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Coordinated activation of antitumor responses of g9d2 and CD8 T-cells by targeting BTN3A with ICT01 in patients with solid tumors: EVICTION trial

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Background

g9d2 T-cells function at the crossroad of innate and adaptive antitumor immunity, infiltrate into most tumors, and are MHC-independent killers of tumors. Butyrophilin (BTN) 3A is an immune checkpoint molecule expressed on tumors and immune cells that is part of the stress response that activates g9d2 T-cells. ICT01, an anti-BTN3A mAb targeting all 3 isoforms of BTN3A, induces pAg-independent g9d2 T-cell activation and *in vitro/vivo* killing of multiple solid and hematologic tumors.

Methods

EVICTION (EudraCT: 2019-003847-31) is a FIH, open-label, basket trial assessing safety, tolerability and activity of ICT01 monotherapy and in combination with pembrolizumab (200 mg IV Q3W), in advanced cancer patients with no available standard of care. Blood samples were collected for target occupancy (TO), immunophenotyping and cytokine analysis (IFNg, TNFa, IL-1b/2/4/6/8/10/12/13). Tumor biopsies (baseline, Day 28) were used for IHC of BTN3A and tumor-infiltrating lymphocytes, and gene expression profiling.

Results

Dose escalation from 20µg to 200mg IV ICT01 Q3W in solid tumor patients (n=32) and 2 dose cohorts of ICT01 (700µg, 2mg) plus Pembro (n=7) were completed without DLTs. First-dose fever and chills (Grade 1/2) were the most common AEs that increased in frequency but not severity with dose, and did not recur. BTN3A TO on circulating T-cells by ICT01 reached 100% within 30 minutes at doses ≥7 mg, which lasted at least 24h (20 mg) or 7 days (≥75 mg). ICT01 induced a >95% decrease from baseline of circulating γ9δ2 T-cells within 30 min post ICT01 (≥2 mg), which was sustained for 21 days at doses ≥75 mg. 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 led to activation and migration of NK and CD8 T-cells out of the blood at doses ≥7 mg. Paired tumor biopsies indicated that high baseline g9d2 T-cell counts were associated with significant ICT01-related intra-tumoral increases in γδ, CD3 and CD8 T-cells, and adaptive immunity using the Immunosign21 gene signature.

Conclusions

ICT01-activated g9d2 T-cells orchestrate a broad antitumor immune response that supports cohort expansion.

Clinical trial identification

NCT04243499; EudraCT: 2019-003847-31.

Legal entity responsible for the study

ImCheck Therapeutics.

Funding

ImCheck Therapeutics.

Disclosure

A. Marabelle: Financial Interests, Personal, Advisory Board: ImCheck. J. de Bono: Financial Interests, Personal, Advisory Board: ImCheck. P. Lorusso: Financial Interests, Personal, Advisory Board: ImCheck. D. Olive: Financial Interests, Personal, Stocks/Shares: ImCheck. P.A. Frohna: Financial Interests, Personal, Full or part-time Employment: ImCheck. All other authors

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