First-in-Human Study of ICT01, an Anti-BTN3A Activating Monoclonal Antibody in Combination with Low Dose IL-2 in Patients with Advanced Solid Tumors (EVICTION-2 Study)

CT179

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Background

ICT01 is an anti-BTN3A mAb that selectively activates γ9δ2 T cells (Fig 1) resulting in remodeling of the tumor microenvironment by activated γ9δ2 T, CD8 T, and NK cells (EVICTION- NCT04243499; AACR 2022 CT188). Response to ICT01 depends on the baseline number of γ9δ2 T cells with many cancer patients having inadequate numbers due to prior chemotherapy and/or the underlying malignancy (Fig 2).

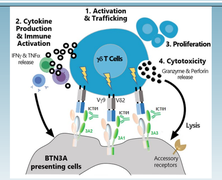


Figure 1. Mode of action of ICT01

Eligibility criteria for the expansion cohorts in EVICTION have been instituted based on the dose-escalation data suggesting that >20K for monotherapy and >5K for the pembrolizumab combination are necessary for responses to ICT01, leading to exclusion of a significant proportion of patients across all indications

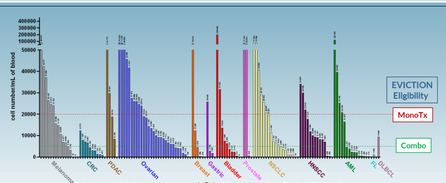
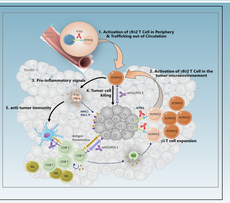


Figure 2. Baseline γ9δ2 T Cells in EVICTION

IL-2 is used to expand γ9δ2 T cells in combination with phosphoantigen (pAg) or zoledronate *in vitro*, which work intracellularly through BTN3A1. Combining ICT01 with IL-2 may provide a novel BTN3A-targeted approach to increase the number of circulating and tumor-resident γ9δ2 T cells in patients for a stronger anti-tumor immune response.



EVICTION-2 Study Design and Population

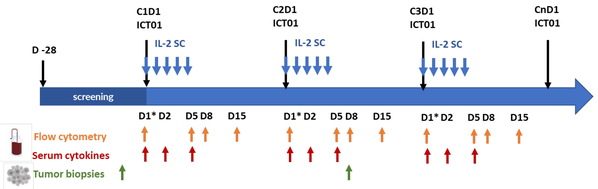
Part 1: Bayesian Dose Escalation
Objectives: Safety & Expansion of γ9δ2 T cells

ICT01 + LDSC IL-2 (21-day cycle)
Colorectal, Ovarian, Prostate cancer and PDAC
N = 16-30

Part 2: Cohort Expansion
Objectives: Safety & Efficacy

ICT01 + LDSC IL-2
Solid Tumor Indication(s)
N = 25/regimen/indication

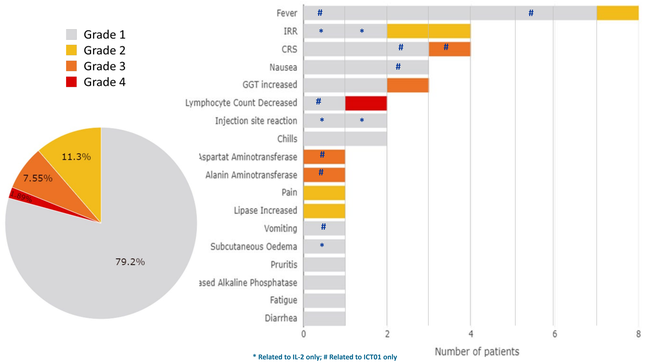
Major Inclusion Criteria
1) Relapsed/refractory patients who have failed at least 2 lines of systemic therapy or who failed first line therapy and are intolerant of or have a contraindication to the standard second line of therapy
2) Willingness to undergo baseline and on-study tumor biopsies
3) ECOG performance status ≤ 1 and life expectancy>3m
4) At least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST)



Cohort	Patient ID Demographics	Cancer Type	Prior Lines Rx	Baseline γ9δ2 T Cells Tumor Burden	Status RECIST/ iRECIST
1 1mg ICT01 1MIU/m² IL-2	01-01-201 65 yo M	CRC	7	8 111	PD W8
	01-01-203 60 yo F	Ovarian	10	192 242	**SD W8 /** PD W16
2 1mg ICT01 2MIU/m² IL-2	01-01-204 67 yo M	CRC	4	15 098	**SD W8** / PD W16
	01-01-206 69 yo F	Ovarian	9	6 789	PD-W16
3 5mg ICT01 1MIU/m² IL-2	01-01-205 56 yo F	CRC	4	19 136	**SD W16/ iuPD W24**
	04-01-202 63 yo M	CRC	6	75 861	PD W8
	05-01-203 66 yo M	PDAC	*3*	5 697	Ongoing C1
5 20mg ICT01 1MIU/m² IL-2	04-01-203 46 yo F	CRC	6	18 468	PD-W8
	05-01-201 66 yo M	PDAC	2	0	Died C1
	05-01-202 58 yo F	Ovarian	4	6 512	Ongoing C2
	05-01-205 69 yo M	Prostate	3	0	Ongoing C3
7 75mg ICT01 1MIU/m² IL-2	01-01-208 66 yo M	CRC	4	6 047	PD-W8
	04-02-201 55 yo M	CRC	4	35 257	Ongoing C2
	05-01-204 68 yo M	Prostate	*5*	9 848	Ongoing C1

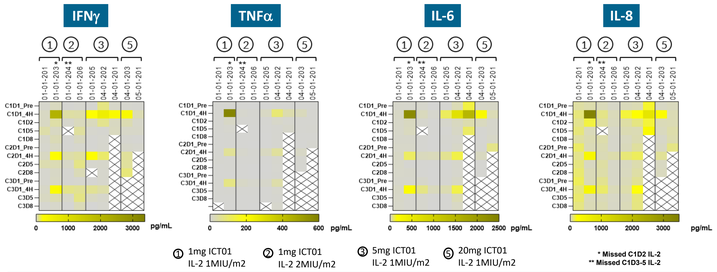
Safety: Treatment Related Adverse Events

No Dose Limiting Toxicities



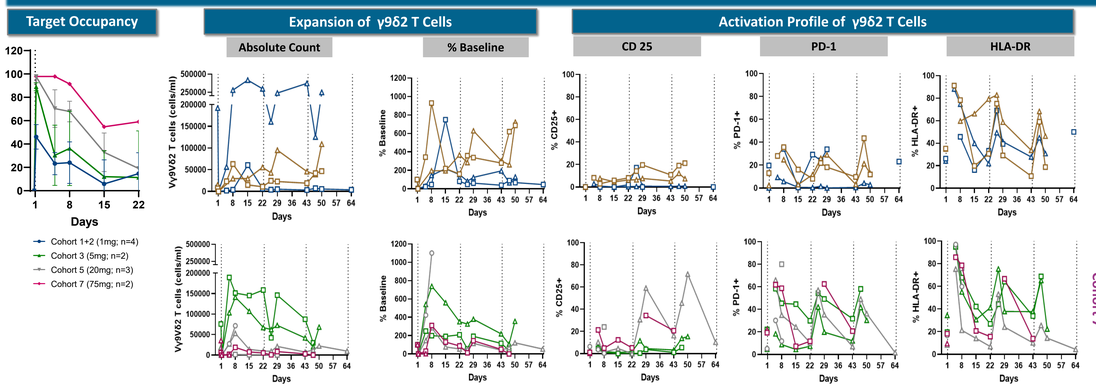
Safety Summary:
1. TEAEs consistent with known safety profile of ICT01 and IL-2, NO new or amplified TEAEs observed.
2. Main TEAEs are IRR, fever, chills and CRS, which self resolve in <24hrs and not different in severity from ICT01 or IL-2 monotherapy

ICT01 + LDSC IL-2 Induces Release of Cytokines

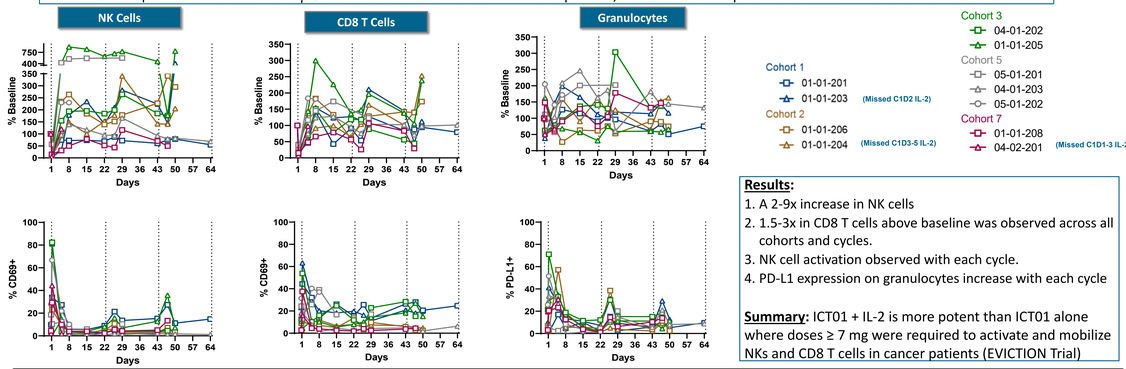


Transient increase in IFNγ, TNFα, IL-6 and IL-8 levels peaking 4H after each dose of ICT01 + LDSC IL-2.

ICT01 + LDSC IL-2 induces Expansion and Activation of γ9δ2 T Cells, NK ,CD8 and Granulocytes



Results: A 2-11 x increase above baseline was observed across all cohorts that peaks between day 5 to 15, which recurs with subsequent cycles. However, Group 5 patient 05-01-201 with 0 γ9δ2 T cells at baseline showed minimal expansion, which identifies a potential exclusion criteria for Part 2.



Results:
1. A 2-9x increase in NK cells
2. 1.5-3x in CD8 T cells above baseline was observed across all cohorts and cycles.
3. NK cell activation observed with each cycle.
4. PD-L1 expression on granulocytes increase with each cycle

Summary: ICT01 + IL-2 is more potent than ICT01 alone where doses ≥ 7 mg were required to activate and mobilize NKs and CD8 T cells in cancer patients (EVICTION Trial)

CONCLUSIONS:

1. **ICT01 + LDSC IL-2 safely induced γ9δ2 T cell expansion in 11/11 evaluable patients across all dose cohorts.**
2. **Expansion of γ9δ2 T cells occurs after 2nd and 3rd cycles, which differentiates this approach from results with pAgs and zoledronate.**
3. **Activation, mobilization and proliferation of CD8 T cells, NKs & granulocytes demonstrate broad immune activation.**
4. **Increased PD-1 and PD-L1 suggest the addition of a CPI may further enhance clinical responses to this regimen (planned for Part 2)**