Evaluation of ICT01, a γ9δ2 T Cell-Activating Monoclonal Antibody, Combined with Venetoclax and Azacitidine in 1L AML (EVICTION Study)

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INTRODUCTION

ICT01 & γ9δ2 T cells

- γ9δ2 T cells are emerging as novel effector cells that harbor strong cytolytic and pro-inflammatory activities, and whose intratumoral presence is associated with a favorable prognosis across solid and liquid cancer patients *(Gentles et al., Nature 2015; Tosolini et al., Oncoimmunology 2017)*.
- ICT01, a first-in-class anti-BTN3A mAb activating γ9δ2 T cells, completed Phase 1 testing in relapsed/refractory (r/r) solid tumors as monotherapy and in combination with pembrolizumab, and as monotherapy in r/r AML and lymphoma (EVICTION NCT04243499).
- ICT01 activates circulating γ9δ2 T, CD8 T, and NK cells that leads to tumor infiltration and remodeling of the TME *(De Gassart et al., STM 2021; Wermke et al., ESMO 2021)* without dose-limiting toxicities and a good safety profile.

Part 1: Dose Escalation
Objectives: Safety & Biomarker-derived Target Engagement

Part 2: Expansion Cohorts
Objectives: Safety & Preliminary Efficacy (ORR)

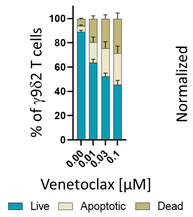
- A. MonoTx Mixed Solid tumor *Bladder, breast, colorectal, gastric, melanoma, ovarian, prostate, PDAC* N = 33 — Completed
  - D. MonoTx in high γ9δ2 T cell pts _ *Ovarian (2L/3L)* — 2 dose levels, IA 10pts/dose
  - E. MonoTx in high γ9δ2 T cell pts _ *mCRPC (2L/3L)* — 2 dose levels, IA 10pts/dose
- B. MonoTx Hematologic *AML, FL, DLBCL* N = 26 — Completed
  - F. *Combo with Ven/Aza _ First-line AML* — 2 dose levels, IA 10pts/dose — Enrolling
- C. Pembro Combo *Bladder, HNSCC, melanoma & NSCLC* N = 40 PD-1 relapsed/refract. — Completed
  - G. Pembro Combo _ *Melanoma CPI-refractory* — 2 dose levels, IA 10pts/dose
  - H. Pembro Combo _ *Bladder Chemotx Failures* — 2 dose levels, IA 10pts/dose
  - I. Pembro Combo _ *HNSCC CPI-refractory* — 2 dose levels, IA 10pts/dose — Enrolling

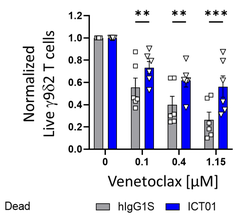
Rationale for using ICT01 in VEN/AZA setting

- ICT01 was **well tolerated** and demonstrated encouraging clinical activity in the **hematologic cancer cohort with a 30% DCR on the 10 patients evaluable at week 8 or beyond** *(Garciaz et al., SITC 2023)* including blast reductions in 3 patients.
- VEN/AZA is the standard of care for patients with newly diagnosed AML who are not candidates for intensive chemotherapy.
- In addition to their anti-leukemic activity:
  - AZA improves cancer cell recognition by immune effector cells through induction of stress ligand expression *(Gang et al., BCJ 2014; Lee et al., Blood 2021)*
  - VEN enhances T cell and NK cell–mediated cytotoxicity against AML blasts *(Lee et al., Blood 2021; Wu et al., Int Immunopharmacol 2022)*

PRECLINICAL RESULTS

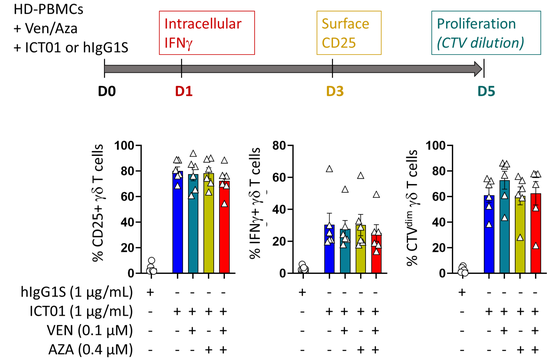
1. ICT01-Mediated Activation of Resting γ9δ2 T Cells Partially Protects them from VEN Induced Cell Death





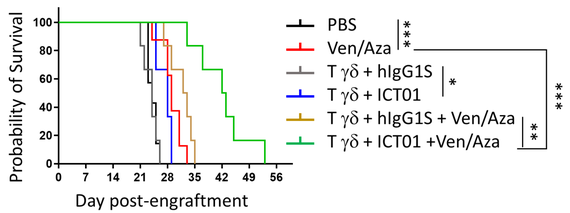
Flow cytometry assessment of VEN effect on γ9δ2 T cell viability in healthy donor (HD)-PBMC cultured *in vitro* for 48 hours with or without ICT01 (1 µg/mL).
2-way ANOVA and Holm-Šídák's multiple comparisons test. ** p<0.01, *** p<0.005

2. Ven and AZA Do Not Interfere with ICT01-Induced Activation of γ9δ2 T cells in HD-PBMC



Flow cytometry assessment of VEN and AZA effect on ICT01-mediated γ9δ2 T-cell activation after *in vitro* culture of healthy donor (HD) PBMC for indicated time

3. Combination of ICT01 and VEN/AZA Significantly Improves γ9δ2 T Cells-Mediated Control of MOLM14 AML Cell Line Growth In Vivo

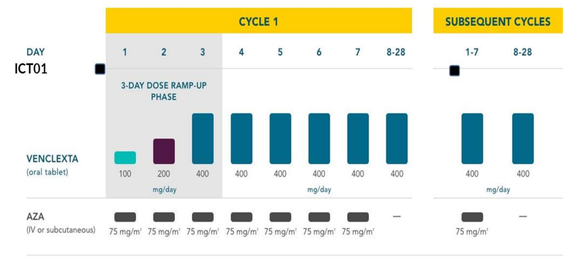


NSG mice engrafted with human AML cell line (MOLM14). From D1, mice received indicated treatments as follow:
- VEN (40mg/kg/day OG 5 days/week for 3 weeks)/AZA (2mg/kg/day IP 5 days/week for 1 week)
- Adoptive transfer of human γ9δ2 T cells ($3x10^6$ cells weekly 4 weeks)
- hIgG1S or ICT01 (1mg/kg IV twice/week 4 weeks)

p values calculated with log-rank (Mantel-Cox) test. *p<0.05, **p<0.005, ***p<0.0005.

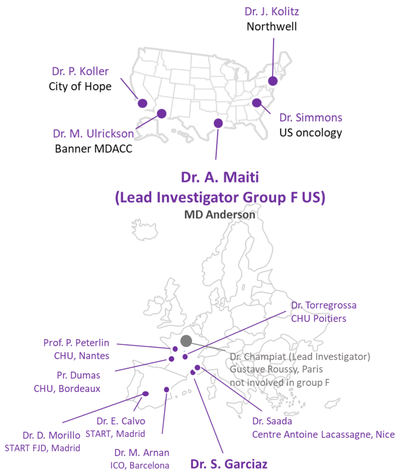
CLINICAL DESIGN

- **AML by WHO criteria, newly diagnosed** in adults aged ≥75, or 18-74 years of age who have comorbidities that preclude use of intensive induction chemotherapy and **are indicated to start VEN/AZA**
- **IV ICT01 10 or 75 mg (n =25/dose group) every 4 weeks**



Continue VENCLEXTA, in combination with azacitidine, until disease progression or unacceptable toxicity.

Graphic not to scale. Each cycle is 28 days.



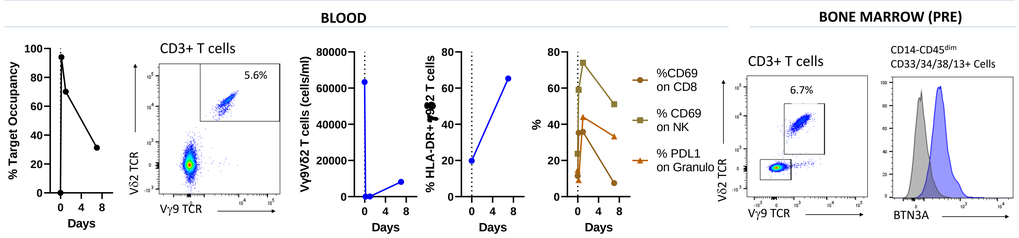
AML CASE STUDY

- 78-yo male diagnosed Sept 2023
- **NPM1**, DNTM3A, IDH2, JAK2, PTPN11 mutations
- **BM**: 25% blasts at diagnosis
- **Dosing:** 10 mg of ICT01 plus VEN/AZA

Clinical Assessments

- **1st Dose:** CRS Grade 3 resolved within 48h with supportive care, including steroids and adrenaline
- **2nd Dose:** pre-treated with 20 mg dexamethasone and no IRR/CRS observed
- **AEs:** Neutropenia G3/4 resolved with Filgastrim
- **BM Day 21: Blasts decreased to 3%,** MRD+ NPM1 3%

BIOMARKERS



ICT01 binds rapidly to BTN3A on leukocytes

Activation & Trafficking of γ9δ2 T Cells and Broad Immune Activation in Peripheral Blood

γ9δ2 T cells well infiltrated & BTN3A well expressed on blasts in BM

CONCLUSION

- **Encouraging results obtained in the EVICTION Phase 1 trial and preclinical demonstration of the benefit of using ICT01 plus VEN/AZA have led to initiation of a Phase 2a expansion cohort in EU and US to evaluate the clinical benefit of this combination in 1L AML patients.**