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
- Small nucleic acid therapies are designed to selectively upregulate therapeutic proteins by recruiting endogenous RNA molecules to target gene, leading to increased expression of naturally processed mRNA
- Transcription factor (C/EBP) LCATR (leucine-coding 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 nanosystem to specifically target the CEBPA gene and has been shown to improve liver function and inhibit HCC tumour growth in preclinical models
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### Methods
- 28 patients were recruited; 10 (35%) patients were still active in study
- Mean follow-up period of 3.5 month (1–20)

### Study Design
- Part 3: Dose escalation to determine maximum tolerated dose
- Part 2: Dose expansion at Recommended Phase 2 Dose

### Pharmacokinetics
- Rapid distribution phase and a slower elimination phase fitted to a linear two-compartment PK model
- Mean terminal elimination half-life 36h (range 10–58h) with dose proportion d_{28} and AUC; constant exposure profile between the first and the second dose; no signs of accumulation for the weekly dosing
- Exposure increases over the 27–140 mg/m² dose range with significant AUC overlap between 98 and 130 mg/m² dose levels

### Safety
- 7 (25%) patients experienced a maximum AE of Grade 1 and 5 (18%) patients experienced a maximum AE of Grade 2, suggesting MTL
- 73% after 20 cycles (1.6 year)
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### Pharmacodynamics
- Significant increased expression of CEBPA mRNA in WBC supports target engagement
- Correlation with a drastic and rapid increase in CEBPA mRNA in WBC upon dosing

### Case Study
- 78 year old female, hepatitis B related cirrhosis, prior trans-arterial chemoembolisation, radiofrequency ablation and liver resection, screened and experimental FGFRi
- Radiological outcome: partial response (42%) at Week 8, confirmed at Week 16 (43%)
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### 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 mRNA in WBC and greater anti-tumour efficacy
- PK for DME dosing well described by linear and dose proportional two-compartment model
- Target engagement supported by increased CEBPA gene expression in WBC driven enhancing target expression

### 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 other major axis
- ECOG performance status 0−1
- At least one measurable liver lesion (≥ 1.0cm)

### Baseline Demographics and Characteristics

<table>
<thead>
<tr>
<th>Characteristics, No. (%)</th>
<th>Total (n=28)</th>
<th>CEBPA expression</th>
<th>ECOG status</th>
<th>Median age, years (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>10 (71)</td>
<td>5 (50)</td>
<td>66 (27 - 86)</td>
<td>70 (71)</td>
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<tr>
<td>Female</td>
<td>18 (64)</td>
<td>9 (50)</td>
<td>12 (43)</td>
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### Key references