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Poster 486a

Sant P. Chawla, MD, FRACP
santchawla@sarcomaoncology.com

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

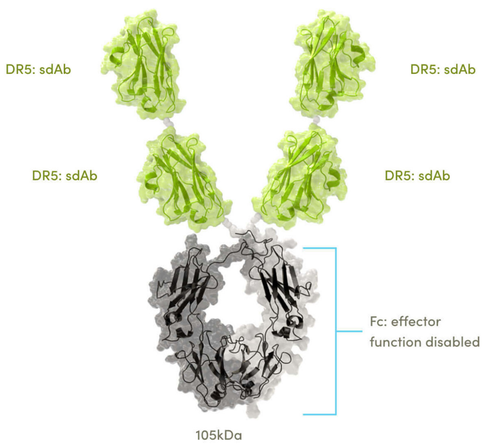
Sant P. Chawla,[1] Garrett Thomas Wasp,[2] Dale Randall Shepard,[3] Jean-Yves Blay,[4] Robin Lewis Jones,[5] Silvia Stacchiotti,[6] Peter Reichardt,[7] Hans Gelderblom,[8] Javier Martin-Broto,[9] Brendan Eckelman,[10] Michelle Darling,[10] Vasily Andrianov,[10] Anthony Paul Conley[11]

[1]Sarcoma Oncology Research Center, Santa Monica, CA; [2]Norris Cotton Cancer Center at Dartmouth-Hitchcock, Lebanon, NH; [3]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; [4]Department of Medical Oncology, Centre Léon Bérard, Lyon, France; [5]Royal Marsden Hospital and Institute of Cancer Research, London, United Kingdom; [6]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [7]Sarcoma Center Berlin-Brandenburg, Helios Klinikum Berlin-Buch, Berlin, Germany; [8]Leiden University Medical Center, Leiden, the Netherlands; [9]Medical Oncology Department, Fundación Jiménez Diaz University Hospital, Madrid, Spain; Institute of Biomedicine of Seville, University of Seville, Seville, Spain; [10]Inhibrx, Inc., La Jolla, CA; [11]The University of Texas MD Anderson Cancer Center, Houston, TX

BACKGROUND

- Chondrosarcomas (CS) are a heterogenous group of malignant bone tumors and the third most common type of primary bone cancer after myeloma and osteosarcoma[1]
  - CS form in the bone cartilage and usually start in the pelvis, scapula, ribs, or the ends of long bones[2]
- The conventional subtype of CS represents 85% to 90% of cases and is typically treated with surgical resection[1]
- However, conventional CS that are unresectable or metastatic are generally resistant to chemotherapy, radiation, and molecular targeted agents, and outcomes remain poor[3]
  - The median progression-free survival (PFS) in patients receiving inactive agents or placebo has historically been <4 months[4]
- Several agents for unresectable or metastatic conventional CS have been evaluated, but most of these have failed, and no systemic therapies have been approved[5-9]
- INBRX-109 is a third-generation, tetravalent agonistic antibody that targets human death receptor 5 (DR5)
  - DR5 is one of 2 pro-apoptotic receptors for the trimeric tumor necrosis factor–related apoptosis-inducing ligand (TRAIL)
  - TRAIL selectively induces programmed cell death in cancer cells with minimal impact on normal tissues and therefore plays an important role in tumor and viral immune surveillance[10]
  - The valency of INBRX-109 was empirically selected to include 4 DR5 binding domains to overcome the limitations of earlier-generation agonists and potently agonize DR5 through efficient receptor clustering, causing cell death

Structure of INBRX-109



- INBRX-109 is based on a single domain antibody (sdAb) platform
  - It consists of 2 identical camelid heavy-chain–only antibody-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[11]

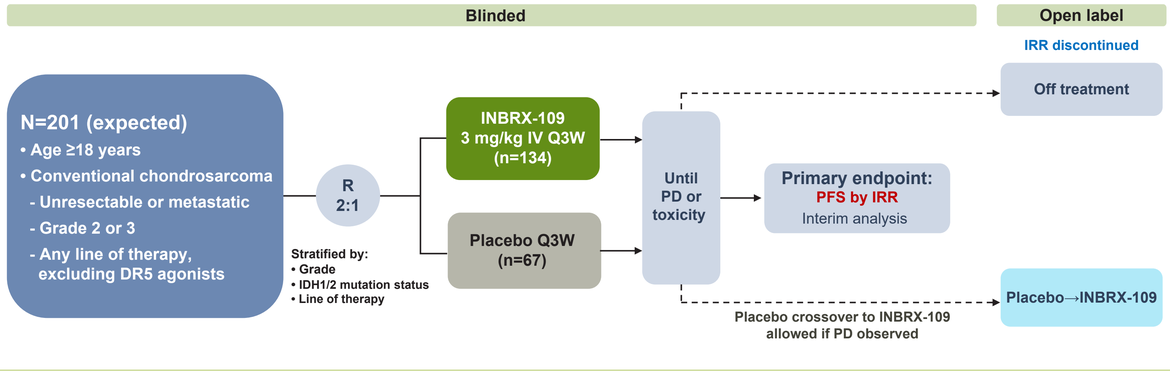
DR5, death receptor 5; Fc, crystallizable fragment; sdAb, single domain antibody.

- As of October 1, 2021, 20 patients with conventional CS were treated with INBRX-109 as part of a phase 1 dose-escalation study (NCT03715933)
  - Of the 18 evaluable patients, 2 (11%) achieved a partial response (PR) and 14 patients (78%) had stable disease (SD); accordingly, the disease control rate (PR + SD) was 89% (16/18)
  - 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 version 1.1; 6 patients (33%) had a decrease of ≥10%
  - Median PFS was 7.4 months
- Given the early clinical activity observed in the phase 1 study and the unmet need in conventional CS, the phase 2 study presented here will evaluate INBRX-109 in unresectable or metastatic conventional CS

METHODS

- ChonDRAgon (NCT04950075) is a multicenter, randomized, blinded, placebo-controlled phase 2 study of INBRX-109 in patients with unresectable or metastatic conventional CS

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 • Conventional chondrosarcoma - Unresectable or metastatic - Grade 2 or 3 per AJCC 8th edition - Any number of prior lines of therapy • Measurable disease by RECIST v1.1 • Radiological progression of disease per RECIST v1.1 criteria within 6 months prior to screening • Adequate hematologic, coagulation, hepatic, and renal function as defined per protocol • ECOG performance status of 0 or 1 • Estimated life expectancy of ≥12 weeks • Availability of archival tissue or fresh cancer biopsy	• Any prior exposure to DR5 agonists • Nonconventional chondrosarcoma (eg, clear-cell, mesenchymal, extraskeletal myxoid, myxoid, and dedifferentiated chondrosarcoma) • Symptomatic active CNS metastases or leptomeningeal disease - Patients with controlled asymptomatic CNS metastases are eligible • Chronic liver diseases, including NASH, NAFLD, alcohol-related liver disease, and cirrhosis - Patients aged <64 years with NAFLD are eligible if adequate hepatic function is confirmed • Patients aged ≥65 years with BMI >30 kg/m^2 • Acute viral or toxic liver disease within 4 weeks prior to first dose of study treatment • Evidence or history of HBV, HCV, or HIV infection

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, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; RECIST, Response Evaluation Criteria in Solid Tumors.

Endpoints

Primary Endpoint

- PFS per RECIST v1.1 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
- PFS by investigator assessment
- ORR, DOR, and DCR per RECIST v1.1 by real-time IRR
- QOL (EORTC QLQ-C30)
- Safety (TEAEs, including SAEs, graded by CTCAE v5.0)
- Immunogenicity of INBRX-109
- PK characterization

CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DOR, duration of response; IRR, independent radiology review; ITT, intention to treat; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

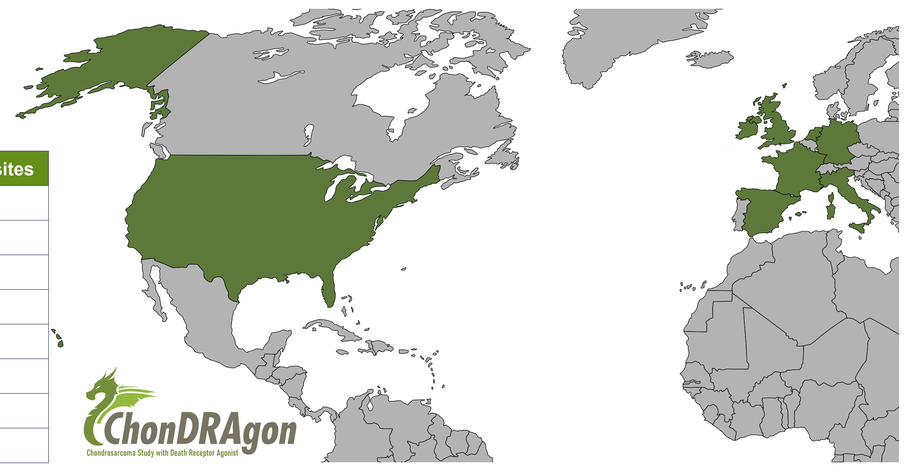
PLANNED ENROLLMENT

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
Netherlands	2
Spain	5
United Kingdom	4



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