Zacks Small-Cap Research

November 30, 2015
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Tyme, Inc. (TYMI - OTC)

TYMI: FDA Accepts IND for SM-88; Set to Initiate Phase 2 Trial in Breast Cancer Patients…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	04/20/2015
Current Price (11/30/15)	$10.75
Target Price	**$14.00**

UPDATE

On November 23, 2015, Tyme, Inc. filed form 10-Q with financial results for the third quarter of 2015. The company exited the quarter with $1.9 million, and subsequent to the end of the quarter received an additional $1.25 million from the maturity of a previously issued promissory note.

Tyme has filed an IND, which was accepted by the FDA, such that the company can initiate a Phase 2 clinical trial of SM-88 in breast cancer patients. We anticipate the trial commencing in the first half of 2016.

The company obtained impressive data from a Phase 1 clinical trial of SM-88 in 30 patients with late-stage, metastatic cancer. If those results can be replicated in the upcoming Phase 2 trial, SM-88 has blockbuster potential.

SUMMARY DATA

52-Week High	**$10.75**
52-Week Low	**$6.25**
One-Year Return (%)	**N/A**
Beta	**N/A**
Average Daily Volume (sh)	**1,879**
Shares Outstanding (mil)	**86**
Market Capitalization ($mil)	**$925**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**0**
Insider Ownership (%)	**N/A**
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 2015 Estimate	**N/A**
P/E using 2016 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	0 A	0 A	0 A
2015	0 A	0 A	0 A	0 E	0 E
2016					0 E
2017					0 E

Earnings per Share

(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014					
2015	-$0.08 A	-$0.02 A	-$0.03 A	-$0.04 E	-$0.16 E
2016					-$0.11 E
2017					-$0.10 E

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WHAT'S NEW

Financial Update

On November 23, 2015, Tyme, Inc. (NASDAQ: TYMI) filed Form 10-Q with financial results for the third quarter of 2015. As expected, the company did not have any revenues in the quarter. Net loss for the third quarter of 2015 was $2.3 million, or $0.03 per share, and consisted of $1.4 million in R&D expense and $1.0 million in G&A expense. Actual cash burn for the quarter was $1.4 million.

The company exited the third quarter of 2015 with approximately $1.9 million in cash and cash equivalents. Subsequent to the end of the third quarter, the company received $1.25 million from a promissory note originally issued in connection with the company's private placement on March 5, 2015. This money was received due to the company submitting an Investigational New Drug (IND) application with the U.S. Food and Drug Administration (FDA) for SM-88, the company's lead drug candidate. We estimate that this will be enough to fund the company for the next six to nine months.

Business Update

Tyme is developing SM-88, a drug cocktail that takes a novel approach to treat intractable, aggressive, metastatic forms of cancer that have proven refractory to traditional strategies, including radiation, surgery, chemotherapy, and targeted therapeutics aimed at known receptor pathways. The company is focused on exploiting the aberrant metabolic characteristics of cancer cells that make them susceptible to subtle shifts in nutrient availability to which normal cells are impervious. Below we provide background on SM-88, the results of the proof-of-concept Phase 1 clinical trial, and what the Phase 2 clinical trial may look like.

Background on SM-88

Tumor cells are metabolically distinct from normal cells as a direct result of the modulation of intracellular signaling pathways that are altered by different genes through mutation and/or increased expression. Altered signaling pathways not only enable cells to adapt to tumor cell metabolism, but several of these metabolic alterations are also essential for malignant transformation (DeBerardinis *et al*., 2008). However, these altered signaling pathways also represent opportunities for therapeutic intervention, as a slight perturbation in nutrient availability is enough to send the cancer cell into distress. SM-88 is based on attacking various points of a cancer cell's unique metabolic profile, and – as opposed to most current cancer treatments that target one or two signaling pathways – it is designed to attack at least three separate metabolic pathways that render the cancer cell incapable of acquiring the necessary nutrients to rapidly divide. This ultimately pushes the cell into senescence or cell death.

Unlike most cancer treatments, which are developed by trained medical researchers and tested in animal models, SM-88 was developed by an engineer – Steve Hoffman (Tyme's current CEO) – who became interested in the manner by which electromagnetic radiation killed tumor cells. He scoured the medical literature in a way that was different from the approach typically taken by classically trained cancer investigators. In this approach, tumor cells were viewed to be vulnerable due to the aberrant nature of their metabolism, and mechanisms defined in the literature were invoked both serially and in parallel to attack tumors using already developed agents. Also unusual was the conscious decision to eschew the use of any preclinical models to test the underlying assumptions in animals. Rather, based upon extensive reading and an effective understanding of the medical literature, a theoretical approach was developed to attack and kill tumor cells selectively while sparing normal cells; and this was then tested in people. Thus far results have been quite encouraging – all while sparing late-stage cancer patients the debilitating side effects associated with chemotherapy, most of which are directly linked to chemotherapy's lack of specificity (i.e., its targeting of any rapidly-proliferating cells).

SM-88 Proof-of-Concept Trial

In November 2011, Luminant Biosciences (the precursor company to Tyme) filed for approval of a clinical trial for SM-88 (then known as SMK) with the Institutional Review Board (IRB) of New York Downtown Hospital. The company enrolled 30 patients with advanced metastatic cancer in the single-center, open-label, proof-of-concept clinical trial. The purpose of the trial was to determine the safety, tolerability, and efficacy of SM-88 in subjects with advanced metastatic cancer. Additional exploratory endpoints were the assessment of progression free survival,

objective response rate, duration of response, overall survival, and patient reported outcomes including health-related Quality-of-Life (QoL) and disease/treatment-related symptoms. Between January and December 2012, 30 subjects were enrolled into the study. The patient population was comprised of patients who failed all available anti-cancer treatments and had the following cancer types: 14 had breast cancer, four had non-small cell lung cancer, three had pancreatic cancer, two had prostate cancer, and one patient had each of small cell lung cancer, hepatic cancer, tongue cancer, appendix cancer, thyroid cancer, colon cancer, and a cancer of unknown origin.

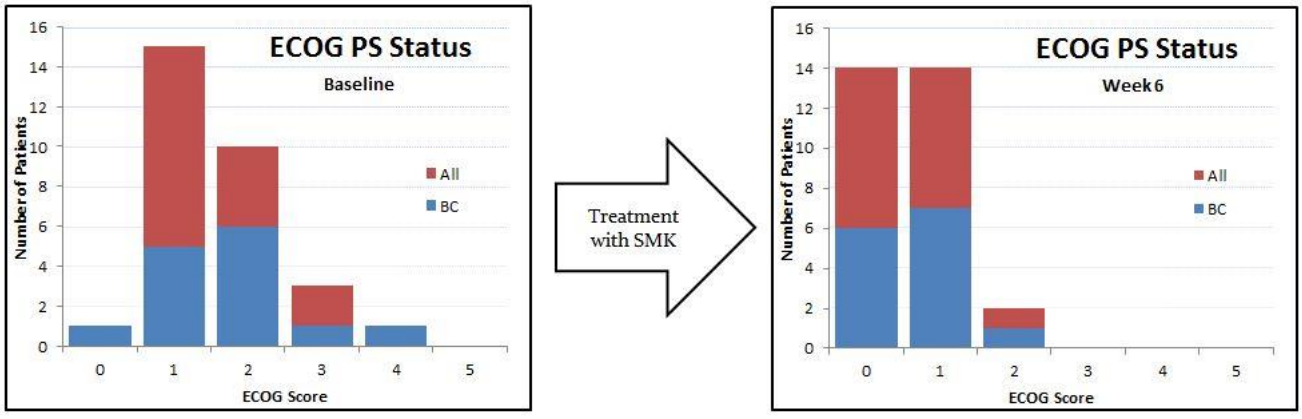
Patients received one to 10 courses of therapy, with each course consisting of daily SM-88 administration, five days per week, for a total of six weeks. The therapy was well tolerated, with all drug related adverse events occurring within the first treatment cycle, with the exception of hyperpigmentation, which eventually occurred in all patients. Drug-related or possibly drug-related adverse events (AEs) were mild-to-moderate, self-limiting, and did not require interventional therapy.

In this study, the most striking findings were on the level of tumor response and patient survival, particularly in the 14 breast cancer patients. In an affidavit filed Feb 5, 2013 with the US Patent and Trademark Office, Jeanetta Stega, MD, PhD (who oversaw the Phase 1 study) stated the following in regards to the 14 breast cancer patients who participated in the Phase 1 study:

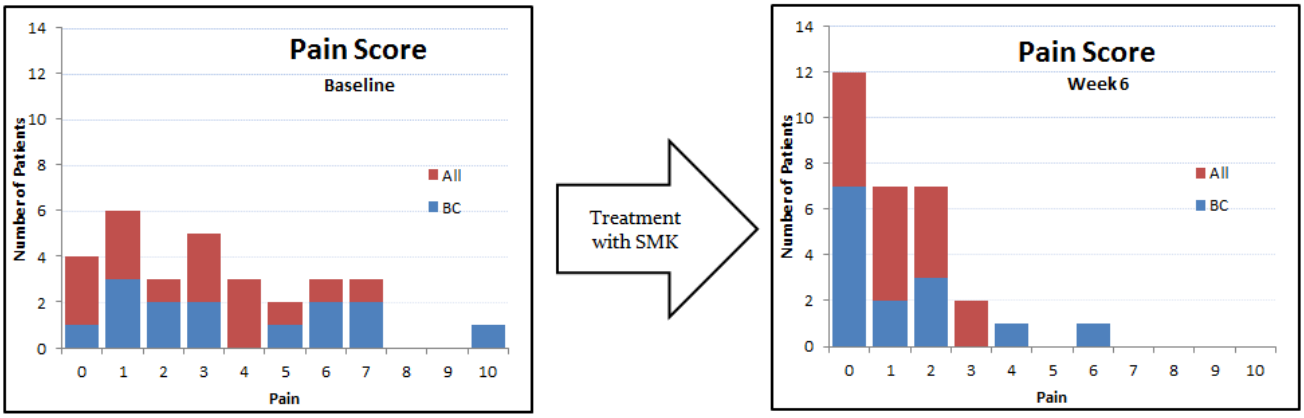
> 8. No disease was detected in three (3) of 14 (21%) with normal physical exam, review of systems, and imaging. Five (5) of 14 (36%) had significant reduction in quantity of tumors and/or size of the largest tumor. Two (2) of 14 (14%) exhibited reduction in quantity of tumors and/or size of the largest tumor. Four (4) of 14 (29%) showed no progression of disease.

Source: Affidavit filed 2/5/13 in support of patent application 13/371,076

Virtually all patients manifested dramatic and rapid improvements in Eastern Cooperative Oncology Group (ECOG) performance status (PS), European Organization for the Research and Treatment of Cancer (EORTC) quality-of-life (QoL) measures, and self-reported pain scores during the first six-week course of treatment. These changes were rapid, dramatic, and durable in nature, as shown in the following charts for all treated patients and for just breast cancer (BC) patients. Once these improvements had occurred, they persisted. Only one patient in this trial entered with an ECOG PS of 0, and 14 patients had a PS of 0 after six weeks of therapy. It is worth noting that the patient with an ECOG PS of 4 improved to a PS of 1 during this time. A dramatic improvement in self-reported pain was seen in all patients. Four patients entered the trial with no pain, which improved to 12 patients by the end of the initial six weeks. The impact of SM-88 therapy on these outcome measures could be considered even more differentiating than the impact on survival, because there are virtually no therapeutic agents currently marketed to treat cancer that are capable of providing these kinds of benefits to patients.

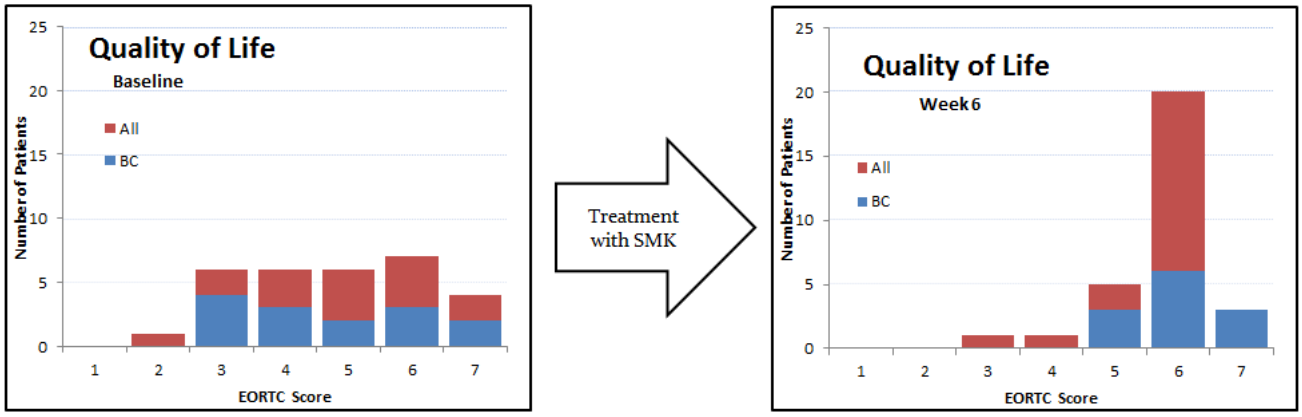


Source: Data from Tyme, Inc. / Chart from Zacks SCR (Napodano)



Source: Data from Tyme, Inc. / Chart from Zacks SCR (Napodano)

The EORTC QLQ C30 quality of life assessment tool incorporates nine multi-item scales, five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. Unlike the pain and performance status scales in which low scores are good, the EORTC QoL goes from 0 = worst QoL to 7 = best QoL. Eleven of the 30 treated patients entered the study with excellent or near-excellent QoL ratings; by the end of the first six weeks, 23/30 patients fell into this category.



Source: Data from Tyme, Inc. / Chart from Zacks SCR (Napodano)

In summary, SM-88 appears to be a safe and well-tolerated therapeutic regimen that induced unexpected increases in survival in a variety of Stage IV patients with many different tumor types, along with rapid and profound improvements in performance status, quality-of-life, and pain outcome measures in all treated patients. It is noteworthy that these responses occurred in “salvage” patients with fully disseminated Stage IV tumors who had failed all prior therapies – many of whom were referred by Memorial-Sloan Kettering Cancer Center (MSKCC) in New York City, as no approved treatment options remained for these patients.

How SM-88 Compares to Other Cancer Treatments

The results shown above are quite impressive when considering they were achieved in patients with Stage IV cancer, and particularly when examining only breast cancer patients. To put the data into context, the following is a summary of Phase 1b data presented by Oncothyreon (Nasdaq: ONTY) in May 2015 compared to the data obtained with SM-88 in breast cancer patients. Oncothyreon is developing ONT-380 for the treatment of metastatic breast cancer in patients who are HER2 positive. The drug is given in combination with Xeloda® (capecitabine) and Herceptin® (trastuzumab). The following table gives a breakdown of the results from that study based on best overall response using RECIST 1.1 criteria.

	ONT-380	SM-88 (breast cancer)
Tumor Response	Number of Patients (n = 32) Evaluable Patients (n = 27)	Number of Patients (n = 14) Evaluable Patients (n = 14)
Complete Response	2 (7.4%)	3 (21.4%)
Partial Response	12 (44.4%)	5 (35.7%)
Stable Disease	9 (33.3%)	6 (42.9%)
Progressive Disease	4 (14.8%)	0 (0.0%)

Sources: Oncothyreon, Inc. and affidavit filed 2/5/13 in support of patent application 13/371,076

While impossible to perform a direct comparison between clinical trials, the data obtained by Tyme in the Phase 1 trial is quite comparable to the data from the ONT-380 clinical trial. It is important to reiterate that ONT-380 is only available for patients who are HER2 positive, which represents approximately 20-25% of all breast cancer patients. SM-88 has no restrictions based on receptor status and thus could potentially be utilized by all breast cancer patients.

Another data set regarding late stage cancer patients that has been recently released involved the study of AG-120, which is being developed by Agios Pharmaceuticals, Inc. (Nasdaq: AGIO). AG-120 is an inhibitor of mutant isocitrate dehydrogenase 1 (IDH1), and the drug is currently being studied in an ongoing Phase 1 study in patients who have cancers with a mutation in the IDH1 gene. The recent data set presented by Agios involved patients who had glioma, intra-hepatic cholangiocarcinoma (IHCC), and chondrosarcomas, all of which are relatively rare. In contrast to the data presented by Tyme, there were no complete responses (CRs) and only one partial response (PR) out of a total of 55 evaluable patients. This represents an overall response rate (ORR) of 2%.

- Chondrosarcoma: Seven of the 11 patients with IDH1 mutant positive chondrosarcoma had stable disease. Five of these patients maintained stable disease for six months or more. The six-month clinical benefit response rate was 5/9 or 56%.
- IHCC: One out of 20 patients with IDH1 mutant-positive IHCC had a partial response (PR) and 11 patients had stable disease. Six of these patients, including one with a PR and five with stable disease, maintained their response for six months or more. The six-month clinical benefit response rate was 6/14 or 43%.
- Glioma: Ten out of 20 patients with IDH1 mutant-positive glioma had stable disease. Four of these patients maintained stable disease for six months or more. The six-month clinical benefit response rate was 4/16 or 25%.
- Other: One of the four patients with other IDH1 mutant positive solid tumors had stable disease.

Lastly, the rights to AG-120 are shared with Celgene, while Tyme currently retains 100% of the rights to SM-88. Looking at the cancer treatment landscape it is apparent that the data seen thus far with SM-88 is highly encouraging, particularly in relation to other cancer treatments at similar stages of development.

IND Accepted by FDA; Phase 2 Clinical Trial To Begin Soon

On October 26, 2015, Tyme announced that the FDA has accepted the company's Investigational New Drug (IND) application for SM-88. The acceptance of the IND means that the company is cleared to initiate a Phase 2 clinical trial. The trial will be a single-arm, open label trial. There are likely to be 10-20 clinical sites involved and the plan is to enroll 80-120 patients. All of the patients will have metastatic breast cancer that is refractory to more than one prior treatment. There will be no selection for patients based on receptor status, thus the trial will enroll patients who are positive or negative for estrogen receptor (ER), progesterone receptor (PR), and HER2.

Patients with metastatic breast cancer represent a very difficult cohort to treat, as the disease is considered incurable once it metastasizes and therapeutic goals are palliative in nature. The median overall survival for patients with metastatic breast cancer is 2-4 years (Chung *et al*., 2003); however, those statistics are for women who are previously untreated. Those with refractory metastatic breast cancer have a much worse prognosis as they have a median overall survival of 8-9 months (Pontiggia *et al*., 1995). While less than 10% of newly diagnosed patients (out of a total of approximately 230,000) will present with locally advanced or metastatic disease (Bernard-Marty *et al*., 2004), approximately 25% of patients diagnosed at earlier stages will relapse with metastatic disease (Metastatic Breast Cancer Network).

Once initiated, we anticipate that the Phase 2 trial will enroll patients fairly quickly, as there are no further treatment options for patients with refractory metastatic breast cancer and the trial is going to take place at between 10 and 20

clinical centers in the U.S. We anticipate that the Phase 2 trial will begin in the first part of 2016. Given an expected survival of 8-9 months for the patients, by the end of 2016 we should have a fairly clear understanding of whether SM-88 is prolonging overall survival since the trial will be open label.

Tyme Makes Multiple Appointments to Medical Advisory Board

During September and October 2015, Tyme made multiple appointments to the company's Medical Advisory Board:

Daniel Petrylak, MD: Dr. Petrylak will oversee the company's clinical trials. He is currently Professor of Medicine, Director of Genitourinary Oncology and Co-Director of the Signal Transduction Research Program at Yale University. Prior to Yale, Dr. Petrylak served as Professor of Medicine at Columbia University Medical Center. He has received several grants and funding support from the National Institutes of Health, private institutions, and the pharmaceutical industry to study cancer treatments and has authored or co-authored more than 100 articles and abstracts in peer reviewed journals.

Mario Eisenberger, MD: Dr. Eisenberger will offer oversight to the company in clinical and medical affairs. He is currently Professor of urology and oncology at Johns Hopkins University School of Medicine, with a practice specializing in the treatment of cancers of the bladder, kidney, prostate, and testicles. Dr. Eisenberger has been listed in *Best Doctors in America* and *Who's Who in the World* along with having an extensive list of publications.

W. Kevin Kelly, DO: Dr. Kelly has been appointed to serve on both the Medical Advisory Board and the Scientific Advisory Board. He is currently Director of the solid tumor division in the Department of Medical Oncology and Associate Director of Translational Research at the Thomas Jefferson University Hospital Kimmel Cancer Center in Philadelphia. Dr. Kelly's main clinical research focus has been in the area of genitourinary cancers and he is a leading expert in the development of novel treatment strategies and targeted agents for prostate cancer and other urologic cancers.

Conclusion and Recommendation

We have chosen to model potential sales of SM-88 solely in late-stage, metastatic breast cancer patients. However, based on what appears to be a broad applicability across multiple tumor types this analysis may ultimately be too restrictive if the results seen in the Phase 1 trial are replicated in a larger clinical trial. The possibility of broader applicability into other types of cancer – e.g., renal cell carcinoma, Ewing's sarcoma, lymphomas and leukemias – could represent sources of upside to our estimates. No revenue from an expanded access program is assumed, which may be conservative – companies like Pharmion and Celgene generated tens of millions of dollars from such programs prior to the actual formal approval of several of their anti-cancer drugs. We estimate peak revenues in the U.S. and E.U. of approximately $3.3 and $3.0 billion, respectively (with a 15% royalty generated through a partnership on sales in the E.U.). We have slightly increased our price target based on no issues identified with the company's IND. We think the shares are worth approximately $14 and we are maintaining a 'Buy' rating.

PROJECTED FINANCIALS

Tyme, Inc.
Income Statement

Tyme, Inc.	2014 A	Q1 A	Q2 A	Q3 A	Q4 E	2015 E	2016 E
SM-88 (Breast Cancer)	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-
Research & Development	$0.8	$0.5	$0.8	$1.4	$2.0	$4.7	$3.0
General & Administrative	$1.8	$1.6	$1.0	$1.0	$1.2	$4.7	$7.5
Other Expenses	$0	$0	$0	$0	$0	$0	$0
Operating Income	($2.6)	($2.1)	($1.8)	($2.3)	($3.2)	($9.4)	($10.5)
Operating Margin	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	($0.1)	($3.5)	$0.0	$0.0	($0.1)	($3.6)	($0.1)
Pre-Tax Income	($2.7)	($5.6)	($1.8)	($2.3)	($3.3)	($13.0)	($10.6)
Income Taxes Paid	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($2.661)**	**($5.6)**	**($1.8)**	**($2.3)**	**($3.3)**	**($13.0)**	**($10.6)**
Net Margin	-	-	-	-	-	-	-
Reported EPS	**($1,330)**	**($0.08)**	**($0.02)**	**($0.03)**	**($0.04)**	**($0.16)**	**($0.11)**
YOY Growth	-	-	-	-	-	-	-
Basic Shares Outstanding	0.0	73.4	86.0	86.0	88.0	83.4	93.0

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

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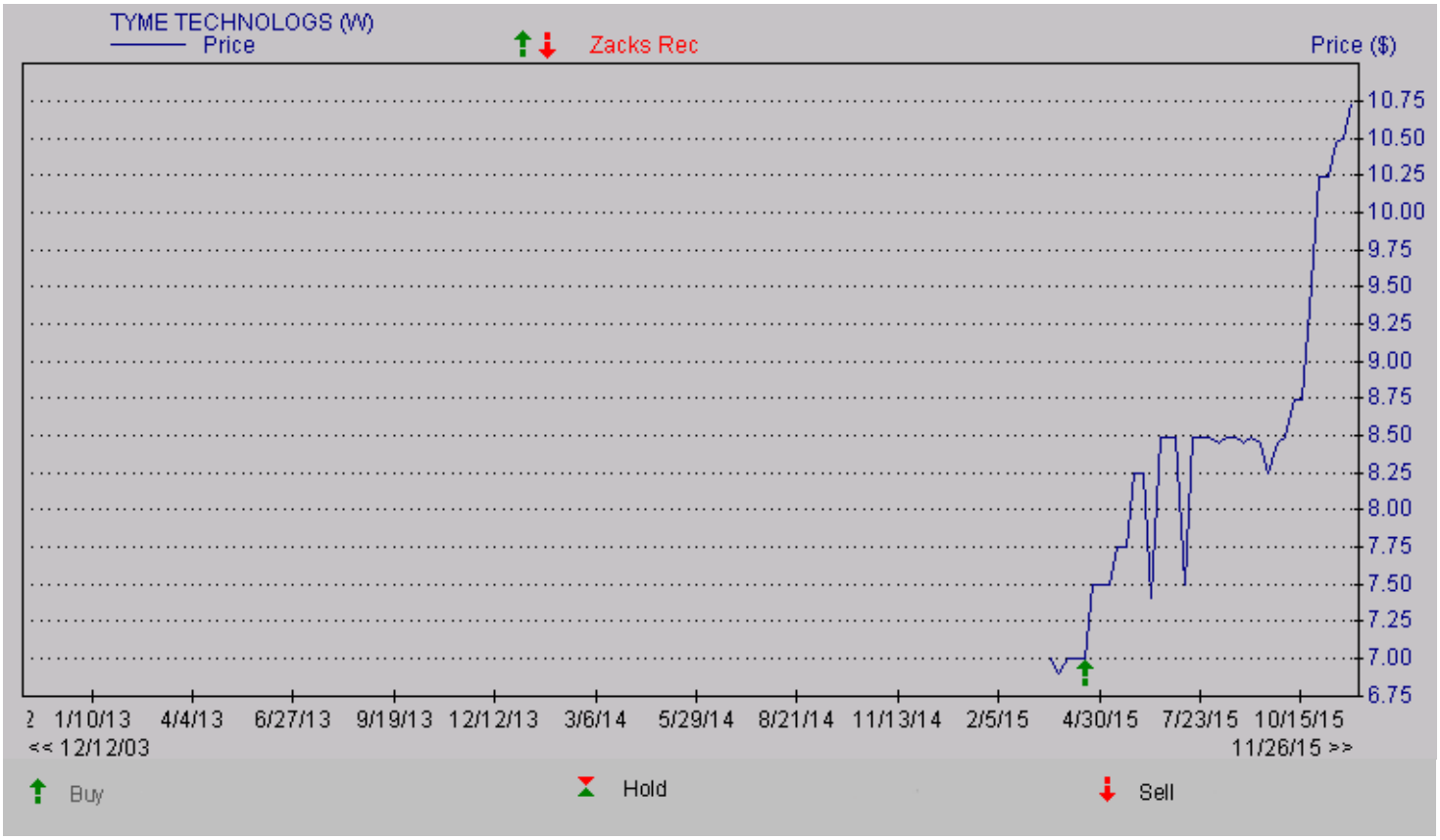
HISTORICAL ZACKS RECOMMENDATIONS



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Buy/Outperform: The analyst expects that the subject company will outperform the broader U.S. equity market over the next one to two quarters.
Hold/Neutral: The analyst expects that the company will perform in line with the broader U.S. equity market over the next one to two quarters.
Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

The current distribution is as follows: Buy/Outperform- 25.7%, Hold/Neutral- 56.1%, Sell/Underperform – 14.4%. Data is as of midnight on the business day immediately prior to this publication.