AB-101, an Allogeneic, Non-Genetically Modified, Natural Killer (NK) Cell Therapy, Evaluated as Monotherapy or in Combination with Rituximab in R/R Non-Hodgkin Lymphoma

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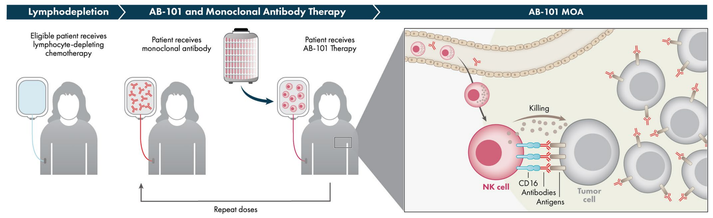
Introduction

AB-101 is a non-genetically modified, cord blood-derived, allogeneic, cryopreserved NK cell therapy, which has been optimized for combination with monoclonal antibody (mAb) therapy through the antibody-dependent cellular cytotoxicity (ADCC) mechanism. Many cancer patients are unable to mount a robust ADCC response, rendering mAb therapy less effective for these patients. To improve anti-tumor activity and ADCC enhancement, cord blood units used for the manufacturing of AB-101 are preselected to ensure:

- High-affinity variants of CD16 (158V/V polymorphism)[1] to potentially enhance ADCC via combinations with mAbs, and
- KIR-B haplotype[2] for enhanced innate activity in the allogeneic setting.



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.[3]

- To date, the therapeutic potential of multi-dose NK-cell/mAb combinations has not been fully assessed due to limited scale of cell production.
- AB-101 is a highly scaled product candidate that is being investigated in the outpatient setting, without the requirements for hospitalization or prolonged safety observations compared to genetically modified cell therapies.

Study Design

Key Inclusion Criteria
- r/r CD20+ B-cell malignancies
- Received ≥2 prior lines of therapy
- ECOG PS 0 or 1
- Prior CAR-T permitted
- No prior allo TX or CNS involvement

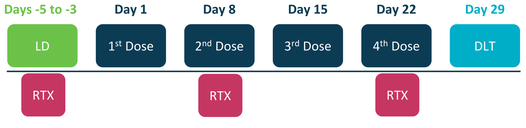
Endpoints:
- Safety and tolerability
- Anti-tumor activity
- Pharmacokinetics

NCT04673617

Lymphodepletion
- Fludarabine 30mg/m2
- Cyclophosphamide 250 or 500 mg/m2
- LD Cycles 1 and 2 only

AB-101
- 4 doses per 28-day cycle
- 1B or 4B cell per dose (dose finding)
- administration of IL-2 after AB-101

Rituximab *(combination only)*
- 375mg/m2 per dose
- 3 doses Cycle 1 and Cycle 2
- 2 doses Cycle 3 and Cycle 4



Monotherapy: Limited to one treatment cycle to assess safety, tolerability and PK without the influence of a mAb.

Combination with Rituximab: Up to 4 treatment cycles in the absence of toxicity or progressive disease. All AB-101 administrations (up to 16 doses) are conducted in the outpatient setting.

AB-101 is a US multi-center study and a first in human trial to investigate the safety, tolerability, and anti-tumor activity with AB-101 ± Rituximab (anti-CD20 mAB) in patients with advanced B-cell malignancies.

Demographics & Baseline Characteristics

	Monotherapy N = 15	Combination N = 9	Total N = 24
Age, median years (range)	**66 (29-80)**	**71 (59-74)**	**67 (29-80)**
Sex (n; % male)	**9 (60)**	**5 (56)**	**14 (58)**
Diagnosis (n, %)			
DLBCL	6 (40)	6 (67)	12 (50)*
FL	5 (33)	2 (22)	7 (29)^
MCL	2 (13)	1 (11)	3 (13)
WM	2 (13)	0	2 (8)
Prior Lines, median (range)	**5 (2-11)**	**4 (3-6)**	**4 (2-11)**
Prior CAR-T therapy (n, %)	7 (47)	8 (89)	15 (63)
Prior auto transplant (n, %)	2 (13)	2 (22)	4 (17)
Refractory/Relapsed# (n, %)			
Refractory	10 (67)	6 (67)	16 (67)
Relapse < 6mos	2 (13)	1 (11)	3 (12)

*1 subject was primary mediastinal BCL; ^ includes 1 subject with transformed FL

Patients who were treated with AB-101 alone or with Rituximab were heavily pretreated and had a poor prognosis. Approximately 2/3 of patients had aggressive B-NHL. Patients had received a median of 4 (range: 2-11) prior lines of therapy. 63% were treated with prior CAR-T therapy, 67% were considered refractory to last therapy and 12% had relapsed within the first 6 months from last therapy. Of interest, in the combination cohort, prior CAR-T usage was 89% in an elderly population (median of 71y).

Safety and Tolerability

MedDRA	Monotherapy (n=15) Any Grade n (%)	Monotherapy (n=15) Grade 3+ n (%)	Combination (n=9) Any Grade n (%)	Combination (n=9) Grade 3+ n (%)
Any AE	**15 (100%)**	**15 (100%)**	**9 (100%)**	**8 (89%)**
Lymphopenia	7 (47%)	7 (47%)	8 (89%)	8 (89%)
Neutropenia	9 (60%)	9 (60%)	6 (67%)	6 (67%)
Nausea	10 (67%)	0	3 (33%)	0
Leukopenia	6 (40%)	6 (40%)	5 (56%)	5 (56%)
Fatigue	6 (40%)	1 (7%)	4 (44%)	0
IRR	2 (13%)	0	4 (44%)	1 (11%)
Pyrexia	4 (27%)	0	2 (22%)	0
Night sweats	2 (13%)	0	3 (33%)	0
Headache	4 (27%)	0	0	0

Table 1 Most common AEs at any grade in ≥25% in either monotherapy or combo therapy cohorts.

Cell Therapy associated AEs, n (%)		Monotherapy (N = 15)	Combination (N = 9)
ICANS	Grade 1	0 (0)	0 (0)
	Grade ≥ 2	0 (0)	0 (0)
CRS	Grade 1	2 (13%)	0 (0)
	Grade ≥ 2	0 (0)	0 (0)
GvHD	Grade 1	0 (0)	0 (0)
	Grade ≥ 2	0 (0)	0 (0)
AB-101-related IRR	Grade 1	2 (13%)	1 (11%)
	Grade ≥ 2	1 (7%)	0 (0)

AE, adverse event; CRS, cytokine release syndrome; ICANS, Immune Effector Cell-associated Neurotoxicity Syndrome; IRR, Infusion Related Reactions

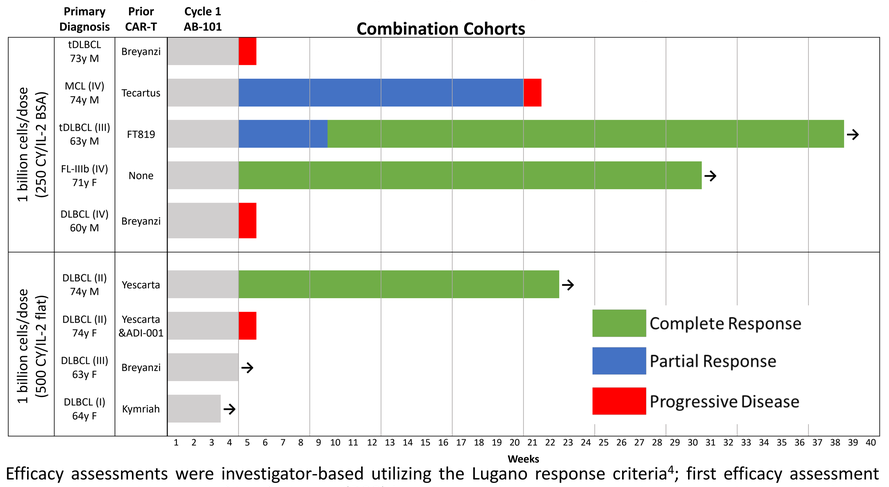
Table 2 Overview of AEs often associated with allogeneic Cell Therapy.

- AB-101 was well tolerated at 1 and 4 billion cells per dose, with successful administration of up to 16 doses of AB-101 in outpatient setting.
- Myelosuppression was the most common Grade ≥ 3 toxicity, which is consistent with standard lymphodepletion regimens and was manageable with standard of care.
  - No prolonged cytopenias were observed.
- No observations of ICANS/neurotoxicity or GvHD were noted even after 16 doses per patient.
- Two (8%) patients had AEs of CRS, based on Grade 1 fevers which resolved within 5-24 hours without the usage of steroids and/or tocilizumab.
- The most common monotherapy SAEs reported were febrile neutropenia (n=2, both Grade 3) and malignant neoplasm progression (n=3; one Grade 2 and two Grade 3).
- There were no treatment-related AEs leading to discontinuation of AB-101. At this time, there are no relevant safety/tolerability differences noted between AB-101 alone or in combination with Rituximab.

Translational Findings

- Lymphodepletion led to an increase in cytokine levels such as MCP-1, IL-7 and IL-15; a comparison between Cy250 vs Cy500 indicated a significant increase in IL-15 levels with Cy500.
- As expected, lymphodepletion (Cy250 and Cy500) depleted peripheral immune cells up to day 8. No clinically meaningful difference in the depth of lymphodepletion or cell recovery kinetics was observed between Cy250 vs Cy500.
- So far, no evidence of B-cell mediated immunogenicity in either monotherapy or combination cohorts.

Preliminary Response/Efficacy



Efficacy assessments were investigator-based utilizing the Lugano response criteria[4]; first efficacy assessment was conducted at the end of the first cycle (D29) in both cohorts, and subsequent assessments were conducted 1-3 months thereafter.

Monotherapy: Efficacy is an exploratory endpoint for the AB-101 monotherapy cohorts and limited to 1 cycle of treatment to assess safety, tolerability and AB-101 PK/PD characteristics without the influence of mAbs.

The Objective Response Rate (ORR) in 13 efficacy evaluable patients treated with AB-101 alone was 38.5% overall (including 3 CRs and 2 PRs).

Combination Therapy: The ORR in 7 efficacy evaluable patients treated with AB-101 plus Rituximab was 57.1% overall, including 3 CRs and 1 PR. At the time of the data cut, 3 patients had ongoing responses and were progression free for 5+, 7+ and 9+ months.

Efficacy is currently limited to the 1 billion per dose cohort; the 4 billion combination cohort will start enrolling in June.

Conclusions

- AB-101 alone or with Rituximab is safe and well tolerated.
  - Myelosuppression, consistent with Cy/Flu Lymphodepletion, was the most common Grade 3+ toxicity.
  - There were no observations of ICANS, GvHD or clinically meaningful CRS.
- AB-101 was successfully administered for up to 16 consecutive doses in the outpatient setting.
- The current study population is older, median age of 67, and is heavily pretreated.
  - Median of 4 prior lines of therapy.
  - Overall prior CAR-T usage of 63% (combination cohorts = 89%).
  - 67% of patients were refractory to last line of treatment and 12% relapsed within 6 months.
- Early signs of activity: 4 of 7 (57%) evaluable patients responded in the combination cohort with AB-101.
  - Complete and durable responses were observed in DLBCL and FL after prior CAR-T failure.
  - Responses were also observed with monotherapy (33%), trending to higher responses in the higher doses of AB-101.
- The study is ongoing and actively enrolling at the 4 billion combination dose level, which may potentially improve the activity noted in this poster.

References

1. 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.
2. 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.
3. Rogers P, Yang B, Kim H, et al. 306 Evaluation of AB-101, an allogeneic cord blood-derived natural killer (NK) cell therapy, as an ADCC enhancer in hematologic and solid tumors. Journal for Immuno Therapy of Cancer 2022;10:doi: 10.1136/jitc-2022-SITC2022.0306
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Disclaimer

1. *Poster includes data entered as of 27APR2023. The trial is ongoing, and data is subject to change.*

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