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
- Mediates JAK/STAT3, PI3K/AKT and MAPK signaling pathways

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/LIFR signaling
- Inhibits downstream STAT3 activation and LIF-induced cell death
- Drives reprogramming of STZ via modulation of immunosuppressive macrophages and effects on Tregs, CD8 T and NK cells

ELEVATED LIF EXPRESSION IS ASSOCIATED WITH POOR PROGNOSIS

STUDY RATIONALE

DOSE ESCALATION (all tumor solid tumors)

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 5 first 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

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

DOSE 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

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 assess pharmacodynamic 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

- Phase 1a study enrolling advanced solid tumors patients
- The study will be conducted in an investigator-initiated 3+3 design
- Flat dose of MSC-1 administered intravenously once qw

MSC-1-105 study

- Open-label, Phase 1 study enrolling advanced solid tumors patients
- The study will be conducted in an investigator-initiated 3+3 design
- Flat dose of MSC-1 administered intravenously once qw

DOSE ESCALATION (all tumor solid tumors)

- Drug escalation 75 mg as cohort 1 → 225 mg as cohort 2 → 750 mg as cohort 3 → 1,125 mg as cohort 4

MSC-1-101 study

- Study conducted in an investigator-initiated 3+3 design
- Flat dose of MSC-1 administered intravenously once qw

- LIF EXPRESSION ASSOCIATED WITH POOR PROGNOSIS

DEMONOGPHICS & PRIOR THERAPY

DOSE EXPANSION (LIF-High)

- Patients with high LIF levels
- Patients with LIF levels > 1000 pg/ml
- Patients with LIF levels > 600 pg/ml

- Drug escalation 75 mg as cohort 1 → 225 mg as cohort 2 → 750 mg as cohort 3 → 1,125 mg as cohort 4

- Drug escalation completed as of 12/17/2019, 10 patients enrolled

- Median Age (range)
- Female sex
- Race

- Proportion of patients with baseline LIF levels above 1000 pg/ml
- Proportion of patients with baseline LIF levels above 600 pg/ml

MSC-1-101 PK/PD

- Total LIF levels in patient serum increase with MSC-1 treatment
- Total LIF levels reach peak levels 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

- Dose escalation completed as of 06/2019, 6 patients enrolled

CONCLUSIONS

REFERENCES

6. Albrengues C et al. 2015 PMID: 26626376
7. Lui et al. Oncotarget 2014 PMID: 24551391

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