**LEUKEMIA INHIBITORY FACTOR (LIF)**
- A multifunctional 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 JAKSTAT3, 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 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 therapies).

**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 PI3K/AKT in vitro and in vivo.
- Drives reprogramming of TME through modulation of immunosuppressive macrophages and of several immune cell types.

**ROLE IN MALIGNANCY**
- LIF is highly expressed in a sub-set of many solid tumors.
  - GBM
  - NSCLC
  - Ovarian CA
  - CRC
  - Pancreatic Ca
- LIF over-expression correlates to poor prognosis.

**MSC-1 IN SYNGENEIC MODELS**
- MSC-1 inhibited tumor growth in multiple syngeneic models.
- Tumor growth in NSCLC and colon cancer (Yu 2014).
- High LIF expression correlates with poor prognosis.
- Complex role in tumor development and progression.
  - Low LIF
  - High LIF

**MSC-1 REPROGRAMS TUMOR MICROENVIRONMENT**
- MSC-1 increased frequency of intratumoral immune cells and activation status.

**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 treatment.
- 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**
- 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 Q2W.

**STUDY DESIGN**
- DOSE ESCALATION
  - MTD/OBD
  - 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 every 12 weeks thereafter until confirmed progression disease or patient withdrawal.

**REPRESENTATION IN TREATMENT**
- Tumor associated macrophages (M2) were reprogrammed towards a pro-inflammatory phenotype.
- Low LIF
- High LIF

**ENTRY CRITERIA**
- Symptomatic or unstable brain metastasis
- Prior systemic therapy within 4 weeks of 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 (N=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
  - Antithrombotic treatment for a thromboembolic event

**REFERENCES**

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