A FIRST-IN-HUMAN PHASE 1/2 CLINICAL TRIAL OF SIRP<sup>α</sup> LOW ACTIVATED MACROPHAGES (SIRPANT-M) FOR THE TREATMENT OF R/R-NHL

1SIRPant Immunotherapeutics, Hummelstown, PA, USA; 2Develotron, LLC, Hillsborough, NH, USA; 3BBCR, Cambridge, MA, USA

Background: The development of cellular immunotherapy for the treatment of aggressive tumors has reached an innovation bottleneck. While 300 INDs and 6 BLAs occupy this space in the US, nearly all of the underlying technologies target single tumor-associated antigens and nearly all utilize terminal effector cells. Development of SIRPant-M<sup>TM</sup> challenges this status quo. By leveraging the cells that drive the immune response—macrophages—SIRPant-M initiates both polyclonal T cell and polyclonal antibody responses that effectively target tumor neo-antigens (rather than tumor-associated antigens). While requiring no genetic modifications or transgenes, SIRPant-M launches a multi-modal polyclonal immune response that remodels the tumor microenvironment (TME) into a pro-inflammatory niche and provides effective targeting of cancer cells throughout the body from both cellular and humoral angles. This is accomplished by licensing the macrophages to effectively mount immune responses even in adverse conditions (such as the TME) by modulating the activity of SIRPa, a negative regulator of pro-inflammatory macrophage function. Administration of focal external-beam radiotherapy (XRT) as an adjuvant to SIRPant-M further sensitizes cancerous cells to phagocytic elimination (through irradiation-mediated upregulation of CD47 and calreticulin that leads to collateral sensitivity), unmasks tumor neoantigens, and provides supplemental pro-inflammatory signals in situ to foster durable anti-cancer immunity. Based on exhaustive pre-clinical studies characterizing this treatment approach, a Phase I first-in-human clinical trial was designed to test the hypothesis that autologous SIRPant-M macrophages are safe, tolerable, and effective in treating patients with relapsed/refractory non-Hodgkin’s lymphoma (R/R-NHL). The trial also tests the secondary hypothesis that SIRPant-M treatment yields a broad and robust polyclonal adaptive immune response.

Methods: This multi-center, open-label study will evaluate the safety and tolerability of SIRPant-M monotherapy alone or coupled with focal XRT in 12–24 participants with R/R-NHL who have progressed on prior therapies. SIRPant-M is manufactured from autologous monocytes isolated by apheresis that are differentiated into macrophages and modified with Phag-oAct<sup>TM</sup> to generate activated SIRP-α-low macrophages. The study will contain four patient groups that will receive either low or high dose of SIRPant-M with or without focally-administered XRT. Each group will have up to 6 participants. SIRPant-M will be intratumorally administered. An SRC will review any adverse events and DLTs. Blood samples and biopsies will be collected for multi-parameter analyte detection, multiplex flow cytometry, scRNA sequencing, and ctDNA analysis to investigate safety, pharmacodynamics, and mechanism of action.

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