ICT01, an anti-BTN3A mAb that activates γ9δ2 T cells, plus interleukin-2: a potent and promising combination for cancer immunotherapy

Aude De Gassart1, Patrick Brune1, Suong Le1, Sophie Agaugué1, Emmanuel Valentin1, Jennifer Sim2, Daniel Olive1, Paul Frohna1, René Hoe1

1. ImCheck UPMPS, CNRS UMR 7258, Marseille, France; 2. Institut Pasteur, Marseille, France. *Integrated Biology GmbH, Basel, Switzerland. **INSERM U1088, Centre de Recherche en Cancérologie de Marseille (CRCM), Immunology & Cancer, Institut Paul-Sabatier, Aix-Marseille Université, France

Background: γδ T-cells are attractive targets for cancer immunotherapy given their strong cytolytic and pro-inflammatory cytokine secretion activities, and the association between tumor proliferation and positive prognosis. ICT01 is a novel cytokine variant that activates γδ2 T-cells in a phosphoantigen (pAg)-independent manner. ICT01 is currently in a Phase 1/2a study in solid and hematologic tumors (NCT04243499).

IL-2 has been shown to expand γδ2 T-cells in vitro and in non-human primates in the presence of pAgγδ2. Considering the MOA of ICT01 (Figure below), our hypothesis was that the combination of ICT01 plus IL-2 would induce selective, profferative effects on γδ2 T-cells as an approach to potentiate γδ2 T-cell mediated cancer immunotherapy.

1. IL-2 Significantly Enhances ICT01-Mediated γδ2 T Cell Proliferation in Human and Cynomolgus PBMCs in vitro

2. ICT01+IL-2 Induces γ9δ2 T Cell Expansion in NCG Mice Engrafted with Hu-PBMCs

3. ICT01+ IL-2 Induces Significant Expansion & Long-term Activation of γ9δ2 T Cells in Cynomolgus Monkey

4. No Effect of ICT01 on NK, or CD4 and CD8 T Cells While IHC Shows γ9δ2 T Cells in Several Organs in ICT01+IL-2 Treated Cynos

RESULTS:

- γδ2 cell activation with trafficking in <30 min
- Cytokines lead to activation of other immune cells, including T cells, APCs, & B cells
- Proliferation under appropriate conditions (e.g., presence of IL-2, IL-15)
- γδ2 cytokotic activity by γδ2 T cells requires 2nd signal from stressed/malignant/infected cells

RESULTS: Flow cytometry analysis of mouse blood revealed a 5-5 fold increase in human γδ2 T-cell number in the combination groups compared to ICT01 or IL-2 alone treated animals, with γδ2 T-cell frequency reaching ~35% of the CD3+ T-cell compartment.

RESULTS: Expansion and activation of peripheral γδ2 T-cells from ~1% at baseline to 10-30% of T cells on Day 8 in the combination treatment arms, which was not observed with IL-2 alone.

RESULTS: No ICT01+IL-2 effect observed on other immune cell populations

- Trend towards higher numbers of γδ2 T-cells in several organs in ICT01+IL-2 treated monkeys. However, since these were healthy monkeys there was little expectation for a significant build up in any single organ/tissue.

ADDITIONAL OBSERVATIONS:

- No evidence for a systemic cytokine release syndrome at any time point.
- No evidence for cytokotic effects on normal BTN3A expressing cells in blood or tissues.
- Adverse effects (AEs) with variable severity were observed (hypercycosity, anemia, and reversible prolongation of activated partial thromboplastin time, and reversible changes in clinical chemistry (decreased albumin and total protein, increased creatinine and triglycerides)
- Most AEs were reversible and commonly associated with IL-2 alone but mostly pronounced in the ICT01+IL-2 groups.

These toxicities were not reported in the 4-week GLP toxicity study with ICT01 alone at IV doses up to 100 mg/kg/week.

Conclusion and Clinical Perspectives

These results demonstrate that ICT01+IL-2 profoundly and selectively expands and activates γδ2 T cells, which is not observed with IL-2 alone.

The clinical combination of ICT01 plus a lymphoproliferative cytokine (e.g., IL-2) or a novel cytokine variant may be a powerful therapeutic approach for maximizing the immunotherapeutic potential of γδ2 T cells. Currently, a new monkey study is ongoing to identify a safe and pharmacologically active combination of ICT01 + IL-2 or one of the novel cytokine variants.

References:


