Abstract 2523: A Phase 1a Dose Escalation Study of PY159, a Monoclonal Antibody Targeting TREM1, Triggering Receptor Expressed on Myeloid Cells 1

Winer I1, Patnaik A2, Barve M3, Kummer S4, Schenk EL5, LoRuocco PM6, Yeko O7, Fu S8, Jachan N9, Myers M9, Liang L10, Deegan D10, Jackson L10, Li Y10, Reyno L11, Chamberlain M10

1Karmanos Cancer Institute Detroit MI, 2START San Antonio TX, 3Mary Crowley Cancer Research Dallas TX, 4Oregon Health and Science University Knight Cancer Institute Portland OR, 5University of Colorado Aurora CO, 6Yale University New haven CT, 7Massachusetts General Hospital Boston MA, 8University of Texas MD Anderson Cancer Center Houston TX, 9Pionyr Immunotherapeutics South San Francisco CA

Purpose: To characterize the safety of PY159, an agonist antibody to Triggering Receptor Expressed on Myeloid cells 1 (TREM1) that engagers immunosuppressive human myeloid cells, as a single agent and in combination with pembrolizumab in subjects with advanced refractory solid tumors including subjects with no refractory to immune checkpoint inhibitors.

Methods: Two strata were evaluated, PY159 and in combination with 200 mg of pembrolizumab using an accelerated 3+3 dose escalation study design. During dosing onward every 4 weeks. Dosis assessment was established by RECIST 1.1, performed every 6 weeks. The single agent stratum included 7 doses of PY159 (range 0.01 to 10 mg/kg). The combination stratum included 4 dose levels of PY159 (range 0.3 to 10 mg/kg). Pharmacokinetics were evaluated at specific time points. Archival tumor tissues were analyzed for TREM1 expression by immunohistochemistry. Based on preclinical immunohistochemistry data, HR+/HER2- and triple-negative breast cancer, gastric cancer, pancreatic cancer, head and neck cancer, non-small cell lung cancer, and gynecological cancers were evaluted.

Results: 37 subjects (median age 65 years range 29-95), 22 females and 15 males with an ECOG PS >2 were enrolled and all 7, 4 were radiographically evaluable (1 withdrew consent, 2 sustained a TEAE, and 1 with a DLH, an asymptomatic Grade 3 thrombosis), 20 subjects received single agent PY159 and 17 received PY159 in combination with pembrolizumab. 4 subjects experienced a Grade 3 TARE, 14a low immune related reaction, 15A Grade 1 AEs, 16S (related to, 20 of AEs), and 2 immune related adverse event (arthritis). There were on SUAs, 5 subjects had sustained high GRAE resulting in discontinuum. TREM1 levels in the tumor ranged from 0.1 to 20 ng/mL. Pharmacokinetic parameters were linear beyond the 0.3 mg/kg dose, dose proportional with a half-life of 9-5 days, and unaffected by pembrolizumab. Radiographic response included 2 partial responses (1 each in an ovarian and pancreatic cancer) and unaffected in 37.8% (31/37) of subjects experienced at least one TRAE. • No clinically relevant neutropenia

Conclusions: PY159 was well tolerated, with an acceptable safety profile, as a single agent and in combination with pembrolizumab. A dose expansion was derived and enrollment in 7 pre specified cancers is ongoing.

Safety Summary and Adverse Events

- 100% (37/37) of subjects experienced at least one TEAE
- 20 (51.4%) subjects experienced a Grade 3 TEAE and 3 (8.1%) experienced a Grade 5 TEAE
- 83.8% (31/37) of subjects experienced at least one TRAE
- 4 subjects (10.8%) experienced a Grade 3 TARE, 14 low immune related reaction, 15A Grade 1 AEs, 16S (related to, 20 of AEs), and 2 immune related adverse event (arthritis). There were on SUAs, 5 subjects had sustained high GRAE resulting in discontinuum. TREM1 levels in the tumor ranged from 0.1 to 20 ng/mL. Pharmacokinetic parameters were linear beyond the 0.3 mg/kg dose, dose proportional with a half-life of 9-5 days, and unaffected by pembrolizumab. Radiographic response included 2 partial responses (1 each in an ovarian and pancreatic cancer) and unaffected in 37.8% (31/37) of subjects experienced at least one TRAE. • No clinically relevant neutropenia

PY159 is safe and well tolerated across 7 dose levels (0.01-10 mg/kg) as a single agent and 4 dose levels (0.01-3 mg/kg) in combination with a fixed dose of pembrolizumab.

PY159 pharmacokinetics at doses above 0.3 mg/kg are linear, dose proportional, and have a half-life ranging from 4.2-9.4 days.

PY159 expression by IHC from 33 evaluable archival tumor specimens across multiple cancers ranged from 0-15% with a median of 0.5% TREM1 expression modestly correlated with M2-like (CD68+CD163+) TAMs.

Best Radiographic Response: Partial Response and Stable Disease

Subject | Cancer | Dose Level (mg/kg) | Prior Therapies | Prior Therapy Last Therapy | Duration (Wk) | Best Response | Archival TREM1 (%) | Archival TAM-M2 (%)
---|---|---|---|---|---|---|---|---
104-2001 | Breast | 6.03 | 3L | HER2- | Single | 9/12 | PD | No | 36/108 | SD | NE | NE
107-2004 | Pancreatic | 3.0 | Single | 3L | | 2/SD | No | 2/12 | PD | 20 | 7.29 | 0.1 | 0.2
102-2005 | Ovarian | 0.1 | Single | 3L | | 11/SD | Yes | 11/SD | PD | 1 | 9.2 | 0.1 | 0.2
103-2003 | Pancreatic | 0.1 | Single | 3L | | 5/SD | 3 | 5.63 | 0.3 | 0.12
102-2002 | HSNC | 0.03 | Single | 3L | | 4/SD | Yes | 4/SD | PD | 0.15 | 3.4 | 0.2 | 0.1
105-2002 | HSNC | 0.03 | Single | 3L | | 2/SD | Yes | 12/6 SD | PD | 7 | 50.7 | 0.1 | 0.2
104-2009 | Pancreatic | 0.3 | Combination | 3L | | 4/12 | PD | 2/12 | PD | 0.5 | 2.3 | 0.1 | 0.1
102-2004 | HSNC | 0.03 | Combination | 3L | | 2/PR | Yes | 4/12 SD | PD | 3 | 4 | 0.1 | 0.1
111-2006 | Pancreatic | 0.03 | Combination | 3L | | 3/SD | 4 | 17.7 | 0.1 | 0.2
104-2014 | HSNC | 0.03 | Combination | 3L | | 3/SD | Yes | 7/21 SD | PD | 0 | 1.2 | 0.1 | 0.1
107-2006 | Ovarian | 0.8 | Combination | 3L | | 8/PR | No | 8/24 PR | PD | 15 | 39 | 0.1 | 0.1

Changes from Baseline in Target Lesion Size

- Waterfall plots show best change from baseline in sum of diameters (0-100%)
- Overall response can be different as neither new lesion or non-target lesion(s) are considered.
- Subjects without complete target measurement are not included.
- Spider plot shows longitudinal change from baseline across subjects with a response of Stable Disease or better.