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 PI3Kδ 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 PI3Kδ 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
- 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. Toxicity units are weighted scores combining the severity, frequency, and duration of each side effect.

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
Tebentefusp	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=4	NHL 20 mg n=4	ST 40 mg n=4	ST 80 mg n=4	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

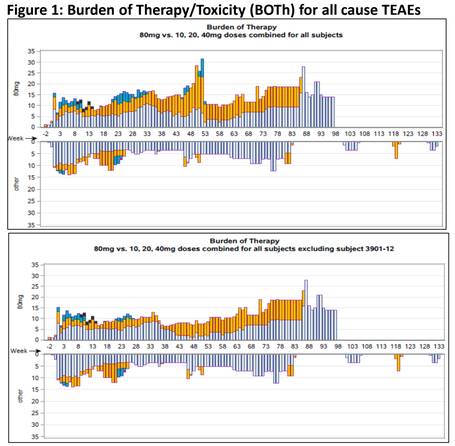

Figure 1: All Cause TEAEs - Long-term treatment with roginolisib shown for Grade 1 (grey), Grade 2 (orange), Grade 3 (blue) for patients receiving 80 mg (n= 28) vs all other dose levels (n=16). y-axis: toxicity units quantify the cumulative impact of a patient's adverse effects during treatment (x-axis).

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

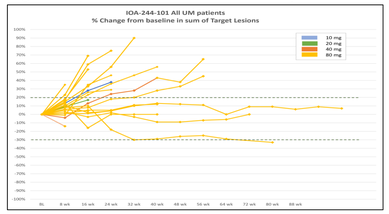

Figure 2: Spider plot of % change in target lesions for all UM patients with measurable disease as per RECIST 1.1 by dose level (dotted lines: PD, +20%, and PR, -30%)

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

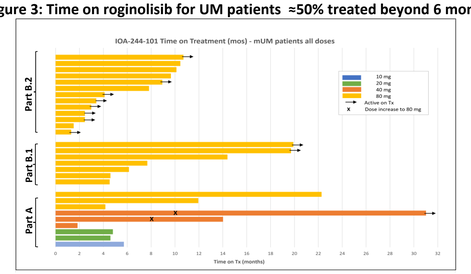

Figure 3: Swimmer Plot (Napoleon Plot) for patients with uveal melanoma (n=29). As of 12th of May 2023, 11/29 pts (38%) continue on roginolisib.

Part A: Patients (n=9) from the dose escalation are shown at the four initial dose levels (see color-matched dose levels). Black "x" indicate intra-patient dose escalation.

Part B.1: Patients of the initial dose expansion at 80 mg QD (n=7)

Part B.2.: Patients of the remaining dose expansion 80 mg QD (n=13)

Figure 4: Proteomic analysis of plasma cytokine/chemokine

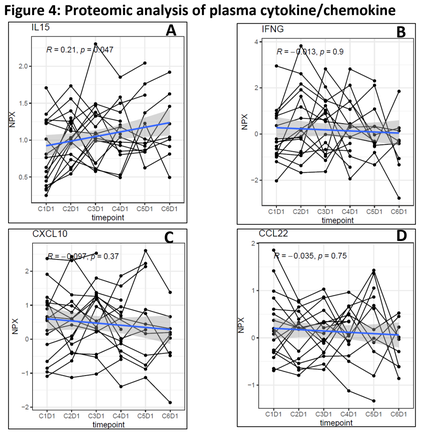

Figure 4: Plasma Chemokine and Cytokines (O-Link Panel): Panel A-C Plasma levels of IL15, IFNG (IFNγ), CXCL10 increase in the first 28 days for most patients (blue line=median). Panel D: The Treg cell inducing chemokine CCL22 is reduced. The increase of IL-15, IFNγ and CXCL10 are consistent with previously reported increases of CD8 T effector cells, and the reduction of CCL22 coincides with the decline in Treg cells (Di Giacomo et al. ESMO-IO 2022). (X-axis: Each of 28 days is denoted C1 etc; y-axis: NPX levels based on O-Link reports)

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

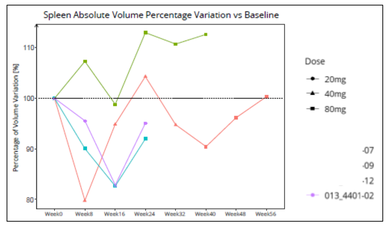

Figure 5: A treatment-related reduction of spleen volume is observed in 3/4 patients. Occurs within normal ranges and recover within several cycles.

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)

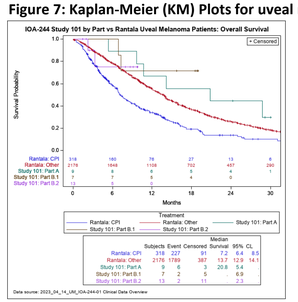

Figure 7: Patients treated with roginolisib have extended time on treatment (ToTx), beyond progression, due to the favourable toxicity profile.

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 yet 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)

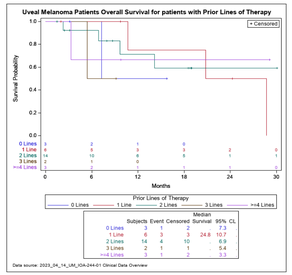

Figure 8: Evolving survival curves based on numbers of prior lines of treatment. 88% of patients with prior Tx having received at least one CPI (Part A, B.1 and B.2).

Blue:	no prior	(n=3)
Red:	1 prior	(n=6)
Green:	2 prior	(n=14)
Brown:	3 prior	(n=2)
Purple:	≥4 prior	(n=3)

CONCLUSIONS/Next steps

- 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
- Long term administration of roginolisib (>6 months) translates to encouraging Overall Survival (>20 months)
- Correlation studies with mass cytometry (e.g., Treg, CD8) are ongoing

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Trial NCT04328844 is ongoing -Sponsored by iOnctura SA