#316

THE EVICTION STUDY:

Preliminary Results in Solid Tumor Patients with ICT01, a First-in-Class, γ9δ2 T Cell Activating Antibody Targeting Butyrophilin 3A

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ImCheck therapeutics

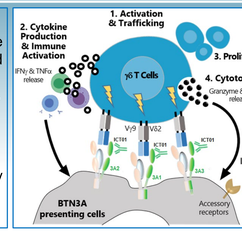
Introduction:

Gamma delta (γδ) T cells constitute a small subset of circulating T cells that, unlike αβ T cells, recognize non-MHC restricted antigens and present with innate and adaptive immune response features. γ9δ2 T cells are the predominant population among γδ T cells in the blood and are major players of the immunosurveillance for malignancies and infections. Their anti-tumor immune response is triggered by the binding of phosphoantigens (pAgs), overexpressed within malignant and infected cells, to the intracellular domain of Butyrophillin 3A1 that leads to a conformational change in the extracellular domain and subsequent recognition by and activation of γ9δ2 T cells. γ9δ2 T cell infiltration into solid tumors has been associated with a positive prognosis (Gentles, 2015), making them an attractive target for the next generation of anti-cancer immunotherapeutics.

Based on the above observations, ImCheck Therapeutics is developing ICT01, a humanized mAb that binds to the extracellular domain of all 3 isoforms of BTN3A and induces pAg-independent γ9δ2 T cell activation, for the treatment of patients with solid or hematologic tumors. See MOA Figure EVICTION (NCT04243499; EudraCT: 2019-003847-31) is an international, , multi-center, Phase I/IIa, first-in-human, open-label, clinical trial. Its objectives are to assess the safety, tolerability and activity of IV doses of ICT01 as monotherapy and in combination with pembrolizumab (KEYTRUDA®), in patients with advanced-stage, relapsed/refractory cancer. The study design is shown in Figure 1A.

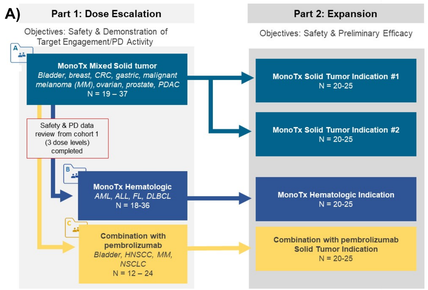
Following Competent Authority and Ethics Committee approvals, the study is being conducted at 6 cancer centers in France, Belgium, Spain, Germany, and the UK, with sites in the US expected to join before the end of 2020.
Following signed informed consent, patients receive ICT01 (dose range: 20 mg to 200 mg) every 3 weeks for up to 12 months with potential for prolonged treatment in responders. A detailed biomarker plan is shown below in Figure 1B, which includes tumor biopsies at baseline and 7 days after the 2nd dose of ICT01 (Day 28), multiple whole blood samples for immunophenotyping by flow cytometry and serum for cytokine, PK and ADA analysis.

Cohort 1 of solid tumor patients (n=6) has been enrolled, treated, and followed for analysis of safety, Dose Limiting Toxicities and pharmacodynamic activity, with the preliminary results presented below.



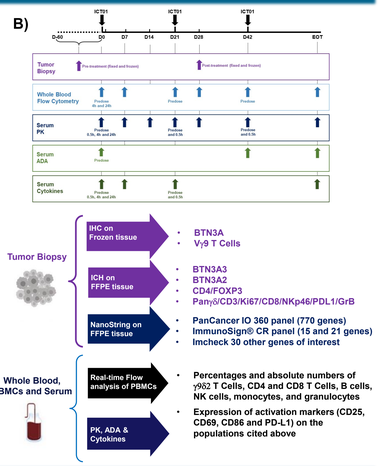
ICT01 MOA
Binds to all three BTN3A isoforms triggering: 1) γ9δ2 T-cell activation and trafficking from the circulation within 30 minutes, 2) Production of IFNγ and TNFα leading to immune cell activation, 3) Proliferation in the presence of cytokines, and 4) Cytotoxic attack of malignant cells that express a 2nd necessary signal.

1) EVICTION Design and Biomarker Collection & Analysis Plans



Major Inclusion Criteria

1) Male or female (non-pregnant, non-lactating) aged ≥18 years
2) Relapsed/refractory patients with histologically or cytologically confirmed diagnosis of advanced-stage or recurrent cancer
3) Willingness to undergo baseline and on-study tumor biopsies
4) ECOG performance status ≤ 1 with life expectancy > 3 months
5) At least 1 measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST)/ Response Evaluation Criteria in Lymphoma (RECIL) or >5% marrow blasts in leukemia
6) Patients must have no available standard of care for their disease, as determined by the treating Investigator
7) No anti-cancer therapy within 28 days or 5 times elimination half-life prior to dosing



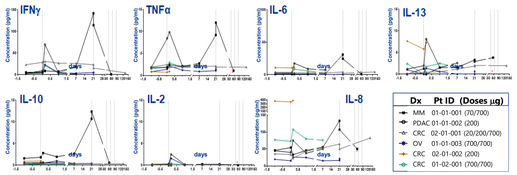
2) Encouraging Safety and Tolerability of Single and Multiple Doses of ICT01

Patients in Cohort 1 that received 2 doses of ICT01, including at least 1 dose of 700 μg, and followed for 21 days after the 2nd dose were considered evaluable for DLTs. **There were no DLTs or related SAEs in Cohort 1.**

Diagnosis	Age (years)	Sex	ICT01 Dose(s)*	Prior Anti-cancer Regimens	Possibly/Related AEs
Colorectal	50	M	20/200/700 μg	8	Dyspnea, Fatigue, Rash, Anemia, TSH increase/ Hypothyroidism
Malignant Melanoma	41	F	70/ 700 μg	8**	Arthralgia, Chills, Fever
PDAC	64	M	200 μg	2	Fever
Colorectal	65	M	200 μg	7	None
Ovarian	54	F	700/700 μg	6	Knee hematoma/pain
Colorectal	67	F	700/700 μg	4	None

***ICT01 is administered IV over 30 min. **Includes 3 courses of Ipilimumab/Nivolumab**

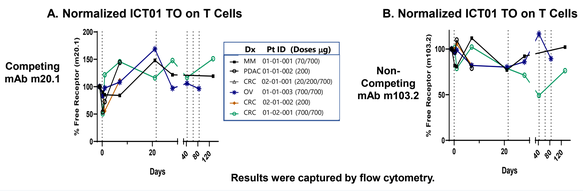
3) No Cytokine Release Syndrome



Summary of Cytokine Results

1. All cytokine levels were very low.
2. IFNγ, TNFα and IL-8 transiently trended up in this cohort
3. IL-12p70, IL-1β & IL-4 levels remained below the level of detection.
4. The MM patient had the highest number of γ9δ2 T cells at baseline, which may be related to the higher levels of cytokines.

4) Target (BTN3A) Occupancy within 30 Minutes Post ICT01 Dosing



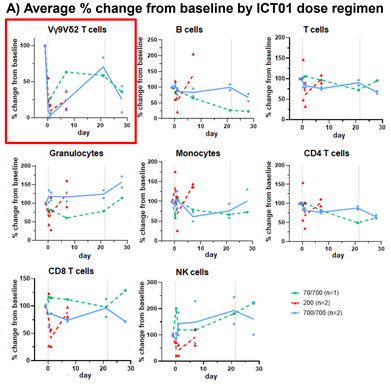
Results were captured by flow cytometry.

Summary of Target Occupancy

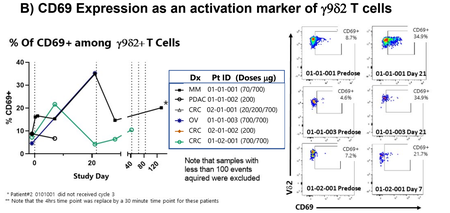
1. TO on T cells ranged from ~10 to 50% across the range of doses tested at 0.5-24h post dose
2. The available ICT01 binding site on BTN3A returned back towards or above baseline by Day 7 post dose
3. BTN3A by the non-competing mAb showed variability across patients
4. Pending PK data will help the interpretation of the TO data

5) Rapid, Selective Activation and Trafficking of γ9δ2 T Cells Post ICT01

A) Average % change from baseline by ICT01 dose regimen



B) CD69 Expression as an activation marker of γ9δ2 T cells

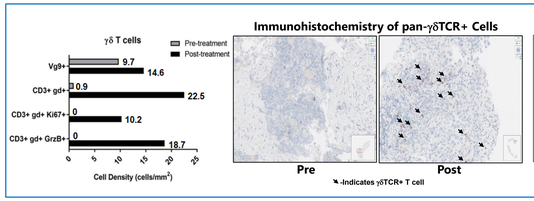


Methods: Fresh whole blood samples were stained with a 13-color immunophenotyping panel and analyzed by flow-cytometry.

Summary of Activation & Trafficking Post ICT01

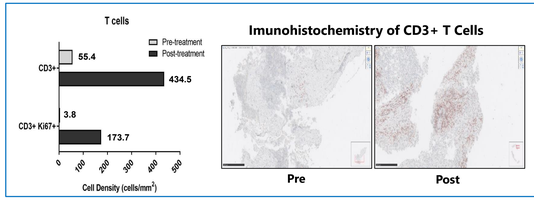
1. A dose dependent effect of γ9δ2 T cell activation and trafficking out of the circulation was observed within 30 min and reached a maximum effect at 24hrs.
2. No activation or trafficking was observed for any other immune cell population.
3. γ9δ2 T cells recovered by Days 7 and 21, and showed another drop following the second dose of ICT01 that demonstrates continued sensitivity to the ICT01 MOA
4. Pending PK data will help the interpretation of the PD data.

6) Increase in the Number of Activated &Proliferating γδ T Cells and CD3+ T Cells 7 Days Post 2nd Dose of ICT01 (700μg) in a Melanoma Patient



Summary of γδ T Cells in Tumor

1. 51% increase in Vγ9+ density over baseline
2. 25x increase in CD3+/pan-γδTCR+ cell density
3. Most CD3+/pan-γδTCR+ cells are activated post ICT01 treatment
4. Since it is only 1 patient, these results need to be confirmed in additional patients.



Summary of CD3+ T Cells in Tumor

1. ~8x Increase in density over baseline in tumor
2. ~45x Increase in proliferating CD3+
3. Similar trends with CD8 and CD4 T cells.
4. Since it is only 1 patient, these results need to be confirmed in additional patients.

7) SUMMARY & CONCLUSION

SAFETY: Single and multiple ICT01 doses ranging from 20 to 700μg were well-tolerated and did not induce CRS in patients with solid tumors.

PD ACTIVITY: The flow and IHC data demonstrate that ICT01 is active at doses as low as ~1 μg/kg (70 μg) and that humans may be more sensitive to the effects of ICT01 than Cynos.

(*See ICT01 PK-PD Modeling in Poster #539 De Gassart et al.*)

Furthermore, the limited IHC data suggest that ICT01 may increase the number and activation status of CD3, CD4 and CD8 T cells in tumors, which suggests that ICT01 may have a unique and powerful MOA by activating γ9δ2 T cells **AND** αβ T cells that results in a more complete anti-tumor immune response.

These promising safety and PD results supported dose escalation to 2 mg in Group A (solid tumors) and the initiation of enrollment for Group B (hematologic malignancies) and Group C (pembrolizumab combination) in EVICTION.

Currently, Dose Cohort 3 (7 mg) is enrolling in Group A.

REFERENCES

1. Gentles AJ, Newman AM, Liu CL, et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. *Nature Medicine*. 2015;21(8):938–945.