748 PHASE 1/2 STUDY OF THE HEXAVALENT OX40 AGONIST INBRX-106 ALONE AND IN COMBINATION WITH PEMBROLIZUMAB IN SELECT SOLID TUMORS

[1]Rachel E Sanborn*, [2]Muhammad Furqan, [2]Doug Laux, [3]Manish Sharma, [4]Daniel Olson, [5]David Berz, [6]Ralph J Hauke, [7]Erminia Massarelli, [8]Conor Steuer, [9]Elizabeth Davis, [9]Wade T Iams, [10]Jonathan Thompson, [11]John Hamm, [12]Vasily Andrianov, [12]Brianne O'Neill, [12]Yaiza Diaz De Durana, [13]Anthony W Tolcher. *[1]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA; [2]University of Iowa, Carver College of Medicine, Iowa City, IA, USA; [3]START Midwest, Grand Rapids, MI, USA; [4]University of Chicago Comprehensive Cancer Center, Chicago, IL, USA; [5]Valkyrie Clinical Trials, Los Angeles, CA, USA; [6]Nebraska Cancer Specialists, Omaha, NE, USA; [7]City of Hope, Duarte, CA, USA; [8]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [9]Vanderbilt University Medical Center, Nashville, TN, USA; [10]Medical College of Wisconsin, Milwaukee, WI, USA; [11]Norton Healthcare, Louisville, KY, USA; [12]Inhibrx, Inc, La Jolla, CA, USA; [13]NEXT Oncology, San Antonio, TX, USA*

Background OX40 is a member of the TNF receptor superfamily and a key costimulatory molecule. OX40 signaling can increase T-cell survival, augment clonal expansion of antigen-specific effector and memory T-cell populations, and inhibit regulatory T-cell–induced immunosuppression, making it an attractive therapeutic target. The endogenous trimeric OX40 ligand binds to 3 OX40 molecules to trigger downstream signaling; however, higher-order clustering of OX40 mediates more potent immune stimulation. INBRX-106 is an empirically designed, hexavalent, agonistic, single-domain antibody specific to OX40; the optimized valency of INBRX-106 can enhance OX40 clustering and elicit greater activation of pathways that promote antitumor immunity than bivalent and tetravalent agonists.[1] A murine INBRX-106 surrogate showed antitumor activity in mouse tumor models resistant or responsive to checkpoint inhibitors (CPIs). Combination with a PD-1 antagonist increased tumor growth inhibition. We describe a phase 1/2 study evaluating INBRX-106±pembrolizumab in select solid tumors.

Methods This open-label, 4-part, phase 1/2 study (NCT04198766) of INBRX-106±pembrolizumab in patients with locally advanced unresectable or metastatic solid tumors (N≈333) is enrolling in the US (figure 1). Dose escalation (part 1, INBRX-106; part 3, combination) has been completed; the recommended phase 2 dose (RP2D) is being assessed in dose-expansion cohorts (part 2, INBRX-106; part 4, combination). Eligible patients are naive to OX40 agonists with disease that progressed despite all standard therapies or who have no alternative treatment options (except CPI-naive cohorts). Parts 2 and 4 include patients with non-small cell lung cancer (NSCLC), melanoma, head and neck squamous cell carcinoma, gastric or gastroesophageal junction adenocarcinoma, renal cell carcinoma, transitional (urothelial) cell carcinoma, or microsatellite instability (MSI)–/tumor mutation burden (TMB)–high solid tumors. In part 2, any PD-L1 combined positive score (CPS) is permitted in the 3 basket cohorts; patients in a fourth cohort (PD-L1+ NSCLC) require a tumor proportion score (TPS) ≥50% or TMB ≥10 mutations/Mb. Part 4 includes 2 PD-L1+ (CPS ≥1) basket cohorts (1 CPI relapsed/refractory; 1 CPI naive) and 2 CPI-relapsed/refractory PD-L1+ NSCLC cohorts (1 TPS ≥1%; 1 TPS ≥50% or TMB ≥10 mutations/Mb); 3 dosing regimens will be evaluated in the CPI-relapsed/refractory NSCLC cohort requiring TPS ≥50%. Additionally, a basket cohort of mismatch repair–deficient or MSI-high solid tumors and a cohort of uveal melanoma (both CPI relapsed/refractory) will be included.

Primary objectives are safety and determination of the maximum tolerated dose and/or RP2D of INBRX-106±pembrolizumab. Secondary objectives include pharmacokinetics, immunogenicity, and preliminary antitumor activity per RECIST.

Trial Registration ClinicalTrials.gov identifier, NCT04198766

REFERENCE

1. Rowell E, Kinkead H, Torretti E, *et al.* INBRX-106: A novel hexavalent anti-OX40 agonist for the treatment of solid tumors. *J Immunother Cancer*. 2021;**9**. Abstract 856.

Ethics Approval The study protocol was reviewed and approved by the institutional review board at each participating institution; all patients provided written informed consent.

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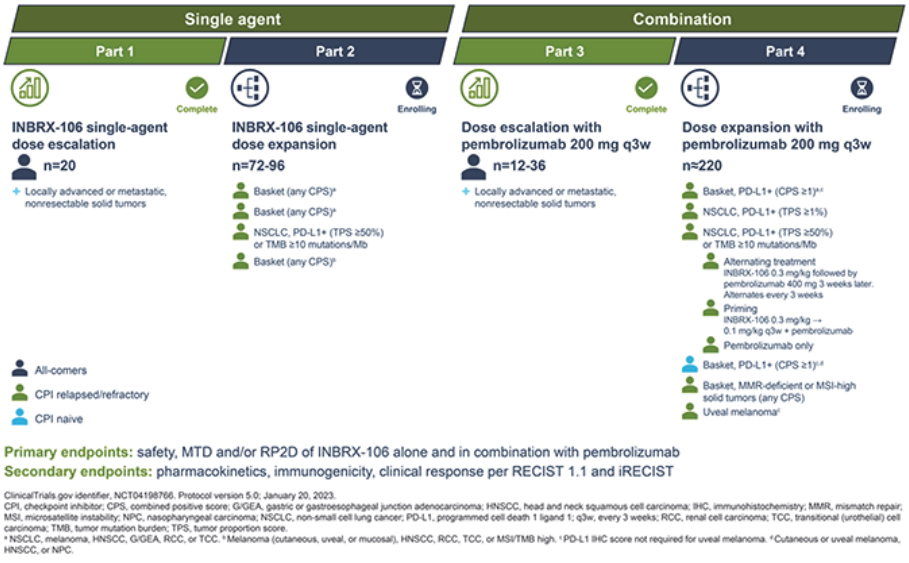

Abstract 748 Figure 1 Phase 112 study of the hexavalent OX40 agonist INBRX-106 as a single agent and in combination with pembrolizumab in patients with locally advanced or metastatic solid tumors

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