A First-in-Human (FIH) Phase 1 Study of the Anti-LILRB4 Antibody IO-202 in Relapsed/Refractory (R/R) Myelomonocytic and Monocytic Acute Myeloid Leukemia (AML) and R/R Chronic Myelomonocytic Leukemia (CMML) (NCT04372433)

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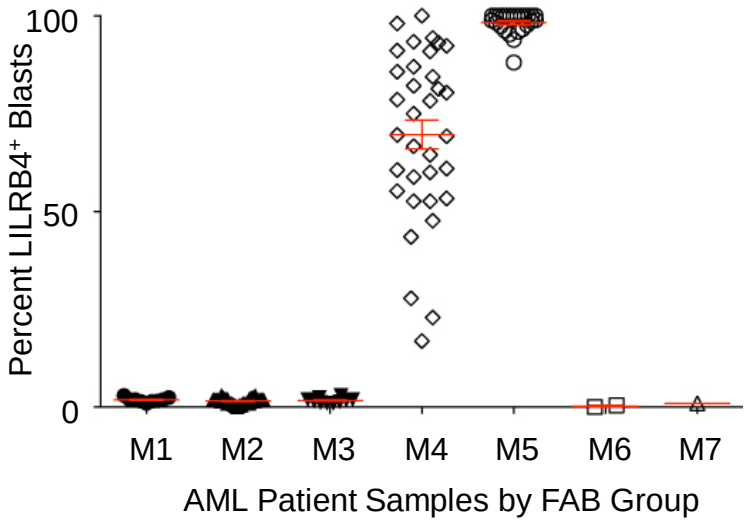
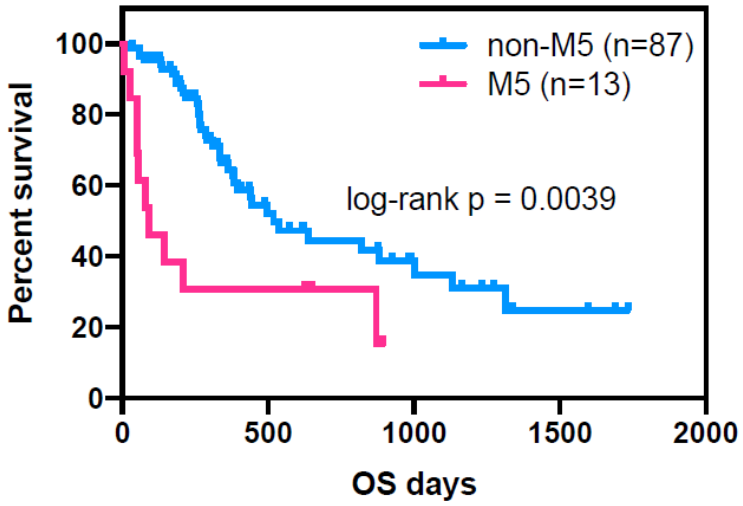
Monocytic AML Expresses LILRB4 and Is Associated With Resistance To Venetoclax Treatment

LILRB4 Expression in Subsets of AML



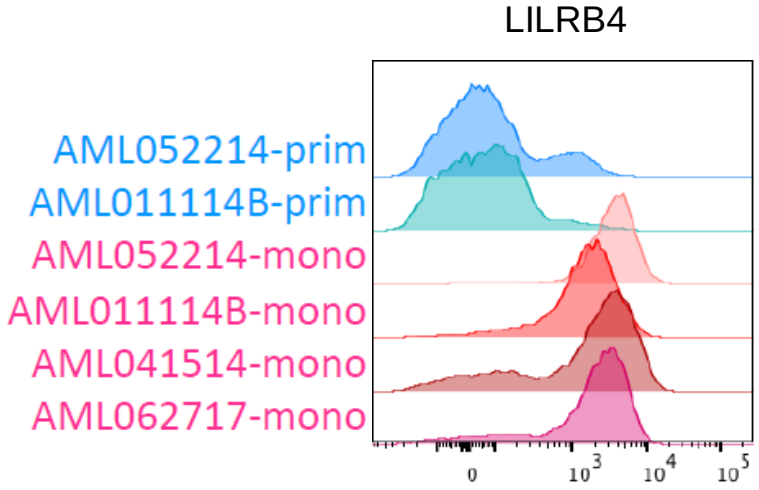
FAB = French–American–British classification; In WHO 2016 classification, M4 = acute myelomonocytic leukemia, M5 = acute monocytic/monoblastic leukemia

Overall Survival of AML Patients Treated with Venetoclax + Azacitidine[1]



Median Overall Survival	
M5 Patients	**89 days**
Non-M5 Patients	518 days

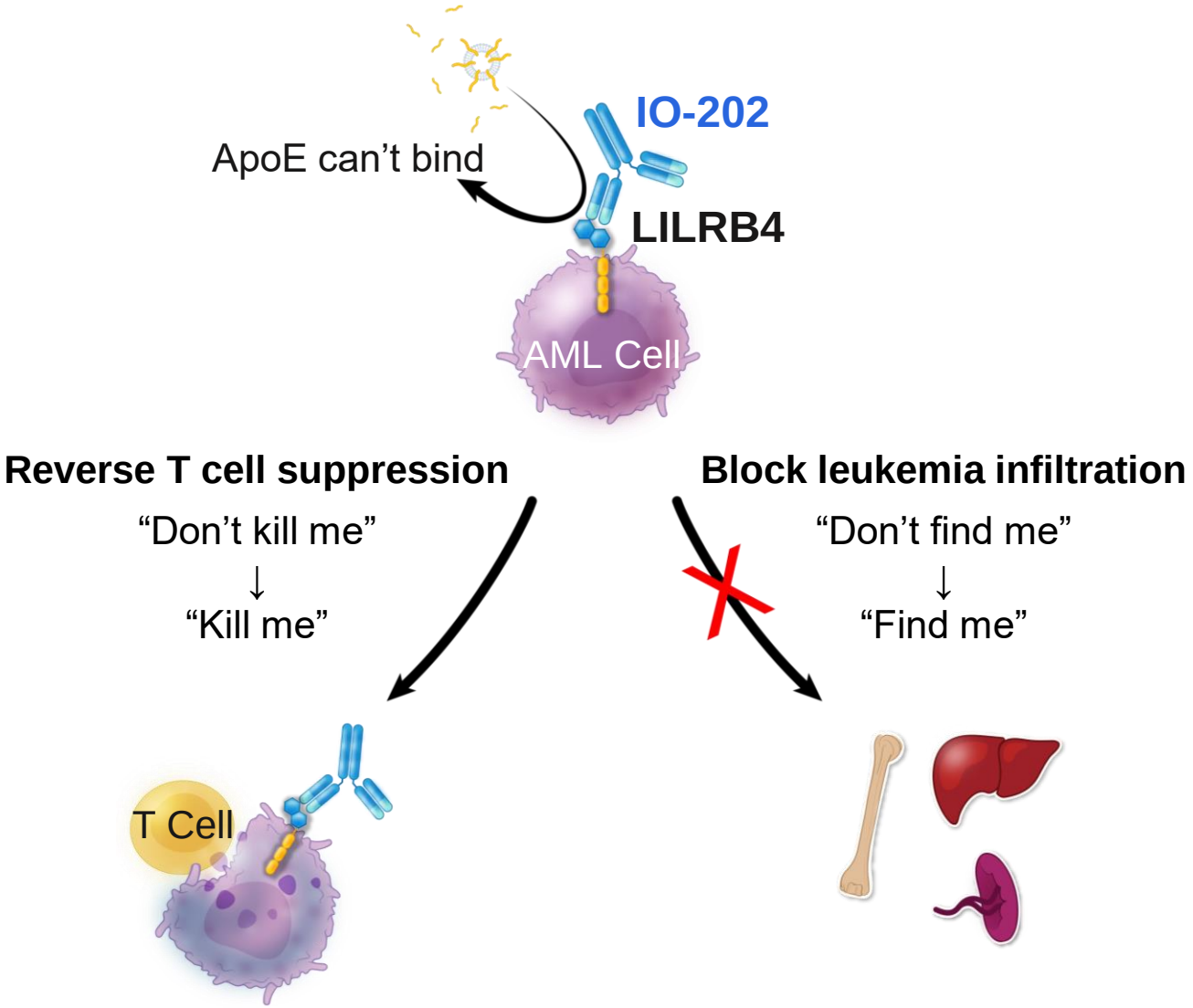
Samples from Resistant Patients Express High Levels of LILRB4[2]



Primitive AML	Dominant mono-AML
AML052214	AML041514
AML011114B	AML062717

[1]Cancer Discovery 10:536–51 (2020); [2]Craig Jordan, personal communication

IO-202 is the **First T-Cell Activator** for AML



"Kill me"

- Enhances antigen presentation of AML cells
- Activates cytotoxic T cells
- Elevates pro-inflammatory cytokines

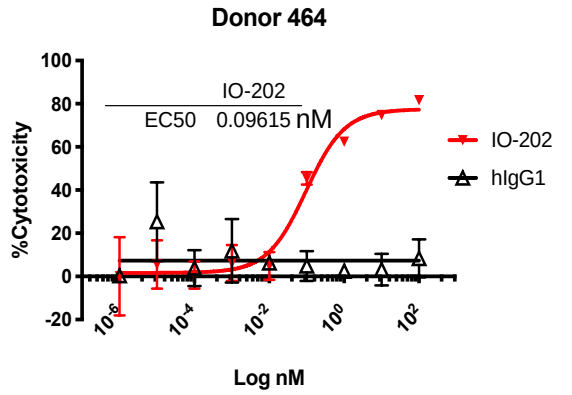
"Find me"

- Blocks AML blast infiltration into tissues (e.g., bone marrow and extramedullary sites)

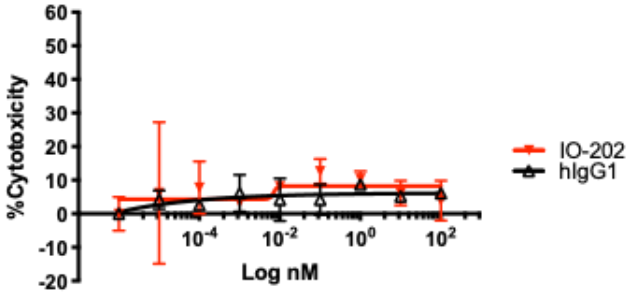
IO-202 Activates T-Cell Cytotoxicity against Human AML Cells, but not Normal Monocytes, and Blocks Leukemia Cell Infiltration

IO-202 activates T-cell cytotoxicity against THP-1 in co-cultures of THP-1/pan T cells

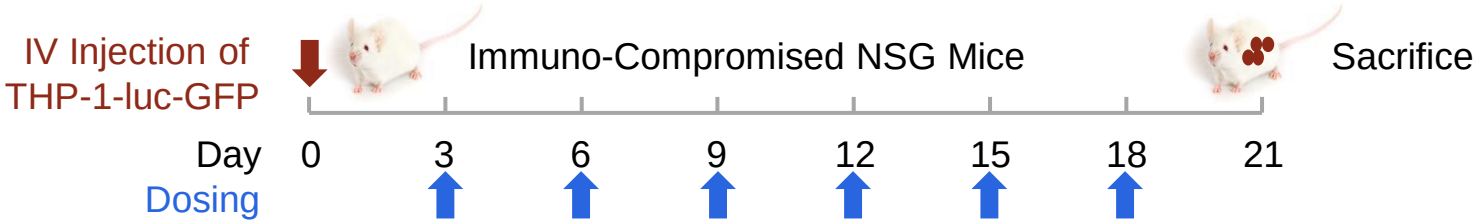
Representative co-culture of pan T cells with THP-1

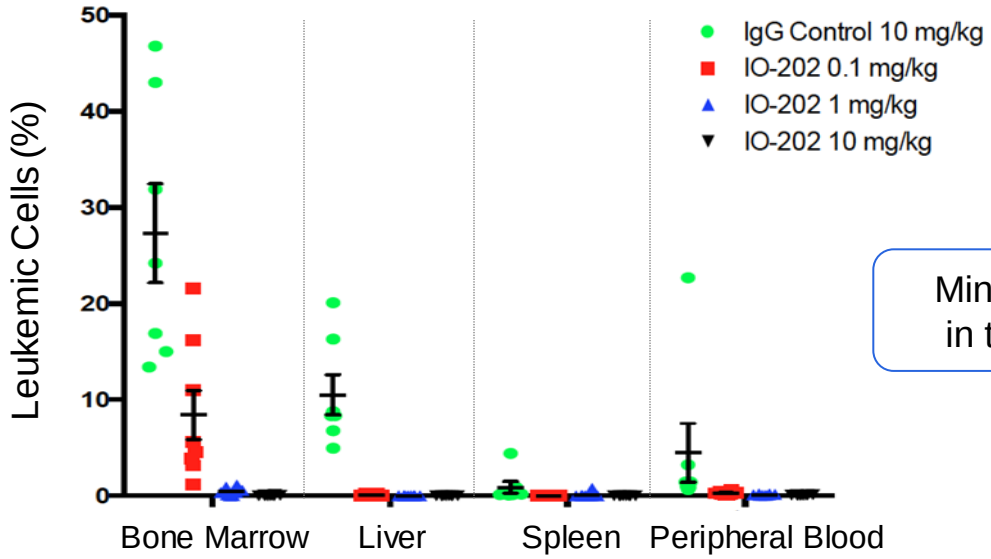


Representative co-culture of pan T cells with allogenic monocytes



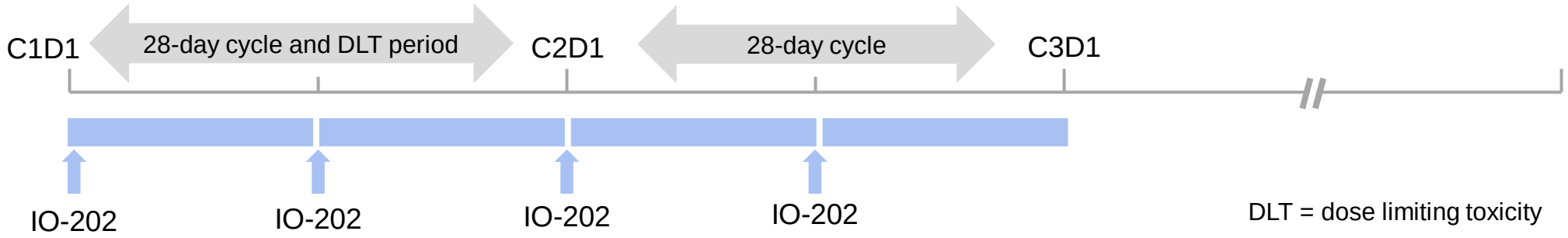
IO-202 blocks leukemia cell infiltration





Minimal Efficacious Dose in this model: 0.1 mg/kg

IO-202 Phase 1 Study Design



Design Features

- Relapsed/Refractory (R/R) myelomonocytic and monocytic/monoblastic AML and CMML (dose escalation only)
- DLT period of 28 days; 3+3 dose escalation
- Expansion cohorts of IO-202 monotherapy and IO-202 + HMA (future amendment)
- Additional combinations, including newly diagnosed patients after proof of concept achieved (future amendment)

Key Inclusion & Exclusion Criteria

- Key inclusion criteria include: 1) Age ≥ 18; 2) Relapsed AML with myelomonocytic or monoblastic/monocytic differentiation or CMML and has failed treatment with available active therapies; 3) adequate renal/hepatic function; and 4) ECOG 0-2.
- Key exclusion criteria include: 1) HSCT within 60 days, on calcineurin inhibitors, or chronic GVHD; 2) chemotherapy, radiotherapy, or investigational agents within 7 days; 3) significant cardiac disease; 4) active infection; 5) uncontrolled CNS leukemia; and 6) hyperleukocytosis (≥ 25 x 10^9/L, although hydroxyurea is permitted).

Biomarker Plan for AML

- Blast reduction
- Exploratory PD biomarkers:
  - T-cell counts and activation status
  - LILRB4 expression and occupancy by IO-202
  - Serum cytokines (TNF-α, IFN-g, CCL2/MCP-1, IL-1α, IL-1β, IL-1ra, IL-2, IL-6, IL-8, IL-10, and CXCL2/Groβ)
- Gene mutation status, global gene expression profiles, immunophenotype, minimal residual disease (MRD)
- Other potential prognostic markers (cytogenetics) in leukemic blasts and plasma will be explored

Assessments and Biostatistics

- The RP2D of IO-202 may be selected based on the totality of the following:
  - The MAD, or the MTD, which is defined as the highest dose level in which the rate of DLTs is < 17% in 6 patients
  - PK and/or PD results
  - The occurrence, nature, and severity of toxicities occurring during the DLT evaluation period (i.e., first 28 days of treatment)
  - Anti-leukemia activity
- Descriptive statistics for treatment-emergent adverse events, clinical laboratory studies, ECG,VS, PK data; correlations between PK and PD data
- Response assessment using AML (Dohner, 2017) and CMML (Savona, 2015) response criteria
- Time to event endpoints will be estimated using Kaplan-Meier methods
- Stopping rules for the dose expansion cohort are proposed when DLTs exceed 20% for a cohort size of 1, maximum number of 20 patients and minimum number of patients of 5 before stopping. The DLT rate will be estimated using a Beta(1,1) prior and continuously calculating the Probability (DLT > 0.20). If ever the Pr(DLT > 0.20) > 0.8, then the study will pause for review of toxicities.