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

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Abstract

Purpose: To characterize the safety of PY159, an agonist antibody to Triggering Receptor Expressed on Myeloid cells 1 (TREM1) that reprograms immunosuppressive intratumoral myeloid cells, as a single agent and in combination with pembrolizumab in subjects with advanced refractory solid tumors including subject's 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. Dosing was intravenous once every 3 weeks. Disease assessment by RECIST 1.1 was performed every 6 weeks. The single agent stratum included 7 dose levels 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 specified 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 gynecologic cancers were studied.

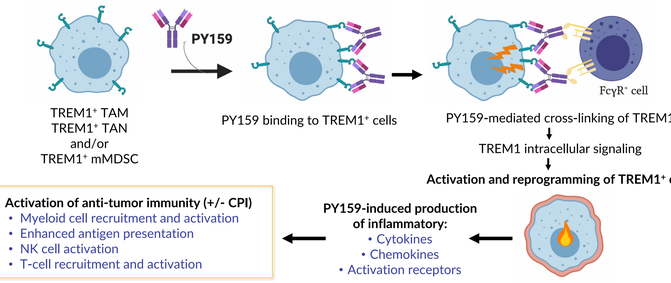
Results: 37 subjects (median age 65 years [range 29-86], 22 females and 15 males) with an ECOG PS <2 were enrolled and all, but 4 were radiographically evaluable (1 withdrew consent, 2 sustained a TEAE, and 1 with a DLT, an asymptomatic Grade 3 transaminitis). 20 subjects received single agent PY159 and 17 received PY159 in combination with pembrolizumab. 4 subjects experienced a Grade 3 TRAE, 14 a low-grade immune related reaction, 18 a SAE (related in 2), and 14 an immune related adverse event (arthralgias). There were no SUSARs. 5 subjects sustained high-grade TRAE resulting in discontinuation. TREM1 levels in the tumor ranged from 0-15%. Pharmacokinetic parameters were linear beyond the 0.3 mg/kg dose, dose proportional with a half-life of 8–9 days, and unaffected by pembrolizumab. Radiographic response included 2 partial responses (1 each in an ovarian and pancreatic cancer subject) and stable disease in 9 subjects ranging in duration from 12–96+ weeks. Two subjects continue receiving PY159.

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

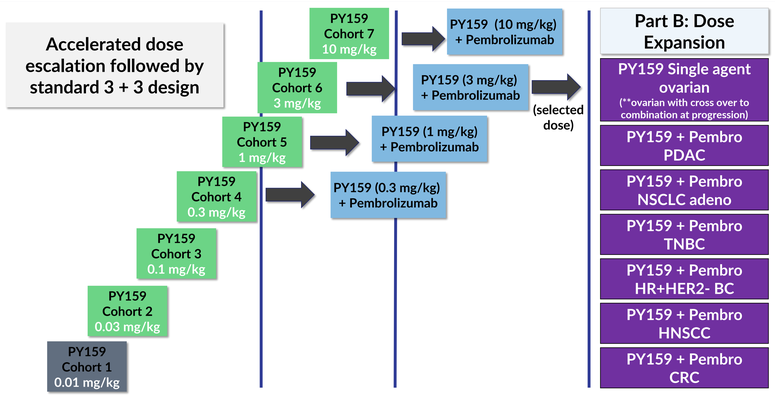
Myeloid Tuning™ and Tumor Destruction

- Pionyr developed a humanized afucosylated IgG1 monoclonal antibody (PY159) that binds TREM1, a myeloid cell immune checkpoint, found on the surface of myeloid cells.
- With enhanced FcγR binding, PY159 is designed to cross-link TREM1 and induce signaling downstream of TREM1 and DAP12 in TREM1-expressing myeloid cells.
- PY159 induces phospho-signaling in TREM1 expressing cells, promotes production of cytokines including CXCL10 and IFN gamma and chemokines including CCL2, CCL3, and CCL4 in human peripheral blood leukocytes, and upregulates cell surface CD40, HLA-DR, and costimulatory molecules CD80 and CD86 on monocytes.
- PY159 repolarizes intratumoral immunosuppressive myeloid cells, including M2-like anti-inflammatory tumor associated macrophages (TAMs), monocytes (monocytic myeloid derived suppressor cells, mMDSCs), and neutrophils (TANs) within the TME to become proinflammatory to promote anti-tumor immunity
- TREM1 expression is associated with poor outcome in many tumor types and targeting TREM1 with PY159 (alone and/or in combination with a CPI) has anti-tumor effects in multiple preclinical mouse tumor models.

PY159 Mechanism of Action: Targeting TREM1 to Reprogram Immunosuppressive Myeloid Cells



PY159 First-in-Human Trial Design: Simultaneous Determination of Safety as a Single Agent and in Combination With Pembrolizumab



Patient Demographics, Prior Therapies, and Cancer Type (N=37)

Demographics	Overall
Age (years)	
Median (min, max)	65 (29, 86)
<50	2 (5.4%)
50-64	15 (40.5%)
≥ 65	20 (54.1%)
Gender	
Female	22 (59.5%)
Male	15 (40.5%)
Race	
White	31 (83.8%)
Black	4 (11.1%)
Other	2 (5.6%)

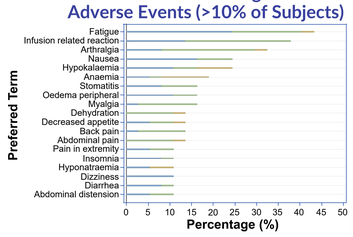
Prior cancer therapy	Number
Surgery	29 (78.4%)
Radiotherapy	15 (40.5%)
Systemic therapy	37 (100%)
I-O based therapy	14 (37.8%)
Median lines of prior therapy	4
Median lines of prior metastatic therapy	3

Cancer	Overall
Breast (HR+HER2-)	2 (5.4%)
Breast (TNBC)	1 (2.7%)
Cervical	2 (5.4%)
Endometrial	1 (2.7%)
Head and Neck (SCC)	6 (16.2%)
Lung (SCC)	3 (8.1%)
Ovarian	7 (18.9%)
Pancreatic	12 (32.4%)
Salivary gland (Parotid ACC)	2 (5.4%)
Vulvar	1 (2.7%)

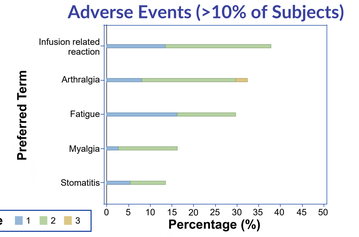
Safety Summary and Adverse Events

- 100% (37/37) of subjects experienced at least one TEAE
  - 20 (54.1%) 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 TRAE (1 each hypotension, hyponatremia, arthralgias, transaminitis)
- 18/37 subjects (48.6%) experienced a total of 24 SAEs
  - All but 2 unrelated (1 each, Grade 2 IRR, recrudescence; Grade 1 irAE pneumonitis)
- 1 DLT (2.7%) (asymptomatic transient Grade 3 biochemical ALT increase [irAE])
- 15 Grade 1/2 infusion-related reactions (IRRs) in 14/37 (37.8%) subjects reported
- 3 unrelated and 2 related TEAEs resulted in PY159 drug discontinuance
- 37.8% (14/37) subjects with rheumatologic irAEs (arthralgia/myalgia syndrome)
- 3 (8.1%) subjects with other irAE
  - 1 Grade 1 asymptomatic irAE pneumonitis by CT
  - 1 Grade 3 asymptomatic elevation of ALT (transaminitis)
  - 1 Grade 2 Sweet's syndrome biopsy documented (dermatitis)
- No clinically relevant neutropenia

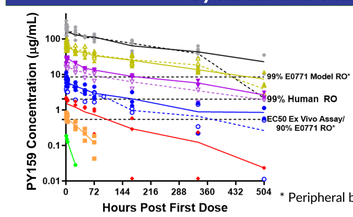
Treatment-Emergent Adverse Events (>10% of Subjects)



Treatment-Related Adverse Events (>10% of Subjects)



Cycle 1 PK Data for Dose Escalation PY159



* Peripheral blood RO

- PY159 exhibits target mediated drug disposition (TMDD) at lower doses;
- TMDD appears saturated at doses ≥ 0.3 mg/kg
- Dose proportional PK observed at ≥ 0.3 mg/kg (single agent)
- Terminal half-life ranged from ~4.2 to 9.4 days once target is saturated (0.3 to 10 mg/kg dose levels)
- Peripheral RO observed over the dosing interval in cohorts ≥ 1 mg/kg

Dose Level (mg/kg)	Subjects (n)	$t_{1/2}$ (day)	C_{max} (µg/mL)	t_{max} (day)	AUC_{0-t} (day*µg/mL)	$AUC_{0-\infty}$ (day*µg/mL)	V_z (mL/kg)	CL (mL/h/kg)	C_{max}/D (kg*µg/mL/mg)	$AUC_{0-\infty}$/D (day*kg*µg/mL/mg)
0.01, single	1	0.380	0.186	0.0417	0.0903	0.106	51.8	3.94	18.6	10.6
0.03, single	3	1.26	0.678	0.0417	0.943	1.18	47.7	1.17	22.6	39.3
0.1, single	3	2.13	1.64	0.0417	6.86	6.92	56.4	1.14	16.4	69.2
0.3, single	3	6.82	7.29	0.0625	38.7	46.0	67.2	0.335	24.3	153
1, single	3	8.75	27.8	0.160	177	215	58.6	0.195	27.8	215
3, single	3	8.06	73.2	0.0417	461	551	66.0	0.240	24.4	184
10, single	3	9.43	181	0.0903	1210	1700	85.1	0.292	18.1	170
0.3, combo	3	4.33	6.64	0.0417	19.3	31.4	65.8	0.490	22.1	105
1, combo	3	8.03	17.1	0.0417	108	145	82.7	0.327	17.1	145
3, combo	6	8.71	75.6	0.0804	487	651	59.1	0.211	25.2	217
10, combo	4	4.24	248	0.0573	1340	1410	46.0	0.302	24.8	141

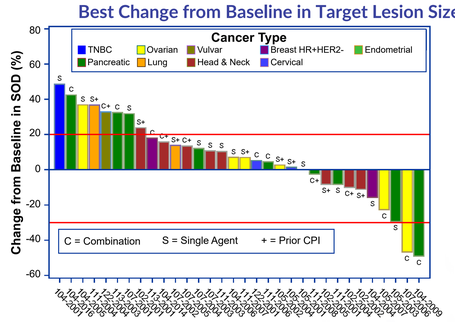
Best Radiographic Response: Partial Response and Stable Disease

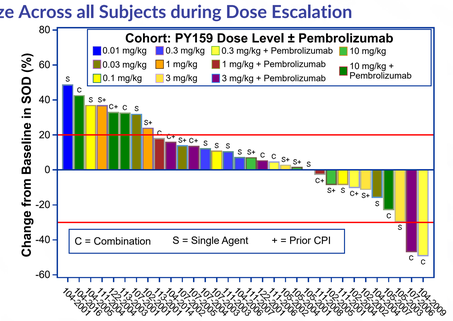
- 37 subjects enrolled
  - 7 single agent and 4 combination cohorts
  - 4 unevaluable for response
  - 2 active subjects
  - 2 subjects treated beyond progression^
- 22 progressive disease or death (66.7%)
  - TREM1 expression median <1%, range 0-10%
- 9 stable disease + 2 PR (33.3%)
  - Median 12 weeks, range 12-105+ weeks
  - TREM1 expression median 2%, range <1%-15%

Subject	Cancer	Dose Level (mg/kg)	Prior Therapies (n) /Response to Last Therapy	Prior CPI	Duration of Stable Disease Cycle/ Weeks	Best Response	Archival TREM1 Expression (%)	Archival TAMs M2 Expression (%)
104-2004	Breast HR+HER2-	0.03, Single Agent	9/PD	No	36/108+	SD	NE	NE
107-2004	Pancreatic	0.3, Single Agent	2/SD	No	4/12	SD	2.0	7.29
105-2002	Ovarian	3.0, Single Agent	11/SD	Yes	4/12	SD	<1	9.2
105-2003	Pancreatic	3.0, Single Agent	5/PD	No	4/12	SD	3	5.63
102-2002	HNSCC	3.0, Single Agent	4/PD	Yes	4/12	SD	0.5	12.14
102-2005	HNSCC	10, Single Agent	2/PD	Yes	12/36	SD^	7	50.7
104-2009	Pancreatic	0.3, Combination	2/PD	No	14/42 in C22	PR^	0.5	2.3
102-2004	HNSCC	0.3, Combination	2/PR	Yes	4/12	SD	3	4.4
111-2008	Pancreatic	1.0, Combination	3/SD	No	4/12	SD	2	17.7
104-2014	HNSCC	3.0, Combination	3/SD	Yes	7/21	SD	0	1.2
107-2006	Ovarian	3.0, Combination	8/PR	No	8/24	PR	15	39

Changes from Baseline in Target Lesion Size

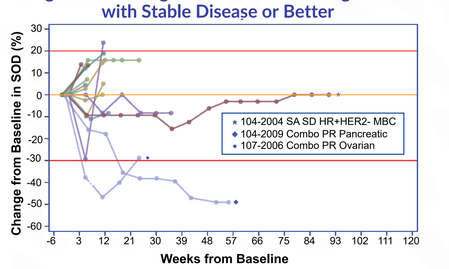
Best Change from Baseline in Target Lesion Size Across all Subjects during Dose Escalation





- Waterfall plots show best change from baseline in sum of diameters (SOD) for target lesions.
- 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 among subjects with a response of Stable Disease or better

Longitudinal Change from Baseline among Patients with Stable Disease or Better



Conclusions

- PY159 is safe and well tolerated across 7 dose levels (0.01-10 mg/kg) as a single agent and 4 dose levels (0.3-10 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.
- TREM1 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 has been stable disease in 9 subjects (25.7%: duration range 12-114 weeks) and partial response in 2 subjects (5.7%, duration range 24-42 weeks).
- A recommended dose for expansion of 3 mg/kg has been determined and 7 prespecified expansion cancer cohorts are currently enrolling.