Abstract 377526: A Phase 1a Dose Escalation Study of PY314, a TREM2 (Triggering Receptor Expressed on Myeloid Cells 2)-Targeting Monoclonal Antibody

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Abstract

Purpose: To characterize the safety and tolerability of PY314 (a monoclonal antibody that depletes immunosuppressive macrophages in tumors) as a single agent and in combination with pembrolizumab in subjects with advanced refractory solid tumors, including those refractory to checkpoint inhibitors if approved for that indication.

Methods: We evaluated single-agent PY314 and the combination of PY314 with 200 mg pembrolizumab in subjects with advanced solid tumors using a 3+3 dose escalation study design. Subjects were given intravenous doses once every 3 weeks. Disease progression was monitored using the RECIST 1.1 criteria every 6 weeks. Each stratum included 4 dose levels of PY314 (1, 3, 10, and 20 mg/kg). Pharmacokinetics were evaluated at specified time points. Archived tumor tissues were analyzed for TREM2 expression by immunohistochemistry. Based on preclinical evaluation of TREM2 expression, we evaluated patients with HR$^+$HER2$^-$ or triple-negative breast tumors, colorectal cancer, renal cell cancer, non-small cell lung cancer, and gynecologic cancers.

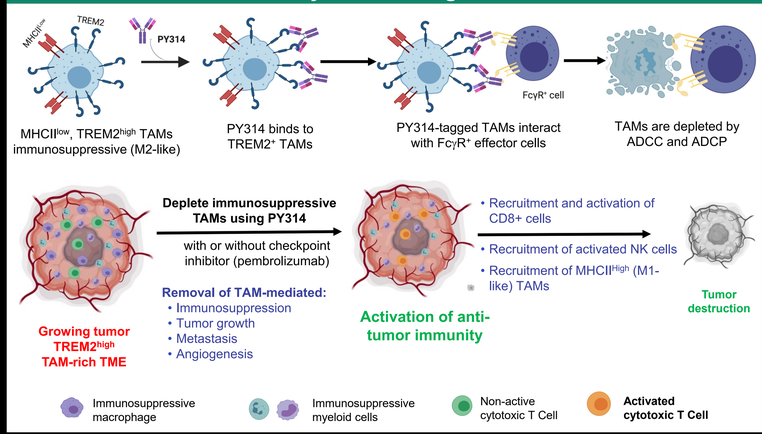
Results: 28 subjects (median age, 60 years; range, 26–76 years old; 22 female and 6 male) with an ECOG PS <2 were enrolled. All but 1 subject, who withdrew consent after dosing, were evaluated. 15 subjects were given single-agent PY314, and 13 subjects were given the combination of PY314 and pembrolizumab. There were no infusion-related reactions, dose limiting toxicities, suspected serious adverse reactions, or high-grade treatment-related adverse events (TRAEs) that resulted in treatment discontinuance. 12 subjects had at least 1 TRAE; in all but 1 subject these were low grade. One subject had a treatment-related immune system disorder. 8 subjects had serious adverse events, all unrelated to treatment. TREM2 expression in archived tumor tissues ranged from 0.0 to 20%. PY314 pharmacokinetics were linear, dose proportional, unaffected by concomitant pembrolizumab, and had a half-life of 8–9 days. The best radiographic response was stable disease, observed in 11 subjects (39.3%), which ranged in duration from 9 to 42 weeks. 6 subjects with stable disease have progressed and 5 remain on treatment. (Data in abstract reported as of February 12, 2022)

Conclusions: PY314 was well tolerated and has an excellent safety profile as a single agent and in combination with pembrolizumab. A recommended dose for expansion was derived and enrollment of subjects with 6 prespecified cancers is underway.

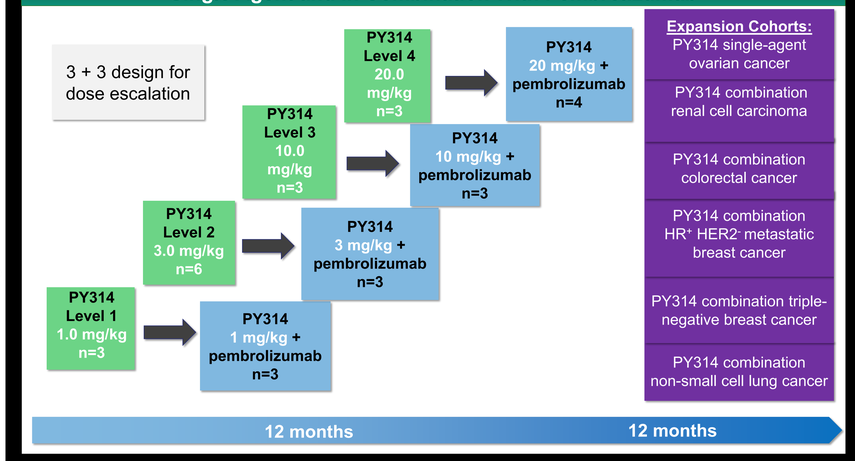
Introduction

- The target of PY314, TREM2, is a transmembrane protein expressed on a subset of myeloid cells, namely macrophages (including microglia), some dendritic cells, and osteoclasts.
- TREM2 is highly expressed on immune-suppressive tumor-associated macrophages (TAMs) within the tumor microenvironment (TME), where it functions as a negative regulator of inflammatory responses.
- Analysis of *TREM2* mRNA in Pionyr's archived tumor specimens and in The Cancer Genome Atlas (TCGA) revealed that TREM2 is upregulated in tumor tissues compared with adjacent non-tumor tissues. Collectively, TAMs express higher levels of TREM2 than macrophages in non-tumor tissues. These findings indicate that agents designed to target TREM2 would have minimal off-target effects in tumor and non-tumor tissues.
- Myeloid inhibitory cells such as TAMs can limit responses to checkpoint inhibitors, chemotherapy, irradiation, and angiogenesis inhibitors by secreting immunosuppressive factors and inhibiting T-cell–mediated responses against tumors.
- Higher numbers of TAMs within the TME (specifically M2-like suppressive TAMs) are associated with shorter survival times of patients with different types of cancer. There is a negative correlation between tumor tissue level of *TREM2* mRNA and patient survival in a variety of cancer types, suggesting its involvement in tumor progression.
- Agents that shift the balance of inhibitory myeloid cells towards more inflammatory functions should promote anti-tumor immune responses in the TME. Targeting the upregulated expression of TREM2 on M2-like suppressive TAMs could be a mechanism for depleting these cells from the TME.
- Pionyr developed a humanized IgG1 afucosylated monoclonal antibody (PY314), which specifically binds human TREM2 and balances the TME ('Myeloid Tuning') by specifically depleting TREM2+ TAMs, via antibody-dependent cell-mediated cytotoxicity (ADCC) and/or antibody-dependent cellular phagocytosis (ADCP) (Binnewies M. et al., *Cell Reports,* 2021).

PY314 Mechanism of 'Myeloid Tuning' and Tumor Destruction



PY314 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

Demographics	Overall (n=28)
Age (years)	
Median (min, max)	60 (26, 76)
Age < 50	9 (32.1%)
Age 50–64	8 (28.6%)
Age ≥ 65	11 (39.3%)
Sex	
Female	22 (78.6%)
Male	6 (21.4%)
Race	
White	22 (78.6%)
Black	4 (14.3%)
Hawaiian	1 (3.6%)
Other	1 (3.6%)

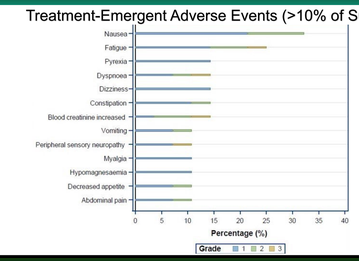
Prior therapy	Number (%)
Surgery	25 (89.3%)
Radiotherapy	13 (46.4%)
Systemic	28 (100%)
Median number	4
Checkpoint inhibitor	8 (28.6%)
Metastatic setting	24 (85.7%)
Median number	3

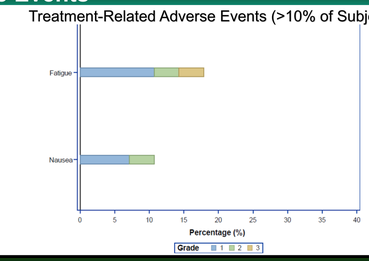
Primary Cancer Type	Overall (n=28)
Breast (HR$^+$HER2$^-$)	4 (14.3%)
Breast (triple negative)	1 (3.6%)
Cervical	1 (3.6%)
Colon	3 (10.7%)
Endometrial	3 (10.7%)
Kidney (clear cell)	3 (10.7%)
Lung (adenocarcinoma)	1 (3.6%)
Ovarian	6 (21.4%)
Rectal	6 (21.4%)

Safety Summary

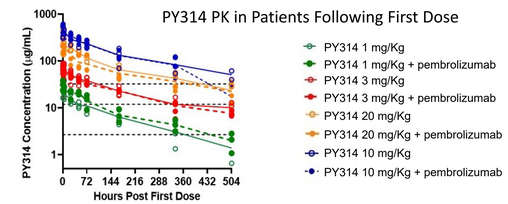
- 25 subjects (89.3%) had at least 1 treatment-emergent adverse event (TEAE)
  - 11 subjects (39.3%) had at least 1 grade-3 TEAE
- 12 subjects (42.9%) had at least 1 treatment-related AE
  - 1 subject (3.6%) had TEAE higher than grade 3 (fatigue)
- 11 subjects had unrelated serious AEs
- No dose-limiting toxicity was observed
- No subject discontinued treatment for a PY314-related AE
- No infusion-related reactions were observed
- 4 subjects had grade-1 or -2 immune-related AEs:
  - 3 polymyalgia-like syndromes
  - 1 mastitis-like syndrome
- No organ-specific toxicities were observed (pancreas, lung, bone)

Adverse Events





Cycle 1 PK Data for Dose Escalation PY314



- Increase in PY314 dose led to dose-proportionate increase in exposure
- Terminal half-life ranged from ~5 to 9 days
- The combination of PY314 + pembrolizumab does not appear to affect exposure levels

Dose Level (mg/kg)	Number of subjects	λ_z (1/day)	$t_{1/2}$ (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)
1, single agent	n=3	0.124	5.78	25.3	0.0625	127	139	63.6	0.329	25.3	139
3, single agent	n=6	0.0929	8.75	76.6	0.122	419	560	66.5	0.238	25.5	187
10, single agent	n=3	0.0907	8.64	295	0.0417	1490	1810	67.0	0.241	29.5	181
20, single agent	n=3	0.0955	7.44	467	0.111	2740	3310	67.4	0.274	23.4	165
1, combination	n=3	0.128	5.45	31.2	0.0417	156	175	47.9	0.253	31.2	175
3, combination	n=3	0.0848	8.25	66.1	0.0417	431	523	68.1	0.240	22.0	174
10, combination	n=3	0.0767	9.08	218	0.0903	1090	1480	98.4	0.317	21.8	148
20, combination	n=4	0.156	4.62	529	0.0781	2790	2790	49.4	0.309	26.4	139

Best Radiographic Response: Stable Disease

- **28 subjects enrolled**
  - 4 single-agent cohorts
  - 4 combination cohorts
- **28 evaluable for response**
  - 11 with stable disease (39.3%)
  - TREM2 expression by immunohistochemistry ranged from 0 to 15% (median 3%), based on manual immune scoring of TREM2-positive myeloid cells in total tumor area.
  - TREM2 expression correlated with infiltration of M2-like (CD68+CD163+) TAMs in the TME.
  - Data reported as of May 13, 2022

Subject	Cancer	Dose level (mg/kg)	Number of Prior treatments/ Response to Last Therapy	Prior Checkpoint Inhibitor Therapy	Duration of Stable Disease Cycle/ Weeks	TREM2 Expression in Archival Tumor Specimens	Archival M2 TAMs (image analysis)
104-1002	endometrial	1, single agent	5/progressive disease	yes	6/18	0%	1.4%
103-1003	renal cell carcinoma	3, single agent	3/toxicity	yes	6/18	0%	1.1%
103-1002	ovarian	3, single agent	6/stable disease	no	14/42	5%	0%
103-1004	endometrial	10, single agent	3/stable disease	no	4/12	3%	12.1%
105-1003	endometrial	20, single agent	4/progressive disease	yes	4/12	15%	9.1%
108-1001	rectal	3, combination	8/progressive disease	no	4/12	4%	11.2%
104-1008	rectal	3, combination	5/progressive disease	no	8/24	1%	1.4%
104-1009	ovarian	10,combination	3/progressive disease	no	7/21	1%	3.5%
109-1001	rectal	20, combination	5/stable disease	yes	3/12	5%	8.87%
108-1004	ovarian	20, combination	2/progressive disease	no	4/12	1%	3%
104-1011	renal cell carcinoma	20, combination	6/progressive disease	yes	6/18	15%	10%

Conclusions

- PY314 is safe and well tolerated across 4 dose levels (1–20 mg/kg), both as a single agent and in combination with a fixed dose (200 mg) of pembrolizumab.
- PY314 pharmacokinetics are linear and dose proportional, the half-life is 5–9 days, and there is no evidence of pembrolizumab interference.
- In 25 evaluable archival tumor specimens, median TREM2-positivity was 3% (range, 0 to 20%); 20/25 (80%) had positive TREM2-target expression above 0, consistent with expression across multiple cancers.
- The best radiographic response observed has been stable disease in 39% of subjects, ranging from 12 to 42 weeks.
- 10 mg/kg of PY314 was determined to be the recommended dose for expansion. Studies in 6 expansion cohorts (triple-negative or HR$^+$HER2$^-$ breast, non-small cell lung, renal cell, colorectal, and ovarian cancers) are enrolling.