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Myeloid targeting antibodies PY159 and PY314 for platinum-resistant ovarian cancer

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ABSTRACT

Background Novel treatment options are required in patients with platinum-resistant ovarian cancer (PROC). Myeloid-derived suppressor cells promote a hostile tumor microenvironment and are associated with worse clinical outcomes in PROC. We evaluated the safety and preliminary efficacy of PY159, an agonist antibody to Triggering receptor expressed on myeloid cells-1 (TREM1) that reprograms immunosuppressive intratumoral myeloid cells, and PY314, an antagonist antibody to Triggering receptor expressed on myeloid cells-2 (TREM2) that depletes tumor-associated macrophages, as single agents and in combination with pembrolizumab in subjects with PROC.

Methods PY159 and PY314 were individually evaluated in patients with PROC. Patients were treated with monotherapy (PY159 3 mg/kg or PY314 10 mg/kg), based on the recommended dose for expansion derived from the phase 1a studies. At the time of first progression, patients could continue study drug and crossover to combination therapy with pembrolizumab (200 mg) every 3 weeks at the discretion of the investigator. Disease assessment by Response Evaluation Criteria in Solid Tumor version 1.1 was performed every 6 weeks.

Results 17 patients were enrolled in the PY159 study (median age 67, range 22–77; median prior therapies 6, range 2–18) and 16 patients in PY314 (median age 65.5, range 49–81; median prior therapies 4, range 2–10). 7 patients in PY159 and 8 patients in PY314 crossed over to combination therapy. Safety events included the following: treatment-related adverse events occurred in 15 patients (88.2%) in PY159 and 9 patients (56.3%) in PY314. Infusion-related reactions occurred in 6 patients (35.3%) in PY159 and 3 patients (18.8%) in PY314. Immune-related adverse events occurred in 13 patients (76.5%) in PY159 (arthralgias) and 1 patient (6.3%) in PY314 (diarrhea). Serious adverse events occurred in 6 patients (36.3%) in PY159 (1 related) and 12 patients (75%) in PY314 (all unrelated). The best radiographic response in PY159 was stable disease in 8/16 patients (50%; median 16 weeks, range 9–33), and in PY314, it was stable disease in 8/16 patients (50%; median 12 weeks, range 6–36). Median PFS was 2.76 months and 2.69 months in PY159 and PY314, respectively. There were no responses in the crossover arm.

Conclusions Both PY159 and PY314 were well tolerated, with an acceptable safety profile, as both single agents and in combination with pembrolizumab. Both agents warrant further investigation in heavily pretreated PROC.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

⇒ There is an urgent and unmet need for efficacious and tolerable treatment options for platinum -resistant ovarian cancer.

⇒ Immune checkpoint inhibitors have shown limited efficacy in ovarian cancer, partly due to a hostile tumor microenvironment that suppresses the activity of cytotoxic immune engagers.

⇒ Murine models and translational data have shown a detrimental effect of tumor -associated macrophages (TAMs) and myeloid -derived suppressor cells (MDSCs) and either depletion or reprogramming of these cells haves led to improved outcomes in experimental models.

WHAT THIS STUDY ADDS

⇒ We aimed to test the hypothesis that either repolarizing TAMs or MDSCs towards a more inflammatory phenotype or depleting them from the tumor microenvironment would improve outcomes in platinum -resistant ovarian cancer. We evaluated PY159, a monoclonal antibody that binds to TREM1 expressed on TAMs and MDSCs leading to repolarization towards an inflammatory and anti-tumor phenotype, and PY314, a monoclonal antibody that binds to TREM2 on TAMs leading to depletion in the tumor microenvironment in a phase 1 clinical trial. PY159 and PY314 were evaluated in two independent studies as monotherapy or in combination with pembrolizumab on disease progression.

⇒ PY159 and PY314 were well tolerated, and immune -related adverse events were mitigated with glucocorticoids. Both PY159 and PY314 led to stable disease in platinum -resistant ovarian cancer.

BACKGROUND

In 2023, there were estimated to be ~19 000 new cases of ovarian cancer diagnosed and ~13 000 deaths from this disease.[1]

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides clinical proof of concept for TAM and MDSC modulation in a heavily pretreated population of patients with platinum -resistant ovarian cancer. The mechanisms of action and side effect profiles of PY159 and PY314 lends itself to combination therapy with cytotoxic chemotherapy or immunotherapy which could be explored in future clinical trials.

For high-grade ovarian cancer (HG-OVCA), about 80% of patient respond to standard therapy with carboplatin and taxanes in the upfront setting; however, about 20% are platinum refractory (ie, progressive disease on upfront therapy) at diagnosis. Additionally, most patients will recur within 2 years of primary treatment even with newer maintenance strategies, with many becoming platinum resistant at first or second recurrence.[2 3] Once platinum resistance has developed, overall response rates to chemotherapy are generally in the 10%–30% range and decrease progressively over time. Overall survival is generally 1–2 years once a patient becomes platinum resistant.[2 4] The only significant advance in this treatment setting in over a decade was the antibody drug conjugate mirvetuximab soravtansine which improved median overall survival by about 4 months compared with chemotherapy.[5] Given this, newer treatments are needed. One significant area of investigation has been the tumor microenvironment (TME) and specifically targeting pathways leading to immune evasion. Historically, monotherapy responses to immune checkpoint inhibitors are 10%–15% in OVCA with many studies currently examining a broad range of monotherapy and combination therapies but still with lower than anticipated responses.[6 7]

Recently, there has been significant interest in investigation of the myeloid lineages, their interactions with the TME, and the mechanisms whereby this leads to resistance to both conventional and targeted therapies including immuno-oncology (IO) agents.[8–14] PY159 and PY314 are being developed in this space.

PY159 is an agonist afucosylated humanized monoclonal antibody (mAb) that binds to triggering receptor expressed on myeloid cells-1 (TREM1), a member of the immunoglobulin variable domain receptor superfamily. This receptor is expressed primarily on neutrophils, monocyte subsets, and tissue macrophages, as well as intratumoral immunosuppressive myeloid cells, including tumor-associated macrophages (TAMs), monocytic myeloid-derived suppressor cells (MDSCs), and tumor-associated neutrophils. Binding leads to a proinflammatory state and promotion of antitumor immune responses.[15–17]

PY314 is a separate, antagonistic, humanized afucosylated glycoengineered IgG1κ mAB targeting triggering receptor expressed on myeloid cells-2 (TREM2), a transmembrane protein expressed on a subset of myeloid cells and enriched on myeloid suppressive cells, particularly M2-like anti-inflammatory TAMs. In this case, antagonism of the TREM2 receptor leads to depletion of suppressive TAMs within the TME and creates a similar proinflammatory state with promotion of antitumor immune response as with PY159.[18–22]

Both agents were investigated in separate phase IA dose escalation studies as well as dose expansion phase IB cohorts. The recommended phase 2 doses of PY159[23] and PY314[24] were established in their individual dose-escalation studies based on safety, receptor occupancy, and in vitro cytotoxicity assays. This report documents the outcomes of these two distinct trials in patients with HG-serous OVCA.

PATIENTS AND METHODS

A total of 17 patients were enrolled to the ovarian cancer expansion cohort for PY159 and 1 patient withdrew consent due to toxicity during cycle 1. All 17 patients were included in safety analysis and 16 patients were included in the efficacy analysis. In the PY314 monotherapy expansion cohort, 16 patients were enrolled. Three patients withdrew their consent, 1 withdrew due to fistula unrealted to therapy, 2 withdrew for adverse events. All 16 patients were included in the safety and efficacy analysis. 11 sites in the USA participated in the trial. Inclusion criteria for study entry included adults greater than 18 years of age, an Eastern Cooperative Oncology Group performance status of 0–2, histologically proven epithelial ovarian, fallopian tube or primary peritoneal carcinoma, provision of an archival and fresh biopsy tumor samples for TREM1 or TREM2 immunohistochemistry analysis, documented disease progression on standard of care therapies with known platinum resistance, Response Evaluation Criteria in Solid Tumor version 1.1 (RECIST 1.1) measurable disease, absence of brain metastases, no autoimmune disease requiring disease-modifying therapy, resolution of prior treatment-related toxicity to Grade 1 or less (Grade 2 allowed for alopecia, endocrinopathies on replacement hormone therapy, and peripheral neuropathy), normal organ function, estimated life expectancy greater than 3 months, no recent surgery (28 days interval for major and 7 days for a minor surgery from time to first dose), and no limit on prior therapies. Exclusion criteria included patients with germ cell, stromal cell, neuroendocrine or carcinosarcoma histology, uncontrolled intercurrent illness, decompensated liver disease as evidenced by hepatic encephalopathy or coagulopathy, active angina or Class III or IV CHF (NYHA CHF Functional Classification System) or clinically significant cardiac disease within 12 months of first dose of study drug, any anticancer therapy within 21 days (dependent on the agent and drug half-life), of first dose of study drug, history of a concurrent or second malignancy, known HIV infection or AIDS, known positive hepatitis B surface antigen test, known positive hepatitis C antibody test, history of long QT syndrome or whose corrected QT interval (QTc) measured (Fridericia method) at screening is prolonged (>500 milliseconds), active infection requiring treatment within 7 days prior to

first dose of study drug, and history or evidence of clinically significant disorder, condition, or disease that, in the opinion of the investigator or medical monitor would pose a risk to patient safety or interfere with the study evaluations, procedures, or study completion.

Study procedures

Both studies received approval from the Institutional Review Boards of the respective institutions. All participants gave consent to participate. All patients for the dose expansion cohorts of PY159 and PY314 signed informed consent for study participation. The recommended phase 2 dose of PY159 was determined to be 3 mg/kg on day 1, administered as an intravenous infusion over 30 min with premedication to mitigate infusion-related reactions every 21 days. In a separate dose escalation study, the recommended phase 2 dosing of PY314 was declared as 3 mg/kg on day 1, administered as an intravenous infusion over 30 min without premedication every 21 days. During the 28-day screening window, patients underwent a laboratory assessment for eligibility as well as a contrast CT of the chest, abdomen, and pelvis to determine RECIST 1.1 defined target and non-target lesions. Following review of protocol-mandated studies obtained during screening, patients enrolled in the ovarian cancer expansion cohorts of the respective trials. The cycle length was 21 days and response assessment was performed once every 42 days. Patients with stable or an objective radiographic response continued treatment as tolerated until disease progression, toxicity, or consent withdrawal. Patients with progression of disease at first assessment were eligible to cross over to combination therapy with pembrolizumab if deemed appropriate by the treating investigator. In patients who crossed over in the respective PY159 and PY314 studies, pembrolizumab was administered 30 min after PY159 or PY314 at a fixed dose of 200 mg over 30 min infusion every 3 weeks.

Table 1 Summary of baseline characteristics from PY159 and PY314 ovarian cancer cohorts

	PY159 (n=17)	PY314 (n=16)
Age—years		
Median (range)	67 (22–77)	65.5 (49–81)
<50	1 (5.9%)	1 (6.3%)
50–65	5 (29.4%)	7 (43.8%)
≥65	11 (64.7%)	8 (50.0%)
Race		
Asian	1 (5.9%)	1 (6.3%)
Black	1 (5.9%)	2 (12.5%)
Other	0 (0.0%)	1 (6.3%)
White	15 (88.2%)	12 (75.0%)
Prior lines		
Median (range)	6 (2–18)	4 (2–10)
<3	1 (5.9%)	1 (6.3%)
≥3	16 (94.1%)	15 (93.7%)
Prior bevacizumab		
Yes	12 (58.8%)	12 (75%)
No	5 (17.6%)	4 (25%)
Unknown	0 (23.5%)	2 (12.5%)
Prior immune checkpoint inhibitor		
Yes	4 (23.5%)	7 (43.8%)
No	13 (76.5%)	9 (56.2%)
Prior PARP inhibitor		
Yes	11 (64.7%)	6 (37.5%)
No	6 (35.3%)	8 (50%)
Unknown	0 (0.0%)	2 (12.5%)
Mutational status		
BRCA1/2 mut	3 (17.6%)	1 (6.3%)
HRD/LOH	3 (17.6)	1 (6.3%)
Unknown	3 (17.6%)	2 (12.5%)

HRD, homologous recombination deficiency; LOH, loss of heterozygosity.

Study endpoints

The primary endpoints of both PY159 and PY314 expansion cohorts were to determine the incidence of adverse events (AEs) alone and in combination with pembrolizumab for patients who crossed over to the combination cohorts; identified as safe, tolerable, and providing target therapeutic exposure. Secondary endpoints included determining the pharmacokinetic (PK) profile of PY159 and PY314 as measured by standard PK parameters, measures of antitumor activity/disease status from baseline including objective response rate (ORR), clinical benefit rate (CBR), and duration of response (DOR) as defined by RECIST 1.1, and the incidence of antidrug antibody formation. Exploratory endpoints were identification of TREM1 and TREM2 in archival tissue, pre-treatment biopsies, and on-treatment biopsies by protein expression as determined by immunohistochemistry using proprietary anti-TREM1 or anti-TREM2 monoclonal antibodies. Expression was determined by a manual scoring system wherein the percent of macrophages and neutrophils staining for TREM1 or TREM2 in the tumor intervening stroma per the total number of cells (both stromal and tumor) was calculated.

Statistical analyses

There were no formal statistical hypotheses or sample-size calculations for the ovarian cancer dose expansion cohorts for PY159 or PY314. Descriptive statistics were used throughout. Efficacy variables were analyzed in the intention-to-treat population (all enrolled patients). Time-to-event parameters were analyzed using descriptive and Kaplan-Meier statistics. Categorical variables were summarized by

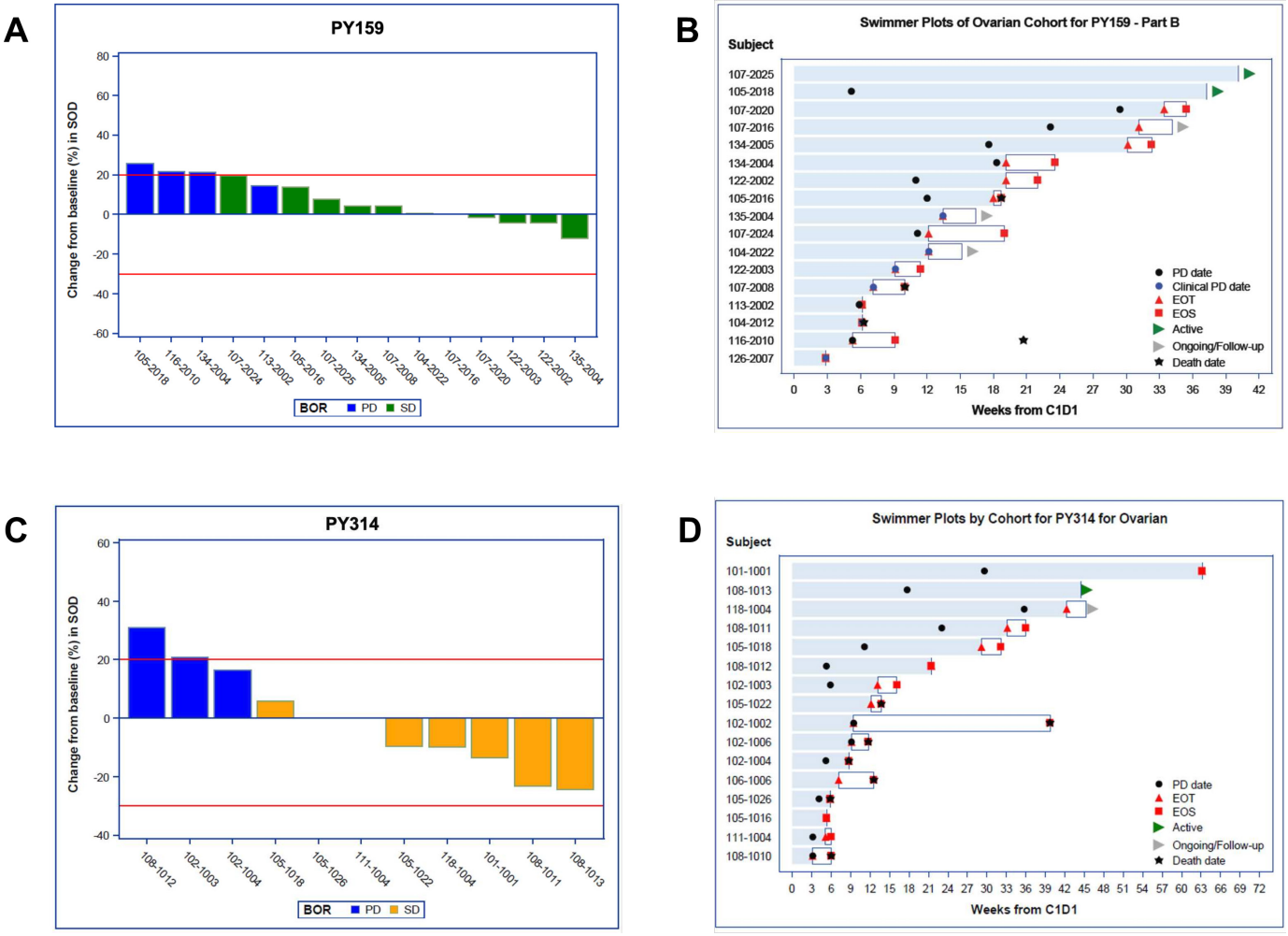

Figure 1 Response assessments after treatment with PY159 or PY314 in the dose expansion cohorts. (A) Waterfall plot and (B) swimmer's plot depicting duration of response for all evaluable patients treated in the expansion cohort of PY159. (C) Waterfall plot and (D) swimmer's plot depicting duration of response for all evaluable patients treated in the expansion cohort of PY314.

frequency distributions and continuous variables were summarized by descriptive statistics.

Safety data was analyzed for all patients who received at least 1 dose of PY159 or PY314. Adverse events were summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. All AEs were classified according to the National Cancer Institute CTCAE version 5.0. Separate tabulations were produced for all treatment-emergent AEs (TEAEs), treatment-related AEs (TRAEs; those considered by the investigator as at least possibly drug related), serious adverse events (SAEs), discontinuations due to AEs, and AEs of at least CTCAE Grade 3 severity.

RESULTS

Patients and demographics

From February 2022 to November 2022, a total of 17 patients and 16 patients were enrolled to the expansion cohorts of PY159 and PY314, respectively. The characteristics of enrolled patients in both trials are shown in table 1. The median age of patients in the PY159 and PY314 studies was 67 years (range, 22–77) and 65.5 years (49 – 81) respectively. 15 (88.2%) and 12 (75%) patients enrolled to PY159 and PY314 identified as white non-Hispanic, respectively. The median number of prior lines of treatment in PY159 was 6 (range, 2–18) and 4 (2 – 10) in PY314. In PY159 and PY314, 16 (94.1%) and 15 (93.7%) patients had received more than three prior lines of cytotoxic therapy, and all were platinum resistant. In the PY159 expansion study, 12 (58.8%) had received prior bevacizumab, 11 (64.7%) had received a prior PARP inhibitor, and 4 (23.5%) had been previously treated with an immune checkpoint inhibitor. In the PY314 expansion study, 12 (75%) patients had previously received bevacizumab, 6 (37.5%) had received a PARP, and 7 (43.8%) had been previously treated with an immune checkpoint inhibitor. There were 6 (35.3%) and 2 (12.5%) patients with BRCA or Homologous Deficiency Repair pathway mutations in PY159 and PY314 respectively.

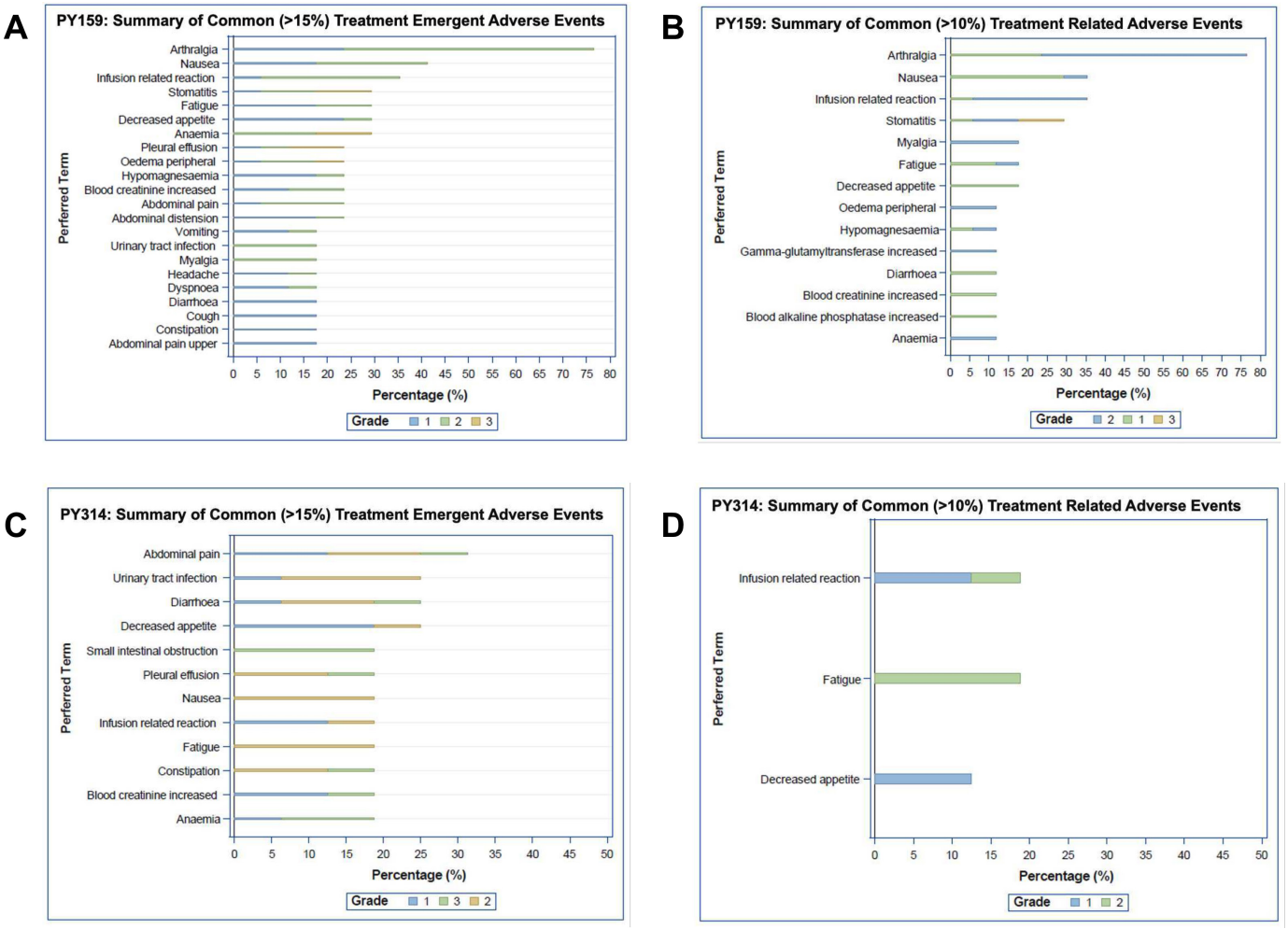

Figure 2 Adverse events. (A) Summary of treatment-emergent adverse events and (B) treatment-related adverse events by RECIST 1.1 criteria for all patients treated in the expansion cohort of PY159. (C) Summary of treatment-emergent adverse events and (D) treatment-related adverse events by RECIST 1.1 criteria for all patients treated in the expansion cohort of PY314. RECIST 1.1, Response Evaluation Criteria in Solid Tumor version 1.1.

Response

The best radiographic response observed with either PY159 or PY314 was stable disease. Of the 16 evaluable patients in PY159, 8 (50%) patients had stable disease with a median duration of 16 weeks (range, 9–33) (figure 1A,B). At the time of study termination, 2 patients remained on treatment. The median PFS for patients in the PY159 expansion study was 2.76 months (95% CI, 1.35 to 5.32). In PY314, 16 patients were evaluable for response. Eight (50%) patients had stable disease with a median duration of response of 12 weeks (range, 6–36 weeks) (figure 1C,D). One patient remained on treatment at study termination. The median PFS for patients treated with PY314 was 2.69 months (95% CI, 1.18 to 4.07).

At first progression, 7 patients in the PY159 expansion cohort crossed over to combination therapy with pembrolizumab. There were no objective responses in the crossover cohort and all 7 patients progressed, although 2 of these 7 patients achieved stable disease past progression. The median time to second progression was 3 weeks (range, 3–15 weeks). Eight patients on the PY314 study crossed over to pembrolizumab combination at first progression. There were no objective responses although stabilization of disease occurred in 5 of these 8 patients. The median time to second progression was 6 weeks (range, 3–27 weeks).

Adverse Events

PY159

All 17 (100%) patients had at least one TEAE of Grade 1 or 2. Grade 3 TEAEs occurred in 8 (47.1%) patients. The most common TEAEs occurring in >15% of patients are shown in figure 2A and online supplemental table 1. TRAEs occurred in 15 (88.2%) patients. TRAEs occurring in >10% of patients are shown in figure 2B and online supplemental table 2. Grade 1 or 2 TRAEs occurred in 13 (76.5%) and Grade 3 events occurred in 2 (11.8%) patients. SAEs occurred in 6 (35.3%) patients, with Grade 1 and 2 events occurring in 2 (11.8%) patients and Grade 3 events in 3 patients (17.6%). There was 1 fatal adverse event of pericardial effusion unrelated to PY159. Table 2

Table 2 Summary of SAE and irAE from the PY159 and P314 ovarian cancer cohorts

	PY159, no. (%)		PY314, no. (%)	
Immune-related adverse events	All grades	Grade ≥3	All grades	Grade ≥3
Arthralgia	13 (76)	0	–	–
Stomatitis	5 (29)	2 (12)	–	–
Myalgia	3 (18)	0	–	–
Arthritis	1 (6)	0	–	–
Fatigue	1 (6)	0	–	–
Hypothyroidism	1 (6)	0	–	–
Fever	1 (6)	0	–	–
Decreased appetite	1 (6)	0	–	–
Dermatitis	1 (6)	0	–	–
Erythema	1 (6)	0	–	–
Immune-mediated dermatitis	1 (6)	0	–	–
Diarrhea	–	–	1 (6)	0
Serious adverse events				
Pericardial effusion	2 (12)	1 (6)*	–	–
Enterovesical fistula	1 (6)	0	–	–
Immune-related dermatitis	1 (6)	0	–	–
Pleuritic chest pain	1 (6)	0	–	–
Urinary tract infection	1 (6)	0	1 (6)	0
Plural effusion	2 (12)	2 (12)	1 (6)	0
Urinary tract obstruction	–	–	1	1 (6)
Gastroenteritis	–	–	1 (6)	0
Nausea	–	–	1 (6)	0
Pain	–	–	1 (6)	0
Acute kidney injury	–	–	1 (13)	1 (6)
Acute small bowel obstruction	–	–	3 (19)	3 (19)
Leukocytosis	–	–	1 (6)	0
Intestinal perforation	–	–	2 (6)	2 (13)*
Septic shock due to UTI	–	–	1 (6)	1 (6)
Takatsubo's cardiomyopathy	–	–	1 (6)	1 (6)*†
Acute respiratory failure	–	–	1 (6)	1 (6)*†
Tonsillitis	–	–	1 (6)	1 (6)
Nephropathy	–	–	1 (6)	1 (6)
Thrombophlebitis	–	–	1 (6)	1 (6)
Upper GI hemorrhage	–	–	1 (6)	1 (6)

*Grade 5.
†These toxicities occurred in the same patient.
GI, gastrointestinal; irAE, immune-related adverse event; SAE, serious adverse event; UTI, urinary tract infection.

shows a list of SAEs and immune-related adverse events (irAEs). Arthralgias, stomatitis, and myalgia were irAEs of special interest, occurring in 13 (76.5%), 13 (76.5%), and 5 (29.4%) of patients respectively.

PY314

All 16 (100%) patients experienced at least 1 TEAE of Grade 1 or 2. There were 12 patients (75%) who experienced Grade 3 TEAEs. The most common TEAEs occurring in >15% of patients are shown in figure 2C and online supplemental table 1. TRAEs occurred in 9 (56.3%) patients. Grade 1 and 2 TRAEs occurred in 4 (25%) patients and Grade 3 TRAEs occurred in 2 (12.5%) patients. TRAEs occurring in >10% of patients are shown in figure 2D and online

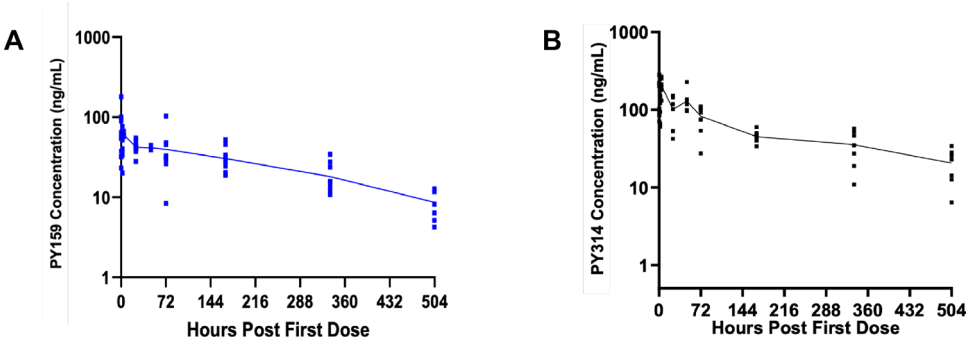

Figure 3 Plasma concentration-time profile after (A) 3 mg/kg of PY159 and (B) 10 mg/kg of PY314.

supplemental table 2. SAEs occurred in 12 (75%) patients, with Grade 1 and 2 events occurring in 3 (18.8%) patients and Grade 3 events occurring in 10 patients (62.5%). There were 2 unrelated fatal adverse events on this study. One patient had a fatal bowel perforation, and another patient developed stress cardiomyopathy and respiratory failure, both felt to be related to underlying disease. Table 2 summarizes the complete list of SAEs and irAEs.

Pharmacokinetics and exploratory TREM1/2 analysis

Pharmacokinetic data was available for 11 patients and 9 patients from the TREM1 and TREM2 expansion cohorts, respectively. For patients who received PY159, the mean maximum concentration (C_{max}, ± SD) was 78.8 µg/mL±38.9 and the mean time to maximum concentration (T_{max}) was 7.92 hours±21.36 (figure 3A**,** online supplemental table 1). The half-life was 8.8 days±2.5. For PY314, the mean C_{max} (±SD), (T_{max}), and $t_{1/2}$ were 198 µg/mL±64, 6.72 hours±15.6, and 8.2 days±4.6, respectively (figure 3B, online supplemental table 2). No antidrug antibodies to PY159 or PY314 were detected. There was no association between PY159 or PY314 exposure and toxicity or clinical outcomes. No pharmacokinetic data was obtained on patients who crossed over to the pembrolizumab combination arm in both studies.

The expression of TREM1 and TREM2 was also evaluated in the PY159 and PY314 expansion studies respectively. In PY159, TREM1 expression was available for 9 (52.9%) patients (figure 4). In 2 patients, TREM1 expression was similar between archival tissue and pre-treatment biopsy. TREM1 expression increased in 2 patients following treatment with PY159. There was no definitive relationship given small numbers between treatment response and TREM1 expression (figure 4). TREM2 expression was available in 15 (93.8%) patients on the PY314 expansion study (figure 4). TREM2 expression varied between archival tumor samples and pre-treatment biopsies in all available patients. Three out of 4 (75%) patients with a decrease in post-treatment TREM2 compared with pre-treatment expression had stable disease (figure 4).

DISCUSSION

To our knowledge, this is the first report of targeting tumor infiltrating macrophages (TAMs) in OVCA as an attempt to overcome resistance to immunotherapy in this disease.

Prior attempts at the use of single agent immunotherapy in platinum-resistant ovarian cancer have had limited effect, likely secondary to the complex interplay between the TME, cancer cells, and infiltrating immune cells. Specifically, it is felt that immunosuppressive myeloid populations within the TME employ a multitude of mechanisms to undermine antitumor immunity and to directly promote tumor growth, even in the setting of immunotherapy use leading to resistance. Combining multiagent drugs to overcome this resistance is likely key, although the best combinations of agents are yet to be determined.[13 14 25 26] Limited combination therapy trials with reported outcomes with other immunotherapy agents or conventional chemotherapies (mostly in expansion cohorts or phase II although some phase III have occurred), in both platinum sensitive and resistant disease, have yet to demonstrate significant activity, notwithstanding some modest activity. In general, patients in these trials have seen significantly less chemotherapy, on average, than the patients treated in either the PY159 or the PY314 study presented here.[27–35]

While targeting tumor-associated macrophages is a mechanism that is garnering more interest in OVCA treatment and multiple trials are underway, no trials to date have reported on outcomes in this space (reviewed in Truxova *et al*)[26] as many of the agents tested have cross-activity in many aspects of the TME. The contemporary agents PY159 and PY314 have been demonstrated to be more specific myeloid-directed monoclonal antibody therapies, ideally suited to evaluate the therapeutic impact of TAM modulation in OVCA.

Both PY159 and PY314 achieved adequate plasma concentrations based on the phase Ia data and PK analyses and in the current study and both PY314 and PY159 monotherapy led to a CBR of 50% (best response as noted stable disease) with an acceptable safety profile and overall were well tolerated. While patients were allowed to cross-over on progression to a combination with pembrolizumab, no responses were noted in this arm although a few patients achieved stable disease when crossing over to combination therapy.

PY159

Subject	Best response	% TREM1 expression		
		Archival	Pre-treatment	Post-treatment
104-2012	PD	0.03	12.04	30.18
122-2002	SD	0.03	0.63	0.04
122-2003	SD	3.39	2.37	n/a
107-2016	SD	0.90	1.55	0.93
107-2020	SD	0.02	1.95	0.09
134-2004	PD	0.0	0.91	0.32
105-2018	PD	2.01	2.53	5.21
104-2022	SD	0.07	0.15	0.17
134-2005	SD	0.02	3.12	2.69

PY314

Subject ID	Best response	% TREM2 expression		
		Archival	Pre-treatment	Post-treatment
102-1002	PD	9.3	n/a	n/a
101-1001	SD	1.1	12.6	4.4
102-1003	PD	0.6	2.7	1.6
105-1016	SD	33.8	15.5	8.3
105-1018	SD	4.8	9.1	n/a
105-1022	SD	18.3	4.3	n/a
102-1006	PD	6.2	4.6	2.6
108-1010	PD	2.9	10.7	n/a
108-1011	SD	8.2	6.7	n/a
105-1026	PD	2.0	15.5	n/a
111-1004	PD	0.3	12.7	n/a
108-1012	PD	13.7	n/a	13.5
118-1004	PD	2.0	1.1	4.3
108-1013	SD	0.2	12.7	3.6

Figure 4 TREM1/2 expression and best response. Summary of response and TREM1% in pre/post-treatment biopsies in patients from PY159 trial, and summary of response and TREM2% in pre/post-treatment biopsies in patients from PY314 trial. TREM1, triggering receptor expressed on myeloid cells 1; TREM2, triggering receptor expressed on myeloid cells 2.

In the exploratory analysis of post-treatment depletion of TREM1/2, patients with SD did appear to have reduced levels of both receptors; however, in this small phase Ia/b study, the number of patients with post-treatment biopsies was too small to confirm association with response to therapy. Our understanding of TREM1 and TREM2 biology continues to evolve. For instance, inhibition of TREM1 via small molecule inhibitors and short interfering RNA suppressed tumor growth and metastasis in a preclinical model of hepatocellular carcinoma.[36] It is conceivable that competing effects of TREM1 agonism on myeloid cells and tumor cells led to the findings in this study. A similar observation has been made in Head and Neck squamous cell carcinoma where TREM2 expression on multinucleated giant macrophages portends a favorable prognosis.[37] In this situation, TREM2 antagonism could facilitate disease progression. A limitation of our study is the absence of tissue-based pharmacodynamic biomarkers beyond baseline and on-treatment TREM1/2 expression. Identification of immune cell infiltrates, or subset analysis of which TREM2-positive myeloid lineage cells were depleted in patients with stable disease on this study could have yielded information that refined our understanding of TREM1/2 biology in ovarian cancer and potentially guide future combination therapy strategies.

While this study and its interpretation are limited secondary to a small sample size and a heavily pretreated population, some of whom had received immunotherapy, both PY159 and PY314 were well tolerated and demonstrated reasonable safety profile as single agents and in combination with pembrolizumab. Given the CBR in heavily pretreated platinum-resistant ovarian cancer, these agents warrant additional investigation in combination with IO agents with consideration of scheduling (i.e. up-front inclusion) and with additional targeted and conventional agents in this difficult to treat patient population with limited options.

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