SYNOPSIS

Title of study: A Phase 1 Multicenter, Open-label, Dose-escalation and Dose-expansion Study to Evaluate the Safety, Pharmacokinetics, Pharmacodynamics, Immunogenicity and Antitumor Activity of MSC-1 in Patients with Advanced Solid Tumors

Investigational product: MSC-1

Sponsor: Northern Biologics, Inc., 101 College Street TMDT 11-301, Toronto, ON M5G 1L7 Canada

Investigators: [redacted]

Publications: none

Period of study: 21 May 2018 (date of first informed consent) to 23 September 2019 (date of final poststudy observation).

Phase of development: Clinical Phase 1

Objectives:

The primary objectives of the dose-escalation part of the study were:

- • To evaluate the safety and tolerability of MSC-1 in adult patients with advanced solid tumors.
- • To determine a recommended dose for MSC-1 monotherapy for further evaluation in the expansion part of the study in patients with advanced solid tumors.

The primary objective of the dose-expansion part of the study was:

- • To assess the preliminary antitumor activity of MSC-1 monotherapy as measured by objective response rate (ORR) according to standard criteria (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1).

The secondary objectives of the study were:

- • To confirm the recommended phase 2 dose (RP2D) and dosing regimen of MSC-1 for further development.
- • To assess the type, incidence, severity, timing, seriousness, and relatedness of adverse events (AEs) and laboratory abnormalities.

- • To characterize the pharmacokinetics (PK) of MSC-1.
- • To assess other efficacy parameters in patients with advanced solid tumors including disease control rate (DCR) and progression-free survival (PFS) by RECIST 1.1.
- • To assess the development of human anti-drug antibodies (ADAs) to MSC-1.

The exploratory objectives of the study were:

- • To characterize the pharmacodynamics (PD) effects of MSC-1 in the tumor, for example, but not limited to, assessment of:
  - o Leukemia inhibitory factor (LIF) expression by immunohistochemistry (IHC).
  - o Tumor immune infiltrate using single or multiplex IHC, for instance:

[redacted]

  - o Changes in circulating tumor marker eg, serum LIF.

[redacted]

  - o Changes in pSTAT3 levels in peripheral blood mononuclear cells (PBMCs) consistent with modulation of the LIF pathway.

[redacted]

Methodology:
MSC-1-101 was an open-label, 2-part, first-in-human, Phase 1, dose-finding study designed to determine the safety, tolerability, PK, PD, and proof-of-concept of MSC-1 in subjects with advanced solid tumors. The study consisted of a dose-escalation phase and a dose-expansion phase, however, the planned dose-expansion phase in LIF_{High} tumors, defined as tumors with intra-tumoral LIF levels in the upper 50^{th} percentile, was cancelled by the Sponsor because the enrollment of 41 subjects in the dose-escalation portion of the study allowed for a robust evaluation of safety and the establishment of the RP2D of MSC-1 for future development in combination with other cancer therapies.
After providing informed consent, subjects were assessed for study eligibility at the Screening visit (Days -28 to -1). For Cohorts 1 and 2 (75 and 225 mg MSC-1 once every 3 weeks [Q3W]), an accelerated titration dose-escalation scheme (enrolling 1 evaluable subject per cohort with expansion in the event of Grade ≥ 2 toxicity) was used. For Cohorts 3, 4, and 5 (750, 1125, and 1500 mg MSC-1 Q3W, respectively) the dose-escalation followed a 3 + 3 design whereby if none of the 3 subjects experienced a dose-limiting toxicity (DLT), another 3 subjects were treated at the next higher dose level. Up to a maximum of 12 additional subjects could have been enrolled in Cohorts 3 to 5. MSC-1 was administered intravenously until disease progression, the subject no longer derived clinical benefit, unmanageable toxicity, withdrawal of consent, or study termination.
A DLT was defined as a Grade 3 AE per Common Terminology Criteria for Adverse Events v4.03, within 21 days of starting treatment that was considered at least possibly related to MSC-1 based upon the determination of the Investigator (and agreed upon at the subsequent safety/dose-escalation meeting with the Data Review Committee [DRC]), with some exceptions as defined in the protocol. Any drug-related Grade 4 or greater toxicity was considered a DLT. MSC-1 treatment was to have been permanently discontinued in subjects who incurred a drug-related Grade 4 AE.
The maximum tolerated dose (MTD) was defined as the dose level below the dose level that was associated with DLTs in 2 out of 3 subjects (or 2 out of 6 subjects).
Number of subjects (planned and analyzed):
Approximately 14 to 48 subjects were anticipated for the dose-escalation part of the study. Forty-one subjects were enrolled in the study and were included in the Safety, PK, and PD Populations and 38 subjects were included in the Efficacy Population. Three subjects were not included in the Efficacy Population as they did not have at least 1 post-treatment tumor assessment.
Diagnosis and main criteria for inclusion and exclusion:
Male and female subjects were 18 years of age or older with advanced, unresectable solid tumors, for which there was no curative therapy and had progressed on standard-of-care (SOC) treatment, were intolerant to or had no available SOC or found SOC unacceptable and had a life expectancy of ≥ 12 weeks.

Investigational product, dose and mode of administration, lot number:

MSC-1[redacted] Subjects were observed for at least 6 hours after the end of the first infusion and for 2 hours after the end of the subsequent infusions for symptoms of infusion-related reactions (IRRs) such as fever, chills, or other infusion-related symptoms.

Intra-subject dose escalation was allowed.

Duration of treatment:

The treatment duration was until disease progression, the subject no longer derived clinical benefit, unmanageable toxicity, withdrawal of consent, or study termination.

Criteria for evaluation:

Safety:

Adverse events, vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory evaluations, physical examination, body weight, Eastern Cooperative Oncology Group (ECOG) performance status, and ADAs.

Pharmacokinetics:

Blood samples for the analysis of serum concentrations of MSC-1.

Pharmacodynamics:

Blood samples for the measurement of LIF, [redacted]

Exploratory tumor biomarkers for establishing the effects of MSC-1 on LIF expression by IHC, STAT3 signaling, [redacted] and CD8 T-cells using single or multiplex IHC. Archival tissue was collected for evaluation of LIF expression and exploratory biomarker analyses for all subjects.

A semi-mechanistic PK/PD calibrated model was used to predict drug exposure and reduction of non-drug-bound LIF in tumor for each subject in response to various MSC-1 dose amounts and schedules for the same subject population.

Efficacy

Tumor response was assessed according to RECIST 1.1.

Statistical methods:
Summary statistics were presented for the safety, PK, PD, and efficacy data.
The ORR and DCR was calculated along with its 95% confidence interval determined by the Clopper-Pearson method. The median and range of PFS and time-to-response were estimated from the Kaplan-Meier survival curve and summarized by cohort.
Summary - Conclusions:
Subject disposition:
Forty-one subjects were enrolled in the study and received at least 1 dose of MSC-1. Treatment was discontinued for all subjects due to radiographic disease progression (35 subjects), clinical disease progression (4 subjects), withdrawal of consent (1 subject), or death (1 subject).
No subjects experienced DLT. For the 750 to 1500 mg MSC-1 cohorts more than 3 subjects were enrolled to further evaluate safety, PK, and PD findings. Ten subjects were enrolled in the 750 and 1125 mg dose cohorts and 18 subjects were enrolled in the 1500 mg dose cohort.
Safety results:
All subjects experienced treatment-emergent AEs (TEAEs) with 23 subjects (56.1%) experiencing TEAEs that were ≥ Grade 3. There was no trend across doses in the number of subjects experiencing TEAEs.
Nineteen out of 41 subjects (46.3%) had TEAEs that were considered by the Investigator to be related to MSC-1 administration. There was no trend across doses in the number of subjects experiencing drug-related TEAEs. For all dose levels the drug-related TEAEs were Grade 1 or Grade 2 in severity, except for 1 drug-related TEAE of Grade 3 aspartate aminotransferase increased in the 75 mg MSC-1 cohort.
No subjects experienced a DLT. No subjects were withdrawn from the study due to drug-related TEAEs and dosing was delayed for 1 subject due to TEAEs. Two subjects experienced low grade IRR and after recovery, both subjects could continue treatment with MSC-1. Nineteen subjects experienced at least 1 serious adverse event (SAE) and 5 of the SAEs were fatal. Four subjects died due to disease progression and 1 subject experienced sudden death reported by the Investigator as not related to study drug. Only 1 SAE of osteonecrosis of jaw, in a subject with head and neck cancer, was considered by the Investigator to be related to MSC-1. The Investigator cited acute and chronic oral sequel of head and neck radiation therapy and prior treatment with denosumab as an alternative explanation for the event.
There were no trends identified with respect to clinical laboratory shifts and AEs associated with clinical laboratory findings. Several subjects had increases in hepatic liver enzyme and bilirubin levels, however, no subjects had liver function tests that met the Hy's Law criteria. Two subjects had increased hepatic enzyme levels that were considered by the Investigator to be related to MSC-1 administration, however, enzyme levels for these subjects were above the reference range prior to the first infusion. No subjects had abnormal hematology or urinalysis findings that were considered related to MSC-1 administration.

There were no dose-related trends in the number of subjects experiencing changes in vital signs of potential clinical importance and in ECOG performance status scores. No 12-lead ECG findings were clinically significant. Eight subjects had physical examination findings that were considered to be clinically significant, and the findings, which were also recorded as AEs were not considered to be related to MSC-1 administration. MSC-1 had a benign immunogenicity profile with only 2 subjects showing positive and very low ADA titers over the course of treatment.

Pharmacokinetic results:

For nearly all 41 subjects, MSC-1 time to maximum measured concentration (t_{max}) was reached within 4 hours of the start of infusion (3 hours after the end of infusion) and then serum concentrations declined in a generally biphasic manner. At the lowest dose (75 mg), the geometric mean of estimated terminal half-life was 7.0 days. At the higher doses, the geometric mean half-life values were relatively consistent around 13 days. MSC-1 exposure parameters are near dose-proportional at doses from 225 mg to the highest dose, 1500 mg.

While total clearance (CL) was highest at the lowest dose, at higher doses, CL was relatively stable at 11.9 to16.6 mL/h, or 0.29 to 0.40 L/day. The volume of distribution at steady-state at doses above 75 mg was 5 to 7 L. Visual inspection of trough serum concentrations suggest MSC-1 steady-state is attained at treatment Cycle 4, and that there is a 1.6-fold increase in MSC-1 concentrations at steady-state compared to the first administration of MSC-1.

Pharmacodynamic results:

Peripheral pharmacodynamic evaluation

Predose free LIF could only be measured for 4 out of 41 subjects, and these levels were all below 9 pg/mL. Total LIF concentrations (LIF stabilization) were detected in all 41 subjects treated with MSC-1. Total LIF generally increased to a relatively stable level for each subject by the end of the second treatment cycle, although cycle-to-cycle total LIF measurements for most subjects were variable. The inter-subject variability for total LIF levels was also high.

Tumor pharmacodynamic evaluation

Tumor biomarkers were measured in 10 pre-/on-treatment biopsies obtained at the top 2 dose levels of MSC-1 tested (1125 and 1500 mg) and an archival-/end of treatment biopsy pair. A single on-treatment biopsy was additionally collected from a pancreatic tumor subject who reported improvements in symptoms and displayed evidence of tumor shrinkage, indicative of a positive response to MSC-1. All but 1 of the 10 pre-/on-treatment biopsy pairs were obtained from the same metastatic lesion. MSC-1 impacted pSTAT3 signaling and M1:M2 skewing, biomarkers proximal to the effects of LIF, in the majority of tested subjects. MSC-1 also induced substantial increases in the frequency of CD8 T-cells in a subset of subjects.

Semi-mechanistic PK/PD human evaluation of MSC-1 in solid tumors

On a Q3W schedule, a dose of 750 mg or higher was required to reduce average non-drug-bound tumor LIF levels below 20% of baseline for more than 80% of subjects.

the 1500 mg Q3W IV dose with MSC-1, the median average tumor LIF occupancy was predicted to be 96.7%.

Efficacy

Evidence of clinical activity was noted, with 13 subjects (34.2%) having stable disease based on RECIST 1.1. The percentage of subjects with stable disease was similar for the 750, 1125, and 1500 mg MSC-1 cohorts (30.0% to 37.5%). The remainder of the subjects had progressive disease. Nine subjects had stable disease for at least 2 consecutive tumor assessments and the DCR was 23.7%. The overall median PFS was approximately 6 weeks, with 9 subjects having PFS greater than 16 weeks. The time-to-response could not be calculated as no subjects had an objective response (complete response or partial response).

Conclusions:

- • MSC-1 was considered to be safe and tolerable in subjects with advanced solid tumors.
- • No DLTs were detected. The MTD was not reached and the RP2D is 1500 mg MSC-1 given every 3 weeks.
- • MSC-1 has a PK profile typical for an antibody and high levels of peripheral LIF target engagement were detected in all subjects throughout the Q3W treatment cycle.
- • MSC-1 treatment showed evidence of LIF signaling inhibition and immunological reprogramming in tumors supporting the therapeutic hypothesis of MSC-1.
- • Fatigue and nausea were the most frequently reported drug-related TEAEs. Two subjects experienced an IRR. One SAE of osteonecrosis of jaw was considered to be related to MSC-1 administration.
- • No subjects had liver function tests that met the Hy's Law criteria. Two subjects had increased hepatic enzyme levels that were considered to be related to MSC-1 administration and there were no abnormal hematology or urinalysis findings that were considered related to MSC-1 administration.
- • There were no dose-related trends in the number of subjects experiencing changes in vital signs of potential clinical importance and in ECOG performance status scores. No 12-lead ECG findings were clinically significant.
- • MSC-1 had a benign immunogenicity profile with only 2 subjects showing positive and very low ADA titers over the course of treatment.
- • Based on RECIST 1.1, the best overall response (BOR) was stable disease for 13 subjects (34.2%), the other subjects had a BOR of progressive disease. Nine subjects had stable disease for least 2 consecutive tumor assessments and the DCR was 23.7%.
- • The overall median PFS was approximately 6 weeks, with 9 subjects having PFS of > 16 weeks.