P322

A Randomized, Placebo-Controlled, Phase 2 Trial of INBRX-109 in Unresectable or Metastatic Conventional Chondrosarcoma

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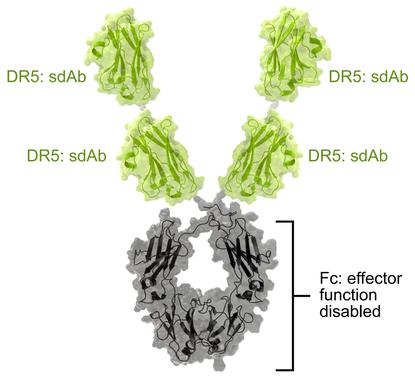
INTRODUCTION

- Chondrosarcomas are a heterogeneous group of malignant bone tumors and the third most common type of primary bone cancer after myeloma and osteosarcoma[1]
  - Chondrosarcomas form in the bone cartilage and usually start in the pelvis, scapula, ribs, or the ends of long bones[2]
- The conventional subtype of chondrosarcoma represents 85% to 90% of cases and is typically treated with surgical resection[1]
- However, treatment for unresectable or metastatic conventional chondrosarcoma is limited, and prognosis remains poor[3]
  - Unresectable or metastatic conventional chondrosarcoma is generally resistant to chemotherapy and radiation, and standard molecular targeted agents are not available[3]
  - Median progression-free survival (PFS) in patients receiving ineffective agents or placebo has historically been <4 months[4]
- Several agents for unresectable or metastatic conventional chondrosarcoma have been evaluated, but most have been ineffective, and no systemic therapies have been approved[5-9]

INBRX-109 Mechanism of Action

- INBRX-109 is a third-generation, tetravalent, agonistic antibody that targets human death receptor 5 (DR5), 1 of 2 proapoptotic receptors for the trimeric tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) (**Figures 1** and **2**)
  - TRAIL selectively induces apoptosis in cancer cells while sparing normal tissues and therefore plays an important role in tumor and viral immune surveillance[10]
  - Targeting DR5 may hold great promise in chondrosarcoma, as suggested by the clinical activity previously observed with dulanermin (recombinant TRAIL)[11]

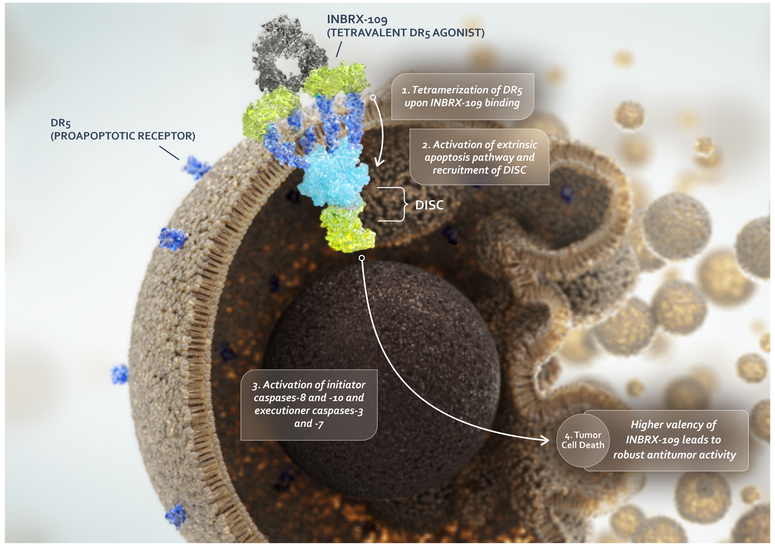
Figure 1. Structure of INBRX-109



- INBRX-109 is based on a single-domain antibody (sdAb) platform
  - It consists of 2 identical camelid heavy-chain–only antigen-binding domains targeting DR5
  - These domains are joined end to end with an effector-silenced Fc constant domain based on human immunoglobulin G1
- By way of our sdAb platform, INBRX-109 eliminates recognition by preexisting antidrug antibodies (ADAs), lessening the potential for hyperclustering
  - Previous tetravalent DR5 agonists failed in the clinic due to hepatotoxicity, likely due to hyperclustering by ADAs[12]

DR5, death receptor 5; sdAb, single-domain antibody.

Figure 2. INBRX-109 Mechanism of Action



INBRX-109: tetravalent DR5 agonist

- INBRX-109 is a tetravalent, agonistic antibody against DR5, a proapoptotic receptor widely expressed on tumor cells
- The tetravalent format of INBRX-109 was selected as an optimal balance of DR5 agonism on tumor vs normal cells, enabling robust cancer-biased cell death while avoiding hyperclustering and concomitant hepatotoxicity observed with previous multivalent DR5 candidates

DISC, death-inducing signaling complex; DR5, death receptor 5.

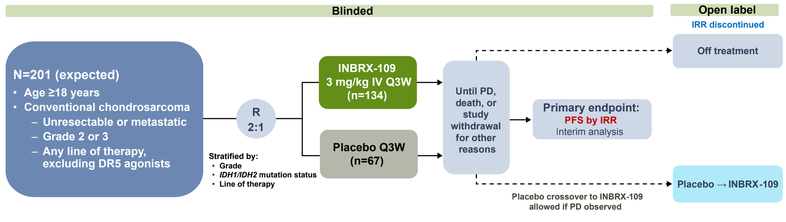
OBJECTIVE

- INBRX-109 is currently in clinical development in an ongoing phase 1 dose-escalation study (NCT03715933) with dedicated single-agent expansion cohorts in chondrosarcoma, nonconventional chondrosarcoma, synovial sarcoma, malignant pleural mesothelioma, gastric adenocarcinoma, and colorectal adenocarcinoma as well as chemotherapy combination cohorts in malignant pleural mesothelioma, pancreatic adenocarcinoma, and Ewing sarcoma
- In an early assessment of the phase 1 study (October 1, 2021), INBRX-109 demonstrated clinical activity with a manageable safety profile in 20 patients with chondrosarcoma[13]
  - The disease control rate (complete response + partial response [PR] + stable disease [SD]) was 89% (16/18); 2 patients (11%) achieved a PR and 14 patients (78%) had SD
  - Notably, 11 of the 18 patients (61%) had a reduction in the sum of target lesions as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; 6 patients (33%) had a decrease of ≥10%
  - Median PFS among patients with chondrosarcoma was 7.4 months (historical PFS, <4 months)[4]
  - Among all 116 patients treated with INBRX-109 in the phase 1 study, any-grade hepatotoxicity was observed in 13 patients (11%); grade ≥3 liver-related adverse events occurred in 5.2% of patients
- Updated results as of May 26, 2022 confirmed these results and indicated activity in conventional chondrosarcoma (see CTOS 2022 presentation P043 for updated information)
- Given the early clinical activity observed in the phase 1 study and the unmet need in conventional chondrosarcoma, a phase 2 study (ChonDRAgon; NCT04950075) of INBRX-109 in unresectable or metastatic conventional chondrosarcoma has been initiated

METHODS

- ChonDRAgon is a multicenter, randomized, blinded, placebo-controlled phase 2 study of INBRX-109 in patients with unresectable or metastatic conventional chondrosarcoma (**Figure 3**)
- Eligible patients will be randomized 2:1 to receive either INBRX-109 at a dose of 3 mg/kg every 3 weeks (Q3W; n=134) or placebo (n=67)
  - Patients will be stratified by grade, isocitrate dehydrogenase 1/2 [*IDH1*/*IDH2*] mutation status, and line of therapy
- Treatment with INBRX-109 or placebo will continue until disease progression, death, or study withdrawal for other reasons
- Patients in the placebo arm who experience documented disease progression verified by central real-time independent radiology review (IRR) will have their treatment assignment unblinded and will be able to cross over to open-label INBRX-109
  - Patients will receive INBRX-109 until subsequent disease progression; tumor assessments will not be submitted for central IRR
  - Assessments for the crossover population will be analyzed separately
- The primary efficacy endpoint is PFS assessed by real-time IRR, using RECIST 1.1
  - PFS is defined as the time from randomization to the first observation of documented disease progression or death due to any cause, whichever occurs first

Figure 3. ChonDRAgon (NCT04950075) Study Design



DR5, death receptor 5; IDH, isocitrate dehydrogenase; IRR, independent radiology review; IV, intravenous; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized.

Inclusion/Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years	• Any prior exposure to DR5 agonists
• Conventional chondrosarcoma	• Nonconventional chondrosarcoma (eg, clear cell, mesenchymal, extraskeletal myxoid, myxoid, and dedifferentiated chondrosarcoma)
– Unresectable or metastatic	• Symptomatic active CNS metastases or leptomeningeal disease
– Grade 2 or 3 per AJCC 8th edition	– Patients with controlled asymptomatic CNS metastases are eligible
• Any number of prior lines of therapy	• Chronic liver diseases, including NASH, NAFLD, alcohol-related liver disease, and cirrhosis
• Measurable disease by RECIST 1.1	– Patients aged <64 years with NAFLD are eligible if adequate hepatic function is confirmed
• Radiological progression of disease per RECIST 1.1 within 6 months prior to screening	• Patients aged ≥65 years with BMI >30 kg/m^2
• Adequate hematologic, coagulation, hepatic, and renal function as defined per protocol	• Acute viral or toxic liver disease within 4 weeks prior to first dose of study treatment
• ECOG performance status of 0 or 1	• Evidence or history of HBV, HCV, or HIV infection
• Availability of archival tissue or fresh cancer biopsy	

AJCC, American Joint Committee on Cancer; BMI, body mass index; CNS, central nervous system; DR5, death receptor 5; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; RECIST, Response Evaluation Criteria in Solid Tumors.

Endpoints

Primary Endpoint

- PFS per RECIST 1.1 assessed by central real-time IRR in the ITT population
  - PFS is defined as the time from randomization to disease progression or death due to any cause, whichever occurs first

Secondary Endpoints

- Overall survival in the ITT population
- PFS per RECIST 1.1 by investigator assessment
- Overall response rate, duration of response, and disease control rate per RECIST 1.1 by real-time IRR
- QOL (European Organisation for Research and Treatment of Cancer QLQ-C30)
  - QOL will also be measured using the EQ-5D-5L, PGI-C, and PGI-S questionnaires (exploratory endpoint)
- Safety (treatment-emergent adverse events, including serious adverse events, graded by Common Terminology Criteria for Adverse Events version 5.0)
- Immunogenicity of INBRX-109
- Pharmacokinetic characterization

IRR, independent radiology review; ITT, intent-to-treat; PFS, progression-free survival; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; QOL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.

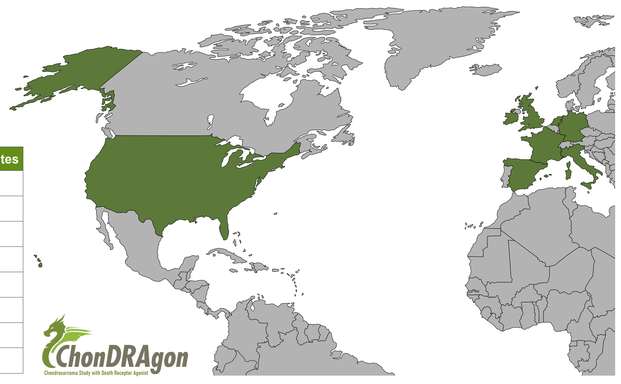
Planned Enrollment

If interested in participating in this clinical trial, please contact Michelle Darling or Kevin Bayer at clinicaltrials@inhibrx.com

8 countries

51 sites

Country	No. of sites
United States	30
France	3
Germany	2
Ireland	1
Italy	4
The Netherlands	2
Spain	5
United Kingdom	4



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