First-in-human, first-in-class phase I trial of MTL-CEBPA, a RNA oligonucleotide targeting the transcription factor C/EBP-α in patients with advanced hepatocellular cancer (OUTREACH)

Debashis Sarker¹, Ruth Plummer², Bristi Basu³, Tim Meyer⁴, Kai-wen Huang⁵, Jeffry Evans⁶, Mikael Sodergren⁷, Duncan Spalding⁷, Yuk-Ting Ma⁸, Daniel Palmer⁹, Cheng Ean Chee¹⁰, Nagy Habib ⁷,¹¹

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

• Honoraria: Bayer, Pfizer, Ipsen, MSD, Eisai

• Consulting/Advisory Role: Novartis, Ipsen, Eisai, Blueprint Medicines

• Travel/Accommodations/Expenses: Ipsen, MiNA Therapeutics, Bayer, Eisai
Small Activating RNAs

- Small activating RNAs (saRNAs) are short double stranded oligonucleotides designed to selectively upregulate their target gene by transcriptional activation.
- saRNAs recruit endogenous transcription complexes to a target gene, leading to increased expression of naturally processed mRNA.
C/EBP-a (CCAAT/enhancer-binding protein alpha) acts on both cancer and myeloid cells

1. Tumour suppressor in solid tumours
   - Deregulation of C/EBP-a expression reported in a variety of human cancers
   - In HCC, C/EBP-a reported to inhibit cell proliferation, cell motility and metastasis
   - CEBPA knock-in mice have reduced susceptibility to HCC
   - CEBPA up-regulation by saRNA inhibits tumour growth in multiple tumour models
     - Key reference: Lourenço and Coffer, Oncogene, 2017

2. Differentiator of tumour immune microenvironment
   - C/EBP-a regulates hematopoiesis by inducing myeloid differentiation
   - In tumour bearing mice, C/EBP-a is downregulated in MDSC
   - CEBPA knock-out mice have increased MDSC count and tumour infiltration, and tumour vascularisation and growth
   - Elevated expression of C/EBP-b (inhibitor of C/EBP-a) in TAM (34 pts of which 14 HCC)
     - Key reference: Mackert et al, Scientific Reports, 2017

3. Regulator of liver homeostasis
   - CEBPA down-regulated in Hepatic Stellate Cells and Liver Fibrosis
   - CEBPA knock-out mice have impaired liver function
   - CEBPA over-expression ameliorates liver fibrosis in CCl4 mice
   - CEBPA up-regulation by saRNA improves liver function in multiple preclinical models
     - Key reference: Rebye et al, Hepatology, 2014
MTL-CEBPA: First-in-class activator of C/EBP-a

Small activating RNA targeting CEBPA gene + NOV340 SMARTICLES® liposome → MTL-CEBPA

Published pre-clinical data across range of liver and cancer models
Voutilä et al, Molecular Therapy, 2017 | Reebye et al, Oncogene, 2018
OUTREACH Phase I clinical trial

| Design | Open label, First in Human dose escalation in cohorts of 3 patients  
|   | Open label dose expansion at RP2D in up to 25 pts |
| Indications | Advanced HCC (primary liver tumours) |
| Objectives | Primary: To determine the safety of administering MTL-CEBPA to patients with liver tumours  
|   | Secondary: To determine the RP2D; characterise the PK of MTL-CEBPA; characterise the PD of MTL-CEBPA; to increase serum albumin and/or decrease serum bilirubin |
| Administration | 60min I.V. infusion  
|   | 4 week cycles |
| Dose cohorts | QWx3: 0.8 → 1.3 → 1.9 → 2.6 → 3.5 → 4.3 mg/kg  
|   | BIWx3: 1.9 mg/kg  
|   | TIWx3: 1.9 → 3.5 mg/kg |
Study Inclusion Criteria and Demographics

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)
• Life expectancy greater than 3 months at the time of the recruitment
• Platelets ≥ 60 x 10^9/L

<table>
<thead>
<tr>
<th>Characteristics, No. (%)</th>
<th>Total (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>65 (27 - 80)</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (77)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (23)</td>
</tr>
<tr>
<td>ECOG:</td>
<td></td>
</tr>
<tr>
<td>PS=0</td>
<td>15 (38)</td>
</tr>
<tr>
<td>PS=1</td>
<td>23 (59)</td>
</tr>
<tr>
<td>PS=2</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Tumour Type:</td>
<td></td>
</tr>
<tr>
<td>HCC</td>
<td>34 (87)</td>
</tr>
<tr>
<td>Secondary HCC</td>
<td>5 (13)</td>
</tr>
</tbody>
</table>
### MTL-CEBPA Safety

- **MTL-CEBPA was well tolerated with no DLTs at the maximum administered dose of 160mg/m² QW**
- **Treatment-related AEs (all grades) that occurred in more than 10% of patients were fatigue (23.7%), thrombocytopenia (13.2%), anaemia (13.2%), elevated AST (13.2%), elevated ALP (10.5%), hypoalbuminaemia (10.5%), increased ALT (10.5%) and increased bilirubin (10.5%)**
- **Only 4 (9%) patients discontinued treatment due to possible drug-related toxicities**
- **Based on combination of safety, PK and PD recommended dose for further evaluation is 130mg/m² weekly**

<table>
<thead>
<tr>
<th>Most Frequent TEAEs ≥20% Pts</th>
<th>% Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>33.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30.8</td>
</tr>
<tr>
<td>Anemia</td>
<td>23.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20.5</td>
</tr>
<tr>
<td>Increased ALP</td>
<td>20.5</td>
</tr>
<tr>
<td>Increased AST</td>
<td>20.5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20.5</td>
</tr>
</tbody>
</table>
Pharmacokinetics
Pharmacodynamics: MTL-CEBPA clinical proof of mechanism

Increase in CEBPA mRNA in patient WBCs

Reversible increase in patient neutrophils (n=5, QW at 70 mg/m2)

Myeloid progenitor cells into monocyes and granulocytes so increase in neutrophils expected based on CEBPA biology
Decrease of peripheral MDSCs following MTL-CEBPA administration

FACS analysis (Monocytic and PMN-MDSC) from WBC of MTL-CEBPA treated patients at Day 2

Peripheral myeloid derived suppressor cells (MDSCs)- both monocytic and polymorphonuclear are suppressed within 24 hours following MTL-CEBPA administration in patients (n=2).
OUTREACH: maintained partial response for 2 years

- 78 year old female, hepatitis B related cirrhosis, prior TACE, radiofrequency ablation and liver resection, sorafenib and experimental FGFR4 antibody
- Radiological outcome: partial response (-75%) durable 2 years

Response biomarkers: mRNA expression in WBC
Therapeutic rationale of MTL-CEBPA + Sorafenib combination in advanced HCC

Evidence that targeting myeloid cells can improve efficacy of Sorafenib in HCC

- Sorafenib treatment increases suppressive myeloid cell tumour infiltration in HCC patients
- Targeting myeloid cells in mouse HCC tumour models increases anti-tumour activity of Sorafenib
  - Tang lab – depletion of Tumour Associated Macrophages with clodrolip or zoledronic acid
  - Duda lab – reduction of myeloid cell tumour infiltration with CXCR4 inhibition (+/- anti-PD1)
  - Ann-Li Cheng lab – depletion of Myeloid Derived Suppressor Cells with anti-Ly6G

MTL-CEBPA improves tumour growth inhibition of Sorafenib in DEN model of HCC

<table>
<thead>
<tr>
<th>Week 1</th>
<th>PBS</th>
<th>MTL-CEBPA</th>
<th>MTL-CEBPA</th>
<th>Sorafenib</th>
<th>MTL-CEBPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 2</td>
<td>PBS</td>
<td>–</td>
<td>MTL-CEBPA</td>
<td>Sorafenib</td>
<td>Sorafenib</td>
</tr>
</tbody>
</table>
MTL-CEBPA repopulates tumour microenvironment, associated with subsequent complete response to sorafenib

Dramatic reduction in pro-tumour / immuno-suppressive CD163+ M2 macrophages in HCC biopsy

Complete Response of HCC and lung mets (ongoing response 1yr +)
Ongoing Phase IB study of MTL-CEBPA in combination with sorafenib in advanced HCC

- **Sequential** up to 20 pts
  - MTL-CEBPA 130 mg/m² QW (2 months)
  - Sorafenib 400 mg BID

- **Co-administration** up to 20 pts
  - MTL-CEBPA 130 mg/m² QW + Sorafenib 400 mg BID

**Primary endpoints**
- Objective response rate
- Safety and tolerability

**Secondary endpoints**
- Complete response rate
- Disease control rate
- Progression free survival
- Overall survival
- Biomarkers
# Phase I/II trial of MTL-CEBPA in combination with pembrolizumab in HCC and solid tumors

<table>
<thead>
<tr>
<th>Duration</th>
<th>Q4 ’19 to Q4 ’21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Open label</td>
</tr>
<tr>
<td></td>
<td>Phase 1 – 2 cohort ascending dose 3+3</td>
</tr>
<tr>
<td></td>
<td>Phase 2 – up to 90 patient expansion cohort at Recommended Phase 2 Dose</td>
</tr>
<tr>
<td>Indications</td>
<td>Patients with any solid tumour refractory to standard of care</td>
</tr>
<tr>
<td></td>
<td>Naïve to Immune Checkpoint Blockade</td>
</tr>
<tr>
<td>Objectives</td>
<td>Primary: Safety and tolerability (Phase 1), Objective Response Rate (Phase 2)</td>
</tr>
<tr>
<td></td>
<td>Secondary: PK in plasma and WBC; PD in WBC and paired biopsies; FACS in WBC; DCR rate, DCR, PFS, OS</td>
</tr>
<tr>
<td>Administration</td>
<td>1 cycle = Pembrolizumab per label claim and MTL-CEBPA once weekly (i.v.) with a total of 6 injections over two months</td>
</tr>
<tr>
<td>Clinical sites</td>
<td>Up to 20 specialised centres and university hospitals</td>
</tr>
</tbody>
</table>
Conclusions

• MTL-CEBPA is the first small activating RNA therapeutic and the first drug targeting CEBP-a to enter clinical trials
• MTL-CEBPA is well tolerated with no maximum tolerated dose; based on combination of safety, PK and PD recommended dose for further evaluation is 130mg/m² weekly
• MTL-CEBPA shows target engagement with increase in C/EBP-a mRNA expression in WBCs
• Initial evidence of clinical response in patients with advanced HCC, including complete responses in patients subsequently treated with sorafenib
• Hypothesise that MTL-CEBPA sensitises tumours to sorafenib by repopulating tumour immune microenvironment
• HCC MTL-CEBPA+Sorafenib combination study is ongoing; pembrolizumab combination study planned in HCC and other solid tumours to commence Q4 2019
Acknowledgements

• The patients and their families who participated in this study
• Clinical research teams at the treating sites
• 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

Clinical investigators
King's College London – Debashis Sarker
University College London – Tim Meyer
Newcastle – Ruth Plummer
Cambridge – Bristi Basu
NTUH – Kai-Wen Huang
Glasgow – Jeff Evans
Imperial College – Duncan Spalding
Birmingham – Yuk-Ting Ma
Liverpool – Daniel Palmer
NUHS – Cheng Ean Chee