MiNA Therapeutics

Open label, randomised, phase 2 study to evaluate the safety and efficacy of sorafenib with or without MTL-CEBPA, an immune-modulatory saRNA upregulating C/EBP-a, as second line treatment in advanced hepatocellular carcinoma (OUTREACH 2)

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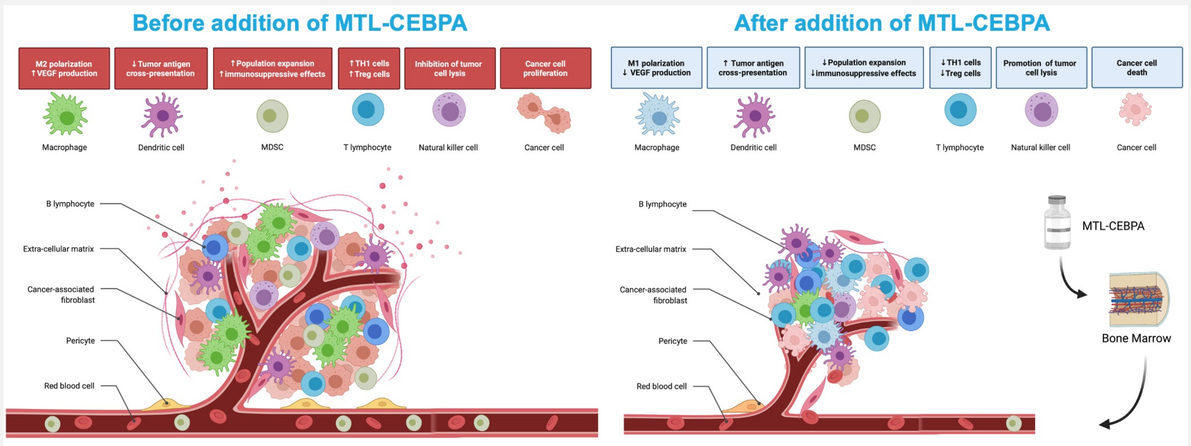
Background

There is a paucity of clinical outcome data relating to second line treatment options for unresectable HCC in patients who have progressed on atezolizumab and bevacizumab. Sorafenib and other tyrosine kinase inhibitors (TKIs) have been adopted as standard of care in second line having previously demonstrated modest clinical benefit in first line setting (1, 2). Tumour infiltration of myeloid derived suppressor cells (MDSC) has been associated with worse prognosis in solid organ malignancies, including HCC, and primary resistance to multiple treatments including TKIs (3, 4). C/EBP-α is a master regulator of myeloid cells and knock-out of C/EBP-α in preclinical models led to expansion and infiltration of myeloid derived suppressor cells in the tumour microenvironment (5, 6). MTL-CEBPA is a small activating RNA (saRNA) that has been shown to increase expression of C/EBP-α and reduce immune suppression in the tumour microenvironment (7, 9). Emerging clinical data from a Phase 1b study of MTL-CEBPA in combination with sorafenib demonstrated a favourable safety and tolerability profile and encouraging initial clinical activity in patients with viral aetiology and no prior exposure to TKIs, with an overall response rate of 26.7% and complete response rate of 13.3% (8, 9).

Proposed mechanism of MTL-CEBPA

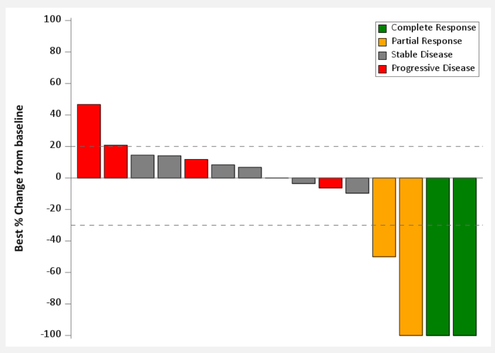


Preclinical and translational data have validated an immunological mechanism of action of MTL-CEBPA that potentiates response to a range of anti-cancer therapies. Data demonstrates that MTL-CEBPA reduces immune suppression in the tumor microenvironment by specifically upregulating C/EBP-a master regulator in myeloid immune cells (7, 8).

MTL-CEBPA demonstrated promising activity in Phase 1

A Phase 1/1b study of MTL-CEBPA (OUTREACH 1) demonstrated a favourable safety and tolerability profile and preliminary clinical activity as a single agent, and in combination with sorafenib in patients with viral aetiology and no prior exposure to TKIs.

MTL-CEBPA + Sorafenib activity in HCC (viral aetiologies, no prior TKI) (9)
- 26.7% ORR
- 2 CR, 2 PR, 7 SD

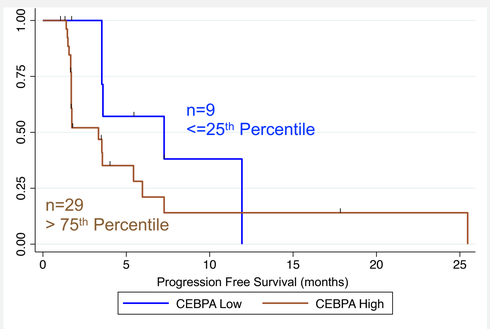


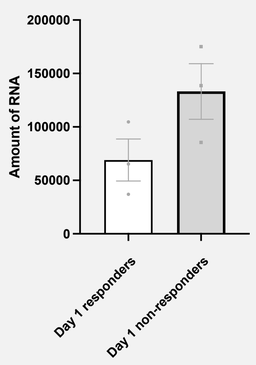
MTL-CEBPA single agent activity in HCC (all aetiologies) (8)
- 5.6% ORR
- 2 PR, 15 SD

Potential responder biomarker identified in Phase 1

Retrospective analysis suggested target gene expression in WBC may predict outcomes of patients treated with MTL-CEBPA and Sorafenib.

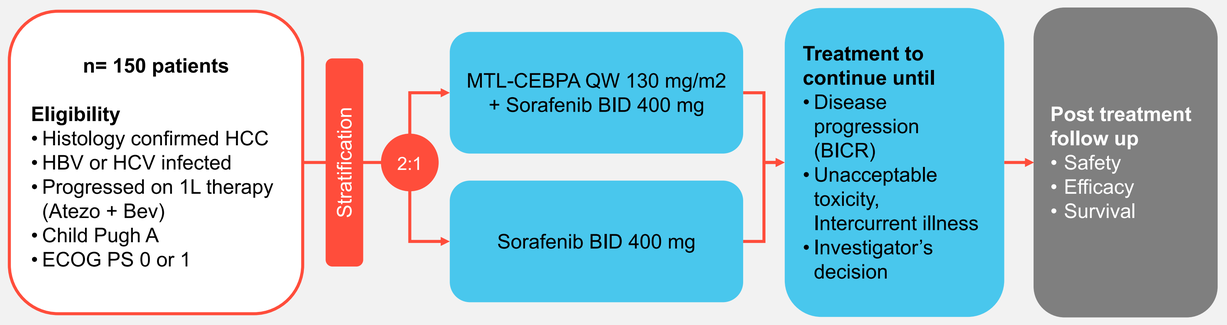
- Low levels of CEBPA mRNA at baseline correlated with improved PFS
- Low levels of CEBPA mRNA at baseline observed in responder patients





- Subgroup analysis in OUTREACH 2 pre-planned to further explore potential as predictive biomarker

OUTREACH 2 study design



OUTEACH 2 is an open label, two-arm global multicentre study with 2:1 randomisation between MTL CEBPA + sorafenib (n=100) and sorafenib alone (n=50), stratified by ALBI (albumin-bilirubin) grade (1 vs >1) and geographic region (Asia vs Rest of World) as a second line treatment in participants with histologically confirmed advanced HCC and a background of Hepatitis B or C who have previously failed treatment of atezolizumab in combination with bevacizumab. The study will include participants with Child-Pugh A score, ECOG 0-1 and BCLC stage C or stage B if not amenable or refractory to locoregional therapy and not amenable to a curative intent.

Study treatments

MTL-CEBPA + Sorafenib arm
- MTL-CEBPA i.v. infusion once weekly for each 28 day cycle. Infusion on Day 1, 8, 15 with rest on Day 22
- Sorafenib oral twice daily from Day 8

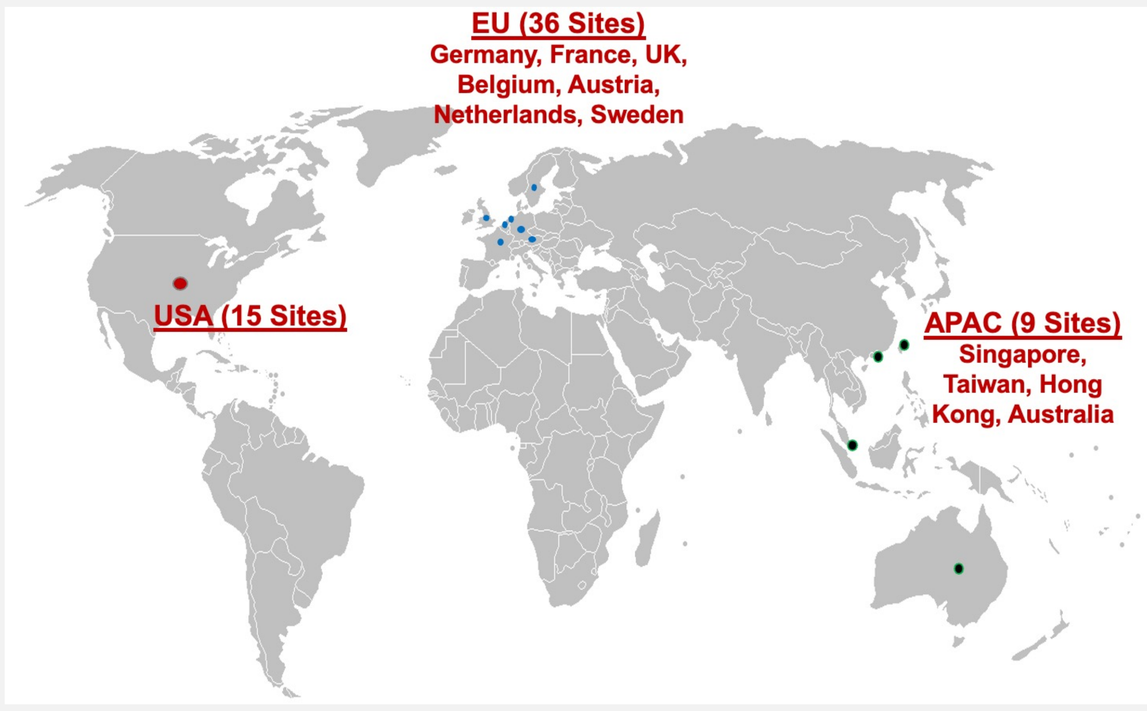
Sorafenib arm
- Sorafenib oral twice daily from Day 1

Outcome measures

Primary:
- PFS of MTL-CEBPA in combination with sorafenib compared to sorafenib alone as determined by BICR using RECIST v1.1

Secondary:
- Efficacy (BOR, ORR, DoR, TTR and changes in tumour size) of MTL-CEBPA in combination with sorafenib compared to sorafenib alone as assessed by BICR by RECIST 1.1
- Overall Survival (OS) of MTL-CEBPA in combination with sorafenib compared to sorafenib alone
- Consistency in tumour-based efficacy endpoints between BICR and Investigator assessment
- Safety and tolerability
- Health-related quality of life (HRQoL) assessed by EORTC-QLQ-C30 and EORTC-QLQ-HCC18 QOL

Investigator sites



As of August 4th 2022 the study is open to recruitment in Austria, Belgium, Singapore, Taiwan, UK, USA.

References

1. Finn et al, 2020 2. Kudo et al, 2018 3. Veglia et al, 2018 4. Chang et al, 2018 5. Lourenco et al, 2017 6. Mackert et al, 2017 7. Voutila et al, 2017 8. Sarker et al, 2020 9. Hashimoto et al, 2021