γ9δ2 T-cell activation and azacitidine-venetoclax for older/unfit adults with newly diagnosed acute myeloid leukemia induces high rates of complete remission: Preliminary efficacy, safety, pharmacodynamics and dose selection of ICT01 in the phase 1 study EVICTION

Poster # **CT024**

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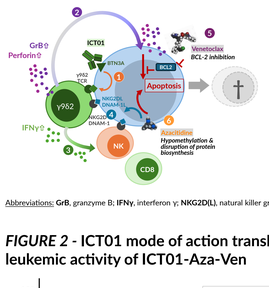
BACKGROUND

- Acute myeloid leukemia (AML) impairs immunosurveillance by circumventing target recognition and cytotoxic T cell responses, which is partly counteracted by immunomodulatory effects of azacitidine-venetoclax (Aza-Ven).
- γ9δ2 T-cell (γ9δ2TC) are known to drive graft-versus-leukemia efficacy.
- ICT01 – a first-in-class, anti-butyrophilin 3A monoclonal antibody – selectively activates γ9δ2TCs promoting direct anti-leukemic cytotoxicity and immunomodulation (**Figure 1**).
- ICT01-mediated γ9δ2TC activation is dose dependent, safe, tolerable and modestly effective as monotherapy in immunocompromised contexts of dose-escalation studies.[1]
- ICT01-mediated γ9δ2TC activation is maintained under Aza-Ven co-administration and induces synergistic anti-leukemic efficacy and favorable immunomodulatory effects *in-vivo* (**Figure 2**).

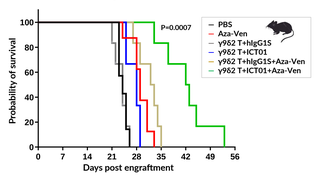
FIGURE 1 **- Azacitidine-venetoclax sensitize AML blasts mounting synergistic ICT01-mediated anti-leukemic effect via activated γ9δ2 T, NK and CD8 cells**



1. ICT01-induced active BTN3A$^{(AML)}$ engages with γ9δ2 TCR
2. Direct cytotoxicity via GrB/perforin pathway[2,3]
3. IFNγ secretion$^{[γ9δ2TC]}$ activates CD8 & NK cells ⇨downstream immunological cascade[4]
4. **Co-receptor**$^{[γ9δ2]}$ **⇔ligand**$^{[target]}$ interaction (e.g., NKG2D[L], DNAM-1[L], ICAM1) lead to **cytolysis** of AML blasts[4,5]
5. In addition to BCL-2 inhibition, immuno-modulation by **venetoclax** overcomes GrB/perforin resistance of AML blasts and enhances the anti-leukemic efficacy of γ9δ2, NK and CD8 T cells[6–8]
6. In addition to hypomethylation, immuno-modulation by **azacitidine** improves immune-effector–cell recognition of AML blasts through NKG2DL (secondary stress ligand) induction and dsDNA accumulation.[8–10]

Abbreviations: **GrB**, granzyme B; **IFNγ**, interferon γ; **NKG2D(L)**, natural killer group 2 member D (ligand).

FIGURE 2 **- ICT01 mode of action translates into synergistic *in-vivo* anti-leukemic activity of ICT01-Aza-Ven**



Abbreviations: **Aza-Ven**, azacitidine-venetoclax; **hIgG1S**, control antibody; **MOLM14**, AML cell line; **NSG**, NOD Scid Gamma mouse; **PBS**, Phosphate Buffered saline.

Design: NSG mice engrafted with human MOLM14 cell line and treated with **azacitidine** (2 mg/kg/day for 5d/wk for 1wk), **venetoclax** (40 mg/kg/day for 5d/wk for 3 wks), adoptive transfer of human **γ9δ2 T cells** (3×10^6 cells QW IV for 4 wks), and **ICT01** or **hIgG1** (1 mg/kg BIW IV for 4 wks). P-value (γ5T-ICT01-Aza-Ven vs. Aza-Ven), log-rank test.

STUDY DESIGN

Main eligibility criteria
- Adults with newly diagnosed AML ineligible for induction chemotherapy
- No t(15;17), t(8;21), inv(16), or t(16;16)
- No history of myeloproliferative neoplasms, polycythemia vera, chronic myeloid leukemia with or without BCR-ABL1 translocation, or AML with BCR-ABL1 translocation.

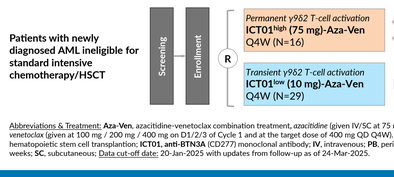
Primary Endpoint
- Complete response (CR) rate according to the *European LeukemiaNet* (ELN) 2022 criteria[11]

Efficacy assessments (ELN 2022 criteria)
- CR rate= percentage of patients with CR
- CRc rate= percentage of patients with CR, CR with partial hematological recovery (CRh) or CR with in-complete hematological recovery (CRi)
- EE= Efficacy evaluable population (***interim dataset***)

Safety – Treatment-emergent adverse events (TEAE)

Biomarkers
- BTN3A expression on AML blasts in BM
- Cytokine secretion (IFNγ, TNFα)
- Number and activation of γ9δ2TCs in PB and BM.

FIGURE 3 **- Study design of dose-optimizing/efficacy-estimating cohorts**



Abbreviations & Treatment: **Aza-Ven**, azacitidine-venetoclax combination treatment, *azacitidine* (given IV/SC at 75 mg/m^2 on D1–7 Q4W); **D**, day; *venetoclax* (given at 100 mg / 200 mg / 400 mg on D1/2/3 of Cycle 1 and at the target dose of 400 mg QD Q4W). **BM**, bone marrow; **HSCT**, hematopoietic stem cell transplantation; **ICT01, anti-BTN3A** (CD277) monoclonal antibody; **IV**, intravenous; **PB**, peripheral blood; **Q4W**, every four weeks; **SC**, subcutaneous; Data cut-off date: 20-Jan-2025 with updates from follow-up as of 24-Mar-2025.

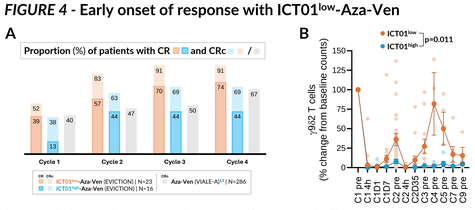
RESULTS

TABLE 1 **- Patient demographics**

Variables	Safety population ICT01^{low}-Aza-Ven (N=29)	ICT01^{high}-Aza-Ven (N=16)	Pooled (N=45)
Age [median (range)]	**76 (51-87)**	**75 (64-84)**	**76 (51-87)**
< 75 years [n(%)]	12 (41)	7 (44)	19 (42)
≥ 75 years [n(%)]	17 (59)	9 (56)	26 (58)
Male [n(%)]	**17 (59)**	**7 (44)**	**24 (53)**
ECOG performance status [n(%)]			
0 or 1	23 (79)	9 (56)	32 (71)
2 or 3	5 (17)	6 (38)	11 (25)
Missing	1 (4)	1 (6)	2 (4)
Bone marrow blasts [% (range)]	**40 (7-98)**	**34.5 (9-82)**	**40 (7-98)**
< 30 %	11 (38)	8 (50)	19 (42)
≥ 30-50%	8 (28)	2 (12)	10 (22)
≥ 50%	9 (31)	6 (38)	15 (33)
Missing	1 (3)		1 (2)
Revised ELN risk 2024 [n(%)][12]			
Favorable	9 (31)	3 (19)	12 (27)
Intermediate	15 (52)	5 (31)	20 (44)
Adverse	5 (17)	8 (50)	13 (29)

Abbreviations: **Aza-Ven**, azacitidine-venetoclax combination treatment; **ELN**, European Leukemia Network; **ICT01low/high**, ICT01 10 mg/75 mg Q4W.

FIGURE 4 **- Early onset of response with ICT01^{low}-Aza-Ven**



Abbreviations: **Aza-Ven**, azacitidine-venetoclax combination treatment; **CR**, complete remission; **CRc**, composite complete remission (CR+CRh+CRi); **CRh**, CR with partial hematological recovery; **CRi**, CR with incomplete hematological recovery; **ICT01low/high**, 10 mg/75 mg ICT01 Q4W

A. **High response rate with ICT01^{low}-Aza-Ven**, superior to the response observed with ICT01^{high}-Aza-Ven.
B. **Continued dosing of ICT01^{high} leads to sustained depletion of γ9δ2 T cells**, suggesting (over)activation-induced cell death (AICD).

FIGURE 5 **– Greatest relative decrease of AML blasts from baseline**

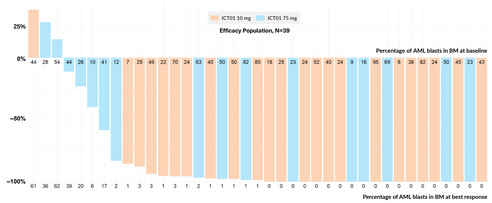
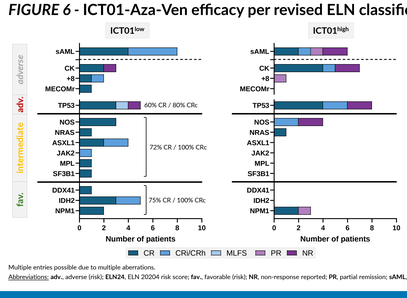
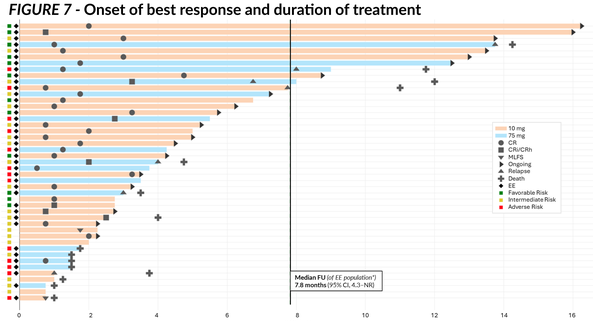


FIGURE 6 **- ICT01-Aza-Ven efficacy per revised ELN classification[12]**



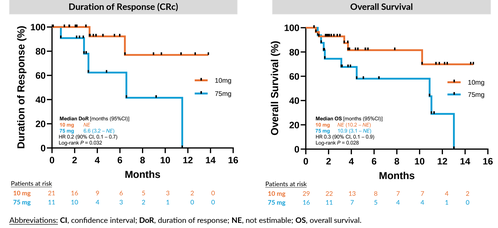
Multiple entries possible due to multiple aberrations.
Abbreviations: **adv.**, adverse (risk); **ELN24**, ELN 20204 risk score; **fav.**, favorable (risk); **NR**, non-response reported; **PR**, partial remission; **sAML**, secondary AML.

FIGURE 7 **- Onset of best response and duration of treatment**



*Complete Disease Assessments in Cycle 1 and initiation of Cycle 3.
Abbreviations: **CI**, confidence interval; **FU**, follow up; **EE**, Efficacy Population.

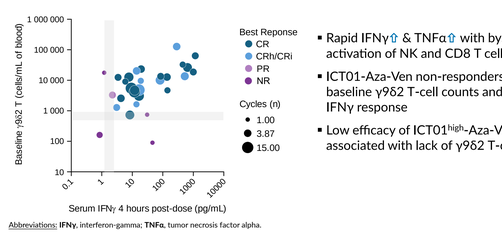
FIGURES 8 **- Kaplan-Meier Analysis of treatment duration and overall survival**



Abbreviations: **CI**, confidence interval; **DoR**, duration of response; **NE**, not estimable; **OS**, overall survival.

- At a median follow-up of 7.8 months, differential CR and CRi/CRh rates for ICT01^{low} and ICT01^{high} shown in **Figure 4** appear to translate into differential median DoR and OS outcomes.
- DoR and OS at this stage are immature with 30 (67%) of 45 patients still ongoing.

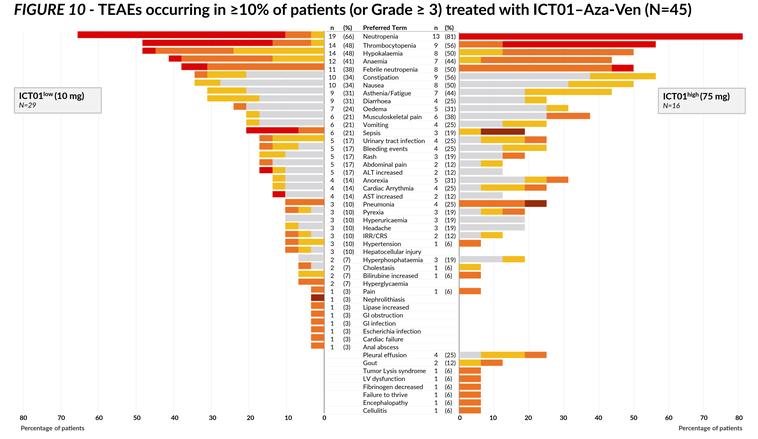
FIGURE 9 **- Evidence for a relationship/association between proposed mode of action and clinical data**



- Rapid IFNγ⇧ & TNFα⇧ with bystander activation of NK and CD8 T cells (not shown)
- ICT01-Aza-Ven non-responders have low baseline γ9δ2 T-cell counts and low-level IFNγ response
- Low efficacy of ICT01^{high}-Aza-Ven is associated with lack of γ9δ2 T-cell recovery

Abbreviations: **IFNγ**, interferon-gamma; **TNFα**, tumor necrosis factor alpha.

FIGURE 10 **- TEAEs occurring in ≥10% of patients (or Grade ≥ 3) treated with ICT01–Aza-Ven (N=45)**



CTCAE categories: ■ Grade 1 | ■ Grade 2 | ■ Grade 3 | ■ Grade 4 | ■ Grade 5.
Abbreviations: **CRS**, cytokine release syndrome; **GI**, gastrointestinal; **LV**, left ventricular; **IRR**, infusion-related reaction.

Summary of safety findings

- No new safety signal for ICT01 and for ICT01-Aza-Ven; less infectious events with ICT01^{low} versus ICT01^{high}
- ICT01^{low} shows less neutropenia (70% vs. 98% Aza-Ven[16]), and less febrile neutropenia (37% vs. 43% Ven/Aza) with potential ICT01-induced MCL1-mediated protection of granulocytes[4]
- Low rates of CRS/IRR with dexamethasone prophylaxis
- Only 1 event of TLS, managed clinically without sequelae
- Low 30-day mortality (3%)
- Overall, 4 deaths due to pneumonia and sepsis, and 1 death due to preexisting chronic kidney disease; all deaths 'unlikely'/'not related' to ICT01

⇨ **No ICT01-related mortality, low incidence of dose modifications and study drug discontinuations**

CONCLUSIONS

- **ICT01^{low}-Aza-Ven generated very high CR & CR/CRi rates across molecular AML subtypes**
- **Although survival analysis are not informative to date, a differential median OS is assessed for ICT01^{low} as compared with ICT01^{high}**
- **Safety of ICT01-Aza-Ven is clinically well manageable with typical Aza-Ven hematotoxicity and low 30-day mortality**
- **ICT01^{low}-Aza-Ven exhibited a favorable benefit–risk profile; RP2D of ICT01 is 10 mg Q4W in combination with Aza-Ven**
- **ICT01^{low} induced rapid γ9δ2TC activation and immune cascade, indicating the contribution of ICT01 to Aza-Ven efficacy**
- **γ9δ2TCs became almost undetectable on ICT01^{high}, suggestive of AICD, and likely explaining efficacy similar to Aza-Ven.**

SCAN ME

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