Background OX40 is a member of the TNF receptor super-family 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 clustering and elicit greater activation of pathways that promote antitumor immunity than bivalent and tetravalent OX40 agonists. INBRX-106 is an empirically designed, hexavalent, agonistic, single-domain antibody specific to OX40; the optimized valency of INBRX-106 can enhance clustering and elicit greater activation of pathways that promote antitumor immunity than bivalent and tetravalent OX40 agonists. INBRX-106 is 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 clustering and elicit greater activation of pathways that promote antitumor immunity than bivalent and tetravalent OX40 agonists.

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)-mismatch repair (MMR)-deficient or MSI-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 ≥10%, 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

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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Phase 1/2 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