Zacks Small-Cap Research

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Pieris Pharmaceuticals, Inc. (PIRS-NASDAQ)

PIRS: PRS-343 Shows Efficacy in Humanized Mouse Cancer Model…

Based on our probability adjusted DCF model that takes into account potential future revenues from PRS-080, PRS-060, and PRS-343, PIRS is valued at $8/share. This model is highly dependent upon the clinical success of those products and will be adjusted accordingly based upon future clinical results.

Current Price (05/18/16)	$1.68
Valuation	**$8.00**

OUTLOOK

On May 12, 2016 Pieris Pharmaceuticals (PIRS) announced financial results for the first quarter of 2016. The company recognized $1.2 million in revenue from the recently signed agreement with Roche. Net loss for the quarter was $4.2 million, or $0.10 per share, and the company exited the quarter with approximately $31.2 million in cash and cash equivalents, which should be sufficient to fund operations for at least the next 12 months.

Pieris recently presented *in vivo* results for the company's lead immunooncology product, PRS-343, at the 2016 AACR Annual Meeting. The data show PRS-343 to be effective in a humanized mouse xenograft model using SKOV-3 cells. These first *in vivo* results are a positive first step for Pieris as it seeks to develop the Anticalin® platform into a number of different immunooncology applications.

SUMMARY DATA

52-Week High	**$4.40**
52-Week Low	**$1.26**
One-Year Return (%)	**-45.81**
Beta	**1.60**
Average Daily Volume (sh)	**142,375**
Shares Outstanding (mil)	**40**
Market Capitalization ($mil)	**$67**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**44**
Insider Ownership (%)	**2**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2016 Estimate	**N/A**
P/E using 2017 Estimate	**N/A**

Risk Level	**Above Avg.,**
Type of Stock	**Small-Blend**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	0.2 A	0.2 A	0.4 A	2.1 A	2.9 A
2016	1.2 A	1.2 E	1.2 E	1.2 E	4.8 E
2017					12.0 E
2018					15.0 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2015	-$0.13 A	-$0.12 A	-$0.10 A	-$0.07 A	-$0.41 A
2016	-$0.10 A	-$0.12 E	-$0.12 E	-$0.12 E	-$0.46 E
2017					-$0.32 E
2018					-$0.30 E

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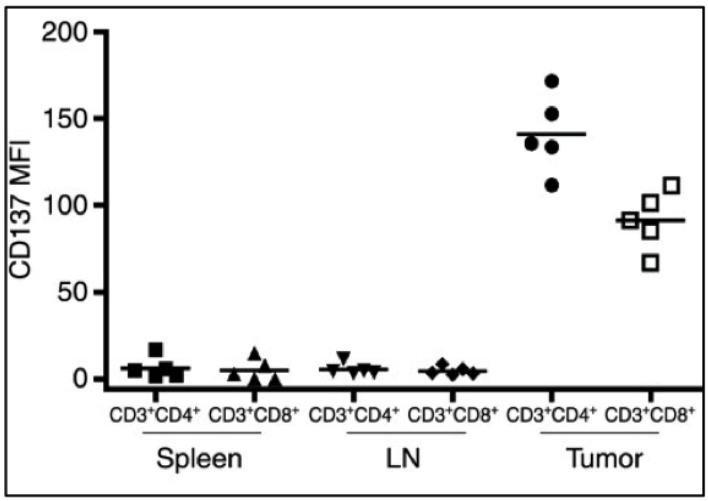
***In Vivo* Data Presented for PRS-343 at 2016 AACR Meeting**

On April 17, 2016, Pieris Pharmaceuticals, Inc. (PIRS) presented the first *in vivo* data for PRS-343, the company's lead immunooncology (IO) compound at the 2016 AACR Annual Meeting. The data showed that PRS-343 was safer and more effective than a reference anti-CD137 antibody and supported the proposed mechanism of action of tumor-specific T-cell activation.

PRS-343

PRS-343 is a bispecific compound that contains a CD137-specific Anticalin® genetically linked to a HER2-specific monoclonal antibody (trastuzumab), and is the lead compound from the company's IO program. CD137 is expressed on activated CD8+ T-cells. Since CD8+ T-cells play a pivotal role in tumor immunity, enhancing CD137 costimulation could promote the generation of protective antitumor immune responses. This idea has been validated through enhanced immunogenicity in tumor cells engineered to express CD137 ligand (Mogi *et al*., 2000) or anti-CD137 antibodies (Ye *et al*., 2002). Unfortunately, the use of systemic anti-CD137 antibodies can result in severe side effects such as liver toxicity (Grade 4 hepatitis), which resulted in the cancellation of a Phase 1 clinical trial (Yao *et al*., 2013). Thus, Pieris is utilizing the HER2-specific antibody to localize T-cell activation inside the tumor microenvironment, which could help to mitigate potential systemic toxic effects.

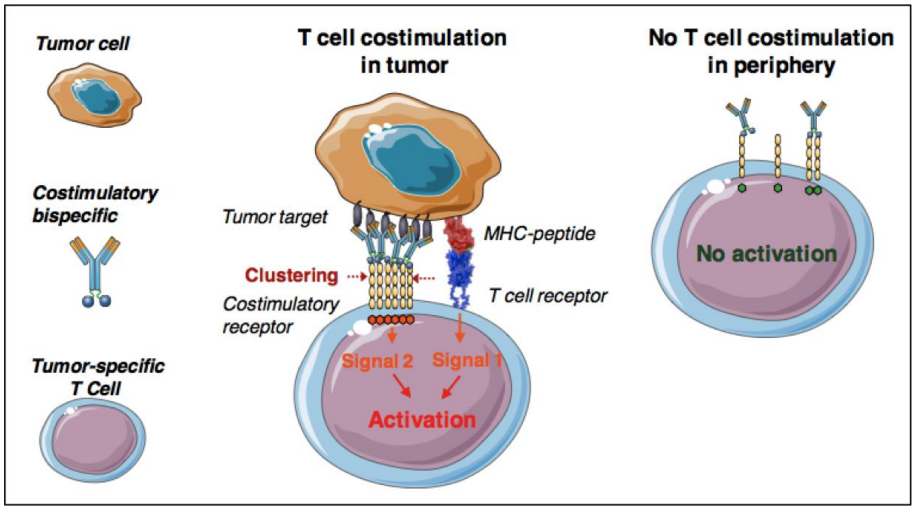
Another important aspect of CD137 is that it is preferentially expressed in high levels on intratumoral T-cells (Palazón *et al*., 2012). This is shown in the following graph, where CD4+ and CD8+ T-cells were extracted from the spleen, lymph nodes, and tumor of mice bearing CT26 tumors (murine colon cancer). Only T-cells purified from tumors showed expression of CD137, whereas T-cells from other locations from the same mice did not show increased expression of CD137.



Source: Palazón *et al*., 2012

These data were further corroborated in tissue samples from patients with ovarian cancer (Ye *et al*., 2014). Results from that study showed that tumor-infiltrating lymphocytes (TILs; found in the tumor microenvironment) and tumor-associated lymphocytes (TALs; found surrounding the tumor microenvironment) naturally expressed higher levels of CD137 than circulating T cells. In addition, CD137-expressing TILs, but not PD-1 positive or PD-1 negative CD137-negative cells, possessed autologous tumor reactivity both *in vitro* and *in vivo*. All told, there is significant data to support the use of CD137-targeting therapeutics as anti-cancer agents.

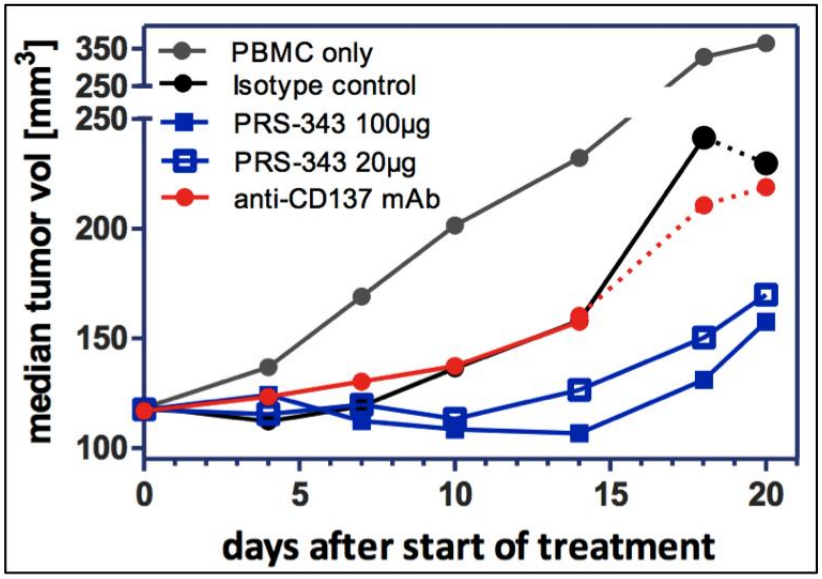
The CD137 directed T-cell response is generated through a "clustering" phenomenon, where the more CD137 molecules that are activated together in a group leads to a greater activation signal. For PRS-343, this "clustering" occurs because of the overexpression of HER2 (tumor target) on the tumor cell surface. By bringing together the tumor cell and the T-cell, the T-cell receptor can then interact with any peptides presented on the tumor cell surface through the major histocompatibility complex (MHC), further enhancing the anti-tumor response by the T-cell. This is all depicted in the following graphic.



Source: Hinner *et al*., 2015

In Vivo *Data in Humanized Mouse Model*

To test the efficacy of PRS-343, Pieris utilized NOG mice, which are immunocompromised and allow for the engraftment of human cells that can then proliferate and differentiate (Ito *et al*., 2002). The mice were engrafted with SKOV-3 cells, a human ovarian cancer cell line, which highly expresses HER2. Once the SKOV-3 tumors reached approximately 120 mm^3, the mice were engrafted with human peripheral blood mononuclear cells (PBMC; to act as a surrogate immune system) and treatment began one hour later. Groups of ten mice were treated with either placebo, isotype control antibody, PRS-343 (20 µg), PRS-343 (100 µg), or anti-CD137 antibody for a total of three treatments each seven days apart (Days 0, 7, 14). On Day 20, tumors from two mice for each group were collected and analyzed for the presence of human T-cells. The following figure shows the tumor growth for the five groups of mice.

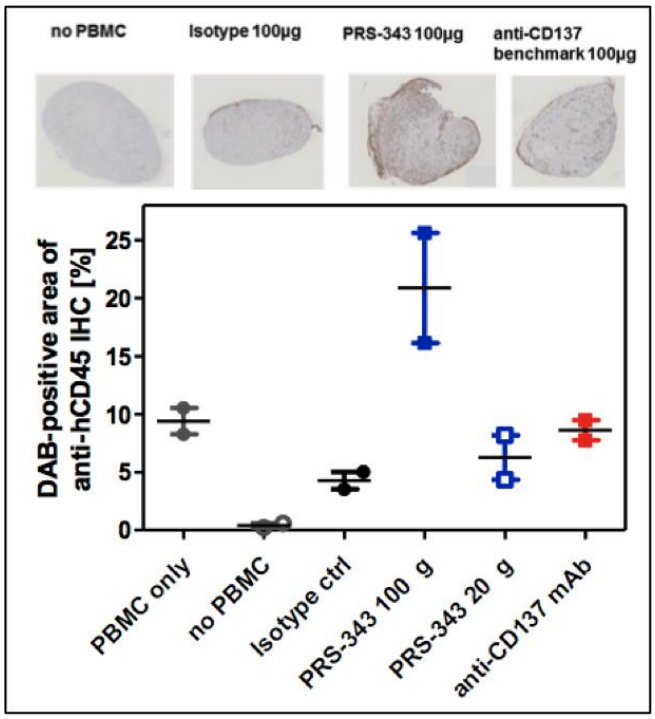


Source: Hinner *et al*., 2016

The data show that PRS-343 at both doses inhibits tumor growth, and even causes tumor regression for the first two weeks at the 100 µg dose. This is in stark contrast to the placebo treated mice that exhibited almost linear tumor growth for the three weeks of the experiment. The anti-CD137 antibody appeared to have some effect on tumor growth, however it's difficult to determine how much since those mice faired very similarly to the isotype control-treated mice.

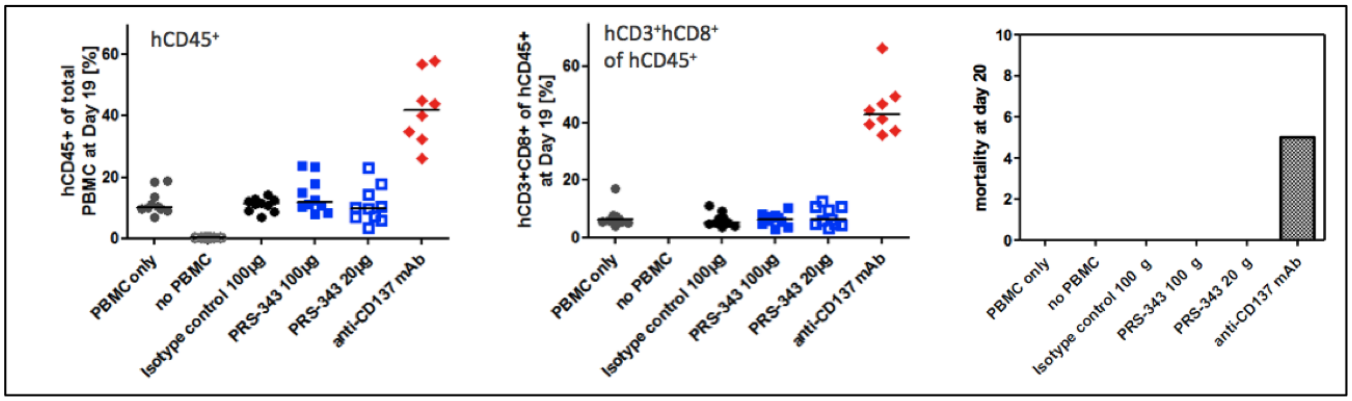
A closer look at the tumor cell population gives credence to the notion that PRS-343 is in fact working as proposed. Tumor sections were stained for CD45 (a marker expressed on all leukocytes), with the results showing that mice

treated with the 100 µg dose of PRS-343 showed higher infiltration of CD45-positive cells in the tumor than mice treated with the 20 µg dose of PRS-343, the anti-CD137 antibody, or the isotype control. While there is a sizeable population of tumor infiltrating lymphocytes (TILs) in the tumors of PRS-343 treated mice, it was not determined what specific cell types make up that population (i.e., CD8+ T-cells/CD4+ T-cells/NK cells/etc.)



Source: Hinner *et al*., 2016

Perhaps the most interesting data to be reported by Pieris in this presentation was the toxicity data concerning the anti-CD137-treated animals. The following figures show the percentage of CD45+ cells amongst the PBMC cell population on Day 20 of the experiment. Mice treated with anti-CD137 antibody had a very high percentage of CD45+ cells (left panel), with almost 50% of those cells being CD8+ T-cells (middle panel). The net result of this was that a very high percentage of the anti-CD137-treated mice developed graft versus host disease and 50% of them died spontaneously or had to be sacrificed prior to Day 20 (right panel).



Source: Hinner *et al*., 2016

These results are very important in that they show peripheral activation of anti-CD137 can lead to toxic side effects, which as mentioned above was seen in a Phase 1 study of an anti-CD137 antibody that had to be discontinued due to toxicity. PRS-343 does NOT cause activation or expansion of peripheral T-cells, thus from a safety standpoint these data allude to the fact that PRS-343 may have a cleaner safety profile than previously tested anti-CD137 monoclonal antibodies. This exemplifies another advantage of the Anticalin® platform, which is the ability to target certain antigens in a unique manner that would otherwise be more difficult with a traditional monoclonal antibody approach.

PRS-080 Update

PRS-080 is an Anticalin® that targets hepcidin, a 25 amino acid peptide produced in the liver and excreted into the bloodstream where it binds to ferroportin, an iron transporter found on duodenal enterocytes, reticuloendothelial macrophages, and hepatocytes (Donovan *et al*., 2006). Binding of hepcidin to ferroportin induces its internalization and degradation, resulting in iron accumulation in enterocytes, macrophages, and the liver. Hepcidin expression is induced by inflammatory cytokines, which is hypothesized to result in the sequestration of iron from invading pathogens (Babitt *et al*., 2010). This increased hepcidin expression results in many of the hallmarks of chronic diseases, including iron sequestration, hypoferremia, and anemia.

Pieris is developing PRS-080 as a treatment for functional iron deficiency (FID) in anemic patients with chronic kidney disease (CKD), which is a progressive loss of kidney function over a period of months or years. FID in CKD patients is characterized by low circulating iron levels that limits erythropoiesis even when these patients have sufficient iron stores in their body. These patients have low serum transferrin (a measure of circulating iron) and normal or high serum ferritin (a marker of body iron stores). FID is characteristic of a chronic inflammatory state, which in CKD patients may be due to an increased incidence of infections and/or the induction of inflammatory cytokines by the hemodialysis procedure.

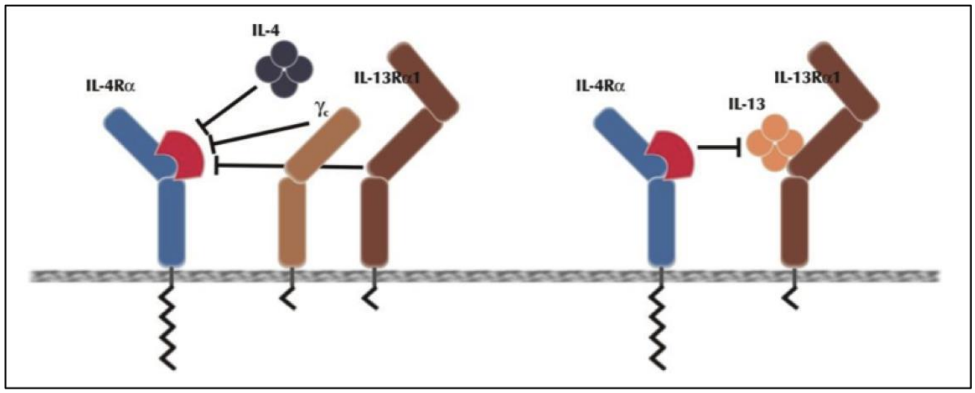
The company presented results at the American Society of Hematology (ASH) 2015 annual meeting from a placebo controlled, double blind, Phase 1 study, which consisted of six cohorts of healthy volunteers treated with ascending doses of PRS-080 in of 0.08, 0.4, 1.2, 4.0, 8.0, and 16.0 mg/kg (NCT02340572). Six patients in each cohort received drug while two patients received placebo through a two hour intravenous infusion. A total of 39 adverse events (AEs) were reported during or after treatment in 22 subjects. All AEs were mild or moderate and there were no serious AEs reported. Importantly, there were no infusion reactions or hypersensitivities noted during the study. In addition, no anti-drug antibodies were detected from participants treated with PRS-080.

A decrease in free hepcidin was noted beginning one hour after administration of PRS-080 along with a transient increase in serum iron concentration and transferrin saturation. Serum iron concentrations reached approximately 50 µM in individual subjects but did not increase further with increasing dose. The normal range for serum iron concentration is approximately 11-30 µM. We believe this is a very important data point to come out of this trial, because if PRS-080 is able to increase normal iron levels to above normal, it stands to reason that it should be able to increase anemic patients iron levels to within the normal range.

The company is currently conducting a single ascending dose Phase 1b clinical trial of PRS-080 in hemodyalisis-dependent patients with end-stage renal disease (ESRD), with results from this first-in-patient study expected by the end of 2016. Following that trial, the company will move quickly into a multiple ascending dose trial in order to evaluate the effects on hemoglobin levels. We believe results from the multi-dose trial will be reported in mid-2017. With approximately 180,000 dialysis patients worldwide having functional iron deficiency, we estimate PRS-080 could have greater than $1 billion in peak sales.

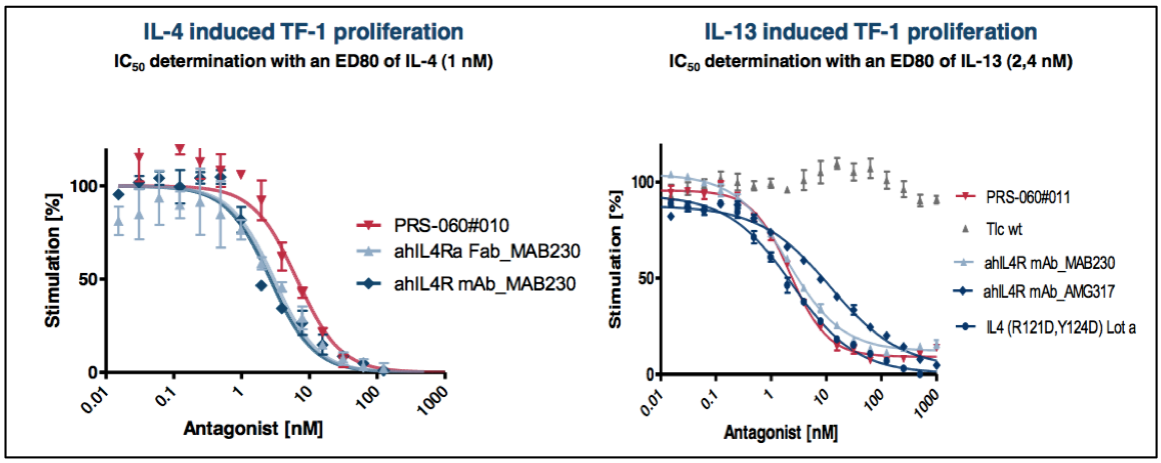
PRS-060 Update

PRS-060 is an Anticalin® that has very high affinity for the alpha subunit of the IL-4 receptor (IL-4Ra; Kd ~ 20 pM) and does not bind to the related cytokine receptors IL-6R, IL-18R, and IL-23R. By targeting IL-4Ra, PRS-060 inhibits binding of both IL-4 and IL-13, as depicted in the following graphic.



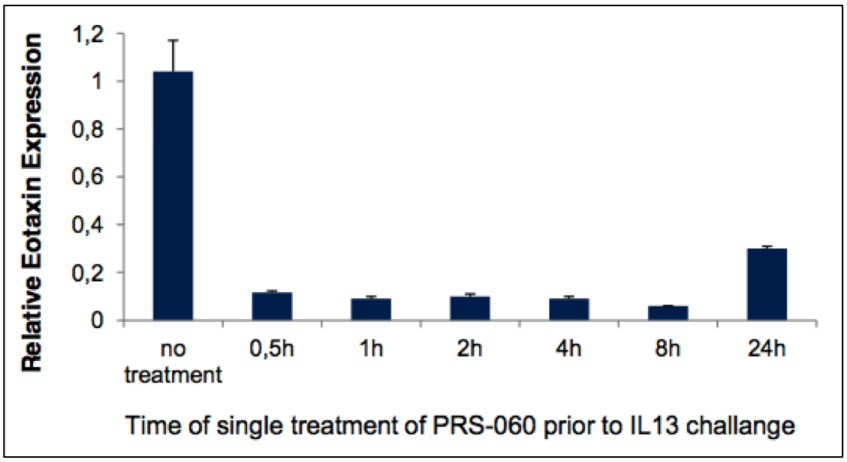
Source: Hohlbaum *et al*., 2011

The inhibition of IL-4 and IL-13 binding by PRS-060 was shown in a series of preclinical experiments involving erythroleukemic (TF-1) cells that proliferate upon stimulation with a wide range of cytokines. The cells were preincubated for 30 min with PRS-060 or other IL-4Ra antagonists prior to stimulation with IL-4 (left) or IL-13 (right). Cell proliferation was measured five days after treatment and graphed as a function of increasing amounts of IL4Ra antagonist. The results show that PRS-060 is able to inhibit both IL-4 and IL-13 dependent proliferation.



Source: Hohlbaum *et al*., 2011

Pieris has formulated PRS-060 for pulmonary delivery by inhalation, which further shows the flexibility of the Anticalin® platform as monoclonal antibodies are currently unable to be dosed through inhalation. Efficacy of inhaled PRS-060 is shown in the following graphic, in which eotaxin expression (a marker of airway inflammation) was induced by administration of IL-13 to the lungs of mice after pre-treatment with inhaled PRS-060. The data shows that eotaxin expression is inhibited for up to 24 hours following a single inhaled dose of PRS-060.



Source: Pieris Pharmaceuticals, Inc.

IL-4Ra is a clinically validated target for the treatment of asthma, as shown by clinical trial results with the IL-4Ra specific monoclonal antibody dupilumab, which is being developed by Regneron Pharmaceuticals (REGN) and Sanofi. The results from a Phase 2a study showed that treatment with dupilumab resulted in a significant decrease in asthma exacerbations and an improvement in the ACQ5 score that was maintained through 12 weeks of treatment (Wenzel *et al*., 2013). In April 2016, the results of a pivotal Phase 2b study of dupilumab in adults with asthma were published in *The Lancet* (Wenzel *et al*., 2016). The results showed the study met its primary endpoint of improving lung function in both unselected severe asthma patients and those with “allergic” asthma. Dupilumab is administered subcutaneously, and in both studies the most common adverse events were injection-site reaction, nasopharyngitis, and upper respiratory tract infection. While dupliumab has shown clinical efficacy in treating asthma, we believe administering PRS-060 through inhalation could offer a number of potential advantages, including lower systemic side effects, a smaller dose, and a more convenient dosing method.

Currently, PRS-060 is still in preclinical development with the final IND enabling studies being conducted in 2016 in preparation for a first-in-man study to be initiated in the first half of 2017. With well over 1 million potential patients worldwide, PRS-060 has blockbuster potential.

Update on Collaborations

On April 18, 2016, Pieris entered into a license and transfer agreement with Enumeral Biomedical Holdings, Inc. pursuant to Enumeral's anti-PD-1 antibody program ENUM 388D4 for its potential use as a multispecific protein containing an Anticalin® protein. Pieris paid Enumeral a license fee of $250,000 and is required to pay an additional $750,000 by May 31, 2016 to continue the agreement. If Pieris continues the license agreement, Pieris will have a 12-month option to license an additional antibody program under the same terms as the ENUM 388D4 program. Total development milestones of $37.8 million are possible along with net sales milestone payments of up to $67.5 million for an Anticalin® product that contains ENUM 388D4. Pieris will also pay Enumeral a low-to-lower middle single digit royalty on net sales. Anti-PD-1 antibodies are fast becoming the cornerstone of immunooncology combination products, and we believe acquiring the rights to anti-PD-1 antibodies is a smart move by Pieris as the company will likely utilize them to develop additional immunooncology assets.

Financial Update

On May 12, 2016, Pieris announced financial results for the first quarter of 2016. The company recognized $1.2 million in revenue, which was comprised of $0.8 million recognized from the $6.5 million upfront payment from Roche for the immunooncology collaboration and $0.4 million for research and development services provided to Roche in relation to the immunooncology collaboration. Net loss for the first quarter was $4.2 million, or $0.10 per share, and included $3.2 million in R&D expenses and $2.0 million in G&A expenses. Pieris exited the first quarter with approximately $31.2 million in cash and cash equivalents, compared to $29.3 million as of December 31, 2015. The increase in cash was due to the $6.5 million upfront payment from Roche offset by operating expenses for the first quarter. We believe the company's current cash position should be sufficient to fund operations for at least the next 12 months.

Conclusion and Valuation

The first *in vivo* data presented by Pieris on PRS-343 shows that the compound exhibits anti-tumor activity with a mechanism of action consistent with CD137 activation only in the tumor microenvironment. The importance of site-specific activation by PRS-343 is exemplified by the toxicity seen in mice treated with an anti-CD137 antibody that developed graft versus host disease, leading to 50% mortality prior to the end of the experiment.

The data presented on PRS-343 further reinforce our positive opinion of PIeris and the Anticalin® platform. The true power of the platform is exemplified by the ability to completely differentiate an anti-CD137 targeted treatment using an Anticalin® from an anti-CD137 antibody approach in terms of safety and efficacy in a humanized mouse model. We believe that the more data the company accumulates on Anticalin®-based compounds the better, as it's only a matter of time before the potential for the company becomes evident to the investment community. We have constructed a probability adjusted discounted cash flow model that takes into account potential future revenues from PRS-080, PRS-060, and PRS-343. This model leads to a valuation for Pieris of $8/share.

PROJECTED FINANCIALS

Pieris Pharmaceuticals, Inc.
Income Statement

Pieris Pharma	2015 A	Q1 A	Q2 E	Q3 E	Q4 E	2016 E	2017 E	2018 E
PRS-080	$0	$0	$0	$0	$0	$0	$0	$0
PRS-060	$0	$0	$0	$0	$0	$0	$0	$0
PRS-343	$0	$0	$0	$0	$0	$0	$0	$0
PRS-050	$0	$0	$0	$0	$0	$0	$0	$0
PRS-110	$0	$0	$0	$0	$0	$0	$0	$0
PRS-NN	$0	$0	$0	$0	$0	$0	$0	$0
PRS-SNY	$0	$0	$0	$0	$0	$0	$0	$0
Licensing & Collaborative	**$2.9**	**$1.2**	**$1.2**	**$1.2**	**$1.2**	**$4.8**	**$12.0**	**$15.0**
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$2.9**	**$1.2**	**$1.2**	**$1.2**	**$1.2**	**$4.8**	**$12.0**	**$15.0**
CoGS	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
R&D Expense	$8.2	$3.7	$3.7	$3.8	$3.8	$15.0	$18.0	$20.0
SG&A Expense	$8.4	$2.0	$2.2	$2.2	$2.3	$8.7	$9.0	$10.0
Other Expenses	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($13.7)	($4.4)	($4.7)	($4.8)	($4.9)	($18.8)	($15.0)	($15.0)
Operating Margin	*-466.6%*	*-351.4%*	*-391.7%*	*-400.0%*	*-408.3%*	*-387.5%*	*-125.0%*	*-100.0%*
Total Other Income	($0.2)	$0.2	($0.0)	($0.0)	($0.0)	$0.2	($0.2)	($0.2)
Pre-Tax Income	($13.9)	($4.2)	($4.7)	($4.8)	($4.9)	($18.6)	($15.2)	($15.2)
Taxes & Other	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*100%*	*100%*
Net Income	($14.1)	($4.2)	($4.7)	($4.9)	($4.9)	($18.6)	($15.2)	($15.2)
Reported EPS	**($0.41)**	**($0.10)**	**($0.12)**	**($0.12)**	**($0.12)**	**($0.46)**	**($0.32)**	**($0.30)**
YOY Growth						-	-	-
Shares Outstanding	34.4	39.8	40.5	41.0	42.0	40.8	47.0	50.0

Source: Zacks Investment Research, Inc. *David Bautz, PhD*

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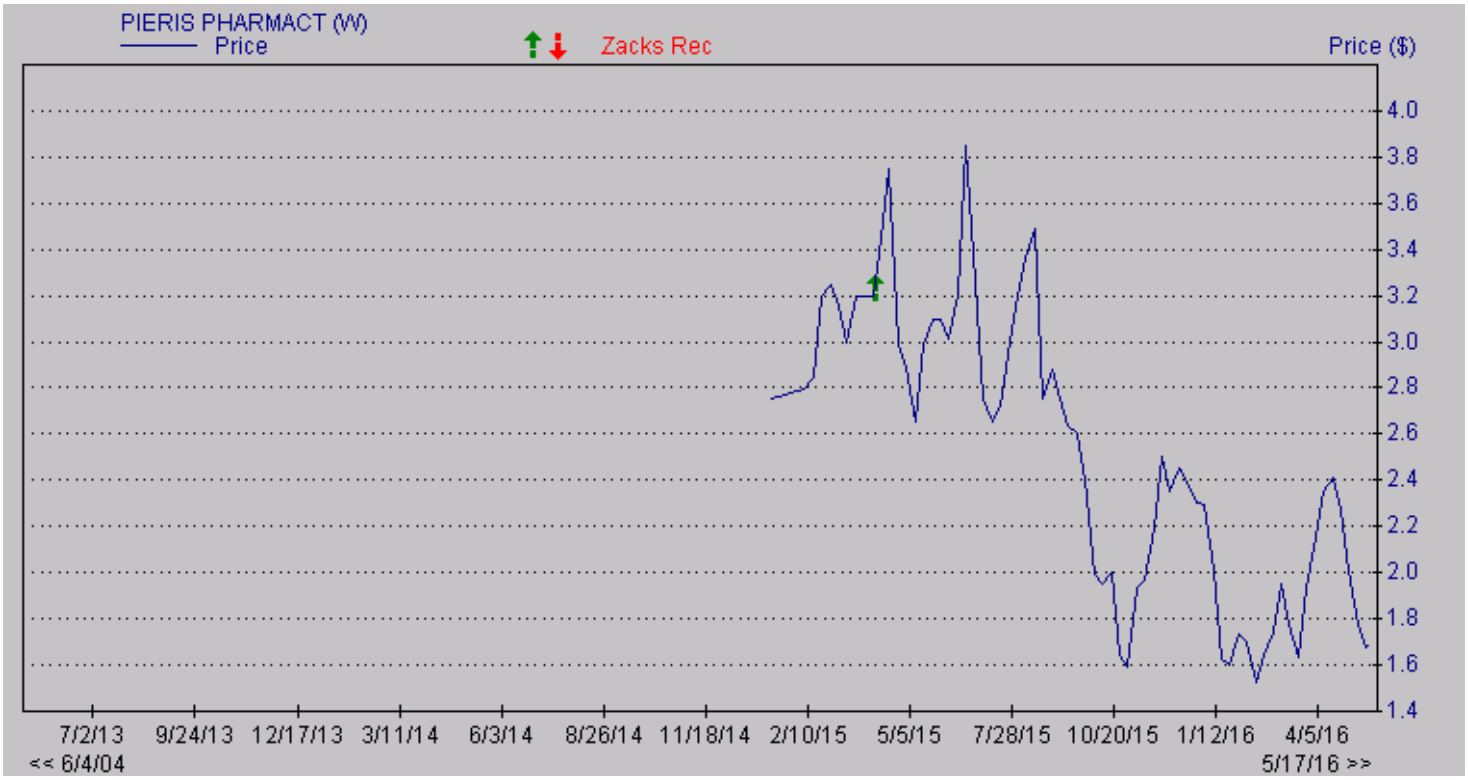
HISTORICAL STOCK PRICE



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