

A PHASE 1 TRIAL OF IO-202, AN ANTAGONIST ANTIBODY TARGETING MYELOID CHECKPOINT LILRB4 (ILT3), AS MONOTHERAPY AND IN COMBINATION WITH PEMBROLIZUMAB IN ADULT PATIENTS WITH ADVANCED RELAPSED OR REFRACTORY SOLID TUMORS

¹Aung Naing, ²John Powderly, ³Meredith Pelster, ⁴Alexander Spira, ⁵Reva Schneider, ⁶Paul Woodard, ⁶Luke Chung, ⁶Elizabeth Wieland, ⁶Sydney Ray, ⁶Kyu Hong, ⁶Tao Huang, ⁶X Charlene Liao, ⁶Hong Xiang, ⁷Heinz-Josef Lenz, ⁶Wen Hong Lin*. ¹MD Anderson Cancer Center, Houston, TX, USA; ²Carolina BioOncology Institute, Huntersville, NC, USA; ³Sarah Cannon Research Institute at Tennessee Oncology, Nashville, TN, USA; ⁴Virginia Cancer Specialists, Fairfax, VA, USA; ⁵Mary Crowley Cancer Institute, Dallas, TX, USA; ⁶Immune-Onc, Palo Alto, CA, USA; ⁷USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA

Background Most patients with advanced solid tumors relapse after T-cell checkpoint blockade despite of immunotherapy becoming the mainstream with the approvals of T-cell checkpoint inhibitors. Myeloid checkpoint inhibition is a new approach to immunotherapy.

Leukocyte immunoglobulin-like receptor subfamily B member 4 (LILRB4) is a myeloid checkpoint with its expression restricted to monocytes or monocyte-derived cells^{1,2,3} and in normal antigen presenting cells. LILRB4 functions as a negative regulator of immunity through interaction with its ligands, apolipoprotein E and fibronectin^{1,2,4,5,6}. Blockade of LILRB4 has the potential to enhance anti-tumor T cell activities.

IO-202 is a IgG1 monoclonal antibody that binds to LILRB4 to block ligand interactions and inhibits the function of LILRB4. In vitro, IO-202 treatment of immune cells increases pro-inflammatory responses and enhances antigen presenting cell phenotypes. IO-202 has been studied at a first-in-human, phase1 study in acute myeloid leukemia and chronic myelomonocytic leukemia patients (IO-202-CL-001) up to 30 mg/kg IV Q2W with no observed dose limiting toxicity (DLT), which provided sufficient data supporting the starting dose of 250 mg.

Methods This trial (NCT05309187) is a Phase 1, dose-escalation, dose-expansion, safety, and pharmacokinetic (PK) evaluation of IO-202 alone and plus pembrolizumab in patients with advanced solid tumors. Up to 36 patients will be enrolled in the dose-escalation portion (Part 1) and up to 168 patients will be enrolled in the dose-expansion portion (Part 2). IO-202 will be administered IV Q3W, with a 21-day DLT evaluation period. In Part 1, patients will be treated with increasing doses of IO-202 alone and plus pembrolizumab using the modified Toxicity Probability Interval method; the combination cohorts will start once the 1st monotherapy dose has cleared the DLT window and be conducted independently. In Part 2, patients will be treated with IO-202 RP2D plus pembrolizumab 200 mg IV Q3W.

The primary objective is to assess safety and tolerability of IO-202 alone and plus pembrolizumab in patients with advanced solid tumors, to estimate the maximal tolerated dose or maximum administered dose and select the recommended phase 2 dose (RP2D). Secondary objectives include characterizing PK for IO-202 alone or plus pembrolizumab; and assessing efficacy of IO-202 plus pembrolizumab in various solid tumors. Biomarker evaluation includes changes in immune cell markers, LILRB4 expression and receptor occupancy.

Statistical analyses will be descriptive. Tabulations will be produced for appropriate disposition, demographics, baseline characteristics, safety, PK, pharmacodynamic, and clinical activity parameters. To date, one patient has been treated with IO-202 without DLT.

Trial Registration NCT05309187

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Ethics Approval The trial has been approved by the Advarra IRB on January 18, 2022, with the Advarra IRB ID of Pro00060224. All the subjects will give informed consent before being enrolled into this trial and any study related procedures.

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