A Phase 1, First-in-Human, Open Label, Dose Escalation, Dose Expansion Study of MSC-1, a Humanized Anti-LIF Monoclonal Antibody, in Patients with Relapsed/Refractory Metastatic Solid Tumors

David Hyman,1 Irene Braña,2 Anna Spreafico1, Naimish Pandya2, Kimberly Hoffman3, Robin Hallett4, Patricia Giblin5, Angus Sinclair5, Judit Anido6, Isabel Huber-Ruano6, Ada Sala7, Monica Pascual8, Vanessa Chiganças2, Jeanne Magram9, Robert Wasserman4, Joan Seoane2

1Memorial Sloan Kettering Cancer Center, New York, NY; 2Vall D’Hebron Institute of Oncology, Barcelona, Spain; 3Princess Margaret Cancer Center, Toronto, Canada; 4Northern Biologics, Inc. Toronto, Canada

**BACKGROUND AND PRECLINICAL**

**LEUKEMIA INHIBITOR FACTOR (LIF)**
- A multi-functional cytokine and part of the IL-6 family of cytokines
- Binds to its specific receptor (LIFR) and recruits gp130 to form high affinity receptor complex
- Activates downstream signaling pathways that regulate proliferation and survival
- Induces JAK/STAT3, PKB/Akt, and MAPK signaling pathways
- Complex role in tumor development and progression
  - Increases the migration and invasion abilities of tumor cells and promotes metastasis
  - Described role in regulating multiple immune cell types found within TME, including T-eff, T-reg, Th17 cells, as well as Myeloid cells
- Promotes the activity of cancer initiating cells (CICs)
- Increases resistance to anti-cancer therapy (chemotherapy and radiation therapy)

**ROLE IN MALIGNANCY**
- LIF is highly expressed in a sub-set of many solid tumors
- Promotes the activity of cancer initiating cells (CICs)
- Activates downstream signaling pathways that regulate proliferation and survival
- Binds to its specific receptor (LIFR) and recruits gp130 to form high affinity receptor complex
- Increases the migration and invasion abilities of tumor cells and promotes metastasis
- Described role in regulating multiple immune cell types found within TME, including T-eff, T-reg, Th17 cells, as well as Myeloid cells

**MSC-1 — ANTI-LIF MONOCLONAL ANTIBODY**
- First-in-class, humanized IgG1 monoclonal antibody
- Binds to LIF with high affinity and specificity
- Functions as a potent LIF antagonist
- Inhibits downstream pSTAT3 in vitro and in vivo
- Drives reprogramming of TME through modulation of immunosuppressive macrophages and of several immune cell types

**STUDY RATIONALE**
- LIF is a pleiotropic cytokine over-expressed in multiple solid tumors and hypothesized to play a role in tumor growth, progression and resistance to standard anti-cancer treatments
- It is hypothesized that in patients with advanced solid tumors, treatment with MSC-1 will lead to effective blocking of LIF signaling and reprogramming of the tumor microenvironment causing increased immune-mediated anti-tumor effect
- It is further hypothesized that administration of MSC-1 will be sufficiently well tolerated to enable further development subsequent to the completion of this Phase 1 study

**KEY STUDY OBJECTIVES**
- To explore the relationships between PK, pharmacodynamics and MSC-1 exposure to patient safety and anti-tumor activity
- To assess whether high tumor LIF expression correlates with anti-tumor activity
- To characterize pharmacodynamic effects of MSC-1 in the periphery and in the tumor
- To characterize impact of MSC-1 treatment on exploratory biomarkers

**STUDY DESIGN**
- Open-label, Phase 1 study enrolling advanced solid tumor patients
- The study will be conducted in an accelerated titration 3 + 3 design
- Flat dose of MSC-1 administered intravenously once Q3W

**DOSE ESCALATION**

**DOSE EXPANSION (LIF-High)**

**RESPONSE ASSESSMENTS**
- Anti-tumor response will be assessed by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines
- Assessments to be performed at baseline and every 6 weeks for first 6 months and then every 12 weeks thereafter until confirmed progression disease or patient withdrawal

**SAFETY ASSESSMENTS**
- Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
- To be assessed continuously during the study and for 30 days after the last treatment

**REFERENCES**

**ENTRY CRITERIA**

**KEY INCLUSION CRITERIA**
- Histologically proven relapsed / refractory advanced, unselectable solid tumor
- Measurable disease as per RECIST 1.1 criteria
- Identification of archival tumor sample for LIF expression analysis
- ECOG 0 or 1
- Weight > 37.5 kg
- Life expectancy ≥ 12 weeks
- Men and women ≥ 18 years of age
- Adequate organ function
- Signed Informed Consent

**KEY EXCLUSION CRITERIA**
- Symptomatic or unstable brain metastasis
- Prior systemic therapy within 4 weeks of study entry
- Prior radiation therapy or significant surgery within 21 days to study entry
- Ascites or pleural effusion requiring large volume para- or pleurocentesis within 4 weeks of study entry
- Patients currently receiving immunosuppressive therapy, except inhaled corticosteroids
- Uncontrolled or clinically significant cardiovascular or pulmonary disease
- Grade 3 or 4 peripheral neuropathy (NCI CTCAE v4.03)
- Vaccination with live virus vaccine 4 weeks from initiation
- Positive for hepatitis B or C or HIV
- Second primary malignancy not in remission > 2 years
- Anticoagulation therapy for a thromboembolic event

**STUDY RATIONALE**

**PRIMARY OBJECTIVE**
- To evaluate the safety and tolerability of MSC-1 in patients with advanced solid tumors
- To determine the recommended dose for MSC-1 monotherapy
- To assess the preliminary anti-tumor activity, as measured by ORR, of MSC-1 according to RECIST 1.1 criteria

**SECONDARY OBJECTIVES**
- To characterize the PK and immunogenicity of MSC-1
- To assess efficacy parameters in patients with advanced solid tumors, including DCR & PFS by RECIST 1.1

**KEY EXPLORATORY OBJECTIVES**
- To explore the relationships between PK, pharmacodynamics and MSC-1 exposure to patient safety and anti-tumor activity
- To assess whether high tumor LIF expression correlates with anti-tumor activity
- To characterize pharmacodynamic effects of MSC-1 in the periphery and in the tumor
- To characterize impact of MSC-1 treatment on exploratory biomarkers

Presented at the Society for Immunotherapy of Cancer (SITC) 32nd Annual Meeting, November 8–12, 2017, National Harbor, MD

©2017 Northern Biologics, Inc. All rights reserved.