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): April 17, 2016

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
(Address of principal executive offices, including zip code)

Registrant's telephone number, including area code: 857-246-8794

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))

Item 7.01 Regulation FD Disclosure.

On April 17, 2016, Pieris Pharmaceuticals, Inc. presented a poster on PRS-343 preclinical data at the American Association for Cancer Research annual meeting in New Orleans, Louisiana. The poster is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated by reference herein.

The information disclosed in this Item 7.01 is being furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities under that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act except as expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits

(d) *Exhibits.*

99.1 Poster of Pieris Pharmaceuticals, Inc.

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: April 18, 2016

PIERIS PHARMACEUTICALS, INC.

By: /s/ Darlene Deptula-Hicks
Name: Darlene Deptula-Hicks
Title: Chief Financial Officer

EXHIBIT INDEX

Exhibit No.	Description
99.1	Poster of Pieris Pharmaceuticals, Inc.

Exhibit 99.1

Costimulatory T-cell engagement by the CD137/HER2 bispecific PRS-343 leads to strong anti-tumor effect in humanized mouse model

Marlon J. Hinner, Rachida-Siham Bel Aiba, Corinna Schlosser, Alexander Wiedenmann, Andrea Allersdorfer, Thomas J. Jaquin, Gabriele Matschiner, Sven Berger, Ulrich Moebius, Christine Rothe, Shane A. Olwill

Pieris Pharmaceuticals, Inc., 255 State Street, Boston, Massachusetts

Abstract

Background. CD137 (4-1BB) is a key costimulatory immunoreceptor and a member of the TNF-receptor (TNFR) superfamily. While multiple lines of evidence show that CD137 is a highly promising therapeutic target in cancer, current mAb-based approaches are not designed to achieve a tumor-target driven activation and may display toxicity and a limited therapeutic window due to peripheral T cell and NK cell activation. To overcome this limitation, we generated PRS-343, a CD137/HER2 bispecific that is designed to promote CD137 clustering by bridging CD137-positive T cells with HER2-positive tumor cells, thereby providing a potent costimulatory signal to tumor antigen-specific T cells.

Methods. Anticalin® proteins are 18 kD protein therapeutics derived from human lipocalins. We utilized phage display to generate an Anticalin protein binding to CD137 with high affinity and specificity. PRS-343 was obtained by genetic fusion of the CD137-specific Anticalin protein to a variant of the HER2-targeting monoclonal antibody trastuzumab with an engineered IgG4 backbone.

Results. The bispecific fusion PRS-343 targets CD137 and HER2 with nearly identical affinities compared to the parental building blocks, and is capable of binding both targets simultaneously. We show ex vivo that T cells are efficiently activated when incubated with PRS-343 and HER2-positive cells, and that the activation is HER2-dependent. The in vivo activity of PRS-343 was investigated utilizing a humanized mouse model with a tumor cell-line-derived, HER2-positive xenograft. When tumors had reached a predefined size, mice received human PBMC via an intravenous route and weekly intraperitoneal injections of PRS-343 or controls for three weeks. We found that PRS-343 led to strong tumor growth inhibition and a significantly better response compared to either isotype control or anti-CD137 benchmark mAbs. The data, which include phenotyping of peripheral and intra-tumoral lymphocytes, support the envisaged mode of action of tumor-localized costimulatory T cell activation.

Conclusion. We report potent costimulatory T-cell engagement of the immunoreceptor CD137 in a HER2-dependent manner, utilizing the CD137/HER2 bispecific PRS-343. Compared to known CD137-targeting antibodies in clinical development, this approach has the potential to provide a more localized activation of the immune system with higher efficacy and reduced peripheral toxicity. The positive functional ex vivo and in vivo data of PRS-343 as well as the excellent developability profile support investigation of its anti-cancer activity in clinical trials.

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

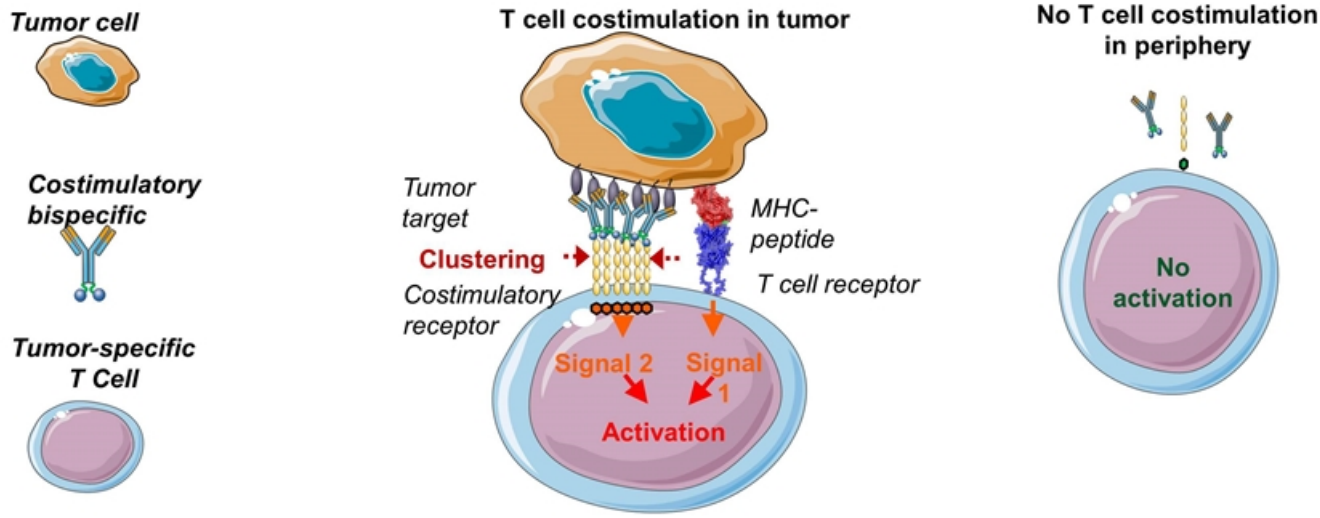


Figure 1. Concept of costimulatory T cell engagement: Within a patient´s tumor, tumor-specific T cells are bridged with tumor cells by a costimulatory bispecific. The resulting clustering of the costimulatory T cell receptor provides a local co-activatory signal to the T cell, further enhancing its T cell receptor (TCR)-mediated activity and leading to tumor destruction. Toxic side effects are expected to be manageable, as target-negative cells do not lead to costimulation of T cells due to a lack of target-mediated receptor clustering, and healthy tissue is spared by tumor-costimulated T cells due to the absence of a primary, TCR-mediated signal.

CD137 – the prime costimulatory receptor

Background

- CD137 is mainly expressed on activated CD4+ and CD8+ T cells, activated B cells, and natural killer (NK) cells
- CD137 activation occurs via clustering by cell-surface expressed CD137 ligand (predominantly found on antigen-presenting cells)
- CD137-costimulated T- and NK-cells display enhanced proliferation, proinflammatory cytokine expression and killing capacity

Target validation

- CD137 is a validated marker for tumor-reactive T cells in man[1]
- Anti-CD137 mAbs improve expansion of $CD8^+$ melanoma TIL in adoptive T cell therapy[2]
- CD137 downstream signaling is key to success in clinical CAR-T[3,4]
- CD137 costimulation in NK-cells is currently evaluated in clinical trials[5]
- CD137 expression is localized in the tumor microenvironment[6]
- Costimulatory T cell engagement via CD137 has been demonstrated using aptamer technology[7]

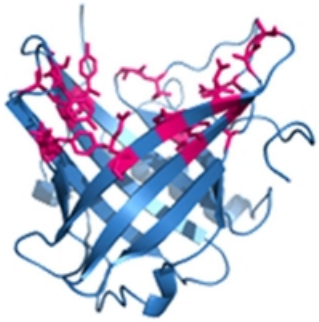
Building block: Anticalin targeting CD137

Discovery

- Phage display of lipocalin library against CD137, followed by affinity maturation

Binding to CD137

- K_D = 2.3nM (SPR)
- EC50(FACS) = 5.9nM
- Non-competitive binding vs CD137L



Biophysical properties

100% monomeric expression
T_M =74°C (DSC)
Fully stable after 1 week at 37°C in
PBS pH7.4, human plasma or mouse plasma

Functional activity

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

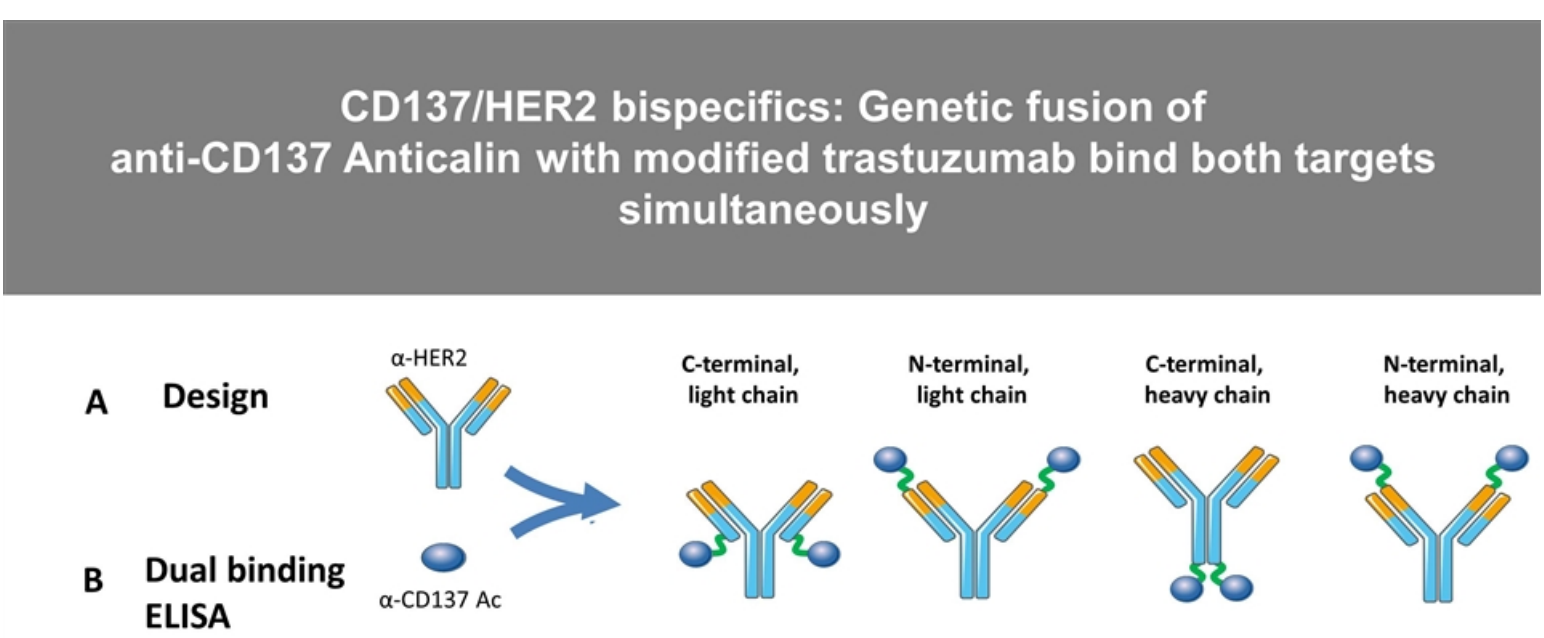
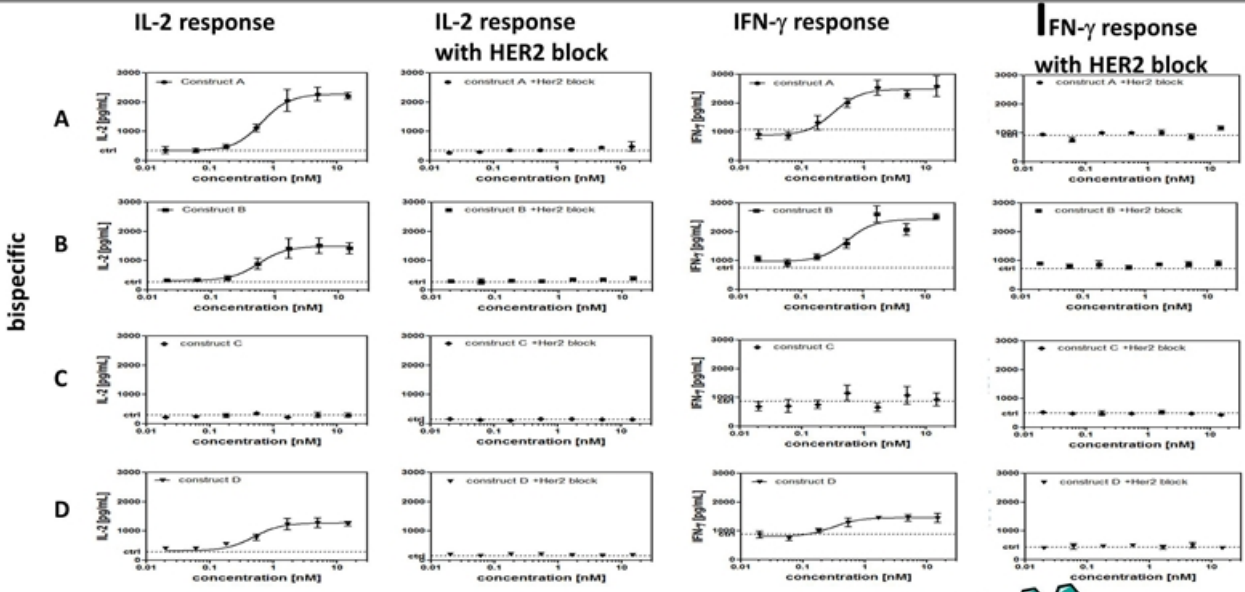


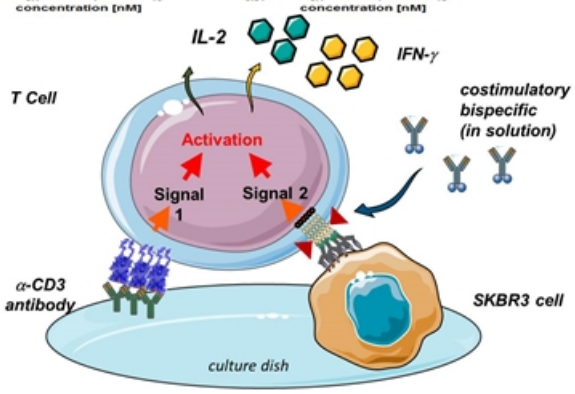
Figure 2. Design and dual target binding of four CD137/HER2 bispecifics. (A) Design: genetic fusions of backbone-engineered trastuzumab to the anti-CD137 Anticalin were generated to either one of the four termini of the antibody. The IgG1 backbone of trastuzumab was exchanged for an engineered IgG4 backbone. (B) Dual binding: CD137/HER2 bispecifics are capable of binding both targets at the same time according to Sandwich ELISA.

Potent costimulatory T cell activation is dependent on both HER2 binding and bispecific geometry

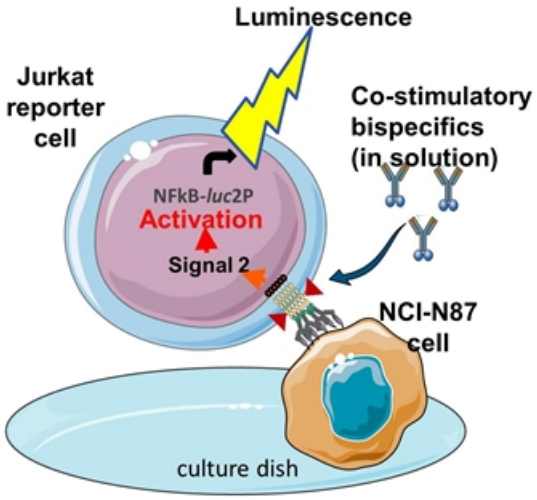


Brief methods.

SKBR3 tumor cells were grown overnight on 96-well plates that had been precoated with anti-CD3 antibody. The next day, T cells purified from healthy donor PBMC were added to the wells together with the titrated CD137/HER2 bispecific molecules (constructs A-D). After three days in culture, IL-2 and IFN-g levels in the culture supernatants were measured by an Electrochemoluminescence immunoassay. The experiment was performed also in the presence of an excess of trastuzumab to inhibit the binding of CD137/HER2 bispecifics to the SKBR3 cells.



Drug candidate PRS-343 activates CD137 pathway only in presence of HER2-expressing cells



Brief methods.
HER2^{high} expressing NCI-N87 tumor cells were grown overnight on 96-well plates. Jurkat NF-κB reporter cells, over-expressing CD137 and carrying a NF-κB-Luciferase reporter gene, were then added to the plates together with the titrated CD137/HER2 bispecific construct PRS-343 (A) or anti-CD137 benchmark (B). After incubation, the T cell reporter signal was measured by luminescence. The impact of CD137-targeting on CD137 downstream signaling was also investigated in the absence of tumor cells at a single concentration of CD137 agonists (10nM).

- CD137 downstream signaling activation by the CD137/HER2 bispecific drug candidate PRS-343 was investigated by an NF-κB-luciferase reporter assay
- PRS-343 strongly activated the CD137 pathway in the presence of HER2^{high} NCI-N87 target cells; no activation occurred in the absence of NCI-N87 tumor cells
- An anti-CD137 benchmark activated the CD137 pathway both in the absence and presence of tumor cells

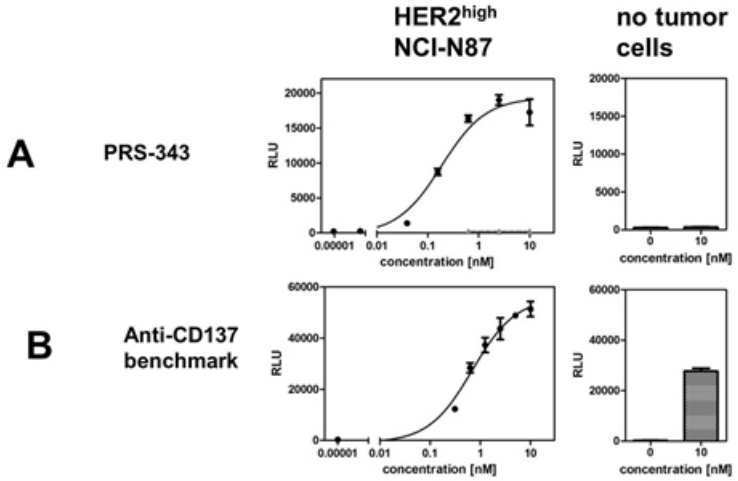


Figure 4. Activation of the CD137 signaling pathway in Jurkat T cells was measured by an NF-kB-Luciferase reporter assay. The luminescence signal was used as a relative measure of CD137 pathway activation. (A) PRS-343 drug candidate (solid line), negative control trastuzumab (light grey dashed line). (B) Anti-CD137 benchmark.

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

- Immuno-compromised mice engrafted with HER2-positive tumor cells (SKOV-3) were injected with human PBMC and treated over 3 weeks with PRS-343 or controls
- PRS-343 treatment at high dose (100µg/wk) and low dose (20µg/wk) resulted in stronger tumor growth inhibition (TGI) compared to isotype control or anti-CD137 benchmark
- IHC staining for the human lymphocyte marker CD45 shows increased frequency of human TIL for high dose PRS-343 – low dose PRS-343 does not show this effect
- Taken together these data are consistent with dual functionality of PRS-343
    - CD137-mediated activity: Expansion of TIL's in the tumor microenvironment suggests tumor-localized costimulatory T cell activation by PRS-343
    - HER2-mediated activity: TGI is observed with 20ug PRS-343, in the absence of TIL expansion, suggesting this activity may be driven by HER2 antagonism

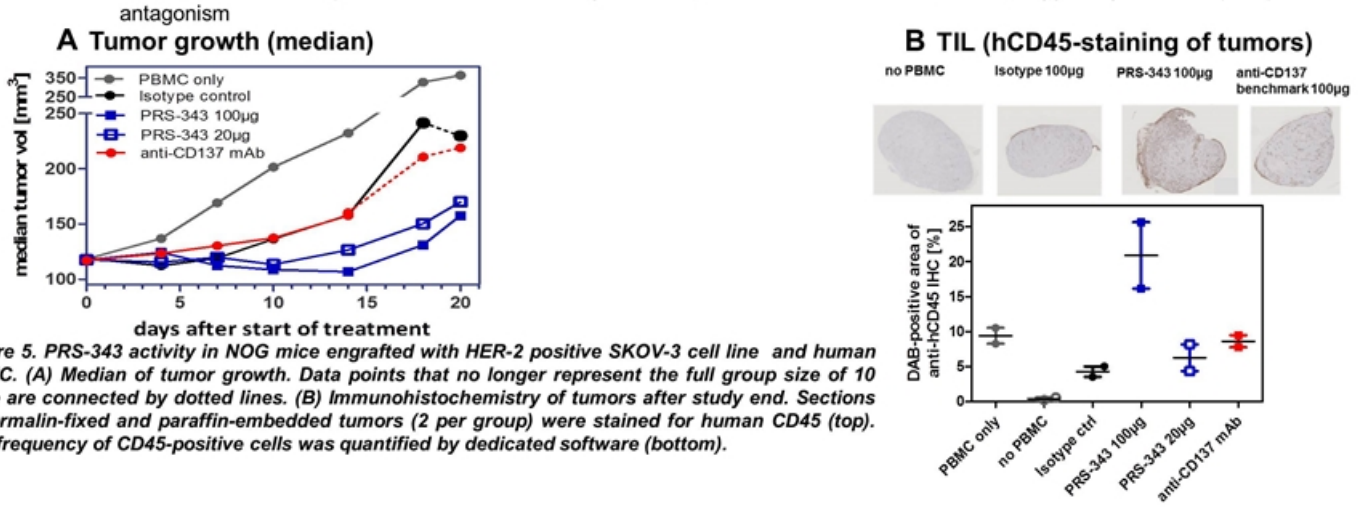
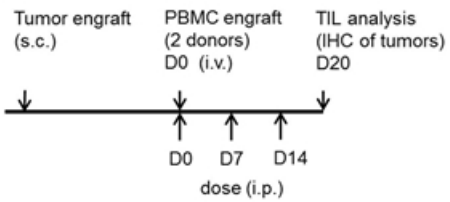


Figure 5. PRS-343 activity in NOG mice engrafted with HER-2 positive SKOV-3 cell line and human PBMC. (A) Median of tumor growth. Data points that no longer represent the full group size of 10 mice are connected by dotted lines. (B) Immunohistochemistry of tumors after study end. Sections of formalin-fixed and paraffin-embedded tumors (2 per group) were stained for human CD45 (top). The frequency of CD45-positive cells was quantified by dedicated software (bottom).

Brief methods. NOG mice were subcutaneously (s.c.) injected with SK-OV-3 cells and tumors were allowed to grow to an average of 120mm^3 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 (20µg or 100µg) or control. Tumor growth was recorded twice weekly. Tumors from two mice were harvested on day 20 post treatment and assessed for infiltration of human T cells by immunohistochemistry.



Safety in humanized mouse model: PRS-343 avoids CD8⁺ T_{eff} expansion in periphery unlike CD137 mAb

- Anti-CD137 mAb treatment led to accelerated graft-versus-host disease with significant mortality compared to control and PRS-343 groups on study day 20
- PBMC phenotyping results indicate that anti-CD137 mAb mortality is caused by strongly increased expansion of CD8⁺ human effector T cells in anti-CD137 group compared to control or PRS-343 groups

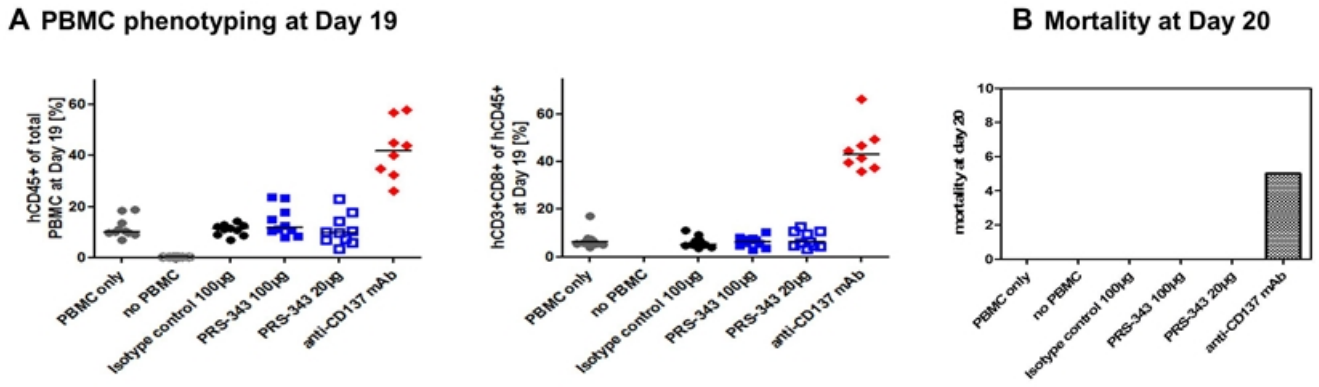


Figure 6. PBMC phenotyping and mortality in humanized NOG mouse SKOV-3 tumor model. (A) PBMC phenotyping. PBMC were isolated from mouse blood samples taken on day 19 after PBMC engraftment and analysed by multicolor FACS for human surface markers CD45, CD3 and CD8. (B) Mortality. Plotted values correspond to number of mice per group of ten that died spontaneously or needed to be sacrificed based on defined general condition criteria.

PRS-343 exhibits pharmacokinetics comparable to trastuzumab in mice and primates

- In mice, terminal half-life of PRS-343 at a dose of 10mg/kg lies at 21 days compared to 13 days for trastuzumab
- In cynomolgus monkey, the terminal half-life of PRS-343 at a dose of 3mg/kg lies at 99 hours compared to 86 hours for trastuzumab

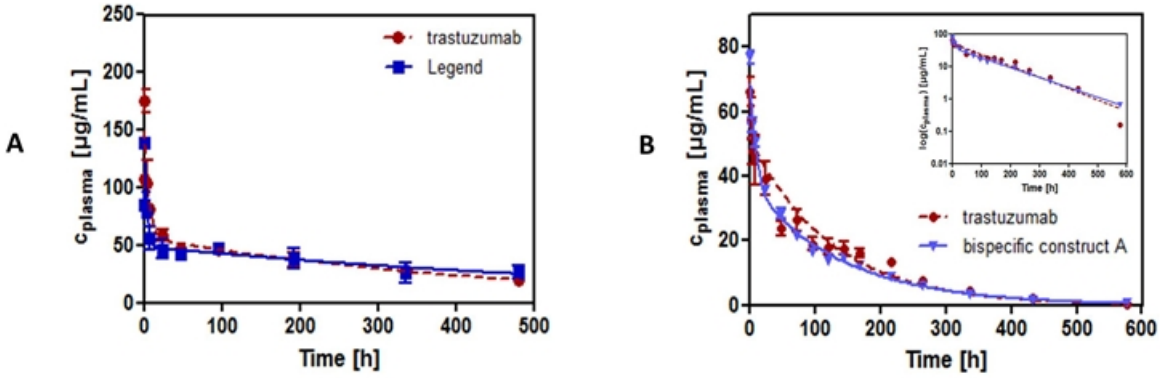


Figure 7. Pharmacokinetics of PRS-343 compared to trastuzumab: (A) Male CD-1 mice (3 mice per time point) were injected intravenously with test articles at a dose of 10mg/kg. (B) Male cynomolgus monkeys received test articles as an intravenous infusion at a dose of 3mg/kg. Drug levels were detected using Sandwich ELISA.

Summary

- **Four CD137/HER2 bispecifics were generated based on genetic fusion of a high-affinity CD137-binding Anticalin and modified trastuzumab, displaying**
  - **Excellent drug-like properties**
  - **Simultaneous target engagement with an affinity comparable to parental building blocks**
  - **Differential ability to activate T cells based on bispecific geometry**
  - **Long, antibody-like terminal in vivo half-life**

- **The drug candidate, PRS-343, displays a differentiated profile when compared to benchmark CD137-targeting antibodies**
  - **In vitro: PRS-343 induces strong T cell activation via tumor target-dependent costimulatory T cell engagement**
  - **In vivo: PRS-343 leads to increased density of hCD45^{+} cells in the tumor, which supports a mode of action based on local activation of tumor-specific T cells**
  - **In vivo: PRS-343 avoids the systemic peripheral activation of CD8+ T cells observed with benchmark CD137 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**

References.
[1] Ye, Q. et al., Clin Canc Res 2014 Jan 1; 20(1):44-55. [2] Chacon, J. A. et al., PloS One 2013 8(4):e60031. [3] Kalos, M. et al., Sci Transl Med 2011 Aug 10; 3(95): 2-21. [4] Maude, S. L. et al., N Engl J Med 2014 Oct 16; 371(16):1507 – 1517. [5] Kohrt, H. et al, J Clin Invest. 2012 Mar;122(3):1066-75.[6] Palazon, A. et al., Cancer Discovery: 2012 (2): 608 – 623. [7] Pastor F. et al., Mol Ther. 2011 Oct;19(10):1878-86. [8] Mukai, Y. et al., Sci Signal.: 2010 (3): ra83. [9] Press, M. F. et al., Oncogene: 1990 5(7):953-62.
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