Enhancing the Anti-tumor Immunity and Therapeutic Potential of ICT01 a Butyrophilin 3A γ9δ2 T Cell-Activating Monoclonal Antibody with Low Dose IL-2 in Patients with Advanced Solid Tumors: The EVICTION-2 Trial

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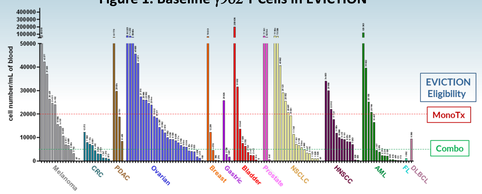
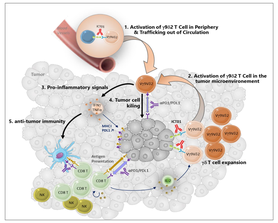
INTRODUCTION: ICT01 is an anti-BTN3A mAb that selectively activates γ9δ2 T cells inducing a robust antitumor immune response of the innate and adaptive immune systems that leads to solid tumor infiltration of activated γ9δ2 T cells, CD8 T cells, and NK cells. (EVICTION trial (NCT04243499); SITC 2021, #503). The pharmacodynamic effects of ICT01 are dependent on an adequate population of γ9δ2 T cells, which is highly variable and lacking in most advanced cancer patients (Fig 1).

Figure 1. Baseline γ9δ2 T Cells in EVICTION



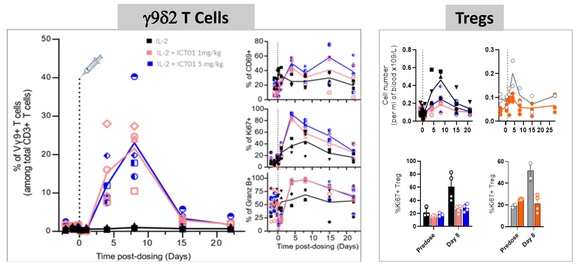
Eligibility criteria for the expansion cohorts in EVICTION have been instituted based on the dose-escalation data suggesting that >20K for monotherapy and >5K for the pembrolizumab combination are necessary for responses to ICT01. Both of these lead to exclusion of a significant proportion of patients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

IL-2 is commonly used to expand γ9δ2 T cells in combination with phosphoantigen or zoledronate *in vitro*, which work intracellularly through BTN3A1. Therefore, 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. This would create more tumor-infiltrating γ9δ2 T cells for a stronger anti-tumor immune response that potentially leads to improved clinical outcomes for patients (See schematic to the right).



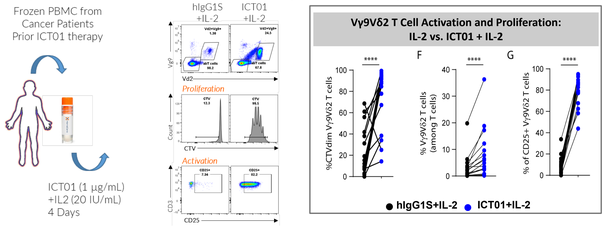
1. Non-Clinical Data Supporting the Combination of ICT01 + IL-2

A. Non-human primates received a single IV dose of ICT01 on Day 0 + SC IL-2 on Days 0-4, or IL-2 alone



Results: ICT01 + LDSC IL-2 safely and selectively induces γ9δ2 T cell proliferation in NHPs while blunting IL-2 mediated expansion of Tregs

B. Vγ9Vδ2 T Cells from Cancer Patients are Responsive to ICT01 plus IL-2 Ex Vivo



2. EVICTION-2 Study Design and Objectives

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

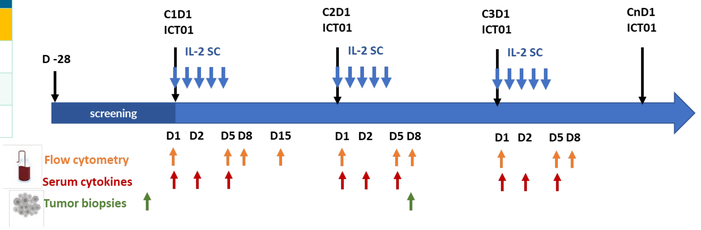
ICT01 + LDSC IL-2
Solid Tumor Indication(s)
N = 25/regimen/indication

Major Inclusion Criteria

1) ≥18 years
2) 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 with histologically or cytologically confirmed diagnosis of:
3) Willingness to undergo baseline and on-study tumor biopsies
4) ECOG performance status ≤ 1 and life expectancy>3m
5) At least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST)

ICT01 IV Dose + Daily IL-2 SC (n=2*)	
1) 1 mg + 1MIU/m²	2) 1 mg + 2MIU/m²
3) 5 mg + 1MIU/m²	4) 5 mg + 2MIU/m²
5) 20 mg + 1MIU/m²	6) 20 mg + 2MIU/m²
7) 75 mg + 1MIU/m²	8) 75 mg + 2MIU/m²

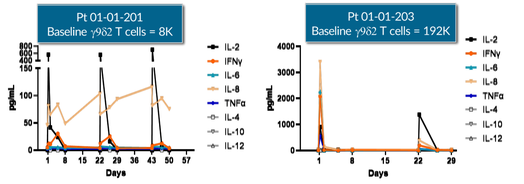
*n will be expanded to 6 if a DLT is observed and once an active regimen is observed



3. Safety: Drug Related Adverse Events

Cohort Regimen	Pt ID Demographics	Diagnosis Prior Treatment	AE Term	Grade	Onset	Related to ICT01	Related to IL-2	Status
1 mg ICT01 + 1MIU/m² IL-2	01-01-201 65yo M	CRC/2017 7 Lines	Injection site reaction	2	C1, C2	No	Yes	WD PD C4
	01-01-203 60yo F	Ovarian/2011 10 Lines	1. Infusion-related reaction (chills, fever, fatigue, hypoxia, hypotension, lumbar pain)	2	C1	Yes	Yes	Ongoing C6
			2. Increased GGT	1	C1	Yes	Yes	
			3. Increase Alkaline Phosphatase	1	C1	Yes	Yes	
			4. Headache	1	C2	Yes	No	
			5. Infusion-related reaction	1	C2	No	Yes	
			6. Constipation	2	C2	No	No	
1 mg ICT01 + 2MIU/m² IL-2	01-01-204 68yo M	CRC/2017 5 Lines	1. Hemoptysis	2	C1	No	No	Ongoing C4
			2. Infusion-related reaction (fever)	1	C1	Yes	Yes	
	01-01-206 70yo F	Ovarian/ ?? Unknown	None	-	-	-	-	Ongoing C2
5 mg ICT01 + 1MIU/m² IL-2	01-01-205 56yo F	CRC/2017 5 Lines	1. Fever	2	C1	Yes	Yes	Ongoing C2
			2. Chills	1	C1	Yes	Yes	
			3. Headache	1	C1	Yes	Yes	
			4. Fatigue	1	C1	No	Yes	
	04-01-201 55yo F	PDAC/2021 6 Lines	1. Fever	1	C1	Yes	Yes	Death due to stroke
			2. Nausea	1	C1	Yes	No	
			3. Stroke with secondary bleeding	2	C1	No	No	
	04-01-202 63yo M	CRC/2021 6 Lines	1. CRS (fever, hypertension)	1	C1	Yes	Yes	Ongoing C1

Cohort 1 Cytokines: IRR in Pt 203 related to higher γ9δ2 T cells & cytokines

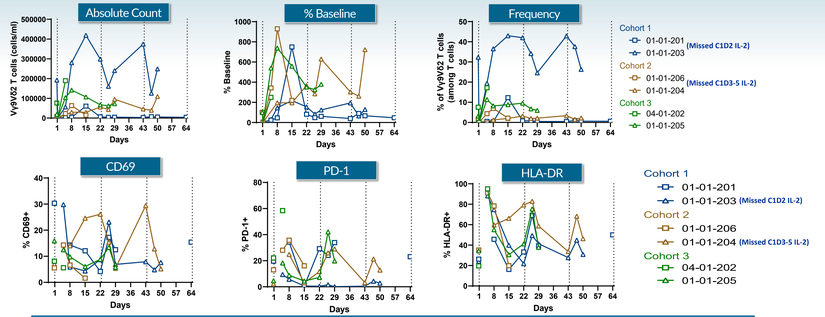


Safety Summary:

1. **No DLTs in first 3 dose cohorts.**
2. **TEAEs are consistent with known safety/AE profile of ICT01 and IL-2, with NO new or amplified TEAEs observed.**
3. **Cytokine release is related to the first dose TEAEs of IRR, fever, chills and CRS, which self resolve in <24hrs and has been previously observed with ICT01 in the EVICTION trial.**

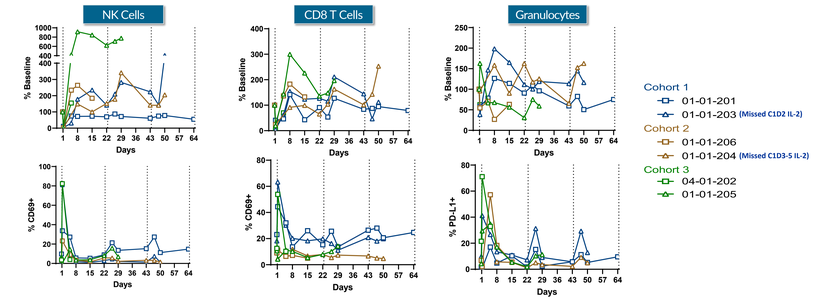
4. Pharmacodynamic Effects: Flow Cytometry of Peripheral Immune Cells

A. ICT01+IL-2 Induces Activation, Migration, and Expansion of Circulating γ9δ2 T Cells



Results: A 2-9x increase above baseline was observed across all cohorts, which seems to peak by day 8 to 15, and can recur with subsequent cycles. T

B. ICT01+IL-2 Induces Activation, Migration and Expansion of Circulating NKs and CD8 T Cells, and Activates Circulating Granulocytes



Results: These results demonstrate that the combination of ICT01 + IL-2 is more potent than ICT01 alone where doses ≥ 7 mg were required to similarly mobilize NKs and CD8 T cells in cancer patients (EVICTION Trial)

5. Summary & Conclusions

1. Low dose ICT01 + IL-2 safely induced γ9δ2 T cell expansion in 6/6 evaluable patients.
2. Expansion of γ9δ2 T cells seems to occur after 2nd and 3rd cycles, which may differentiate this approach from previous approaches with synthetic phosphoantigens and zoledronate. More patient data needed to confirm.
3. Activation, mobilization and proliferation of CD8 T cells, NKs & granulocytes demonstrate broad immune activation.
4. Part 1 dose escalation expected to be completed in Q1 2023 with launch of expansion cohorts in Q2 2023.