducing CCL22 levels
- Correlation studies with mass cytometry (Treg, CD8 and NK cell population) are ongoing
- Long term administration of roginolisib (>6 months) translates to encouraging Overall Survival (>20 months)

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Trial NCT04328844 is ongoing -Sponsored by iOnctura SA