Evaluation of AB-101, an Allogeneic Cord Blood-derived Natural Killer (NK) Cell Therapy, as an ADCC Enhancer in Hematologic and Solid Tumors

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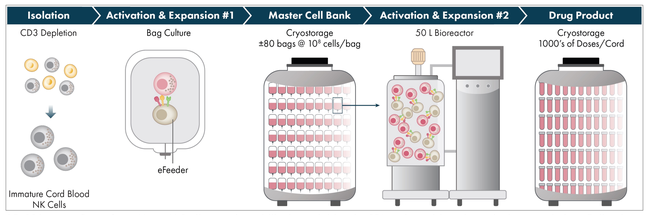
Introduction

AB-101 is a non-engineered, allogeneic, off-the-shelf, cryopreserved cord blood-derived natural killer (NK)-cell therapy in development as a cancer therapeutic. A highly scaled manufacturing process enables production of 1000s of doses from a single donor cord blood unit (CBU). AB-101 has been optimized for combination with monoclonal antibodies (mAbs) to enhance antibody-dependent cellular cytotoxicity (ADCC) and anti-tumor responses through selection of key attributes in the CBU. These include a KIR-B haplotype[1] and natural high-affinity variant of CD16 (158V/V polymorphism)[2], which are associated with improved anti-tumor activity and ADCC enhancement. Administration of AB-101 to patients in combination with mAbs has the potential to enhance the ADCC response, thereby increasing anti-tumor activity. Here we present preclinical data to support development of AB-101 in combination with mAbs as an ADCC enhancer in hematologic malignancies and solid tumor indications.

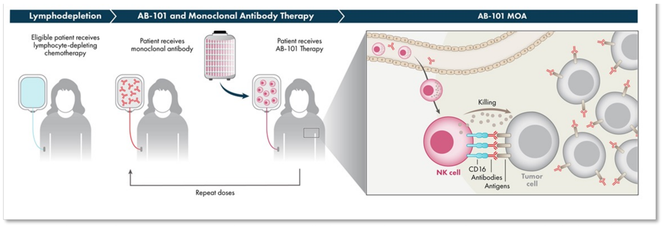
Methods



AB-101 manufacturing- Uses U.S. licensed umbilical cord blood (CB) units with selected characteristics. Following isolation, NK cells are expanded utilizing a proprietary engineered feeder cell (eFeeder) used to derive a master cell bank, followed by a bioreactor-based large-scale NK cell expansion and activation process to produce pure NK cells. High and consistent expression of the 158V/V CD16 is achieved in the AB-101 drug product, without the requirement for engineering of the cells. The scale of production potentially enables hundreds to thousands of patients to be treated from a single donor CBU.

In vitro characterization of AB-101 included evaluation of the purity and expression of cell surface markers by flow cytometry. In vitro ADCC assays were performed at various effector to target ratios against hematologic (Raji, ARH-77, Ramos) tumors in combination with Rituximab or Obinutuzumab. In addition, AB-101 efficacy was assessed in vivo in B-cell lymphoma (Raji, Ramos) xenograft models. These data supported the initiation of a clinical trial (NCT04673617) assessing AB-101 as monotherapy and in combination with Rituximab in patients with Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma.

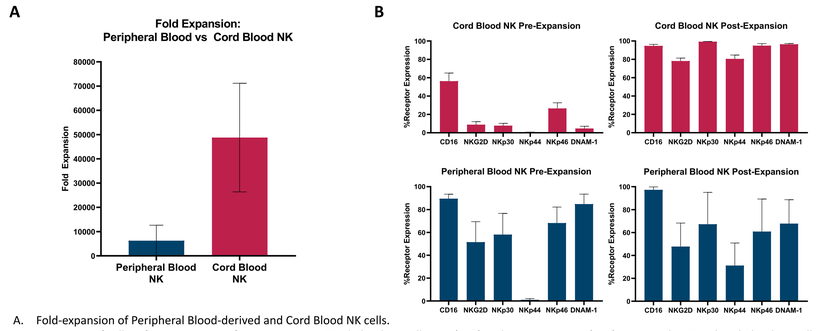
AB-101 was also characterized in solid tumor cell lines (Breast-MDA-MB-468, Ovarian-SKOV-3) in the presence of approved therapeutic antibodies (Cetuximab and Trastuzumab) demonstrating the potential for additional combinations.



AB-101 Mechanism of Action as an ADCC Enhancer – NK cells that can enhance a patient's ADCC, or antibody-dependent cellular cytotoxicity, response when undergoing monoclonal antibody therapy for either hematological or solid tumors.

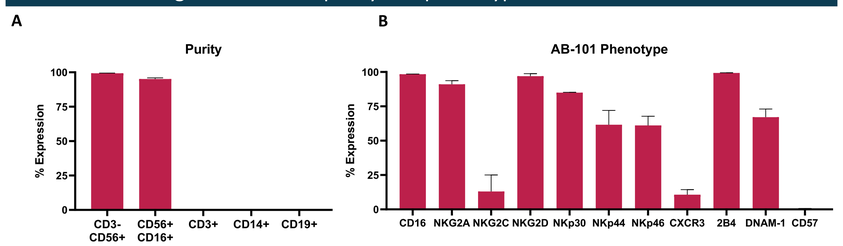
Results

Figure 1. Cord blood has significant advantage over peripheral blood as NK source



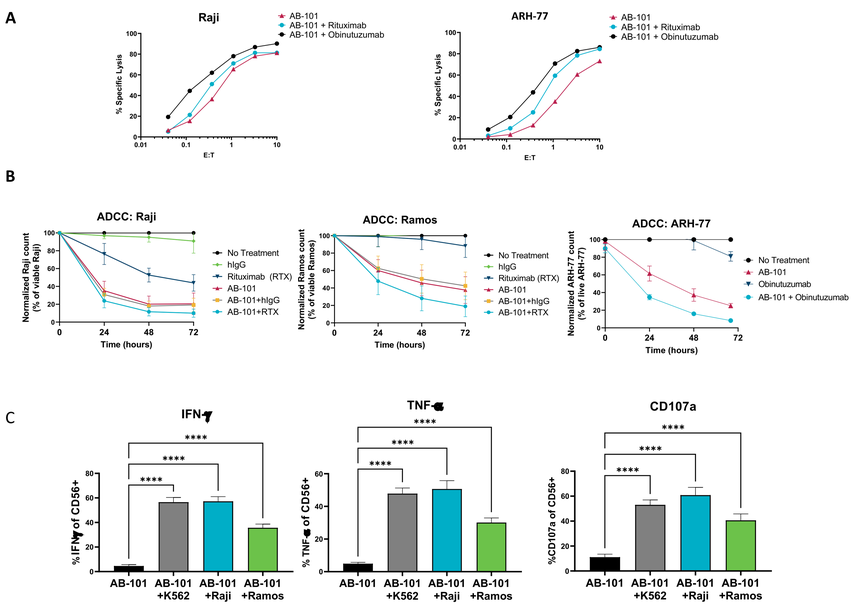
A. Fold-expansion of Peripheral Blood-derived and Cord Blood NK cells.
B. Frequency of cell surface expression of NK receptors on Cord Blood NK cells pre- (n=3) and post-expansion (n=8) compared to Peripheral Blood NK cells pre- (n= 17) and post- (n=40) expansion. Data are plotted as the mean ± SD.

Figure 2. AB-101: purity and phenotypic characterization



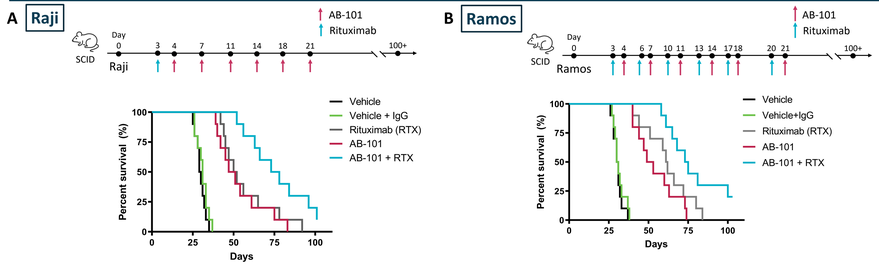
A. AB-101 characterization and frequency of NK cells (CD3-CD56+), (CD16+CD56+).
B. Frequency of cell surface expression of NK receptors was assessed on AB-101 gating on CD3-CD56+ cells. Data are plotted as the mean ± SEM.

Figure 3. Enhanced ADCC with AB-101 + anti-CD20 mAbs, Rituximab and Obinutuzumab



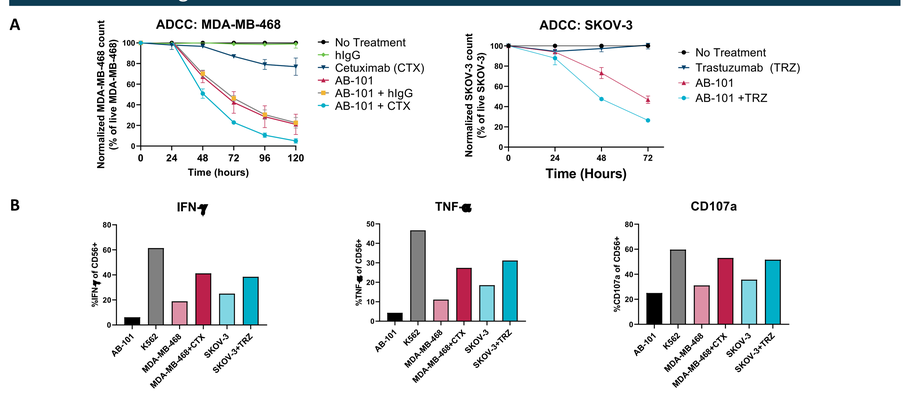
A. Cytotoxicity of AB-101 alone and in combination with anti-CD20 monoclonal antibodies (Rituximab and Obinutuzumab) against lymphoma cell lines.
B. Long-term cellular cytotoxicity of AB-101 alone and in combination with Rituximab or Obinutuzumab or isotype control (hIgG) against CD20+ tumor cell lines (Raji, Ramos and ARH-77) over 72hours at a 1:1 Effector:Target (E:T) ratio.
C. AB-101 was stimulated for 4 hours with tumor targets at a 1:1 E:T ratio. Following stimulation, cells were collected, and degranulation (CD107a) and cytokine secretion were analyzed by flow cytometry. Plots show the mean ± SEM.

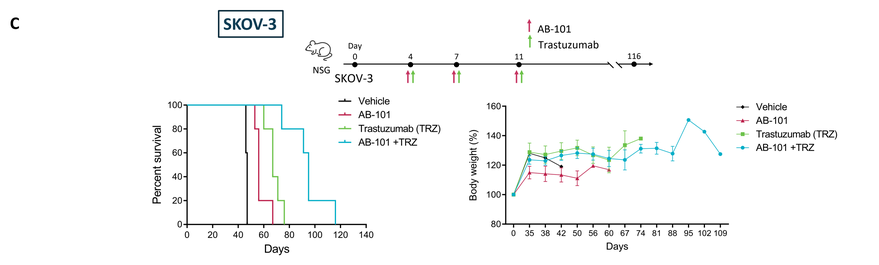
Figure 4. AB-101 demonstrates enhanced in vivo anti-tumor activity



A. Experimental design: Raji B-lymphoma model (IV) in SCID mice administered vehicle, vehicle + IgG (0.01μg), Rituximab (0.01μg), AB-101 (2x10^7), or AB-101 (2x10^7) + Rituximab (0.01μg). A total of 6 doses of AB-101 and 1 dose of Rituximab were given. Kaplan-Meier survival curve is representative of % survival in each group.
B. Experimental design: Ramos lymphoma model (IV) in SCID mice administered vehicle, vehicle + IgG (0.01μg), Rituximab (0.3μg), AB-101 (2x10^7), or AB-101 (2x10^7) + Rituximab (0.3μg). A total of 6 doses of AB-101 and 6 doses of Rituximab were given. Kaplan-Meier survival curve is representative of % survival rate in each group.

Figure 5. AB-101 demonstrates enhanced ADCC in solid tumors





A. Long-term cellular cytotoxicity of AB-101 alone and in combination with Cetuximab (1μg/mL) or isotype control (hIgG) against an EGFR+ breast (MDA-MB-468) tumor cell line and AB-101 alone or in combination with Trastuzumab (1μg/mL) in HER2+ ovarian (SKOV-3) tumor cell line over 72-120 hours at a 3:1 E:T ratio (MDA-MB-468) or 1:1 E:T ratio (SKOV-3). Data are plotted as the mean ± SEM.
B. AB-101 was stimulated for 4 hours with tumor targets at a 1:1 E:T ratio. Following stimulation, cells were collected, and degranulation (CD107a) and cytokine secretion were analyzed by flow cytometry.
C. Experimental design: 1x10^6 SKOV-3 tumor cells were inoculated by intraperitoneal (IP) administration on day 0 in NSG mice, followed by IP administration of vehicle, Trastuzumab (5mg/kg) , AB-101 (2x10^7), or AB-101 + Trastuzumab on day 4, 7, 11. Kaplan-Meier survival curve is representative of % survival in each group (left). No differences were observed in body weight between groups (right).

Conclusions

Data presented herein suggests that AB-101, a highly scaled, cryopreserved, allogeneic NK cell product, has potential to be an effective therapy in combination with mAbs as an ADCC enhancer in hematologic malignancies and solid tumor indications.

References

1. Cooley, S., et al., Donors with group B KIR haplotypes improve relapse-free survival after unrelated hematopoietic cell transplantation for acute myelogenous leukemia. Blood, 2009. 113(3): p. 726-32.
2. Musolino, A., et al., Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu-positive metastatic breast cancer. J Clin Oncol, 2008. 26(11): p. 1789-96.