P1116 - SAFETY, PHARMACOKINETIC (PK), PHARMACODYNAMIC (PD) AND ACTIVITY OF THE HIGHLY SELECTIVE PHOSPHOINOSITIDE 3-KINASE INHIBITOR DELTA (PI3Kd) INHIBITOR IOA-244 IN PATIENTS WITH FOLLICULAR LYMPHOMA (FL)

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BACKGROUND

- In a parallel dose escalation study in patients with solid tumours, IOA-244 has shown a favourable toxicity profile (Di Giacomo et al. 2021).
- IOA-244 was investigated in patients with Follicular Lymphoma (FL-NHL) and data from the first dose level are presented.
- 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.

Reference

•Tarantelli, C.; Argnani, L.; Zinzani, P.L.; Bertoni, F. PI3K Inhibitors as Immunomodulatory Agents for the Treatment of Lymphoma Patients. Cancers **2021**, 13, 5535. https://doi.org/10.3390/ cancers13215535

•Wang et al. Wang and Ke Journal of Hematology & Oncology 2011, 4:50

•Di Giacomo et al. Annals of Oncology (2021) 32 (suppl_7): S1428-S1457. 10.1016/annonc/annonc787

Figure 1

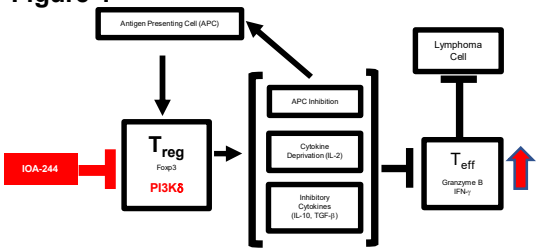

Figure 1: IOA-244 is designed to selectively block PI3Kδ in T_{reg} cells. By blocking the function of T_{reg}, the suppressive function on T_{eff} cells is released and consequently T_{eff} are enabled to attack lymphoma cells

Figure 2

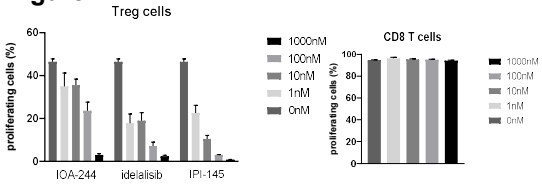

Figure 2: IOA-244 inhibits the proliferation of human T_{regs}, while retaining the T_{eff} proliferation

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 upregulation on basophils in relationship to exposure
- To document any antitumor activity, including overall response rate (ORR), duration of response (DoR), progression free survival (PFS) and overall survival (OS)

METHODS

Design:

3+3 cohort dose escalation

By cohort re-assessment of PK and PD to inform and confirm the predictive non-clinical PK/PD model

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 FL-NHL

Adequate organ functioning

Assessments:

Toxicities graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

Standard laboratory, haematology and chemistry

RECIST 1.1. based evaluation (ORR)

Benefit/Risk for Recommended Phase 2 Dose (RP2D)

Figure 3

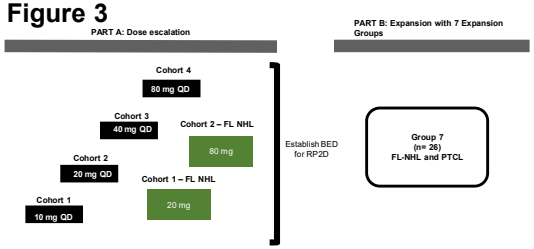

Figure 3: IOA-244 was investigated in a First-in-Human (FiH) dose escalation (PART A) to determine the Biologically Effective Dose (BED). The BED of 80 mg QD was used for the Recommended Phase 2 Dose (RP2D). Once the RP2D was determined, Part B of the study was initiated consisting of 7 expansion cohorts. At the same time a dose escalation of the BED dose range was investigated in patients with FL-NHL: Cohort 1-FL-NHL at 20 mg QD and Cohort 2-FL-NHL at 80 mg QD.

RESULTS

Demography and Baseline Characteristics

Follicular Lymphoma (FL-NHL)	20 mg QD (n = 4)
Age (median)	64.0
Sex (m/f)	2/2
Time since initial Dx (y)	12.4 (3.2 – 16.4)
# Prior treatments	1 (1-7)

Safety

All causality TEAEs by System Organ Class	Overall (n)	10 mg ST (n)	20 mg ST (n)	20 mg FL (n)	40 mg ST (n)	80 mg ST (n)
Evaluable Patients	27	4	4	4	4	11
Any Grade TEAE	25	4	3	4	4	10
Any Grade ≥3 TEAE	2	1	0	1	0	4
Disease Progression						
Grade 3/4	0	1	0	0	0	1
Diarrhoea						
Grade 3/4	1	0	0	0	0	1
Investigations						
Grade 3/4	4	0	0	1	0	3
ALT increase						
Grade 3/4	2	0	0	0	0	2
AST increase						
Grade 3/4	2	0	0	0	0	2
Respiratory						
Grade 5*	2	1	0	0	1	1
Dyspnoea						
Grade 5*	1	0	0	0	0	0
Pulmonary embolism						
Grade 5*	1	0	0	0	1	0

*The CTCAE Grade 5 toxicities observed were associated with tumour progression in patients with mesothelioma and not considered related to treatment

Drug-related TEAE Organ system/Preferred Term (MedDRA)	10 mg ST	20 mg ST	20 mg FL	40 mg ST	80 mg ST	Overall
Patients evaluable / dosed	2/4	1/4	3/4	2/4	2/11	8/27
Grade 1 (Mild)						
Any drug-related TEAE (# events)	3	1	5	5	2	16
Blood & Lymphatic Disorders	0	0	1	0	0	1
Anaemia	0	0	1	0	0	1
Nervous System Disorders	1	0	0	2	0	4
Dysgeusia	1	0	0	0	0	1
Headache	0	0	0	1	0	1
Lethargy	0	0	0	1	0	1
Parasthesia	0	0	0	0	1	1
Gastrointestinal Disorders	0	0	1	2	1	4
Diarrhoea	0	0	1	2	0	3
Vomiting	0	0	0	0	1	1
General Disorders	0	1	0	0	0	1
Asthenia	0	1	0	0	0	1
Investigations	0	0	3	0	0	3
ALT increased	0	0	1	0	0	1
AST increased	0	0	1	0	0	1
BUA increased	0	0	1	0	0	1
Metabolism & Nutrition Disorders	1	0	0	0	0	1
Decreased Appetite	1	0	0	0	0	1
Musculoskeletal & Connective Tissue Disorders	0	0	0	0	1	1
Arthralgia	0	0	0	0	1	1
Skin & Subcutaneous Tissue Disorders	1	0	0	0	0	1
Dry skin	1	0	0	0	0	1
Grade 2 (Moderate)						
Any drug-related TEAE (# events)	0	0	2	0	2	4
Gastrointestinal Disorders	0	0	0	0	1	1
Diarrhoea	0	0	0	0	1	1
Eye Disorders	0	0	0	1	0	1
Uveitis	0	0	0	1	0	1
Investigations	0	0	2	0	0	2
ALT increase	0	0	1	0	0	1
Platelet Count decrease	0	0	1	0	0	1
Grade 3 (Severe)						
Any drug-related TEAE (# events)	0	0	1	0	0	1
Investigations	0	0	1	0	0	1
Platelet Count decrease	0	0	1	0	0	1
Grade 4/5						
Any drug-related TEAE (# events)	0	0	0	0	0	0

Figure 4

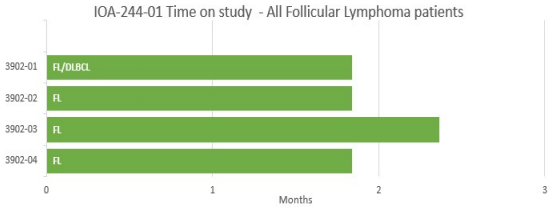

Figure 4: At the 20 mg QD dose, 4 patients were treated beyond the DLT period of 28 days. There was no dose interruption or omission. No PR or CR based on Lugano criteria were observed and patients were discontinued due to clinical progression.

Figure 5

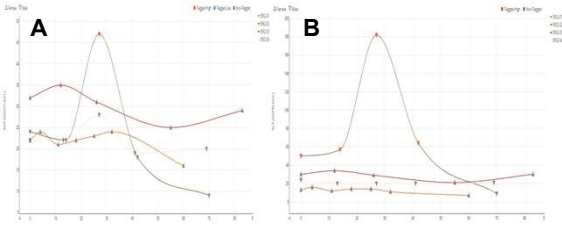

Figure 5: All 4 patients showed normal AST (**Panel A; U/L**) and ALT levels (**Panel B; U/L**). One patient had a transient increase in AST and ALT (3902-02), which subsequently returned to baseline, while patient continued to receive IOA-244 without any other drug intervention

Figure 6

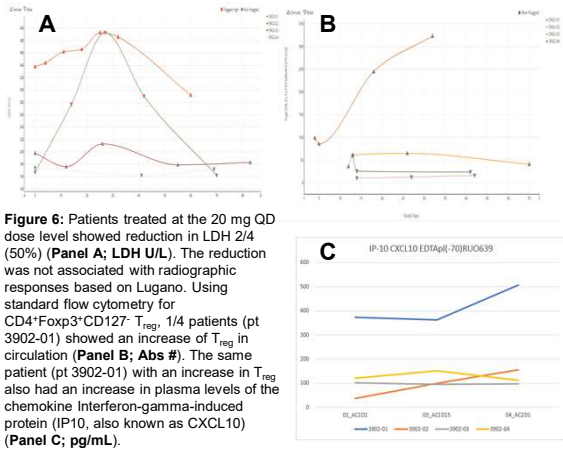

Figure 6: Patients treated at the 20 mg QD dose level showed reduction in LDH 2/4 (50%) (**Panel A; LDH U/L**). The reduction was not associated with radiographic responses based on Lugano. Using standard flow cytometry for $CD4^+Foxp3^+CD127^-$ T_{reg}, 1/4 patients (pt 3902-01) showed an increase of T_{reg} in circulation (**Panel B; Abs #**). The same patient (pt 3902-01) with an increase in T_{reg} also had an increase in plasma levels of the chemokine Interferon-gamma-induced protein (IP10, also known as CXCL10) (**Panel C; pg/mL**).

CONCLUSION

- At 20 mg QD liver enzyme elevations are transient and do not require treatment interruptions or omissions. This is consistent with observations in patients with solid tumors, including patients with liver metastases (Di Giacomo et al ESMO-IO 2021)
- Patients are currently being treated at 80 mg QD
- At 20 mg QD no dose-limiting toxicities were observed
- PK and ADME profile pending and expected to be favourable as in patients with solid tumours (Di Giacomo et al ESMO-IO 2021)
- Effect of IOA-244 on T_{reg} in FL-NHL continues to be explored

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Study Ongoing and Data Not Fully Validated