an open label, randomised, phase 2 study to evaluate the safety and efficacy of mtl-cebpa administered in combination with sorafenib or sorafenib alone, in TKI naïve participants with previously treated advanced hepatocellular carcinoma (HCC) and hepatitis B or hepatitis C virus (outreach2)

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We compare the efficacy and safety of the new medication MTL-CEBPA in combination with sorafenib with the efficacy and safety of sorafenib alone. Sorafenib is already being used for the treatment of HCC.

Ethical review	Approved WMO
Status	Pending
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON51314

Source
ToetsingOnline

Brief title
MTL-CEBPA with sorafenib versus sorafenib alone in participants with HCC.

Condition

- Viral infectious disorders
- Hepatobiliary neoplasms malignant and unspecified

Synonym
advanced liver cancer in association with viral infections

Research involving
Human

Sponsors and support

Primary sponsor: MiNA Alpha Limited Translation & Innovation Hub,
Source(s) of monetary or material Support: Industry sponsor MiNA Alpha Ltd

Intervention

Keyword: hepatocellular carcinoma (HCC), MNA-3521-014-RNDZ, outreach2

Outcome measures

Primary outcome

To compare PFS of MTL-CEBPA in combination with sorafenib compared to sorafenib alone as determined by BICR and assessed using RECIST v1.1 guidelines.

Secondary outcome

To compare efficacy of MTL-CEBPA in combination with sorafenib compared to sorafenib alone as assessed by BICR for the following: Best Objective Response (BOR), Objective Response Rate (ORR), Duration of Response (DoR), Time to Response (TTR), and changes in tumour size.

To compare OS of MTL-CEBPA in combination with sorafenib compared to sorafenib alone.

To assess consistency in tumour-based efficacy endpoints between BICR and

Investigator assessment.

To evaluate the safety and tolerability profile of MTL-CEBPA when administered

in combination with sorafenib and compared to sorafenib alone.

To compare the health-related quality of life (HRQoL) of MTL-CEBPA in

combination with sorafenib compared to sorafenib alone as assessed by

EORTC-QLQ-C30 plus EORTC-QLQ-HCC18 QOL questionnaires.

Study description

Background summary

MTL-CEBPA is made of two strands of ribonucleic acid (RNA). RNA is a substance that carries and gives information to genes, which are structures that carry the information needed to make the different parts of our cells. The drug MTL-CEBPA sends a message to a particular gene to work harder to produce the proteins necessary to make sure the liver works properly.
Previous research has shown that MTL-CEBPA was safe to give in humans and can have an anti-cancer effect by slowing down tumour growth. The current thinking is that MTL-CEBPA works in combination with other anti-cancer drugs. In this study, called OUTREACH2, MTL-CEBPA is combined with another drug sorafenib.

Sorafenib is a type of targeted therapy approved for the treatment of liver cancer. Sorafenib*s category of drug is called a multi kinase inhibitor. Sorafenib works by blocking signals in the cancer cells that make them grow. Blocking the signals causes the cells to die. Sorafenib can also stop cancer cells developing new blood vessels. This reduces their supply of oxygen and nutrients, so the tumour shrinks or stops growing.

Study objective

We compare the efficacy and safety of the new medication MTL-CEBPA in combination with sorafenib with the efficacy and safety of sorafenib alone. Sorafenib is already being used for the treatment of HCC.

Study design

Phase II, randomised, open label, two-arm, comparative study. This is an interventional, parallel study with active control, run across multiple centres.

Randomisation: Participants will be randomised in a 2:1 ratio in 2 groups between MTLCEBPA + sorafenib (100 participants) and sorafenib alone (50 participants).

Intervention

Participants will be assigned to two groups to receive MTL-CEBPA + sorafenib or sorafenib monotherapy in a 2:1 randomisation scheme.

Stratification: ALBI (albumin-bilirubin) grade (1 vs >1) and geographic region (Asia vs Rest of World).

MTL-CEBPA will be administered once a week (QW) at a dose of 130 mg/m2 by i.v. infusion over 60 minutes for 3 weeks followed by a rest period of 1 week (4 weeks = one cycle) and continued until study treatment discontinuation criteria are met.

Sorafenib will be administered orally starting on Cycle 1 Day 1 for participants in the sorafenib monotherapy group and on Day 8 for participants in the MTL-CEBPA + sorafenib group, at the approved dose of 400*mg (2 x 200 mg tablets) twice daily (BID). Sorafenib will be administered following MTL-CEBPA administration on days when both drugs are administered and continued until study treatment discontinuation criteria are met.

Study burden and risks

Subject will visit the hospital for screening visit and during cycle 1 visits on day 1,2,8,15 and for additional cycles on day 1.8.15. and 22.
per cycle weekly infusion with MTL-CEBPA the first 3 weeks and sorafenib daily dose as of day 8 of first cycle.
or if sorafenib alone group dialy dose of sorafenib from day 1.
every three weeks completion of questionnaires estimated 10 to 15 minutes but subject should take as long as needed.
every 8 weeks CT scan
blood samples taken at all visits
subject can consent to optional tumor biopsies at screening and during treatment.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Written informed consent obtained prior to any specific trial-related procedure.
2. Male or female 18 years or older.
3. Histologically confirmed advanced HCC with cirrhosis in a participant with a history of hepatitis B and/or C. Participants with past or ongoing HCV infection will be eligible for the study. Participants must have completed their treatment at least 1 month prior to starting study intervention and their HCV viral load below the limit of quantification. Participants who are HCV Ab positive but HCV RNA negative due to prior treatment or natural resolution will be eligible. Participants with past or controlled ongoing hepatitis B will be eligible as long as their HBV viral load is less than 500 IU/mL prior to first dose of study drug. Participants on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study intervention.
4. Child-Pugh classification A.
5. Unsuitable for liver tumour resection and/or refractory to loco-regional

therapy.
6. Not eligible for liver transplantation.
7. Had progression or recurrence of HCC following previous treatment with atezolizumab in combination with bevacizumab. Participants with progression or recurrence of HCC on non-atezolizumab anti-PD-1/PD-L1 inhibitors and non bevacizumab anti-VEGF agent in combination or as any as single agents, and no prior treatment with atezolizumab and bevacizumab, are eligible.
8. Naïve to tyrosine kinase inhibitors, including sorafenib, regorafenib, cabozantinib, and lenvatinib.
9. Participants with BCLC stage C disease. BCLC Stage B will be allowed if not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach (Appendix B).
10. Eastern Cooperative Oncology Group performance status of 0 or 1.
11. Has the ability to swallow and retain oral medication.
12. Life expectancy greater than 3 months at time of recruitment.
13. At least one measurable liver lesion (RECIST v1.1) assessed by the investigator.
14. Platelet count >70 x109/L.
15. Serum albumin >=28g/L.
16. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <=5 x the upper limit of normal (ULN).
17. Bilirubin <=50 µmol /L.
18. White Blood Cell (WBC) >=2.0 x 109/L.
19. Absolute neutrophil count >=1.5 x 109/L.
20. Haemoglobin >=9.0 g/dL.

Exclusion criteria

1. Child-Pugh classification B and C.
2. Participants without a history of hepatitis B and/or hepatitis C.
3. Participants with fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtype HCC.
4. Participants with no prior therapy who are eligible for first-line treatment with atezolizumab in combination with bevacizumab.
5. Participants who received investigational drug(s) within the last 30 days prior to study treatment initiation.
6. Participants with clinically significant ascites.
7. Any episode of bleeding from oesophageal varices or other uncontrolled bleeding including
clinically meaningful epistaxis within the last 3 months prior to study treatment initiation.
8. Clinically diagnosed hepatic encephalopathy in the last 6 months unresponsive to therapy.
9. Participants with a history of gastrointestinal haemorrhage or perforation.
10. Has known active CNS metastases and/or carcinomatous meningitis.

Participants with previously treated such metastases may participate provided they are radiologically stable for at least 4 weeks by repeat imaging performed during study screening, clinically stable and without requirement of steroid treatment for at least 28 days prior to first dose of study intervention. MRI brain scan are required for all participants with stable brain metastases at screening (CT scan will be allowed if MRI is contraindicated).
11. Participants administered with serum albumin within the last 7 days prior to the first study treatment administration.
12. Known infection with human immunodeficiency virus (HIV) with CD4+ T-cell counts <350 cells/µL or with a history of AIDS-defining opportunistic infection. No HIV testing is required unless mandated by local health authority.
13. Received a live vaccine within 30 days prior to the first dose of study treatment. Live vaccines include, but are not limited to: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
14. Known other malignancy that is progressing or has required active treatment in the last 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death such as early-stage cancers treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, or in situ breast cancer that has undergone potentially curative therapy.
15. Participants presenting with a baseline prolongation of QT/QTc interval defined as repeated demonstration of a QTc interval >=450ms (males) and >=460ms (females) using Fridericia*s correction formula.
16. Participants with a screening diastolic blood pressure >90 mm Hg.
17. Clinically significant cardiovascular disease within 12 months from first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability.
Note: Medically controlled arrhythmia would be permitted.
18. Major surgery within the last 30 days prior to study treatment initiation. If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.
19. Participants with a history of organ transplantation
20. Diagnosis of immunodeficiency or receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2022
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	MTL-CEBPA
Generic name:	MTL-CEBPA
Product type:	Medicine
Brand name:	Nexavar
Generic name:	sorafenib
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	23-03-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	17-05-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-09-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-005431-23-NL
CCMO	NL80197.000.22