

64th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

605. MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

DR-01, a Non-Fucosylated Anti-CD94 Antibody, Depletes Leukemic Cells in Ex Vivo and In Vivo Models of Large Granular Lymphocyte Leukemia

Kelly Shi, PhD^{1,*}, Cindy Tan^{2,*}, Lu Bai^{2,*}, Jennifer Richardson, PhD DABT^{2,*}, Andy Deng, PhD^{2,*}, Matthias Will, MD², Michael Brehm, PhD^{3,*}, Dale Greiner, PhD^{4,*}, Leonard Shultz, PhD^{5,*}, Antonella Teramo, PhD^{6,*}, Renato Zambello, MD^{7,*}, David J Feith, PhD^{8,*}, Thomas P. Loughran Jr, MD⁹, Nenad Tomasevic, PhD^{2,*}

¹Dren Bio, Inc., San Carlos, CA

²Dren Bio, Inc., Foster City,

³University of Massachusetts Medical School, Worcester, MA

⁴UMass Med. School, Worcester, MA

⁵The Jackson Laboratory, Bar Harbor, ME

⁶Department of Medicine (DIMED), Hematology and Clinical Immunology Branch, Padova University School of Medicine, Padova, Italy

⁷Veneto Institute of Molecular Medicine (VIMM), Padova, Italy

⁸University of Virginia Cancer Center, University of Virginia, Charlottesville, VA

⁹Division of Hematology & Oncology, Department of Medicine, University of Virginia, Charlottesville, VA

*Asterisk with author names denotes non-ASH members.

Abstract Large granular lymphocyte leukemia (LGLL) is a rare leukemia more frequently occurring in the elderly population with three major subtypes: T-LGLL, chronic lymphoproliferative disorder of NK cells (CLPD-NK) and aggressive NK cell leukemia (ANKL). Over 50% of patients develop complications including severe neutropenia, thrombocytopenia and anemia, thus predisposing patients to opportunistic infections. In addition, treatments are limited to standard immunosuppressive therapy such as methotrexate, cyclosporine or cyclophosphamide, with complete response rates of only 50% or less for each agent. Thus, novel and effective therapies for LGLL patients are critically needed.

Dren Bio is developing DR-01, a non-ligand blocking, non-fucosylated monoclonal antibody targeting CD94. CD94 is a type II transmembrane receptor identified on mature, cytotoxic lymphocytes such as healthy NK and terminally differentiated CD8 T cells. In the context of disease, CD94 is known to be upregulated on LGLL cells. DR-01 functions through depletion of target cells via antibody-mediated cellular cytotoxicity (ADCC) by means of fratricide, a method in which the same cell type induces ADCC on each other. Through characterization of DR-01 using various ELISA and cell-based assays, DR-01 was determined to bind with nanomolar affinity to CD16a (EC50: 0.04 µg/mL) and to CD94 on healthy human donor NK cells, cynomolgus monkey NK cells and LGLL cells (EC50: 0.5-1 nM). DR-01 induces potent, dose-dependent depletion of CD94+ cells in ex vivo ADCC assays (IC50: 1 ng/mL) of peripheral blood mononuclear cells (PBMCs) from healthy and diseased individuals. Furthermore, DR-01 has been shown to be well tolerated in a 4-week dose-range finding and Good Laboratory Practice (GLP) study in cynomolgus monkeys from 5-100 mg/kg on a weekly dosing regimen.

A 12-color flow cytometry panel was applied to a cohort of patient LGLL PBMCs to profile CD94 expression and other cytotoxic markers associated with the disease, including CD16, CD57 and functional binding partners of CD94 such as NKG2A and NKG2C. CD94 was identified on 97% (37/38) of patient samples screened, ranging from 400 to 725,000 receptors per cell. All patient leukemic cells expressed variable levels of CD16 and CD57. NKG2A and NKG2C were present in over 5% of total leukemic cells in 37% (14/38) and 21% (8/38) of patient samples, respectively. In addition, DR-01 was able to deplete LGLL leukemic cells with high potency and in a dose-dependent manner in a functional ADCC assay (IC50: 1-10 ng/mL). The mechanism of fratricide was demonstrated through degranulation of the leukemic population via expression of CD107a. Cytokine profiling results are pending.

To demonstrate in vivo efficacy of DR-01 in a disease model of LGLL, humanized NSG-Tg(hIL-15) mice engrafted with patient LGLL splenocytes were utilized. Optimal splenocyte engraftment (5-20% human CD45+ cells in blood) was achieved within 3

weeks post-inoculation with 10 million PBMCs per pre-sublethally irradiated mouse. The engrafted leukemic population partially preserved the CD94 expression profile from the patient leukemic cells and was successfully depleted (>90%) in blood, bone marrow, spleen and liver 1-week post-treatment with a single dose of DR-01 at 5mg/kg. Overall, DR-01 is a non-fucosylated anti-CD94 antibody with high affinity and potent leukemic cell depleting ability ex vivo and in vivo. The favorable toxicity profile of DR-01 in cynomolgus monkeys precede clinical studies in LGLL patients. Additional profiling and evaluation of DR-01 in LGLL patient samples ex vivo as part of a pre-phase I study is ongoing. A phase I/II trial has been initiated to assess the safety and efficacy of DR-01 in previously treated LGLL patients.

Disclosures **Shi:** Dren Bio, Inc.: Current Employment. **Tan:** Dren Bio, Inc.: Current Employment. **Bai:** Dren Bio, Inc.: Current Employment. **Richardson:** Dren Bio, Inc.: Current Employment. **Deng:** Dren Bio, Inc.: Current Employment. **Will:** Dren Bio, Inc.: Current Employment; Amgen: Current equity holder in publicly-traded company; BMS: Current equity holder in publicly-traded company; BEAM Therapeutics: Current equity holder in publicly-traded company; Fate Therapeutics: Current equity holder in publicly-traded company; Innoviva: Current equity holder in publicly-traded company; Iovance Therapeutics: Current equity holder in publicly-traded company; Regeneron: Current equity holder in publicly-traded company; Lilly: Current equity holder in publicly-traded company; Uniqure: Current equity holder in publicly-traded company; Zymeworks: Current equity holder in publicly-traded company. **Brehm:** Dren Bio, Inc.: Consultancy; Blue Rock Therapeutics: Consultancy; The Jackson Laboratory: Consultancy, Research Funding. **Greiner:** Dren Bio, Inc.: Consultancy; Blue Rock Therapeutics: Consultancy; Swib: Consultancy; The Jackson Laboratory: Consultancy, Research Funding. **Shultz:** Blue Rock Therapeutics: Consultancy; Dren Bio, Inc.: Consultancy; ORNA: Consultancy. **Teramo:** Dren Bio, Inc.: Consultancy. **Zambello:** Janssen: Membership on an entity's Board of Directors or advisory committees; Bristol Myers Squibb: Membership on an entity's Board of Directors or advisory committees; GlaxoSmithKline: Membership on an entity's Board of Directors or advisory committees; Takeda: Membership on an entity's Board of Directors or advisory committees; Sanofi: Membership on an entity's Board of Directors or advisory committees; Amgen: Membership on an entity's Board of Directors or advisory committees. **Feith:** AstraZeneca: Research Funding; Kymera Therapeutics: Honoraria; Recludix Pharma: Research Funding. **Loughran:** Dren Bio, Inc.: Current holder of stock options in a privately-held company, Membership on an entity's Board of Directors or advisory committees; Kymera Therapeutics: Honoraria; Recludix Pharma: Current holder of stock options in a privately-held company, Membership on an entity's Board of Directors or advisory committees; Keystone Nano: Current holder of stock options in a privately-held company, Membership on an entity's Board of Directors or advisory committees; Prime Genomics: Current holder of stock options in a privately-held company, Membership on an entity's Board of Directors or advisory committees. **Tomasevic:** Dren Bio, Inc.: Current Employment.

<https://doi.org/10.1182/blood-2022-159242>