DEVELOPING PLACENTAL CD34+-DERIVED NATURAL KILLER CELLS WITH HIGH AFFINITY AND CLEAVAGE RESISTANT CD16 (CYNK-101) IN COMBINATION WITH AVELUMAB FOR ENHANCED THERAPY AGAINST PD-L1+ SOLID TUMORS

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Background Natural killer (NK) cells play a key role in antibody dependent cellular cytotoxicity (ADCC) via their CD16 Fc receptor. NK cell therapies can be targeted to tumors via tumor specific antibodies. Celularity Inc. is developing human placental CD34+-derived, cryopreserved, off-the-shelf, allogenic NK cells (CYNK-101) with a high IgG binding affinity and proteinase cleavage resistant CD16 variant (CD16VP) for cancer treatment. We hypothesize that expression of CD16VP on CYNK-101 augments its anti-tumor ADCC activity.

Methods Here, we evaluated anti-tumor activity of CYNK-101 in combination with Avelumab, an anti-PD-L1 antibody, against PD-L1+ lung, breast, and bladder cancer cell lines. Furthermore, the PI3-kinase inhibitor Wortmannin was used to investigate the molecular mechanism underlying CYNK-101-mediated cytotoxicity.

Results In vitro ADCC activity of CYNK-101 against PD-L1+ targets was assessed in combination with Avelumab. At 4h, at an effector to target (E:T) ratio of 5:1, CYNK-101 displayed increased cytotoxicity against the lung cancer cell line NCI-H1975, 56.7 ± 19.3% with Avelumab vs. 37.3 ± 6.4% with IgG control (n=6 donors, p<0.05). For the breast cancer cell line MDA-MB-231, cytolyis with Avelumab at the 5:1 ratio was 64.4 ± 17.1% vs. 51.1 ± 15.7% with IgG control (n=6 donors, p<0.005). For the bladder cancer cell lines, the cytolyis with Avelumab compared to IgG control was 78.3 ± 16.9% vs. 10.4 ± 20.2% for 5637 (p<0.005), 57.8 ± 22.8% vs. 37.2 ± 19.4% for T-24 (p<0.005), and 38.1 ± 20.0% vs. 28.7 ± 14.3% for RT-112 (p<0.05, respectively (n=6 donors). CYNK-101 in the presence of Avelumab also secreted significantly higher levels of GM-CSF and IFN-gamma when co-cultured for 24h with NCI-H1975 and MDA-MB-231 compared to that of the IgG control (n=6 donors, p<0.05). The enhanced cytotoxicity of CYNK-101 was PI3-kinase pathway dependent as Wortmannin (0.1 μM) significantly decreased the 24h cytotoxicity for NCI-H1975 with Avelumab from 92.4 ± 13.1% to 66.3 ± 16.7% at the E:T ratio of 5:1, such a decrease was also observed at E:T ratios from 2.5:1 to 0.6:1 (n=3 donors, p<0.05).

Conclusions Our results demonstrate that CYNK-101 has enhanced Avelumab-mediated ADCC activity against PD-L1+ tumor cell lines, such as lung, breast, and bladder cancers. Further development of the combinational therapy for PD-L1+ solid tumor indications is warranted.