Abstract 4601

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 carcinoma (HCC)

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Background

- Immunosuppressive myeloid cells are important cellular actors in the tumor microenvironment that suppress T cell response and promote tumor growth
- Reducing myeloid cells immunosuppression has been demonstrated to improve the effectiveness of a range of cancer therapies including checkpoint inhibitors and sorafenib
- **MTL-CEBPA is the first intervention to specifically increase C/EBP-α master regulator of myeloid cell differentiation and is being developed as a combination agent in cancer**
- In a first-in-human Phase 1 study in 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 Can Res, 2020)
- After discontinuation of MTL-CEBPA, three out of five patients experienced durable, radiological complete response (CR) to off-study sorafenib treatment
- 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 in patients with advanced hepatocellular carcinoma (HCC)

Treatment
- MTL-CEBPA administered once weekly by intravenous infusion over 60 minutes at 90 or 130 mg/m2
- Sorafenib administered 400mg BID
- 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 NASH 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 liver 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 (unless otherwise denoted) are preliminary and based on a data cut-off of Feb 1, 2020

Baseline Demographics/Characteristics

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

	All n = 36	TKI naive viral n = 16	TKI naive non-viral n = 11	TKI experienced viral n = 5	TKI experienced non-viral n = 4
Age, years	66.2	66.3	67.7	57.0	64.7
Sex, male	88%	88%	82%	100%	100%
Race					
Asian	57%	88%	37%	40%	25%
White	31%	12%	54%	20%	50%
Other	12%	0%	9%	40%	25%
Aetiology					
Viral, HBV | HCV	22% | 33%	44% | 56%	–	20% | 80%	–
Non-viral, NAFLD | Alcohol | Other	20% | 8% | 17%	–	55% | 27% | 18%	–	50% | 0% | 50%
ECOG, 0 | 1	67% | 33%	81% | 19%	55% | 45%	40% | 60%	75% | 25%
Extrahepatic sites, yes	19%	13%	18%	20%	50%
AFP >200, yes	42%	56%	9%	100%	0%
Child Pugh, A5 | A6 | B7 | B9	72% | 19% | 3% | 3%	67% | 19% | 0% | 7%	64% | 27% | 9% | 0%	80% | 20% | 0% | 0%	100% | 0% | 0% | 0%
Prior Immune Checkpoint Inhibitors	8%	6%	18%	0%	0%
Prior Loco-regional Therapies	58%	67%	45%	60%	50%

Table 1. Demographics (Safety Analysis Set)

Best Objective Response

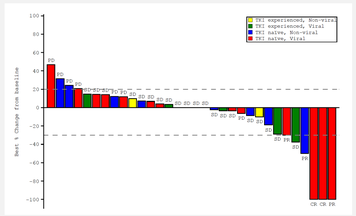

Fig 1. Best % change in tumor size

	TKI naïve Viral HCC n = 16	TKI naïve Non-viral HCC n = 11	TKI experienced Viral HCC n = 5	TKI experienced Non-viral HCC n = 4
Complete Response	2	–	–	–
Partial Response	2	1	–	–
Stable Disease	3	5	5	3
Progressive Disease	2	–	–	–
Total evaluable	9	6	5	3
Non-evaluable (withdrawn)	4	5	–	–
Non-evaluable (ongoing)	3	–	–	1

Table 2. Best Objective Response

Complete Responses

Patient 1- 65yrs, male, HCC, HBV carrier (Child Pugh A5). Diagnosed with HCC in November 2017. Patient was TKI naïve prior to study treatment.
- Previous HCC treatment consisted of Doxorubicin HCL on 16Apr2018 40mg and Surgery (LT Laparoscopic Adrenal Adrenalectomy) on 15May2018
- At study screening, patient had (1) target lesion in the liver left lobe measuring 12mm in the longest diameter assessed by CT scan (31Jan2019). Sum of longest diameters at screening: 12mm
- First dose of IMP (MTL-CEBPA) infused on 19Feb2019; patient compliant with the sorafenib prescription (400mg daily) with no missed doses during Cycles 1 & 2
- Cycle 2 Day 22 tumor assessment completed on 10Apr2019. Overall response: Complete Response as per RECIST 1.1

Patient 2 - 55yrs, male, HCC with cirrhosis developed on a background of hepatitis C, Child-Pugh A. Patient was TKI naïve prior to study treatment.
- Previous HCC treatment consisted of TACE on 10Dec2018
- At study screening patient had (2) target lesions in the liver left lobe and liver right lobe measuring 30mm and 18mm respectively in the longest diameter assessed by CT scan (18Jun2019)
- First dose of IMP (MTL-CEBPA) infused on 02Jul2019. Patient received (2) cycles of MTL-CEBPA as per protocol with no missed doses. The patient was also compliant with the sorafenib prescription with no missed doses during Cycles 3 and 4
- Cycle 2 Day 22 tumor assessment was completed on 20Aug2019. Overall response: Progressive Disease as per RECIST 1.1
- Cycle 4 Day 22 tumor assessment was completed on 15Oct2019. Overall response: Complete Response as per RECIST 1.1 (non-viable tumor confirmed by biopsy); CR still maintained as of 07Mar2020

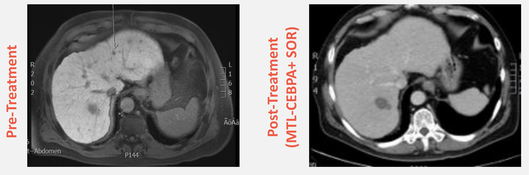

Fig 2. Treatment with MTL-CEBPA (QW) + Sorafenib (Co-administration)

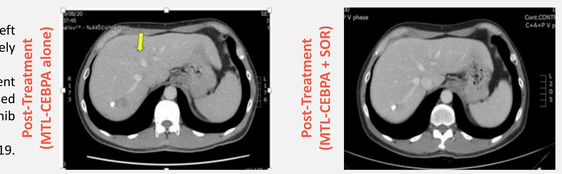

Fig 3. Treatment with MTL-CEBPA (QW) + Sorafenib (Sequential)

Discussion

- MTL-CEBPA is a novel agent designed to target immuno-suppressive myeloid cells and enhance the activity of anti-cancer treatment
- MTL-CEBPA is generally very well tolerated in combination with sorafenib when administered both concomitantly or sequentially
- Pharmacokinetics of MTL-CEBPA are unaltered 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 sensitize tumors to cancer treatments by repopulating tumor microenvironment from immuno-suppressive to pathogen patrolling myeloid cells
- The results validate the continued development of MTL-CEBPA as a combination therapy in HCC and further investigation is planned
- Separately a Phase 1b study has been initiated in combination with pembrolizumab in patients with advanced solid tumors (NCT04105335)

References
1. Voutila J, et al. *Development and Mechanism of Small Activating RNA Targeting CEBPA, a Novel Therapeutic in Clinical Trials for Liver Cancer.* Mol Ther. 2017; 25(12):2705-2714; 2. Reebye V et al. *Gene activation of CEBPA using saRNA: preclinical studies of the first in human saRNA drug candidate for liver cancer*. Oncogene. 2018. 3216-3228. 3. Sarker et al. *MTL-CEBPA, a small activating RNA therapeutic up-regulating C/EBP-α, in patients with advanced liver cancer: a first-in-human, multi-centre, open-label, phase I trial.* Clin Canc Res. 2020
Study References: Clinicaltrials.gov: NCT02716012; UK NIHR CRN ID:20332 (CANC 4818)
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Safety

- Overall the combination therapy was very well tolerated
- Changes in liver function tests were generally transient; overall there were no significant changes in LFTs at the end of the first and second cycles of treatment compared to baseline
- No AEs resulted in treatment withdrawal
- 15 serious adverse events (SAEs) reported in 10 patients
- No serious TEAEs led to treatment withdrawal and 8 led to a drug interruption

Treatment Emergent Adverse Events – all causality, n (%)	Co-admin n = 22		Sequential n = 14	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Diarrhea	9 (41)	0 (0)	4 (29)	0 (0)
Fatigue	6 (27)	0 (0)	5 (36)	0 (0)
Fever	5 (23)	0 (0)	3 (21)	0 (0)
PPE	6 (27)	0 (0)	3 (21)	0 (0)
GGT increased	4 (18)	2 (9)	0 (0)	0 (0)
ALP increased	5 (23)	1 (5)	0 (0)	0 (0)
AST increased	4 (18)	1 (5)	2 (14)	1 (7)
Decreased appetite	4 (18)	0 (0)	4 (29)	0 (0)

Table 3. Treatment (MTL-CEBPA)-emergent adverse events

Pharmacokinetics

- Plasma CEBPA-51 concentration vs. time profiles are available for 12 patients treated with concomitant MTL-CEBPA (n=3, 90 mg/m²; n=9 130 mg/m²) and sorafenib (400-800 mg QID)
- Although not powered to detect the potential interference of sorafenib on the PK of CEBPA-51, mean concentration vs time profiles of CEBPA-51 are very similar for the monotherapy and combination therapy cohorts (see comparison with monotherapy at 130 mg/m² dose)

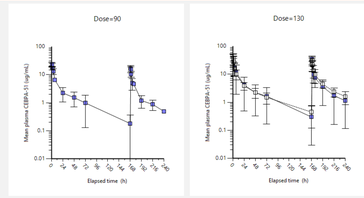

Fig 4. Plasma concentrations of CEBPA-51

Treatment and Response Duration

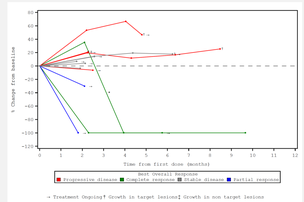

Fig 5. % Change in target tumor size in TKI naïve pts

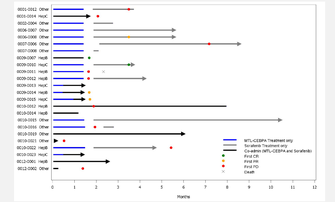

Fig 6. Duration of treatment in TKI naïve patients

Mechanism of Action

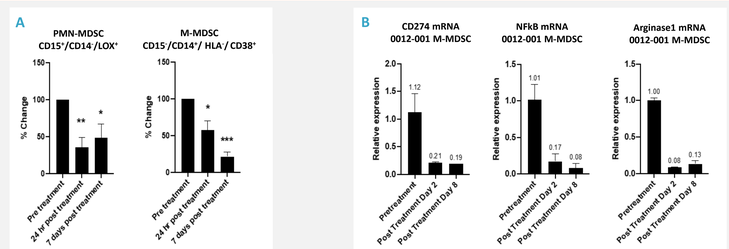

Fig 7. (A) Circulating MDSC Levels isolated by flow cytometry (B) Expression of key factors from isolated MDSCs

- After excluding lineage (CD3⁺/CD19⁺/CD56⁺). Population of monocytic (CD66⁻/CD14⁺/HLA-DR⁻/LO/CD15⁻/CD11b⁺/CD38⁺) and polymorphonucleic MDSCs (CD66⁺/CD14⁻/CD15⁺/CD11b⁺/LOX1⁺) significantly decreases after MTL-CEBPA treatment
- Gene expression analysis of monocytic MDSC shows downregulation of immunosuppressive markers CD274, Arginase 1 and NFkB