English Protocol Synopsis

Sequential or up-front triple treatment with durvalumab, tremelimumab and bevacizumab for non-resectable hepatocellular carcinoma (HCC) patients (MONTBLANC)

EU CT number	2024-511439-84-00
EudraCT number	2022-001201-48

Study site(s) and number of patients planned

This study will randomize approximately 83 patients, with no prior systemic therapy for hepatocellular carcinoma (HCC) and not eligible for locoregional therapy. A number of 10 study sites are planned to be involved.

Study duration	
Start of the trial	First initiation of first site (30 Mar 2023)
Estimated date of first patient enrolled	Q2 2023 (FPI: 12 Apr 2023)
Estimated recruitment period	24 months
Individual treatment duration	Up to 24 months
Follow-up duration	For a period of 24 months after randomization of last patient
Estimated date of last patient completed	Q1 2027
End of the study	LPLV, last visit within 24 months after randomization of last patient

Study design

This is a randomized, open-label, multi-center, international, Phase II study to assess the efficacy and safety of sequential or up-front triple treatment with durvalumab, tremelimumab and bevacizumab for non-resectable hepatocellular carcinoma.

Patients will be randomized in a 1:1 ratio combination therapy with durvalumab 1500 mg plus tremelimumab 300 mg x 1 dose followed by bevacizumab upon radiological progression or in the absence of objective response after the second staging (i.e., after 4 months since treatment initiation) (Arm A) or to combination therapy with durvalumab 1500 mg plus tremelimumab 300 mg x 1 dose followed by bevacizumab, which will be initiated on Cycle 2 (Arm B).

Patients will be stratified according to macrovascular invasion (yes versus no), and etiology of liver disease (viral etiologies versus others).

Objectives

Primary objective:	Outcome measure:
To assess the efficacy of Arm A and of Arm B vs. historical control	Objective response rate (ORR)

Secondary objective:	Outcome measure:
To assess the efficacy of Arm A and of Arm B	• Overall survival (OS) • Progression-free survival (PFS) • Time to progression (TTP) • Objective response rate acc. to BICR (ORR-BICR) • Duration of response (DOR) • Disease control rate (DCR) • Proportion of patients alive at 18 months (OS-18m) • Proportion of patients alive at 24 months (OS-24m) • Progression-free survival from escalation treatment (PFS-E) • PFS on next treatment • TTFS (time to failure of strategy)
To assess disease-related symptoms, impacts and health-related quality of life (HRQoL) in Arm A and in Arm B	• European Organisation for Research and Treatment of Cancer (EORTC) 30-item core quality of life questionnaire (QLQ-C30): Change compared to baseline, Time to deterioration in global health status/Quality of life and functioning scales • EORTC 18-item hepatocellular cancer health-related quality of life

Secondary objective:	Outcome measure:
	questionnaire (QLQ-HCC18): Change compared to baseline
To investigate the deterioration of liver function	• Time to deterioration of liver function, defined as time from randomization to worsening of CTCAE grade compared with baseline and persisting for ≥ 30 days for any of these parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, and international normalized ratio (INR)

Safety objective:	Outcome measure:
To assess the safety and tolerability profile across both treatment arms	Adverse events and laboratory findings.

Exploratory objectives:	Outcome measures:
To assess the efficacy of Arm A and of B using immune-related Response Evaluation Criteria in solid tumors (irRECIST) and modified Response EvaluationCriteria in Solid Tumors (mRECIST) for HCC	PFS, TTP, ORR, DCR, DCR-16w, DCR-24w and DOR according to irRECIST and mRECIST and by Blinded Independent Central Review, if performed
To investigate the relationship between the progressive changes in alpha-fetoprotein (AFP) levels and efficacy parameters	Association of AFP expression level with: OS, PFS, TTP, ORR, DOR, DCR, DCR-16w and DCR-24w according to RECIST 1.1 using Investigator assessments
To investigate the efficacy of Arm A and of Arm B by baseline gene expression.	Association of interferon gamma and immune-related gene expression, as measured by messenger RNA (mRNA) levels from baseline tumor biopsies and blood, with OS, PFS, TTP, ORR, DOR, DCR, DCR-16w and DCR-24w according to RECIST 1.1 using Investigator assessments

Exploratory objectives:	Outcome measures:
To investigate the efficacy of treatment in both treatment arms by biomarkers that may correlate with drug activity or identify patients likely to respond to treatment.	Association of intratumoral immune cell numbers (specifically cluster of differentiation (CD)8+ T-cells), circulating tumor deoxyribonucleic acid (ctDNA), and/or tumor mutations with • OS • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w and DOR, according to RECIST 1.1 using Investigator assessments
To investigate the efficacy of both treatment arms in patients who are at low risk of early mortality based on baseline characteristics	• OS
To assess the efficacy of both treatment arms in the overall population and in the population defined by programmed cell death ligand 1 (PD-L1) expression	• OS • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w and DOR, according to RECIST 1.1 using Investigator assessments
To assess physician-reported patient outcome in ECOG performance status of Arm A and of Arm B	• ECOG
To assess the predictive value of imaging baseline features (arterial hypervascularization, atypical contrast dynamics (MRI), diffusion restrictions (MRI), infiltrative pattern (as defined by peritumoral hypointensity on hepatobiliary imaging (MRI) and by peritumoral hypervascularization), T2 hyperintensity (MRI), tumor uptake of hepatobiliary contrast media in hepatobiliary phase (MRI), tumor size, presence of ascites	• OS • PFS, TTP, ORR, DCR, DCR-16w, DCR-24w and DOR

Target patient population

The study population includes patients 18 years of age or older with advanced HCC, Barcelona Clinic Liver Cancer Stage B (not eligible for locoregional therapy) or stage C, and Child-Pugh A classification liver disease. Patients must not have received any prior systemic therapy for

HCC. Each patient should meet all the inclusion criteria and none of the exclusion criteria for this study.

Escalation of treatment

Patients who received durvalumab plus tremelimumab in Arm A and subsequently have evidence of PD, or no objective response after the second staging, will be treated with tremelimumab once and start additional treatment with bevacizumab, provided they meet eligibility criteria as described in Section 7.5 of the protocol.

Rechallenge option with tremelimumab

Patients who received durvalumab plus tremelimumab and are benefiting from study drug(s) in the Investigator' s opinion, and subsequently have evidence of PD with or without confirmation according to RECIST 1.l during the bevacizumab-containing portion of their regimen can be rechallenged with tremelimumab, provided they meet eligibility criteria for rechallenge, as described in Section 7.5 of the protocol.

Duration of treatment

Patients in all treatment arms should, wherever possible, continue to receive their initially assigned treatment to disease progression.

At the Investigator's discretion, patients in all treatment arms who are undergoing the bevacizumab-containing portion of their regime may continue receiving treatment until progressive disease (PD) by RECIST 1.1 is confirmed on a follow-up scan as per Confirmation of Radiological Progression criteria.

Patients in both arms with confirmed PD who, in the Investigator's opinion, continue to receive benefit from their assigned treatment and meet the criteria for treatment in the setting of PD may continue to receive their assigned treatment. However, patients who develop progression in target lesions (TLs) after a clear response to therapy as defined by RECIST 1.1 will not be permitted to continue therapy.

Tumor assessments

Tumor assessments, based on RECIST 1.1, will be performed every 8 weeks (±1 week) for the first 48 weeks relative to the date of randomization and then every 12 weeks (±1 week) thereafter until RECIST 1.1-defined radiological progression is confirmed by a follow-up scan, if clinically feasible, as per Confirmation of Radiological Progression criteria. Patients who continue treatment beyond radiological progression should continue with tumor assessments on their regular imaging schedule for the duration of their treatment.

Post study treatment

Patients who continue to receive benefit from their assigned treatment may continue the treatment in the follow-up outside the study.

Investigational product, dosage, and mode of administration

Arm A. Durvalumab 1500 mg plus tremelimumab 300 mg x 1 dose followed by addition of bevacizumab 15mg/kg upon detection of radiological progression or in the absence of objective response after the second staging (i.e. after 4 months since treatment initiation). Durvalumab 1500 mg plus tremelimumab 300 mg x l dose will be administered on cycle 1 followed by durvalumab 1500 mg Q4W starting 4 weeks after the first and final infusion of the combination therapy until PD or in the absence of objective response at the second staging (i.e. after 4 months since treatment initiation), unacceptable toxicity, or any other discontinuation criteria are met.

In case of PD or in the absence of objective response after the second staging, another tremelimumab 300 mg x l dose will be administered plus durvalumab 1500 mg and bevacizumab 15mg/kg combination. Additional one-shot tremelimumab as well as bevacizumab treatment will be initiated as soon as possible after detection of progressive disease or the absence of objective response, on a day which may or may not coincide with the day of the next scheduled administration of durvalumab. Durvalumab 1500 mg Q4W will be continued with the addition of bevacizumab 15mg/kg Q3W.

Arm B. Durvalumab 1500 mg plus tremelimumab 300 mg x 1 dose followed by bevacizumab 15mg/kg. Durvalumab 1500 mg plus tremelimumab 300 mg x l dose will be administered on cycle 1 followed by durvalumab 1500 mg Q4W and bevacizumab 15mg/kg Q3W starting 4 weeks after the first and final infusion of durvalumab plus tremelimumab until confirmed PD, unacceptable toxicity, or any discontinuation criteria are met.

Statistical methods

Efficacy analyses

The primary endpoint of this study is ORR, which will be determined with respect to the best response throughout the study-specific treatment, which includes the bevacizumab-containing portion of the treatment in arm A. The secondary endpoints are OS, PFS, TTP, ORR-BICR, DOR, DCR, OS-18m, OS-24m, PFS-E, PFS on next treatment, and TTFS. All tumor-assessment-related endpoints will be analyzed using Investigator assessments according to RECIST 1.1.

Efficacy data will be summarized and analyzed on an intent-to-treat (ITT) basis, and the treatment arms will be analyzed on the basis of randomized treatment, regardless of the treatment actually received. Patients who are randomized but do not subsequently go on to receive study drug(s) are included in the ITT population.

Sample size estimate

The study is sized to characterize the ORR benefit of Arm A and Arm B separately vs. historical controls from the HIMALAYA trial treated with combined durvalumab and tremelimumab (STRIDE regimen). The primary endpoint is ORR. It is planned to include n=83 patients in this study. Due to 15% non-informative dropouts a total of n=70 patients (n=35 in each arm) will be evaluable. We assume an ORR of 20.1% for the historic control and using a two-sided significance level of 0.05 and Power of at least 80%. With n=35 evaluable patients it is possible to show as alternative hypothesis an ORR of 42.8% for patients undergoing up-front or escalated triple treatment.

Safety analysis

Safety data will be summarized descriptively and will not be formally analyzed.

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study, to ensure the integrity of the study. The first IDMC safety review will occur once 5 and 10 patients respectively will have completed 2 treatment cycles with durvalumab / tremelimumab / bevacizumab.

Once the two safety analyses have been accomplished, the IDMC will conduct regular meetings twice a year (starting six months after second safety analysis) for the duration of the study until the last IMPs are administered.

Further meetings may be scheduled at any time at the request of a member of the IDMC and/or the sponsor.