# A Phase 3, Randomized, Double-blind Study of Adjuvant Nivolumab versus Placebo for Participants with Hepatocellular Carcinoma Who Are at High Risk of Recurrence after Curative Hepatic Resection or Ablation

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This study has been transitioned to CTIS with ID 2023-508726-10-00 check the CTIS register for the current data. Objectives of the studyPrimary ObjectiveTo compare recurrence-free survival (RFS)(based on BICR assessment) of nivolumab versus placebo...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Hepatobiliary neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON56028

**Source**
ToetsingOnline

**Brief title**
CA209-9DX

### Condition

- Hepatobiliary neoplasms malignant and unspecified

**Synonym**
hepatocellular carcinoma, liver cancer

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Bristol-Myers Squibb
**Source(s) of monetary or material Support:** Pharmaceutical industry

## Intervention

**Keyword:** ablation, high risk, nivolumab, resection

## Outcome measures

### Primary outcome

Recurrence free survival (RFS), defined as the time from randomization to the first documented disease recurrence (ie, intrahepatic recurrence of primary tumor or occurrence of a new HCC primary tumor, or extrahepatic recurrence) or death (by any cause), whichever occurs first.

### Secondary outcome

• Overall survival (OS), defined as the time between the date of randomization and the date of death (by any cause).

• Time to recurrence (TTR), defined as the time from randomization to the first documented disease recurrence (ie, intrahepatic recurrence of primary tumor or occurrence of a new HCC primary tumorr or extrahepatic recurrence).

# Study description

### Background summary

Hepatocellular carcinoma is the sixth most common cancer worldwide and the second leading cause of cancer-related death. The global incidence has continuously increased, with roughly 700,000 new cases diagnosed worldwide annually. The incidence varies geographically largely due to variations in

hepatitis B and C virus infection. Most cases arise in eastern Asia and sub-Saharan Africa, where the dominant risk factor is chronic infection with hepatitis B virus (HBV), while in North America, Europe, and Japan, infection with hepatitis C virus (HCV), together with alcohol use are the main risk factors for HCC.
HCC is a highly lethal cancer with a mortality-to-incidence rate ratio of 0.98 and 5-year survival rates of approximately 5%-6%. Factors such as late diagnosis, underlying liver dysfunction, and an aggressive and heterogeneous tumor biology have been identified as reasons for poor outcomes.
Moreover, the prognosis is further compromised because of the low effectiveness of available treatments, which emphasizes the need for early diagnosis and more effective therapies in HCC.

Treatment of HCC is challenging because the disease is highly heterogeneous with different etiologies, varying approaches to diagnosis and treatment, and variations in responses to therapy. The patient*s underlying liver function has an important influence on HCC treatment decisions. A total of 90% of HCC patients have an underlying cirrhosis requiring management of both the malignancy and the cirrhosis. Additionally, many patients require ongoing support for concomitant underlying disease such as HBV or HCV or non-viral related liver disease (eg, non-alcoholic
steatohepatitis), making HCC treatment strategies and management even more complex.

Surveillance programs for early detection of HCC in high-risk populations and improvement of therapeutic modalities have increased the likelihood of potentially curative treatments contributing to significant improvements of survival rates in this population. Unfortunately, despite remarkable improvements, the long-term prognosis, even after curative treatment, remains unsatisfactory. The 5-year risk of recurrence exceeds 70% after resection or local ablation, and most of the recurrences (especially those that appear early during follow-up) are due to tumor dissemination
and have a more aggressive biological pattern as compared to primary tumors, jeopardizing the survival of this population. In this context, preventing recurrence with effective neoadjuvant or adjuvant therapies, particularly in those patients at higher risk of recurrence, represents a
significant high unmet medical need in HCC. Up until now, attempts to address this need have proven largely unsuccessful, with no treatments showing benefits in randomized studies, which results in a lack of current standard of care (SOC) in the adjuvant setting.

At this time, curative therapies for primary tumors remains the best chance to cure patients with localized HCC. However, survival rates particularly in those patients with high risk of recurrence remain poor, and novel therapeutic approaches are needed to improve prognosis in
this population.

## Study objective

This study has been transitioned to CTIS with ID 2023-508726-10-00 check the CTIS register for the current data.

Objectives of the study
Primary Objective
To compare recurrence-free survival (RFS)(based on BICR assessment) of nivolumab versus placebo in all randomized participants.

Secondary Objectives
• To compare overall survival (OS) of nivolumab versus placebo in all randomized participants.
• To evaluate time to recurrence (TTR) (based on BICR assessment) of nivolumab versus placebo in all randomized participants.

## Study design

Phase 3, randomized, double-blind study of nivolumab monotherapy versus placebo in participants who have undergone curative liver resection or ablation, following a first diagnosis of hepatocellular carcinoma (HCC), and who are at high risk for recurrence.
About 883 patients, will be enrolled in this study, for 530 being treated.
Randomized patients will receive nivolumab 480 mg or placebo every 4 weeks.
Patients will have 50% chance to receive nivolumab and 50% chance to receive the placebo.
Patients will undergo screening procedures prior to first treatment to assess if they are eligible to take part in the study. A pre-treatment tumor sample to determine biomarkers is required to be submitted prior to randomization for patients who undergo a resection and is optional for patients who undergo local ablation.
Nivolumab and placebo will be given by a 30 min infusion.
Throughout the study, patients will have the following procedures: up to 2 biopsies, CT/MRI scans, physical exams, ECGs, vital signs, blood sampling and pregnancy testing. They will also have to complete questionnaires regularly.
On-study tumor assessments will be done every 12 weeks from randomization for the first 2 years and will continue every 24 weeks thereafter until disease recurrence.
All patients will receive their treatment until their cancer returns (as evaluated by CT scan or MRI), unacceptable toxicity, or if they withdraw their consent to continue the treatment, whichever comes first.
Patients will be expected to receive their treatment for a maximum of 1 year and be in follow-up for 5 years.
Follow-up: after stopping their treatments, patients will be asked to come back to the hospital for 2 follow-up visits, at 30 and 100 days after their last dose of study treatment, respectively.

Additional visits (approximately every 3 months) after follow-up visits (survival visits).

## Intervention

The medical interventions include treatment with nivolumab or placebo. Nivolumab will be supplied by the sponsor.

Patients will be randomised 1:1 to:
• Arm A: nivolumab 480 mg as a 30 minute infusion every 4 weeks (Q4W)
• Arm B: placebo as a 30 minute infusion every 4 weeks (Q4W)

Treatment, in the absence of recurrence (confirmed by BICR), unacceptable toxicity, or
withdrawal of consent, will be continued for a maximum of 1 year total duration.

## Study burden and risks

As part of the trial, patients will be expected to attend multiple clinic visits where they will undergo physical examinations, vital sign measurements, blood tests for safety assessment, pregnancy testing (for females of child bearing potential) and monitoring for adverse events & serious adverse events. Patients will be asked to complete questionnaires (FACT-Hep & EQ-5Q-3L) about their quality of life. Blood will also be collected at certain visits for research purposes (PK, immunogenicity and biomarker studies). If ablation and a tumor biopsy occurred no longer than 3 months ago, archival tumor tissue will be sent to a central laboratory for analysis of biomarkers. Otherwise the tumor biopsy obtained during the resection or ablation procedure will be obtained and sent to central laboratory. A tumour biopsy will be performed at disease recurrence. Patients will undergo radiographic assessment by CT or MRI at screening, every 12 weeks for the first 2 years, then every 24 weeks for up to a maximum of 5 years until disease recurrence (confirmed by Blinded Independent Review Committee). The frequency of visits and number of procedures carried out during this trial would be typically considered over and above standard of care. The procedures are carried out by trained medical professionals and every effort will be made to minimise any risks or discomfort to the patient.
Treatment for cancer often has side effects, including some that are life threatening. To assure an ongoing favourable risk/benefit assessment for patients enrolled onto the study, an Independent Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of patients enrolled in the study.
BMS will conduct rigorous safety monitoring to ensure patients safety by regularly & systematically reviewing safety data; the reported safety events

will be closely followed-up; sites and study investigators will receive training on the implementation of nivolumab toxicity management strategies. New immune system targeted therapy (immunotherapies) such as nivolumab could potentially provide clinical benefit and improvements in the outcomes for patients with this disease. However, with all experimental drugs and clinical trials, there are known and unknown risks. Study medication and procedure related risks are outlined in the patient information sheet in detail to ensure the patients are fully informed before agreeing to take part in the study.

# Contacts

**Public**
Bristol-Myers Squibb

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GB
**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

- Males and females, ages 18 or older
- Participants must have a first diagnosis of hepatocellur carcinoma (HCC)

amenable for management with curative intent by resection or local ablation. Cytological or histological confirmation prior to randomization is required.
• Participants are eligible to enroll if they have non-viral related-HCC, or if they have HBV-HCC, or HCV-HCC defined as follows:
- Non-HBV non-HCV related HCC
- HBV-HCC:
o Resolved HBV infection (detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV DNA, and undetectable HBV surface antigen), OR
o Chronic HBV infection (detectable HBV surface antigen or HBV DNA). Participants with chronic HBV infection must be on antiviral therapy and must have HBV DNA < 500 IU/mL
- HCV-HCC:
o Resolved HCV infection (detectable antibody), OR
o Chronic HCV infection (detectable HCV RNA)
• Participants are eligible to enroll if they have undergone:
- Hepatic resection and have the following tumor characteristics:
o Up to 3 tumors, at least one > 5 cm, and with no evidence of macrovascular invasion
o Up to 3 tumors, none > 5 cm but with confirmation of microvascular invasion or poorly/undifferentiated HCC (G3-G4) in the pathological report
o > 3 tumors, none > 5 cm, and with no evidence of macrovascular invasion
- Local ablation [radiofrequency ablation (RFA) or microwave ablation (MWA)]:
o Solitary tumor > 3 cm <= 5 cm
o Multiple tumors (up to 4), none > 5 cm
• Participants must have complete resection (R0) documented in the pathology report, OR must have achieved radiologically documented complete response after local ablation (RFA or MWA)
• For participants who have undergone resection, tumor tissue obtained from the resected site of disease at the time of hepatic resection is required for randomization. For participants who have undergone local ablation, submission of tumor tissue obtained from a biopsy performed prior to ablation (within 3 months) or at the time of ablation is optional.
• All participants are required to have imaging studies confirming disease-free status at least 4 weeks after resection or ablation, and within 4 weeks prior to randomization. BICR confirmation of disease-free status is required for randomization.
• Child-Pugh Score 5 or 6
• ECOG PS 0 or 1
• Adequate liver function: Albumin > 2.8 g/dL and Bilirubin < 3 mg/dL and AST/ALT < 5xULN

## Exclusion criteria

Target Disease Exceptions:
• Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC

• Prior recurrence of HCC
• Any evidence of tumor metastasis or co-existing malignant disease
• Participants showing evidence of macrovascular invasion on imaging tests
• Participants who have undergone a liver transplant or those who are in the waiting list for liver transplantation at study entry

Medical Conditions:
• Active co-infection with:
• Chronische hepatitis B & C [detectable HBV surface antigen (HBsAg) or HBV DNA and HCV RNA], OR
• Hepatitis D infection in participants with chronic hepatitis B
• Known history of positive HIV or AIDS

Prior/Concomitant Therapy:
• Participants previously receiving any prior therapy for HCC, including loco-regional therapies, before or after resection or ablation
• Participants receiving or expected to receive IFN-based therapies during the study period
• Participants who have received a live/attenuated vaccine within 30 days of randomization

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 03-03-2020 |
| Enrollment: | 4 |
| Type: | Actual |

### Medical products/devices used

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| Product type: | Medicine |
| Brand name: | Opdivo |
| Generic name: | Nivolumab |
| Registration: | Yes - NL outside intended use |

## Ethics review

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| Approved WMO Date: | 24-06-2019 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 29-08-2019 |
| Application type: | First submission |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 04-03-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 10-03-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 05-11-2020 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 16-10-2021 |
| Application type: | Amendment |

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| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 08-11-2022 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 28-08-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 31-08-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 13-12-2023 |
| Application type: | Amendment |
| Review commission: | BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen) |
| Approved WMO Date: | 21-12-2023 |
| 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 | CTIS2023-508726-10-00 |
| EudraCT | EUCTR2017-002755-29-NL |
| ClinicalTrials.gov | NCT03383458 |
| CCMO | NL70215.056.19 |