A POTENT, CD8 T CELL TARGETED IL-2 A-KINE WITH A BROAD THERAPEUTIC WINDOW INDUCES ANTITUMOR IMMUNITY IN SYNGENEIC AND HUMANIZED MOUSE TUMOR MODELS

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Background High dose IL-2 therapy induces complete and durable responses in a small subset of patients with metastatic melanoma and renal cell carcinoma. Severe toxicity, including capillary leak syndrome, limits its therapeutic use and requires inpatient treatment at specialized centers. High dose IL-2 therapy induces activation of regulatory T cells (Tregs), potentially limiting its efficacy. IL-2 variants engineered to avoid the high affinity IL-2 receptor on Tregs and other cells involved in systemic toxicity, are in advanced clinical trials. However, monotherapy efficacy has been reported only in small numbers of patients. Other approaches limit the activity of IL-2 to the tumor microenvironment, ignoring the opportunity to directly stimulate immune responses in secondary lymphoid organs. We engineered a conditionally active IL-2 variant (A-Kine) that requires targeting to specific receptors expressed on selected immune cells. Herein, we evaluate the activity of IL-2 A-Kines targeted to CD8+ T cells (CD8-ALN2) in syngeneic and humanized mouse tumor models.

Methods Mice were subcutaneously inoculated with MC38 or CT26 tumor cells. Once tumor growth was established, mice were treated with mouse CD8-ALN2 (mCD8-ALN2), untargeted-ALN2, or vehicle. CD34+ humanized NSG mice were subcutaneously inoculated with RL lymphoma or MDA-MB-231 breast tumor cells. Once tumor growth was established, mice were treated with human CD8-ALN2 (hCD8-ALN2), untargeted-ALN2, or vehicle. Tumor growth was measured, and tissues were analyzed by flow cytometry.

Results mCD8-ALN2 treatment induced significant MC38 tumor growth inhibition and up to 80% complete responses (CRs), while tumors in mice treated with untargeted-ALN2 grew as rapidly as vehicle-treated controls. CD8 T cell activation and expansion was observed in blood, spleen, and tumors following mCD8-ALN2 treatment, but not in response to untargeted-ALN2. Immune-depletion studies demonstrate a critical role for CD8+ but not CD4+ T cells. mCD8-ALN2 treatment also resulted in CRs in the CT26 colon carcinoma model, and inhibited tumor growth in B16 melanoma and Panc carcinoma models. Tumor growth inhibition was also observed in CD34+ humanized mice implanted with RL lymphoma or MDA-MB-231 breast tumors following hCD8-ALN2 treatment but not in mice treated with untargeted-ALN2. Consistent with antitumor efficacy, CD8 T cell activation and expansion was observed in the blood of hCD8-ALN2 treated mice.

Conclusions Selective stimulation of CD8 T cells with conditionally active CD8-ALN2 resulted in significant antitumor efficacy in syngeneic and humanized mouse tumor models. These data warrant the further development of hCD8-ALN2 for cancer immunotherapy.

Ethics Approval All animal experiments followed the Federation of European Laboratory Animal Science Association guidelines and were approved by the Ethical Committee of Ghent University. Approval numbers: ECD 20–40 and ECD 18/40.