Abstract CT188

ICT01, an anti-Butyrophilin 3A Targeted mAb Activating γ9δ2 T cells, Induces Immune Remodeling of the Tumor Microenvironment and Clinical Responses in Combination with Pembrolizumab in Patients with Advanced Solid Tumors who Failed Prior Checkpoint Inhibitor Therapy: EVICTION Trial

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Abstract

Background: γ9δ2 T cells are part of the innate-like immune response to malignancies and have the ability to bridge to the adaptive immune response via cytokine release (e.g., IFNγ and TNFα). Butyrophilin 3A is a novel checkpoint molecule that is required to activate γ9δ2 T cells and the target of a monoclonal antibody ICT01. ICT01 induces activation and migration of γ9δ2 T cells from the circulation to induce immune remodeling of the tumor microenvironment (TME) at doses ≥ 700 µg (AACR 2021, CT034). In vitro studies demonstrated that ICT01 induces upregulation of PD-1 on γ9δ2 T cells and that the combination with pembrolizumab leads to enhanced cancer cell killing, providing scientific rationale for evaluating this combination.

Methods: EVICTION is an ongoing Phase 1/2a, international, open-label trial with Group C assessing ICT01 plus pembrolizumab (200mg IV Q3W) in patients with bladder cancer, HNSCC, melanoma, or NSCLC who failed ≥1 checkpoint inhibitor (CPI). Pharmacodynamic activity was monitored by immunophenotyping and cytokine level analysis. Tumor biopsies (baseline, Day 28) were used for immunohistochemistry of BTN3A and tumor-infiltrating lymphocytes, and gene expression profiling. Efficacy evaluations by irRECIST 1.1 were conducted every 8 weeks.

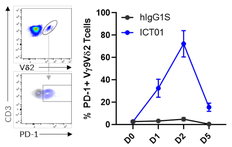
Results: Group C patient cohorts have been enrolled and treated with ICT01 doses of 700µg, 2mg, 7mg, 20mg or 75mg (n=30), with the 200mg cohort enrolling currently. To date, no DLTs have been observed with the combination. First-dose fever and chills (Grade 1/2) were the most common AEs that increased in frequency up to 75mg (100%, n=6), without any increase in severity, and rarely recur with subsequent dosing. ICT01+pembrolizumab induced trafficking of >95% of circulating γ9δ2 T cells within 30 min post ICT01 (≥700 µg), which was sustained for 21 days at 75mg. Transient, dose-dependent increases in serum cytokines at 30 min (TNFα) or 4h (IFNγ) post-dose were correlated with baseline γ9δ2 T cell counts and returned to baseline by 24 hrs post dose. Baseline γ9δ2 T cells also correlated with increases in tumor infiltration of γδ, CD3, and CD8 T cells, confirming the ability to remodel the TME, and the potential to select/enrich patients with higher baseline γ9δ2 T cell counts. Sixteen patients (9/16 pembro-experienced; 5/16 received >1 prior CPI) were efficacy-evaluable at ICT01 doses up to 20 mg at ≥Week 8 by RECIST1.1 with a disease control rate of 44% (including 3 confirmed PRs: bladder (2mg), melanoma (2mg), NSCLC (7mg)), with the Ipi/Nivo-refractory melanoma patient with PR also achieving a CR on their non-target lesion brain metastasis. Data from the 75 and 200mg cohorts will be presented.

Conclusion: The immune remodeling of the TME by ICT01-activated γ9δ2 T cells leads to clinical benefit in CPI-relapsed/refractory patients when used in combination with pembrolizumab. The RP2D of ICT01 will be selected and combination expansion cohorts launched in mid 2022.

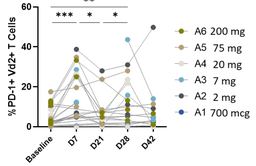
1. Rationale & Study Design

ICT01 activation of γ9δ2 T cells increases surface expression of PD-1 in vitro (A) and in cancer patients treated in Group A of EVICTION (B). Combination with an anti-PD-1 (i.e., pembrolizumab) enables full activation of the γ9δ2 T cells and the newly recruited CD8 T cells, which enhances killing of cancer cells in vitro (data not shown).

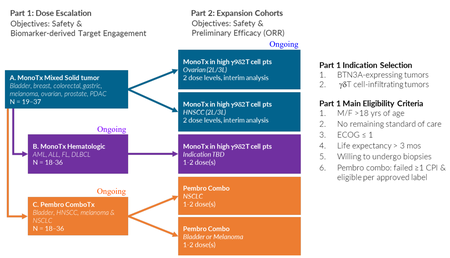
A. Expression of PD-1 in huPBMC



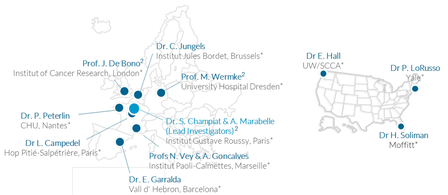
B. ICT01 Increases PD-1 Expression in Patients



EVICTION Trial Design



Participating Study Centers



2. Safety Results

Group C ICT01 + Pembro Type of Event	700 µg ICT01 N=4 n (%) E	2 mg ICT01 N=8 n (%) E	7 mg ICT01 N=8 n (%) E	20 mg ICT01 N=8 n (%) E	75 mg ICT01 N=6 n (%) E	200 mg ICT01 N=4 n (%) E
TEAEs	3 (75.0%) 37	7 (87.5%) 51	7 (87.5%) 71	8 (100.0%) 83	6 (100.0%) 49	4 (100.0%) 17
TEAEs Considered Related to Study Drug[1]	3 (75.0%) 11	6 (75.0%) 13	7 (87.5%) 17	7 (87.5%) 51	6 (100.0%) 32	4 (100.0%) 15
Related TEAEs Leading to Study Discontinuation	0	0	0	0	0	0
TEAEs Graded at Least Severe	2 (50.0%) 2	4 (50.0%) 8	3 (37.5%) 9	5 (62.5%) 6	2 (33.3%) 3	1 (25.0%) 1
SAEs	2 (50.0%) 2	2 (25.0%) 3	2 (25.0%) 5	3 (37.5%) 6	4 (66.7%) 5	1 (25.0%) 1
TESAEs	2 (50.0%) 2	2 (25.0%) 3	2 (25.0%) 5	3 (37.5%) 6	4 (66.7%) 5	1 (25.0%) 1
DLTs	0	0	0	0	0	0
AESIs	0	0	0	0	0	0
Related Fatal TEAEs	0	0	0	0	0	0

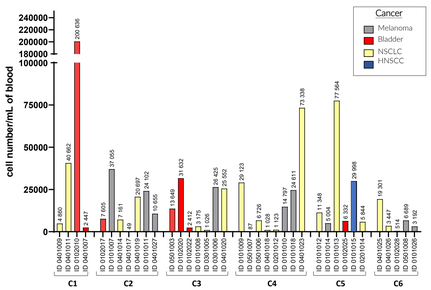
Comparison of Common (>10%) Related TEAEs in Solid Tumor Patients

Group A ICT01 MonoTx Preferred Term	20-700 µg (N=6) n (%)	2 mg (N=5) n (%)	7 mg (N=4) n (%)	20 mg (N=5) n (%)	75 mg (N=7) n (%)	200 mg (N=6) n (%)	Overall (N=33) n (%)
Pyrexia	2 (33%)	3 (60%)	0	4 (80%)	7 (100%)	3 (50%)	17 (52%)
Chills	0	1 (20%)	0	1 (20%)	5 (71%)	3 (50%)	9 (27%)
Asthenia	0	0	3 (75%)	0	2 (29%)	1 (17%)	6 (18%)
Arthralgia	2 (33%)	0	1 (25%)	0	0	3 (33%)	6 (18%)
Nausea	0	0	1 (25%)	2 (40%)	1 (14%)	1 (17%)	5 (15%)
Vomiting	0	0	1 (25%)	2 (40%)	0	1 (17%)	4 (12%)
Fatigue	1 (17%)	0	0	1	1 (14%)	2 (33%)	4 (12%)

Group C Pembro Combo Preferred Term	700 µg (N=4) n (%)	2 mg (N=8) n (%)	7 mg (N=8) n (%)	20 mg (N=8) n (%)	75 mg (N=6) n (%)	200 mg (N=4) n (%)	Overall (N=36) n (%)
Pyrexia	0	2 (29)	2 (25)	5 (63)	6 (100)	2 (50)	17 (47)
Chills	0	1 (12)	3 (38)	3 (38)	3 (50)	1 (25)	11 (31)
Asthenia	1 (25)	1 (12)	3 (38)	1 (12)	1 (17)	0	7 (19)
Vomiting	0	1 (12)	0	2 (25)	1 (17)	0	4 (11)
Fatigue	0	0	1 (12)	2 (25)	1 (17)	0	4 (11)
Nausea	0	0	1 (12)	2 (25)	1 (17)	0	4 (11)
Hypoxia*	0	0	1 (12)	2 (25)	0	1 (25)	4 (11)

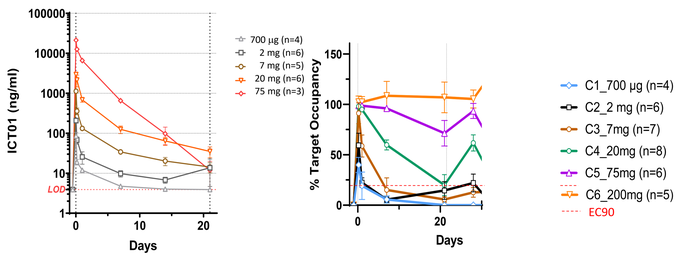
Safety Summary: No DLTs or significant safety signals have been observed to date. The most common TEAEs in solid tumor patients treated with ICT01 (alone and in combo with pembrolizumab) are fever, chills and asthenia that are part of an Infusion-Related Reaction (IRR) that is usually observed with only the 1st cycle. The events are self-limited and can generally be managed by paracetamol/acetaminophen, although steroids and antihistamines have been used in some patients. Tocilizumab has not been needed for any of these IRRs.

3. Baseline γ9δ2 T Cells by Cohort & Cancer



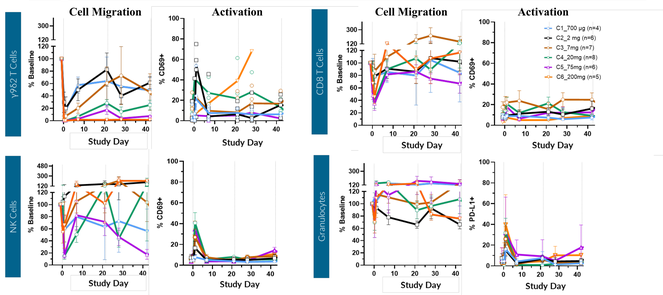
Summary: There is a wide range of baseline γ9δ2 T cell counts in Group C, range: 49 – 200K cells/mL. Only 14 of the 37 patients enrolled have >20K cells/mL, which is an eligibility criteria being tested in the ICT01 monotherapy expansion arms (blue boxes on study design). Since this patient population is very heterogeneous, we have not identified predictors of baseline γ9δ2 T cell counts.

4. ICT01 Exposure and Target Occupancy



Summary: Following a 30-min IV infusion there is a rapid Cmax that is reflected by rapid TO, which remains above the EC90 threshold for the 21-day dosing interval at ICT01 doses ≥ 20 mg. Doses ≤7 mg drop below the EC90 and provide intermittent activation while the higher doses induce constant activation of γ9δ2 T cells that is reflected in the migration patterns (See next section).

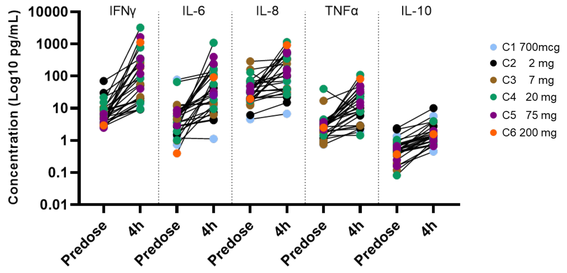
5. Activation & Migration of Multiple Immune Cell Populations Post ICT01/Pembrolizumab Treatment



Flow Cytometry Summary:

1. γ9δ2 T cells migrate rapidly post dose with nearly 100% migration observed at all doses tested, with the duration of effect being dose dependent.
2. Effects on CD8 and NK cells are observed at 7mg and higher, with peak effects observed at 75 mg.
3. Activation of granulocytes was observed at all doses, although the migration out of the blood was minimal.
4. The peak effect on γ9δ2 T cells was observed 30 minutes post treatment, while the peak effect on CD8 and NK cells was observed at 24 hours post treatment. These data suggest that there is a step after γ9δ2 T cell activation that is required to create these effects, which we have identified as being cytokine-mediated.

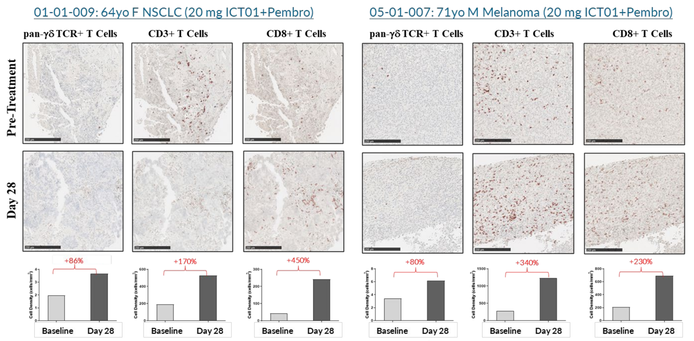
6. Increased Circulating Cytokine Levels



Cytokine Levels post Cycle 1:

1. Activated γ9δ2 T cells release TNFα and IFNγ as part of their ability to expand the anti-tumor immune response within the innate immune system (NK cells) and bridge to the adaptive immune system (CD8 T cells), respectively.
2. IL-6 and IL-8 tended to increase post treatment and declined back to baseline within 24 hours post treatment.
3. IL-10 levels increased post treatment but remained very low overall.

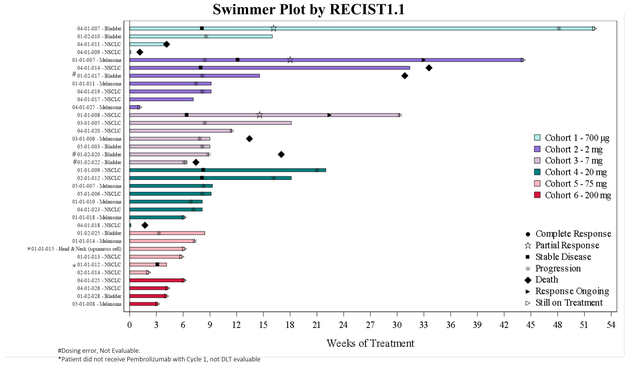
7. Tumor Biopsy: Enhanced Immune Cell Infiltration



Patient 01-01-009 failed 5 prior lines of tx, including pembrolizumab in 2020; baseline γ9δ2 T cells = 29K (Section 3)
Patient 05-01-007 failed 3 prior lines of tx, including ipilimumab in 2020 followed by pembrolizumab in 2020; baseline γ9δ2 T cells = 87

8. Clinical Activity

Swimmer Plot by RECIST1.1

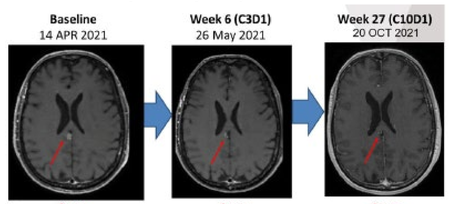


#Dosing error, Not Evaluable.
*Patient did not receive Pembrolizumab with Cycle 1, not DLT evaluable

Solid Tumor Patients with Disease Control of Better at ≥Week 8 by RECIST1.1

Patient ID Demographics ICT01 Dose/Start	Cancer Dx Date	Prior Therapies	Baseline γ9δ2 T Cells	Baseline Sum of Target Lesions (n)	Best Response	Status
04-01-007 57yo M 700 mcg/2 mg 22-FEB-21	Bladder (2015)	1.Gem/Cis 11/15-1/16 2.Gem/Cis 11/16-1/17 **3.Nivolumab** 10/18-11/19 (PD) 4.Gem/Carbo 2/20-6/20	2447	11 (1)	Confirmed PR	PD with NNML W48
01-01-007 60yo F 2 mg 14-APR-21	Melanoma (2019)	**1. Nivolumab** 4/20-12/20 **Ipilimumab** 7/20-10/20 (PD liver/spleen, SD on lymph nodes) 2. Mektovi 1/21-4/21	37065	58 (2)	Confirmed PR (CR brain met, not a target lesion)	Ongoing C17
01-01-008 61yo M 7 mg 5-JUL-21	NSCLC (2017)	1. Cis/Pemetrexed/ Denosumab 9/17-3/18 **2. Nivolumab** + radiotx 4/18-10/20 (PR of visceral lesions, PD on bone mets)	3175	15 (1)	Confirmed PR	PD W32 (No RECIST) C11
04-01-014 64yo F 7 mg 27-APR-21	NSCLC (2013)	1. Carbo/Pemetrexed/**Pembrolizumab** 2/19-4/19 2. Pemetrexed 5-11/19 **Pembrolizumab** 5/19-4/20 3. Docetaxel/Navgatref 6/20-2/21	7161	44 (2)	SD	Died Wk 34 C10
01-01-009 64yo F 20 mg 8-SEP-21	NSCLC (2019)	1. Carbo/Taxol 2019 **2. Pembrolizumab** 3/20-9/20 3. Gem 9/20-2/21 4. Taxol 2/21-3/21 5. Vinorelbine 4/21-7/21	29123	95 (1)	SD	PD W22 C7
02-01-012 61yo F 20 mg 23-SEP-21	NSCLC (2020)	1. Cis/Pemetrexed 2/20-4/20 2. Cis/Vinorelbine 5/20-6/20 **3. Atezolizumab** 2/21-8/21	1123	65 (2)	SD	Withdrawn by PI iuPD, W16 C6
01-01-015 50yo F 75 mg 21-Dec-2021	HNSCC (2011)	1. Cis/5-FU/Cetuximab 3/18-7/18 **2. Nivolumab** 1/19-unk/19 3. Carbo/Taxol/Olaparib 1/20-3/21 4. Investigational anti-integrin+ADC 4/21-11/21	29998	40 (1)	SD	Withdrawn by PI iuPD—oral pain W12 C4
01-01-018 53yo F 20 mg 4-Jan-2022	Melanoma (2019)	**1. Nivolumab** 6/21-10/21 **Ipilimumab** 8/21-10/21	24611	104 (1)	SD	Ongoing C4

CR of Brain Metastasis in Ipi/Nivo Refractory Metastatic Melanoma (01-01-007)



Conclusions

1. The combination of ICT01 plus pembrolizumab was well tolerated without any DLTs or safety concerns observed to date. The most common TEAEs are consistent with an IRR, which is a well-described event for pembrolizumab.
2. No immune-related AESI were reported.
3. Activation & migration of γ9δ2 T cells in the blood was observed at all ICT01 doses within 30 minutes post dose.
4. Activation & migration of CD8 T cells and NK cells in the blood were observed at doses ≥ 7 mg ICT01 and appear to be mediated by release of IFNγ and TNFα from activated γ9δ2 T cells.
5. Peripheral immune activation was reflected by infiltration of tumors by γδ, CD3 and CD8 T cells.
6. Clinical responses in these CPI failure patients were observed across multiple different solid tumors at ICT01 doses as low as 2 mg, suggesting that the complementary mechanisms of action lead to an increased anti-tumor immune response.

The expansion arms of EVICTION are planned to commence by mid 2022 after selection of the RP2D and target patient populations.