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MSC-1 is a First-in-Class Humanized Monoclonal Antibody that Modulates the Tumor Microenvironment by Inhibiting the Novel Cancer Immunotherapy Target, LIF

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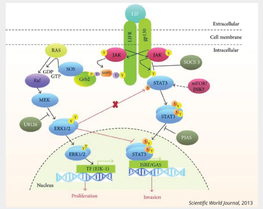
BACKGROUND AND PRECLINICAL

LEUKEMIA INHIBITORY FACTOR (LIF)

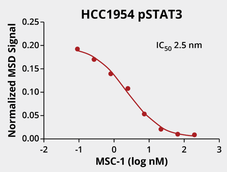
- A multi-functional cytokine and part of the IL-6 family of cytokines
- Binds to its specific receptor (LIFR) and recruits gp130 to form high affinity receptor complex
- Activates downstream signaling pathways that regulate proliferation and survival
  - Induces JAK/STAT3, PI3K/AKT and MAPK signaling 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 Teff, Treg, 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)



Schema of the proposed LIF signaling pathway. LIF triggers activation of JAK/STAT and MAPK pathways independently, resulting in different cell-responses: increase of invasiveness and proliferation, respectively.

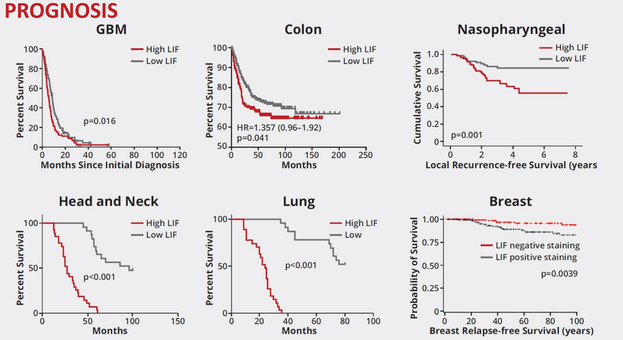
MSC-1 – ANTI-LIF MONOCLONAL ANTIBODY

- First-in-class, humanized IgG1 monoclonal antibody
- Binds to LIF with high affinity and specificity
- Functions as a potent LIF antagonist through blockade of LIF/gp130 binding
- Inhibits downstream pSTAT3 *in vitro* and *in vivo*
- Drives reprogramming of TME through modulation of immunosuppressive macrophages and effects on Tregs, CD8 T and NK cells



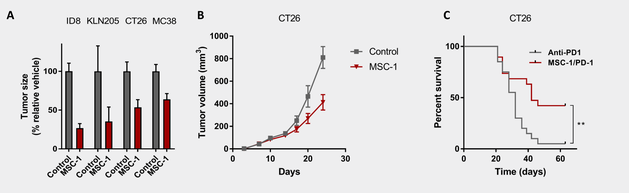
Representative IC_{50} dose-inhibition curve of LIF-induced pSTAT3 with MSC-1 treatment in HCC1954 breast cancer cell line.

ELEVATED LIF EXPRESSION IS ASSOCIATED WITH POOR PROGNOSIS



High LIF expression correlates with poor prognosis. High LIF transcript levels are associated with poor outcome in GBM and colon cancer [Yu 2014]. High circulating serum LIF protein levels correlates with poor outcome in nasopharyngeal cancer [Liu 2013]. C) High intratumoral LIF protein expression correlates with poor outcome in head and neck, lung and breast cancer [Albrengues 2014, Li 2014].

MSC-1 SHOWS PRE-CLINICAL ACTIVITY AS MONOTHERAPY AND COMBINED WITH CHECKPOINT BLOCKADE



Treatments: 15 mg/kg 2QW MSC-1; 10mg/kg 2QW anti-PD1

A. Monotherapy efficacy (tumor growth inhibition) was observed across 4 syngeneic mouse tumor with MSC-1 treatment. **B.** MSC-1 treatment significantly slows tumor growth in the CT26 tumor model. **C.** MSC-1 and anti-PD1 combination therapy induces durable regressions relative to anti-PD1 monotherapy

STUDY RATIONALE

- LIF is a pleotropic 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

KEY STUDY OBJECTIVES

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

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 (PD) and MSC-1 exposure to patient safety and 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 AND PATIENTS TREATED

- 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

MSC-1-101 study

DOSE ESCALATION
(all comer solid tumors)

MTD / OBD

DOSE EXPANSION
(LIF-High)

NSCLC | Ovarian Cancer | Pancreatic Cancer | Basket

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

DOSE LEVELS AND NUMBER OF PATIENTS TREATED

DOSE ESCALATION
Accelerated Titration/3+3 Design
(n = 41)

1500 mg Q3W (n = 6)	1500 mg Q3W (n = 12)
1125 mg Q3W (n = 3)	1125 mg Q3W (n = 7)
750 mg Q3W (n = 3)	750 mg Q3W (n = 7)
225 mg Q3W (n = 1)	ESCALATION EXPANSION
75 mg Q3W (n = 2)	
ESCALATION	

ESCALATION EXPANSION
- Additional PK/LIF stabilization data
- LIF levels by IHC in biopsies
- Assessment of PD modulation by multiplex IHC in biopsies:
  - CD206/CD163/CCL22 & CD68/MHCII (LIF biology)
  - pSTAT3 (LIF signaling)
  - CD8/FoxP3/CD68 & CD8/PD1 (Anti-tumor immune response)
- Additional patients may be enrolled at these dose levels to further evaluate safety, PK & PD; enrollment will occur only after initial safety

- Dose escalation completed as of 06Mar2019, 41 patients enrolled

ENTRY CRITERIA

KEY INCLUSION CRITERIA

- Histologically proven relapsed/refractory advanced, unresectable 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
- Adequate organ function

KEY EXCLUSION CRITERIA

- Symptomatic or unstable brain metastasis
- Prior systemic therapy within 4 weeks of study entry
- 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
- Uncontrolled or clinically significant cardiovascular or pulmonary disease
- Grade 3 or 4 peripheral neuropathy (NCI CTCAE v4.03)

DEMOGRAPHICS & PRIOR THERAPY

PATIENT DEMOGRAPHICS (N=34)

Median Age (Range)	63.5 (36-78)
Gender, N (%)	
Male	18 (53%)
Female	16 (47%)
Race, N(%)	
Caucasian	28 (82%)
Black	4 (12%)
Asian	2 (6%)
Tumor type, N (%)	
Pancreatic	10 (29%)
Colorectal	5 (15%)
Prostate	3 (9%)
Head and Neck	3 (9%)
Cholangiocarcinoma	2 (6%)
Ovarian	2 (6%)
NSCLC	2 (6%)
Appendix	2 (6%)
Melanoma	1 (3%)
Uterine Liposarcoma	1 (3%)
Myxoid Liposarcoma	1 (3%)
Paraganglioma	1 (3%)
Squamous Cell of the Anus	1 (3%)

PRIOR SYSTEMIC ANTI-CANCER THERAPY (N=34)

Number of Prior Treatments, N	Number of Subjects (%)
1	3 (8.8%)
2	9 (26.4%)
3	10 (29.4%)
4	4 (11.8%)
5	4 (11.8%)
6	2 (5.9%)
7	0
8	1 (2.9%)
9	1 (2.9%)

PRIOR RADIATION THERAPY (N=34)

Number of Prior Treatments, N	Number of Subjects (%)
1	8 (23.4%)
2	9 (26.4%)

Data cut-off: 25Feb2019

DLT DEFINITON & SAFETY SUMMARY

- During 21 days post C1D1 as assessed by PI in agreement with DRC as possibly related to MSC-1
- Any drug-related grade ≥ 3 AE
- AEs with a clear-cut alternative explanation and pre-specified, self-limited grade 3 AEs may be deemed non-DLT, including:
  - Fatigue, nausea, vomiting or diarrhea that resolves to Grade ≤ 2 within 72 hrs with appropriate medical therapy
  - Transient (lasting ≤ 72 hrs) Grade 3 biochemical abnormalities that are considered clinically insignificant
  - Grade 3 neutropenia lasting ≤ 72 hrs
  - Grade 3 thrombocytopenia without clinically significant bleeding
- A drug-related AE of any grade that delays the start of C2D1 > 14 days may be considered a DLT by the DRC

SUMMARY OF ADVERSE EVENTS (AEs)

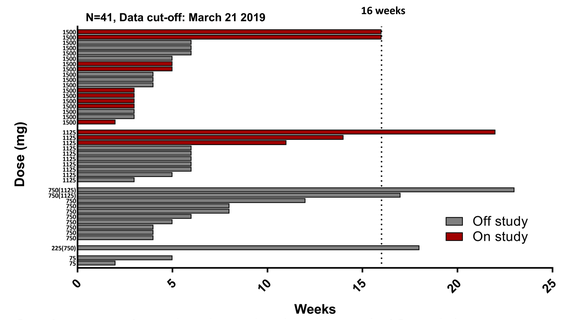
Data cut-off: 25Feb2019

	Cohort 1 25mg (N = 2)	Cohort 2 225 mg (N = 1)	Cohort 3 750mg (N = 10)	Cohort 4 1125mg (N=10)	Cohort 5 1500mg (N = 11)	Total (N = 34)
Number of Subjects with Adverse Events (AEs). N (%)	2	1	10	8	6	27 (79.4%)
Number of Subjects with Grade ≥ 3 AEs. N (Total AEs)	2 (10)	0	6 (11)	1 (1)	1 (1)	10 (23)
SAEs	8	0	8	0	2	18
Fatal AEs*	1	0	1	0	0	2
Infusion Related AEs	0	1	1	0	0	2
DLTs during C1 (21d)	0	0	0	0	0	0
Delayed DLTs	0	0	0	0	0	0
AEs Causing MSC-1 Interruption	0	0	1	1	0	2
AES Causing MSC-1 Discontinuation	0	0	1	0	0	1
AES causing MSC-1 Dose modification	0	0	0	0	0	0
Number of Subjects with possible MSC-1 related AEs. N (Total AEs)	0	1 (2)	4 (8)	3 (9)	3 (5)	11 (24)
MSC-1 Related SAEs	0	0	0	0	0	0

There were 20 Grade 1 and 4 Grade 2 AEs possibly related to MSC-1; AEs seen in more than one patient include 6 patients with fatigue, 2 patients with anorexia, and 2 patients with nausea

*Disease related: 1 multiorgan failure in a subject with metastatic pancreatic cancer; 1 cardiac arrest in a subject with metastatic NSCLC and hypoxia

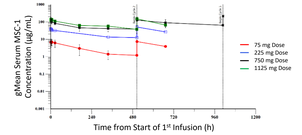
PATIENT STATUS



- 6 patients experienced prolonged stable disease (≥ 16 weeks)
- Pancreatic Ductal Adenocarcinoma patient with 4 lines of post-initial recurrence treatment currently remains on study (> 22 weeks). Subject achieved initial improvements in pain control (analgesia decreased) and resumed traveling. In addition, subject had reductions in CA19-9 levels which remain below baseline through treatment course. Currently stable disease is their best response. CA19-9 levels below:

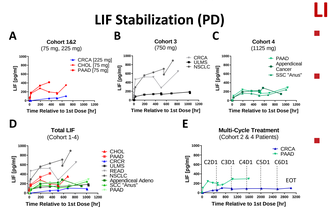
Tumor Markers	Baseline	Cycle(C) 3	C5	C6	C7	C8
CA 19-9 (U/mL)	1658	1069	1224	1395	1397	1106

MSC-1-101 PK/PD



PHARMACOKINETICS (PK)

- MSC-1 exhibits linear PK over the dose range of 75 – 1125 mg q3weeks
  - Half-life estimate is ~15 days



Total LIF levels in patient serum after first doses of MSC-1: **(A-C)** separated by dose cohorts, **(D)** all dose cohorts combined and **(E)** after multiple doses of MSC-1.

LIF STABILIZATION (PD)

- Total LIF levels in patient serum increase with MSC-1 treatment.
- Total LIF levels appear to reach saturation in patients with prolonged MSC-1 treatment.
- Large variability in total LIF levels of individual patients, potentially due to: diverse tumor types, inherent biological differences within tumor types and amount of tumor burden

CONCLUSIONS

- 41 patients enrolled in dose escalation (first patient dosed 04Jun2018; last patient dosed 06Mar2019)
- No Dose Limiting Toxicities observed; 24 AEs (20 grade 1 and 4 grade 2) were reported as possibly related to MSC-1 by the investigator
- Overall favorable PK profile (through 1125 mg dose) with estimated terminal half life of ~15 days and suggestion of durable peripheral LIF saturation in some patients
- Efficacy signal observed as prolonged stable disease (≥ 16 weeks) in multiple patients and decrease in tumor markers (CA19-9)
- Tumor biomarker and additional peripheral PK/LIF stabilization analyses are ongoing

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