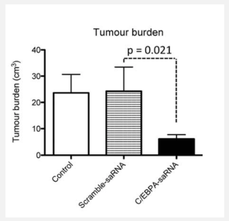
# Preliminary results of a first-in-human, first-in-class phase I study of MTL-CEBPA, a small activating RNA (saRNA) targeting the transcription factor C/EBP-α in patients with advanced liver cancer

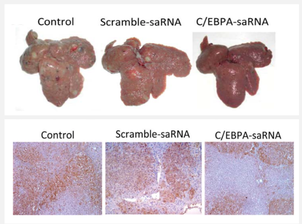
**Debashis Sarker,[1] Ruth Plummer[2], Bristi Basu[3], Tim Meyer[4], Kai-wen Huang[5], Jeff Evans[6], Duncan Spalding[7], Yuk-Ting Ma[8], Daniel Palmer[9], Cheng Ean Chee[10], Nagy Habib[11,7]**

[1]King's College London, London UK; [2]Sir Bobby Robson Cancer Trials Research Centre, Newcastle Upon Tyne, UK ; [3]Addenbrooke's Hospital, Cambridge, UK ; [4]University College London, London, UK ; [5]National Taiwan University Hospital, Taipei City, Taiwan [6]Beatson West of Scotland Cancer Centre, Glasgow, UK; [7]Department of Surgery & Cancer, Imperial College London, UK; [8]Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, UK; [9]Clatterbridge Cancer Centre, Liverpool, UK; [10]National University Health System, Singapore; [11]MiNA Therapeutics Limited, London, UK

## 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**



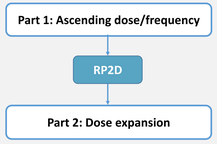




## Methods

- 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*

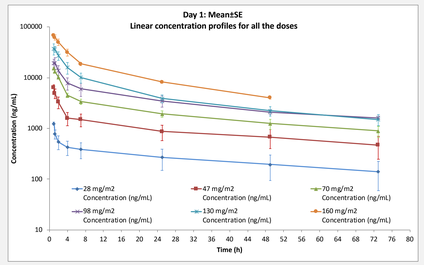
## Safety

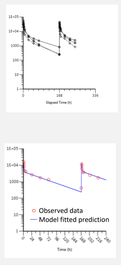
- 7 (25%) patients experienced a maximum AE of Grade 1 and 5 (18%) patients experienced a maximum AE of Grade 2, suggesting MTL-CEBPA was well tolerated in patients with late-stage HCC or secondary liver cancer
- 7 (25%) patients experienced Grade ≥3 AE recorded as either possibly or probably treatment-related (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

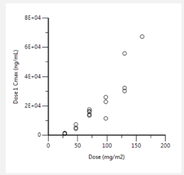
| AE Category, Grade ≥3 (n>1) | No. (%) |
|---|---|
| Hyperbilirubinaemia | 3 (11) |
| Elevated GGT | 3 (11) |
| Hypophosphataemia | 3 (11) |
| Anaemia | 2 (7) |
| Hypertension | 2 (7) |

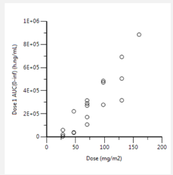
## Pharmacokinetics

- 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



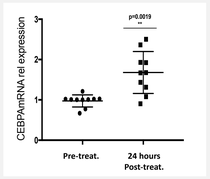



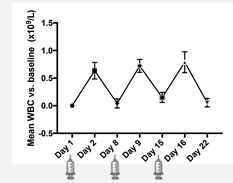

## Pharmacodynamics

- 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)**

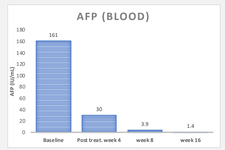


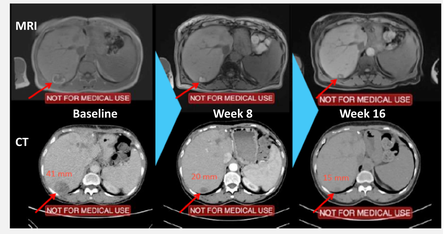

**WBC vs baseline following dosing at 70 mg/m² QW (n=5)**



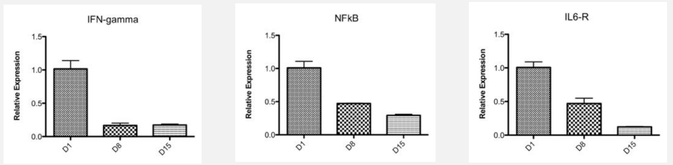

## Case Study

- 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

**Acknowledgements:** The UK sites receive support from Cancer Research UK and Department of Health as Experimental Cancer Medicine Centres. Financial support for the study was also provided by NIHR Biomedical Research Centre awards.
The study is sponsored by MiNA Alpha Ltd. We would like to thank the participating patients and their families for volunteering to take part in the study, all co-investigators, clinical and nursing staff for the conduct of the study. We also thank David Collin and Joanna Nicholls who contributed to this poster.

**References**
1. Reebye V et al. A novel RNA oligonucleotide improves liver function and inhibits liver carcinogenesis in vivo. Hepatology 2014;59:216-227; 2. 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 Dec 6;25(12):2705-2714; 3. Zhao X, et al. Treatment of Liver Cancer by C/EBPA saRNA. Adv Exp Med Biol. 2017;983:189-194; 4. 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 Mar 7. doi: 10.1038/s41388-018-0126-2.

**Study References:** Clinicaltrials.gov: NCT02716012; UK NIHR CRN ID:20332 (CANC 4818)
**Contact:** outreach@minatx.com