ICT01 plus Low Dose SC IL-2 Produces a Robust Anti-Tumor Immune Activation in Advanced Cancer Patients (EVICTION-2 Study)

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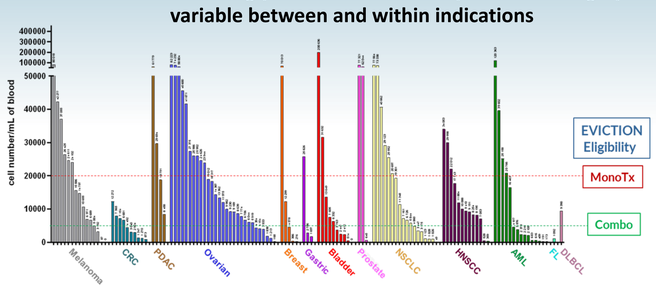
1. Background

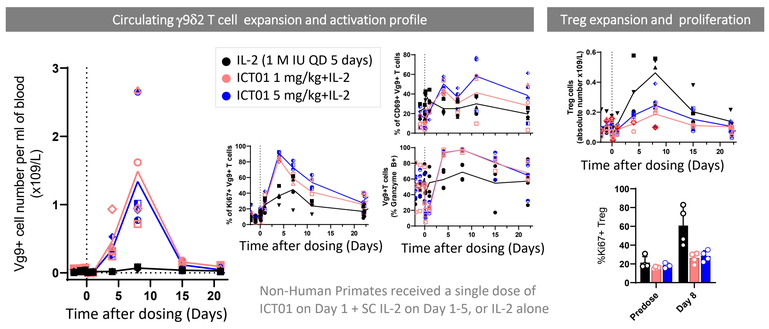
γ9δ2 T cell tumor infiltration is associated with a positive clinical prognosis. The anti-BTN3A mAb, ICT01, selectively activates γ9δ2 T cells resulting in remodeling of the TME by activated γ9δ2 T, CD8 T, and NK cells (EVICTION-NCT04243499). Response to ICT01 depends on baseline γ9δ2 T cells with many cancer patients having inadequate numbers. Eligibility criteria for the expansion cohorts in EVICTION have been instituted based on baseline γ9δ2 T cells leading to exclusion of a significant proportion of patients.

Interleukin-2 (IL-2, Proleukin®) is an approved cancer immunotherapy shown to expand γ9δ2 T cells in humans when combined with phosphoantigen or zoledronate that decreased over multiple cycles. 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 resulting in a stronger anti-tumor immune response.

Baseline circulating γ9δ2 T cells in cancer patients are highly variable between and within indications

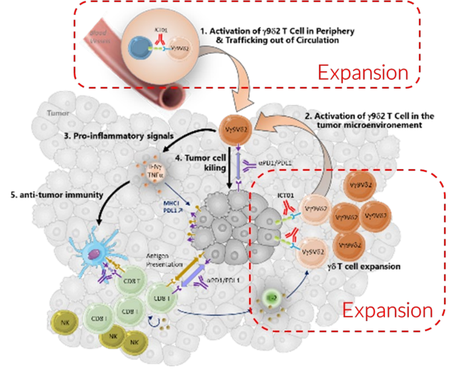


ICT01 + LDSC IL-2 selectively increase circulating γ9δ2 T cells in Non-Human Primates while blunting IL-2-mediated expansion of Tregs



Non-Human Primates received a single dose of ICT01 on Day 1 + SC IL-2 on Day 1-5, or IL-2 alone

Proposed MoA



2. Study Design Part 1 Dose Escalation

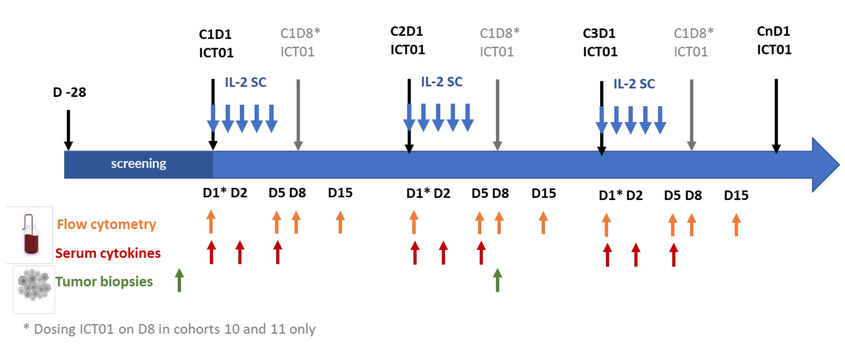
Phase 1/2a EVICTION-2 clinical trial: ICT01 (IV Q3W) with Proleukin® (1 or 2 MIU/m² SC Day 1-5) for the first 3 cycles, continued alone thereafter.

Major Inclusion Criteria

1) ≥18 years
2) Colorectal, Ovarian, Prostate Cancer and PDAC
3) 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
4) 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 (CnD1) + Daily IL-2 SC	
Cohort 1: 1mg + 1 MIU/m² (n=2)	Cohort 2: 1mg + 2 MIU/m² (n=2)
Cohort 3: 5mg + 1 MIU/m² (n=5)	*Cohort 4: 5mg + 1 MIU/m²*
Cohort 5: 20mg + 1 MIU/m² (n=2)	*Cohort 6: 20mg + 1 MIU/m²*
Cohort 7: 75mg + 1 MIU/m² (n=2)	*Cohort 8: 75mg + 1 MIU/m²*

N = patients dosed with at least one dose of ICT01 with LDSC IL2 (09 oct 2023)

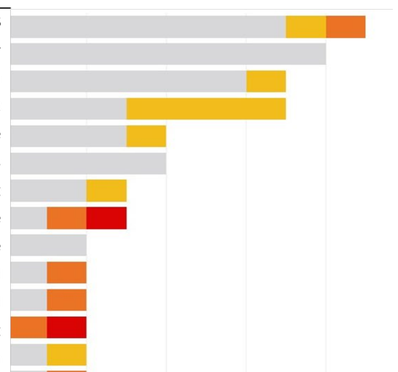


* Dosing ICT01 on D8 in cohorts 10 and 11 only

3. ICT01 + LDSC IL-2 has a Favorable Safety Profile

ICT1-related Adverse Events (> 1 patient)

N	(%)	#Events	Preferred term
9	39%	16	CRS
8	30%	12	Fever
7	35%	7	Nausea
7	30%	12	IRR
4	17%	4	Fatigue
4	17%	6	Chills
3	13%	5	Vomiting
3	13%	3	Lymphocyte count decrease
2	9%	2	Loss of appetite
2	9%	5	ASAT increased
2	9%	3	ALAT increased
2	9%	2	Lymphocyte count decrease worsening
2	9%	3	Pain
2	9%	2	GGT increased



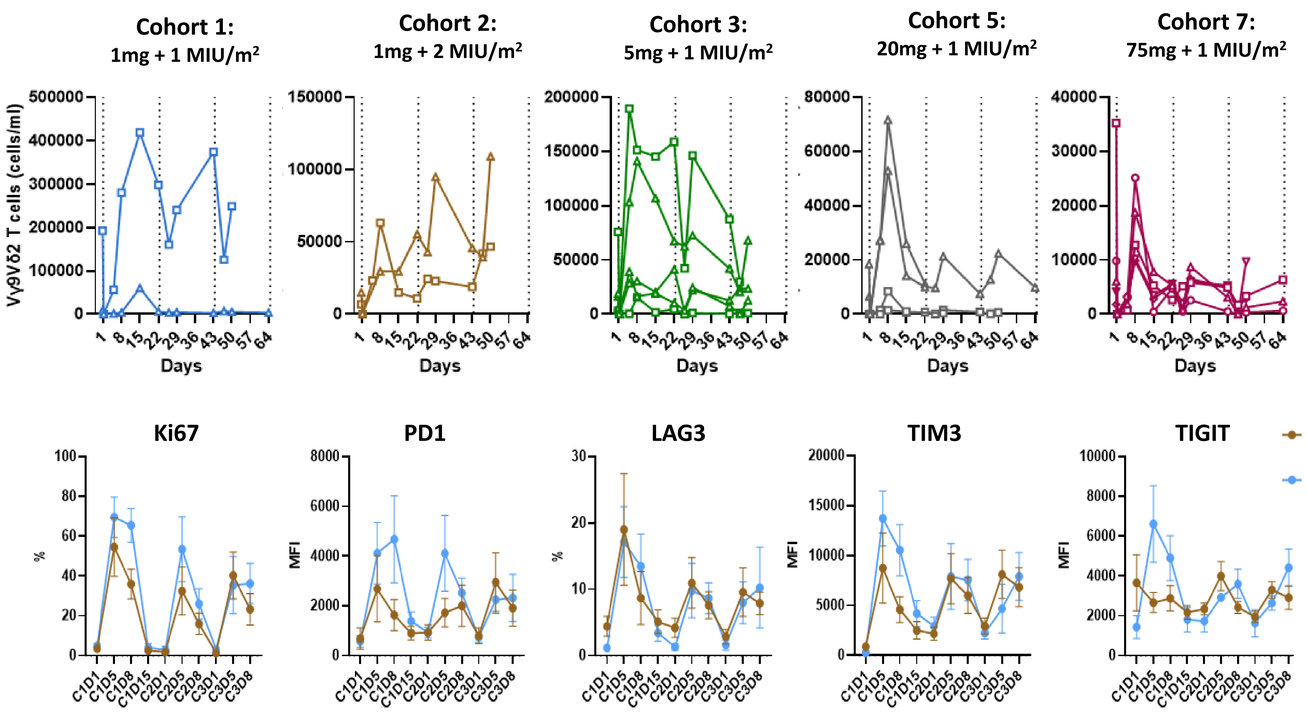
Total patients dosed (N) =23 (Sep 2023)

Combination of ICT01 with LDSC-IL-2 has a good safety profile, with no dose limiting toxicities. Most frequent treatment-related adverse events are cytokine release syndrome (CRS) and infusion related reaction (IRR) that are similar to those observed with ICT01 monotherapy (EVICTION-NCT04243499) , mostly Grade 1 and 2, observed also at 2nd and 3rd cycle

Cohort	Patient ID	Dx	Baseline γ9δ2 T Cells	RECIST/ iRECIST
1 1mg ICT01 1MIU/m² IL-2	01-01-201	CRC	8 111	PD W8
	01-01-203	Ovarian	192 242	SD W8/PD W16
2 1mg ICT01 2MIU/m² IL-2	01-01-204	CRC	15 098	SD W8/PD W16
	01-01-206	Ovarian	6 789	PD W16
3 5mg ICT01 1MIU/m² IL-2	01-01-205	CRC	19 136	SD W16/iuPD W24
	04-01-202	CRC	75 861	PD W8
	05-01-203	Pancreas	**5 697**	SD W8/PD W16
	05-01-207	Prostate	**3 014**	iuPD W8/PD W16
	04-01-205	Pancreas	**16 377**	PD W8
5 20mg ICT01 1MIU/m² IL-2	04-01-203	CRC	18 468	PD W8
	05-01-201	PDAC	0	ND
	05-01-202	Ovarian	6 512	ND
	05-01-205	Prostate	**0**	SD W8/PD W16
7 75mg ICT01 1MIU/m² IL-2	01-01-208	CRC	6 047	PD W8
	04-02-201	CRC	35 257	PD W8
	05-01-204	Prostate	9 848	PD W8
	04-01-204	Pancreas	4 165	SD W24
	01-01-209	Ovarian	1 800	PD W8

4. Effect of ICT01+LDSC IL-2 on Expansion and Activation of Circulating γ9δ2 T cells, NK, CD8 T cells and Tregs

Expansion, proliferation and activation of γ9δ2 T Cells



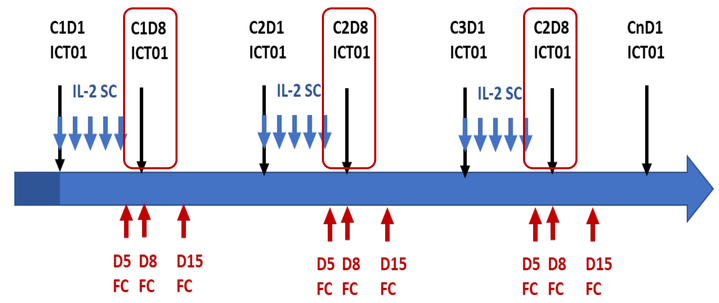
ICT01 combination with LDSC IL-2 induces a 2-14x increase of γ9δ2 T cell count above baseline across all cohorts peaking at day 8 to 15 expansion, reoccurring in subsequent cycles.

γ9δ2 T cell expansion is associated with increase in proliferation marker (Ki67) and increased expression of surface immune checkpoint receptors.

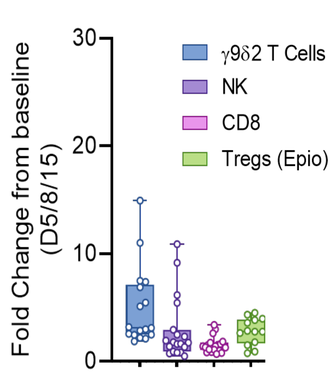
New dosing regimen

To further activate the expanded γ9δ2 T cells an alternative ICT01 dosing regimen ICT01 administration was introduced. Low dose ICT01+LDSC IL2 is used to trigger γ9δ2 T cell expansion (D1).
An additional ICT01 dose is added at the peak of expansion (D8) to trigger activation and migration of a large number of γ9δ2 T cells

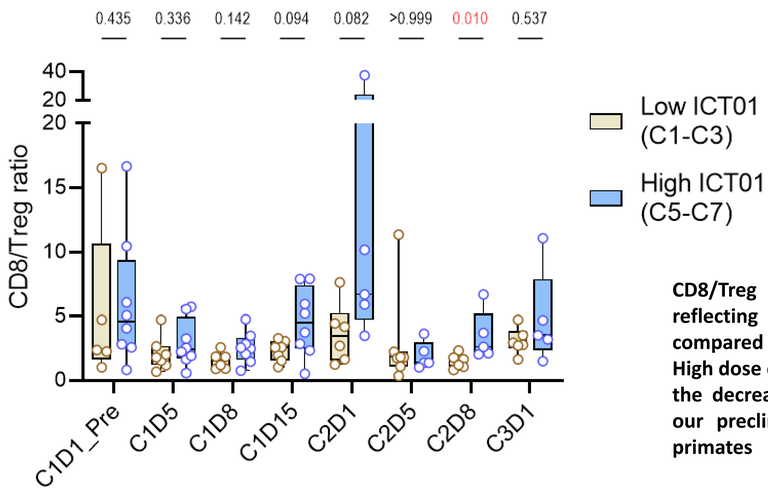
ICT01 IV Dose (CnD1 and C1-3D8) + Daily IL-2 SC	
Cohort 10: 5mg/5mg + 1 MIU/m² (n=2)	Cohort 11: 5mg/20mg + 2 MIU/m² (n=2)



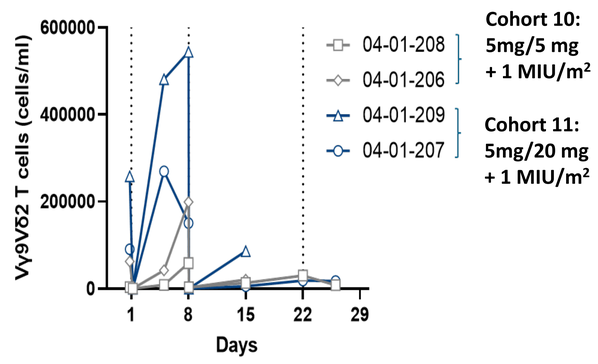
Expansion of γ9δ2 T, NK, CD8 Cells and Tregs



ICT01 combination with LDSC IL-2 induces increase in blood γ9δ2 T cells (3.1 fold), Tregs (2.8 fold), NK cells (1.7 fold) and CD8 T cells (1.4 fold).



CD8/Treg ratio decreases post ICT01+IL-2 reflecting superior expansion of Treg as compared to CD8 T cells in peripheral blood. High dose of ICT01 (20 or 75mg) tends to limit the decrease of CD8/Treg ratio in line with our preclinical observations in non-human primates



The expansion of γ9δ2 T cells at D8 following low dose of ICT01 on day 1 was confirmed. Adding a second dose of ICT01 at peak of expansion results is rapid migration of circulating T cells, hence confirming that these expanded cells γ9δ2 are still ICT01-responsive

5. Conclusion

The selective expansion of γ9δ2 T cells observed in preclinical studies has been confirmed in patients with advanced-stage solid tumors with a beneficial safety profile. ICT01 plus LDSC IL-2 produces a broad anti-tumor immune response that is durable across multiple treatment cycles, which appears different to prior attempts to expand γ9δ2 T cells with bisphosphonates or phosphoantigens.