A first-in-human phase 1 study of IO-202 (anti-LILRB4 mAb) in acute myeloid leukemia (AML) with monocytic differentiation and chronic myelomonocytic leukemia (CMML) patients

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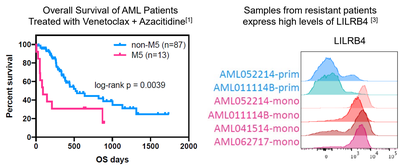
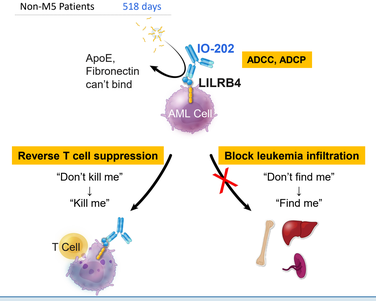
INTRODUCTION

Monocytic AML represents approximately 10-20% of AML and is often associated with extramedullary disease, hyperleukocytosis, and venetoclax-resistance [1].

LILRB4 (also known as ILT3, CD85K, and LIR5) is an immune inhibitory receptor whose expression in patients with AML with monocytic differentiation negatively correlates with overall survival [2-3].

IO-202 is a humanized IgG1 monoclonal antibody with high affinity and specificity towards LILRB4, and blocks LILRB4 binding to its known ligands apolipoprotein E (ApoE) and fibronectin. IO-202 has three mechanisms of action (MOA) in hematologic malignancies, including ADCC or ADCP, activation of T cell cytotoxicity, and reduction of leukemia tissue infiltration in nonclinical models [4]. FDA has granted Fast Track designations for IO-202 for the treatment of relapsed or refractory (R/R) AML and CMML.





OBJECTIVES

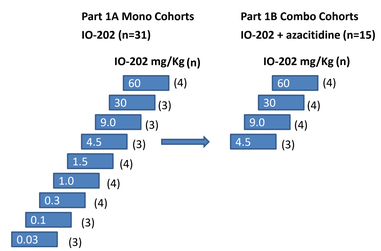
The primary objective of the study is to assess safety and tolerability of IO-202 in successive cohorts of patients with relapsed or refractory (R/R) AML with monocytic differentiation and R/R CMML and estimate the maximum tolerated dose (MTD) or maximum administered dose (MAD) and determine the recommended Phase 2 dose (RP2D).

We hereby report the clinical trial data of using IO-202 from the dose escalation (Part 1) stage of the first-in-human phase 1 study in AML and CMML patients (IO-202-CL-001; NCT04372433).

METHODS

In Part 1 of the study, patients with R/R AML with monocytic differentiation, or R/R CMML were enrolled to receive IO-202 in escalating dose levels (0.03 to 60 mg/kg) as monotherapy and in combination with azacitidine (AZA). IO-202 is administered on day 1 and day 15 of each 28-day cycle, and AZA is administered 75 mg/m^2 IV or SC on days 1-7 of each 28-day cycle in patients treated in the combination cohorts. The first 28-day cycle is defined as the dose-limiting toxicity (DLT) period. Safety, tolerability, pharmacokinetics, immunogenicity, clinical activity and pharmacodynamic (PD) biomarkers were assessed.

Number of patients enrolled



Cohorts	AML	CMML	Total
Monotherapy	26	5	31
Combo + AZA	10	5	15
Total	**36**	**10**	**46**

Enrollment:
As of May 2023, 46 R/R patients (AML n=36, CMML n=10) were treated in Part 1 with IO-202 monotherapy (9 cohorts; n=31) or in combination with AZA (4 cohorts; n=15).

RESULTS

Efficacy:

- IO-202 monotherapy: efficacy in both AML and CMML patients.
- IO-202 combination therapy: efficacy in both AML and CMML patients.
  - AML: 1 out of 2 AML patients with LILRB4^{high} expression achieved a complete remission for over 10 months (the other one received a low dose of 1 mg/kg), in a population with an average survival of 3 months
  - CMML: 3 out of 5 CMML patients achieved clinical benefits including Optimal Marrow Response

	AML (n=36)	CMML (n=10)
IO-202 Monotherapy	Partial Remission (9 mg/kg)	Clinical Benefit >1y (0.1--> 0.3 mg/kg)
IO-202 + Azacitidine	Complete Remission >10m (30 mg/kg)	• Optimal Marrow Response >3m (60 mg/kg) • Partial Remission (4.5 mg/kg) • Clinical Benefit (9 mg/kg)

Safety:

Treatment Emergent Adverse Event (TEAE) Summary

Number of subjects with events (%)	IO-202 Monotherapy (n=31)	IO-202 + AZA (n=15)
Any grade Treatment-Emergent AE	31 (100%)	15 (100%)
Grade 3-5	28 (90.3%)	13 (86.7%)
Led to Discontinuation	5 (16.1%)	1 (6.7%)
Serious	24 (77.4%)	10 (66.7%)
Serious and Led to Discontinuation	5 (16.1%)	1 (6.7%)
Led to Death	8 (25.8%)	2 (13.3%)

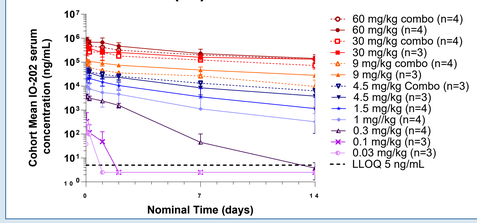
Grade ≥3 adverse events of the most common TEAE (observed in >20% of patients at any grades) were leukocytosis (n=9), febrile neutropenia (8), sinus tachycardia, epistaxis, hypokalemia and hyponatremia (1 each) in monotherapy; febrile neutropenia (4), nausea, vomiting, fatigue (2 each), and hypotension (1) in IO-202 + AZA.

No study deaths have been assessed as related to IO-202 administration. No DLTs were observed, and the maximum tolerated dose was not reached.

List of Adverse Events (# of events shown) led to Discontinuation or Death regardless of Causality

System Organ Class	Preferred Term	Monotherapy (n=31)		Combination (n=15)	
		Led to Discontinuation	Death	Led to Discontinuation	Death
Blood and lymphatic system	Leukocytosis	1	1		
Cardiac disorders	Cardiac arrest		1		
	Cardio-respiratory arrest		1		
General disorders and administration site conditions	Chest pain	1			
	Fatigue	1			
	Multiple organ dysfunction syndrome				1
Infections and infestations	Klebsiella infection		1		
	Pneumonia fungal		1		
	Pseudomonas infection		1		
Injury, poisoning and procedural complications	Contusion	1			
Neoplasms benign, malignant and unspecified	Leukemic infiltration			1	1
Psychiatric disorders	Hallucination	1			
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	1	1		
	Respiratory distress		1		
	Respiratory failure	1	2		

Pharmacokinetics (PK):



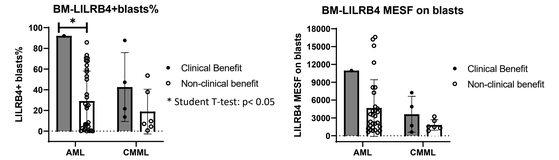
Preliminary observed group mean (+/-SD) IO-202 serum concentration versus time data following IV administration on Cycle 1 Day 1 (Figure on left) indicate:

- IO-202 has non-linear clearance from 0.03 mg/kg to 60 mg/kg due to target mediated drug disposition
- Dose-normalized exposure was similar in the dose range from 9 to 60 mg/kg

RESULTS (CONTINUED)

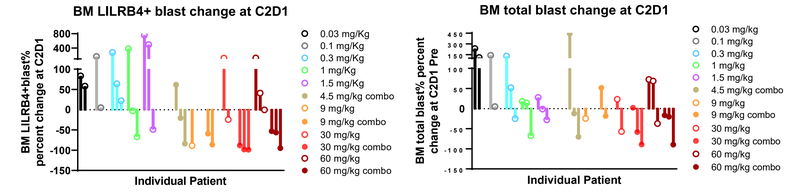
Pharmacodynamics (PD) Biomarkers:

Correlation of clinical responses with baseline LILRB4 was observed in AML patients, but not in CMML patients



Number of MESF (Molecules of Equivalent Soluble Fluorochrome) can be translated into LILRB4 copy number
Clinical Benefit is defined as PR or better in AML, and Clinical Benefit or better in CMML
The PR patient has no baseline BM data, therefore only AML CR patient data shown

Bone Marrow LILRB4-positive blast reduction and total blast reduction are observed in majority of patients at higher doses



CONCLUSIONS

- IO-202 is safe and well tolerated up to 60 mg/kg Q2W as monotherapy and in combination with AZA.
- Encouraging responses, including monotherapy activity, ongoing CR in a R/R AML patient with high LILRB4 expression, and PR and Optimal Marrow Response in R/R CMML patients, were observed.
- The biomarker data support the mechanisms of action, patient selection, and selection of RP2D.
- The durable CR in AML and the encouraging results of Optimal Marrow Response in CMML warrant moving IO-202 to the Part 2 expansion phase with a strategy to select AML patients with high LILRB4.

IO-202 Phase 1 Part 2 Expansion Cohorts:

- Cohort 2A, n=10-20, 2-stage: R/R LILRB4^{high} monocytic AML: IO-202 + AZA
- Cohort 2B, n=10-20, 2-stage: Newly diagnosed CMML: IO-202 + AZA
- Cohort 2C, n=10-20, 2-stage: Newly diagnosed unfit LILRB4^{high} monocytic AML: IO-202 + AZA + venetoclax

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UT Southwestern has a financial interest in Immune-Onc Therapeutics in the form of equity and licensing.

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