129 DEVELOPMENT OF AB-201, A NOVEL ALLOGENEIC ANTI-HER2-SPECIFIC CAR-NK CELL THERAPY FOR THE TREATMENT OF HER2+ TUMORS

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Background Human Epidermal Growth Factor Receptor 2 (HER2), is a receptor tyrosine kinase that is highly expressed on the surface of many solid tumors. While many patients derive meaningful benefit from the approved HER2-directed therapies, most will eventually suffer relapse or progression of their disease highlighting the need for additional treatment options. Currently there are no FDA-approved cellular therapies targeting HER2. Over the past decade, however, cellular therapy has been shown to be a viable treatment option in different cancer types. Here we present AB-201, an off-the-shelf, cryopreserved cord blood (CB)-derived HER2 chimeric antigen receptor (CAR)-natural killer (NK) cell therapy as a safe, active, and readily available option for patients with HER2+ solid tumors.

Methods AB-201 is comprised of ex vivo expanded allogeneic CB-derived NK cells that have been genetically modified to express a HER2-directed CAR and presented as a cryopreserved infusion-ready product. The manufacturing process utilizes a feeder-cell line engineered to express factors specifically identified as supportive to NK cell expansion and a lentiviral transduction step to introduce the HER2 CAR construct. In vitro characterization of AB-201 included evaluation of the purity and expression of cell surface markers by flow cytometry and short- (4 hour) and long-term (over 5 days) cytotoxicity assays in the presence of HER2+ tumor cell lines at various effector to target ratios. In addition, AB-201 efficacy was assessed in vivo in established ovarian (intraperitoneal, SKOV-3), breast (intraperitoneal, HCC1954) and gastric (subcutaneous, N87) xenograft models in NSG mice.

Results HER2 CAR expression was detected in 93.1% of AB-201 cells. AB-201 is 97.9% CD3-/CD56+ cells and 94.6% CD56+/CD16+. Further characterization of AB-201 demonstrated high expression of NK activating receptors such as NKG2D, NKp30, NKp46, and DNAM-1 and expression of the chemokine receptor, CXCR3. AB-201 demonstrated concentration-dependent and HER2 targeted short-term cytotoxic activity and sustained long-term cell killing against the tumor cell lines SKOV-3, HCC1954, and NCI-N87. Efficacy, as evidenced by a significant reduction in bioluminescent signal or tumor volume, was observed in all xenograft models. A significant survival benefit over non-transduced NK cells or trastuzumab controls was demonstrated in the HCC1954 model.

Conclusions Data presented herein suggests that AB-201, a highly pure and readily expandable HER2-directed CAR NK cell product, has potential to be an effective therapy in the treatment of HER2+ tumors.

Ethics Approval The animal studies were conducted in accordance with an Institutional Animal Care and Use Committee-approved protocol and with the approval of an IACUC committee at each center where the studies took place

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