ForPatients
by Roche

Advanced Liver CancersHepatocellular Carcinoma (HCC)

A clinical trial to look at how safe and effective different combinations of immunotherapy-based treatments are at reducing tumour size in people with advanced liver cancers

A Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients With Advanced Liver Cancers (Morpheus-Liver)

Trial Status	Trial Runs In	Trial Identifier
Recruiting	7 Countries	NCT04524871 2020-001743-10 GO42216

The information is taken directly from public registry websites such as ClinicalTrials.gov, EuClinicalTrials.eu, ISRCTN.com, etc., and has not been edited.

Official Title:

A Phase Ib/II, Open-Label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients With Advanced Liver Cancers (Morpheus-Liver)

Trial Summary:

This is a Phase Ib/II, open-label, multicenter, randomized umbrella study in participants with advanced liver cancers. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, modify the participant population, or introduce additional cohorts of participants with other types of advanced primary liver cancer. Cohort 1 will enroll participants with locally advanced or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy for their disease. Eligible participants will initially be randomly assigned to one of several treatment arms (Stage 1). Participants who experience loss of clinical benefit or unacceptable toxicity during Stage 1 may be eligible to receive treatment with a different treatment combination (Stage 2). When a Stage 2 treatment combination is available, this will be introduced by amending the protocol.

Hoffmann-La Roche Sponsor	**Phase 1/Phase 2** Phase

NCT04524871 2020-001743-10 GO42216
Trial Identifiers

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Eligibility Criteria:

Gender	Age	Healthy Volunteers
All	#18 Years	No

1. Why is the MORPHEUS-liver clinical trial needed?

Hepatocellular carcinoma (HCC) is the most common type of liver cancer. Most people are first diagnosed with HCC once it has spread to surrounding tissues or lymph nodes (known as ‘advanced HCC’) or to other parts of the body (known as ‘metastatic HCC’).

The standard first treatment for HCC that cannot be removed with surgery (known as ‘unresectable’ HCC) is cancer immunotherapy (‘CIT’, such as atezolizumab plus bevacizumab), which helps the body’s immune system to destroy cancer cells. The anti-cancer activity of CITs may be boosted when different treatments are given at the same time – as CIT combinations. New CIT combinations are needed to improve health outcomes for people with advanced HCC.

This clinical trial aims to compare the effects, good or bad, of different combinations of CIT in people with locally advanced or metastatic HCC. As the trial progresses, the safety and effectiveness of other new treatment combinations may be tested.

2. How does the MORPHEUS-liver clinical trial work?

This clinical trial is recruiting people with HCC. People can take part if they have advanced, metastatic or inoperable HCC. People who take part in this clinical trial (participants) will be given one of several CIT combinations (consisting of at least one CIT drug) for as long as it can help them. If participants have unacceptable side effects to the CIT combination. or their disease gets worse, they may be given a different CIT combination if one is available, and if they agree to it. The clinical trial doctor will see participants regularly. These hospital visits will include checks, such as a tumour assessment scan, to see how the participant responds to treatment and any side effects they may have. The tumour assessment scans will occur every 6 weeks for the first 48 weeks of the trial and then every 6 or 12 weeks after that. After the final dose of treatment, the clinical trial doctor will follow-up with participants about every 3 months for as long as they agree to it. Participants’ total time in the clinical trial will depend on how they tolerate treatment and how their cancer responds to treatment, which could be up to more than 1 year. Participants can stop trial treatment and leave the clinical trial at any time.

3. What are the main endpoints of the MORPHEUS-liver clinical trial?

The main clinical trial endpoint (the main result measured in the trial to see if the treatment combinations have worked) is the number of participants with either cancer that has reduced in size or no detectable cancer (known as the ‘objective response rate’).

The other clinical trial endpoints include:

- The length of time between the start of treatment and cancer getting worse (known as ‘progression free survival’)
- How long participants live (known as ‘overall survival’)
- The amount of time between cancer getting better from treatment and then getting worse (known as ‘duration of response’)
- How many participants have tumours that stay the same or reduce in size for at least 3 months (known as ‘disease control rate’)

4. Who can take part in this clinical trial?

People can take part in this trial if they are at least 18 years old and have advanced, metastatic or unresectable HCC and have not been treated for it with drugs that affect the whole body (known as ‘systemic’ treatment). People who have had treatments that are given to the tumour directly, such as surgery or radiotherapy, are allowed to take part.

People may not be able to take part in this trial if they have HCC that has spread to the brain or spinal cord and causes symptoms, rare types of HCC (such as fibrolamellar HCC and sarcomatoid HCC) or have certain other medical conditions such as infections, autoimmune, heart or lung disease. People who have previously been given certain treatments, including CITs, or who are pregnant or breastfeeding or are intending to become pregnant during the clinical trial, are not able to take part. There are other specific criteria that participants may need to meet to be given a particular CIT treatment combination in this clinical trial.

5. What treatment will participants be given in this clinical trial?

Participants will be given a combination of CITs. The combinations may include atezolizumab plus bevacizumab with or without: tiragolumab, tocilizumab, TPST-1120 or ADG126, or may be a combination of RO7247669 plus bevacizumab. Treatment combinations will be given by mouth (orally) or as an infusion into a vein every 3 or 4 weeks depending on the CIT combination.

Participants will be placed in a CIT combination treatment group randomly (by chance) depending on the safety criteria they meet and the number of groups available. Participants may also receive treatment with tocilizumab as an infusion into the vein, if they experience certain side effects (called ‘cytokine release syndrome’) during the clinical trial.

This is an open-label trial, which means everyone involved, including the participant and the clinical trial doctor, will know the clinical trial treatment the participant has been given.

6. Are there any risks or benefits in taking part in this clinical trial?

The safety or effectiveness of the experimental treatment or use may not be fully known at the time of the trial. Most trials involve some risks to the participant. However, it may not be greater than the risks related to routine medical care or the natural progression of the health condition. People who would like to participate will be told about any risks and benefits of taking part in the clinical trial, as well as any additional procedures, tests, or assessments they will be asked to undergo. All of these will be described in an informed consent document (a document that provides people with the information they need to decide to volunteer for the clinical trial).

Risks associated with the clinical trial

Participants may have side effects (an unwanted effect of a drug or medical treatment) from the drugs used in this clinical trial. Side effects can be mild to severe, even life-threatening, and vary from person to person. Participants will be told about the known side effects of CITs and possible side effects based on human and laboratory studies or knowledge of similar drugs. CITs will be given by mouth (orally) or as an infusion into a vein (intravenous infusion). Participants will be told about known side effects of intravenous infusion and will be closely monitored during the clinical trial; safety assessments will be performed regularly.

Potential benefits associated with the clinical trial

Participants' health may or may not improve from participation in the clinical trial. Still, the information collected may help other people with similar medical conditions in the future.

Inclusion Criteria:

Stage 1

- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 within 7 days prior to randomization
- Locally advanced or metastatic and/or unresectable hepatocellular carcinoma (HCC) with diagnosis confirmed by histology/cytology or clinically by American Association for the Study of
- Liver Diseases criteria in cirrhotic patients
- Child-Pugh class A within 7 days prior to randomization
- Disease that is not amenable to curative surgical and/or locoregional therapies
- No prior systemic treatment for HCC
- Life expectancy >= 3 months
- Availability of a representative tumor specimen that is suitable for determination of PD-L1 and/or additional biomarker status via central testing

Stage 1 and Stage 2

- Measurable disease according to Response Evaluation Criteria in Solid Tumors v1.1
- Adequate hematologic and end-organ function within 7 days prior to initiation of study treatment
- Documented virology status of hepatitis, as confirmed by screening tests for hepatitis B virus - (HBV) and hepatitis C virus (HCV)

- Negative HIV test at screening
- For women of childbearing potential: agreement to remain abstinent or use contraception and for men: agreement to remain abstinent or use contraception, and agreement to refrain from donating sperm

Stage 2

- ECOG Performance Status of 0, 1, or 2
- Ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity not related to atezolizumab or RO7247669 or loss of clinical benefit as determined by the investigator while receiving Stage 1 treatment
- Availability of a tumor specimen from a biopsy performed upon discontinuation of Stage 1 (if deemed clinically feasible)

Exclusion Criteria:

Stage 1

- Prior treatment with CD137 agonists or immune checkpoint inhibitors
- Treatment with investigational therapy within 28 days prior to initiation of study
- Treatment with locoregional therapy to liver within 28 days prior to initiation of study, or non-recovery from side effects of any such procedure
- Untreated or incompletely treated esophageal and/or gastric varices with bleeding or at high risk for bleeding
- Prior bleeding event due to esophageal and/or gastric varices within 6 months prior to initiation of study
- AEs from prior anti-cancer therapy that have not resolved to Grade <= 1 or better, with the exception of alopecia of any grade
- Inadequately controlled hypertension
- History of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease
- History of hemoptysis within 1 month prior to initiation of study
- Evidence of bleeding diathesis or significant coagulopathy
- Current or recent use of asprin (>325 mg/day) or treatment with clopidogrel, dipyramidole, ticlopidine, or cilostazol
- Current or recent use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose
- Core biopsy or other minor surgical procedure within 3 days prior to initiation of study
- History of abdominal or tracheoesophageal fistula, GI perforation, or intra-abdominal abscess, intestinal obstruction and/or clinical signs/symptoms of GI obstruction
- Evidence of abdominal free air not explained by paracentesis or recent surgery
- Serious, non-healing/dehiscing wound, active ulcer, or untreated bone fracture
- Grade >=2 proteinuria
- Metastatic disease involving major airways/blood vessels, or centrally located mediastinal tumor masses of large volume
- History of intra-abdominal inflammatory process
- Radiotherapy within 28 days or abdominal/pelvic radiotherapy within 60 days prior to initiation of study with the exception of palliative radiotherapy to bone lesions within 7 days prior to initiation of study
- Major surgery, open biopsy, or significant traumatic injury within 28 days prior to initiation of study; or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to initiation of study; or anticipation of need for major surgery during study or non-recovery from side effects of any such procedure
- Chronic daily treatment with NSAID
- Eligible only for control arm

Stage 1 and 2

- Fibrolamellar or sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
- History of hepatic encephalopathy
- Moderate or severe ascites
- HBV and HCV coinfection
- Symptomatic, untreated, or actively progressing CNS metastases
- History of leptomeningeal disease
- Uncontrolled tumor-related pain
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures
- Uncontrolled or symptomatic hypercalcemia
- Active or history of autoimmune disease or immune deficiency
- History of IPF, organizing pneumonia, drug-induced or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
- Active TB
- Significant CV disease within 3 months prior to initiation of study, unstable arrhythmia, or unstable angina
- Major surgery, other than for diagnosis, within 4 weeks prior to initiation of study, or anticipated major surgery during study
- History of malignancy other than HCC within 5 years prior to screening
- Severe infection within 4 weeks prior to initiation of study
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known allergy or hypersensitivity to any of the study drugs or any of their excipients Treatment with systemic immunostimulatory, immunosuppressive agents within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study
- Treatment with systemic immunosuppressive medication within 2 weeks prior to initiation of study
- Patients entering Stage 2: immunotherapy-related adverse events that have not resolved to Grade 1 or better or to baseline at time of consent