



The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

722.ALLOGENEIC TRANSPLANTATION: ACUTE AND CHRONIC GVHD, IMMUNE RECONSTITUTION

Impact of Investigational Microbiome Therapeutic SER-155 on Pathogen Domination: Initial Results from a Phase 1b Study in Adults Undergoing Allogeneic Hematopoietic Cell Transplantation (HCT)

Jonathan U. Peled, MD PhD¹, Marcel R.M. van den Brink², Doris M. Ponce, MD MS¹, Satyajit Kosuri, MD³, Nandita Khera, MD⁴, Zachariah DeFilipp⁵, Bina Tejura, MD⁶, David I Lichter, ALM⁶, Mary-Jane Lombardo, PhD⁶, Meghan Chafee, PhD⁶, Jennifer R Wortman, MSc⁶, Timothy Straub, MSc⁶, Emily Walsh, PhD⁶, Augustus Ge, MA⁶, David Lyttle, PhD⁶, Brooke Hasson, PhD⁶, Christopher Ford, PhD⁶, Lisa von Moltke, MD⁶, Matthew Henn, PhD⁶

¹ Adult Bone Marrow Transplantation Service, Memorial Sloan Kettering Cancer Center, New York, NY

² Department of Medicine, Adult Bone Marrow Transplantation Service, Memorial Sloan Kettering Cancer Center, New York, NY

³ University of Chicago Medicine, Chicago, IL

⁴ Mayo Clinic, Phoenix, AZ

⁵ Hematopoietic Cell Transplant and Cellular Therapy Program, Massachusetts General Hospital, Boston, MA

⁶ Seres Therapeutics, Cambridge, MA

Introduction:

During allogeneic hematopoietic cell transplantation (allo-HCT), conditioning regimens disrupt the epithelial barrier of the gastrointestinal (GI) tract and broad-spectrum antibiotics cause microbiome disruption characterized by low microbial diversity and high abundance of pathogens that can dominate gut communities. Microbiome disruption is associated with increased translocation of pathogenic bacteria leading to risk of bloodstream infections (BSIs) and acute graft-vs-host disease (aGvHD). Nonclinical studies have demonstrated that domination with pathogens leads to immune activation and subsequent GvHD following exposure to bacterial antigens in the gut-associated lymphoid tissue [*Jenq 2015 Biol Blood Marrow Transplant*, *Stein-Thoeringer 2019 Science*, *Peled 2020 NEJM*].

SER-155, an oral investigational cultivated microbiome therapeutic comprised of 16 bacterial Firmicutes strains, was designed to engraft in the GI tract, improve GI barrier integrity, and restructure the GI microbiome by introducing bacteria with immunomodulatory and anti-inflammatory properties and driving a reduction in abundance of proinflammatory bacteria [*Halvorsen 2021 OFID*, *2022 Bone Marrow Transplant*]. Herein, we present preliminary clinical data through Day 100 from an open-label cohort of a Phase 1b study in patients undergoing allo-HCT (NCT04995653) and compare the incidence of GI pathogen domination in this cohort to a historical cohort.

Methods:

Study patients received two treatment courses of SER-155 (before conditioning and after neutrophil engraftment), each comprised of microbiome conditioning with 4 days oral vancomycin (to facilitate engraftment of SER-155 strains into the GI microbiome) followed by 10 days of oral SER-155. The primary endpoint was safety. Stool samples collected pre- and post-HCT were used to evaluate secondary endpoints, including engraftment of SER-155 strains (following each course of SER-155) and GI pathogen domination, defined as a relative abundance of a specific taxa at $\geq 30\%$ (*Peled, 2020*). Engraftment of SER-155 strains was assessed via strain-specific molecular probes (NanoString). Relative abundance of *Enterobacteriaceae*, *Enterococcaceae*, *Streptococcaceae* and *Staphylococcaceae* was assessed with whole metagenomic shotgun sequencing (WMS). A *post-hoc* comparison of GI domination was made with a historical cohort of 459 HCT patients with similar patient characteristics from one of the study sites (MSKCC) using stool samples profiled by 16S-amplicon sequencing.

Results:

Fifteen adults (median age 67 years; 54% male) were enrolled and 13 received study drug. SER-155 was generally well-tolerated. Following each course of SER-155, the majority of the 16 strains in SER-155 were detected in evaluable patients (median = 11 strains in 8 patients before conditioning; median = 12 strains in 7 patients after neutrophil engraftment). Between the day of transplant (Day 0) and Day 30, GI domination with potentially pathogenic bacteria occurred in only 1 of 9 (11%) evaluable patients (Figure 1). In contrast, in the historical comparator cohort, 64% of patients (294 of 459) had pathogen domination during the same timeframe, with domination by *Enterococcus* being most common.

Conclusions:

The observation of SER-155 strain engraftment before transplant and low incidence of GI pathogen domination after transplant through Day 30 are encouraging, although these preliminary data are limited by the small size of this open-label cohort of HCT patients. These observations are consistent with the design and preclinical evaluation of SER-155, supporting further development of this investigational cultivated microbiome therapeutic. Enrollment in the second double-blind, randomized, placebo-controlled cohort (approximately 60 participants) has initiated following a preplanned review by the Data Safety Monitoring Committee.

Disclosures Peled: *Postbiotics Plus Research*: Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *MaaT Pharma*: Consultancy; *CSL Behring*: Consultancy; *DaVolterra*: Consultancy; *Seres Therapeutics*: Other: travel reimbursement, intellectual property fee, Research Funding. **van den Brink:** *Nektar Therapeutics*: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Notch Therapeutics*: Consultancy, Current holder of stock options in a privately-held company, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Ceramedix*: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Lygenesis*: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Pluto Immunotherapeutics*: Consultancy, Current holder of stock options in a privately-held company, Honoraria, Membership on an entity's Board of Directors or advisory committees; *DKMS (a non-profit organization)*: Membership on an entity's Board of Directors or advisory committees; *Juno Therapeutics*: Other: IP licensing; *Wolters Kluwer*: Patents & Royalties; *Vor Biopharma*: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *GlaxoSmithKline*: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Da Volterra*: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Thymofox*: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Frazier Healthcare Partners*: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Rheos Medicines*: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Seres Therapeutics*: Consultancy, Current holder of stock options in a privately-held company, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: IP licensing, Research Funding. **Ponce:** *Kadmon/Sanofi Pharmaceuticals*: Membership on an entity's Board of Directors or advisory committees; *Ceramedix*: Membership on an entity's Board of Directors or advisory committees; *Incyte Corporation*: Membership on an entity's Board of Directors or advisory committees, Research Funding; *Evive Biotechnology*: Membership on an entity's Board of Directors or advisory committees. **Khera:** *Incyte*: Honoraria. **DeFilipp:** *Ono Pharmaceuticals*: Consultancy; *Incyte*: Consultancy, Honoraria, Research Funding; *Regimmune*: Research Funding; *Taiho Oncology*: Research Funding; *Sanofi*: Consultancy; *MorphoSys*: Consultancy, Honoraria; *Inhibrx*: Consultancy; *PharmaBiome AG*: Consultancy. **Tejura:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company. **Lichter:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company. **Lombardo:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company. **Chafee:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company. **Wortman:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company. **Straub:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company. **Walsh:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company. **Ge:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company. **Lyttle:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company. **Hasson:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company. **Ford:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company. **von Moltke:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company; *Cara Therapeutics*: Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees. **Henn:** *Seres Therapeutics*: Current Employment, Current equity holder in publicly-traded company.

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