
**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): October 21, 2016

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

Nevada
(State of Incorporation)

001-37471
(Commission
File Number)

EIN 30-0784346
(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))
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Item 7.01 Regulation FD Disclosure.

On October 21, 2016, Pieris Pharmaceuticals, Inc. presented a poster titled “Costimulatory T-cell engagement by PRS-343, a CD137 (4-1BB)/HER2 bispecific, leads to tumor growth inhibition and CD8(+) T-cell expansion in humanized mouse model” at an American Association for Cancer Research conference in Boston, Massachusetts. The poster is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated by reference herein.

Attached hereto as Exhibit 99.2 and incorporated by reference herein is press release regarding presentations at research and development conferences.

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 Industry Conference Presentation of Pieris Pharmaceuticals, Inc., dated October 2016.

99.2 Press Release dated October 20, 2016.

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.

Dated: October 24, 2016

PIERIS PHARMACEUTICALS, INC.

By: /s/ Darlene Deptula-Hicks

Name: Darlene Deptula-Hicks

Title: Chief Financial Officer

EXHIBIT INDEX

Exhibit No.	Description
99.1	Industry Conference Presentation of Pieris Pharmaceuticals, Inc., dated October 2016.
99.2	Press Release dated October 20, 2016.



Costimulatory T-cell engagement by PRS-343, a CD137 (4-1BB)/HER2 bispecific, leads to tumor growth inhibition and CD8(+) T cell expansion in humanized mouse model

Marlon J. Hinner¹, Rachida-Siham Bel Abba¹, Corinna Schlosser¹, Thomas Jaquin¹, Andrea Allersdorfer¹, Sven Berger¹, Alexander Wiedenmann¹, Gabriele Matschiner¹, Julia Schuler¹, Ulrich Moebius¹, Christine Rothe¹, Shane A. O'Neil¹
¹Pieris Pharmaceuticals, Inc., 255 State Street, Boston, Massachusetts; ²Oncost GmbH, Am Flughafen 12, Freiburg, Germany.

Abstract

Background: 4-1BB (CD137) is a potent costimulatory immunoreceptor and a highly promising target for immunostimulatory cancer therapy. Conventional 4-1BB-targeting antibodies, however, suffer from a lack of tumor-selective activity, which may lead to peripheral toxicity and reduce the available therapeutic window. To develop a therapeutic that facilitates a 4-1BB-based activation of T cells that is both tumor-targeted and tumor localized, we have generated PRS-343, a 4-1BB/HER2 bispecific. PRS-343 was made by genetic fusion of a 4-1BB-binding Anticlonal to modified trastuzumab. We have shown previously that PRS-343 targets 4-1BB and HER2 in a bispecific manner and efficiently activates T cells *ex vivo* in the presence of HER2-positive cells. Here, we present *in vivo* proof of concept data and tumor infiltrating lymphocyte (TIL) phenotyping.

Results: We tested PRS-343 efficacy in a humanized mouse model in immunocompromised mice using the SK-OV3 cell line as a HER2-positive antigen. The data indicate that PRS-343 displays dual activity based on monospecific HER2-targeting and bispecific, tumor-localized costimulation of 4-1BB. Tumor response was accompanied by a significantly higher frequency of hCD45(+) TILs as determined by immunohistochemistry (IHC). TIL phenotyping indicated that the rise in TIL frequency was due to an expansion of CD5(+)CD44(+) T cells. Interestingly, we observed neither tumor growth inhibition nor an increase in human TILs with the anti-4-1BB benchmark. In contrast to PRS-343, the anti-4-1BB benchmark displayed an increased toxicity due to accelerated graft-versus-host-disease (GVHD). The accelerated GVHD correlated with CD8⁺ T cell expansion in the peripheral blood. The data therefore support the concept that tumor-localized costimulatory T cell activation by a bispecific such as PRS-343 may lead to higher efficacy and reduced systemic toxicity compared to conventional anti-4-1BB mAbs.

Conclusion: The positive functional *ex vivo* and *in vivo* data of PRS-343 as well as the excellent developability profile supported investigation of its anti-cancer activity in clinical trials. A first-in-patient study is planned to commence in the first half of 2017.

PRS-343 was selected from four 4-1BB/HER2 bispecifics based on functionality

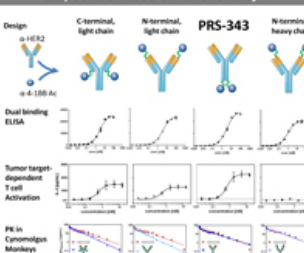


Figure 2. Design and selected functional data of four 4-1BB/HER2 bispecifics. (A) Design: genetic fusion of backbone-engineered trastuzumab to the anti-4-1BB Anticlonal were generated to any of the four regions of the antibody. The IgG1 backbone of trastuzumab was exchanged for an engineered IgG4 backbone. (B) Dual binding ELISA: 4-1BB/HER2 bispecifics are capable of binding both targets at the same time according to Sandwich ELISA. (C) *Ex vivo* T cell activation: 4-1BB/HER2 bispecifics display different capabilities of eliciting IL-2 production by costimulatory engagement (see method description below). (D) Pharmacokinetics of PRS-343 compared to trastuzumab: mice cynomolgus monkeys received oral infusions of a dose of 10mg/kg. Drug levels were detected using Sandwich ELISA.

PRS-343 induces T cell activation when tumor HER2 levels are high, but not at physiological levels

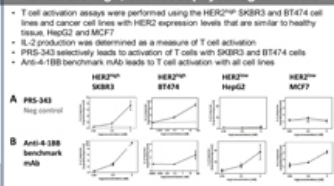


Figure 4. Relative IL-2 induction by 4-1BB-driven T cell activation in the presence of highly HER2-expressing cells (SKOV3, BT20) and cell lines expressing HER2 at a level similar to that of healthy cells (MCF7, Hs5783). (A) 4-1BB/HER2 bispecific (solid line) and negative control trastuzumab (dashed line). (B) Anti-4-1BB benchmark mAb. The experiments were performed as described for Figure 2. The plotted relative IL-2 response corresponds to the ratio of the responses obtained in the presence and in the absence ("background") of test articles.

PRS-343 leads to an expansion of CD8⁺ T_H1 cells in the tumor unlike 4-1BB mAb

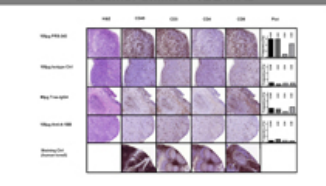


Figure 7. Phenotyping of tumors after study end by immunohistochemistry. Sections of formalin-fixed and paraffin-embedded tumors were stained for human CD45, CD8, CD8+ and CD8-. The frequency of marker positive cells was quantified by dedicated software. The data shows that PRS-343 induces an increase in the frequency of human CD8+ cells in the tumor compared to control. IHC staining was also performed.

PRS-343 activates 4-1BB pathway only in presence of HER2-expressing cells

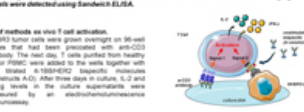


Figure 3. Activation of the 4-1BB signaling pathway in Jurkat T cells was measured by an NF-κB-Luciferase reporter assay. The luminescence signal was used as a relative measure of 4-1BB pathway activation. (A) PRS-343 drug candidate (solid line), negative control trastuzumab (light grey dashed line). (B) Anti-4-1BB benchmark mAb.

Activity in humanized mouse model: PRS-343 leads to TGI and increased hCD45-positive cells in tumor

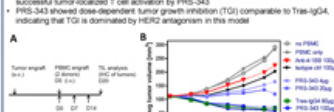


Figure 5. PRS-343 activity in NOD mice engrafted with HER2-positive SK-OV3 cell line and human PBMC. NOD mice were subcutaneously (s.c.) injected with SK-OV3 cells and tumors were allowed to grow for an average of 10 weeks prior to randomization into treatment groups (n=10). Mice were engrafted with fresh human PBMC intravenously (i.v.) into a tail vein and treatment commenced 1 hour later. Mice received 3 weekly intraperitoneal (i.p.) doses of treatment (day 10, 16, 22) or 20mg/kg or 20mg/kg or 20mg/kg. Tumor growth was recorded twice weekly. Tumors from up to six mice were harvested on day 20 post treatment (anti-1BB benchmark mAb; day 17) and assessed for infiltration of human T cells by immunohistochemistry. (A) Diagram of overview. (B) Median of tumor growth. Data points that no longer represent the full group size of 10 mice are connected by dotted lines.

Safety in humanized mouse model: PRS-343 avoids CD8⁺ T_H1 expansion in periphery unlike 4-1BB mAb

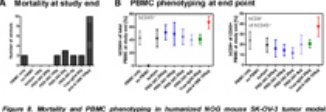


Figure 8. Mortality and PBMC phenotyping in humanized NOD mouse SK-OV3 tumor model. (A) Mortality: Plotted values correspond to number of mice per group of the first three that spontaneously or needed to be sacrificed based on defined general condition criteria. (B) PBMC phenotyping: PBMC were isolated from mouse blood samples taken on day 20 after PBMC engraftment and analyzed by multicolor FACS for human surface markers CD45, CD8 and CD8. PBMC from surviving animals of the group treated with anti-1BB benchmark mAb were phenotyped on day 17.

Concept: tumor-specific and tumor-localized costimulatory activation of T cells

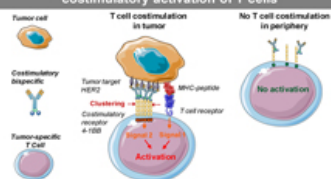


Figure 1. Concept of costimulatory T cell engagement by PRS-343. Within a patient's tumor, tumor-specific T cells are engaged by the costimulatory bispecific PRS-343 which simultaneously binds the tumor target HER2 and the immune receptor 4-1BB. The resulting clustering of 4-1BB provides a local co-stimulatory signal to the T cell, further enhancing its T cell receptor (TCR)-mediated activity and leading to tumor destruction. Tumor cells are expected to be monospecific, as PRS-343 does not induce clustering and activation of 4-1BB in the absence of large-positive cells, and healthy tissue is spared by tumor-co-stimulated T cells due to the absence of a primary TCR-mediated signal.

Building block: Anticlonal targeting 4-1BB

Discovery

- Phage display of IgG library against 4-1BB, followed by affinity maturation
- Binding to 4-1BB

 - K_d = 2.3 nM (SPR)
 - EC50/AC50 = 5.9 nM
 - Non-competitive binding to 4-1BB.

Biophysical properties

- 100% monospecific expression
- T_m = 74°C (DSC)
- Fully stable after 1 week at 37°C in PBS/pH 7.4, human plasma or mouse plasma

Functional activity

- Ex vivo activation of T cells when coated; no activation when in solution

Summary

- PRS-343 is a 4-1BB/HER2 bispecific based on the genetic fusion of a high-affinity 4-1BB-binding Anticlonal and modified trastuzumab
- PRS-343 displays a differentiated profile when compared to a benchmark 4-1BB-targeting antibody
 - Reporter assay: PRS-343 leads to 4-1BB activation in presence of HER2-positive tumor cells, but not in their absence
 - Ex vivo: PRS-343 induces strong T cell activation via tumor target-dependent costimulatory T cell engagement
 - In vivo: PRS-343 displays dual activity based on monospecific HER2-targeting and bispecific, tumor-localized costimulation of 4-1BB, leading to increased density of CD8⁺ cells in the tumor
 - In vivo: PRS-343 avoids the systemic peripheral activation of CD8⁺ T cells observed with benchmark 4-1BB antibody, which supports a better safety profile
- PRS-343 path to clinic: IND-enabling activities are ongoing with an anticipated first-in-patient study planned for the first half of 2017

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PRESS RELEASE

**PIERIS ANNOUNCES PRESENTATIONS AT UPCOMING
R&D CONFERENCES**

BOSTON, MA, October 20, 2016 – Pieris Pharmaceuticals, Inc. (NASDAQ:[PIRS](#)), a clinical-stage biotechnology company advancing novel biotherapeutics through its proprietary Anticalin® technology platform for cancer and other diseases, announced today presentations at two upcoming R&D conferences focused on immuno-oncology.

The details for each presentation are as follows:

American Association of Cancer Research (AACR) Special Conference on Tumor Immunology and Immunotherapy, Boston Marriott Copley Plaza, Boston, MA, October 20 – 23, 2016

Presentation Time: Friday, October 21, 2016, 5:15 pm-7:45 pm, Back Bay room

Presentation: A poster presentation entitled, “Costimulatory T-cell engagement by PRS-343, a CD137 (4-1BB)/HER2 bispecific, leads to tumor growth inhibition and CD8(+) T cell expansion in a humanized mouse model”.

Society of Immunotherapy of Cancer (SITC), Gaylord National Hotel & Convention Center, National Harbor, Maryland, November 9 – 13, 2016

Oral Presentation: An oral presentation entitled “PRS-343, a CD137 (4-1BB)/HER2 Bispecific” will be given on Wednesday, November 9, 2016, 11:50 am

Poster Presentation: New Cancer Immunotherapy - A poster presentation will be presented on Saturday, November 12, 2016, 11:45 am – 1:00 pm and 6:45 pm – 8:00 pm

About Pieris

Pieris Pharmaceuticals is a clinical-stage biotechnology company that discovers and develops Anticalin[®] protein-based drugs to target validated disease pathways in a unique and transformative way. Our pipeline includes immuno-oncology multi-specifics tailored for the tumor micro-environment, an inhaled Anticalin protein to treat uncontrolled asthma and a half-life-optimized Anticalin protein to treat anemia. Proprietary to Pieris, Anticalin proteins are a novel class of protein therapeutics validated in the clinic and by partnerships with leading pharmaceutical companies. Anticalin[®] is a registered trademark of Pieris. For more information visit www.pieris.com.

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