A PHASE III, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY OF ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY) PLUS BEVACIZUMAB VERSUS ACTIVE SURVEILLANCE AS ADJUVANT THERAPY IN PATIENTS WITH HEPATOCELLULAR CARCINOMA AT HIGH RISK OF RECURRENCE AFTER SURGICAL RESECTION OR ABLATION

Published: 08-01-2020
Last updated: 21-09-2024

This study has been transitioned to CTIS with ID 2023-504303-86-00 check the CTIS register for the current data. Primary objective:To evaluate the efficacy of atezolizumab plus bevacizumab compared with active surveillance on the basis of recurrence...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON54966

Source
ToetsingOnline

Brief title
WO41535 IMbrave050

Condition

- Other condition

Synonym
hepatocellular carcinoma; liver cancer

Health condition

carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland NL
Source(s) of monetary or material Support: F. Hoffman-La Roche

Intervention

Keyword: ATEZOLIZUMAB (ANTI-PD-L1 ANTIBODY), BEVACIZUMAB, HEPATOCELLULAR CARCINOMA

Outcome measures

Primary outcome

Primary endpoint:

1. RFS

Secondary outcome

Secundary endpoint

1. OS rate at 24 months and 36 months

2. OS

3. RFS as determined by the investigator

4. TTR

5. Time to EHS or macrovascular invasion

6. RFS after randomization as determined by the investigator and by an IRF,

among patients in the PD-L1-high subgroup

7. Incidence and severity of adverse events, with severity determined according

to NCI CTCAE v5.0

8. Change from baseline in targeted vital signs

9. Change from baseline in targeted clinical laboratory test results

10. Serum concentration of atezolizumab at specified timepoints

11. Prevalence of anti-drug antibody (ADAs) to atezolizumab at baseline and

incidence of ADAs to atezolizumab during the study

Study description

Background summary

Liver cancer is the fifth most common cancer, accounting for 7% of all cancers, and the second most frequent cause of cancer-related death globally, with 854,000 new cases and 810,000 deaths per year. Hepatocellular carcinoma (HCC) represents approximately 90% of primary liver cancers and thus represents a significant global public health issue. On the basis of annual projections, the World Health Organization estimates that in excess of 1 million people will die from liver cancer in 2030 (Villanueva 2019).
The majority of HCCs occur in patients with underlying liver disease, mostly as a result of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection or alcohol abuse. HBV infection accounts for the majority of HCC cases worldwide; however, in Western countries and Japan, HCV is the main cause of HCC (Villanueva 2019). Universal HBV vaccination and wide implementation of direct-acting antiviral agents against HCV are likely to change the etiologic landscape of HCC. However, the incidence of non-alcoholic fatty liver disease (NAFLD), which is a risk factor for HCC, is increasing

worldwide and NAFLD will soon become a leading cause of liver cancer in Western countries (Villanueva 2019).

Study objective

This study has been transitioned to CTIS with ID 2023-504303-86-00 check the CTIS register for the current data.

Primary objective:
To evaluate the efficacy of atezolizumab plus bevacizumab compared with active surveillance on the basis of recurrence-free survival (RFS).

Secondary objectives:
1. To evaluate the efficacy of atezolizumab plus bevacizumab compared with active surveillance on the basis of overall survival (OS), RFS after randomization as determined by the investigator and by an Independent Review Facility (IRF), time to recurrence (TTR), OS rate at 24 months and 36 months, Time to extrahepatic spread or macrovascular invasion after randomization
2. To evaluate the safety of atezolizumab plus bevacizumab compared with active surveillance
3. To characterize the PK profile of atezolizumab when given in combination with bevacizumab
4. To evaluate the immune response to atezolizumab

Study design

This is a Phase III, global, multicenter, open-label, two-arm, randomized study designed to evaluate the efficacy and safety of adjuvant therapy with atezolizumab plus bevacizumab compared with active surveillance in patients with completely resected or ablated HCC who are at high risk for disease recurrence.Patients who have undergone surgical resection may have received 1 cycle of adjuvant TACE prior to study entry (randomization), if deemed appropriate by the investigator and if consistent with local standards of care (see Section 4.1.1 in the protocol for details).
The definition of high risk is based on composite criteria including size of the largest tumor, number of tumors, and presence of either microvascular invasion (defined as the presence of tumor emboli within the central vein, the portal vein, or large capsular vessels) or poorly differentiated microscopic appearance (histologic Grade 3 or 4). The criteria for high risk of HCC recurrence used in this study are presented by type of curative treatment in Table 2 in protocol.

Study burden and risks

There are several potentially curative or palliative approaches to the treatment of HCC,

including surgical resection and ablation.

Liver resection provides an opportunity for long-term, cancer-free survival and represents the primary curative treatment option for patients with HCC deemed to be surgical candidates. Eligibility for curative resection is typically based on disease stage as well as assessment of functional liver reserve; however, the concept of "resectability" varies significantly depending on local clinical practice and guidelines. Local ablative strategies such as radiofrequency ablation (RFA) and microwave ablation (MWA) are potentially curative options typically offered to patients with very early or early stage HCC who are not candidates for resection (Villanueva 2019). As compared with resection, ablation has fewer complications but provides worse local control for larger tumors (Villanueva 2019).

Tumor recurrence is a major post-procedural complication associated with both resection and ablation, with 50% to 70% of patients experiencing recurrence by 5 years (Villanueva 2019). The risk of HCC recurrence after curative intervention is primarily related to the number of tumors and tumor characteristics at the time of surgery or ablation, such as size, degree of differentiation, and the presence of vascular invasion.

For patients harboring one or more of these high-risk features (tumor size, tumor number, vascular invasion, poorly differentiated tumor), the prognosis following curative intervention is poor. In one study, 5-year disease-free survival rates following resection were 26% in patients with large/multinodular HCC and 18% in patients with macrovascular invasion (Zhong et al. 2015). Five-year survival rates were 42% in patients with large/multinodular HCC and 18% in patients with macrovascular invasion.
In a retrospective analysis, 5-year recurrence-free survival (RFS) rates following resection were 13% versus 34% in patients with and without microvascular invasion, respectively (Shen et al. 2018). In addition, histologic tumor grade has been shown to influence survival after resection, with patients harboring poorly

differentiated tumors
having a worse prognosis compared with patients with moderately or well-differentiated
tumors (Pawlik et al. 2005; Martins-Filho et al. 2017).

For patients with high-risk disease, effective and well-tolerated adjuvant therapies are needed in order to prevent disease
recurrence and to increase cure rates.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- For the 1st, 2nd, 5th, and 10th patients at each site: Medical Monitor approval prior to randomization in order to monitor adherence to key

eligibility criteria
- Age >= 18 years
- Participants with a first diagnosis of HCC who have undergone either a curative resection or ablation within 4-12 weeks of randomization (not applicable for crossover)
- Documented diagnosis of HCC that has been completely resected or ablated (not applicable for crossover).
- Absence of major macrovascular (gross vascular) invasion and of the portal vein (Vp3 or Vp4) or any grade of macrovascular invasion in the hepatic vein or inferior vena cava (not applicable for crossover)
Note: Patients undergoing resection with minor vascular invasion of the portal vein (Vp1 or Vp2) as detected by either imaging or pathological examination are allowed
- Absence of extrahepatic spread as confirmed by CT or MRI scan of the chest abdomen, pelvis, and head prior to and following curative procedure
- Full recovery from surgical resection or ablation within 4 weeks prior to randomization
- High risk for HCC recurrence after resection or ablation
- For patients who received post-operative transarterial chemoembolization: full recovery from the procedure within 4 weeks prior to randomization
- For patients with resected HCC, availability of a representative baseline tumor tissue sample
- Negative HIV test at screening
- Documented virology status of hepatitis, as confirmed by screening hepatitis B virus (HBV) and hepatitis C virus (HCV) tests
- For patients with active HBV: HBV DNA < 500 IU/mL during screening, initiation of anti-HBV treatment at least 14 days prior to randomization and willingness to continue anti-HBV treatment during the study
- For patients enrolled in the extended China enrollment phase: current resident of mainland China and of Chinese ancestry
- Performance of an esophagogastroduodenoscopy either before resection or ablation as part of pre-procedure work-up or during screening, and assessment and treatment of varices of all sizes per local standard of care prior to randomization
- Eastern Cooperative Oncology Group Performance Status of 0 or 1
- Child-Pugh Class A status
- Adequate hematologic and end-organ function
- For women of childbearing potential: agreement to remain abstinent or use contraceptive methods and agreement to refrain from donating eggs for 5 months after the final dose of atezolizumab and for 6 months after the final dose of bevacizumab
- For men: agreement to remain abstinent or use a condom, and agreement to refrain from donating sperm for during the treatment period and for 6 months after the final dose of bevacizumab to avoid

exposing the embryo
Additional Inclusion Criteria for Crossover for Patients in Arm B
- Documentation of unequivocal recurrence as defined by European Association for the Study of the Liver Clinical Practice Guidelines or RECIST v1.1 criteria that is confirmed by the IRF
- For Arm B patients who undergo surgical resection or ablation for first recurrence: full recovery from surgical resection or ablation within 4 weeks prior to Day 1 of Cycle 1
- Availability of a representative tumor specimen obtained at the time of recurrence for exploratory biomarker research
- After recurrence assessments are performed by the investigator and IRF, approval for crossover must be received from the Medical Monitor

Exclusion criteria

- Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
- Recurrent HCC prior to randomization
- Evidence of residual, recurrent, or metastatic disease at randomization (not applicable for crossover)
- Clinically significant ascites
- History of hepatic encephalopathy
- Prior bleeding event due to untreated or incompletely treated esophageal and/or gastric varices within 6 months prior to randomization
- Active or history of autoimmune disease or immune deficiency
- History of idiopathic pulmonary fibrosis, organizing pneumonia, druginduced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to Day 1 of Cycle 1, unstable arrhythmia, or unstable angina
- History of malignancy other than HCC within 5 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death, such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Active tuberculosis
- Severe infection within 4 weeks prior to Day 1 of Cycle 1, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that in the opinion of the investigator, could impact patient safety
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to Day 1 of Cycle 1

- Prior allogeneic stem cell or solid organ transplantation
- On the waiting list for liver transplantation
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 5 months after the final dose of atezolizumab or within 6 months after the final dose of bevacizumab
- Co-infection with HBV and HCV
- Co-infection with HBV and hepatitis D viral infection
- Clinically significant uncontrolled or symptomatic hypercalcemia
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab or bevacizumab formulations
- Any treatment for HCC prior to resection or ablation, including systemic therapy and locoregional therapy such as TACE
- Treatment with a live, attenuated vaccine within 4 weeks prior to Day 1 of Cycle 1, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab
- Treatment with investigational therapy within 4 weeks prior to Day 1 of Cycle 1
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies
- Treatment with systemic immune stimulatory agents within 4 weeks or 5 drug elimination half-lives prior to Day 1 of Cycle 1
- Treatment with systemic immunosuppressive medication within 2 weeks prior to Day 1 of Cycle 1, or anticipation of need for systemic immunosuppressive medication during study treatment
- Inadequately controlled arterial hypertension, based on an average of at least three BP readings at two or more sessions
- History of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease within 6 months prior to Day 1 of Cycle 1
- History of hemoptysis within 1 month prior to Day 1 of Cycle 1
- Evidence of bleeding diathesis or significant coagulopathy
- Current or recent use of aspirin or current or recent treatment with dipyramidole, ticlopidine, clopidogrel, and cilostazol
- Current or recent use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purpose
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to Day 1 of Cycle 1
- History of GI fistula, GI perforation, or intra-abdominal abscess within 6 months prior to Day 1 of Cycle 1
- Evidence of abdominal free air that is not explained by paracentesis or

recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Major surgical procedure within 4 weeks prior to Day 1 of Cycle 1 or anticipation of need for a major surgical procedure during the study
- History of clinically significant intra-abdominal inflammatory process within 6 months
prior to Day 1 of Cycle 1, including, but not limited to, peptic ulcer disease, diverticulitis, or colitis
- Chronic daily treatment with a non-steroidal anti-inflammatory drug

Study design

Design

Study phase:	3
Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-08-2021
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL outside intended use
Product type:	Medicine

Brand name:	Tecentriq
Generic name:	Atezolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-06-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-10-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	13-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-04-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	28-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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
EU-CTR	CTIS2023-504303-86-00
EudraCT	EUCTR2019-002491-14-NL
ClinicalTrials.gov	NCT04102098
CCMO	NL72323.056.19