131P - Safety and Clinical Efficacy of Roginolisib (IOA-244), the First Oral Allosteric Modulator of Phosphoinositide 3-kinase Inhibitor delta (PI3Kδ)

AM Di Giacomo[1], M Simonelli[2], F Santangelo[1], G Amato[1], E Simonetti[1], J Graham[3], M Lahn[4], G Di Conza[4], T Hammett[4], R Zorrilla[4], P Kaur[4], T Ziyang[5], L Tadepally[5], P Brodin[5], M Occhipinti[6], C Carlo-Stella[2], A Santoro[2], P Spiliopoulou[3], TRJ Evans[3]*, M Maio[1]*

[1]University of Siena; Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy, [2]IRCSS Humanitas Research Hospital, Milano-Rozzano, Italy, [3]Beatson West of Scotland Cancer Centre – NHS Greater Glasgow and Clyde, Glasgow, United Kingdom, [4]R&D Department, iOnctura SA, Geneva, Switzerland, [5]Cellular Immunomonitoring Facility, SciLifeLab, Dept. of Women´s and Children´s Health, Karolinska Institutet, Stockholm, Sweden, [6]Radiomics, Liege, Belgium, *Asterix indicates both are senior authors

BACKGROUND

- *PIK3CD* expression is correlated with immune suppressive immune cells, such as T regulatory (T_{reg}) cells
- Highly selective PI3Kδ inhibition results in blocking tumour-cell intrinsic and extrinsic pathways
- Roginolisib is a highly selective oral allosteric modulator of PI3Kδ
- Roginolisib has a unique safety and pharmacodynamic profile

OBJECTIVES

Primary:

Safety and tolerability of escalating doses of roginolisib to the predicted biological effective dose (BED) range

Secondary:

- To assess the pharmacokinetic (PK) profile
- Characterize PD effect as determined by inhibition of CD63 expression on basophils in response to roginolisib.
- Document anti-tumour activity, e.g., overall response rate (ORR), duration of response (DoR), progression free survival (PFS) and overall survival (OS)

Exploratory:

- Changes in circulating immune cell by mass cytometry (Cytometry by Time of Flight, CyTOF).
- Response assessments by radiomics and blood-based proteins

METHODS

Design: 3+3 cohort dose escalation and expansion

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, uveal melanoma and Follicular Lymphoma (FL)
- Adequate organ functioning

Assessments:

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

RESULTS

Table 1. Demography and Baseline Characteristics

	Part A				Part B	
Cohort	10 mg	20 mg	40 mg	80 mg	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
ECOG at Screening						
0	3	4	4	3	18	32
1	1	4	0	5	2	12
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	5
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	3	3

SAFETY

Table 2. All cause and Drug related TEAEs

(As of 12Jun23)	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%)	17 (85%)	41 (93%)
Grade 1	4 (100%)	3 (75%)	4 (100%)	2 (50%)	4 (100%)	4 (100%)	17 (85%)	36 (84%)
Grade 2	3 (75%)	2 (50%)	1 (25%)	2 (50%)	4 (100%)	3 (75%)	13 (65%)	27 (63%)
Grade 3	0	0	1 (25%)	0	3 (75%)	1 (25%)	4 (20%)	9 (19%)
Grade 4	0	0	0	0	0	0	1 (5%)	1 (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%)	8 (40%)	17 (39%)
Grade 1	2 (50%)	1 (25%)	3 (75%)	2 (50%)	0	0	8 (40%)	15 (34%)
Grade 2	0	0	1 (25%)	1 (25%)	0	0	3 (15%)	5 (11%)
Grade 3†	0	0	1 (25%) [a]	0	0	1 (25%) [b]	1 (5%) [c]	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; TEAEs – Treatment emergent adverse events
*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[a], 80 mg FL – Neutrophil decrease[b], lipase increase[c]

No serious TEAEs considered related to Roginolisib were observed

Figure 1: Low Dose Interruptions, Reductions and Modifications with Roginolisib (by Cycle)

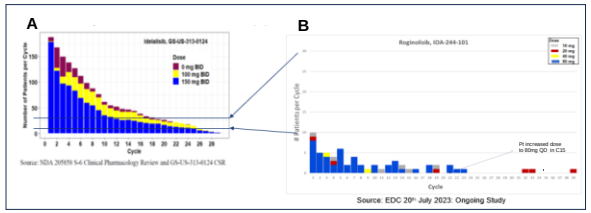

Figure 1: Dose interruptions comparison between idelalisib (Panel A) and roginolisib (Panel B) (1 patient on roginolisib discontinued due to undiagnosed uveitis from a prior pembrolizumab treatment)

EFFICACY

Figure 2: Time on Treatment and Overall Survival In Uveal Melanoma (n=29)

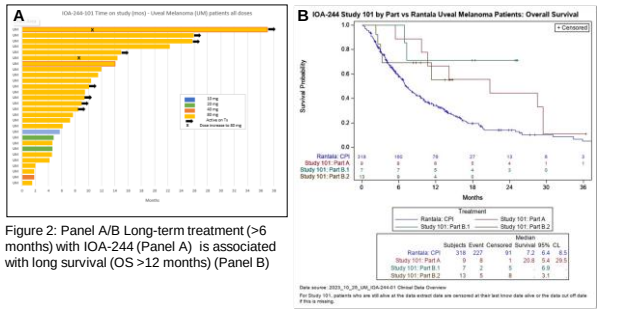

Figure 2: Panel A/B Long-term treatment (>6 months) with IOA-244 (Panel A) is associated with long survival (OS >12 months) (Panel B)

Rantala ES, Hernberg M, Kivelä TT. Overall survival after treatment for metastatic uveal melanoma: a systematic review and meta-analysis. Melanoma Res. 2019 Dec;29(6):561-568

EXPLORATORY STUDIES

Figure 3: Mass Cytometry of Peripheral Blood Immune Cell and Associated Plasma Protein Changes

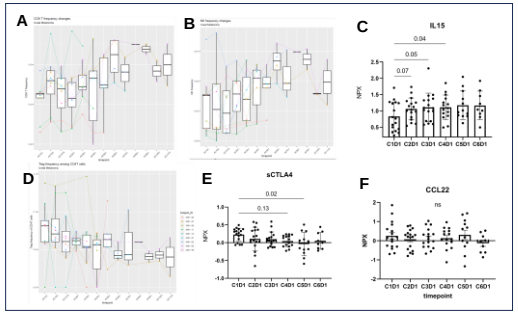

Figure 3: Mass Cytometry data show an increase of peripheral blood CD8⁺ T cells and NK Cells (panel A and B). This coincides with increase in plasma IL-15 levels (O-Link; Panel C). Simultaneously, T_{reg} cells are reduced (Panel D) along with plasma sCTLA-4 (Panel E). For CCL22 (Panel F) there is an initial decrease at Cycle 2 Day 1.

Figure 4: Changes in Target Lesions (RECIST 1.1) and Serum LDH levels

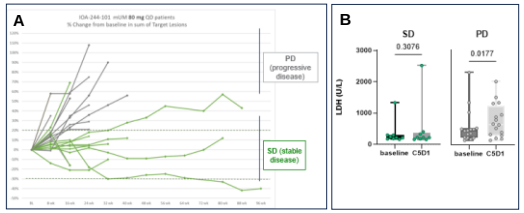

Figure 4: Panel A: Spider plot representing decrease or increase of target lesions by RECIST1.1 for patients with either SD (green lines) or PD (grey lines) at Cycle 5. Panel B: LDH levels in patients with SD and PD at Cycle 5 indicating that patients with PD are having a possible tumour growth.

Figure 5: Plasma Protein Changes (O-Link Panel) Indicate that patients with SD at Cycle 5 have increased immune competency

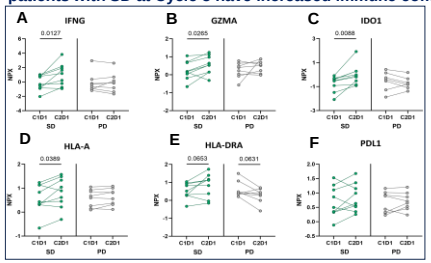

Figure 5: Patients with SD at Cycle 5 up-regulate IFN-γ and IFN-γ-associated proteins in their plasma after 1 cycle of Roginolisib therapy (C2D1). No changes were observed in the PD patients. Statistics were performed by using paired t-test.

Figure 6: Changes Of Activated T cells in Patients with SD and PD at Cycle 5 (by Flow Cytometry)

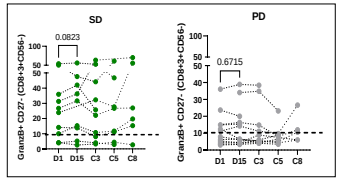

Figure 6: Flow cytometry analysis of activated CD8⁺ T cells (Granzyme B⁺/CD27⁻ (% of CD8⁺ T cells) measure in the peripheral blood of patients at baseline (D1) and after roginolisib treatment.

Figure 7: Radiomics-based Analyses – 56 y.o. Female with Stage IV UM

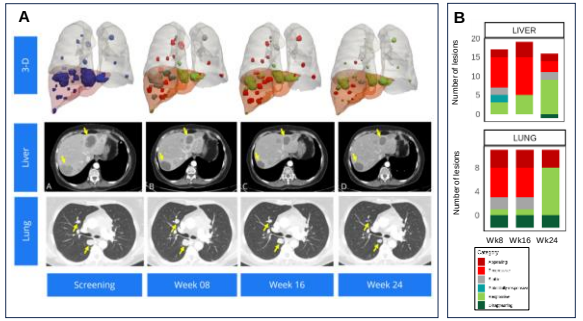

Figure 7: Lesion changes over time (3-D rendering, CT liver/lung) in a patient with uveal melanoma (80 mg QD) (Panel A and B). Colour scale represents responses of lesions with green indicating responses)

Table 3: Summary of lesion number per response category (radiomics-based ROI)

ROI	RESPONSE STATUS FROM BASELINE					
	Appearing	Progressive	Stable	Potentially Responsive	Responsive	Disappearing
LUNG	3	0	0	0	8	-2
LIVER	2	3	2	0	9	-1

CONCLUSIONS

- Roginolisib is well tolerated at the 80 mg QD dose
- Long term administration (>6 months) translates into encouraging OS in uveal melanoma superior to historical OS in patients previously treated with an immune checkpoint inhibitor: 59% (17/29) were treated for >6 months, with 65% (11/17) showing an OS of >12 months (ongoing)
- Patients can be characterised by 2 populations based on clinical and pharmacodynamic outcomes
- **Stable disease (SD) by Cycle 5 Population:** elevated activated T cells at baseline and a PD response to roginolisib indicative of increased immune competency (↑IFNg,↑GZMA,↑HLA-DRA, HLA-A), immune modulation (↑IDO1, ↑PD-L1) and good disease control (e.g., low LDH, stable on imaging)
- **Progressive disease (PD) by Cycle 5 Population:** low activated T cells at baseline, no immunocompetency pharmacodynamic changes on treatment and with signs of disease progression (e.g., increasing LDH, progressive disease on imaging)
- Patients with SD at Cycle 5 show rebalancing of their T Cell effector function

Presenter´s email: annamaria.digiacomo@unisi.it

NCT04328844 - Sponsored by iOnctura SA