ICT01, an anti-BTN3A mAb, and NL-201, an alpha-independent IL-2/IL-15 agonist, combine to elicit a potent anti-tumor response by synergistically stimulating Vγ9Vδ2 T cell activation and proliferation

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Background γδ2 T-cells are attractive mediators of cancer immunotherapy due to their strong cytolytic and pro-inflammatory activities and the positive correlation between tumor infiltration and good prognosis [1,2]. ICT01, a novel anti-BTN3A mAb activating γδ2 T-cells, is being evaluated in a Phase 1/2a clinical study (NCT04243499) [3,4]. Previous studies have shown that IL-2 (Proleukin®) promotes γδ2 T-cells expansion following ICT01 stimulation, which may be clinically useful given that γδ2 T-cells are normally <5% of total T-cells [5]. However, the severe toxicity of IL-2 has limited its widespread use. NL-201 is a de novo alpha-independent IL-2/IL-15 agonist that preferentially stimulates CD8 T and NK cell proliferation at low concentrations, enabling a potentially wider therapeutic index than IL-2, and is being evaluated in a Phase 1 clinical study (NCT04659629) [6,7]. Here, we explore the potential of ICT01 and NL-201 to synergistically stimulate the activation and proliferation of γδ2 T-cells.

Methods Flow cytometry was used to assess IL-2R signaling (pSTAT5), and γδ2 T-cell activation and expansion after in vitro culture of huPBMCs with ICT01, NL201 or the combination. Tumor cell killing activity was monitored upon co-culture of huPBMCs with tumor cell lines (Incucyte). In vivo pharmacology was performed in NCG mice engrafted with 20x10⁶ huPBMCs and treated with ICT01 (1 mg/kg IV), NL201 (250 ng/kg IV) or the combination. Immune cells were phenotyped by flow cytometry in blood and organs collected at sacrifice (Day 16).

Results NL-201 is ~100X more potent than IL-2 in triggering IL-2R signaling in γδ2 T-cells, without preferential activity on Tregs. NL-201 plus ICT01 induces synergistic expansion of γδ2 T-cells, approaching ~50% of T-cells after 5 days versus ~10% with single agents. In addition, the combination of NL-201 and ICT01 promotes γδ2 T-cell effector memory differentiation, in contrast to IL-2, which induces primarily central memory phenotype. Importantly, NL-201 enhances ICT01-mediated killing of cancer cells by γδ2 T-cells. In mice, a dose-dependent expansion of peripheral γδ2 T-cells from ~1–2% at baseline to up to 40% of T-cells was observed in the ICT01+NL-201 combination groups. Consistently, γδ2 T-cell number and frequency increase in spleen and lungs of the ICT01+NL-201 treated animals as compared to controls. Expanded γδ2 T-cells in the combination groups display an effector memory phenotype, confirming our in vitro results.

Conclusions These results demonstrate the ability of the ICT01+NL-201 combination to synergistically trigger γδ2 T-cell activation, expansion and anti-tumor activity and support clinical evaluation of this combination as a novel therapeutic approach for cancer patients.

REFERENCES

Ethics Approval All procedures involving animals described in this study have been reviewed and approved by the local ethic committee (CELEAG) and the French Ministry of Research.

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