Preliminary results of a first-in-human, first-in-class phase I study of MTL-CEBPA, a small activating RNA (saRNA) targeting the transcription factor C/EBP-α in patients with advanced liver cancer

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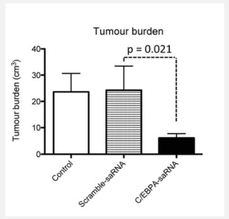
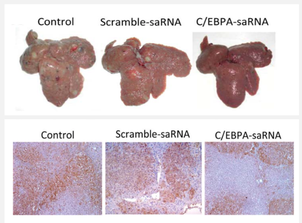
Background

- saRNAs are small oligonucleotide drugs designed to selectively upregulate therapeutic proteins by recruiting endogenous transcription complexes to a target gene, leading to increased expression of naturally processed mRNA
- Transcription factor C/EBP-α (CCAAT/enhancer-binding protein alpha) is a leucine zipper protein which acts as a master regulator of liver homeostasis and multiple oncogenic processes including cell cycle control, proliferation and angiogenesis
- MTL-CEBPA comprises a double stranded RNA payload formulated inside a SMARTICLES® liposomal nanoparticle to specifically target the CEBPA gene and has been shown to improve liver function and inhibit HCC tumour growth in preclinical models (Reebye et al, Hepatology, 2014; Voutila et al, Molecular Therapy, 2017; Reebye et al, Oncogene, 2018)
- **MTL-CEBPA is the first saRNA and the first drug targeting C/EBP-α to enter clinical trials**



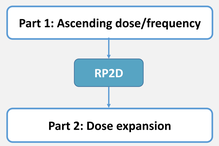


Methods

- 4 week cycle (3 weeks dosing + 1 week rest)
- MTL-CEBPA administered by intravenous infusion over 60 minutes
- Pre-medication may be administered to prevent infusion reactions
- AE, PK and PD assessed
- Radiological response determined by RECIST 1.1 every 8 weeks (2 cycles)
- All data are preliminary and based on a cut-off of March 31, 2018

Study Design

- International multi-centre, open-label, Phase 1 in two parts
- Part 1: 3+3 dose escalation: QW and BIW
- Part 2: dose expansion at Recommended Phase 2 Dose



MTL-CEBPA (mg/m2)	No. Recruit. Patient (n=28)
QW Dosing	**23**
28	4
47	4
70	3+3
98	3
130	3
160	3
BIW Dosing	**5**
70	5

Key Inclusion Criteria

- Unresectable, histologically confirmed HCC or secondary liver cancer
- HCC only recruited from cohort 3± prior sorafenib
- Child-Pugh class A /B with no clinically apparent ascites
- ECOG performance status 0–1
- At least one measurable liver lesion (≥ 1.0cm)

Baseline Demographics and Characteristics

- 28 patients were recruited; 10 (36%) patients were still active in study
- Mean follow-up period of 3.5 month (1 – 20)

Characteristics, No. (%)	Total (n=28)	Characteristics, No. (%)	Total (n=28)
Median age, years (range)	66 (27 - 80)	**ECOG status:**	
Gender: Male	20 (71)	PS=0	12 (43)
Female	8 (29)	PS=1	16 (57)
Tumour type/ Aetiology		**Child-Pugh score (HCC only, n=23)**	
Colorectal	4 (14)	A5	17 (74)
Ampullary	1 (4)	A6	3 (13)
HCC with cirrhosis	20 (71)	B7	3 (13)
- HBV	7 (25)	**Median prev. lines of therapy (range)**	2 (1 - >5)
- NAFLD/ NASH	4 (14)	Colorectal/ Ampullary / Fibrolamellar	4 (2 - >5)
- ALD	2 (7)	HCC (excluding fibrolamellar)	1 (1 - 3)
- HCV	3 (11)	**HCC specific therapy cohorts (any line)**	
- Aetiology undefined	4 (14)	prior TKI	16 (57)
HCC non-cirrhotic (NASH)	1 (4)	prior ICB	9 (32)
HCC Fibrolamellar	2 (7)	prior FGFRi	3 (11)

TKI: tyrosine kinase inhibitor; ICB: immune checkpoint blockade; FGFRi: fibroblast growth factor receptor inhibitor

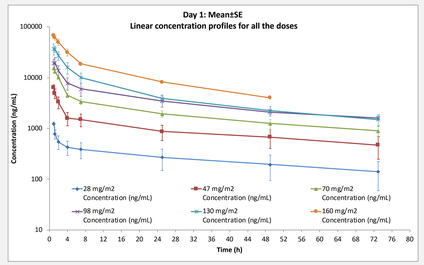
Safety

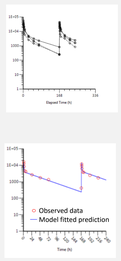
- 7 (25%) patients experienced a maximum AE of Grade 1 and 5 (18%) patients experienced a maximum AE of Grade 2, suggesting MTL-CEBPA was well tolerated in patients with late-stage HCC or secondary liver cancer
- 7 (25%) patients experienced Grade ≥3 AE recorded as either possibly or probably treatment-related (thrombocytopaenia, hypophosphataemia, anaemia, elevated AST, elevated GGT, hyperbilirubinaemia, infection, fatigue and acute coronary syndrome)
- Presumed drug toxicity led to treatment discontinuation in 3 (11%) patients after median of follow-up of 2 months (1 – 3):
  - 1 patient with secondary liver cancer experienced a Grade 3 dose limiting toxicity at 70 mg/m² of hyperbilirubinaemia after one dose
  - 1 patient with HCC experienced Grade 3 Acute Coronary Syndrome at 70 mg/m² after one dose
  - 1 patient with HCC experienced Grade 3 elevated GGT at 70 mg/m² dose in Cycle 3 Day 8

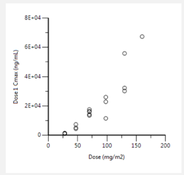
AE Category, Grade ≥3 (n>1)	No. (%)
Hyperbilirubinaemia	3 (11)
Elevated GGT	3 (11)
Hypophosphataemia	3 (11)
Anaemia	2 (7)
Hypertension	2 (7)

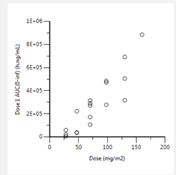
Pharmacokinetics

- Rapid distribution phase and a slower elimination phase fitted to a linear two-compartment PK model
- Mean terminal elimination half-life 36h (range 19-56h) with dose proportional C_{max} and AUC; consistent exposure profile between the first and the second dose ; no signs of accumulation for the weekly dosing
- Exposure increases over the 27 – 130 mg/m² dose range with significant AUC overlap between 98 and 130 mg/m² dose levels





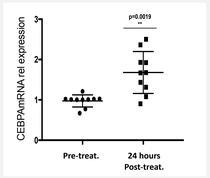




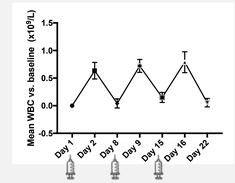
Pharmacodynamics

- Significant increased expression of CEBPA mRNA in WBC supports target engagement
- Significant and repeated increase in WBC vs baseline consistent with C/EBP-a dependent granulopoiesis

CEBPA mRNA expression in WBCs (n=10)

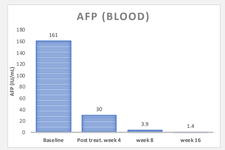


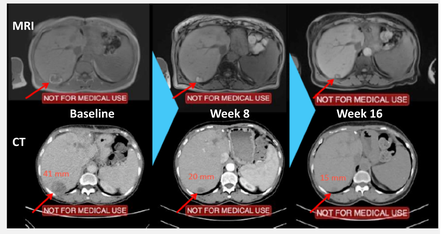
WBC vs baseline following dosing at 70 mg/m² QW (n=5)



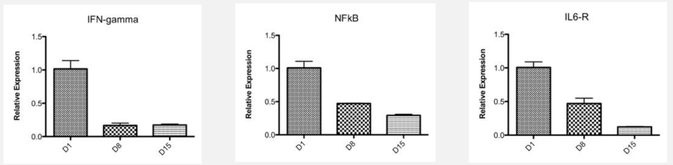
Case Study

- 78 year old female, hepatitis B related cirrhosis, prior trans-arterial chemoembolisation, radiofrequency ablation and liver resection, sorafenib and experimental FGFR4 antibody
- Radiological outcome: partial response (-42%) at Week 8, confirmed at Week 16 (-63%)
- Correlation with a drastic and rapid decrease of AFP tumour marker versus baseline
- Maintained response (-73%) after 20 cycles (1.6 year)





Response biomarkers: mRNA expression in WBC



Discussion

- 3+3 ascending doses with MTL-CEBPA weekly is well tolerated.
- Alternative dosing schedules now enrolling based on preclinical data suggesting increased up regulation of CEBPa and greater anti tumour efficacy
- PK for QW dosing well described by linear and dose proportional two-compartment model
- Target engagement supported by increased CEBPA gene expression in WBC driving enhanced granulopoiesis

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Study References: Clinicaltrials.gov: NCT02716012; UK NIHR CRN ID:20332 (CANC 4818)
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