UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): November 9, 2018

PIERIS PHARMACEUTICALS, INC.
(Exact Name of Registrant as Specified in its Charter)

Nevada	**001-37471**	**EIN 30-0784346**
(State of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

255 State Street, 9th Floor
Boston, MA 02109
United States
(Address of principal executive offices, including zip code)

Registrant's telephone number, including area code: 857-246-8998

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (17 CFR §230.405) or Rule 12b-2 of the Securities Exchange Act of 1934 (17 CFR §240.12b-2).

Emerging Growth Company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01: Regulation FD Disclosure.

On November 9, 2018, Pieris Pharmaceuticals, Inc. presented preclinical data regarding PRS-344. The poster is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated by reference herein.

The information set forth under this “Item 7.01. Regulation FD Disclosure,” including the exhibits attached hereto, shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, nor shall it be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, except as shall be expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits

(d) *Exhibits.*

99.1 Conference Poster, Dated November 9, 2018.

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

PIERIS PHARMACEUTICALS, INC.

Dated: November 9, 2018

/s/ Allan Reine

Allan Reine

Chief Financial Officer

Simultaneous costimulatory T-cell engagement and checkpoint inhibition by PRS-344/ONC0055, a 4-1BB / PD-L1 bispecific compound for tumor localized activation of the immune system

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Background

Multiple lines of evidence show that 4-1BB (CD137), a key costimulatory immunoreceptor, is a highly promising therapeutic target in cancer. Current antibody-based approaches showed immune cell activation not only in tumor tissues but also in the periphery, associated with dose-limiting on-target toxicity and a limited therapeutic window. To overcome this limitation, we generated PRS-344/ONC055, a 4-1BB/PD-L1 bispecific Anticalin®/antibody fusion protein. PRS-344/ONC055 is designed to promote 4-1BB clustering on 4-1BB-positive T cells only in presence of PD-L1 expressing cells. PD-L1, the primary ligand of the T-cell receptor PD-1, is widely expressed in the tumor microenvironment resulting in an inhibitory interaction with PD-1. Combining 4-1BB-induced T-cell co-stimulation and expansion with anti-PD-L1 mediated immune checkpoint blockade may overcome the limitation of single agent therapy and offer benefit to ICP-resistant or non-responsive patients. PRS-344/ONC0055 not only merges the potential of a combinatorial therapy in one molecule but also favors the localized activation of antigen-specific T cells in the tumor microenvironment, potentially reducing peripheral toxicity.

Here we provide a preclinical dataset demonstrating that PRS-344/ONC0055 is capable of providing strong 4-1BB-mediated T-cell co-stimulation that is strictly PD-L1 dependent and requires simultaneous TCR signaling thereby restricting T cell activation to antigen-specific, tumor-localized T cells. PRS-344/ONC0055 provides good target binding properties and pharmacokinetics supporting further development of this drug.

This program is part of the strategic alliance between Pieris and Servier.

Concept: Tumor-localized co-stimulatory T cell activation combined with checkpoint blockade

PRS-344/ONC0055 clusters 4-1BB only in the presence of PD-L1^{high} expressing tumor and/or antigen-presenting cells in the tumor microenvironment or tumor-draining lymph node. At the same time, blocking the PD-1/PD-L1 interaction further increases T cell responsiveness. However, no clustering of 4-1BB is expected in the periphery where PD-L1 expression levels are low.

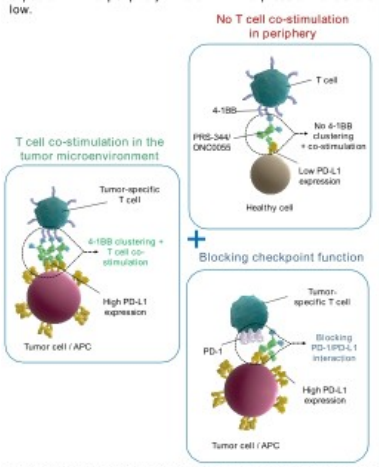


Figure 1. Concept of tumor-localized co-stimulatory T cell activation combined with immune checkpoint blockade. A) Low PD-L1 expression in the periphery is not able to sufficiently cluster 4-1BB which is required to ensure 4-1BB signaling. This results in a reduced risk of peripheral toxicity. B) High PD-L1 expression in the tumor microenvironment, presented on tumor cell and/or APCs, leads to sufficient 4-1BB clustering resulting in a tumor-localized T cell co-stimulation, further enhancing TCR signaling of tumor-specific T cells. C) At the same time, the co-inhibitory PD-1/PD-L1 pathway is efficiently blocked, abrogating suppression of tumor-specific T cells.

PRS-344/ONC0055 is capable of robust target engagement

PRS-344/ONC0055 bispecific demonstrates comparable target binding properties to 4-1BB and PD-L1 as the respective single building blocks and is capable to bind both targets simultaneously.

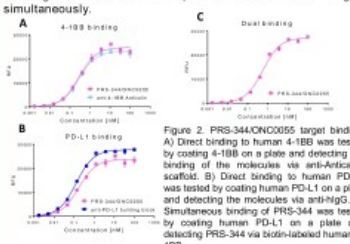


Figure 2. PRS-344/ONC0055 target binding. A) Direct binding to human 4-1BB was tested by coating 4-1BB on a plate and detecting the binding of the molecules via anti-Anticalin-scaffold. B) Direct binding to human PD-L1 was tested by coating human PD-L1 on a plate and detecting the molecules via anti-hIgG. C) Simultaneous binding of PRS-344 was tested by coating human PD-L1 on a plate and detecting PRS-344 via biotin-labeled human 4-1BB.

PRS-344/ONC0055 recognizes functional relevant epitopes

PRS-344/ONC0055 bispecific effectively competes with PD-1 /PD-L1 binding and shares an overlapping 4-1BB binding epitope with clinically active anti-4-1BB benchmark mAb.

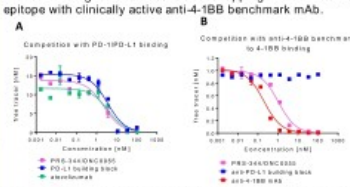


Figure 3. A) Competition to PD-1/PD-L1 binding was assessed in an ELISA based format using coated human PD-1 and human PD-L1-Fc as a tracer. Detection was performed with anti-hIgG. B) Competition with an anti-4-1BB benchmark mAb was assessed in an ELISA based format using coated anti-4-1BB benchmark mAb and human 4-1BB-biotin as a tracer. Detection was performed via ExtrAvidin-HRP.

PRS-344/ONC0055-mediated costimulation is highly effective and PD-L1 dependent

4-1BB clustering and downstream signaling mediated by PRS-344/ONC0055 in presence of a PD-L1-positive cell line are significantly stronger than those of the benchmark anti-4-1BB mAb and are strictly PD-L1 dependent

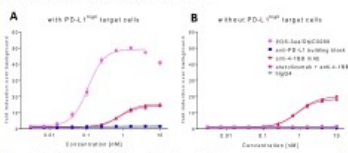


Figure 4. PRS-344/ONC0055-mediated co-stimulatory activity was measured in a Jurkat-4-1BB-NF-κB reporter cell line. A) in presence or B) absence of PD-L1-positive colon cancer cell line RKO.

PRS-344/ONC0055 bispecific retains full checkpoint blockade capacity

PRS-344/ONC0055 retains checkpoint blockade activity similar to anti-PD-L1 mAb building block and atezolizumab

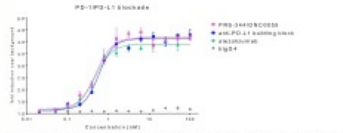


Figure 5. PD-1/PD-L1 checkpoint blockade activity was assessed in a Jurkat-PD-1-NFAT reporter cell line co-cultured with PD-L1 expressing CHO cells.

PRS-344/ONC0055 demonstrates synergistic effect in T cell activation

The combination of atezolizumab and anti-4-1BB benchmark demonstrates the strong synergistic effect of T cell co-stimulation and checkpoint blockade in T cell activation. With PRS-344/ONC0055, this synergistic effect is massively increased.

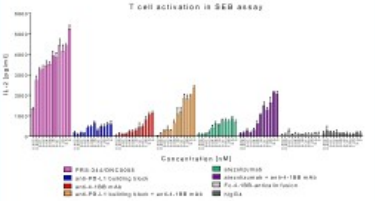


Figure 6. PBMCs from healthy blood donors were stimulated with 0.1 ng/ml SEB in presence of various concentrations of constructs. After 3 days, IL-2 secretion levels were measured from the supernatant. Exemplary data is shown. Background IL-2 levels was 35 pg/ml (PBMC + SEB without constructs). No increase in IL-2 secretion observed when PBMC were not activated with SEB (not shown).

PRS-344/ONC0055-mediated T cell activation is PD-L1 dependent and only occurs in combination with TCR activation

PRS-344/ONC0055-mediated co-stimulation is strictly PD-L1 dependent, reducing the risk of peripheral toxicity. In addition, co-stimulation only occurs in combination with simultaneous TCR signaling, further restricting PRS-344/ONC0055-mediated co-stimulation to antigen-specific T cells.

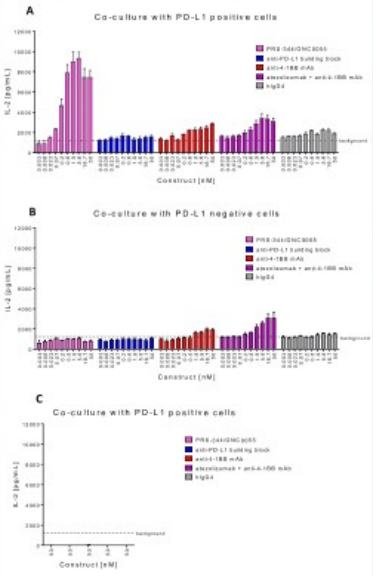


Figure 7. Pan T cells from healthy blood donors were co-cultured in 0.25 µg/ml anti-CD3 mAb coated plates in presence of various concentrations of constructs with A) PD-L1 transfected CHO cells or B) mock transfected CHO cells. C) 50 nM of each construct were added to Pan T cells co-cultured with PD-L1 transfected CHO cells in absence of anti-CD3 mAb which is activating TCR signaling. Background = Pan T cells + anti-CD3 mAb + target cell line.

PRS-344/ONC0055 induces an effective CD8 T cell response in a mixed lymphocyte reaction

PRS-344/ONC0055 induces an effective CD8 T cell response in MLR shown by secretion of several cytokines and cytotoxic molecules which is superior to combination of benchmarks.

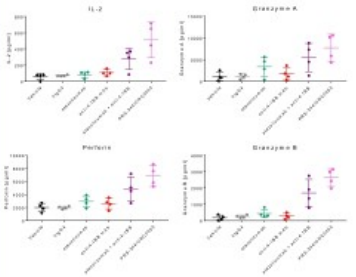
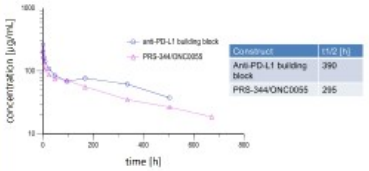


Figure 8. CD8 T cells were co-cultured for 6 days with mature monocyte-derived dendritic cells from another healthy blood donor. Cytokine secretion was measured from the supernatant. Results are shown for IL-2, Granzyme A, Granzyme B and Perforin. Similar results were obtained for IFNγ, TNFα, GM-CSF, IL-13, IL-5, soluble FasL, MIP-1α and MIP-1β. No change in secretion levels observed for IL-6. Graphs show results of 4 different donors.

PRS-344/ONC0055 displays antibody-like pharmacokinetics in mice

The mab-like half-life of the anti-PD-L1 mAb building block is preserved within PRS-344/ONC0055.



Construct	t1/2 [h]
Anti-PD-L1 building block	390
PRS-344/ONC0055	295

Figure 9. PK was analyzed in male CD1 mice of about 6 weeks of age. Animals were injected with 10 mg/kg of the respective construct and plasma samples taken at the indicated timepoints. ADA-positive samples were removed and a non-compartmental analysis performed.

Conclusion

- PRS-344/ONC0055 is a 4-1BB/PD-L1 bispecific based on the genetic fusion of a high-affinity 4-1BB-binding Anticalin® moiety and an anti-PD-L1 mAb.
- Target binding is retained in the bispecific format and both arms of the PRS-344 bispecific are functional.
- PRS-344/ONC0055-mediated 4-1BB activation is strictly PD-L1 dependent potentially reducing the risk of peripheral toxicity. Furthermore, 4-1BB co-stimulation only occurs in combination with simultaneous TCR signaling further reducing the risk of peripheral toxicity by limiting co-stimulation to antigen-specific T cells.
- PRS-344/ONC0055 induces an effective CD8 T cell response by secretion of several cytokines and cytotoxic molecules.
- PRS-344/ONC0055 demonstrates strong synergistic effect in T cell activation which is more pronounced than the combination of benchmarks.
- In mice, PRS-344/ONC0055 displays antibody-like pharmacokinetics.

The here-reported preclinical data support proceeding to further development of PRS-344/ONC0055.