HaNK, a cytotoxic human high affinity natural killer cell line, exerts enhanced ADCC mediated by avelumab (an anti-PD-L1 antibody) against multiple human tumor cell lines

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Purpose: Immune checkpoints have been implicated in the down-regulation of antitumor immunity. Anti-PD-1/PD-L1 checkpoint inhibitory monoclonal antibodies (mAbs) can restore immune function in the tumor microenvironment, and have demonstrated clinical benefit in patients with melanoma, Hodgkin’s lymphoma, lung and bladder cancers, and other tumor types. In addition to its checkpoint inhibitory function, avelumab, a fully human IgG1 anti-PD-L1 mAb, can mediate antibody-dependent cellular cytotoxicity (ADCC) to lyse human tumor cells in the presence of natural killer (NK) cells. NK cells can be used for cancer therapy. However, obtaining sufficient numbers of functionally active NK cells from patients is technically challenging since only about 10% of the population expresses on NK cells the high-affinity FcR that provides maximum ADCC. One alternative is to use established NK cell lines that have antitumor activity. High-avidity NK cells (haNK), provided by NantKwest, derived from the human NK cell line NK-92, are genetically engineered to express high-affinity human CD16 (FcγRIIIA-V158) and transduced with the human IL-2 gene. In addition, haNK cells have little inhibitory killer-cell immunoglobulin-like receptor (KIR) expression, a unique feature that may be a factor in their high cytolytic activity against a broad range of malignancies. We report here our investigation of 1) whether haNK cells used in combination with avelumab can lyse human tumor cells via the ADCC mechanism, and 2) the factors that may influence this cytotoxic activity.

Materials and Methods: Cell lines used in our experiments included human carcinomas of the head and neck, cervix, bladder, and skin, as well as prostate and pancreatic cancers. haNK cells irradiated with 10 Gy were used as effector cells at various effector-to-target-cell ratios in all experiments. Four- and 18-hour 111In release assays were performed to evaluate ADCC activity.

Conclusions: Our results show that 1) haNK cells can lyse a range of human carcinoma cells when avelumab is used to target PD-L1 expression; 2) the addition of anti-C16 neutralizing antibody significantly inhibits ADCC lysis, implicating C16 ligation as a major mechanism of action for ADCC lysis mediated by haNK and avelumab; and 3) in combination with avelumab, haNK cells mediate significantly higher levels of ADCC lysis than do NK cells isolated from healthy donor PBMCs.

These results provide a rationale for using haNK cells in combination with avelumab or other ADCC mediating cytokotic mAbs to treat human malignancies.