#119P Long-term safety evaluation of roginolisib (formerly IOA-244), a highly selective phosphoinositide 3-kinase inhibitor delta (PI3Kδ), in a Phase I First in Human (FIH) study

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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 a allosteric modulator and as a highly selective PI3Kδ inhibitor

Hypothesis:
Due to its unique mechanism of action, roginolisib has a favourable toxicity profile compared to first generation PI3Kδ inhibitors

OBJECTIVES

Primary:
Safety and tolerability of escalating doses of roginolosib to the predicted biological effective dose (BED)

Secondary:
- Assess the pharmacokinetic (PK) profile
- Document antitumor activity, such as time on treatment, overall survival (OS)

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)
- 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 .
The daily burden estimate is based on number and severity of adverse events (AEs) and a combination of incidence and severity.
Traditional analysis of AEs gives a static interpretation, BOTh provide a more dynamic view on burden of toxicity on pts

Reference: Abdulahad et al. Contemporary Clinical Trials Communications 4 (2016) 186e191

RESULTS

Demography and Baseline Characteristics

Cohort	10 mg	20 mg	40 mg	80 mg	Overall
N	4	8	4	8	24
Age (median)	73.5	54.5	70.0	61.5	65.0
Sex (m/f)	4/0	3/5	2/2	2/6	11/13
Primary Diagnosis					
Uveal Melanoma	1	2	3	3	9
Mesothelioma	1	1	0	0	2
Melanoma	2	1	1	1	5
Follicular Lymphoma	0	4	0	4	8
Median prior Tx	2 (1-3)	3 (1–7)	2 (1-3)	2 (1-5)	2 (1-7)

Solid tumour: n=16 (4 at each dose level). NHL-FL: n= 8 (4 at 20 and 80 mg dose level)

Safety

	10 mg n=4	20 mg n=8	40 mg n=4	80 mg n=8	Overall n=24
All Causality TEAEs					
Any Grade n patients (%)	4 (100%)	7 (87%)	4 (100%)	6 (75%)	21 (87%)
Grade 1	4 (100%)	7 (87%)	2 (50%)	6 (75%)	19 (79%)
Grade 2	3 (75%)	3 (37%)	2 (50%)	5 (62%)	13 (54%)
Grade 3	0	1 (13%)	0	4 (50%)	5 (21%)
Grade 4	0	0	0	0	0
Grade 5*	1 (25%)	1 (13%)	1 (25%)	0	3 (13%)
Drug-related TEAEs					
All TEAEs related to IOA 244 n patients (%)	2 (50%)	4 (50%)	2 (50%)	1 (13%)	9 (38%)
Grade 1	2 (50%)	4 (50%)	2 (50%)	0	8 (33%)
Grade 2	0	1 (25%)	1 (25%)	0	2 (8%)
Grade 3†	0	1 (25%)	0	1 (25%)	2 (8%)
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0

*The CTCAE Grade 5 toxicities observed were associated with tumour progression and **NOT** considered related to treatment.
†The Grade 3 related TEAEs were transient and resolved whilst continuing on treatment with roginolosib. 20 mg NHL-FL – Platelet Count decrease, 80 mg NHL-FL – Neutrophil decrease

Figure 1: Serum Transaminase and LDH

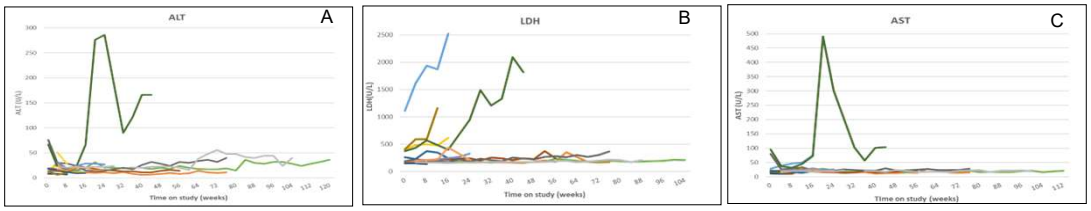
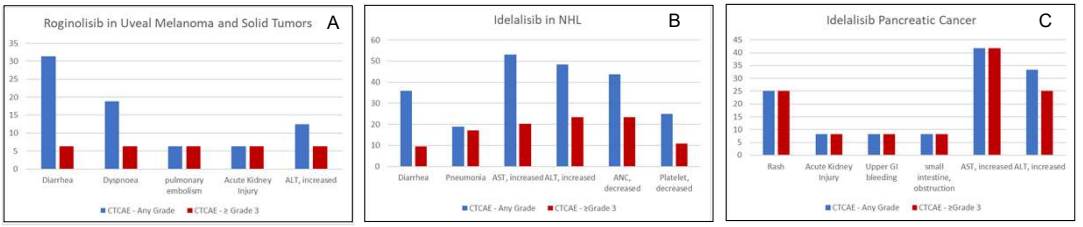


Figure 1 Panel A-C:
Roginolisib was given without dose modifications in patients treated for more than 4 months. ALT (A), LDH (B), and AST (C) remain unchanged during treatment unless where progression is observed in the liver.

Figure 2: All Cause Toxicity for Roginolisib compared to 1st Generation PI3Kδ Inhibitors (AEs in more than 10% of Frequency)



Flinn et al 2014 - Blood. 2014;123(22):3406-3413

Borazanci et al. The Oncologist 2020;25:e1604–e1613

Figure 2 Panel A-C:
All-cause toxicity of roginolisib (A) compared to FiH dose study data for idelalisib in NHL (B) and pancreatic cancer (C). Idelalisib has a similar toxicity profile in haematologic and solid tumour

Figure 3: Burden of Therapy/Toxicity (BOTh)

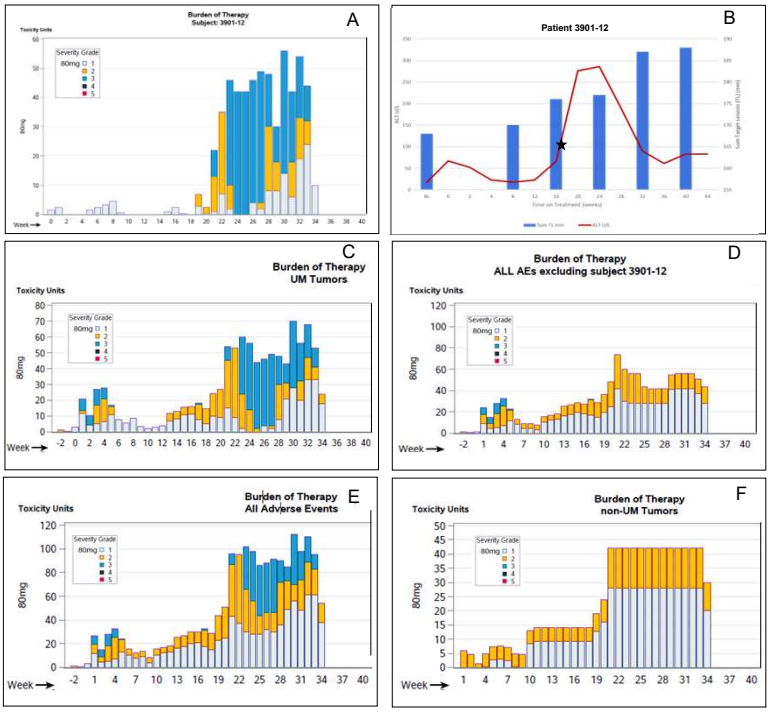


Figure 3 Panel A-F: Long-term treatment with roginolisib shown for Grade 1 (grey), Grade 2 (orange), Grade 3 (blue) all-cause toxicity (A, C-F). Panel B: one patient with uveal melanoma had an initial increase and reduction in ALT (red curve) coinciding with viral infection★. Increase in metastases burden is also shown (blue bars). Removing this patient (D and F) identifies this patient as the main driver for Grade 3 toxicity evaluation in uveal melanoma.

Figure 4: Long-term Administration of Roginolisib Translates to Clinical Benefit

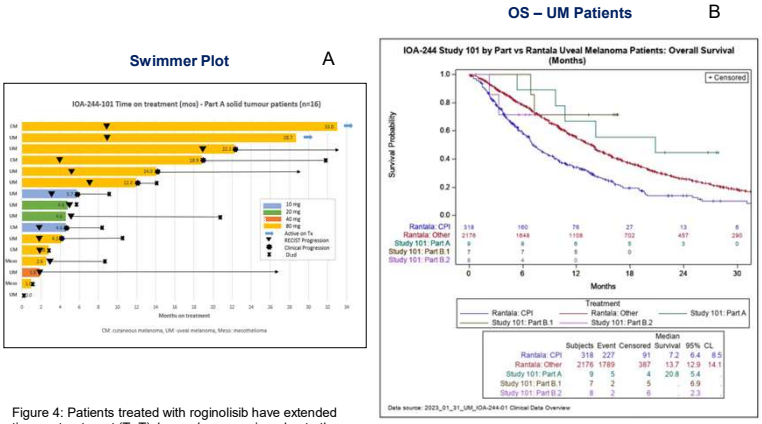


Figure 4: Patients treated with roginolisib have extended time on treatment (ToT), beyond progression, due to the favourable toxicity profile (A). This extended ToT translates to long OS for patients treated in the dose escalation part, initial expansion cohort and final expansion cohort (B).

CONCLUSIONS

- Roginolisib monotherapy has a favourable toxicity profile compared to 1st generation PI3Kδ Inhibitors (especially in patients treated >6 months)
- BOTh evaluation highlights the toxicity profile in patients over time
- Long term administration of roginolosib (>6 months) translates to encouraging Overall Survival (>20 months)

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