Zacks Small-Cap Research

April 20, 2015
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Tyme, Inc. (TYMI - OTC)

TYMI: Initiating Coverage of Tyme, Inc.; Unique Anti-Cancer Platform Targeting Metabolic Features of Cancer…

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	04/20/2015
Current Price (04/20/15)	$7.00
Target Price	**$12.00**

INITIATION

We are initiating coverage of Tyme, Inc. with a Buy rating and a $12.00 price target.

Tyme is a clinical stage pharmaceutical company developing highly targeted cancer therapeutics to treat a wide range of oncology indications. The company's lead candidate is SM-88, a drug cocktail that is designed to induce metabolic stress to specifically kill cancer cells.

SM-88 is a combination of four drugs (three of which are approved for other indications) that work synergistically to target unique metabolic features of cancer cells. The cocktail has been tested in 30 Stage IV cancer patients, with only two patients experiencing progressive disease during the trial.

SUMMARY DATA

52-Week High	**$7.00**
52-Week Low	**$5.25**
One-Year Return (%)	**33**
Beta	**N/A**
Average Daily Volume (sh)	**2150**
Shares Outstanding (mil)	**86.0**
Market Capitalization ($mil)	**602**
Short Interest Ratio (days)	**0**
Institutional Ownership (%)	**16**
Insider Ownership (%)	**66**
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 E	0 E	0 E	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	-$0.01 E	-$0.01 E	-$0.01 E	-$0.01 E	-$0.04 E
2016					-$0.07 E
2017					-$0.10 E

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WHAT'S NEW

Initiating Coverage



We are initiating coverage of Tyme, Inc. (TYMI) with a Buy rating and a $12.00 price target. Tyme's lead product is SM-88, 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.

Tyme has taken an accelerated approach to clinical development by formulating a combination regimen based on existing approved drugs. The treatment is based in part on an observation, originally noted by Otto Warburg in the 1920's, that cancer cells take up glucose at a much higher rate than normal cells and secrete most of the glucose-derived carbon as lactate, a process known as the "Warburg effect". This shift in metabolism from the typical manner in which energy is utilized and transported within cells (oxidative phosphorylation) to a more wasteful system in which energy is derived simply from breaking down glucose (glycolysis) is a unique feature of cancer cells that can be utilized to increase metabolic stress inside the cell. Unlike many other companies focusing on drug development, Tyme has elected to repurpose existing drugs for the creation of its combination regimen, bypassing animal proof-of-concept studies that often turn out to be of dubious predictive value in order to assess the effectiveness of its approach directly in human patients.

Thus far, Tyme has conducted a proof-of-concept clinical study in 30 salvage patients – individuals with late-stage disease who have run out of other treatment options – that demonstrated a benign safety profile and robust tolerability, while also showing intriguing indications of differentiated efficacy. In particular, Tyme's SM-88 regimen has shown the potential to achieve durable complete responses (100% clearance of cancer cells) and substantial increases in survival as well as the ability to improve patients' well-being, which contrasts markedly to the side effects typical of traditional chemotherapy (hair loss, nausea, anemia, neutropenia, immune system compromise, and gastrointestinal problems that can render patients entirely unable to eat solid food). The data generated thus far may indicate that SM-88 represents a potentially best-in-class approach to cancer therapy from both a safety and efficacy standpoint. Furthermore, it appears that SM-88 has clinical activity against a wide array of cancer types, regardless of the tissue or organ of origin, and that it possesses the ability to address both solid and liquid tumors. Such broad-based activity with the kind of safety profile that the company has seen thus far may position SM-88 above many existing treatments as well as some of the late-stage therapeutic approaches currently being developed, such as chimeric antigen receptor T-cell immunotherapy (CAR-T) approaches, checkpoint inhibitors, and targeted enzyme inhibitors.

The company is currently in the process of assembling a formal Investigational New Drug (IND) filing, which it expects to file with the U.S. Food and Drug Administration (FDA) within the next two to three months. If accepted, this filing should allow for the initiation of a formal Phase 2 clinical trial that could enroll 80 – 120 metastatic breast cancer patients and potentially generate sufficient clinical efficacy data to permit the firm to request Breakthrough Therapy designation and possibly accelerated review and approval, although that is far from certain at this time. Tyme is also planning to pursue the establishment of an Expanded Access program for SM-88, which would be aimed at facilitating the availability of the regimen to late-stage patients who have exhausted all other options.

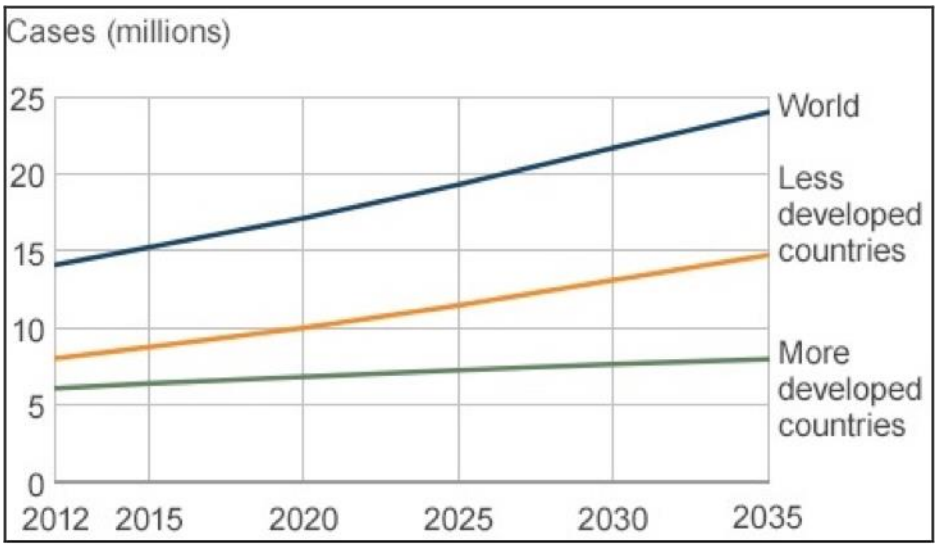
As of March 5, 2015, Tyme had approximately $5.6 million in cash following the completion of a private placement transaction with an institutional investor that raised $6.8 million. These funds are being deployed to drive the filing of the IND and to conduct the Phase 2 clinical trial of SM-88. Tyme eventually intends to pursue the development of SM-88 across multiple cancer types in order to optimize the potential clinical benefit of this therapeutic approach; however, they are choosing to initially focus on metastatic breast cancer.

INVESTMENT THESIS

Cancer

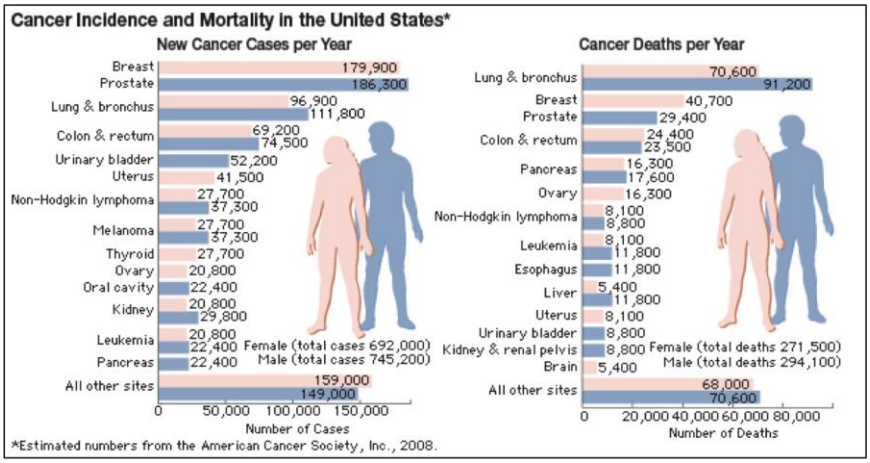
Memorably referred to as “The Emperor of All Maladies” in Siddhartha Mukherjee’s award-winning non-fiction book of the same name, cancer has long been considered a major unmet medical need. Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer is caused by external factors, such as tobacco use, infectious organisms, and unhealthy diet, and internal factors, such as inherited genetic mutations, hormones, and immune conditions. These factors may act together or in sequence to cause cancer. Ten or more years often pass between exposure to external factors and detectable cancer. Treatments include surgery, radiation, chemotherapy, hormone therapy, immune therapy, and targeted therapy (drugs that specifically interfere with cancer cell growth).

Globally, approximately 14 million people are estimated to develop cancer in 2015, with roughly six million in developed countries and eight million in developing countries (American Cancer Society). This number has been projected to grow to approximately 22 million cancer cases and 13.2 million deaths worldwide by 2030, driven by the aging of the global population and continued prevalence of environmental factors, such as tobacco consumption, which represent known drivers of cancer. It is estimated that roughly 1.7 million individuals develop one or another form of cancer each year in the U.S., and that approximately 600,000 deaths occur each year in the U.S. from these various malignancies. The National Cancer Institute (NCI), which was originally established in 1937 with an annual budget of $700,000, currently spends approximately $6 billion each year to research and develop cures for the different types of cancer that are now known to develop. Virtually every organ and tissue type in the human body is potentially prone to the development and uncontrolled proliferation of aberrant cells, which is the hallmark of cancer.



Source: American Cancer Society

While there are an estimated 15 million Americans currently living with cancer or who have survived cancer (i.e., achieved remission from disease), the continued increase in incidence rates and the fact that cancer remains one of the leading causes of death globally mean that cancer remains a significant unmet medical need and a considerable public health problem. One in every eight deaths is due to cancer; it is the leading cause of death in developed countries and the second-leading cause of death (after heart disease) in developing nations (World Health Organization). Existing therapeutic approaches are often either only palliative (addressing the symptoms without meaningfully enhancing survival) or marginally effective (adding a few months or even only weeks to the patient’s expected survival time), while remaining highly burdensome from a safety and tolerability perspective. The consequences of chemotherapy and radiation are well known to the public as most people know of someone who has received either treatment. Safe, effective treatment of cancer today remains more of a challenge than ever.



Source: National Cancer Institute

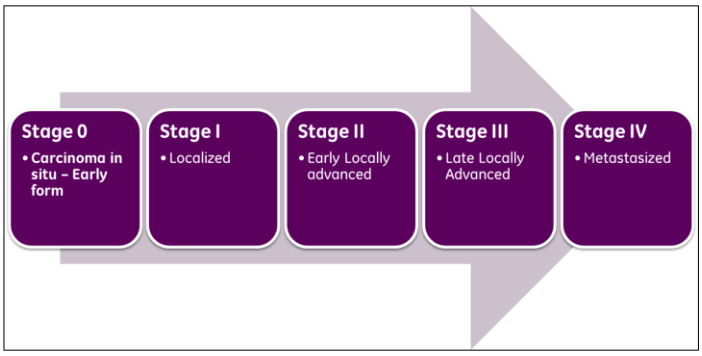
…Cancer Survival Rates Highly Dependent on Cancer Stage…

Staging refers to determining how much cancer is in a patient's body along with where it is located. Oncologists use staging to help plan treatment and to predict a patient's prognosis. While most cancers are staged, some, such as leukemia (cancer of the blood), are not staged as they are spread throughout the body.

While many staging systems have been developed, the most widely used is the TNM Classification of Malignant Tumors, which is maintained by the Union for International Cancer Control (UICC) such that there is one globally recognized standard for classifying cancer. In the TNM system, each cancer is assigned a letter or number to describe the tumor, node, and metastases.

- **T** stands for the original (primary) **tumor**.
  - **Tx =** tumor can't be measured.
  - **T0** = no evidence of a primary tumor.
  - **Tis** = carcinoma *in situ* (cancer cells only growing in superficial layer of tissue with no growth into deeper tissues.
  - **T1, T2, T3, T4** = describes tumor size and/or amount of spread; the larger the T number, the larger the tumor and/or more it has grown into nearby tissue.
- **N** stands for **nodes**. It tells whether the cancer has spread to the nearby lymph nodes.
  - **Nx =** lymph nodes can't be evaluated.
  - **N0** = no cancer in nearby lymph nodes.
  - **N1, N2, N3** = describes the size, location, and/or the number of nearby lymph nodes with cancer; the higher the N number, the greater the cancer spread to nearby lymph nodes.
- **M** stands for **metastasis**. It tells whether the cancer has spread to distant parts of the body.
  - **M0** = no sign of distant cancer spread.
  - **M1** = cancer has spread to distant organs or tissues.

Once the T, N, and M values have been determined they are combined to assign an overall stage. For most cancers, the stage is a Roman numeral from I to IV, where stage IV is the highest and means that the cancer is more advanced and has spread.



Source: md-health.com

- Stage 0. Also known as carcinoma *in situ*, this is an early form of cancer where there is a flat lesion but no invasion of malignant cells into the surrounding tissue. Although this can develop into full-blown cancer, some doctors do not consider this as cancer but "pre-cancer."

- Stage I. Tumors in this stage are usually smaller than 2 centimeters (cm) in diameter and are localized to their site of origin. Lymph nodes are not affected and there is no sign of metastasis (spreading to other parts of the body).

- Stage II. Tumors in this stage measure 2-5 cm, but are still localized to their site of origin since they have not invaded other tissues or metastasized. Local lymph nodes may be affected. Stage II tumors are considered to be locally advanced tumors.

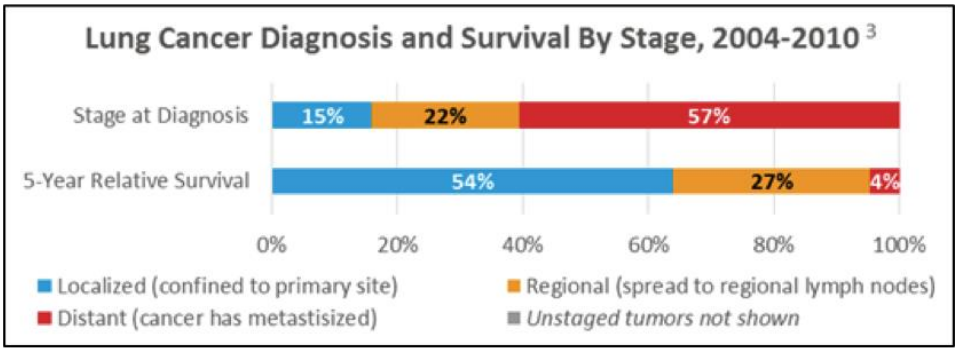
- Stage III. Tumors in this stage are fairly large, measuring more than 5 cm in diameter. This late, locally advanced stage affects nearby lymph nodes and it may be difficult to differentiate from stage II cancer.

- Stage IV. Tumors in this stage may be of any size, affecting nearby lymph nodes and showing evidence of metastasis to other organs or regions of the body. A secondary cancer may develop during this stage. The overall physical and mental health of the patient may be affected and the historical survival rate is very low. The outlook for patients diagnosed at this point in the disease represents the most clarifying indication of the importance of catching cancer early, before metastasis has occurred and prior to the possible development of drug resistance-conferring mutations.

Cancer stage is assigned when a person is first diagnosed before any treatment is given. An important point to remember is that the stage does not change over time no matter if the cancer shrinks, grows, spreads, or reappears after treatment. The cancer is still referred to by the stage when it was first diagnosed; however, additional information may be added to better describe the current situation. For example, a woman diagnosed with Stage II breast cancer that had the cancer respond to treatment and disappear only to return and spread to her bones still has Stage II breast cancer. The current diagnosis would just be amended to say "Stage II breast cancer with bone metastases".

Cancer survival rates are often used to describe what percentage of patients with a certain cancer would be expected to be alive after a given length of time. Cancer statistics are often expressed in terms of five-year overall survival. For instance, if the five-year survival rate for a given cancer was 78%, that means 78 out of 100 people diagnosed with that cancer would be alive after five years, while 22 out of every 100 would be dead.

The survival rates for patients diagnosed with Stage IV cancer are decidedly sobering. The following chart shows what percentage of lung cancer diagnoses are made for each stage along with the five-year survival rates for those stages (Localized is considered Stage I or II, Regional is Stage III, and Distant is Stage IV). The survival rates plummet for patients diagnosed with late-stage disease.



Source: American Lung Association

The above chart demonstrates that, while the prognosis for surviving lung cancer if it is caught in the early stages – before it has metastasized (i.e. spread from its initial location to other sites in the body) – is relatively good, the likelihood of remaining alive five years post-diagnosis if the cancer is already Stage IV is very poor (only 4%). This underscores the significance of the problem remaining today despite the fact that cancer patients overall are living six times longer now than they were in the 1970s (NIH Factsheet on Cancer).

Essentially all Stage IV cancers are associated with a grim prognosis compared to earlier stages of the disease. While the five-year survival rate is only an estimate, as many factors influence the progression of disease, the following table summarizes the very low five-year survival rates for different types of Stage IV cancers, with the data showing a clear need for better treatment options for these patients.

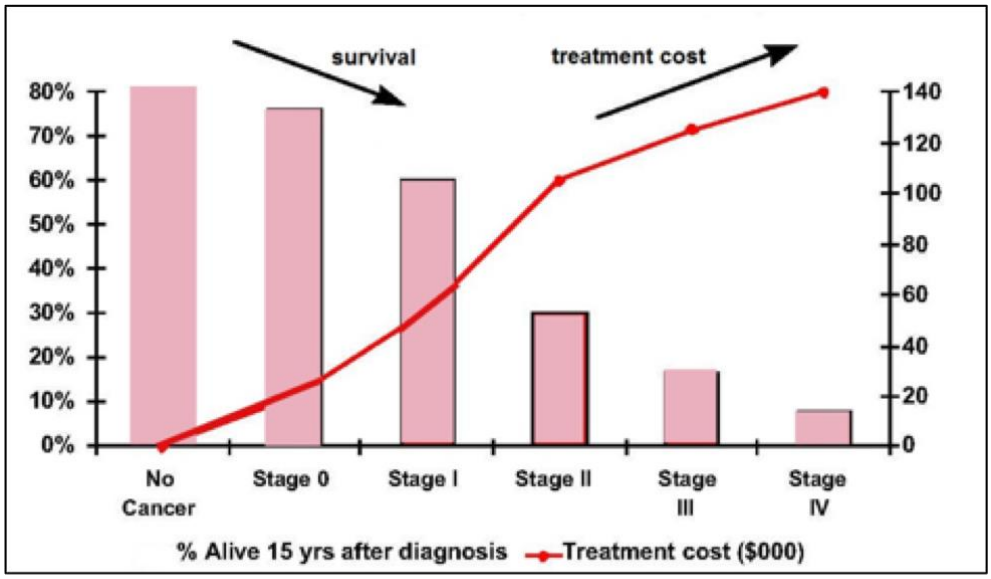
Stage IV Cancer Type	5 Yr. Survival Rate (%)
Brain (e.g. glioblastoma multiforme)	< 20%
Breast (typically metastatic)	16%
Colon / Colorectal	8-15%
Liver (e.g., hepatocellular carcinoma):	
Primary Tumor	30%
Secondary Tumor	0%
Ovarian cancer	17%
Pancreatic cancer	4%
Prostate cancer (typically castration-resistant)	33%
Skin cancer (e.g. melanoma)	15-20%
Stomach / gastric cancer	5%

Source: md-health.com

…Cost of Treating Late Stage Cancer Patients…

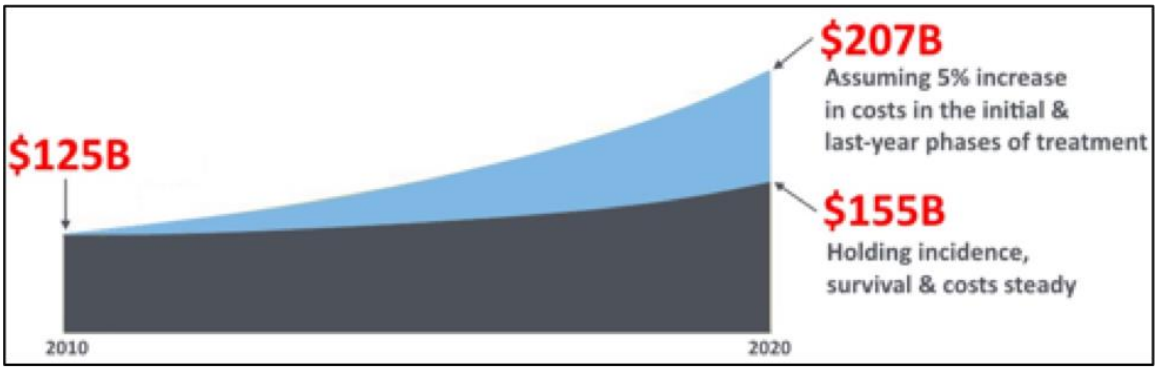
Another issue plaguing the treatment of late-stage cancer patients is that of cost to the healthcare system. In 2009, more than 20% of health care spending was on behalf of just 1% of the population, while 5% of the population accounted for nearly half of all spending (NIHCM, 2012). Accordingly, advances in treatment of the sickest of the sick are likely to result in disproportionately large benefits to the healthcare system in the U.S.

As shown in the figure below, even though the survival rates for patients with late-stage cancer diagnoses remain very low, the costs associated with their care have only increased in recent years. Therefore, a meaningful treatment option for patients with late-stage types of cancer that could boost survival rates while also improving well-being and reducing reliance on other healthcare cost drivers (e.g., pain medications and supportive care) could provide substantial and durable pharmacoeconomic benefits.



Source: National Cancer Institute

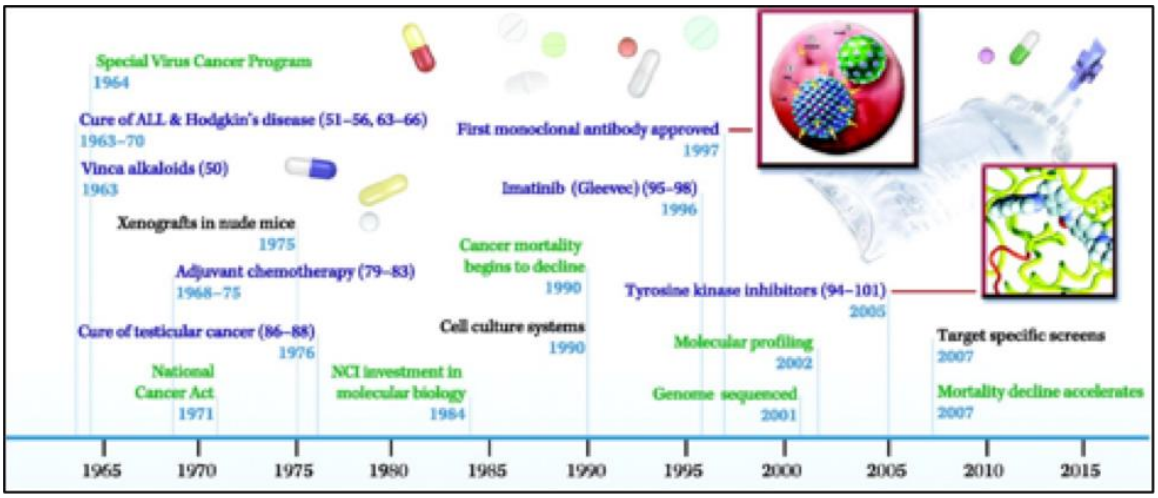
As shown in the following figure, the projected cost of spending on cancer treatment indicates that exponential growth lies ahead (Mariotto *et al*., 2011). Simply put, unless a substantial change occurs in the way cancer is addressed among those patients who are diagnosed later in the course of their disease (i.e., Stage IV), caring for these patients is likely to create an insurmountable burden for the U.S. healthcare system. The situation demands curative regimens, not palliative or marginally effective therapeutics.



Source: Mariotto *et al*., 2011

…Current Treatment Options Insufficient for Late Stage Cancer Patients…

The standard-of-care treatment for cancer diagnosed at its earliest stages involves localizing the problem. Typically, patients will undergo surgical intervention to remove a tumor with the hope that the cancerous tissue can be removed entirely before it has a chance to spread. Surgery is often accompanied by radiation (external beam, intraoperative, or brachytherapy). Both surgery and radiation can be deployed in combination with chemotherapy. Treatment of cancer if detected early is typically successful, as judged by the high five-year survival rates for early stage cancers. This has been aided by the huge advancements made in the development of successful cancer treatments, as shown in the chart below.



Source: American Association for Cancer Research

While a multitude of anti-cancer agents has been developed and commercialized over the past 50 years, they remain relatively ineffective when deployed against late-stage cancers and their side effects can be considerable and highly debilitating. In addition, patients with Stage IV cancer and their physicians choose treatment options to extend life, not to find a cure, as there remain few treatment options that offer the possibility of a complete response in a late stage cancer patient. Different types of chemotherapy remain the standard of care for late stage cancer patients, however the side effects of chemotherapy can be substantial and these side effects can impact quality of life, functional independence, and overall well-being. Therefore, **WE BELIEVE** that therapeutics that target late stage cancer are desperately needed as there is a total lack of safe and effective treatments for patients suffering from late stage cancer.

SM-88 Overview

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, with the types of cancer shown below.

1º Site	# Patients
Breast	14
NSLC	4
Pancreas	3
Prostate	2
Small Cell	1
Hepatic	1
Tongue	1
Appendix	1
Thyroid	1
Colon	1
Unknown	1

Source: Tyme, Inc.

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 therapy.

During Cycle 1, 24 (80.0%) subjects experienced at least one AE that was considered by the investigator to be possibly, probably, or definitely related to SM-88. The majority of these AEs were fatigue, which was reported as related in 15 (50.0%) subjects. Other AEs reported as related to SM-88 in greater than 10% of subjects were hyperpigmentation (8 subjects, 26.7%) and pain (4 subjects, 13.3%). No serious adverse events (SAE) were reported during Cycle 1 and there were no subject discontinuations due to an AE. Most AEs of fatigue started within two weeks of the onset of treatment and had durations ranging from 1.5 to 3 weeks. Two of those events resolved within one day and approximately one-third were still ongoing at the end of treatment. Three of the events were reported as moderate in severity and the rest were mild. The following table lists all reported AEs.

Adverse Events Reported in SMK Phase 1 Trial: 1st Course	
Adverse Event	Number of Patients (30 treated)
Hyperpigmentation	8
Fatigue	15
Lethargy	1
Pain	4
Paresthesia (numbness & tingling)	1
Pigmentation change	2
Pruritus (itching)	1

Source: Tyme, Inc.

It is noteworthy that common side effects of chemotherapy – such as nausea, vomiting, various other gastrointestinal side effects (e.g., GI tract bleeding, constipation, etc.), hair loss, anemia, neutropenia, thrombocytopenia, immune system compromise, and neurotoxicity – were noticeably absent in this trial. The safety profile alone appeared to indicate that the therapy does not adversely impact normal physiological processes or harm normal cells or tissues. Long-term repeat dosing did not appear to increase the toxicity of the regimen, which is also a substantial differentiator compared to chemotherapy.

In this study, the most striking findings were on the level of tumor response and patient survival. The last assessment of tumor responses was performed on November 15, 2013 and at that time 25 of 30 treated subjects were evaluable according to the Response Evaluation Criteria In Solid Tumors (RECIST) classification guidelines (Therasse *et al*., 2000). The results are presented in the following table.

RECIST Results

Tumor Response	Number of Subjects n = 25
Complete Response	2 (8%)
Partial Response	3 (12%)
Stable Disease	18 (72%)
Progressive Disease	2 (8%)

Source: Tyme, Inc.

Evaluation of target lesions according to RECIST is defined by the following:

- ✓ Complete Response (CR): Disappearance of all target lesions
- ✓ Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
- ✓ Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started
- ✓ Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since treatment started or appearance of ≥1 new lesions

Evaluation of non-target lesions according to RECIST is defined by the following:

- ✓ Complete Response (CR): Disappearance of all non-target lesions and normalizing of marker levels
- ✓ Incomplete Response/ Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
- ✓ Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

There are a number of ways to report clinical trial data for cancer therapies (Kogan *et al*., 2008). Objective response rate (ORR) is defined by the FDA as the "proportion of patients with a tumor size reduction of a predefined amount and for a minimum period of time", in other words CR + PR. For the SM-88 trial, there was an ORR of 20%. Perhaps the most striking piece of data from the SM-88 trial was the 72% of patients who achieved stable disease (SD). Interestingly, while most companies (and investors) focus on CR and ORR, a 2009 study from Japan in 602 patients with lung cancer showed very little difference in overall survival between those patients with CR/PR (16.1 months) compared to patients with SD (15.2 months) (Watanabe *et al*., 2009).

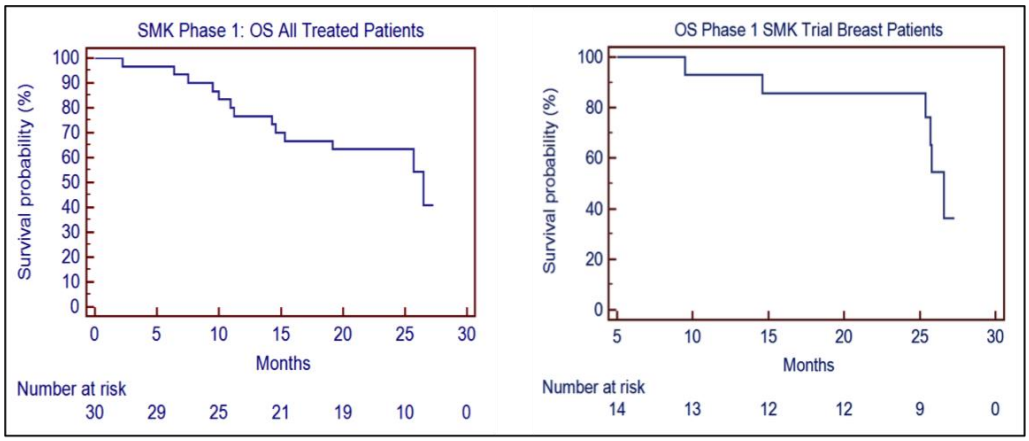
In recent years a number of studies have been reporting the Disease Control Rate (DCR), which is the ORR + SD. For the SM-88 trial, the DCR was 92%. The DCR was shown to be a more powerful predictor of survival than ORR in a lung cancer study (Lara *et al*., 2008) and in analysis of three separate breast cancer studies (Liu *et al*., 2011).

It should be noted that the five of the 30 patients that were not evaluable were excluded not because they were deceased, in fact they are all still alive, but because of the strict criteria that must be met for inclusion that includes having a certain number of scans available for evaluation. The excluded patients were typically missing one of the necessary scans. If included in the last assessment, the five excluded patients included three complete responses and two partial responses. Including these patients in the final analysis lifts the ORR to 33% (10/30) and the DCR to 93% (28/30), results that are quite impressive for a group of patients with Stage IV cancer.

It is impossible to directly compare the data from the SM-88 study to those generated in other oncology trials with different experimental or approved therapies, particularly since there was no control arm in the SM-88 trial. However, it is interesting to compare the data to other studies in patients deemed refractory to at least one line of chemotherapy prior to study entry. In such settings, there are examples such as the following:

- Colorectal cancer: Erbitux (irinotecan-refractory patients): 10.5% PR, 35% SD (Saltz *et al*., 2004).
- Metastatic breast cancer: Tykerb + Herceptin: 10.3% ORR (O'Sullivan *et al*., 2014).
  Perjeta: 3.4% ORR (Zagouri *et al*., 2013).
- Non-small cell lung cancer: Erlotinib: 8.9% ORR (vs. <1% on placebo) (Shepherd *et al*., 2005).

Another intriguing aspect of the data from the first proof-of-concept clinical trial of SM-88 was the long-term survival of the patients from this study. As of June 2014, more than two years after the trial began, 17/30 patients were still alive and 8/14 breast cancer subjects remained alive. Accordingly, median survival had still not been reached either in the overall group or the cohort of patients with breast cancer. In an environment where next-generation therapeutics typically provide only a few extra months or weeks of survival benefit, an approach that seemingly adds years to patients' lives seems to be substantially differentiated. The charts below depict the Kaplan-Meier curves of this population.



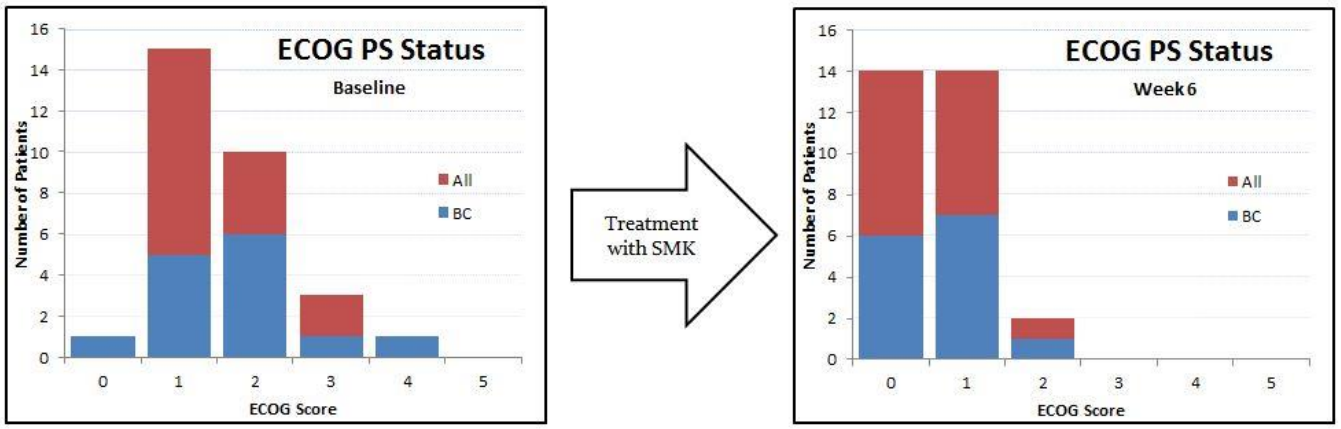
Source: Tyme, Inc.

While there is no current long-term follow-up data from this study available, it is worthwhile pointing out that even if the survival results had not improved at all from the last recorded time point, survival of >2.5 years for patients with Stage IV, disseminated disease that had been heavily pre-treated is unprecedented. The meager survival-promoting effects of currently-marketed anti-cancer agents is well-documented – a notable example is that of the Roche / Genentech drug Avastin® (bevacizumab), which has achieved the following survival results in various heavily pretreated, refractory patient populations:

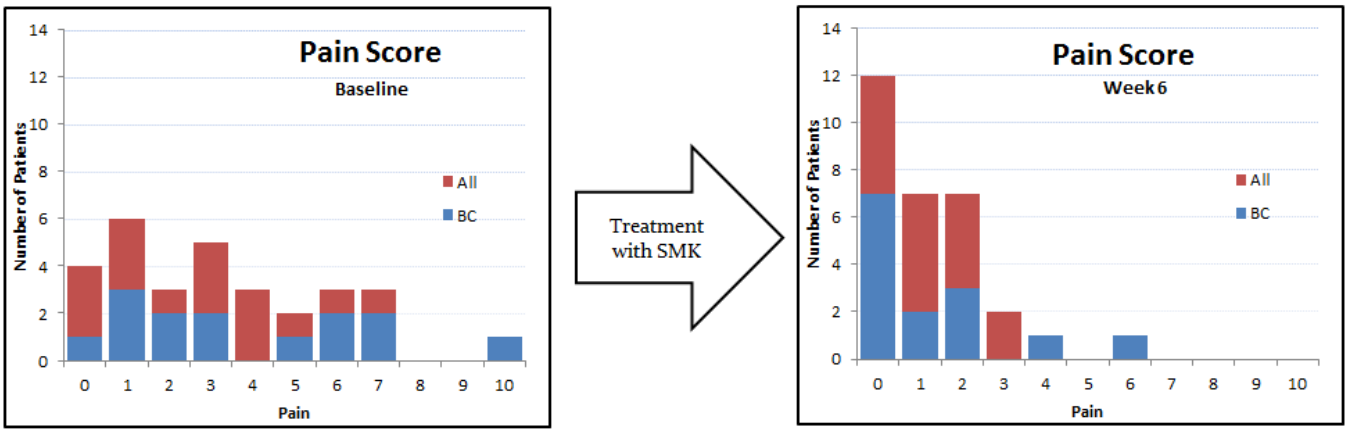
→ Advanced breast cancer: no survival benefit
→ Advanced cervical cancer: ↑ 3.7 months
→ Advanced colorectal cancer: ↑ 2.2 months
→ Advanced lung cancer: ↑ 4 months
→ Advanced glioblastoma: no survival benefit
→ Advanced renal cancer: no survival benefit

Avastin® has been associated with a litany of side effects, including potentially life-threatening blood clots in the lungs, hemorrhages, nausea, vomiting, diarrhea, headaches, dizziness, abdominal pain, and reduced white cell counts. The drug's cost is also a substantial drawback – currently, Avastin® costs over $50,000 per patient for only four to five months of therapy.

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.

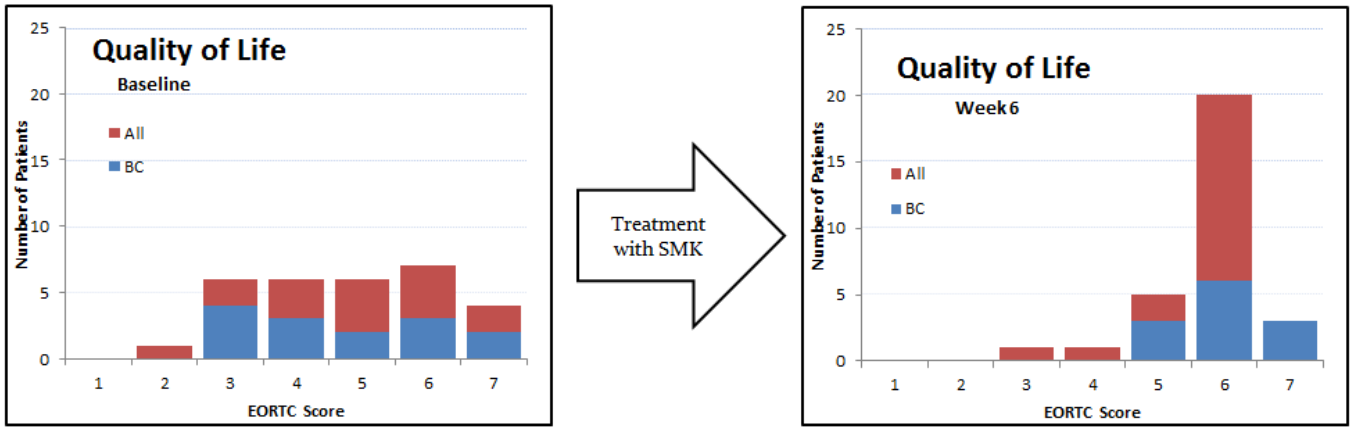


Source: Data from Tyme, Inc. / Chart from Zacks SCR (Napodano)



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)

Anecdotal evidence of efficacy has also been gathered from additional patients, who were treated on a compassionate use basis. Among the more striking cases were:

(1) The report of an 18-year old male with Stage IV Ewing's sarcoma and bone metastases, who had previously been treated aggressively with surgery – including the removal of a kidney – to no avail, and who was also treated with various chemotherapeutic drugs (cyclophosphamide, vincristine, doxorubicin, irinotecan, and temozolomide), without success and who was given weeks to live, yet who exhibited a dramatic response to SM-88 treatment and who is still alive roughly nine months post-SM-88 dosing;

(2) A 22-year old male with Stage IV non-Hodgkin's lymphoma (NHL), who was refractory to radiation, chemotherapy, and targeted therapy (brentuximab vedotin, known by the trade name Adcetris®) at the time of treatment with SM-88, who achieved a complete response after less than two months on treatment;

(3) A 56-year-old male with Stage IV prostate cancer, who experienced normalization of prostate-specific antigen (PSA) levels after only two weeks of treatment with SM-88. The compassionate access experience provides further evidence of the broad-spectrum activity achieved with this approach, as well as the activity across both solid and liquid tumor types.

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.

…Mechanism of Action Hypothesis…

Tyme has a fundamentally different approach to thinking about the origins of cancer that in turn guides the approach taken to both better understand and treat the disease. The insights developed by Tyme are based on the well-established understanding that tumor cells have an altered metabolic profile compared to normal tissue.. Cancer cells do not use the typical method of energy production to generate adenosine triphosphate (ATP) from glucose, in which 32 molecules of ATP are produced from each glucose molecule (oxidative phosphorylation) and about 2% of the utilized oxygen gives rise to free radicals, also known as reactive oxygen species (ROS). Rather, cancer cells rely solely on glycolysis, an inefficient process that only generates two molecules of ATP from each glucose molecule and which gives rise to significantly higher levels of ROS. As a result, cancer cells are continually taking-up nutrients while simultaneously existing on the edge of free radical damage.

They require a very high level of nutrients to burn for energy and for biosynthesis of proteins, lipids, and nucleic acids due to their hyper-proliferative state. Cancer cells have a preferred order to their diet, starting with available glucose and in absence of sugars, the cancer cell will switch to amino acids and ultimately lipids.

Cancer cells' hunger and aberrant energy metabolism create an opportunity to intervene in the tumor cell life cycle in a manner that kills cancer cells without damaging normal healthy tissue. Tyme accomplishes this by using combinations of approved drugs at lower doses than usual and with novel amino acid isomers that have never before been used in man. Tyme has developed a drug methodology that compromises the unique metabolic attributes of cancer cells that ultimately weakens the cancer leading to repeatable induced necrosis of the cancer cells.

In summary:

- The first component of Tyme's proprietary regimen creates an artificial ketogenic state in the body. The cancer cells respond to this signal of loss of available glucose as a food supply and the tumor cells in turn increase their uptake of amino acids. Cancer cells have a preference for certain amino acids, and because the same agent potentiates a system in the cancer cell called LAT1 transfer, the cell can be compelled to less selectively consume nutrients during this induced starvation reaction.
- Tyme provides modified amino acids as part of the treatment regimen that the cell uses avidly, but which are actually non-nutritive. The effect is to impair protein synthesis, thus resulting in an inability for the cancer cell to perform a variety of cellular functions.
- A third component of the regimen stimulates the liver to produce increased cholesterol and related molecules. These lipids are the source of much of the free radical generation in the body, and with the increased uptake of cholesterol and lipids by cancer cells to support the hyper-proliferative state they gain entry into the cell and can be exploited to generate an abundance of free radicals.
- Fourthly, another catalytic molecule is contained in Tyme's SM-88 product that increases the availability of electrons to be used in the generation of free radicals. This has a number of effects, which include:
    - Free radical damage to the cell membrane itself, making the cell leak its contents,
    - Free radical damage to "lipid rafts" in the cell membrane which are scaffolds that anchor a variety of membrane receptors and signaling molecules that regulate cell function,
    - The stimulation of high levels of free radicals in the mitochondria, where ATP is produced and which are sensitive to free radical damage. Polar lipids produce more free radicals than the mitochondria can neutralize and the resultant damage to the mitochondria results in a catastrophic loss of energy production and rapid cell death.

Cancer cells are thus killed in a process that has little effect on healthy tissue, and, with natural agents as the inducers of necrosis, these agents are able to cross the blood-brain barrier (BBB) and other difficult-to-access, boundary-protected organs and tissue.

Since three of the four components of the regimen are based on "repurposed" agents – drugs that have been approved and marketed for many years to treat non-cancer-related conditions – and since these agents are deployed in the context of SM-88 at dosages far below the levels that they are marketed and used at currently, there are unlikely to be safety issues associated with them in the current cancer treatment context. The fourth component of SM-88 is a modified version of an existing, naturally occurring amino acid. The only modification made involves rendering this version non-nutritive. Given these considerations, it appears reasonable to assume that SM-88 can be advanced through clinical development and regulatory review without the safety considerations attendant upon de novo compounds. The multi-factorial nature of SM-88 and the fact that it targets the principles underlying cancer itself – regardless of the cell type or tissue of origin – should enable this therapy to provide benefit across multiple forms of cancer, including both solid and liquid tumors, and evade resistance.

Clinical Development Plan

Tyme is currently in the process of assembling a formal Investigational New Drug (IND) filing, which it expects to file with the U.S. Food and Drug Administration (FDA) within the next two to three months. If accepted, this filing should pave the way for a formal Phase 2 clinical trial that could enroll 80 – 120 metastatic breast cancer patients and potentially generate sufficient clinical efficacy data to permit the firm to request Breakthrough Therapy designation and possibly accelerated review and approval. Tyme is also planning to pursue the establishment of an Expanded Access program for SM-88, which would be aimed at facilitating the availability of the regimen to late-stage patients who have exhausted all other options.

Intellectual Property

Interested readers are invited to review the patent that has been issued to Tyme that goes into greater detail about the approach that Tyme is taking to combat cancer.

- Initial patent granted in the U.S. (#8,481,498)
- Additional international patents filed on compositions and methods

In addition, the company has a number of compositions and methods of use patents and patent applications that are pending, including:

- A novel amino acid isomer not previously used in medicine;
- Novel combinations of amino acids not previously used in medicine, alone, or in combination with other classes of drugs;
- Novel formulations comprised of combinations of different classes of drugs not previously used together in medicine;
- A novel dosage form, in which two existing agents are physically joined to form a new agent that never existed previously;
- A novel device used in the formulation process;
- New methods for the treatment of disease;
- New methods of use for existing agents

It should be noted that the nature of the Tyme regimen permits two principal layers of intellectual property protection to be invoked – that pertaining to the mechanistic theory underlying SM-88 in cancer, and that concerning the components of the regimen, which are protected either from a method of use standpoint (since none of them have ever been deployed in cancer before) or from a market exclusivity standpoint. Therefore, the commercial window for SM-88 should last well beyond 2030. Additional patent claim awards could strengthen the current coverage and even extend the commercial window further. Formulation patent claims could also be sought, given the potential for the product to be formulated for both injection as well as oral delivery (once-daily) routes.

Regulatory Pathway Considerations

An important aspect of the Tyme product development approach is the potential applicability of the 505(b)(2) regulatory pathway. This type of application is one of three established categories of New Drug Application (NDA), and it is a pathway to approval that can potentially save pharmaceutical sponsors both time and money. In addition to the 505(b)(2) pathway, there are the typical *de novo* NDA, which is used for novel drugs, and the Abbreviated New Drug Application (ANDA), used by generic filers to obtain approval for generic versions of existing drugs.

The 505(b)(2) pathways can be considered a hybrid of the *de novo* NDA and the ANDA, containing aspects of both pathways, and is defined in the Federal Food, Drug and Cosmetics Act as an NDA containing investigations of safety and effectiveness that are being relied upon for approval and were not conducted by or for the applicant, and for which the applicant has not obtained a right of reference. These applications differ from the typical NDA (described under Section 505(b)(1) of the Act), in that they allow a sponsor to rely, at least in part, on the FDA's findings of safety and/or effectiveness for a previously approved drug (the "reference drug"). The 505(b)(2) pathway is relevant to Tyme because three of the four components of SM-88 are currently-approved compounds.

The FDA recently promulgated a "Breakthrough Therapy" designation for therapeutic approaches that provide a significant and meaningful improvement in outcomes for serious and life-threatening conditions over existing therapeutic modalities. While Breakthrough Therapy designation must be applied for by the sponsors of such product candidates, it can if awarded permit substantial expediting of regulatory review by the agency in the U.S. The vast majority of Breakthrough Therapy designations that have been granted – since this status was formulated under Section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) of July 2012 – have been for anti-cancer drugs. Accordingly, it is possible that Tyme could obtain expedited processing for SM-88 if it applied for and received Breakthrough Therapy designation. Applications for Breakthrough Therapy status are typically reviewed within 60 days of submission. The reduction in approval time for product candidates given this designation can be substantial. Instead of taking 12 – 14 months to process a standard New Drug Application, the FDA can approve a Breakthrough Therapy-designated product within three months.

Potential Risks to our Thesis

Commercialization risks. Tyme does not have a track record of successfully commercializing products. The company's long-term future and ability to sustain operations will be heavily dependent upon its ability to advance SM-88 and potentially facilitate its commercialization, either through forward-integration or the enlistment of a commercial partner. If the company is unable to monetize the SM-88 product opportunity, it could face difficulties in continuing operations.

Clinical risks. Drug development is an inherently risky business, requiring significant investment of both time and capital. The company's only source of potential revenue, SM-88, could fail to demonstrate adequate safety or efficacy in its targeted clinical indications – notably, metastatic breast cancer and other late-stage cancer types. Such failure could decrease the company's innate value and adversely impact our valuation.

Regulatory risks. Even if Tyme were to be successful in developing SM-88 through the envisaged Phase 2 program, there is a possibility that additional information and/or additional trials could be required by regulators to address any lingering safety or efficacy concerns. If this occurred, it could significantly delay revenue generation going forward, and could materially impact forecasts. Accordingly, therefore, future regulatory submissions for approval of this and other candidates may be delayed from reaching the market due to agency requests for further data or agency decisions indicating that the efficacy and safety data furnished by Tyme is not adequate to justify marketing authorization. Regulatory agencies could also elect not to accord Tyme Breakthrough Therapy status or permit the company to establish an Expanded Access Program, potentially preventing Tyme from generating revenue near-term with SM-88.

Intellectual property risks. Tyme's sole development program, SM-88, is currently protected by a single issued U.S. patent that was issued in June 2013. Additional patent applications are pending or being filed. Since the company's approach involves the use of existing drugs that have lost composition-of-matter protection, competitors may seek to emulate Tyme by attempting to develop similar regimens. It is not certain whether Tyme's intellectual property would wholly preclude such attempts.

Financial risks. Tyme recently completed a ~$6.8 million financing transaction concomitant with the consummation of its reverse merger. Its current available financial resources could be sufficient to complete its regulatory filing for permission to initiate a Phase 2 trial of SM-88 but are unlikely to be sufficient to fund additional clinical development work. Additional sources of capital could include: follow-on offerings, warrant exercises, and/or income from licensing transactions. While unlikely, it is possible that Tyme may not be able to raise cash at all.

Reimbursement risks. Recently, reimbursement agencies have grown more wary of systematically reimbursing for drugs that are deemed to provide marginal benefit at excessive cost. If Medicare spending growth continues to outpace GDP growth, and the government's ability to fund healthcare becomes impaired, changes may be made to reimbursement policy that would negatively affect the firm's business, despite what may be a compelling pharmacoeconomic value proposition inherent in SM-88.

MANAGEMENT & BOD PROFILES

Steven Hoffman – Chief Executive Officer

Mr. Hoffman has served as Chief Executive Officer of Tyme since its formation in July 2013 and as a cofounder and senior leader of Tyme's precursor, Luminant, since its formation in September 2011. In such roles and continuing with his position as Chief Executive Officer and Chief Science Officer of Tyme, Mr. Hoffman supervises the development of the company's product candidates. He has over 25 years experience in management and technical positions with companies in the chemistry, aerospace, and laser optics fields. Prior to the establishment of Luminant, Mr. Hoffman was a co-founder and, from 1993 to 2007, Chief Technology Officer of Mikronite Technologies Group Inc., a developer, licensor, and marketer of material surfacing technologies for various manufacturing processes and applications. At Mikronite, Mr. Hoffman supervised the implementation of proprietary technology. He has received numerous patents and has pending other patent applications, including a patent and three patent applications that have been assigned to Tyme. His efforts on behalf of Mikronite were recognized by The Home Depot and Lowe's with a Best New Product award and an Innovative Technology award from the New Jersey Manufacturers Association. Mr. Hoffman attended New York University and Rutgers University with a concentration in mechanical engineering from 1980 to 1984 and continued his studies under the direct supervision of the chairman of the physics department at the University of Michigan specializing in physics and electro-optics.

Michael Demurjian – Chief Operating Officer

Mr. Demurjian has served as Chief Operating Officer of Tyme since its formation in July 2013 and as a cofounder and senior leader of Tyme's precursor, Luminant, since its formation in September 2011. In such roles and continuing with his position as chief operating officer of Tyme, Mr. Demurjian leads the research teams in development, studies and data collection for our submissions to regulatory authorities, including the FDA. Prior to the establishment of Luminant, Mr. Demurjian was a co-founder and, from 1993 to 2007, Director of Marketing of Mikronite Technologies Group, Inc., a developer, licensor, and marketer of material surfacing technologies for various manufacturing processes and applications. At Mikronite, Mr. Demurjian established all marketing activities and functions, marketing research and analysis, marketing strategy, implementation planning, project, process, and vendor management, organizational management, and leadership. His efforts on behalf of Mikronite were recognized by The Home Depot and Lowe's with a Best New Product award and an Innovative Technology award from the New Jersey Manufacturers Association. Mr. Demurjian received a BA in Economics from New York University in 1986.

Patrick G. LePore, M.B.A. – Independent Director

Patrick G. LePore, retired, last served as Chairman, CEO and President of Par Pharmaceuticals, Inc. (NYSE: PRX) from September 2006 through November 2012. Par is a fully integrated healthcare company focusing on the development, licensing, manufacturing and distributing of generic and branded drugs. The company employs approximately 1,500 people with facilities in New York, California and Chennai India. Its brand division, Strativa, is comprised of 150 pharmaceutical representatives. Through Mr. LePore's leadership, Par increased its value and market presence during his tenure culminating in its sale to Texas Pacific Group (TPG), in a private equity transaction, for $50.00 per share or approximately $2 billion. Mr. LePore transitioned to Chairman of the new company beginning in November 2012. His leadership in the pharmaceutical industry has spanned both private and public sectors with board and operational experience in each. His experience includes building and running a large pharmaceutical service business as well as a fully integrated manufacturing business. Mr. LePore's unique background makes him one of a handful of pharmaceutical executives with an in-depth knowledge of the branded (ethical pharmaceuticals), generics and pharmaceutical service industries. He began his career with Hoffmann-La Roche and then founded Boron LePore and Associates, a medical communications company, which he took public in 1997 and was eventually sold to Cardinal Health in 2002. As an accomplished and respected life science executive, Mr. LePore has extensive experience in all areas of executive management including human resources, executive development, strategic planning, mergers and acquisition, business development, investor relations and corporate governance. He also brings over 30 years of industry relationships to the board of Tyme. Throughout his career, Mr. LePore has served on nonprofit and corporate boards. In addition to chairing the Par board, he is currently the Chairman of Agene Bio and serves on the boards of PharMerica (NYSE:PMC), and Villanova University. A graduate of Villanova University, he holds an M.B.A. degree from Farleigh Dickinson University.

Gerald H. Sokol, M.D., M.Sc., FCP – Independent Director

Dr. Jerry Sokol attained his medical degree from Indiana University's Combined Degree Program in Experimental Medicine with a Master's Degree in Pharmacology and an M.D. degree. Dr. Sokol interned in Medicine at Temple University and attended the U.S. Public Health Service Hospital in affiliation with the National Cancer Institute, Johns Hopkins, and the University of Maryland completing training in Internal Medicine. He then completed training at the Massachusetts General Hospital, Harvard Medical School in Radiation Oncology, Medical Oncology and Clinical Pharmacology attaining Board Certification in Internal Medicine, Medical Oncology, Radiation Oncology, Clinical Pharmacology, and later Quality Assurance and Utilization Review. He is also certified in skin cancer medicine from the University of Queensland in Australia. Dr. Sokol has been Chief of Radiation Oncology at the University of South Florida's Tampa General Hospital, and has built or contributed to building over 10 highly successful cancer centers. He is a board member and partner of Florida Cancer Specialists and Research Institute (the largest research group in Florida) consisting of over 190 physicians). Dr. Sokol is a decorated retired captain in the U.S. Navy and served as commanding officer of the unit at the Uniformed Services University. Dr. Sokol currently holds professorships in medicine and pharmacology at that institution. While maintaining a busy medical practice, Dr. Sokol served on the review staff of the FDA for over 27 years as a senior regulatory scientist and officer composing over 300 white papers, IND and NDA reviews, and opinion papers. Dr. Sokol has authored or coauthored over 100 books, book chapters, abstracts and papers on a multitude of clinical issues. He is a lifetime fellow and board member of the American Cancer Society and a fellow of the American College of Clinical Pharmacology.

Timothy C. Tyson, M.B.A. – Independent Director

Tim Tyson is currently President of Alkaloida Chemical Company Zrt. He previously served as Interim Chief Executive Officer of Caldera Pharmaceuticals, Inc. from September 23, 2014 to November 21, 2014. He also served as Interim Chief Executive Officer and Executive Chairman of Aptuit and at Laurus Labs Pvt. Ltd. since August 2008. Mr. Tyson has over 30 years of leadership experience in the pharmaceutical industry. He served as acting Chief Executive Officer of Aptuit LLC since September 2008. He served as the President of ICN Hungary Co., Ltd. (also called as ICN Hungary Ltd.). Most notably, Mr. Tyson served as the Chief Executive Officer of Valeant Pharmaceuticals International (formerly, ICN Pharmaceuticals Inc.) from January 1, 2005 to February 1, 2008. He served as President of Valeant Pharmaceuticals International from November 2002 to February 1, 2008 and served as its Chief Operating Officer from November 2002 to December 2004. He served as President of Global Manufacturing and Supply for GlaxoSmithKline plc from June 1998 to November 2002. From 1997 to 1998, Mr. Tyson served as GlaxoSmithKline's Vice President and General Manager of Business Operations. During his 14-year tenure at GlaxoSmithKline, he served in a variety of roles with broad international and domestic responsibilities, including significant management experience running two divisions: Glaxo Dermatology and Cerenex Pharmaceuticals. He was responsible for managing all sales and marketing for the U.S. operations, where he launched 32 new products, eight of which became blockbuster drugs. He received a Master in Business Administration and Master in Public Administration from Jacksonville State University in 1979 and 1976, respectively. He is also a 1974 graduate of West Point.

Tommy G. Thompson, M.B.A. – Advisor

Tommy Thompson currently is the Chairman and Chief Executive Officer of Thompson Holdings, and former United States Health and Human Services (HHS) Secretary and four-term Governor of Wisconsin. From 2005 until 2009, Governor Thompson served as a senior advisor at the consulting firm Deloitte LLP and was the founding independent chairman of the Deloitte Center for Health Solutions. From 2005 to early 2012, Governor Thompson served as a senior partner at the law firm of Akin, Gump, Strauss, Hauer, & Feld LLP. Governor Thompson served as Chairman of the Board of Directors of Logistics Health, Inc. from January 2011 to May 2011, and served as President from February 2005 to January 2011. He currently serves on the boards of the following public companies: Physicians Realty Trust and TherapeuticsMD, Inc., each as Chairman of the Board; Centene Corporation, C.R. Bard, Inc., Cytori Therapeutics, Inc., TherapeuticsMD, Inc. and United Therapeutics Corporation.

VALUATION AND RECOMMENDATION

We are initiating coverage of Tyme, Inc. (OTC: TYMI) with a Buy rating and a price target of $12.00. Tyme is a clinical-stage pharmaceutical company focused on discovering and developing highly targeted cancer therapeutics for a broad range of oncology indications. The company takes a fundamentally different approach to both thinking about and treating cancer. This is exemplified in the lead product, SM-88, which is a proprietary drug cocktail containing four components (three of which are currently marketed drugs, while the other is an isomer of a naturally occurring amino acid) that work in concert to target the unique metabolic features of cancer cells and ultimately subject the cancer to increased oxidative stress and cell death.

SM-88 performed remarkably well in a Phase 1 proof-of-concept clinical trial involving 30 heavily pretreated, Stage IV, fully disseminated metastatic patients – individuals with late-stage disease who had run out of other treatment options. Treatment with SM-88 showed a benign safety profile and solid tolerability along with intriguing indications of differentiated efficacy. In particular, SM-88 has shown the potential to achieve durable complete responses (i.e., remission) and substantial increases in survival, as well as the ability to improve patients' well-being, which contrasts markedly to the side effects typical of traditional chemotherapy. The data observed thus far may indicate that SM-88 represents an entirely new metabolism-based therapeutic approach to cancer therapy from both a safety and efficacy standpoint. Furthermore, it appears that SM-88 has clinical activity against a wide array of cancer types, regardless of the tissue or organ of origin, or immunological status, and that it possesses the ability to address both solid and liquid tumors. Such broad-based activity with the kind of safety profile that the firm has seen thus far may position SM-88 above many existing treatments as well as some of the late-stage approaches currently being developed, such as chimeric antigen receptor T-cell immunotherapy (CAR-T) approaches, checkpoint inhibitors, and targeted enzyme inhibitors.

…Initially Targeting Metastatic Breast Cancer…

In the Phase 1 clinical trial, 14 of the 30 patients had metastatic breast cancer, thus Tyme has elected to initially focus on this cohort of patients for the Phase 2 trial. The company is currently in the process of finalizing an Investigational New Drug (IND) application for submission to the NDA. The trial will likely be a multi-center study involving 80-120 Stage IV breast cancer patients who have failed multiple prior chemotherapeutic/targeted treatments.

According to the American Cancer Society, there were approximately 230,000 cases of invasive breast cancer diagnosed among women in 2013. It is estimated that between 6-10% of those cases are Stage IV at the time of diagnosis, and of the cases that are diagnosed as Stages I-III, approximately 25% will have recurrence with metastases (Metastatic Breast Cancer Network). This represents an initial target population of approximately 76,000 patients.

…Substantial Growth Potential…

One of the most important findings from the Phase 1 study was the fact that SM-88 appeared to have activity against a wide range of cancers regardless of the tissue or organ of origin. This means that Tyme could generate significant peak sales with SM-88, given the drug's possible deployment in both solid and liquid tumor types. While most oncology drugs are being targeted towards smaller and smaller patient populations, usually with the aid of diagnostic biomarkers that are designed to predict responsiveness, the Tyme approach appears to be universal to all forms of cancer, irrespective of the tissue of origin or immune status. It exploits the aberrant metabolic characteristics that differentiate all cancer cells – regardless of tissue type or organ of origin – from normal tissue.

In addition to the wide potential applicability, SM-88 has already demonstrated a more favorable safety profile vs. Avastin® and similar "targeted" therapeutics. Since it is based on existing approved agents being administered at low doses there does not seem to be a significant likelihood of greater toxicity being revealed in future clinical trials.

Several of the world's top-selling drugs are anti-cancer agents, e.g. Avastin® (bevacizumab). Sales of Avastin® are projected to exceed $7.5 billion by 2018. Herceptin® (trastuzumab) is a breast cancer drug specifically for patients that harbor overexpression of the cell surface receptor HER2, which occurs in approximately 20-30% of breast cancers (Bange *et al*., 2001). Even with the limited patient population, Herceptin® still generated approximately $6.6 billion in revenue in 2013.

Herceptin® was originally approved in part based on data showing that it increased overall survival in HER2 overexpressing metastatic breast cancer patients who had received no prior treatment for metastatic disease from 20.3 months to 25.1 months (Herceptin Prescribing Information). Another study involving patients with HER2 overexpressing metastatic breast cancer that had relapsed following one or more prior chemotherapy regimens for metastatic disease reported an ORR of 14% with a 2% CR rate and a 12% PR rate. The results from the Phase 1 trial of SM-88 far exceeded results seen with Herceptin®, thus replication of those results in a larger patient cohort could potentially drive SM-88 to be not just a treatment for late-stage metastatic cancer patients, but a front-line therapy for early stage patients. This scenario could make SM-88 a potential blockbuster drug while not even factoring in additional indications.

…Valuation Methodology…

We have chosen to conservatively 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 are estimating pricing of SM-88 in relation to the per cycle cost of Tykerb® (lapatinib), a tyrosine kinase inhibitor developed and commercialized by GlaxoSmithKline that is currently deployed as second-line therapy in metastatic breast cancer. Tykerb® is priced at roughly $6,000 per 30-day cycle. We estimate SM-88 will cost $10,000 per cycle in the U.S. and $8,000 per cycle in the E.U. In addition, we are projecting a median seven cycles of therapy to be administered per patient. The combination of Tykerb® and Xeloda® (capecitabine), another broadly-utilized chemotherapy drug, carries a per-cycle cost of nearly $11,000, thus our pricing appears to be in-line with other widely used agents. However, given the relatively low survival benefit typically associated with Tykerb® in late-stage patients – not to mention its side effect profile – there may be the possibility for higher per cycle pricing, particularly in light of the pharmacoeconomic benefit argument that may be made for an agent that both provides substantial survival benefits as well as enhancement of patient well-being, thus reducing reliance on supportive care, painkillers and other cost drivers.

We model for Tyme to initiate a Phase 2 trial in late 2015, a Phase 3 trial in 2017, with an NDA filing in 2018 and approval in the U.S. in 2019, with approval in the E.U. coming in 2020. It should be noted that exceptional results, like those seen in the Phase 1 trial, in a larger group of patients could warrant expedited approval of SM-88 after the Phase 2 trial is completed under the FDA's accelerated approval program (perhaps through evidence of tumor shrinkage in patients). While this is certainly a possibility, we choose to conservatively estimate that SM-88 will go through the normal approval process and all three phases of clinical testing.

Given a 20% discount rate, a 30% chance of approval, 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 arrive at a net present value for SM-88 in metastatic breast cancer of approximately $1.1 billion. We add in the company's current cash total ($5 million) and an estimated $50 million in capital requirements to arrive at a present value of approximately $1.05 billion. The company currently has 86.5 million shares outstanding, thus equating to a fair value for the stock of approximately $12 and we are assigning a 'Buy' rating to the shares.

PROJECTED FINANCIALS

Tyme, Inc.
Income Statement

Tyme, Inc.	2014 A	Q1 E	Q2E	Q3 E	Q4 E	2015 E	2016 E	2017 E
SM-88 (Breast Cancer)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
SM-88 (Indication #2)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
SM-88 (Indication #3)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$0.8	$0.3	$0.3	$0.4	$0.5	$1.5	$3.0	$5.0
General & Administrative	$1.8	$0.5	$0.5	$0.5	$0.6	$2.1	$4.0	$6.5
Other Expenses	$0	$0	$0	$0	$0	$0	$0	$0
Operating Income	($2.6)	($0.7)	($0.8)	($0.9)	($1.1)	($3.5)	($7.0)	($11.5)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	($0.1)	($0.0)	($0.0)	($0.0)	($0.0)	($0.1)	($0.1)	($0.1)
Pre-Tax Income	($2.7)	($0.7)	($0.8)	($0.9)	($1.1)	($3.6)	($7.1)	($11.6)
Income Taxes Paid	$0	$0	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($2.661)**	**($0.7)**	**($0.8)**	**($0.9)**	**($1.1)**	**($3.6)**	**($7.1)**	**($11.6)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($1,330)**	**($0.01)**	**($0.01)**	**($0.01)**	**($0.01)**	**($0.04)**	**($0.07)**	**($0.10)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	0.0	86.0	90.0	92.0	95.0	90.8	100.0	120.0

Source: Zacks Investment Research, Inc. *Jason Napodano, CFA*

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