P1114 - HIGHLY SELECTIVE ALLOSTERIC MODULATOR OF THE PHOSPHOINOSITIDE 3-KINASE DELTA (PI3KΔ) ROGINOLISIB (IOA-244) IN A DOSE ESCALATION STUDY OF PATIENTS WITH REFRACTORY/RELAPSED FOLLICULAR LYMPHOMA (FL)

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INTRODUCTION

- Roginolisib (IOA-244) has shown a favourable toxicity and ADME profile in over 40 patients (pts) with both solid tumours and Non-Hodgkin´s lymphoma – follicular lymphoma (NHL-FL).
- As part of the First-in-human (FiH) dose escalation study, pts with NHL-FL were treated with the RP2D to determine whether same treatment regimen can be used in either solid or FL pts *(Di Giacomo et al 2021).*
- Roginolisib (IOA-244) is a PI3Kδ inhibitor designed to specifically target T regulatory (T_{reg}) cells in malignancies and to enhance the T effector (T_{eff}) cells function in patients.

Figure 1

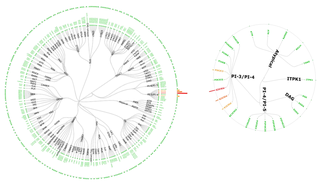

Figure 1: Roginolisib is a Highly Selective PI3Kδ Inhibitor

Figure 2

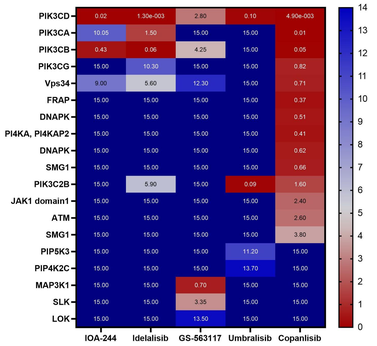

Figure 2: IOA-244 is a unique non-ATP competitive, selective PI3Kδ inhibitor. Heat map presentation of the selectivity of selected PI3Kδ inhibitors: roginolisib (IOA-244), idelalisib, idelalisib´s main metabolite GS-563117, umbralisib and copanlisib - based on activity in Jurkat cell lysate as measured using the KiNativ method *(Johnson et al 2023, Di Conza et al 2022)*

METHODS

Design:

- 3+3 cohort dose escalation
- BED defined as the concentration of IOA-244 at which CD63 is inhibited ≥ 50% area under the Effect (AUE) per 24 hour

Patients Eligibility

- ≥ 18 years of age with the following:
- A performance status of ≤2 on the Eastern Cooperative Oncology Group (ECOG) scale
- Histological or cytological evidence of a diagnosis of cancer that is advanced and/or metastatic disease for mesothelioma, cutaneous and uveal melanoma and NHL-FL
- Adequate organ function

Assessments:

- Toxicities graded according to Common Terminology Criteria for Adverse Events (CTCAE) v 5.0
- Standard laboratory, haematology and chemistry
- Lugano based evaluation (ORR)
- Benefit/Risk for Recommended Phase 2 Dose (RP2D)
- BOTh – Burden of Therapy (Toxicity) (*Abdul-Ahad et al 2016*)

RESULTS

DEMOGRAPHY AND BASELINE CHARACTERISTICS

Table 1: Demographic summary

Cohort	Part A					Part B	Overall
ST: Solid tumour FL: Follicular lymphoma	10 mg ST	20 mg ST	20 mg FL	40 mg ST	80 mg ST	80 mg FL	80 mg ST	
N	4	4	4	4	4	4	20	44
Median Age (range)	74 (52-76)	52 (47 -54)	64 (55 -74)	70 (66-82)	53 (44-59)	74 (65-75)	56 (26-73)	59 (26-82)
Sex (m/f)	4/0	1/3	2/2	2/2	2/2	1/3	10/10	21/23
Primary Diagnosis								
Uveal Melanoma	1	2	0	3	3	0	20	29
Mesothelioma	1	1	0	0	0	0	0	2
Melanoma	2	1	0	1	1	0	0	5
Follicular Lymphoma	0	0	4	0	0	4	0	8
Stage at Screening								
IIIc	0	1	1	0	0	3	0	5
IV	4	3	3	4	4	1	19	39
Median prior Tx	2 (1-3)	4 (1–6)	3 (1–7)	3 (1-4)	2 (1-8)	2 (1-8)	2 (0-8)	2 (0-8)
1st Line Tx								
Pembrolizumab	0	0	0	2	2	0	8	12
Nivolumab	1	1	0	1	1	0	6	10
Nivolumab/Ipilimumab	1	1	0	1	0	0	2	6
Ipilimumab	0	1	0	0	0	0	0	1
Tebentafusp	1	0	0	0	0	0	1	2
Other	1	1	0	0	1	0	0	3
R-CHOP	0	0	2	0	0	1	0	3
R-Bendamustine	0	0	2	0	0	3	2	8
None	0	0	0	0	0	0	0	2

SAFETY

Table 2: Roginolisib All-Cause and Drug Related TEAEs – All patients

	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%) [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, FL: follicular 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[a], 80 mg - neutrophil decrease[b], lipase increase[c]

Table 3: Summary of related TEAEs by CTCAE, PT and SoC – FL

Organ system/Preferred Term (MedDRA)	20 mg FL (n=4)			80 mg FL (n=4)			Overall (n=8)		
	N	%	E	N	%	E	N	%	E
Any related TEAE all grades	**3**	**75%**	**9**	**1**	**25%**	**1**	**4**	**50%**	**10**
Any related TEAE Grade 1 (Mild)	**3**	**75%**	**5**	**0**	**0%**	**0**	**3**	**38%**	**5**
Investigations	**2**	**50%**	**3**	**0**	**0%**	**0**	**2**	**25%**	**3**
Alanine aminotransferase increased	1	25%	1	0	0%	0	1	13%	1
Aspartate aminotransferase increased	1	25%	1	0	0%	0	1	13%	1
Blood uric acid increased	1	25%	1	0	0%	0	1	13%	1
Gastrointestinal disorders	**1**	**25%**	**1**	**0**	**0%**	**0**	**1**	**0%**	**1**
Diarrhoea	1	25%	1	0	0%	0	1	13%	1
Blood and lymphatic system disorders	**1**	**25%**	**1**	**0**	**0%**	**0**	**1**	**13%**	**1**
Anaemia	1	25%	1	0	0%	0	1	13%	1
Any related TEAE Grade 2 (Moderate)	**1**	**25%**	**3**	**0**	**0%**	**0**	**1**	**13%**	**3**
Investigations	**1**	**25%**	**2**	**0**	**0%**	**0**	**1**	**13%**	**2**
Alanine aminotransferase increased	1	25%	**1**	0	0%	**0**	1	13%	1
Platelet count decreased	1	25%	1	0	0%	0	1	13%	1
Blood and lymphatic system disorders	**1**	**25%**	**1**	**0**	**0%**	**0**	**1**	**13%**	**1**
Anaemia	1	25%	1	0	0%	0	1	13%	1
Any related TEAE Grade 3 (Severe)	**1**	**25%**	**1**	**1**	**0%**	**1**	**2**	**25%**	**2**
Investigations	**1**	**25%**	**1**	**1**	**0%**	**1**	**2**	**25%**	**2**
Platelet count decreased	1	25%	**1**	0	0%	**0**	1	13%	1
Neutrophil count decreased	0	0%	0	1	0%	1	1	13%	1
Any related TEAE Grade 4 or 5	0	0%	0	0	0%	0	0	0%	0

PT: preferred term, SoC: system organ class

Figure 3: Burden of Therapy/Toxicity for solid tumour vs NHL-FL patients dosed with roginolisib 80 mg – all cause TEAEs

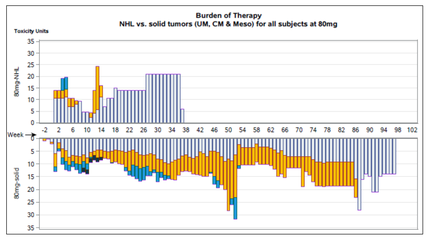

Figure 3: Long-term treatment with roginolisib shown for Grade 1 (grey), Grade 2 (orange), Grade 3 (blue) all-cause toxicity for NHL(n= 8) vs solid tumour (n=36). At 80 mg long term toxicity is similar between solid tumour and NHL patients. (y-axis: toxicity units quantify the cumulative impact of a patient's adverse effects during treatment (x-axis).

Figure 4

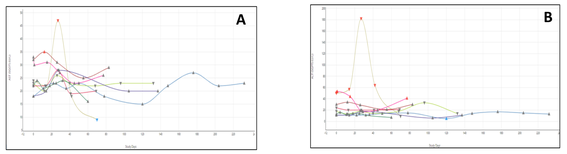

Figure 4: Panel A and B: roginolisib was given without dose modifications in patients treated for up to 8 months. All 8 patients showed normal AST (**Panel A; U/L**) and ALT levels (**Panel B; U/L**). One patient had a transient increase in AST and ALT which subsequently returned to baseline, while patient continued to receive IOA-244 without any other drug intervention

ANTI-TUMOUR ACTIVITY

Figure 5: Time on roginolisib treatment

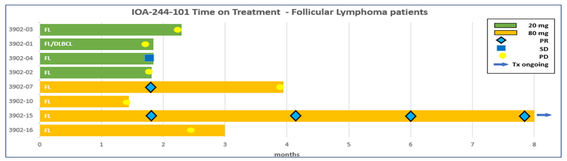

Figure 5: Swimmer plot shows time on roginolisib treatment (mos) and response per investigator assessed Lugano by dose level

Figure 6: PET imaging during treatment

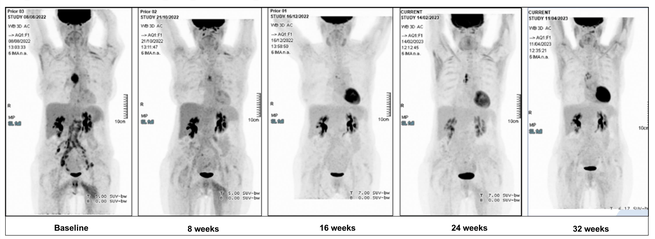

Figure 6: 74 year old female with Stage IV Follicular Lymphoma. Dosed with roginolisib 80 mg, ongoing on treatment for over 8 months. Partial remission as per Lugano criteria observed at 8 weeks and maintained for 6 months.

Figure 7: CT and PET imaging during treatment

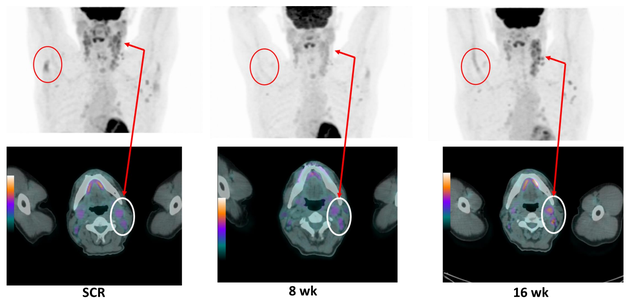

Figure 7: 64 year old male with Stage IV Follicular Lymphoma. Dosed with roginolisib 80 mg for 4 months. Partial remission observed at 8 weeks as per Lugano criteria.

Figure 8

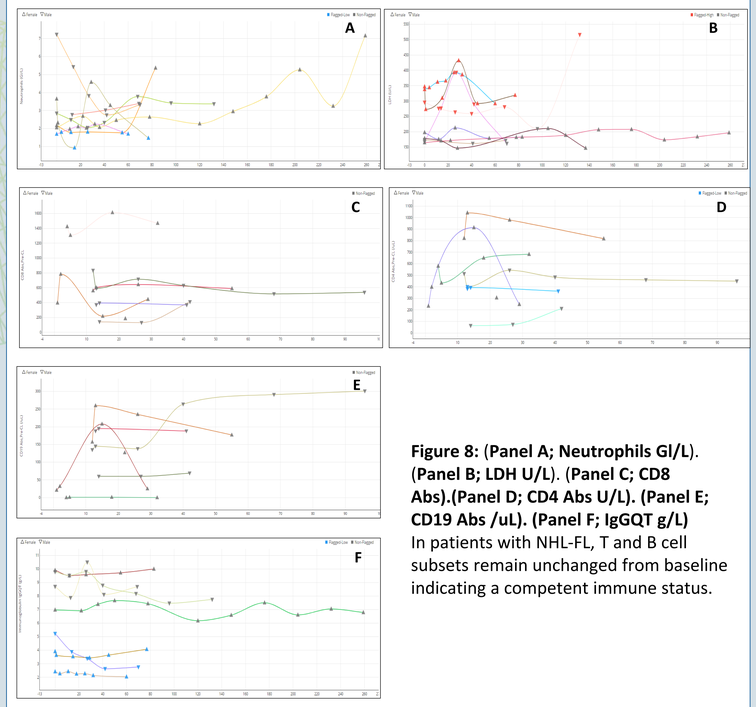

Figure 8: (**Panel A; Neutrophils Gl/L**). (**Panel B; LDH U/L**). (**Panel C; CD8 Abs).(Panel D; CD4 Abs U/L). (Panel E; CD19 Abs /uL). (Panel F; IgGQT g/L)**
In patients with NHL-FL, T and B cell subsets remain unchanged from baseline indicating a competent immune status.

CONCLUSIONS

- Roginolisib monotherapy has a favourable toxicity profile compared to 1st generation PI3Kd Inhibitors (especially in patients treated >6 months) in both solid tumour and FL patients
- Liver enzyme elevations are transient and do not require treatment interruptions or omissions. This is consistent with observations in patients with solid tumours, including patients with liver metastases
- No dose-limiting toxicities were observed
- 80 mg daily dose delivers a response rate consistent with other PI3K inhibitors in lymphoma

ACKNOWLEDGEMENTS

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