

Sequential or upfront triple combination with durvalumab, tremelimumab, and bevacizumab for patients with unresectable hepatocellular carcinoma: the MONTBLANC trial protocol (AIO-HEP-0325/ass)

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Abstract

Background: Immune checkpoint inhibitor (ICI)-based combination therapy has transformed the therapeutic landscape of advanced hepatocellular carcinoma (aHCC). However, durable clinical benefit remains limited to a subset of patients, highlighting the need for approaches that enhance efficacy.

Objectives: The MONTBLANC study presents a novel investigational strategy utilizing triple immunotherapy through the combination of the anti-programmed cell death ligand 1 antibody durvalumab, the anti-cytotoxic T-lymphocyte-associated antigen-4 tremelimumab, and the anti-vascular endothelial growth factor bevacizumab in patients with aHCC.

Methods and analysis: This randomized, open-label, phase II clinical trial examines two distinct therapeutic regimens through parallel study arms: upfront triple-agent administration or doublet therapy with durvalumab and tremelimumab, followed by the addition of bevacizumab upon disease progression or lack of objective radiological response. The primary endpoint is the overall response rate. Secondary endpoints include overall survival, progression-free survival, safety, and patient-reported outcomes.

Ethics: The ethics review boards of all participating sites have approved the study protocol. The trial will be performed in accordance with the Declaration of Helsinki, Good Clinical Practice Standards, and the applicable laws and regulations. All patients must provide written informed consent.

Discussion: The MONTBLANC study aims at guiding the design of future trials in aHCC by assessing efficacy signals of upfront triple or response-adapted treatment escalation with durvalumab, tremelimumab, and bevacizumab.

Trial registration: The MONTBLANC clinical trial is registered at the US National Institutes of Health (ClinicalTrials.gov, NCT05844046) and the European Union Drug Regulating Authorities Clinical Trials Database (clinicaltrialsregister.eu, 2022-001201-48).

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Plain Language Summary

MONTBLANC: durvalumab, tremelimumab, and bevacizumab for hepatocellular carcinoma

Immunotherapy has improved outcomes for patients with hepatocellular carcinoma (HCC), a common form of liver cancer. However, current treatments don't work for every patient, and new strategies are needed to improve the efficacy. The MONTBLANC study is testing a new combination of three immunotherapy drugs, durvalumab, tremelimumab, and bevacizumab, in patients with advanced HCC.

Keywords: bevacizumab, CTLA-4, durvalumab, hepatocellular carcinoma, immunotherapy, PD-L1, tremelimumab, VEGF

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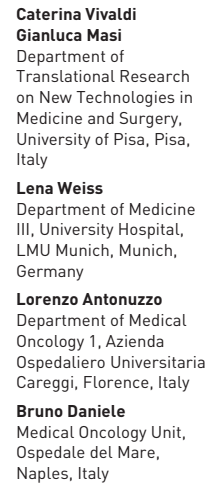
Introduction

Hepatocellular carcinoma (HCC) represents a critical global health challenge, ranking as the third leading cause of cancer mortality.^{1–3} The disease's epidemiology reveals marked geographical variations, primarily driven by differential distribution of risk factors such as hepatitis B (HBV), hepatitis C (HCV), and alcohol consumption.⁴ Recent epidemiological data show a steady increase in cases across North America, Latin America, and Europe,^{5–8} likely attributed to rising rates of alcoholic and metabolic dysfunction-associated steatotic liver disease.^{9–11}

The therapeutic approach to HCC is primarily determined by the disease stage and liver function, as summarized in current guidelines.^{12–14} Potentially curative interventions like surgical resection, liver transplantation, and radiofrequency ablation are viable only for approximately 30% of patients presenting with early-stage disease and preserved hepatic function.^{15,16} For the majority of patients presenting at advanced stages, systemic treatment is the primary therapeutic approach. Sorafenib emerged as the first effective systemic therapy for HCC two decades ago.^{17,18} It remained the first-line standard of care for advanced HCC (aHCC), until the advent of immune checkpoint inhibitor (ICI)-based therapeutic regimens.^{19–21} These advances in immunotherapy leveraged the complex immunobiology of HCC to enhance anti-tumor immunity and improve treatment efficacy.

Immune checkpoint mechanisms in the liver and immunotherapeutic options

The liver possesses a unique immunobiology, characterized by multiple regulatory mechanisms that promote an immunosuppressive niche. Under normal conditions, the liver is inherently tolerogenic to environmental antigens and toxins, preventing inappropriate immune responses to pathogens derived from the gut.²² Clinical and nonclinical data in HCC have revealed an increased presence of immunosuppressive cell populations, such as regulatory T-cells (Tregs) and myeloid-derived suppressor cells, alongside the upregulation of inhibitory signaling molecules, including the immune checkpoints cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1).^{22–24} In addition, HBV and HCV infections have been linked to a higher abundance of Tregs and increased expression of programmed cell death ligand 1 (PD-L1) and PD-1, suggesting a potential role for this pathway in the development of HCC.^{6,22,25,26} Given the immunosuppressive microenvironment of the liver, immune-based therapeutic approaches, especially ICIs, were investigated in liver cancer. The advent of ICI-based immunotherapy has marked a significant advancement in HCC and other malignancies. This approach involves monoclonal antibodies that enhance the antitumor immune response by targeting and inhibiting immune checkpoint pathways, including the PD-1/PD-L1 and CTLA-4 signaling axis.^{27,28}



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Therapeutic strategies targeting these immune checkpoint pathways have had a significant impact across multiple malignancies.³⁴ Monoclonal antibodies such as tremelimumab or ipilimumab (anti-CTLA-4), nivolumab and pembrolizumab (anti-PD-1), and durvalumab (anti-PD-L1) have revolutionized cancer treatment. For HCC, the combined use of the anti-PD-L1 antibody atezolizumab and the vascular endothelial growth factor (VEGF) inhibitor bevacizumab marked a therapeutic breakthrough,³⁵ supporting the concept that immunotherapy efficacy can be enhanced through combining agents targeting separate steps during immune resistance mechanisms (Figure 1). With a median overall survival (mOS) of 19.2 months, this regimen established itself as the new standard of care in HCC treatment.³⁵ By targeting VEGF in conjunction with the PD-1/PD-L1 pathway, this combination strategy aims to mitigate immunosuppressive

mechanisms and enhance immune cell functionality (Figure 1).³⁵ Another key development in the ICI-based systemic treatment of HCC is represented by the positive results of the HIMALAYA trial,³⁶ which explored a dual immune checkpoint blockade strategy. The combination of the anti-PD-L1 antibody durvalumab and the anti-CTLA-4 antibody tremelimumab demonstrated a superior mOS of 16.4 months, compared to 13.8 months with sorafenib therapy.

The pivotal doublet regimens of anti-PD-L1 antibodies with either anti-VEGF or anti-CTLA-4 agents demonstrated that ICI-based combinations have the potential to substantially improve survival in HCC patients. However, responses occur only in a smaller subset of 20%–30% of patients,^{37–40} and outcomes following first-line regimens are poor.^{41,42} Consequently, new strategies are needed to improve patients' outcomes.⁴³ In this regard, triple-combination strategies represent a promising avenue that may substantially advance the therapeutic landscape for HCC patients.

Triplet therapies for HCC

Efforts to extend the benefits of double ICI-based treatment to a triple combination of immunologically active agents require careful consideration of three factors: agent selection, sequencing of administration, and escalation strategy.

Anti-PD-1/PD-L1, anti-CTLA-4, and anti-angiogenic agents (anti-VEGF) demonstrated efficacy in phase III trials of aHCC and were approved and established as standard of care in first-line treatment.^{35,36} Novel ICI targeting alternative pathways, such as T-cell immunoreceptor with Ig and ITIM domains (TIGIT), showed promising results in early phase trials,⁴⁴ but efficacy could not be confirmed in a randomized, phase III trial.⁴⁵ Combinations based on ICI plus broad-spectrum tyrosine kinase inhibitors have so far provided disappointing results.^{46–48} Based on current knowledge, a triple combination therapy using agents that are effective in combination treatment and have distinct, non-overlapping modes of action represents a logical choice.

Regarding the sequence of administration, two strategic approaches are proposed. The first involves synchronous upfront administration of multiple agents, aiming to elicit robust tumor responses while reducing the risk of treatment-resistant clone emergence. This strategy holds

particular relevance, as HCC progression occurs predominantly intrahepatic, which can irreversibly impair liver function in the context of underlying hepatic disease.^{38,49} However, this approach may increase the risk of toxicity. This is a crucial consideration, given the limited tolerance of HCC patients to intensive therapeutic regimens. In addition, severe immune-mediated adverse events (AEs) could lead to permanent discontinuation of immunotherapy in a significant proportion of patients receiving upfront triple therapy. An alternative strategy involves a sequential escalation approach, starting with a doublet regimen and adding a third agent upon radiological progression or failure to elicit an objective radiological response. This method delays triple therapy exposure until progression-associated risks surpass those linked to the increased risk of adverse reactions. This approach may reduce unnecessary exposure to additional agents and their cumulative toxicity in patients responding to doublet therapy, which is particularly relevant given the possibility of long-term survival benefits in these patients.⁵⁰

The third aspect regards the escalation strategy: the traditional approach requires transitioning to a subsequent line of treatment upon detecting radiological progression. However, while no reliable biomarker can predict response in these patients, data from earlier studies in HCC have indicated that early radiological response identifies a patient population with exceptionally long survival.^{51–53} Based on these factors, the MONTBLANC trial implements an alternative design where escalation from an initial regimen of two combined agents to a triple-therapy regimen is prompted by “failure to respond” within a timeframe determined by the estimated time to achieve objective radiological response for the initial doublet.

In summary, the MONTBLANC clinical trial aims to investigate the efficacy and best sequence of anti-PD-L1, anti-CTLA-4, and anti-VEGF for aHCC patients. It compares two approaches: triple therapy or early escalation, and implements the novel strategy of escalating treatment in the absence of an objective radiological response.

Methods and study design

The MONTBLANC clinical trial is a randomized, open-label, multi-center, international phase II study (NCT05844046) to assess the efficacy and safety of either sequential or upfront

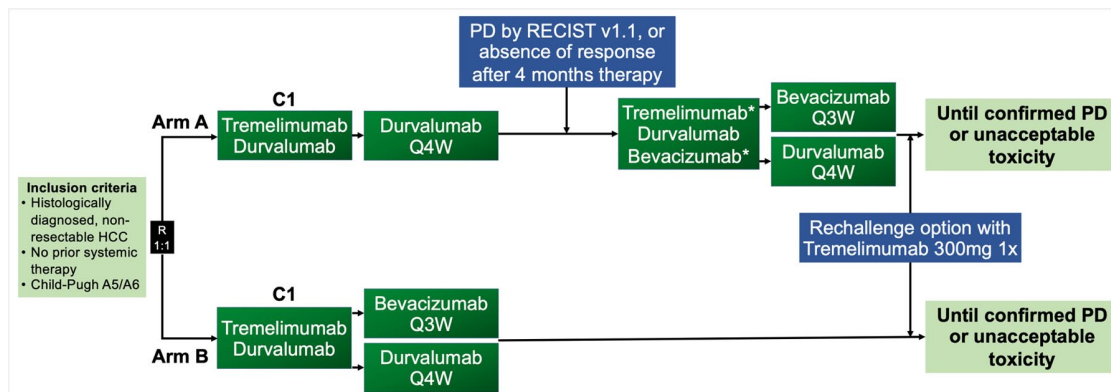


Figure 2. MONTBLANC trial study design. This figure illustrates the treatment timeline for Arms A and B of the MONTBLANC trial. In Arm A, tremelimumab and durvalumab are administered together once, followed by durvalumab Q4W. In case of PD as per RECIST v1.1 or absence of radiological response after 4 months, a single dose of tremelimumab is given along with durvalumab Q4W, and bevacizumab is added Q3W. In Arm B, treatment begins with a single dose of tremelimumab and durvalumab Q4W. At the second cycle of durvalumab, bevacizumab is added and continued Q3W. Both arms include a rechallenge option with tremelimumab if the criteria are met. Treatment ends upon confirmation of PD by RECIST v1.1 or unacceptable toxicity.

*Upon radiological evidence of PD or absence of objective response after the second staging (i.e., after 4 months since treatment initiation), durvalumab will be continued, plus an additional tremelimumab 300 mg 1× dose and bevacizumab 15 mg/kg will be initiated as soon as possible, on a day which may or may not coincide with the day of next scheduled durvalumab.

C1, Cycle 1; HCC, hepatocellular carcinoma; PD, progressive disease; Q3W, every 3 weeks; Q4W, every 4 weeks; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

triple treatment with durvalumab, tremelimumab, and bevacizumab for patients with non-resectable HCC.

Study design

A total of 83 patients with aHCC will be randomized in a 1:1 ratio to two treatment arms. The study population will include patients with Barcelona Clinic Liver Cancer (BCLC) stage B, who are not candidates for locoregional therapy, and with BCLC C. All participants must have Child-Pugh A liver function and no previous exposure to systemic therapy. Randomization will be stratified according to etiology (viral vs non-viral) and the presence of macrovascular invasion. Patients will be randomized independently within each stratum using a web-based tool, based on a computer-generated randomization list developed by the clinical research organization, which will remain uninvolved in the recruitment process.

In both arms, patients will receive combination therapy with durvalumab 1500 mg plus tremelimumab 300 mg as a single dose (Figure 2). In Arm B, durvalumab 1500 mg plus single-shot tremelimumab 300 mg will be administered on cycle 1, after 4 weeks, followed by treatment with

both durvalumab 1500 mg every 4 weeks (Q4W) and bevacizumab 15 mg/kg Q3W. Treatment will be continued until PD, unacceptable toxicity, or any discontinuation criteria are met. The administration of bevacizumab differs in Arm A. Here, durvalumab 1500 mg plus single-shot tremelimumab 300 mg will be administered on cycle 1, followed by monotherapy with durvalumab 1500 mg Q4W. Upon detection of progressive disease (PD) or in the absence of objective response after the second staging, another single shot of tremelimumab 300 mg will be administered, and durvalumab 1500 mg Q4W will be continued with the addition of bevacizumab 15 mg/kg Q3W. The 4-month landmark at which lack of response triggers treatment escalation in Arm A was pre-specified from response-kinetic data in the HIMALAYA trial and confirmed by subsequent analyses showing that the median time to response with STRIDE was ~2 months with a 95% confidence interval of 2–4 months.^{36,50} Since the Response Evaluation Criteria in Solid Tumors (RECIST) assessments are scheduled every 8 weeks, this 4-month landmark aligns with two standard scans.

In case of PD in the bevacizumab-containing part of the study, rechallenge with tremelimumab

300mg once may be considered in patients who meet eligibility criteria for rechallenge. These criteria include the absence of (1) significant, unacceptable toxicity, (2) signs or symptoms indicating clinically significant disease progression with decline of Eastern Cooperative Oncology Group performance status (ECOG PS) >1, and (3) rapid disease progression requiring urgent alternative interventions.

Patients who experience PD after tremelimumab rechallenge may be eligible for treatment beyond progression, provided there was evidence of an objective response in at least one prior staging assessment or lack of progression for at least 6 months. However, progression should not have occurred after a confirmed response in the target lesions. Patients who discontinue therapy due to toxicity, symptomatic deterioration, or initiation of subsequent anticancer treatments will be followed until confirmed disease progression and for survival outcomes.

Key eligibility criteria

Key inclusion and exclusion criteria are summarized in Table 1. Briefly, eligible patients must be 18 years or older with a confirmed diagnosis of HCC that is unresectable and ineligible for locoregional therapy. At least one measurable lesion on computed tomography or magnetic resonance imaging per RECIST version 1.1 is required. Prior locoregional therapy is permitted but must have been completed at least 28 days before the baseline scan. Patients must not have received prior systemic therapy for HCC. Eligible patients must have preserved liver function, defined as Child-Pugh class A, as well as adequate bone marrow and renal function. An ECOG PS of 0 or 1 is required. Excluded are patients with decompensated liver function, such as patients with ascites requiring non-pharmacologic intervention or with hepatic encephalopathy within the past 12 months. Also excluded are patients with active or prior autoimmune or inflammatory disorders in the last 5 years, or those who have received systemic immunosuppressive medications within 14 days prior to the first dose. Patients with the following conditions are also not eligible: Major gastrointestinal bleeding within 4 weeks before randomization, untreated esophageal varices with high bleeding risk, recent surgery, or traumatic injury. A screening gastroscopy is mandatory to assess esophageal varices.

Objectives

The primary endpoint is objective response rate (ORR) and will be assessed as the proportion of patients achieving a complete or partial response per RECIST v1.1, based on each patient's best overall response across the treatment sequence, that is, during durvalumab + tremelimumab and, where applicable, after bevacizumab escalation (Table 2). The choice of ORR as the primary endpoint for this study reflected the evidence available from the most mature OS-by-response data in HCC derived from IMbrave150 (atezolizumab + bevacizumab).⁵¹ Emergent regimen-specific data provided additional rationale for this endpoint choice, as HIMALAYA 5-year analysis demonstrated a graded association between radiographic benefit and long-term OS.⁵⁰ Specifically, the HIMALAYA 5-year update reported OS stratified by multiple response measures: at 60 months, OS was 19.6% overall, 28.7% among patients achieving disease control (CR/PR/SD), and 50.7% among those with >25% tumor shrinkage, demonstrating a graded association between response depth and long-term survival.

Secondary efficacy endpoints include progression-free survival (PFS), OS, time to progression, duration of response, disease control rate, proportion of patients alive at 18 months and 24 months, PFS from escalation treatment, PFS on next treatment, and time to failure of strategy (Table 2). The safety objectives of the MONTBLANC trial are to comprehensively assess the safety and tolerability profile across both treatment arms. Safety endpoints are AEs and AEs of special interest (AESI), including immune-related AEs (irAEs). Other endpoints include patient-reported outcomes (PROs) to assess disease-related symptoms and health-related quality of life, time to deterioration of liver function, and biomarker analyses in correlation with clinical outcomes.

Evaluations

Tumor assessments will be conducted according to RECIST 1.1 criteria every 8 weeks for the first 48 weeks following randomization, and subsequently every 12 weeks until confirmed radiological progression. Patients who continue treatment beyond radiological progression will maintain their regular imaging schedule throughout treatment duration. For patients in Arm A requiring escalation with bevacizumab 15 mg/kg due to

Table 1. Key eligibility criteria for the MONTBLANC trial.

Inclusion criteria

- Patient signed informed consent and is willing to comply with the protocol for the duration of the study
- Age ≥ 18 years
- HCC with confirmed diagnosis
- Unresectable HCC, ineligible for locoregional therapy; BCLC stage B (not eligible for locoregional therapy) or stage C
- Patient must not have received prior systemic therapy for HCC
- At least 1 measurable lesion at baseline (CT or MRI), suitable for repeated assessment per RECIST v1.1. Lesions that have progressed after locoregional therapy may be selected if they meet these criteria
- ECOG performance status of 0 or 1
- Child-Pugh class A
- Adequate bone marrow function (absolute neutrophil count $\geq 1.5 \times 10^9/L$, platelet count $\geq 75 \times 10^9/L$, hemoglobin $\geq 90 g/L$)
- Adequate liver function (including ASAT, ALAT, and AP $\leq 5 \times ULN$, total bilirubin $\leq 2 \times ULN$, INR ≤ 1.6 , albumin $\geq 28 g/L$)
- Adequate kidney function (creatinine clearance $\geq 50 mL/min$ calculated using Cockcroft–Gault formula, urine dipstick for proteinuria $< 2+$)
- If active HBV infection: antiviral therapy to ensure adequate viral suppression (HBV DNA $\leq 2000 IU/mL$) prior to enrollment
- Life expectancy of at least 12 weeks

Exclusion criteria

- Concurrent chemotherapy, study drug, biologic, or hormonal therapy for cancer treatment. Hormonal therapy for non-cancer-related disease is acceptable
- Major surgical procedure or traumatic injury within 28 days prior to the first dose
- Anticipation of major surgery during the study or non-recovery from side effects; local surgery for isolated lesions for palliative intent is acceptable
- History of allogeneic organ transplantation (e.g., liver transplant)
- Hepatic encephalopathy within the past 12 months or requirement for medications to prevent or control encephalopathy
- Clinically meaningful ascites requiring non-pharmacologic intervention (e.g., paracentesis) within 6 months, except for stable diuretic use for ≥ 2 months
- Main portal vein thrombosis (Vp4 thrombosis in the main trunk of the portal vein, with or without blood flow) on baseline imaging
- Symptomatic or uncontrolled hypertension (diastolic $> 90 mmHg$ or systolic $> 140 mmHg$)
- Active or prior autoimmune/inflammatory disorders (e.g., lupus, rheumatoid arthritis, etc.) in the last 5 years, unless discussed with the Study Physician. Exceptions include vitiligo, alopecia, stable hypothyroidism on hormone replacement, chronic skin conditions that do not require systemic therapy, and celiac disease controlled by diet
- Patients co-infected with HBV and HCV, or co-infected with HBV and HDV
- History of another primary malignancy (except for; malignancy treated curatively ≥ 5 years ago with low recurrence risk, prostate cancer stage $\leq T2cN0M0$ without progression, treated non-melanoma skin cancer, or lentigo maligna, treated carcinoma in situ)
- Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
- History of active primary immunodeficiency
- Known to have tested positive for HIV or active tuberculosis infection
- Use of immunosuppressive medication within 14 days before the first dose, except intranasal/inhaled/topical steroids or systemic prednisone $\leq 10 mg/day$
- Major gastrointestinal bleeding within 4 weeks prior to randomization
- Patients with untreated or incompletely treated varices with bleeding or high risk for bleeding
- Evidence of bleeding diathesis or significant coagulopathy
- Current/recent (within 10 days of randomization) use of acetylsalicylic acid (325 mg/day) or use of dipyridamole, ticlopidine, clopidogrel, and cilostazol
- Use of full-dose anticoagulants within 10 days prior to randomization
- Pregnant or breastfeeding patients, or patients of reproductive potential who are not willing to employ effective birth control

Clinical trial registration: NCT05844046 (ClinicalTrials.gov).

ALAT, alanine aminotransferase; AP, alkaline phosphatase; ASAT, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer staging system; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; INR, international normalized ratio; RECIST, Response Evaluation Criteria in Solid Tumors; ULN, upper limit of normal.

Table 2. MONTBLANC trial endpoints.

Primary endpoint
• ORR
Secondary endpoints
• OS, PFS, TTP, ORR-BICR, DOR, DCR, OS-18m, OS-24m, PFS-E, PFS on next treatment, TTFS • Patient-reported outcomes, disease-related symptoms, impacts, and health-related quality of life • Time to deterioration of liver function • Safety: AEs, and AEs of special interest (including irAEs)
Exploratory endpoints
• Efficacy (ORR, PFS, TTP, DCR, DCR-16w, DCR-24w, DOR) as determined by central review according to irRECIST and mRECIST • Biomarker analyses and their correlation with clinical outcomes.
Clinical trial registration: NCT05844046 (ClinicalTrials.gov). AE, adverse events; DCR, disease control rate; DCR-16w, disease control rate at 16 weeks; DCR-24w, disease control rate at 24 weeks; DOR, duration of response; irAEs, immune-related adverse events; ORR, objective response rate; ORR-BICR, objective response rate by blinded independent central review; OS, overall survival; OS-18m, overall survival at 18 months; OS-24m, overall survival at 24 months; PFS, progression-free survival; PFS-E, progression-free survival from escalation treatment; PFS on next treatment, progression-free survival on next line of treatment; RECIST, Response Evaluation Criteria in Solid Tumors; TTFS, time to failure of strategy; TTP, time to progression.

disease progression or absence of objective response at the second staging assessment, a new baseline tumor evaluation will be performed within 28 days before bevacizumab administration. This reassessment may redefine target and non-target lesions, including previously identified new lesions, as per RECIST 1.1 guidelines. Follow-up scans will adhere to the established schedule of every 8 weeks for 48 weeks, followed by every 12 weeks until progression is confirmed. Safety and tolerability will be assessed in terms of AEs (including SAEs), which will be graded according to the Common Terminology Criteria for Adverse Events Version 5.0 classification criteria and documented in the eCRF accordingly. Given that irAEs are a critical concern in ICI-based regimens, potential autoimmune toxicities are considered to be AESI. PROs are assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 and QLQ-HCC18 questionnaires at baseline, every 8 weeks for 48 weeks, and after that at 12-week intervals until the final visit. Translational analyses will be conducted to identify predictive biomarkers through their correlation with clinical outcomes.

Safety

The triple treatment combination of durvalumab, tremelimumab, and bevacizumab is investigated in analogy to several other trials of ICI-based

triplet regimens.^{54–57} The favorable toxicity profiles of the dual combinations durvalumab + tremelimumab,³⁶ durvalumab + bevacizumab,⁵⁸ and atezolizumab + bevacizumab^{55,59,60} suggest that these agents are tolerated also as a triple combination. A relevant example is represented by cohort 6 of the Checkmate 040 trial, which evaluated combined CTLA-4/PD-1-inhibition with ipilimumab/nivolumab and the tyrosine kinase inhibitor cabozantinib, showing a safety profile consistent with those established for the individual drugs in patients with HCC.⁵⁶ A second phase II/III trial with combined PD-L1-/VEGF-/CTLA-4-inhibition using atezolizumab, bevacizumab, and ipilimumab in HCC showed a manageable safety profile.⁵⁷ More recently, the combination of durvalumab, tremelimumab, and bevacizumab in patients with advanced liver cancer (21 biliary tract cancer patients, 6 HCC patients) reported no unexpected toxicities in a phase II study.⁵⁵ Based on the available data, the toxicity profile of combined PD-L1-/VEGF-/CTLA-4-inhibition in the MONTBLANC trial is expected to be manageable.

Two pre-specified interim safety analyses will be conducted per protocol after 5 and 10 patients, respectively, have completed two cycles of durvalumab, tremelimumab, and bevacizumab. These interim safety analyses will be reviewed by an Independent Data Monitoring Committee

(IDMC), which will provide recommendations on whether the study should proceed as planned or be modified/terminated. The study may be stopped if, in the judgment of the Sponsor or the IDMC, patients are placed at undue risk because of clinically significant findings.

Statistics

The primary objective is to evaluate the treatment efficacy of both arms separately against historical controls, with ORR per RECIST 1.1 (investigator-assessed) as the primary endpoint. The study is sized to characterize the ORR benefit of Arm A and Arm B versus historical controls from the HIMALAYA trial. Investigator-assessed ORR was selected as the primary endpoint to ensure direct comparability with the HIMALAYA trial, which also relied on investigator assessment according to RECIST v1.1. A total of 83 patients will be enrolled in this phase II trial, accounting for an anticipated 15% non-informative dropout rate, to yield 70 evaluable patients (35 per arm). The sample size calculation assumes a historical control ORR of 20.1%, employing a two-sided significance level of 0.05 and power of at least 80%. With 35 evaluable patients per arm, the study can detect an alternative hypothesis ORR of 42.8% for patients receiving either upfront or escalated triple therapy. The expected incremental response after adding bevacizumab is calculated by adding early responders on durvalumab, tremelimumab (~20%), to the fraction of non-responders who convert to response after bevacizumab addition, assuming a probability of conversion equal to the response rate under atezolizumab and bevacizumab. According to the sample size calculation, the primary endpoint ORR will be analyzed with an exact binomial test. ORR by blinded independent central review is a pre-specified secondary endpoint. Safety analyses will follow a descriptive approach. Data will be summarized by treatment arm in the safety population, consisting of all patients who received at least one dose of the study drug.

Ethics and guidelines

The ethics review boards of all participating sites have approved the study protocol (Supplemental Table 1). The trial will be performed in accordance with the Declaration of Helsinki, Good Clinical Practice Standards, and the applicable laws and regulations. All patients have to provide written informed consent. Reporting of the

MONTBLANC trial results will adhere to the CONSORT guidelines.⁶¹ This protocol manuscript was prepared in accordance with the SPIRIT guidelines,⁶² as far as applicable to a trial protocol publication. A completed SPIRIT checklist is provided as Supplemental Material.

Discussion

The combination therapies of durvalumab/tremelimumab and atezolizumab/bevacizumab have demonstrated the potential of ICI-based treatments to significantly improve survival rates in patients with HCC. However, the proportion of patients benefiting from these regimens remains limited. In this context, triple-combination strategies offer a promising avenue for advancing the therapeutic landscape of HCC. The MONTBLANC clinical trial is a randomized, open-label, multi-center, international phase II study (NCT05844046) designed to evaluate the efficacy and safety of either sequential or upfront triple therapy with durvalumab, tremelimumab, and bevacizumab in patients with non-resectable HCC. This trial is predicated on the assumption, supported by a consistent and growing body of data, that links treatment response to clinical benefit, an approach underlying the upfront use of three agents in Arm B. An alternative strategy, explored in Arm A, involves escalating treatment only if an early response to a doublet is not observed. This approach examines a less intensive alternative to immediate triplet therapy, as bevacizumab exposure is reserved for patients who do not demonstrate early tumor shrinkage, thereby potentially reducing unnecessary drug exposure for those who respond initially. The primary objective is ORR.

Enrollment in the MONTBLANC trial started in April 2023 and is ongoing. Evaluating the safety and efficacy signals of these two strategies will inform future trial designs by clarifying the relative impact of added toxicity and increased response in the context of treatment escalation for unresectable HCC.

Declarations

Ethics approval and consent to participate

The ethics review boards of all participating sites have approved the study protocol. The trial will be performed in accordance with the Declaration of Helsinki, Good Clinical Practice Standards, and the applicable laws and regulations. All patients

have to provide informed consent before any study-related procedures are conducted.

Consent for publication

Not applicable.

Author contributions

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Competing interests

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Availability of data and materials

The sponsor of the MONTBLANC trial encourages additional scientific analyses based on the

data collected. External data sharing requests will be considered for additional topics not already pursued by the investigators. Researchers can submit a request for individual participant data with a research proposal and a data-sharing agreement to the sponsor for review. All of the anonymized individual participant data collected during the trial can be shared. The study protocol, statistical analysis plan, and informed consent form will also be made accessible.

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Supplemental material

Supplemental material for this article is available online.

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