Zacks Small-Cap Research

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Lion Biotech (LBIO-OTC)

LBIO: Management expansion will accelerate clinical development of TILs---- maintain Outperform rating.

Current Recommendation	**Outperform**
Prior Recommendation	N/A
Date of Last Change	01/05/2014
Current Price (09/18/14)	$7.10
Twelve- Month Target Price	**$15.00**

OUTLOOK

LBIO is an emerging biotech company focused on TILs for the treatment of cancer. TILs have demonstrated compelling efficacy and safety profile in metastatic melanoma patients in physician sponsored clinical trials. We are optimistic about the prospect of TILs technology for the treatment of melanoma and other solid tumors. Lion plans to move TILs to pivotal trials soon and also plans to develop second generation of TILs for cheaper and better product.

Balance sheet remains strong and valuation is attractive at this time.

SUMMARY DATA

52-Week High	**$11.20**
52-Week Low	**$3.49**
One-Year Return (%)	**43.43**
Beta	**4.66**
Average Daily Volume (sh)	**35,765**
Shares Outstanding (mil)	**27**
Market Capitalization ($mil)	**$193**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**55**
Insider Ownership (%)	**43**
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**
Zacks Rank	**N/A**

Risk Level	**High,**
Type of Stock	**N/A**
Industry	**Med-Biomed/Gene**
Zacks Rank in Industry	**N/A**

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	0.00 A	0.00 A	0.00 A	0.00 A	0.00 A
2014	0.00 A	0.00 A	0.00 E	0.00 E	0.00 E
2015					0.00 E
2016					0.00 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	-$1.29 A	-$0.55 A	-$0.19 A	-$0.64 A	-$1.91 A
2014	-$0.11 A	-$0.09 A	-$0.11 E	-$0.11 E	-$0.41 E
2015					-$0.43 E
2016					-$0.47 E

Zacks Projected EPS Growth Rate - Next 5 Years % **N/A**

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WHAT'S NEW

Balance Sheet Remains Strong

The company's balance sheet remained strong. As of June 30, 2014, LBIO held $18.4 million in cash and cash equivalents.

On November 6, 2013, Lion completed a private financing with institutional and other accredited investors for gross proceeds of $23.3 million. After paying the placement agent fees and estimated offering expenses payable by the Company, Lion Biotechnologies received net proceeds of approximately $21.6 million.

At the closing, the Company issued 3,145,300 shares of common stock, 17,000 shares of its new Series A Convertible Preferred Stock, and warrants to purchase a total of 11,645,300 shares of Common Stock.

The purchasers of common stock received warrants to purchase the same number of shares of common stock as such investors purchased in the Private Placement, and the investors who purchased shares of Series A Preferred received warrants to purchase the number of shares of common stock into which the Series A Preferred is initially convertible. The purchase price of each common stock/Warrant unit was $2.00, and the purchase price of each Series A Preferred/Warrants unit was $1,000. The Series A Preferred is convertible into shares of common stock at any initial conversion price of $2.00 per share.

This financing not only boosts the company's balance sheet, but also validates the clinical results to-date and the potential for tumor-infiltrating lymphocyte technology.

With the increased cash, Lion should be able to take the lead T-cell program into a **Phase III** clinical study for metastatic melanoma as well as sponsor several additional combination studies of check point inhibitors and T-cells.

Management Expansion will Accelerate Clinical Development

On August 20, 2014, Lion Biotechnologies (LBIO) hired Elma Hawkins, PhD, MBA, to serve as president and chief operating officer. Her appointment is effective immediately.

Dr. Hawkins has served as Lion's head of clinical development since February 2014. Dr. Hawkins has more than 30 years of experience in biotechnology drug development, corporate development, fundraising and general management, with a special focus on oncology. For the past eight years, she has consulted for various biotechnology companies and financial institutions, and she also served as president of Viridian Pharmaceuticals.

Previously, Dr. Hawkins was president and CEO of Advanced Viral Research, vice chairman of Antigenics and director of corporate development at Genzyme Corporation. Earlier in her career, she held preclinical, clinical and regulatory positions at Warner-Lambert/Parke-Davis Pharmaceuticals and at the Center for the Study of Drug Development at Tufts University. She holds multiple degrees, including a PhD in organic chemistry and an MBA.

On June 23, 2014, Lion Biotechnologies (LBIO) announced that it has appointed **Laszlo Radvanyi**, PhD, as its chief scientific officer (**CSO**).

Dr. Radvanyi is a renowned expert in tumor immunology and adaptive T-cell therapy. In this new position, Dr. Radvanyi will be responsible for developing novel technologies to produce **next-generation TILs** with higher therapeutic potency and reduced manufacturing costs. These technologies will be based on **two different platforms**: one will use clinically sorted TILs to enhance tumor response, and the other will

utilize genetically modified T-cells to modulate expression of specific checkpoint receptors on the cell surface.

As CSO, Dr. Radvanyi will also research additional tumor indications for TILs, including lung, cervical and breast cancer, as the Company continues to advance its clinical programs in **metastatic melanoma**.

Dr. Radvanyi has been conducting clinical research on TILs for ten years, and has more than 25 years of experience studying cellular and molecular immunology. Prior to joining Lion Biotechnologies, he served as professor of melanoma and breast medical oncology at MD Anderson Cancer Center in Houston, TX since 2005. There, he conducted clinical studies on TIL therapy in metastatic melanoma, in addition to performing basic and translational research to identify relevant T-cell therapy biomarkers, enhance the anti-tumor function of expanded T-cells, and improve manufacturing methods for eventual commercialization of T-cell therapy.

Previously, Dr. Radvanyi served as senior scientist in the immunology group at Sanofi-Pasteur in Toronto, where he focused on antigen discovery and developing breast cancer vaccines. He has consulted on immunotherapy development for a number of pharmaceutical companies, and currently serves on the scientific advisory board of Aethlon Medical, Inc. Dr. Radvanyi has authored more than 87 manuscripts, is a reviewer for several journals in the tumor immunology and immunotherapy space, and has sat on many national and international grant review panels. He holds a PhD in clinical biochemistry from the University of Toronto, and completed a post-doctoral fellowship at Harvard Medical School.

With a strong background and rich experience in multiple areas, especially in the immunology and oncology area, we believe the appointment of **Laszlo Radvanyi** and **Dr. Elma Harkins** will accelerate the clinical development of TILs for the treatment of melanoma and expand its clinical utilization for other solid tumors.

Lion Enters into Exclusive License Agreement with Moffitt Cancer Center

In July, 2014, Lion Biotechnologies (LBIO) entered into an exclusive, worldwide license agreement with **Moffitt Cancer Center**.

Under the terms of the agreement, Lion has licensed from Moffitt the rights to develop and commercialize new technologies to enhance **TIL production from melanoma**, which may be applicable to other tumor types that historically have not produced therapeutic TILs.

Moffitt has two provisional patent applications, filed under “Compositions and Methods for Improving Tumor-Infiltrating Lymphocytes for Adoptive Cell Therapy.”

We think this agreement is important to Lion because it gives Lion access to technologies that allow the company to enhance TIL production.

This license agreement represents an expansion of the company’s intellectual property and technology portfolios. Most importantly, the use of these technologies may lead to an extension of the benefits of TIL therapy to address several cancers that have significant unmet medical need.

Also on July 30, 2014, Lion entered into a clinical trial grant agreement with Moffitt Cancer Center to expand an ongoing **Phase I study** of TILs combined with ipilimumab in patients with metastatic melanoma.

Under the agreement, Lion will give Moffitt funding to enroll an additional ten qualified patients into the clinical trial, bringing the total number of subjects to 20. The primary objective of the trial is to evaluate the safety and preliminary efficacy of administering **ipilimumab in combination with TILs** as a first-line therapy for patients with metastatic melanoma. Secondary outcome measures include overall response rate, or tumor shrinkage, and progression-free survival.

New Phase II Data of TILs for Metastatic Melanoma Presented

On April 7, 2014, Dr. Steven A. Rosenberg, Chief of Surgery at the National Cancer Institute (NCI) presented data showing impressive evidence of clinical efficacy from a **Phase II melanoma** clinical trial in a plenary session at the 105th Annual Meeting of the American Association for Cancer Research. LBIO is working with Dr. Rosenberg under a Cooperative Research and Development Agreement (CRADA) to develop and commercialize this novel TIL therapy.

The randomized **Phase II** clinical trial was conducted at NCI in a total of 101 patients with advanced metastatic melanoma, who were equally divided between two treatment groups. Both groups were treated according to standard TIL protocol using chemoablation, but the second group also received total body irradiation.

The new data confirmed that TIL treatment was associated with a high durable objective response rate in patients with **Stage 4 metastatic melanoma**, including many who were refractory to checkpoint inhibitors.

At the time of analysis, 11 of 101 patients from both groups had achieved complete response and 44 had achieved partial response, indicating a combined **ORR of 54%.** Differences between the two treatment groups will be calculable only after all patients have been evaluated later this year. The new data represented a significant improvement over recent clinical data from ipilimumab, marketed by BMS as Yervoy (ORR 10-15%), and anti-PD-1 therapy (ORR 31-41%) in Stage 4 metastatic melanoma patients.

In addition, TILs produced clinically meaningful objective response rates in 19/45 **(ORR 42%)** patients who were ipilimumab refractory, and 5/10 **(ORR 50%)** patients who had previously progressed on anti-PD1. Four patients with prior checkpoint failures had complete responses and continue to be disease free.

We think these data are very impressive, which confirm the results from previous Phase II studies of TILs and underscore the potential of TILs to significantly improve survival and tumor response in patients with advanced metastatic melanoma. We are especially impressed with the findings that TILs have demonstrated meaningful objective response rates in patients who were refractory to Yervoy and checkpoint PD-1 inhibitors.

Recent clinical experience has shown that Yervoy and checkpoint inhibitors are quickly becoming the standard of care for metastatic melanoma, but there are still 50 to 60% percent of patients who do not respond to these agents. The new data from TILs also suggest that TILs in combination with Yervoy or checkpoint inhibitors may further benefit patients with melanoma and other solid tumors.

Current Share Price Does Not Reflect Value

We maintain our Outperform rating on LBIO shares and our 12-month price target is $15.00 per share. We believe current share price does not reflect the value of the Company.

Lion is an emerging biotech company focused on developing and commercializing TIL therapy for cancers with initial target of metastatic melanoma. TIL therapy is an emerging treatment regimen for cancer indications and has demonstrated compelling efficacy and safety profile for the treatment of melanoma.

TIL therapy is so far the most effective treatment for patients with **metastatic melanoma**. With higher response rates than Yervoy (ipilimumab) or IL-2, and longer durations of response than Zelboraf (vemurafenib), TIL therapy carries the potential to transform current outcomes in melanoma, while also defining the way cell-based immunotherapy gets incorporated into mainstream cancer treatment. TIL therapy also has the potential to be applied to **other solid tumors**.

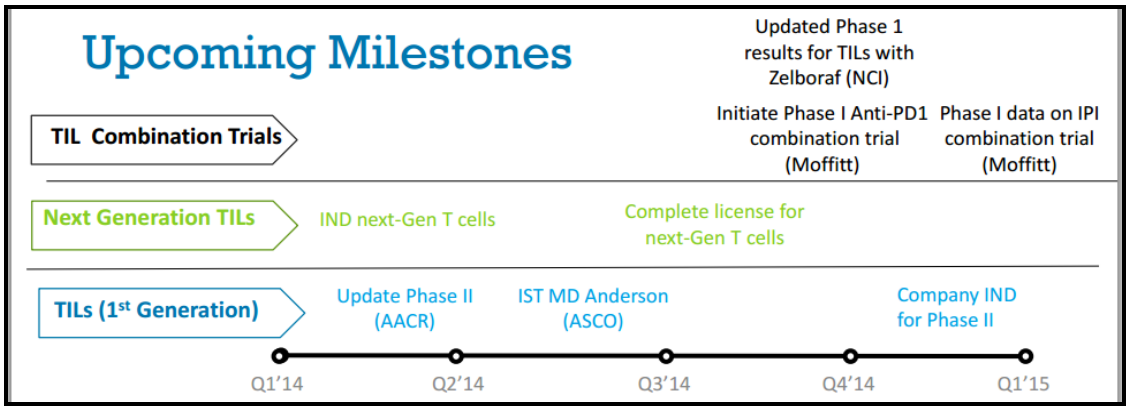
Lion has cooperation agreement with prestigious **National Cancer Institute (NCI)** to develop TIL therapy for melanoma and other cancers.

As the company continues advancing its current clinical programs, it is also developing next generation TILs and an optimized manufacturing process that will enable the production of highly potent, engineered cells at a significantly reduced cost. With unique and versatile technology, promising clinical programs, strong intellectual property, high-profile collaborations and seasoned leadership, we believe Lion has the potential to create meaningful value for its stakeholders.

In terms of valuation, we think Lion's shares are undervalued at current market price. Currently, Lion's shares are trading at about $7 per share, which values the company at $193 million in market cap based on 27 million outstanding shares. We think this is a discount to its peers considering the relatively strong fundamentals.

We understand that valuing a development stage biotech company is not easy. Lion is no exception. Most small biotech companies of development stage are valued from $100 million to $1 billion depending on how advanced the pipeline is and which indications the company is targeting. Lion is a middle stage development biotech company. TIL has finished multiple physician sponsored Phase I/II clinical trials and another PI sponsored Phase II trial is ongoing. Lion expects to have an end of phase II meeting with the FDA in 4Q14 and start pivotal Phase III trial of TIL for metastatic melanoma in 2015. Market is huge for TIL even for melanoma alone. If we consider other solid tumor indications for TIL, the market for TIL will be significantly bigger.

Our price target of $15 values Lion at $405 million in market cap, which we think is still conservative.



OVERVIEW

Lion Biotechnologies, Inc. (**LBIO**) is an emerging biotechnology company focused on developing and commercializing **adoptive cell therapy (ACT)** using autologous tumor infiltrating lymphocytes **(TILs)** for the treatment of melanoma and other solid tumors.

ACT utilizes T-cells harvested from a patient to treat cancer in that patient. TILs, a kind of anti-tumor T-cells that are naturally present in a patient's tumors, are collected from individual patient tumor samples. The TILs are then activated and expanded ex vivo and then infused back into the patient to fight their tumor cells.

ACT using TILs was developed by **Dr. Steven Rosenberg**, Chief of Surgery at the National Cancer Institute **(NCI).** Lion has acquired a worldwide, non-exclusive license for various adoptive cell therapy technologies from the NCI, and entered into a Cooperative Research and Development Agreement **(CRADA)** with the NCI. Pursuant to the agreement, Lion intends to support the in vitro development of improved methods for the generation and selection of TILs, develop approaches for large-scale production of TILs, and conduct clinical trials using these improved methods of generating TILs for the treatment of cancers.

Currently, Lion is also in discussions with the National Institute of Health **(NIH)** to license additional rights to **next generation T-cell technology** that may have higher potency, persist over a longer period of time, require fewer cells, and have a lower manufacturing cost.

TILs therapy is presently available as a physician-sponsored investigational therapy for the treatment of **metastatic melanoma** in the US. Preliminary data in small patient population have demonstrated excellent efficacy and safety profile. Durable response rates have been observed in approximately 50% of metastatic melanoma patients treated with TIL therapy with complete responses of 10%. In addition to melanoma, Lion's TIL technology is potentially applicable to all **solid tumors**.

Manufacturing TILs is currently labor intensive, costly, and time-consuming, which has limited its widespread application. Lion has entered into a Manufacturing Services Agreement with **Lonza Walkersville, Inc**. pursuant to which Lonza has agreed to manufacture, package, ship and handle quality assurance and quality control of the TIL therapy. Lonza has commenced developing a commercial-scale manufacturing process for the TIL therapy. Lion's goal is to develop and establish a manufacturing process for the large-scale production of TILs that is in accord with current Good Manufacturing Practices (cGMP). By providing centralized manufacturing, TILs therapy can be more widely available to a larger number of cancer patients.

Lion is the surviving company between the merger of Lion and Genesis Biopharma, which was the surviving company between the reverse merger of Freight Management Corp. and Genesis Biopharma, Inc. in March 2010. Genesis Biopharma changed its name to Lion Biotechnologies in September 2013 after 1-for-100 reverse stock split of its common stock.

Lion is headquartered in Woodland Hills, California. The company's stocks are traded on OTC under the symbol "LBIO".

INVESTMENT THESIS

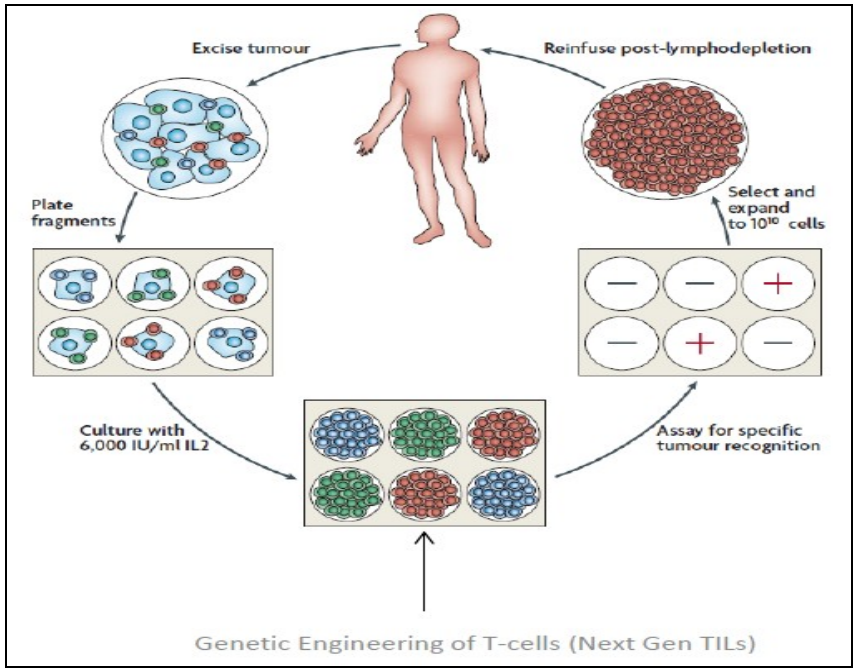
The TIL Technology

Adoptive cell therapy **(ACT)** using autologous tumor infiltrating lymphocytes **(TILs)** was first developed in 1980's by **Dr. Steven Rosenberg**, Chief of Surgery at the National Cancer Institute **(NCI).**

TILs are white blood cells that have left the bloodstream and migrated into a tumor. TILs, when numerous, are considered to be prognostically significant. **Therapeutic TILs** is a preparation of cells, consisting of autologous tumor infiltrating lymphocytes that are manipulated in vitro and, upon administration in vivo, re-infiltrate the tumor to initiate tumor cell lysis. In vitro, TILs are isolated from tumor tissue and cultured with lymphokines such as **interleukin-2**. The therapeutic TILs are then infused into the patient, where, after re-infiltration of the tumor, they may induce lysis of tumor cells and tumor regression. The use of therapeutic TILs is considered a form of **adoptive immunotherapy**.

Patients undergoing TIL therapy must have their tumors surgically resected and then shipped to the company's manufacturing facility, where the TILs are isolated, activated, and expanded to billions in vitro, away from cancer's immune-suppressing effects. These highly activated, potent TILs are then infused

back into the patient, who has been preconditioned to remove all suppressive influences. The TILs are infused into the patient with interleukin-2 (IL-2) to stimulate the immune system.



TIL therapy is emerging to be a powerful treatment option for patients with **metastatic melanoma**. TILs together with high-dose **interleukin 2** have been studied in physician sponsored multiple clinical trials in centers across the world. These physician sponsored studies have consistently demonstrated durable clinical response rates near 50% or more.

Studies also have shown that CD8+ T cells are emerging to be critical for TIL therapy, although the exact subset of CD8+ T cells exhibiting the highest clinical activity in terms of memory and effector markers is still controversial.

At this point of time, a **pivotal phase II or phase III** trial is needed in an attempt to gain regulatory approval of TILs for the treatment of melanoma. Improvements in manufacturing the therapeutic TILs are also needed to reduce cost and increase efficacy. To improve response rate and duration, surrogate and predictive biomarkers are needed to better select suitable patients for TIL therapy.

We think the outlook for TIL therapy for melanoma is quite bright based on current available data. We estimate that TILs therapy will become an important treatment option for melanoma and other solid tumors in the upcoming years. Furthermore, TIL therapy in combination with conventional therapies, such as with BRAF inhibitors, as well as with Yervoy, may further increase efficacy and durable complete response rates for patients with melanoma.

Compelling Efficacy/Safety Data and Competitive Advantages of TILs

TILs therapy is a relatively new cancer therapy regimen, and is currently undergoing physician-sponsored clinical trials for the treatment of **metastatic melanoma** at several institutions, including the NCI, MD Anderson Cancer Center, the H. Lee Moffitt Cancer & Research Institute and Sheba Hospital in Israel.

In **three sequential clinical trials** conducted by **Steven Rosenberg** at National Cancer Institute, 93 patients with measurable metastatic melanoma were treated with TILs in conjunction with interleukin-2 following a lymphodepleting preparative regimen (chemotherapy alone, or with 2Gy or 12Gy radiation). Objective response rate was 49%, 52% and 72% respectively. Twenty of the 93 patients **(22%)** achieved

a complete tumor regression and 19 have ongoing complete regressions beyond three years. **Three and five year survivals** for the entire group were 36% and 29% respectively but for the 20 complete responders were 100% and 93% respectively.

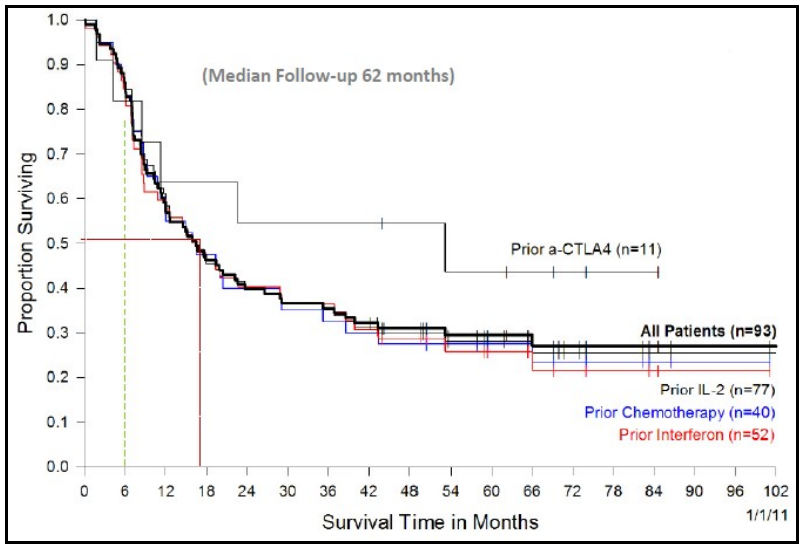
Response rate of TIL Therapy

Treatment	Total	PR	CR	OR (%)
		number of patients (duration in months)		
No TBI	43	16 (37%) (84, 36, 29, 28, 14, 12, 11, 7, 7, 7, 7, 4, 4, 2, 2, 2)	5 (12%) (82+, 81+, 79+, 78+, 64+)	21 (49%)
200 TBI	25	8 (32%) (14, 9, 6, 6, 5, 4, 3, 3)	5 (20%) (68+, 64+, 60+, 57+, 54+)	13 (52%)
1200TBI	25	8 (32%) (21, 13, 7, 6, 6, 5, 3, 2)	10 (40%) (48+, 45+, 44+, 44+, 39+, 38+, 38+, 38+, 37+, 19)	18 (72%)
TOTAL	93	32 (34%)	20 (22%)	52 (56%)

TBI: total body irradiation

Impressive survival benefits were observed even in second line or third line setting.

Overall survival of patients receiving TIL based on prior treatment received

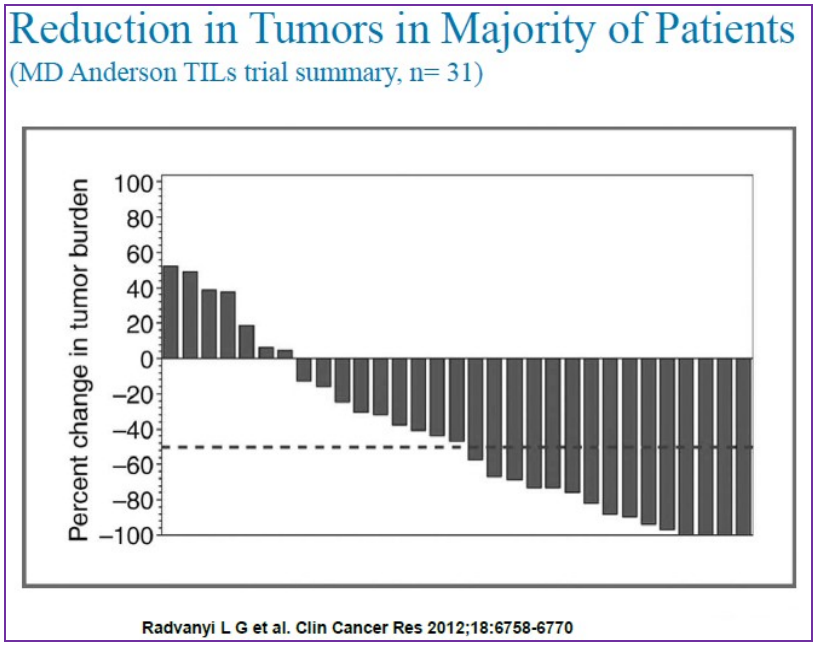


In another PI sponsored clinical trial conducted at MD Anderson Cancer Center, TIL therapy also demonstrated impressive efficacy in patients with **metastatic melanoma.** 31 transiently lymphodepleted patients were treated with their expanded TIL, followed by two cycles of high-dose interleukin (IL)-2 therapy. 15 of 31 (48%) patients had an objective clinical response using immune-related response criteria (irRC) with 2 patients (6.5%) having a complete response.

Of the 15 patients who responded, 12 had 70% or more reduction in their tumor burden and 4 patients had a 100% reduction in measurable tumor burden. Two patients (6.5%) had nonmeasurable bony lesions (complete response) that remained stable throughout the study period.

Progression-free survival of **more than 12 months** was observed for 9 of 15 (60%) of the responding patients. Factors significantly associated with the objective tumor regression included a higher number of

TIL infused, a higher proportion of $CD8^+$ T cells in the infusion product, a more differentiated effector phenotype of the $CD8^+$ population, and a higher frequency of $CD8^+$ T cells coexpressing the negative costimulation molecule "B- and T-lymphocyte attenuator" (BTLA).



Clinical trials conducted at **other institutions** achieved similar results. All clinical trials in small patient populations at different institutions show that durable response rates can be observed in approximately half of metastatic melanoma patients treated with TIL therapy. Complete responses can be seen in about 10% of metastatic melanoma patients treated with TILs.

Summary of Phase I/II Clinical Data at 4 Sites

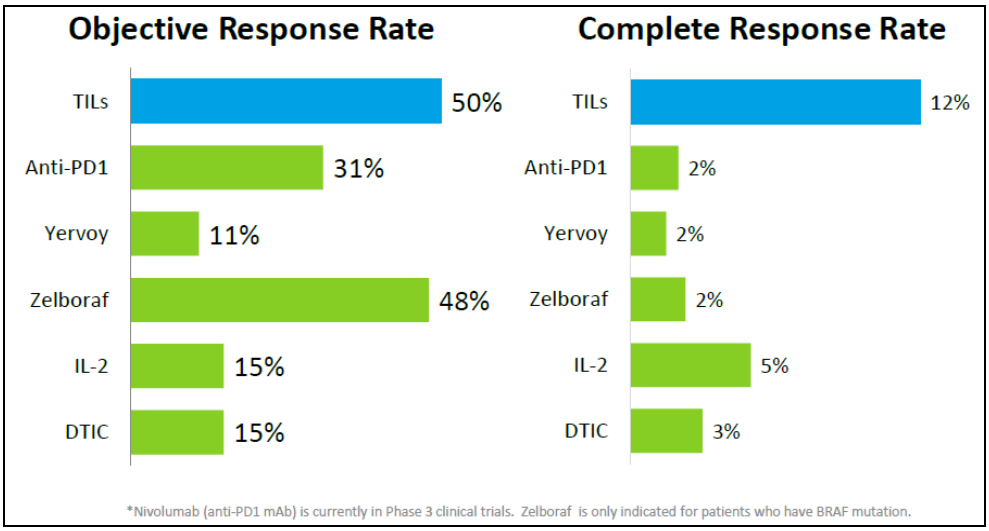
Stage IV Metastatic Melanoma in Patients Refractory to Standard of Care (Second Line Treatment)

	% Patients Achieving Complete Response	% Patients Experiencing an Overall Response (Partial + Complete Response)	Total Patients Treated
Autologous TILs (ACT)			
NCI	12%	49%	43 Patients
MD Anderson	7%	47%	38 Patients
H.L. Moffitt	13%	46%	13 Patients
Sheba Hospital (Israel)	10%	48%	42 Patients
			136 Patients

Objective response rates are usually below 40% for existing treatment regimens approved or under clinical development. For example, objective response rates for Yervoy, IL-2 and DTIC are 11%, 15% and 15% respectively. Zelboraf is an exception, which has an objective response rate of 48%. But Zelboraf is only approved for patients with BRAF mutation. Anti-PD1 has a relatively high objective response rate of 31%, but this candidate is still in clinical trial and its objective response rate is still lower than the 50% objective response rate for TIL.

Furthermore, **complete responses** in melanoma patients are extremely difficult to achieve using existing treatment regimens approved or under clinical development. Complete response rates are usually

between 2-5% for most treatment regimens, way lower than the average 12% complete response rate for TIL. In Dr. Steven Rosenberg's clinical trial, TIL even achieved 22% complete response rate for metastatic melanoma patients.



Development Plan

Based on the positive data from PI sponsored Phase I or II clinical trials, Lion plans to initiate a pivotal **Phase III** registration clinical trial to treat **metastatic melanoma** patients refractory to other treatments with TIL therapy. Subject to receiving FDA clearance for this trial, enrollment for the Phase III trial is expected to begin **in 2015**.

Lion also plans to conduct trials to treat metastatic melanoma **in the frontline setting**, combining TILs with CTLA-4 antibodies, such as ipilimumab (Yervoy®), BRaf inhibitors, such as vemurafenib (Zelboraf®), or PD-1/PD-L1 antibodies, such as nivolumab or lambrolizumab.

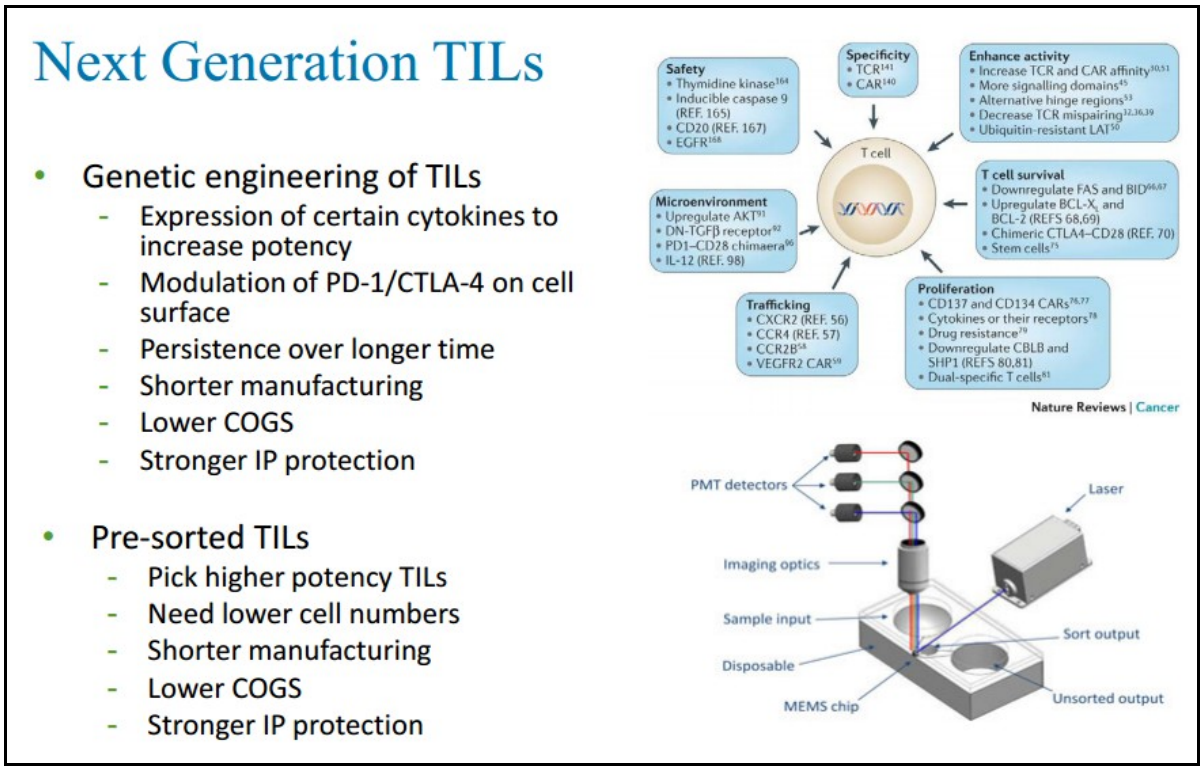
In addition to metastatic melanoma, the company intends to investigate and develop TIL therapy for the treatment of **other cancers** by funding exploratory pilot clinical trials under sponsored research agreements with various medical and research institutions.

TILs Clinical Trial Status

Sponsor	Indication	Phase I	Phase 2	Phase 3
NCI/Lion	2nd line metastatic melanoma	→ Second phase II ongoing		Phase III in 18 months
NCI/Lion	1st line metastatic melanoma in combination with Zelboraf	→		Phase I in progress at NCI
Moffit Cancer Center	1st line metastatic melanoma in combination with Yervoy (BMS)	→	Pilot Trials sponsored by Moffit in collaboration with BMS	
	1st line metastatic melanoma in combination with anti-PD1 Ab (BMS)	→		

Lion is to optimize clinical strategies based on upcoming clinical data from PI sponsored trials. In addition to the planned clinical trials, Lion also plans to engineer a better manufacturing process for therapeutic TILs, which will generate an automated manufacturing process with minimal cellular manipulations and closed systems for manufacturing. This will increase the potency of TIL and reduce cost of goods significantly.

Lion is also working with National Cancer Institute to develop next generation therapeutic TILs for the treatment of cancers. There are two strategies for developing next generation TILs. First strategy is to develop genetically engineered TILs by increasing potency, increasing persistence, and shortening manufacturing. Second strategy is to develop pre-sorted TILs by picking higher potency TILs. Both strategies lead to cheaper and better product.

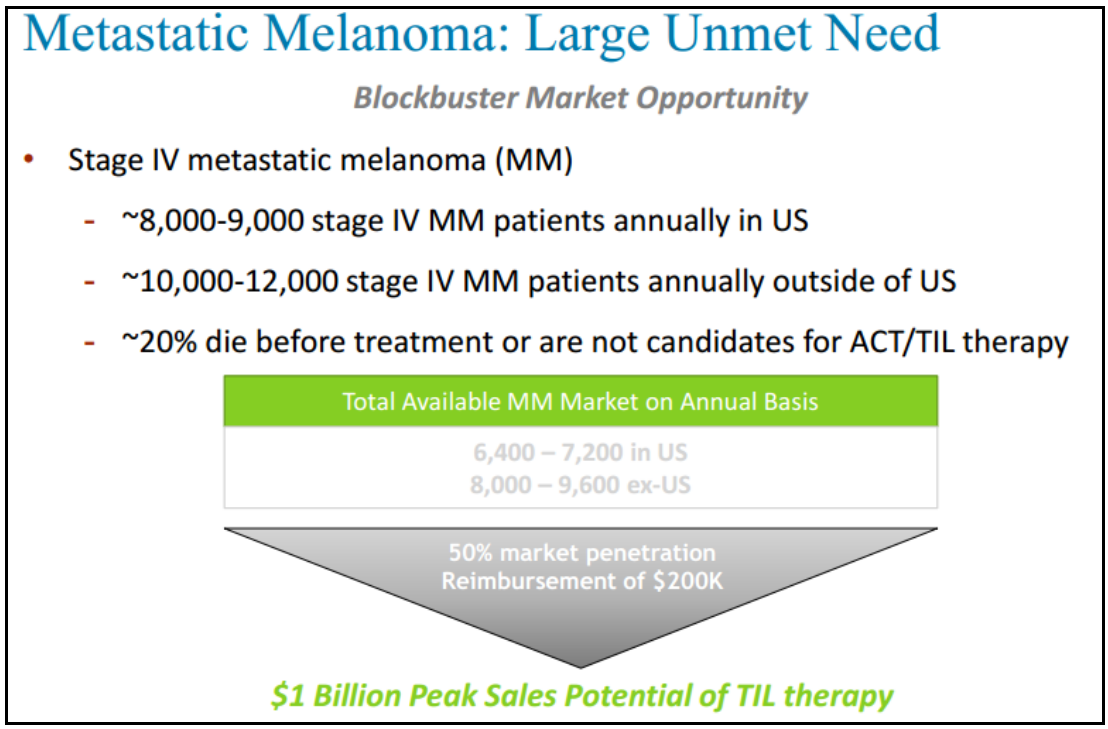


Market Opportunity For TIL Therapy

The initial indication for TIL therapy will be for the treatment of **metastatic melanoma**. From 1975 to 2010, the incidence of melanoma tripled in the United States. The American Cancer Society estimates that about 76,690 new cases of melanoma will be diagnosed and 9,480 Americans are expected to die of melanoma in the United States in 2013.

Based on current estimates of the number of annual deaths due to metastatic melanoma, as many as 7,000 metastatic melanoma patients could be eligible for TIL therapy annually in the United States. The number of metastatic melanoma patients suitable for TIL therapy outside the U.S. is approximately twice that of the U.S. However, the number of eligible patients may significantly increase worldwide if and when TIL therapy is approved.

In addition to melanoma, Lion also plans to develop TIL therapy for other solid tumors. If TIL therapy proves to be effective to treat additional indications, the market opportunity will be significantly larger.



Patients with metastatic melanoma have a poor prognosis with a 5 year survival rate of 5%. Two commonly used therapeutic agents for metastatic melanoma are **dacarbazine** and **interleukin-2**. **Dacarbazine** has an objective response rate of approximately 12% with 2-3% complete response rate that are often transient. **Interleukin-2** has an objective response rate of approximately 16% with 4-6% durable complete response rate.

The US FDA recently approved a few agents for the treatment of metastatic melanoma.

In March 2011, the FDA approved **YERVOY (ipilimumab)** from **Bristol-Myers Squibb** for the treatment of unresectable or metastatic melanoma. Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody. CTLA-4 is expressed on activated T-cells and is a **negative regulator** of T-cell activation. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. By binding CTLA4, ipilimumab enhances T-cell activation.

In a Phase III trial of 676 patients, overall survival was longer with ipilimumab alone compared with tumor vaccine gp100. Patients treated with ipilimumab alone had a median OS of 10 months. Patients treated with gp100 had a median overall survival of 6 months. Patients who received ipilimumab plus gp100 had a median OS of 10 months. Patients treated with ipilimumab alone also had the **best overall response rate** (investigator assessed), of 10.9 percent. Patients treated with the combination of ipilimumab plus vaccine arm had an overall response rate of 5.7 percent. The patients treated with vaccine gp100 alone had an overall response rate of 1.5 percent.

Overall Survival Data for Yervoy

	YERVOY n=137	YERVOY+gp100 n=403	gp100 n=136
Hazard Ratio (vs. gp100) (95% CI)	0.66 (0.51, 0.87)	0.68 (0.55, 0.85)	
p-value	p=0.0026	p=0.0004	
Hazard Ratio (vs. YERVOY) (95% CI)		1.04 (0.83, 1.30)	
Median (months) (95% CI)	10 (8.0, 13.8)	10 (8.5, 11.5)	6 (5.5, 8.7)

In August 17, 2011, the FDA approved **vemurafenib** tablets (**ZELBORAF**, made by Hoffmann-La Roche Inc.) for the treatment of patients with unresectable or metastatic melanoma with the $BRAF^{V600E}$ mutation. ZELBORAF is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with $BRAF^{V600E}$ mutation.

The confirmed, investigator-assessed best overall response rate was 48.4% for ZELBORAF. There were 2 complete responses (0.9%) and 104 partial responses (47.4%).

On May 29, 2013, the FDA approved **dabrafenib (Tafinlar**™ capsule) and **trametinib (Mekinist** tablet), from GlaxoSmithKline, for the treatment of patients with unresectable or metastatic melanoma. Dabrafenib is approved for BRAFV600E mutation, while trametinib is approved for $BRAF^{V600E}$ or ^{V600K} mutation.

The investigator-assessed objective response rates were 52 percent for patients treated with dabrafenib, which included a 3 percent complete response rate. The objective response rates were 22 percent for patients treated with trametinib. None of the 40 patients achieved a confirmed complete response.

The very small number of durable complete response rate makes it unlikely that many patients with metastatic melanoma will be cured utilizing any of these approaches.

Lion's TIL therapy is a totally different treatment regime for melanoma. There are several advantages to TIL therapy. Lymphocytes can obtained from the patient, and large number of lymphocytes can be selected in vitro for high reactivity against tumor antigens, and grow in vitro under conditions that overcome negative factors that normally exist in vivo. It's possible to modify the host prior to the cell infusion to eliminate immune regulatory cells and provide an optimal microenvironment for the infused cells.

TIL has demonstrated compelling efficacy and safety profile in human clinical trials. TIL therapy can also be used in combination with other treatment regimens for melanoma and other solid tumors. We see a blockbuster potential for TIL if approved.

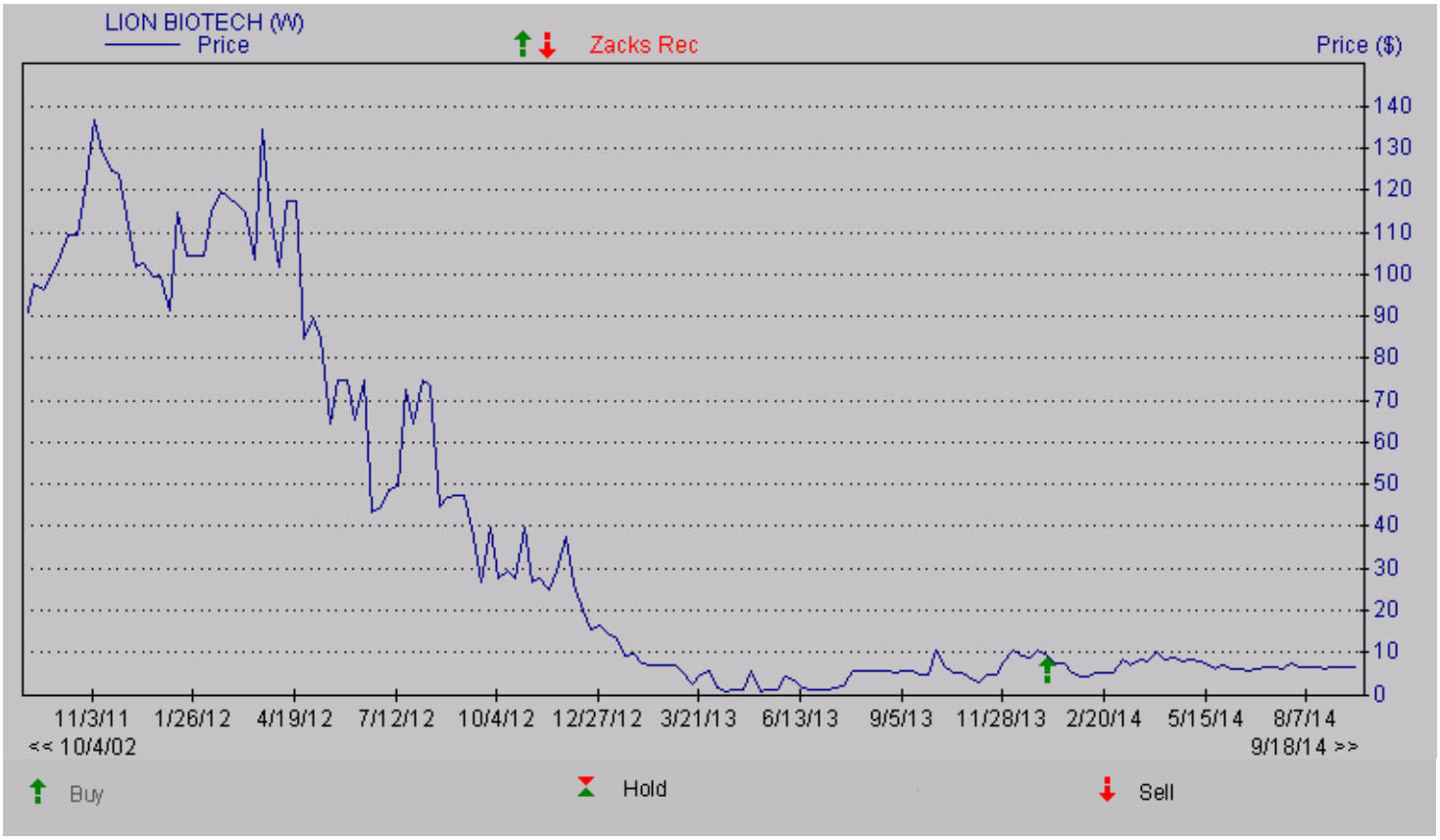
PROJECTED INCOME STATEMENT

	2013 (Dec)					2014E (Dec)					2015E (Dec)	2016E (Dec)	2017E (Dec)	2018E (Dec)
$ in million except per share data	Q1	Q2	Q3	Q4	FY	Q1	Q2	Q3	Q4	FYE	FYE	FYE	FYE	FYE
Grant revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Collaboration revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Product revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$5.00	$25.00
Total Revenues	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$5.00**	**$25.00**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CoGS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	2.50
Gross Income	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$0.00**	**$5.00**	**$22.50**
Gross Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	90.0%
R&D	$0.27	$0.25	$0.25	$0.56	$1.33	$0.30	$0.36	$0.85	$0.90	$2.41	$5.50	$7.50	$9.00	$11.00
% R&D	-	-	-	-	-	-	-	-	-	-	-	-	-	44.0%
SG&A	$0.43	$0.78	$2.46	$0.98	$4.66	$1.96	$1.75	$1.50	$1.75	$6.96	$6.50	$8.00	$10.00	$15.00
%SG&A	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other	$0.00	$0.00	$6.70	$9.96	$16.66	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Operating Income	**($0.7)**	**($1.0)**	**($9.4)**	**($11.5)**	**($22.6)**	**($2.3)**	**($2.1)**	**($2.4)**	**($2.7)**	**($9.4)**	**($12.0)**	**($15.5)**	**($14.0)**	**($3.5)**
Operating Margin	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Other Net	($0.3)	($2.4)	$0.0	($8.5)	($11.2)	$0.0	$0.0	$0.0	$0.0	$0.0	($0.1)	($0.1)	($0.1)	($0.1)
Pre-Tax Income	**($1.0)**	**($3.4)**	**($9.4)**	**($20.0)**	**($33.8)**	**($2.3)**	**($2.1)**	**($2.4)**	**($2.7)**	**($9.4)**	**($12.1)**	**($15.6)**	**($14.1)**	**($3.6)**
Income taxes(benefit)	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.5
Tax Rate	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Reported Net Income	**($1.0)**	**($3.4)**	**($9.4)**	**($20.0)**	**($33.8)**	**($2.3)**	**($2.1)**	**($2.4)**	**($2.7)**	**($9.4)**	**($12.1)**	**($15.6)**	**($14.1)**	**($4.1)**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Net Margin	-	-	-	-	-	-	-	-	-	-	-			
Diluted Shares Out	0.8	6.2	14.2	17.8	9.8	20.8	24.1	22.0	24.0	22.7	28.0	33.0	35.0	38.0
Reported EPS	**($1.28)**	**($0.55)**	**($0.66)**	**($1.12)**	**($3.47)**	**($0.11)**	**($0.09)**	**($0.11)**	**($0.11)**	**($0.41)**	**($0.43)**	**($0.47)**	**($0.40)**	**($0.11)**
One time charge	*$0.00*	*$0.00*	*$6.70*	*$8.46*	*$15.16*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*
Non GAAP Net Income	**($1.0)**	**($3.4)**	**($2.7)**	**($11.5)**	**($18.7)**	**($2.3)**	**($2.1)**	**($2.4)**	**($2.7)**	**($9.4)**	**($12.1)**	**($15.6)**	**($14.1)**	**($4.1)**
Non GAAP EPS	**($1.28)**	**($0.55)**	**($0.19)**	**($0.64)**	**($1.91)**	**($0.11)**	**($0.09)**	**($0.11)**	**($0.11)**	**($0.41)**	**($0.43)**	**($0.47)**	**($0.40)**	**($0.11)**

Source: company filings and Zacks Small Cap Research

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HISTORICAL ZACKS RECOMMENDATIONS



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