A Randomized, Blinded, Placebo-controlled, Phase 2 Study of INBRX-109 in Unresectable or Metastatic Conventional Chondrosarcoma

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This study has been transitioned to CTIS with ID 2024-517528-20-00 check the CTIS register for the current data. Primary objective:• To evaluate the anticancer efficacy of INBRX-109 in the intention-to-treat (ITT) population as measured by…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bone disorders (excl congenital and fractures)
Study type	Interventional

Summary

ID

NL-OMON54090

Source
ToetsingOnline

Brief title
INBRX-109

Condition

- Bone disorders (excl congenital and fractures)

Synonym
Conventional chondrosarcomas, malignant bone tumor

Research involving
Human

Sponsors and support

Primary sponsor: Inhibrx, Inc.

Source(s) of monetary or material Support: Inhibrx;Inc.

Intervention

Keyword: Apoptosis, DR5, INBRX-109, Programmed cell death

Outcome measures

Primary outcome

Primary Endpoint:

Progression free survival per RECISTv1.1 assessed by central real-time independent radiology review (IRR) in the intend-to-treat (ITT) population is the primary endpoint.

Secondary outcome

Secondary Endpoints include overall survival, objective response rate, progression free survival by Investigator assessment, Quality of Life, disease control rate, duration of response, safety, pharmacokinetics and immunogenicity.

Predictive Biomarker Strategy:

Assessment of potential predictive diagnostic biomarkers for INBRX-109 is an exploratory endpoint, and availability of archival tissue or a fresh cancer biopsy is mandatory for enrollment to this study.

Study description

Background summary

Cancer is a disease in which cells in the body grow out of control. Chondrosarcomas are a group of malignant bone tumors and are the third most common type of bone cancers. Conventional chondrosarcomas are often resistant to standard cancer therapies. Currently there are no approved therapies for

unresectable or metastatic conventional chondrosarcoma.

INBRX-109 was specifically created for the treatment of cancer. It works in a similar way as antibodies, which are proteins that are naturally present in the body. Antibodies help the body*s immune system fight diseases such as infections. INBRX-109 works by causing specific cell sensors (called death receptors) to initiate the death of cancer cells (called apoptosis), and it is hoped that this can help in the treatment of patients with unresectable or metastatic conventional chondrosarcomas.

Study objective

This study has been transitioned to CTIS with ID 2024-517528-20-00 check the CTIS register for the current data.

Primary objective:
• To evaluate the anticancer efficacy of INBRX-109 in the intention-to-treat (ITT) population as measured by progression free survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECISTv1.1), assessed by central real-time independent radiology review (IRR), comparing INBRX-109 and placebo.

Secondary objectives:
• To evaluate the anticancer efficacy of INBRX-109 as measured by overall survival (OS) comparing INBRX-109 and placebo.
• To evaluate the anticancer efficacy of INBRX-109 as measured by overall response rate (ORR) per RECISTv1.1, assessed by central real-time IRR, comparing INBRX-109 and placebo.
• To evaluate the anticancer efficacy of INBRX-109 as measured by PFS per RECISTv1.1, by Investigator assessment, comparing INBRX-109 and placebo.
• To evaluate quality of life (QoL), as measured by European Organization for Research and Treatment of Cancer quality of life questionnaire C30 (EORTC QLQ-C30) Pain and Physical Functioning scales, comparing INBRX-109 and placebo.
• To evaluate the anticancer efficacy of INBRX-109 as measured by disease control rate (DCR) per RECISTv1.1, assessed by central real-time IRR, comparing INBRX-109 and placebo.
• To evaluate duration of response (DOR) per RECISTv1.1, assessed by central real-time IRR, comparing INBRX-109 and placebo.
• To evaluate the safety and tolerability of INBRX-109.
• To characterize the pharmacokinetics (PK) of INBRX-109.
• To evaluate the frequency of anti-drug antibodies (ADA), and neutralizing ADAs (NAbs), against INBRX-109 and to explore the potential relationship with safety, PK and efficacy of INBRX-109.

Exploratory objective:
• To evaluate QoL as measured by the EORTC QLQ C30 scales (other than the Pain and Physical Functioning scales), EuroQol Group Five-dimension Questionnaire

(EQ-5D-5L), patient global impression of change (PGI-C) and patient global impression of severity (PGI-S) comparing INBRX-109 and placebo.
• To evaluate the relationship between potential predictive diagnostic response biomarkers and efficacy of INBRX-109.
• To evaluate the anticancer efficacy of INBRX-109 as measured by PFS (by Investigator assessment) for crossover population after treatment with INBRX-109.
• To evaluate the anticancer efficacy of INBRX-109 as measured by ORR (by Investigator assessment) for crossover population after treatment with INBRX-109.

Study design

This is a multicenter, randomized, blinded, placebo-controlled study of intravenous INBRX-109 in patients with unresectable or metastatic conventional chondrosarcoma. Any number of prior lines of therapy and treatments are allowed, with the exception of prior DR5 agonists.

Approximately 201 eligible patients will be enrolled into this study. Patients will be randomized 2:1 to receive INBRX-109 (n=134) or placebo (n=67). Crossover to INBRX-109 at the time of progression is allowed for patients randomized to placebo.

Stratification:
Patients will be stratified for randomization by histologic grade (Grade 2 vs 3; per American Joint Committee on Cancer [AJCC] 8th edition), IDH1 R132/IDH2 R172 status (wildtype vs mutation) and line of systemic therapy (none vs prior).

Blinding:
This is a blinded study; accordingly, the patient, investigator, site staff (except the site pharmacist), sponsor, independent radiology reviewer and biostatistician will be blinded to study arm allocation and will not know whether the patient will receive INBRX-109 or placebo. The site pharmacist will be unblinded to the study arm and will prepare INBRX-109 or placebo for patients as specified by the randomization scheme.

Interim Analysis:
An interim analysis is planned when approximately 50% of the total required number of events occur. During this unblinded interim analysis, data will be assessed by the Data Monitoring Committee (DMC) for sample size re-estimation (SSRE) based on conditional power (CP). The data may also be evaluated for a potential adaptive population enrichment to exclude patients with IDH1 R132 or IDH2 R172 mutations. The maximum number of patients enrolled in the event of a sample size adjustment is planned to be 300 (vs. 201 for study with no sample size adjustment). Additionally, a non-binding futility analysis will be conducted during this interim analysis.

Treatment duration:
Treatment with INBRX-109 or placebo will continue until disease progression (PD), unacceptable toxicities, patient, investigator or sponsor wishes, or failure to comply with study requirements.

Data and Safety Monitoring:
Adverse Events (AEs) will be graded by National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0. (NCI CTCAEv5.0). To supplement routine safety monitoring, an external independent Data Monitoring Committee (DMC) will review safety data approximately every 6 months and the interim analysis results from this study.
Hepatotoxicity will be an AE of special clinical interest.
Concomitant use of potential hepatotoxic medications should be avoided.

Intervention

• Investigational: INBRX-109 at a dose of 3 mg/kg IV every 3 weeks (Q3W; every 21 days [Q21D]). Dose reduction or escalation is not permitted.
• Control: Placebo IV every 3 weeks (Q3W, Q21D).

Study burden and risks

Burden: patients should visit the infusion clinic once every 3 weeks to receive the study treatment by IV infusion. Physical examinations and heart tracing (ECG) will be done and weight, height, and vital signs will be measured. Urine and blood tests will be done to check general health, pregnancy, and to test for HIV and hepatitis B and C. CT and/or MRI scans are performed to assess tumor status and questionnaires about quality of life should be filled in.

Risks: The study drug may have side effects or can cause liver damage in patients.

Benefit: Conventional chondrosarcomas are often resistant to standard cancer therapies. Currently there are no approved therapies for unresectable or metastatic conventional chondrosarcoma, and it is hoped that INBRX-109 treatment can help in the treatment of these patients.

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

To be eligible for study entry patients must satisfy all of the following criteria:
1. Males or females aged >= 18 to <= 85 years.
Note: Potential inclusion of patients who are chronologically older than 85 years, but with Eastern Cooperative Group Performance Status (ECOG PS) 0 and a younger biologic age per comprehensive geriatric assessment, must be based on discussion with the Medical Monitor or Study Director.
2. Conventional (or primary) chondrosarcoma (Note: must be confirmed by local institutional or reference pathology review, but this confirmation is not required for enrollment)
• Metastatic or unresectable (i.e., not amenable to tumor resection with curative intent),
• The availability of archival tissue or a fresh cancer biopsy is mandatory for enrollment.
- Note: A confirmation of IDH mutational status (per Clinical Laboratory Improvement Amendments [CLIA]-certified assay or equivalent) is required for stratification prior to randomization, any status is allowed, i.e. IDH1, IDH2 or wildtype.
• Any number of prior lines of systemic therapy are allowed.
- Note: Since there are no FDA/EMA approved systemic therapies for this

population, patients with unresectable and/or metastatic disease who have not received prior systemic therapy may be eligible, provided that they have exhausted all clinically relevant (localized and/or palliative) treatment options as per investigator*s preference as per local practice guidelines.
• Furthermore, patients with oligometastatic disease (low disease burden, resectable) must have exhausted all clinically relevant options including palliative radiation, surgery or chemotherapy with non-curative intent.
3. Measurable disease by RECISTv1.1.
• Note: Tumor lesions that are located in a previously irradiated (or other locally treated) area will be considered measurable, provided there has been clear imaging-based progression of the lesions since the time of radiation.
4. Evidence of confirmed radiographic disease progression per RECISTv1.1 criteria within 6 months prior to the start of the study treatment
• Note: Potential inclusion of patients with progression, which was not determined or confirmed by RECISTv1.1 (e.g., bone only disease), must be discussed and approved by the Medical Monitor or Study Director.
5. Adequate laboratory parameters:
• Adequate hepatic function:
* AST, ALT and GGT within ULN, and Bilirubin within ULN for patients without liver metastasis.
* AST, ALT and GGT <= 2.5 x ULN, and Bilirubin <= 1.5 x ULN for patients with liver metastasis.
* Exception: Bilirubin <= 2.5 x ULN for patients who have known serum bilirubin increases due to underlying Gilbert*s Syndrome or familial benign unconjugated hyperbilirubinemia.
- Note: As transient elevations in GGT can occur due to nonhepatobiliary etiologies, the test can be repeated during Screening after consultation with the
Medical Monitor.
• Adequate renal function: Creatinine clearance >= 50 mL/min.
• Adequate hematologic function: Absolute neutrophil count (ANC) >= 1500 cells/µL, Platelet count >= 100,000/µL and Hemoglobin >= 8.0 g/dL.
• Coagulation tests: Activated partial thromboplastin time (aPTT) <= 1.5 x ULN and international normalized ratio (INR) <= 1.7 without anti-coagulants.
* Protocol only requires to test for standard coagulation tests. Exception: INR 2 to <= 3 is acceptable for patients on anticoagulation therapy. If a subject is using a DOAC, it will be requested that they adhere to their therapy with standard of care monitoring as needed per local practice.
6. ECOG PS of 0 or 1.
• Exception: Inclusion of non-frail, physically active patients with compromised mobility due to prior cancer surgery (e.g. limb amputation, hemipelvectomy) should be discussed with the Medical Monitor or Study Director.
7. Estimated life expectancy, in the documented judgment of the Investigator, of at least 12 weeks.
8. Recovery from all reversible AEs of previous anticancer therapies to baseline or NCI CTCAEv5.0 Grade 1 or better. Inclusion of patients with other

not clinically significant toxicities (e.g., alopecia, Grade <= 2 sensory peripheral neuropathy or lymphopenia) should be discussed with the Medical Monitor or Study Director.
9. Must have the ability to understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of any study procedures.
• Note: Patients with a personal or financial relationship with the Sponsor, a contractual relationship with the Investigator or the study site, or who are in custody or have been sanctioned by an official or court order will not be eligible to participate.
10. Fertile male patients with female partners of childbearing potential and female patients of childbearing potential must agree to avoid impregnating a partner or becoming pregnant, respectively. They must be willing to use acceptable methods of contraception at least 28 days before the first dose of study treatment until 90 days after the last dose of study treatment.
• A woman is considered of childbearing potential following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.Postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
• A man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy.

Exclusion criteria

Patients will be excluded from the study if one or more of the following criteria is/are applicable:
1. Any prior exposure to DR5 agonists.
2. Receipt of any anti-cancer therapy (including investigational agents) within 4 weeks or within 5 half-lives prior to the first dose of study treatment, whichever is shorter.
• Note: patients who received pazopanib as an immediate prior line, must have a 4 week washout and no evidence of prior or residual hepatotoxicity.
• Note: patients with any history or evidence of Grade >=3 hepatotoxicity on prior anti cancer therapy are excluded.
3. Receipt of radiotherapy (with the exception of palliative localized radiation) within 4 weeks to the first dose of study treatment. Patients must have recovered from all radiation-related toxicities and not require corticosteroids.
• Note: A 1-week washout is required for palliative radiation to non-central nervous system (CNS) disease.
• Note: patients who had prior radiotherapy involving the liver (total calculated dose to the liver >10Gy) are excluded.
4. Receipt of liver-directed therapies (e.g., RFA, TACE/embolization, cryotherapy, SBRT, or others) within 12 months prior to the first dose of study treatment.

• Note: patients who had prior radioembolization with Yttrium-90 beads are excluded.
5. Allergy or sensitivity to INBRX-109 or known allergies to Chinese hamster ovary (CHO) cell-produced antibodies, which in the opinion of the investigator suggest an increased potential for an adverse hypersensitivity to INBRX-109.
6. Non-conventional CS, e.g., clear-cell, mesenchymal, extraskeletal myxoid, myxoid*, and dedifferentiated CS.
• Note: *Conventional CS with myxoid features are considered Grade 2 conventional CS and are allowed in this study.
7. Prior or concurrent malignancies.
• Exception: Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessments of INBRX-109. These cases must be reviewed and discussed with the medical monitor and sponsor for potential inclusion.
8. Symptomatic active CNS metastases or leptomeningeal disease.
• Exception: Patients with asymptomatic CNS metastases are eligible if controlled, defined as >= 4 weeks of stable neurologic function following CNS directed therapy (stereotactic radiotherapy, definitive surgical resection, and/or whole brain radiotherapy); not requiring steroids; and no evidence of CNS disease progression as determined by radiographic imaging within 4 weeks prior to the first dose of study treatment.
• Note: Patients with spinal cord metastases are allowed.
• Note: Patients with untreated, uncontrolled, ongoing spinal cord compression are excluded.
9. Chronic liver diseases including but not limited to NAFLD or NASH, alcohol-related liver disease, cirrhosis, hemochromatosis, Wilson*s disease, alpha-1 antitrypsin deficiency, liver hemangioma, hepatic or biliary autoimmune disorders (e.g., primary biliary cholangitis, autoimmune hepatitis)), history of portal or hepatic vein thrombosis, sinusoidal occlusion syndrome.
• Note: Liver imaging is required for all patients to rule out chronic liver diseases. When NAFLD, NASH, fibrosis, or cirrhosis are suspected, liver MRI or MRE are preferred, and the percentage of liver fat content should be provided. CT scan without contrast (or precontrast, if the baseline tumor assessment scans are used), ultrasound, or transient elastography are acceptable to rule out other chronic liver diseases. If a CT scan is used, the attenuation value of liver and spleen should be provided in HU.
• Exception: The eligibility of the patients with nonclinically significant solitary hemangiomas should be discussed with the Medical Monitor.
• Exception: Patients aged < 45 years with NAFLD detected by imaging may participate in the study, if adequate hepatic function as defined in the inclusion criteria is confirmed. Unclear cases must be reviewed and discussed with the Medical Monitor or Study Director for potential inclusion.
• Note: Patients aged >= 45 years with non-alcoholic fatty liver disease (NAFLD) are excluded from the study.
10. Patients aged >=65 years and with BMI >=30 kg/m2 are excluded from the study. Patients aged >=45 years with HSI >=36 and FLI >=60 are also excluded from the study. If one of the values (HSI or FLI) is in the acceptable range and the

other is above the cutoff, the patient may still be eligible for the study if fatty liver is excluded by liver imaging. These cases must be reviewed and discussed with the Medical Monitor.
11. Acute viral (including hepatitis A, D, E viruses, CMV, EBV) or toxic liver disease within 12 months prior to the first dose of study treatment.
12. Any evidence or history of hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection.
13. Has undergone allogeneic hematopoietic stem cell or bone marrow transplantation within the last 5 years.
• Exception: Patients who have had a stem cell or bone marrow transplant > 5 years ago are eligible for enrollment, as long as there are no symptoms of graft-versus-host disease (GVHD).
14. Major surgery within 4 weeks prior to this study.
15. Clinically significant bacterial, fungal or viral infection requiring anti-infective treatment within 2 weeks prior to this study.
16. Pregnant or nursing females, female patients of childbearing potential, and fertile male patients with female partners of childbearing potential unwilling use acceptable contraception methods at least 28 days before the first dose of study treatment until 90 days after the last dose of study treatment.
17. Any known, documented, or suspected history of illicit substance abuse that would preclude patient from participation, unless clinically justified (i.e., will not interfere with study participation and/or will not compromise study objectives) per judgment of the Investigator and with approval of the Medical Monitor or Study Director.
• Exception: Physician-prescribed medicinal opioids or cannabinoids are allowed for pain management. Cannabinoids are allowed for patients from states/countries that have legalized its use.
• Note: patients with ongoing or prior history of alcoholism are excluded, unless they qualify per LFTs and liver imaging.
18. Any other disease or clinically significant abnormality in laboratory parameters, including serious medical or psychiatric illness/condition likely in the judgment of the investigator to interfere with compliance to protocol treatment/research, or which might compromise the safety of the patient or interfere with participation in the study or compromise the study objective.
Note: patients with the following ongoing comorbid conditions are excluded:
a. Acute deep vein thrombosis or clinically significant pulmonary embolism, not resolved or stable for at least 3 months prior to the start of study treatment.
b. Clinically significant, uncontrolled with medication type 2 diabetes mellitus; metabolic syndrome or pre-diabetes; insulin-resistance (with hemoglobin A1c >6%)
c. Clinically significant, uncontrolled with medication hypothyroidism
d. Clinically significant, uncontrolled with medication hypertension Stage >1
e. Clinically significant, uncontrolled with medication hypertriglyceridemia
f. Hypoxia with oxygen saturation < 92%
g. Encephalopathy Stage >=1
19. Any evidence or history of multiple sclerosis (MS) or other demyelinating disorders. Note: For patients without known or suspected CNS metastases, or any

other neurologic findings, brain imaging is not required at baseline to rule out MS or potential demyelinating disorders.

Study design

Design

Study phase:	2
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):	12-07-2022
Enrollment:	18
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	INBRX-109
Generic name:	INBRX-109

Ethics review

Approved WMO

Date:	08-03-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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Approved WMO Date:	19-05-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	23-06-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	19-08-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	20-12-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	15-04-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	12-05-2023
Application type:	Amendment
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Approved WMO Date:	21-12-2023
Application type:	Amendment
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Approved WMO Date:	08-01-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	25-04-2024
Application type:	Amendment
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Approved WMO Date:	03-05-2024
Application type:	Amendment
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Approved WMO Date:	01-08-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	06-09-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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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	CTIS2024-517528-20-00
EudraCT	EUCTR2021-002635-35-NL
ClinicalTrials.gov	NCT04950075
CCMO	NL78489.058.21