**Abstract**

**Phase 1b dose escalation and cohort expansion study of the novel myeloid differentiating agent MTL-CEBPA in combination with sorafenib in patients with advanced hepatocellular carcina (HCC)**

**Background**

- Immunosuppressive myeloid cells are important cellular actors in the tumor microenvironment that suppress T cell responses and promote tumor growth.
- Reducing myeloid cells immunosuppression has been demonstrated to improve the effectiveness of a range of cancer therapies including TKI.
- MTL-CEBPA is the first intervention to specifically increase CEBPα, a master regulator of myeloid cell differentiation and is being developed as a combination agent in cancer.
- In a first-in-human study of 39 patients, systemic administration of MTL-CEBPA was well tolerated in patients with advanced liver cancer and was demonstrated to activate expression of CEBPA gene in white blood cells and reduce downstream markers of immune suppression (Sarker et al., Clin Cancer Res, 2020).
- After discontinuation of MTL-CEBPA, three out of five patients experienced durable, radiological complete responses (CR) to off-study sorafenib therapy.
- A Phase 1b expansion was conducted to evaluate the safety, tolerability, and efficacy of combination therapy with sorafenib.

**Methods**

**Study design**

- Open label Phase 1b patients in advanced hepatocellular carcinoma (HCC)

**Treatments**

- MTL-CEBPA administered once weekly by intravenous infusion over 45 minutes at 0.15 to 1.8 mg/m²
- Sorafenib administered 400 mg twice daily
- 4 week cycle (3 weeks dosing + 1 week rest)

**Key eligibility criteria**

- Histologically confirmed advanced HCC with cirrhosis resulting from hepatitis B, hepatitis C, alcohol-related liver disease or any other aetiology; OR histologically confirmed advanced HCC resulting from NAFLD with or without cirrhosis.
- Child-Pugh class A or B7
- Life expectancy greater than 3 months at the time of recruitment
- At least one measurable lesion with target lesion size ≥ 1.0 cm as measured by CT scan

**Investigations**

- Safety, PK, and PD
- Radiological response determined by RECIST 1.1 every 8 weeks (2 cycles)
- All data (historically otherwise) are preliminary and based on data cut off on Feb 1, 2020

**Baseline Demographics/Characteristics**

- 16 patients with advanced HCC have been enrolled
- 22 patients were treated with MTL-CEBPA + sorafenib (coadministration)
- 14 patients were treated with MTL-CEBPA followed by sorafenib (sequential administration)

**Results**

- **MTL-CEBPA** is a novel agent designed to target immunosuppressive myeloid cells and enhance the activity of anti-cancer treatment
- **MTL-CEBPA** demonstrated tolerability in combination with sorafenib in the patients who previously been treated both concurrently or sequentially
- Pharmacokinetics of MTL-CEBPA were similar when co-administered with sorafenib
- While the study is non-comparative, the clinical activity observed, including the potential for durable and complete responses, suggest that MTL-CEBPA may potentiate the activity of sorafenib monotherapy
- **MTL-CEBPA** appears to target cancerous microenvironment by repurposing tumor microenvironment from immunosuppressive to pro-angiogenic pattern cells

**Discussion**

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