Zacks Small-Cap Research

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Pieris Pharmaceuticals, Inc. (PIRS - NASDAQ)

PIRS: Plenty of Cash to Continue Development of Anticalin Products…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	04/08/2015
Current Price (08/17/15)	$3.49
Target Price	**$6.00**

UPDATE

On August 12, 2015, Pieris Pharmaceuticals, Inc. announced financial results for the second quarter of 2015. The company reported a net loss of $3.5 million, or $0.12 per share and exited the quarter with $10 million in cash. In July 2015, the company raised gross proceeds of $28.3 million in a public offering.

Pieris recently completed enrollment in the ongoing Phase 1 clinical trial of PRS-080 in healthy volunteers and is planning to present the unblinded data at a scientific conference in the second half of 2015. We anticipate no safety concerns, which will allow for the company to rapidly move into a study of PRS-080 in patients with end stage renal disease.

SUMMARY DATA

52-Week High	**$4.20**
52-Week Low	**$2.50**
One-Year Return (%)	**N/A**
Beta	**N/A**
Average Daily Volume (sh)	**597,603**
Shares Outstanding (mil)	**39**
Market Capitalization ($mil)	**$134**
Short Interest Ratio (days)	**0.10**
Institutional Ownership (%)	**6**
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 2013 Estimate	**N/A**
P/E using 2014 Estimate	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	0 A	0 A	2.1 A	0 A	5.4 A
2015	0.2 A	0.2 A	0.3 E	0.3 E	1.1 E
2016					7.0 E
2017					12.0 E

Earnings per Share
(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-$0.23 A	-$0.20 A	-$0.18 A	-$0.19 A	-$0.71 A
2015	-$0.13 A	-$0.12 A	-$0.16 E	-$0.17 E	-$0.54 E
2016					-$0.58 E
2017					-$0.59 E

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WHAT'S NEW

Financial Update

On August 12, 2015, Pieris Pharmaceuticals, Inc. (PIRS) announced financial results for the second quarter of 2015. The company reported $160,244 in revenue that was received from the European Commission as part of the $6 million grant awarded to the company for the development of PRS-080. Net loss for the quarter was $3.5 million, or $0.12 per share, and was comprised of $1.7 million in R&D and $2.0 million in G&A expenses. Total cash burn was $3.0 million, and the company exited the second quarter of 2015 with approximately $10 million in cash and cash equivalents.

In July 2015, the company raised gross proceeds of $28.3 million through a public offering of 9,090,909 shares of common stock at a price of $2.75 per share and an additional 1,211,827 shares pursuant to the over-allotment option exercised by the underwriters. Oppenheimer & Co. and JMP Securities acted as joint book-running managers for the offering. Roth Capital Partners and Trout Capital acted as co-managers for the offering. We estimate the company will have approximately $35 milllion in cash at the end of the third quarter of 2015, which we believe will be enough to fund operations for at least the next 12 months.

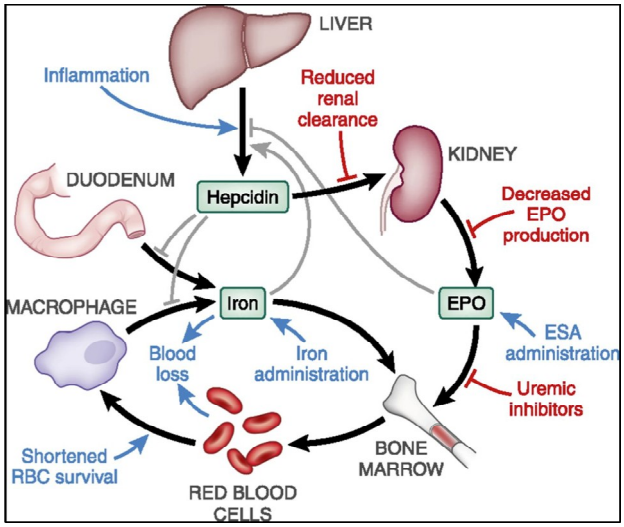
Business Update

Pieris is developing the Anticalin class of biotherapeutic compounds targeting a wide range of medical conditions. Anticalins are a new class of novel, engineered proteins that are based on lipocalins, which are proteins with variable loop regions supported by a rigid framework that bind a wide array of compounds. Pieris scientists have developed a means of modifying the lipocalins to confer unique binding specificities against virtually any biological target, and dubbed the new compounds 'anticalins' (antibody + lipocalin). The company is currently developing PRS-080, which targets hepcidin for the treatment of functional iron deficiency in patients with chronic kidney disease; PRS-060, which targets the interleukin 4 receptor (IL4Ra) for the treatment of asthma; and PRS-343, an immuno-oncology product that works by "stepping on the gas" to ramp up an immune response in the tumor microenvironment.

PRS-080 Update

On June 10, 2015, Pieris announced the completion of enrollment of healthy volunteers in the blinded, placebo controlled Phase 1 study of PRS-080. 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.

PRS-080 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, such as CKD, including iron sequestration, hypoferremia, and anemia.

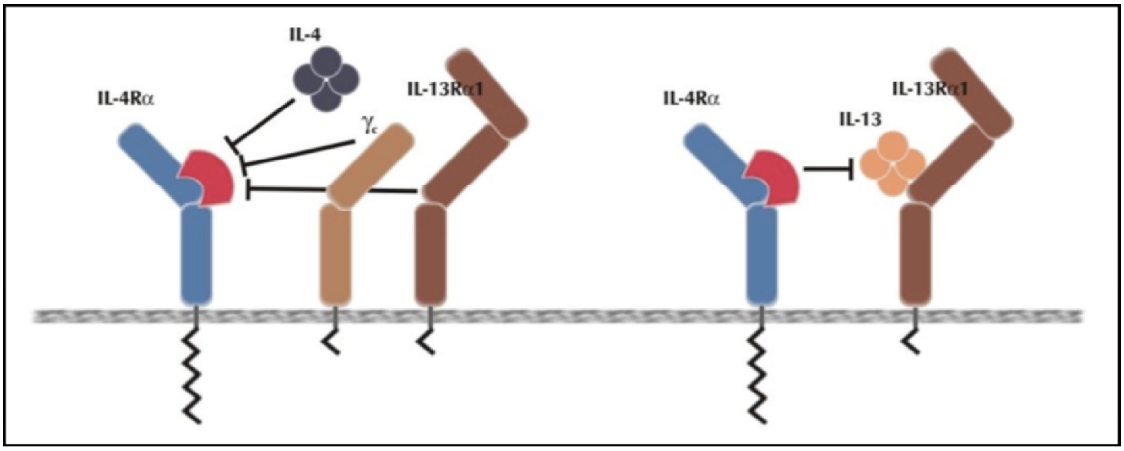


Source: Babitt *et al.*, 2012

Pieris initiated the Phase 1 study of PRS-080 in healthy volunteers in December 2014 (NCT02340572). The trial is a placebo controlled, single ascending dose (0.08 to 16 mg/kg) evaluation of the safety and tolerability of PRS-080 in healthy male volunteers. In the study, no dose-limiting toxicities were observed and a maximum tolerated dose was not reached. The company intends to present the unblinded data at an upcoming scientific conference in the second half of 2015. In addition, Pieris intends to initiate a Phase 1b clinical trial of PRS-080 in end-stage renal disease patients across multiple sites in Europe before the end of 2015. Data from that study should be available in the second half of 2016.

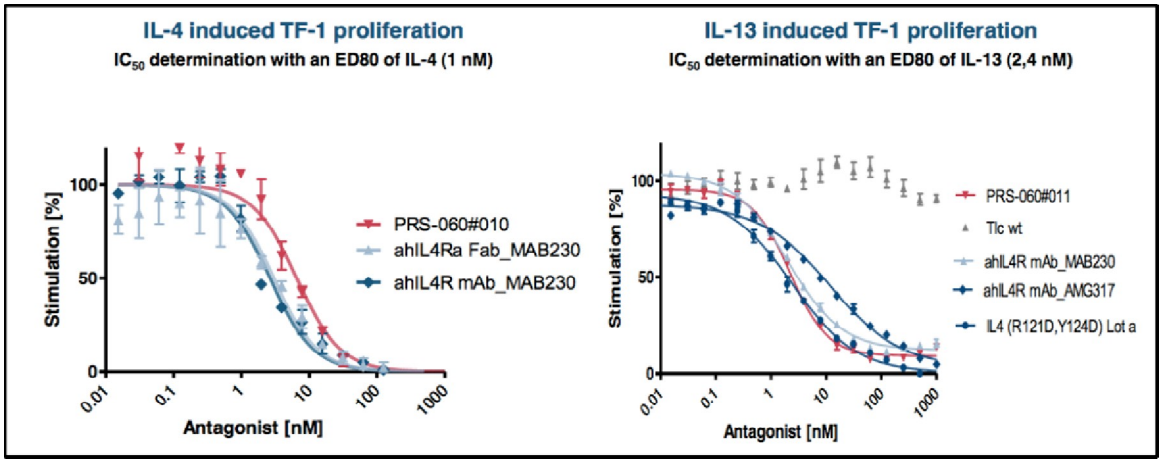
PRS-060 Update

PRS-060 is derived from human tear lipocalin (Lcn1) and has very high affinity for IL4Ra (Kd ~ 20 pM) and does not bind to the related cytokine receptors IL6R, IL18R, and IL23R. By targeting IL4Ra, PRS-060 inhibits binding of both IL-4 and IL-13, as depicted in the following graphic.



Source: Hohlbaum *et al.*, 2011

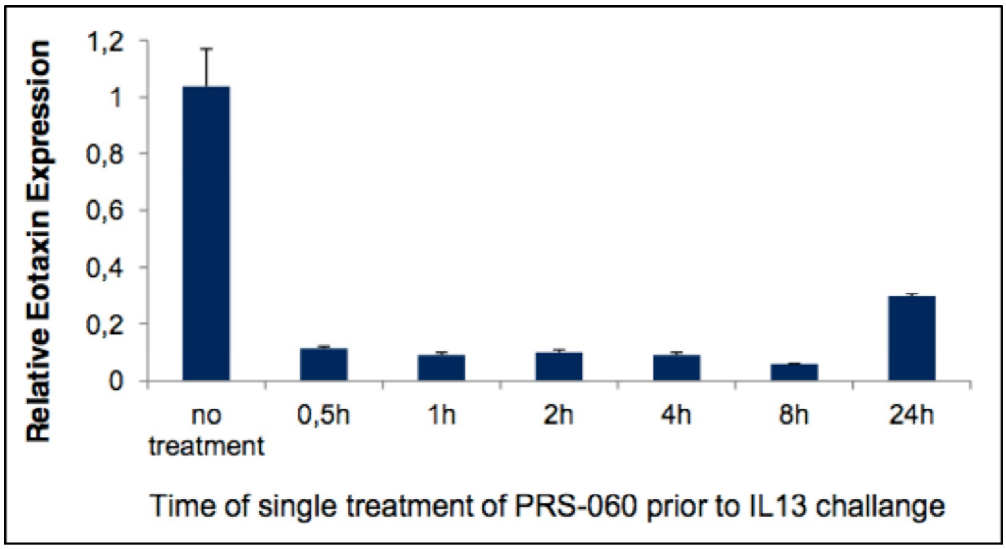
The inhibition of IL-4 and IL-13 binding by PRS-060 was shown in a series of preclinical experiments involving erythroleukemic (TF-1) cells that proliferate upon stimulation with a wide range of cytokines. The cells were preincubated for 30 min with PRS-060 or other IL4Ra antagonists prior to stimulation 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**

One of the advantages that Anticalins® have is their mode of delivery can be modified depending upon the therapeutic target. In the case of PRS-060, which is targeting IL4Ra expression in the lung, inhalation delivery would be optimal as it is likely to decrease the systemic side effects that could arise from a chronic, systemic Th2-targeting medication. Pieris has conducted inhalation studies with PRS-060 in mice and determined that systemic concentration of PRS-060 is minimal when dosed by inhalation. Since most other asthma medications are dosed by inhalation, the ability to dose PRS-060 by inhalation represents a more convenient dosing regimen than monoclonal antibody treatments, which must be administered by injection at a doctor's office or other medical clinic.

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.**

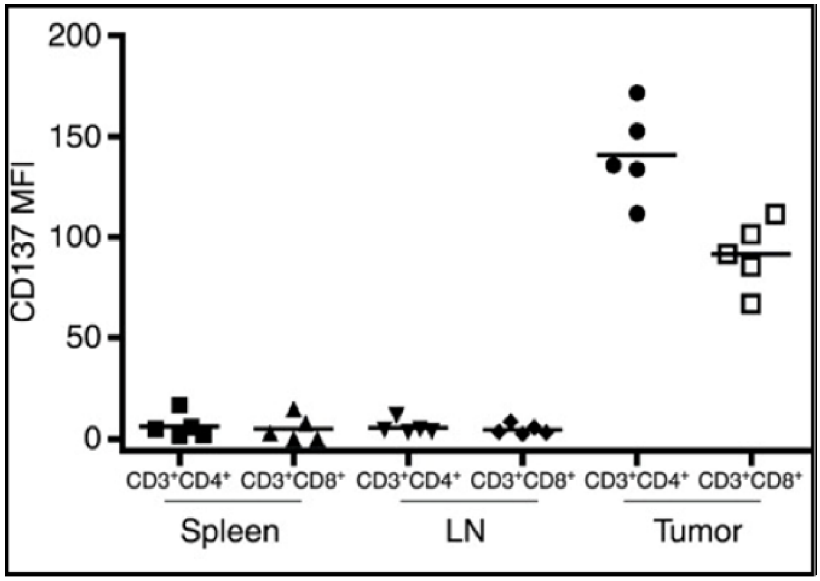
Currently, PRS-060 is still in preclinical development with the final IND enabling studies being conducted in 2015 in preparation for an IND filing in 2016. In support of these studies, Pieris recently announced the receipt of a research grant in collaboration with the University of Melbourne to advance PRS-060 through preclinical studies for inhaled delivery to treat asthmatics.

The current clinical plan calls for Pieris to test PRS-060 in healthy volunteers and then in patients with severe asthma. The goal of these pilot studies is two-fold: 1) the company could establish proof-of-concept for inhaled Anticalins®, which would provide evidence for an additional mode of administration for the company's products outside of subcutaneous and intravenous injections, the way that almost all biological therapies are administered now, and 2) establish that dosing of inhaled Anticalins® is practical and that the compound has the requisite pharmacokinetic/pharmacodynamic profile to be utilized as a therapeutic capable of positively impacting patients symptoms. We estimate that Phase 1 data for PRS-060 could be available in 2017.

PRS-343 Update

PRS-343 is a bispecific compound that contains a CD137-specific anticalin genetically linked to a HER2-specific monoclonal antibody, and is the lead compound from the company's immuno-oncology program. CD137 (4-1BB, TNFSFR9) is a tumor necrosis factor receptor (TNFR) family member with costimulatory function that regulates T-cell proliferation and survival and is expressed on activated CD8+ and CD4+ T-cells (Watts, 2005). 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, the ability to stimulate CD137 in the tumor microenvironment could mitigate these systemic toxic effects.

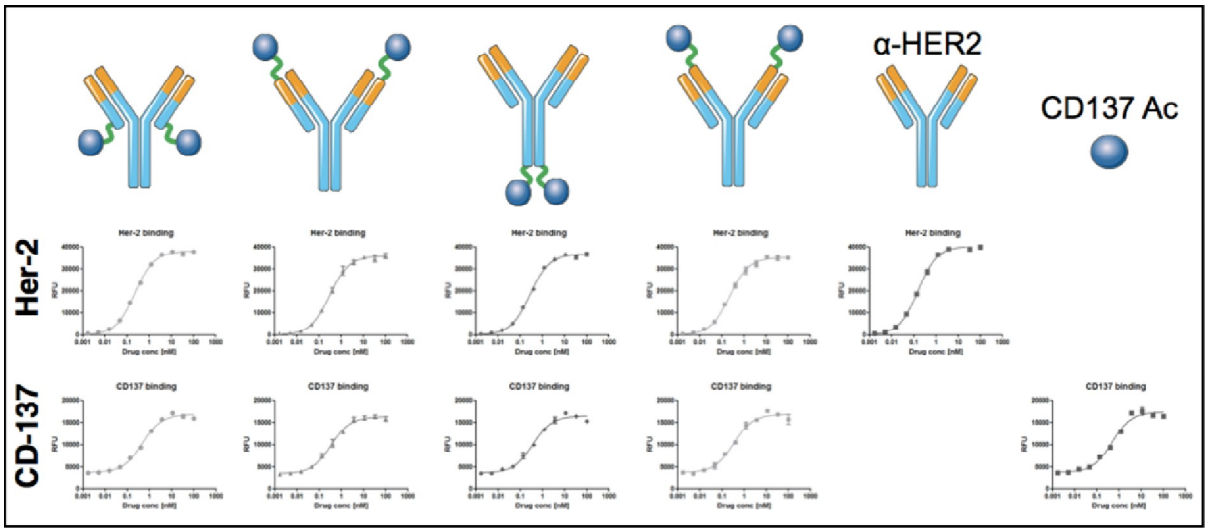
Another important aspect of CD137 is that it is preferentially expressed in high levels on intratumoral T-cells (Palazón *et al*., 2012). This is shown in the following graph, where CD4+ and CD8+ T-cells were extracted from the spleen, lymph nodes, and tumor of mice bearing CT26 tumors. Only T-cells 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**

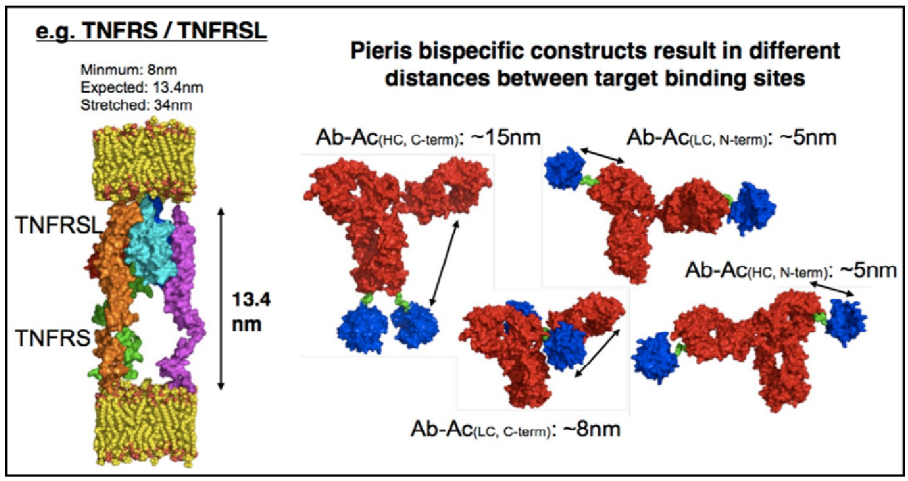
These data were further corroborated in tissue samples from patients with ovarian cancer (Ye *et al*., 2014). Results from that study showed that tumor-infiltrating lymphocytes (TILs; found in the tumor microenvironment) and tumor-associated lymphocytes (TALs; found surrounding the tumor microenvironment) 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.

Pieris has done a number of studies on different CD137-specific anticalin's to identify the lead molecule to advance into clinical testing. The company revealed that this lead compound has a very high affinity for CD137 (~2 nM), activates T-cells in an *ex vivo* model, and binds to CD137 in a "non-competitive fashion". What this means is that binding of the anticalin to CD137 does not interfere with the binding of CD137 and its natural ligand. The flexibility of the anticalin platform is exemplified in the following graphic, which shows that no matter how the anticalin is attached to the monoclonal antibody, both entities retain the ability to bind to their respective ligands with essentially the same affinity.



***Source*: Pieris Pharmaceuticals, Inc.**

Another advantage of the flexibility of the anticalin platform is that the bispecific geometry of the molecule can be manipulated to create different pharmacodynamic effects. This is shown in the following graphic, where multiple distances between HER2 and CD137 binding can be tested to determine the optimal target synapse. Preclinical work such as this is ongoing, with selection of the drug candidate to advance into clinical testing most likely being completed by the end of 2015.



***Source*: Pieris Pharmaceuticals, Inc.**

Collaborations Continue to Reap Benefits for Pieris

On July 8, 2015, Pieris announced the receipt of a third milestone payment for the second program in its discovery and development program with Daiichi Sankyo Company, Limited, and the seventh milestone payment overall under the multi-program collaboration. Pieris did not disclose the amount of the milestone payment, which was triggered by positive *in vivo* proof of concept data and progression of an anticalin drug candidate through a non-GLP toxicity study in non-human primates.

The collaboration with Daiichi calls for Pieris to receive research funding and payments for the achievement of research, preclinical, regulatory, and commercial milestones. A total of €100 million per program in license fees, funding, and milestones is possible, which does not include royalties on sales from marketed anticalin products that arise from the collaboration. Daiichi retains exclusive worldwide marketing rights for all products under the agreement.

Conclusion and Recommendation

We initiated coverage of Pieris in April 2015, and just since that time the company has achieved a number of important milestones, including 1) uplisting to the Nasdaq; 2) improving the balance sheet; and 3) finished dosing of the Phase 1a trial of PRS-080. However, the stock price has not appreciably increased since that time. We believe this will change as the Nasdaq listing should help to increase investor awareness of the company, and once the potential of the anticalin platform is fully appreciated the valuation of the company should significantly increase.

The wide range of diseases being targeted by Pieris is indicative of the flexibility and adaptability of the anticalin platform, and could make Pieris highly sought after by larger biopharmaceutical companies over the next few years, both as a partner or an acquisition candidate. A number of companies with novel protein-binding platforms (most of which have been various monoclonal antibody technologies) have either been acquired or signed lucrative partnership deals over the past few years, as shown in the following table.

Target	Acquirer/Licensor	Date	Total Deal Size
Abgenix	Amgen	December 2005	$2,200 Million
Cambridge Antibody	AstraZeneca	May 2006	$1,070 Million
Genmab	GlaxoSmithKline	December 2006	$2,059 Million
Regeneron	Sanofi-Aventis	November 2007	$1,122 Million
MorphoSys	Novartis	December 2007	$1,000 Million
OncoMed	GlaxoSmithKline	December 2007	$1,400 Million
PDL BioPharma	Bristol-Myers	August 2008	$1,155 Million
Medarex	Bristol-Myers	July 2009	$2,400 Million
Facet Biotech	Abbott Labs	March 2010	$450 Million
Micromet	Amgen	January 2012	$1,160 Million
Genmab	Johnson & Johnson	July 2012	$1,135 Million
MacroGenics	Gilead	January 2013	$1,115 Million
Seattle Genetics	Bayer	June 2013	$520 Million
Amplimmune	AstraZeneca	October 2013	$500 Million
Molecular Partners	Roche	December 2013	$1,061 Million
CytomX	Bristol-Myers	May 2014	$1,242 Million
Dutalys	Roche	December 2014	$489 Million

***Source*: Zacks SCR**

One example from the chart above that really stands out is that of Micromet, which Amgen acquired in January 2012 for $1.1 billion. Micromet was a German company that reverse merged with CancerVax Corporation in 2006. The company developed a novel antibody technology known as Bispecific T-cell engagers (BiTE) that work by binding both a tumor associated antigen and a T-cell receptor. The FDA approved Blinatumomab (BLINCYTO®), a BiTE compound that treats acute lymphoblastic leukemia, in December 2014.

In the first half of 2008, Micromet had a market cap of approximately $80 million. Approximately 4 years later, it was acquired for $1.1 billion, a greater than 13-fold return for investors who got in early. Pieris is a German company that went through a reverse merger and has a novel protein-binding technology that includes a bispecific compound that targets a tumor associated antigen and a T-cell receptor. Pieirs' current market cap is approximately $140 million. Whether the Pieris story will have the same ending as Micromet's remains to be seen, but we believe that the similarities are too great to not consider.

We are very optimistic about the future of Pieris and believe that the anticalin platform is a transformative technology that could lead to a number of novel treatments in a variety of diseases. Our price target is $6 and we continue to believe that investors with a longer-term horizon will be handsomely rewarded by an investment in Pieris.

PROJECTED FINANCIALS

Pieris Pharmaceuticals, Inc.
Income Statement

Pieris Pharma	2014 A	Q1 A	Q2 A	Q3 E	Q4 E	2015 E	2016 E	2017 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	**$5.4**	**$0.2**	**$0.2**	**$0.3**	**$0.3**	**$1.0**	**$7.0**	**$12.0**
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$5.4**	**$0.2**	**$0.2**	**$0.3**	**$0.3**	**$1.0**	**$7.0**	**$12.0**
CoGS	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
R&D Expense	$5.6	$1.5	$1.7	$2.0	$2.4	$7.7	$16.0	$19.0
SG&A Expense	$7.0	$2.4	$2.0	$3.0	$3.3	$10.7	$15.0	$20.0
Other Expenses	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($7.2)	($3.7)	($3.5)	($4.7)	($5.4)	($17.3)	($24.0)	($27.0)
Operating Margin	*-134.2%*	*-1700.8%*	*-2205.7%*	*-1566.7%*	*-1800.0%*	*-1772.8%*	*-342.9%*	*-225.0%*
Total Other Income	($2.7)	($0.0)	$0.0	($0.4)	($0.5)	($0.9)	($2.0)	($2.5)
Pre-Tax Income	($9.8)	($3.7)	($3.5)	($5.1)	($5.9)	($18.2)	($26.0)	($29.5)
Taxes & Other	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*100%*
Net Income	($9.9)	($3.7)	($3.5)	($5.1)	($5.9)	($18.2)	($26.0)	($29.5)
Reported EPS	**($0.71)**	**($0.13)**	**($0.12)**	**($0.13)**	**($0.15)**	**($0.54)**	**($0.58)**	**($0.59)**
YOY Growth	-						-	-
Shares Outstanding	13.9	29.3	29.4	38.5	38.5	33.9	45.0	50.0

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

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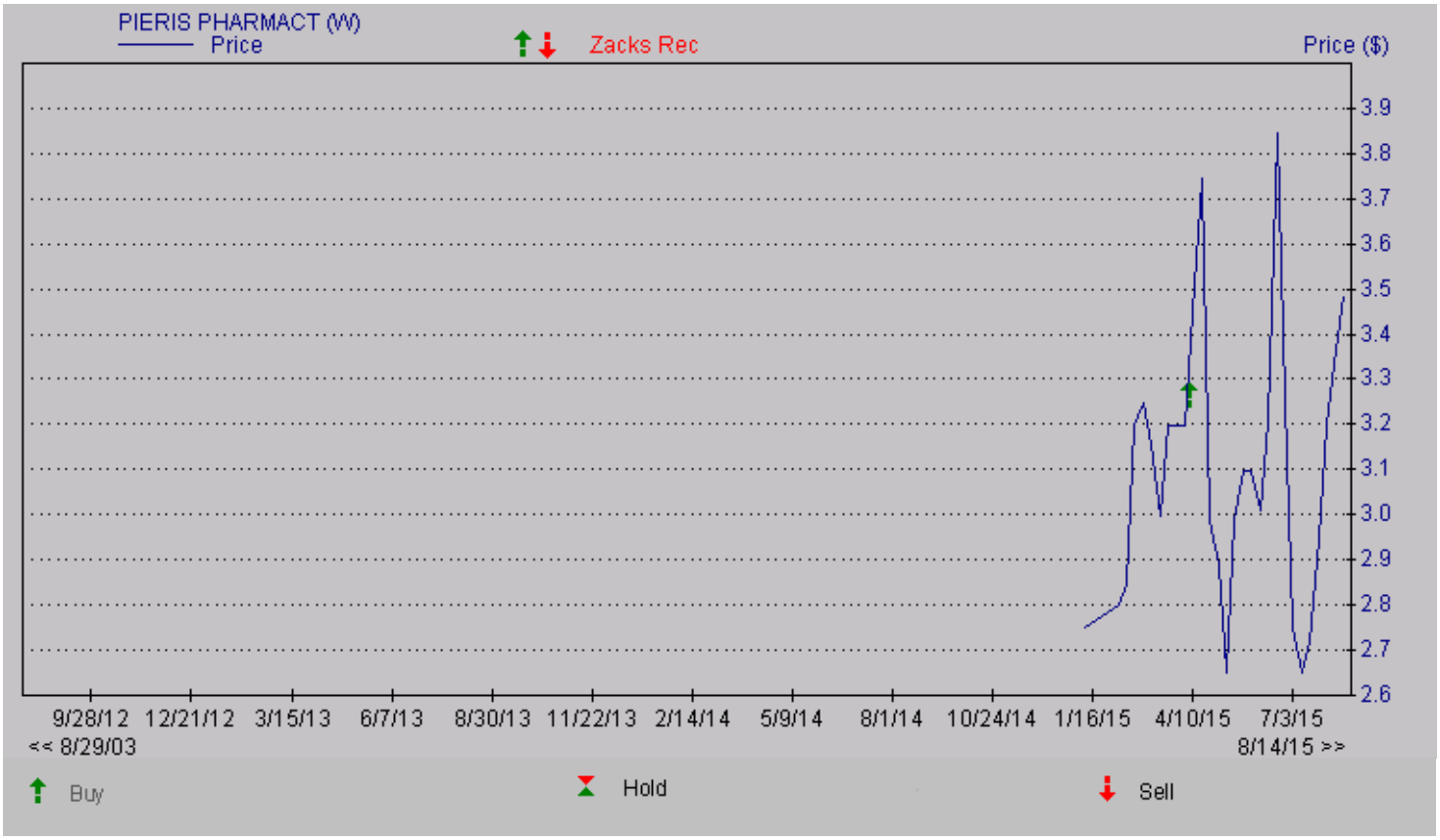
HISTORICAL ZACKS RECOMMENDATIONS



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