Zacks Small-Cap Research

May 15, 2014
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Threshold Pharm (THLD-NASDAQ)

THLD: Unique hypoxia targeted cancer therapy coupled with prodrug platform and late stage candidate – initiating with Outperform

Current Recommendation	**Outperform**
Prior Recommendation	N/A
Date of Last Change	04/27/2014
Current Price (05/14/14)	$3.69
Twelve- Month Target Price	**$9.50**

OUTLOOK

Threshold is a late development stage biopharmaceutical company focused on developing hypoxia targeted cancer therapy. The Company's lead prodrug candidate TH-302 is in a series of clinical trials including two Phase III clinical trials for soft tissue sarcoma and pancreatic cancer respectively.

We model TH-302 to be approved by the FDA in 2016 for soft tissue sarcoma. The Company will be cash flow positive in 2018. Balance sheet remains strong.

We rate Threshold Outperform based on its strong fundamentals.

SUMMARY DATA

52-Week High	**$5.85**
52-Week Low	**$3.62**
One-Year Return (%)	**-34.37**
Beta	**2.27**
Average Daily Volume (sh)	**458,341**
Shares Outstanding (mil)	**59**
Market Capitalization ($mil)	**$226**
Short Interest Ratio (days)	**8.41**
Institutional Ownership (%)	**58**
Insider Ownership (%)	**19**
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 2014 Estimate	**N/A**
P/E using 2015 Estimate	**N/A**
Zacks Rank	**N/A**

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

ZACKS ESTIMATES

Revenue
(in millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	2.9 A	3.2 A	3.2 A	3.2 A	12.5 A
2014	3.7 A	3.7 E	3.9 E	4.0 E	15.2 E
2015					18.5 E
2016					27.0 E

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

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2013	-$0.11 A	-$0.12 A	-$0.08 A	-$0.13 A	-$0.45 A
2014	-$0.14 A	-$0.14 E	-$0.14 E	-$0.15 E	-$0.58 E
2015					-$0.57 E
2016					-$0.54 E

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

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KEY POINTS

- We are initiating coverage of Threshold (THLD) with an Outperform rating. Our 12-month price target is $9.50.

- Threshold is a late development stage biopharmaceutical company focused on developing and commercializing **hypoxia-activated targeted therapy** for cancers.

- Based on targeting the hypoxic tumor microenvironment and the Company's proprietary **prodrug platform** technology, Threshold is developing its lead drug candidate **TH-302**, a prodrug that is activated in the microenvironment of tumor cells with low oxygen concentration (hypoxia). TH-302 is in a series of clinical trials either alone or in combination with other cancer therapeutics, notably chemotherapeutics and antiangiogenics.

- The most advanced clinical trial is the Phase III trial of **TH-302** in combination with **doxorubicin** for soft tissue sarcoma. This trial has completed enrollment and the 235 events (deaths) required to trigger the interim safety and efficacy analyses are projected to be reached in mid-2014. Since the analyses themselves typically take anywhere from 6-12 weeks to complete, we are projecting the analysis should be completed mid-late third quarter. The number of events (434 deaths) required to trigger the primary efficacy analysis is currently projected to be reached in mid-2015 with top-line results expected thereafter. We estimate TH-302 will be approved in late 2016 or early 2017.

- Another advanced clinical trial is a Phase III trial evaluating **TH-302** in combination with **gemcitabine** for **first-line pancreatic cancer.** This trial is still enrolling patients.

- In addition to the two advanced Phase III trials, TH-302 is in more than 10 early to mid-stage clinical trials (Phase I or Phase II) as combination therapy or monotherapy for different cancers. These trials will further validate the clinical utilization of TH302.

- Threshold has a collaboration agreement with Merck KGaA, worth total of $550 million in terms of upfront and milestone payments. Threshold will also receive a **tiered, double-digit royalty** on sales of TH-302 if approved. The Company also has the option to co-commercialize TH-302 in the US. The deal is a major de-risk factor for Threshold. The non-dilutive financing not only boosts its balance sheet, but further validates the Company's technology and clinical programs.

- Beyond TH-302, Threshold is also developing **second generation** of tumor microenvironment targeted therapy for cancers. Though in preclinical development, these new candidates will provide long term growth potential for Threshold.

- Threshold has a strong balance sheet. As of March 31, 2014, the Company had $86.4 million in cash. We estimate current cash balance combined with the potential payment from Merck KGaA could last into 2016 when the Company's TH-302 could be approved for soft tissue sarcoma.

- We think shares of Threshold are undervalued at current market price based on its strong fundamentals. We encourage investors to buy the Company's shares at current level. Risk is also high though at this time since Threshold still needs to navigate through both clinical and regulatory hurdles. But overall, we think Threshold is a risk/reward name for long term investors.

OVERVIEW

Threshold Pharmaceuticals (THLD) is a late development stage biopharmaceutical company focused on discovering and developing **targeted therapy** for cancer.

Threshold's key edge lies on its expertise in the **tumor microenvironment**. The Company is developing **TH-302**, a prodrug targeting **tumor hypoxia**, a common characteristic of the tumor microenvironment. Hypoxia, or low oxygen concentration, is a common feature of the tumor microenvironment in most solid tumors and in the bone marrow of patients with some hematological malignancies. Tumor hypoxia is associated with the development of resistance to traditional anticancer treatments, including chemotherapy and radiotherapy, enhanced metastatic potential, and ultimately treatment failure. Normal healthy tissues, in contrast, are well oxygenated and typically are not hypoxic.

As a prodrug, TH-302 is designed to remain essentially inactive in normal tissues, but to activate under conditions of tumor hypoxia. Upon activation, TH-302 releases **bromo isophosphoramide mustard** (Br-IPM), a potent cytotoxin that kills cells by causing DNA to crosslink.

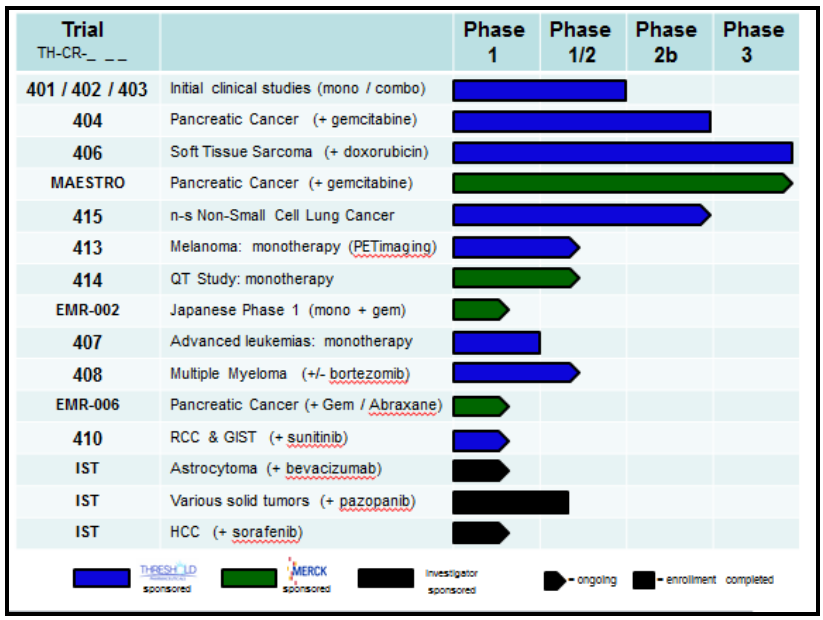
To explore this broad therapeutic potential of TH-302, Threshold is conducting multiple clinical trials to evaluate its safety and efficacy as monotherapy and in combination with currently marketed anticancer drugs, including traditional chemotherapeutic agents and antiangiogenic agents. Currently, TH-302 is being evaluated in two ongoing pivotal **Phase III** clinical trials and multiple earlier-stage clinical trials.

Threshold has a global license and co-development agreement for TH-302 with **Merck KGaA**, with an option to co-commercialize in the United States.

The second lead program is **[18F]-HX4** [flortanidazole (18F)], which is an investigational radiolabeled hypoxia Positron Emission Tomography (PET) imaging agent. The Company initially intends to develop [18F]-HX4 to determine a patient's tumor hypoxia profile, which may identify patients who will best respond to Threshold's hypoxia-targeted therapeutics.

Threshold is also developing second generation of tumor microenvironment targeted therapy. Though in early stage, these new candidates will provide sustainable growth for the Company.

Threshold is headquartered in South San Francisco, California.

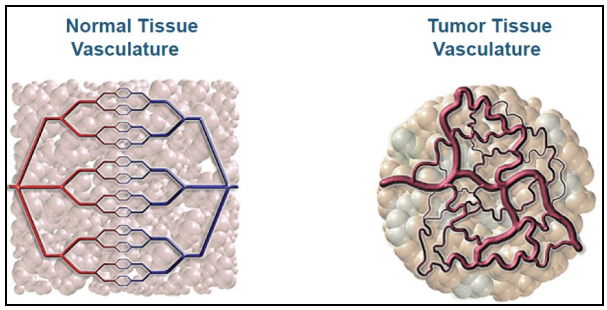


INVESTMENT THESIS

Tumor Hypoxia: An Emerging Target For Cancer Therapy

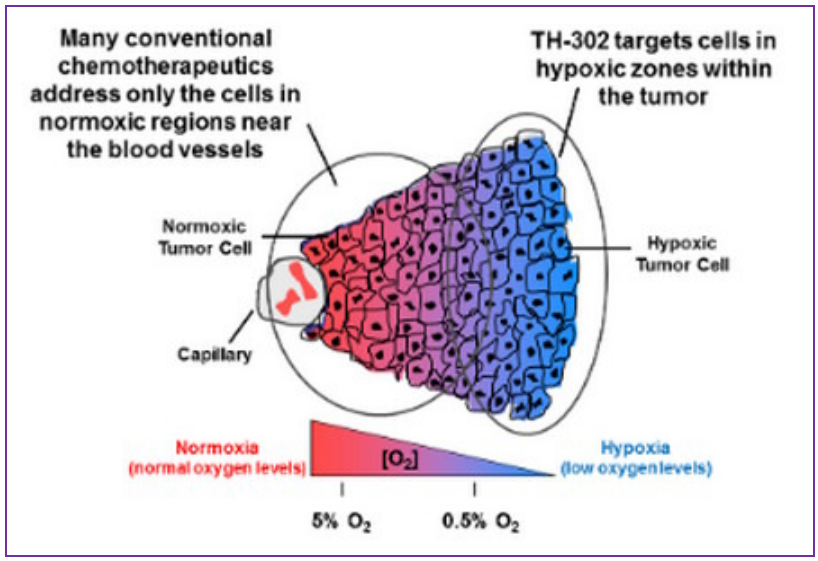
Tumor hypoxia is a common feature of the microenvironment of many solid tumors. Tumor hypoxia is a result of disordered vasculature found in all solid tumors. The network of blood vessels supplying solid tumors is known to be highly irregular and disordered, failing to deliver sufficient oxygen and nutrients to the rapidly dividing cancer cells, whereas normal healthy tissues are typically well oxygenated by virtue of having highly regular and structured arrays of blood vessels.

Common abnormalities in tumor vasculature include a large variation in the distance between the blood vessels that carry oxygen and other vital nutrients as well as “dead-ends” and temporary occlusions. Furthermore, in tumors, the growth of malignant cells is unregulated resulting in these tissues literally outgrowing their blood supply, leading to severe deficiencies in the perfusion of oxygen and nutrients.



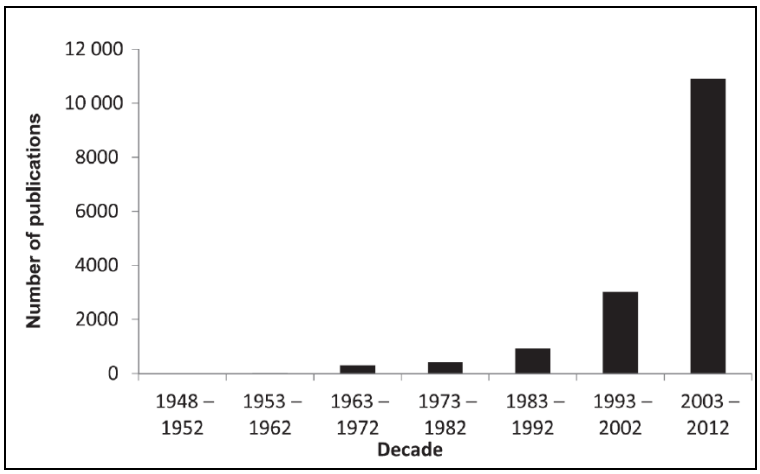
Together, abnormalities in tumor vasculature and the unregulated growth of cancer cells lead to distinctive **hypoxic microenvironments**, which are not found in most normal tissues.

Many traditional anticancer agents are not able to penetrate these hypoxic zones. Furthermore, cells that reside within regions of tumor hypoxia are relatively quiescent in contrast to highly proliferative cells that are the hallmark of cancer. As many traditional cancer therapies work by blocking cell division, they are not effective in killing the non-dividing, quiescent cells within hypoxic zones. In addition, cells subjected to prolonged hypoxia are thought to accumulate the changes in their growth properties and genetic mutations that can lead to **drug resistance**, enhanced **metastatic potential**, and treatment failure , ultimately resulting in compromised clinical outcomes.

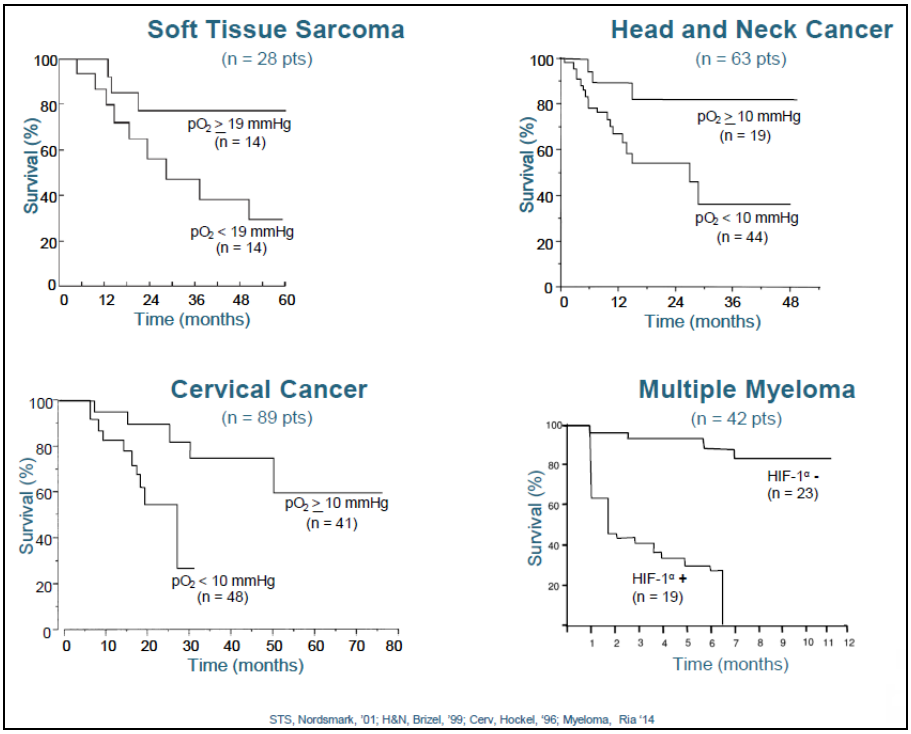


Given the **essential role** of hypoxia in tumor progression, metastasis, and resistance to radiotherapy and standard chemotherapy, and ultimately treatment failure, specific targeting of hypoxic tumor regions is emerging as a significant, high-priority target for effective and durable cancer therapy.

As such, research on tumor hypoxia has exploded in the past decade, which indicates a high interest in tumor hypoxia.



Clinical studies have demonstrated that hypoxia is correlated with poor prognosis. The more the hypoxia is, the worse the prognosis will be as demonstrated in four cancer types below.

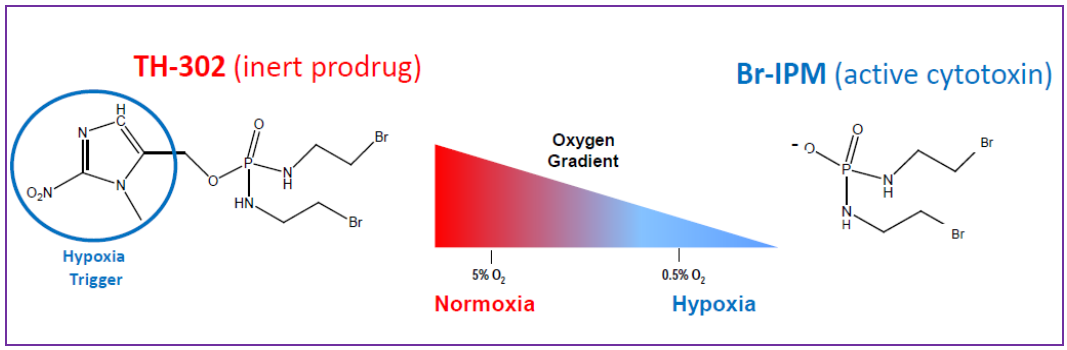


The Prodrug Platform

Threshold's **prodrug** technology is a **platform technology**. A prodrug candidate typically has two distinct parts, **a toxic portion** (the chemotherapeutic toxin) and an attached **trigger** molecule. To prevent general toxicity, the trigger molecule masks the toxin until the prodrug is activated, for example, by the low oxygen concentration in the hypoxic zones of tumors. Once activated, the toxin kills cells in its

vicinity. Threshold has designed prodrug candidates that are triggered only at the very low oxygen levels found in these hypoxic regions. A greater than 100-fold difference in cytotoxicity between cells in normal oxygen levels and hypoxic cells can be achieved.

The Company's lead prodrug candidate is **TH-302,** a prodrug to be selectively activated under the extreme hypoxic conditions in cancer tissue. Within regions of tumor hypoxia, TH-302 releases bromo isophosphoramide mustard (**Br-IPM**), a potent DNA alkylating agent. Br-IPM kills tumor cells by forming DNA crosslinks, rendering cells unable to replicate their DNA and divide as well as interfering with the transcription of DNA to make essential proteins. Once activated in hypoxic tissues, Br-IPM can also diffuse into surrounding oxygenated regions of the tumor and kill cells there via a "bystander effect". Because of its preferential activation in the targeted hypoxic regions of tumors, TH-302 may be less likely to produce broad systemic toxicity seen with untargeted cytotoxic chemotherapies.



Preclinical and clinical data suggest that TH-302 has significant antitumor activity both alone as well as in combination with other cancer therapies that target the rapidly proliferating cells found in normally oxygenated regions of solid tumors. Preclinical studies have also shown enhanced antitumor activity of TH-302 when combined with antiangiogenic agents. The underlying biological rationale for this enhanced activity is based, in part, on evidence that antiangiogenic agents increase levels of tumor hypoxia.

Threshold already completed a monotherapy **Phase I** clinical trial that determined the maximum tolerated dose (MTD), dose limiting toxicities, safety, pharmacokinetics and preliminary efficacy of TH-302 in patients **with advanced solid tumors**. Threshold also completed enrollment in two **combination therapy Phase I/II** clinical trials that determined the maximum tolerated doses, dose-limiting toxicities, safety, pharmacokinetics and preliminary efficacy of TH-302 in combination with four currently approved chemotherapies.

Currently, TH-302 is being evaluated in two Phase III pivotal trials as well as several earlier-stage trials in a variety of solid tumors and hematological malignancies. The most advanced clinical study of TH-302 is a pivotal **Phase III** trial evaluating TH-302 in combination with doxorubicin in patients with **soft tissue sarcoma**. A second ongoing **Phase III** trial is designed to evaluate TH-302 in combination with gemcitabine in patients with advanced **pancreatic cancer**. In addition, several early-stage clinical trials are evaluating the safety and efficacy of TH-302 in a variety of solid and hematologic tumors either as monotherapy or in combination with other anticancer agents including antiangiogenics.

The Deal with Merck KGaA, A Major De-risk Factor

In February 2012, Threshold entered into a global license and co-development agreement for TH-302 with **Merck KGaA**. Under the terms of the agreement, Merck KGaA received co-development rights, exclusive global commercialization rights and provided Threshold an option to co-commercialize TH-302 in the United States.

The deal is worth **total of $550 million** in terms of upfront and milestone payments. To date Threshold has received upfront and milestone payments of $110 million. The Company can earn additional potential

milestone payments of up to $440 million, comprised of $100 million in development and regulatory milestones and $340 million in sales-based milestones.

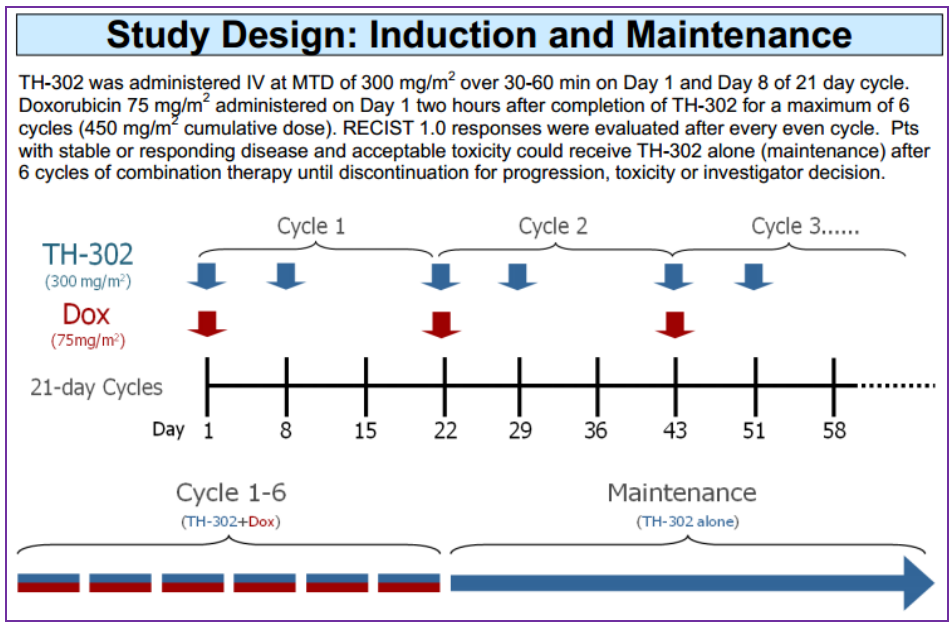
In the United States, Threshold will have primary responsibility for development of TH-302 in the soft tissue sarcoma indication. Threshold and Merck KGaA will jointly develop TH-302 in all other cancer indications being pursued. Merck KGaA will pay 70% of worldwide development costs for TH-302.

Merck KGaA will be responsible for commercialization of TH-302 in the US with Threshold receiving a **tiered, double-digit royalty** on sales. Under the royalty-bearing portion of the agreement, Threshold retains the option to co-promote TH-302 in the United States. Additionally, Threshold retains the option to co-commercialize TH-302 allowing the company to participate in up to 50% of the profits in the United States based on certain revenue tiers. Outside of the United States, Merck KGaA will be solely responsible for the commercialization of TH-302 with Threshold receiving a tiered, double-digit royalty on sales in these territories.

We think the deal with German Merck serves as a major **de-risk event** for Threshold. The license agreement with Merck KGaA not only boosts Threshold's balance sheet in a non-dilutive way, but more importantly validates the Company's technology and clinical programs. With the agreement with Merck KGaA, all the clinical programs will be accelerated going forward.

TH-302 +Doxorubicin for Soft Tissue Sarcoma

Threshold has completed a multi-center, dose-escalation **Phase II trial** (the TH-CR-403 trial) of TH-302 in patients with soft tissue sarcoma (STS). The TH-CR-403 trial was designed to determine the safety, efficacy and pharmacokinetics of TH-302 **in combination with full-dose doxorubicin** in patients with STS followed by TH-302 maintenance monotherapy for patients who had not progressed after six treatment cycles. A total of 91 patients with advanced STS previously untreated with chemotherapy were enrolled.



At the CTOS 2012 annual meeting (Connective Tissue Oncology Society), Threshold presented updated results from the TH-CR-403 trial.

The progression free survival (**PFS**) on study 403 was 6.7 months (Figure 1A). The median PFS after TH-302 maintenance was 3.7 months (Figure1B). The median overall survival (**OS**) on-study 403 was 21.5 months (Figure 2A). The median OS after TH-302 maintenance was 18.0 months (Figure 2B).

The 12-month OS was 73% and the 24-month OS was 44%.

Figure 1A: Progression-free Survival on Study (N=91)

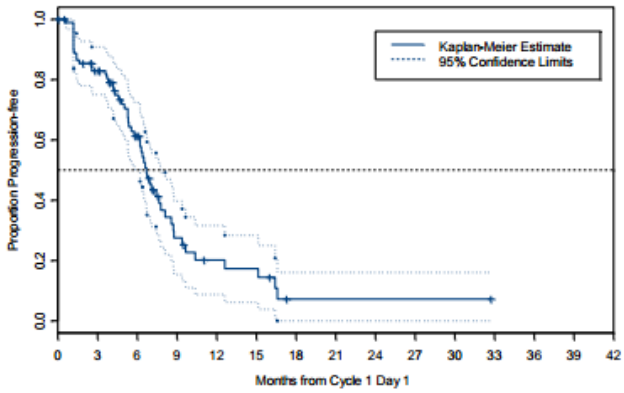


Figure 1B: Progression-free Survival after Initiating Maintenance (N=48)

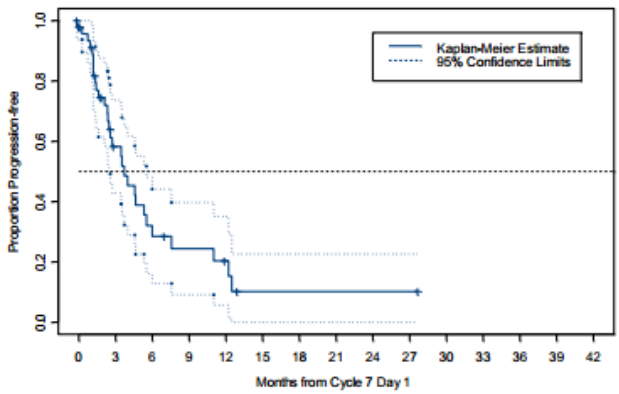


Figure 2A: Overall Survival on Study (N=91)

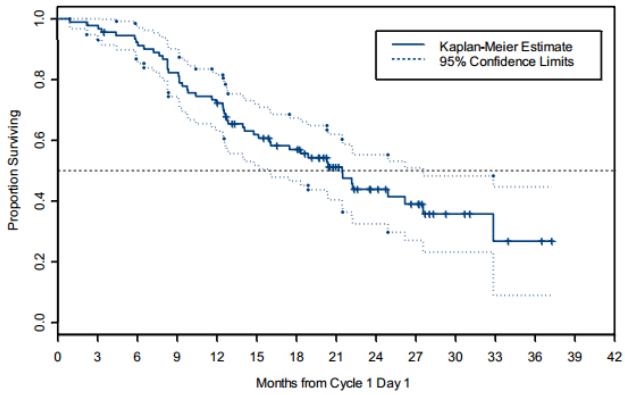
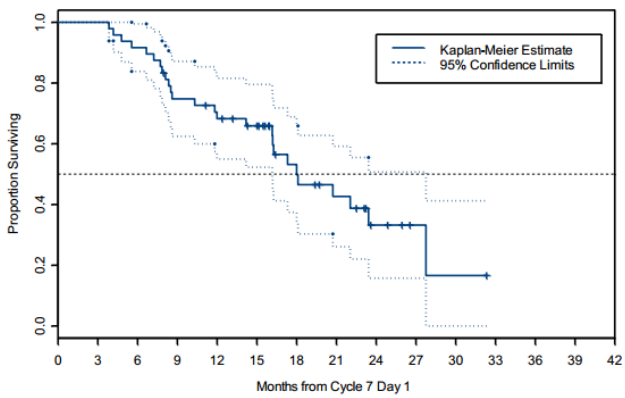


Figure 2B: Overall Survival after Initiating Maintenance (N=48)



Overall best response (partial and complete responses, unconfirmed) for all 91 patients was 36%. Overall response rate for 48 subjects receiving maintenance was 44% following induction and increased to 54% following maintenance (including both induction and maintenance). During the maintenance portion of the study 6 subjects had an upgrade in response category: 5 SDs converting to PR; 1 PR converting to CR.

Best Response (Unconfirmed) to Overall Treatment

	All (N=91*)	Maintenance after Induction (N=48)	Maintenance (N=48)
Best Response			
Complete Response	2 (2%)	1 (2%)	2 (4%)
Partial Response	30 (34%)	20 (42%)	24 (50%)
Stable Disease	43 (48%)	27 (56%)	22 (46%)
Progressive Disease	14(16%)	0 (0%)	0 (0%)
Overall Response Rate (RR) (Partial Response + Complete Response)	32 (36%)	21 (44%)	26(54%)

* Two patients discontinued from treatment for reasons of subject decision (1) and PI decision (1) prior to initial tumor response assessment.

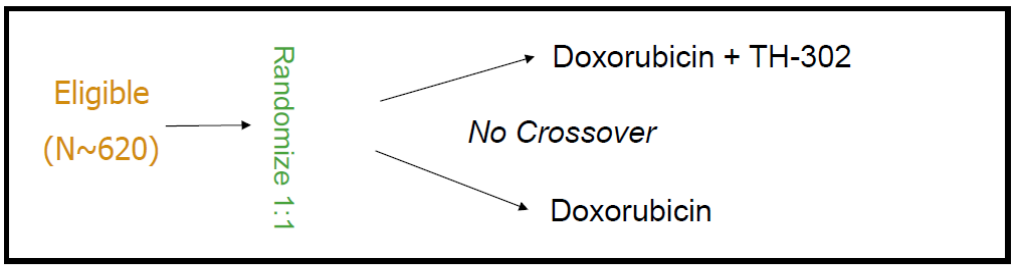
In conclusion, treatment with **TH-302 + doxorubicin** is associated with longer time to progression or death, increased survival, and higher response rates versus historical treatment with doxorubicin alone. The combination of TH-302+doxorubicin (left panel) compares favorably with doxorubicin alone and with doxorubicin in combination with ifosfamide (right panel, Phase III, 455 patients).

	TH-302 + doxorubicin (N=89 evaluable)	Dox (EORTC)	Dox + Ifos (EORTC)
Median Progression-free Survival	6.7 months (95% CI: 6.2 to 8.1 months)	4.6 mo (95% CI: 2.9 – 5.6)	7.4 mo (Δ=2.8) (95% CI: 6.6 – 8.3; p=0.003)
Median Overall Survival	21.5 months (95% CI: 16.0 to 27.6 months)	12.8 mo (95% CI: 10.5 – 14.3)	14.3 mo (Δ=1.5) (95% CI: 12.5 – 16.5; p=0.076)
Survival at 1 year	73% (95% CI: 63% to 82%)	51% (95% CI: 44 – 58)	60% (95% CI: 53 – 66)
Survival at 2 years	44%	~19%	~28%
Best Overall Response (Partial + 2 Complete Responses)	36%	13.6%	26.5%

TH-302 maintenance following induction of TH-302 combined with full dose doxorubicin in soft tissue sarcoma is tolerated with limited hematologic toxicity, manageable skin and mucosal toxicity, no additive renal, hepatic or cardiac adverse events and no cumulative toxicity.

Importantly, the PFS and upgrading of tumor responses indicate a potential additional contribution of TH-302 maintenance.

Based on the positive Phase II study, Threshold initiated a **pivotal TH-CR-406 trial** in partnership with the Sarcoma Alliance for Research through Collaboration (SARC) in September 2011. CR-406 trial is an international, randomized, pivotal **Phase III** trial enrolling patients with metastatic or locally advanced unresectable **soft tissue sarcoma (STS)** who have not previously received chemotherapy outside the adjuvant or neoadjuvant setting. The trial is designed to evaluate the efficacy and safety of TH-302 **in combination with doxorubicin**, compared to doxorubicin alone. The study is under a Special Protocol Assessment (SPA) with the FDA.



Patients	Metastatic or locally advanced unresectable front-line soft tissue sarcoma
Primary Endpoint	Overall survival (OS); 85% power to detect 33% improvement (434 events)
Secondary Endpoints	Overall response rate, progression free survival, duration of response, EFS

The primary endpoint is overall survival; secondary endpoints include efficacy measured by progression-free survival, overall response rate, overall survival at 6 and 12 months, progression free rate at 3 months and progression-free rate at 6 months, duration of response, stable disease or better rate, change in Eastern Cooperative Oncology Group or ECOG and performance status, as well as

assessments of safety and tolerability, pharmacokinetics and biomarkers. The FDA and the European Commission have granted TH-302 **orphan drug** designation for the treatment of soft tissue sarcoma.

In December 2013, Threshold completed the target enrollment of **620 patients**. The enrollment achievement triggered a milestone payment of $12.5 million from Merck KGaA.

Though Threshold will remain blinded to the data from this Phase III trial, an Independent Data Monitoring Committee (IDMC) will conduct an interim efficacy and safety analysis after 235 deaths are reached. The Company's current projections are that the number of events required to trigger the interim safety and efficacy analyses will be reached in **mid-2014**. Since the analyses themselves typically take anywhere from 6-12 weeks to complete, we are projecting the analysis should be completed **mid-late third quarter of 2014**. The interim efficacy analysis is designed to allow for the early termination of the study based on achieving a pre-specified improvement in overall survival and the recommendation of the IDMC. Early termination of the study may also result if the IDMC determines that the 406 trial would be unlikely to meet its primary endpoint of overall survival or if unexpected safety events altering the risk-benefit profile are observed. If the IDMC recommends that the study continue as planned, Threshold will remain blinded to the data until the Company conducts the primary analysis of overall survival after 434 deaths are reached. Unless the IDMC recommends that the study ends early, the number of events (434 deaths) required to trigger the primary efficacy analysis is currently projected to be reached in **mid-2015** with top-line results expected thereafter.

We estimate Threshold will submit a new drug application (NDA) in late 2015 or early 2016. The FDA approval could be in late 2016 or early 2017.

Sarcomas are a group of aggressive cancers of connective tissues of the body. Currently, there are only limited treatment options for sarcomas. **Soft tissue sarcomas** are usually treated with surgery, chemotherapy and radiation or in combination of these modalities.

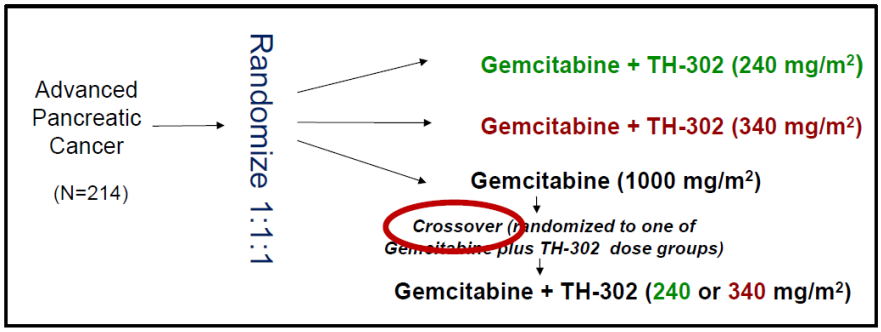
Doxorubicin and **ifosfamide** are the most commonly used chemotherapeutic agents in patients with advanced soft tissue sarcoma, but response rates are generally low and toxicity can be significant. Doxorubicin is the only approved front line therapy with an overall survival rate of approximately 8 months to 12 months, and an overall response rate of approximately 15% to 25%. The most serious toxicity for doxorubicin is the cumulative cardiotoxicity which usually limits the use of doxorubicin.

According to the American Cancer Society, about 12,020 new soft tissue sarcomas will be diagnosed and about 4,740 patients are expected to die of soft tissue sarcomas in the US in 2014.

TH-302 +Gemcitabine for Pancreatic Cancer

Threshold completed a randomized, controlled **Phase IIb** clinical trial of TH-302 **in combination** with **gemcitabine** in patients with **first-line pancreatic cancer** (the 404 trial).

A total of **214 patients** with previously untreated, locally advanced, unresectable or metastatic pancreatic adenocarcinoma were enrolled and treated. Patients were randomized equally into one of three cohorts: TH-302 at a dose of 240 mg/m^2 plus gemcitabine (G+T240) or TH-302 at a dose of 340 mg/m^2 plus gemcitabine (G+T340) or gemcitabine alone. If a patient's cancer progressed while on gemcitabine alone, the patient could crossover and be randomized into one of the TH-302 plus gemcitabine cohorts. The primary efficacy endpoint of the trial was a comparison of progression-free survival between the two pooled combination arms and the gemcitabine alone arm. The secondary endpoints were overall response rate, overall survival, event-free survival, CA 19-9 (a serum biomarker) response rate as well as various safety parameters.



Stratification	Stage: Unresectable locally advanced vs. distant metastases
Primary Endpoint	Progression free survival (PFS); 80% power to detect 50% improvement
Secondary Endpoints	Overall response rate (ORR), overall survival (OS), CA 19-9 response rate as well as various safety parameters

Results from the 404 trial showed a consistent dose effect in terms of improved progression-free survival, increased objective response rate, and decreased CA 19-9 levels in the G+T340 arm compared with the G+T240 and the gemcitabine-alone arms. There was a significant improvement (p=0.008) in progression-free survival associated with 41% reduction of risk for disease progression or death for patients treated with G+T340. This represented a 2.4-month increase in median progression-free survival for patients receiving G+T340 compared with gemcitabine alone. The 12-month overall survival rates were also in favor of the G+T340 treatment group compared with the control arm (38% vs. 26% (p=0.13)). Median overall survival for G, G+T240, and G+T340 was 6.9, 8.7, and 9.2 months, respectively; the differences between treatment groups were not significant, which may be at least partially explained by control arm patients with progressive disease crossing over to one of the G+T treatment arms. In other words, patients receiving gemcitabine alone who crossed over to receive gemcitabine plus TH-302 upon disease progression did contribute to the survival of the control arm. While not statistically significant, the improvement in median overall survival in the gemcitabine plus TH-302 treatment arms was consistent with the improvement in median progression-free survival.

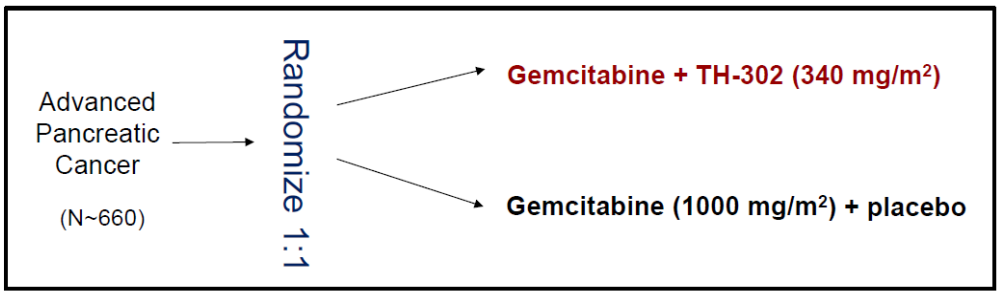
	Gem Alone (N=69)	**Gem + TH-302** 240 mg/m² (N=71)	**Gem + TH-302** 340 mg/m² (N=74)
PFS median (mos) ***1º Endpoint***	3.6	5.6 Δ=2.0 (HR=0.65; p=0.060)	6.0 Δ=2.4 (HR=0.59; p=0.008)
ORR (%)	10	17	26
Mean change in CA 19-9 nadir (U/L)	-523	-4,669	-5,385
# Cycles median	4	5	6
6-Mos Survival (%)	57	69	73
12-Mos Survival (%)	26	37	38
Overall Survival, median (mos)	6.9	8.7 Δ=1.8 (HR=0.96; p=0.827)	9.2 Δ=2.3* (HR=0.955; p=0.800)

**crossover diminished the apparent survival benefit of TH-302*

The most common **adverse events** were fatigue, nausea and peripheral edema, and were similar in frequency across treatment groups. Adverse events leading to discontinuation of study treatment as well as serious adverse events were balanced across all treatment arms. Severe (grade 3/4) myelosuppression was more frequent compared to gemcitabine alone. There was no significant difference in the percentage of patients discontinuing treatment for adverse events across the three treatment arms.

Based on the positive Phase IIb study, in **December 2012,** Threshold partner Merck KGaA initiated the global pivotal **Phase III MAESTRO** clinical trial assessing the efficacy and safety of TH-302 in combination with gemcitabine in patients with previously untreated, locally advanced unresectable or metastatic pancreatic adenocarcinoma. MAESTRO stands for TH-302 in the treatment of MetastAtic or unrESectable pancreaTic adenocaRcinOma.

The MAESTRO trial is a randomized, placebo-controlled, international, multi-center, double-blind Phase III clinical trial of TH-302 plus gemcitabine compared with placebo plus gemcitabine and is expected to enroll **660 patients**. The primary efficacy endpoint is overall survival; the secondary endpoints include efficacy measured by progression-free survival, overall response rate and disease control rate, as well as assessments of safety and tolerability, pharmacokinetics and biomarkers. The study is being conducted under an **SPA** with the FDA.



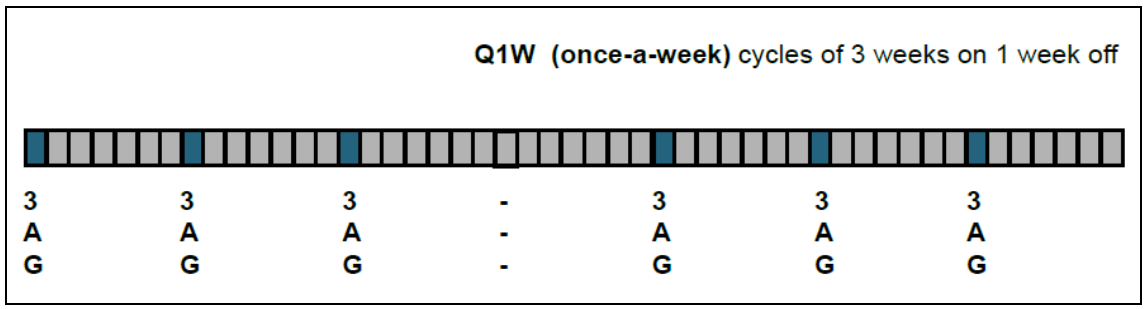
Patients	Metastatic or locally advanced unresectable pancreatic cancer
Primary Endpoint	Overall survival (OS)
Secondary Endpoints	Overall response rate, progression free survival, CA19-9, QOL, pain, safety

Enrollment in the trial is ongoing.

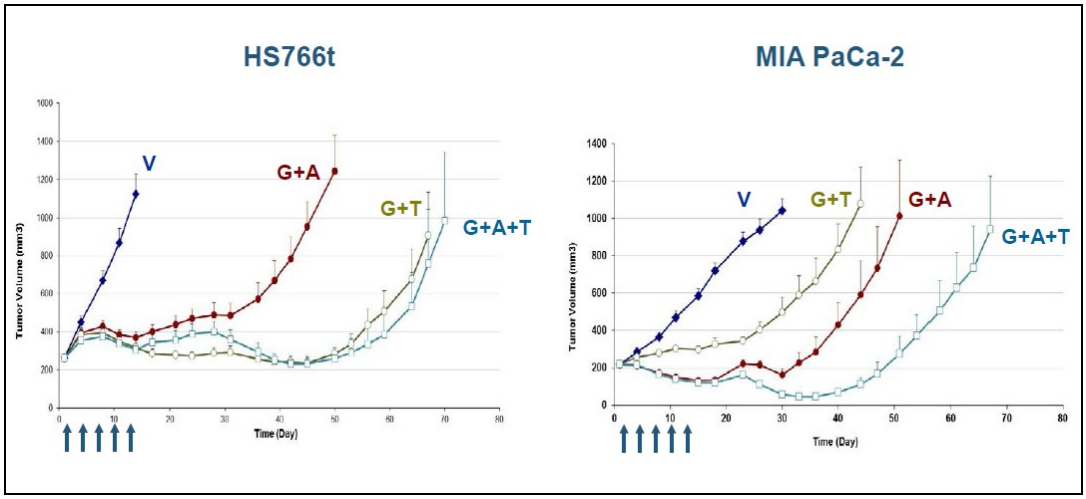
TH-302+Gemcitabine+Abraxane for Pancreatic Cancer

In January 2014, Merck KGaA initiated a **Phase I trial** to evaluate TH-302+Gemcitabine+Abraxane for the 1st line treatment of **pancreatic cancer**. This Phase I trial is an open-label, dose escalation trial. Primary endpoint is to determine maximum tolerated dose. Secondary endpoints include progression free survival, response rate, and duration of response.

All three drugs are given on each dosing day.



The rationale for this triplet trial is that in pancreatic xenograft models (HS766t, and MIA PaCa-2), TH-302 + Gemcitabine + Abraxane was more potent to inhibit the tumor growth compared to G+T or G+A.



This trial will enroll 48 subjects, and final data will be available **in 2016**.

According to the American Cancer Society, about 46,420 people will be diagnosed with pancreatic cancer and about 39,590 people will die of pancreatic cancer in the US in 2014. Pancreatic cancer is the twelfth most common cancer in the U.S. Pancreatic cancer has a low survival rate regardless of stage of disease, with approximately 95% of patients dying from their disease within 5 years.

Gemcitabine is the current **standard of care** for patients with pancreatic cancer with a median overall survival of approximately 6 months and an overall response rate of approximately 8%. The FDA recently approved two other therapeutic agents for the first-line treatment of patients with pancreatic cancer. **Erlotinib (Tarceva)** was approved for the first line treatment of pancreatic cancer **in combination** with gemcitabine with a median overall survival of 6.4 months and overall response rate of 8.6%. **Abraxane** (Nab-paclitaxel) was approved as first–line treatment for metastatic pancreatic cancer **in combination** with gemcitabine. Abraxane plus gemcitabine demonstrated a statistically significant improvement in median overall survival compared to gemcitabine alone (8.5 vs. 6.7 months).

TH-302 for Advanced Melanoma

In August 2013, Threshold initiated a **Phase II** clinical trial to evaluate the efficacy and safety of TH-302 in patients with **melanoma**. Threshold's partner Merck KGaA will fund 70% of development costs associated with this study.

The Phase II trial is a single-arm, multi-center study investigating the clinical efficacy and safety of TH-302 administered at 480 mg/m^2 weekly on a 28-day cycle (three weeks on, one week off) in up to **40 patients** with advanced melanoma. The primary endpoint is three-month progression-free survival. Secondary endpoints include response rate, duration of response, overall survival, safety and evaluation of potential imaging, serum, and tissue biomarkers that may be associated with tumor response and predict for efficacy and safety of TH-302 therapy.

In a previous **Phase I** trial, responses were observed in patients with advanced melanoma treated with TH-302. Out of 34 patients, seven patients (21%) achieved a partial response including patients with BRAF mutant and wild-type tumors, and 12 patients (35%) achieved stable disease yielding a clinical benefit rate of 56%. Median progression-free survival was 3.5 months.

Enrollment in the trial is ongoing.

TH-302 for Leukemia

In June 2010, Threshold initiated a **Phase I (TH-CR-407)** open label clinical trial of TH-302 designed to determine the maximum tolerated dose, dose limiting toxicity, safety, tolerability, clinical activity, and pharmacokinetics of TH-302 in patients with **advanced leukemia**.

The starting dose of TH-302 was 120 mg/m^2 administered daily for 5 days of a 21-day cycle. At the highest dose investigated in this study (550 mg/m^2), two patients developed dose limiting mucosal toxicity. The maximum tolerated daily dose of TH-302 was established at **460 mg/m^2**. Early results of this trial suggested activity of TH-302 monotherapy as evidenced by stabilization or reduction of bone marrow and peripheral blast counts in some patients. Thus, a second dosing regimen was evaluated in which TH-302 was administered as a continuous infusion over a 5-day period.

In December 2013, updated results were presented at the 55th Annual Meeting of the American Society of Hematology (ASH). A total of **49 patients** with previously treated acute myeloid leukemia (AML, n=39), acute lymphoblastic leukemia (ALL, n=9) or chronic myeloid leukemia (CML, n=1) were treated with TH-302. In the **first part** of the trial, a total of 38 patients received 30-minute bolus administration of TH-302 at escalating doses of 120 – 550 mg/m^2 (depending on the dose cohort) daily on days 1-5 of a 21-day cycle. In the **second part** of the trial, a total of 11 patients received TH-302 as a continuous infusion on days 1-5 of a 21-day cycle. Two of three patients treated with continuous infusion of TH-302 (460 mg/m^2/day) experienced dose-limiting toxicities of Grade 3 mucositis or Grade 3 hyperbilirubinemia; continuous administration maximum-tolerated dose was established at **330 mg/m^2/day**.

Two AML patients who received 550 mg/m^2 bolus TH-302 had complete resolution of leukemia cutis. One AML patient at 550 mg/m^2 bolus TH-302 had a complete response with incomplete platelet recovery (CRp), and one AML patient at 440 mg/m^2 bolus TH-302 had a complete response.

The responses observed in these very difficult to treat patients are consistent with the monotherapy activity that has been previously observed in a variety of solid tumors. Threshold has indicated that the potential for further evaluation of TH-302 **in combination with other chemotherapies** for the treatment of advanced leukemia will be assessed.

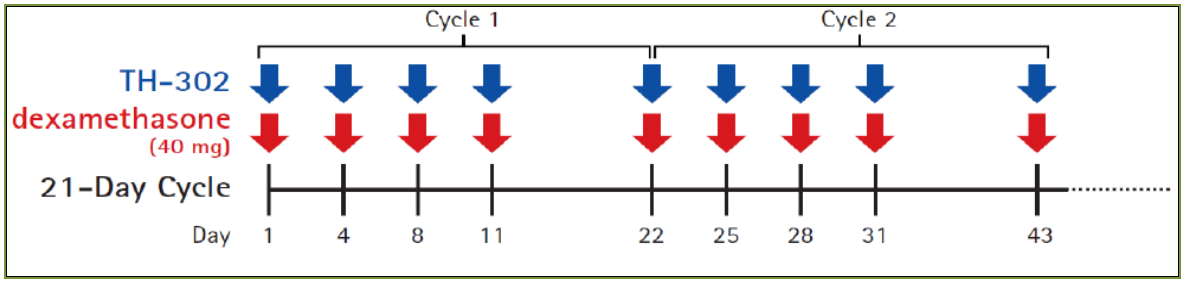
TH-302 for Multiple Myeloma

In March 2012, Threshold initiated a **Phase I/II** (the 408 trial) open label clinical trial of TH-302 to determine the maximum tolerated dose, dose limiting toxicity, safety, tolerability, clinical activity, and pharmacokinetics of TH-302 in patients with **relapsed/refractory multiple myeloma**.

The study has three parts:

- The first part is designed to establish the maximum tolerated dose of TH-302 **in combination with dexamethasone**;
- This MTD of TH-302 will be further evaluated in combination with dexamethasone in additional patients in the second part of the study;
- Lastly, the combination of TH-302 and dexamethasone with **Velcade**® (bortezomib, a proteasome inhibitor currently used to treat patients with multiple myeloma) will be investigated.

The dose of TH-302 administered in the dose escalation portion of the study was 240, 340, or 480 mg/m^2 given on days 1, 4, 8, and 11 of a 21-day cycle, with 40 mg dexamethasone given on the same days as TH-302.



The first part of the Phase I/II trial has been completed. **14 patients** received therapy. These patients were heavily pretreated having received 3 to 11 prior treatments (median of 6.5) and all having received a regimen containing bortezomib, an immunomodulatory agent lenalidomide and/or thalidomide, and an alkylating agent. Patients received one to 19 cycles (median of 4 cycles) of therapy with TH-302 and dexamethasone. **The maximum tolerated dose** was determined to be **340 mg/m^2** TH-302. The most frequent Grade 3/4 side effects were thrombocytopenia, leukopenia, anemia, and neutropenia.

Thirteen patients were evaluable for response. Two patients achieved a partial response and 3 patients achieved a minimal response, with the combination of the 2 types of responses comprising a clinical benefit rate of **38 percent**. Seven patients had stable disease and one patient had progressive disease. Two patients, one with a partial response and one with stable disease, remained on the study for more than one year (13 to 15 months) before discontinuing.

The clinical benefit rate from TH-302 in combination with low dexamethasone for multiple myeloma is comparable to early data as listed below from two of the most recently approved agents for advanced multiple myeloma, i.e., pomalidomide and carfilzomib.

	TH-302 + low dex	**Pomalidomide + low dex**	**Carfilzomib** (single agent)
Stage	Phase 1 dose escalation	Phase 1 dose escalation	Ph 1 dose escalation & expansion
N	13	38 (ITT population)	Escalation: 21 Expansion: 7
Dose & Schedule	240 – 480 mg/m^2 Bi-weekly	2-5 mg/day	1.2 - 27mg/m^2 Bi-weekly
Med Prior Lines	6.5	6	n/a
PR+MR	38%	42%	27%
Subsequent Steps Based Upon Ph 1 Data	TBD	Ex-US Ph 3 and US Registration Ph 2b	Ph 2a/b and Ex-US Ph 3
Current Status	Ph 1 expansion ongoing	US & EU Approved	US Approved

Threshold is currently enrolling patients into the **second part of the trial** in an effort to better characterize the efficacy and safety of TH-302 at 340 mg/m^2 in combination with dexamethasone. The Company expects to complete enrollment of 15 patients around the **middle of 2014**.

The Company expects to initiate the **third part** of the trial to investigate the combination of TH-302 and bortezomib by **year-end 2014**.

There are few treatment options for patients with advanced multiple myeloma that stop responding to bortezomib and lenalidomide, and responses to subsequent salvage therapy have historically been

extremely low. The preliminary results suggest that the combination of TH-302 with dexamethasone is active in some heavily pretreated patients who have failed conventional therapy.

TH-302 in Combination with antiangiogenics

Antiangiogenics are a relatively new class of anticancer therapies that target the tumor vasculature. The goal of antiangiogenic therapy is to "starve" tumors by disrupting the blood vessel network supplying tumors with oxygen and nutrients needed for survival and growth.

While antiangiogenics have proven to be effective for targeted cancer therapy, essentially all tumors eventually become resistant to these treatments. One of the reasons that tumors become resistant to antiangiogenic is that **antiangiogenics may induce tumor hypoxia**. Therefore, co-targeting tumor angiogenesis and tumor hypoxia may be the solution to treatment resistance to antiangiogenics.

Since TH-302 is selectively designed to target tumor hypoxia, the combination of TH-302 with antiangiogenic therapy has the potential to be an effective anticancer treatment. **Preclinical models** demonstrated enhanced antitumor activity of TH-302 when used in combination with antiangiogenic therapies (sunitinib and sorafenib), which was directly related to the amount of hypoxia induced by different doses of these antiangiogenics.

Based on preclinical studies, Threshold is actively exploring the potential of combining TH-302 with antiangiogenic therapies in a variety of tumor types in human clinical trials. Current studies include the following:

- TH-CR-410: A Phase I dose-escalation clinical trial evaluating the safety of TH-302 in combination with sunitinib in patients with advanced renal cell carcinoma (RCC), gastrointestinal stromal tumors (GIST), and pancreatic neuroendocrine tumors (PNET).
- TH-IST-4003: A Phase I/II safety and efficacy study of TH-302 in combination with bevacizumab in patients with recurrent glioblastoma following bevacizumab failure.
- TH-IST-4001: A Phase I dose-escalation study of TH-302 in combination with pazopanib in patients with advanced solid tumors.
- TH-IST-4004: A Phase I/II study of TH-302 in combination with sorafenib in patients with advanced renal cell carcinoma (RCC) and patients with advanced hepatocellular carcinoma (HCC)

TH-302 + Sunitinib for RCC, GIST, and PNET

Threshold is conducting a **Phase I trial (the 410 trial)** evaluating standard full dose **sunitinib** (50 mg) administered daily (Days 1 – 28 of a 6-week cycle) with TH-302 (240 mg/m^2 to 480 mg/m^2) administered on days 8, 15 and 22.

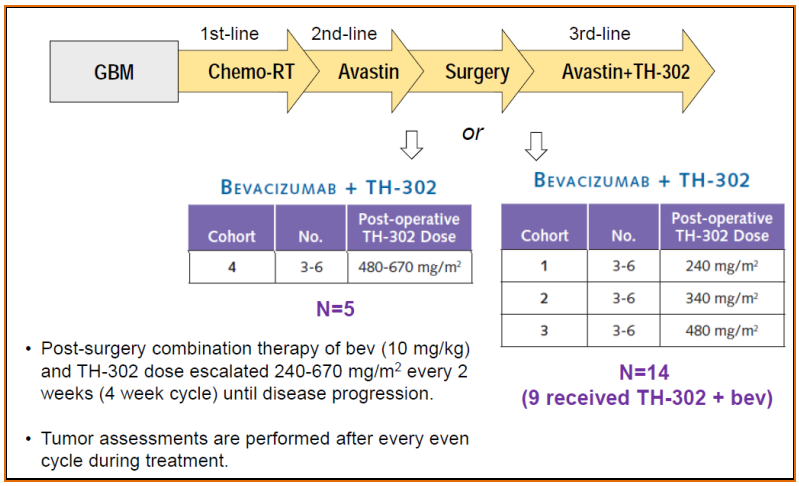
In 2013, preliminary data from the 410 trial were published online in the ASCO 2013 Annual Meeting Proceedings, and updated preliminary results from **12 patients** were reported at the 2013 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. As reported at AACR-NCI-EORTC, no dose-limiting toxicities were observed in the 4 patients treated in the initial cohort at **240 mg/m^2**. One of 6 evaluable patients treated at **340 mg/m^2** had a dose-limiting toxicity of Grade 3 stomatitis. Grade 3 thrombocytopenia and neutropenia were reported in 3 (25%) and 4 (33%) patients, respectively; Grade 4 neutropenia was reported in one patient (8%). Fatigue, nausea, and vomiting were the most common nonhematologic adverse events occurring in 83%, 75%, and 67% of patients, respectively. All cases were grade 1 or 2 except for one report of grade 3 nausea.

Partial responses were achieved by one of four (25%) evaluable GIST patients (confirmed) and three of eight (37.5%) evaluable RCC patients (one confirmed). All four patients with partial responses had received prior sunitinib.

Threshold expects to complete enrollment of additional patients at **480 mg/m^2** in **2H14** to determine the maximum tolerated dose of TH-302 in combination with sunitinib. Plans for further investigation of this combination will be assessed.

TH-302 + Avastin for Glioblastoma

An investigator-sponsored **Phase I/II trial (the 4003 trial)** to evaluate TH-302 in combination with **Avastin**® (bevacizumab) in patients with **recurrent glioblastoma** following bevacizumab failure is ongoing.



Glioblastoma multiforme (GBM), also called glioblastoma, is the most common and most aggressive type of primary brain tumor and accounts for approximately 50% to 60% of all primary brain tumors. It is estimated that 23,130 people were diagnosed with and 14,080 people died of **cancer of the brain and other nervous system** in 2013 in the US.

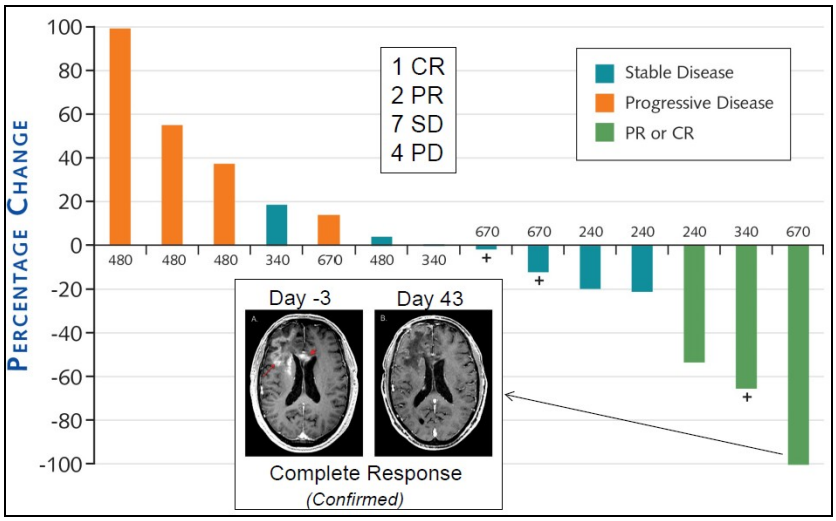
Glioblastomas are among the most aggressively malignant human neoplasms. The median survival time from the time of diagnosis without any treatment is usually less than 1 year. Despite multimodality treatment, median survival is about 14.6 months. The overall 5-year survival is less than 10% with the standard of care today.

Chemotherapy (temozolomide) with radiotherapy (RT) is standard care for newly diagnosed glioblastoma. Avastin (bevacizumab, Roche) is approved in the U.S. for progressive disease following prior therapy. After disease progression on bevacizumab, patients may start a subsequent bevacizumab-containing regimen. These patients typically progress in 5 to 8 weeks.

Treatment Setting	Therapy	Median PFS	Median OS
Newly Diagnosed *first-line setting, after surgical resection*	temozolomide (TMZ) + radiation (RT) followed by maintenance TMZ	~7 months	~15 months *TMZ + RT provides Δ2.5 months benefit over RT alone*
First Recurrence *second-line setting*	bevacizumab	~4 months	~9 months
Second Recurrence *third-line setting*	bevacizumab-containing regimen	~38 days	82 days

Preliminary results from the 4003 trial demonstrated that no dose-limiting toxicity had been reported at doses of TH-302 up to 670 mg/m^2 plus bevacizumab at 10 mg/kg every two weeks.

Preliminary data in 14 patients showed one patient achieved a complete response and two patients achieved partial responses.



Patients continue to be enrolled in the 670 mg/m2 TH-302 cohort.

TH-302 in Combination with Pazopanib for Advanced Solid Tumors

An investigator-sponsored **Phase I trial** (the 4001 trial) has been completed, evaluating TH-302 in combination with pazopanib in patients with **advanced solid tumors**.

Results were reported at the 2013 AACR-NCI-EORTC annual meeting for the 30 patients enrolled with a variety of solid tumors for whom standard therapy or palliative measures were nonexistent or no longer effective. The clinical benefit rate was 76% (n=25 evaluable patients) with three patients with partial responses (12%) and 16 patients with stable disease (64%). The partial responses were observed in patients with neuroendocrine cancer, ovarian cancer, and chondrosarcoma. Treatment-related grade 3 hematological adverse events were reported for neutropenia (7%), thrombocytopenia (7%), and anemia (13%). Treatment-related, grade 2 nonhematologic adverse events included vomiting/nausea/diarrhea (7% grade 3), mucositis (7% grade 3), hand foot syndrome (all grade 2), and hypertension (all grade 2). No grade 4 adverse events have been reported.

Threshold is assessing plans for further investigation of TH-302 in combination with Pazopanib.

TH-302 in Combination with Sorafenib for RCC and HCC

This is an investigator-sponsored **Phase I/II** clinical trial to evaluate **sorafenib** + **TH-302** in advanced renal cell carcinoma (RCC) and advanced hepatocellular carcinoma (HCC).

Primary endpoints include number of dose-limiting toxicity incidents, MTD of sorafenib + TH-302, and overall response rate.

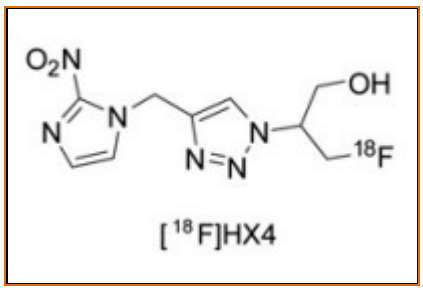
The trial started in May 2012, and is ongoing. Total of 48 subjects will be enrolled in this study. We estimate final data to be presented **later this year**.

[18F]-HX4: A PET Imaging Agent for Hypoxia

Threshold acquired **[18F]-HX4** [flortanidazole (18F)] from Siemens Healthcare in March 2013.

[18F]-HX4 is an investigational Positron Emission Tomography (PET) imaging agent for hypoxia developed by Siemens Healthcare Molecular Imaging to potentially identify and quantify the degree of hypoxia in tumors in vivo.

[18F]-HX4 contains a short-lived radioisotope, 18F, which can be detected in a PET scanner. PET imaging is used to help physicians diagnose and treat cancer and is routinely performed in cancer treatment centers globally. [18F]-HX4 has a 2-nitroimidazole “trigger” that is designed to be activated under the extreme hypoxic conditions generally found in tumors but not typically in normal healthy tissue, therefore it will accumulate more in these hypoxic regions.



Clinical data from Siemens Healthcare have demonstrated the potential of [18F]-HX4 to quantify the degree of hypoxia within different tumors. Threshold initially intends to develop [18F]-HX4 to determine a patient’s tumor hypoxia profile, which may identify patients who will best respond to Threshold’s hypoxia-targeted therapeutics.

[18F]-HX4 is currently being incorporated into some of the Company’s ongoing trials with TH-302. Ultimately, the goal is to get [18F]-HX4 approved as a **companion diagnostic** for hypoxia-targeted drugs.

TH-302 Advantages and Market Opportunities

Anti-hypoxia is an emerging cancer therapy and represents a new approach to targeted therapy. Threshold is a key player in this promising new treatment approach.

Many different approaches are used in treating cancer, including surgery, radiation, chemotherapy, targeted therapy and immunotherapy or a combination of these approaches. But most currently used cancer therapies are focused on killing cancer cells that exhibit rapid division and growth. Such cells are found in regions of the tumor that have an adequate blood supply and therefore receive nutrients and oxygen essential for cell division and growth. However, the vasculature supporting tumors is highly disorganized and irregular. This results in regions of the tumor that do not receive adequate amounts of nutrients and oxygen (**hypoxic zones**).

As we discussed earlier, many traditional anticancer agents are not able to penetrate into the hypoxic zones of tumors or they are not effective on non-dividing hypoxic tumor cells. Moreover, tumor cells in hypoxic regions can develop genetic mutations that lead to drug resistance, enhanced metastatic potential, and, ultimately, treatment failure.

Another disadvantage of current cancer therapies that target rapidly dividing cells is their toxic side effects. Because rapidly dividing cells are also found in many healthy tissues, particularly the gastrointestinal tract, bone marrow and hair follicles, nearly all conventional chemotherapy drugs cause severe side effects.

Threshold's **TH-302** is specifically designed to target cancer hypoxia. Because of its preferential activation in the targeted hypoxic regions of solid tumors, TH-302 may be less likely to produce broad systemic toxicity seen with untargeted cytotoxic chemotherapies.

Threshold has generated clinical data with TH-302 both alone and in combination with multiple anticancer drugs in multiple cancer types. Two classes of cancer therapeutics have been, or are being tested in combination with TH-302: **chemotherapeutics** and **antiangiogenics**. The current total market addressed by chemotherapy and antiangiogenics exceeds $10 billion.

TH-302 is in different stages of development for a variety of cancer indications, including late stage development for **soft tissue sarcoma** and **pancreatic cancer**. Other cancer indications include lung cancer, melanoma, glioblastoma, kidney cancer, liver cancer, gastrointestinal stromal tumors, multiple myeloma, and leukemia.

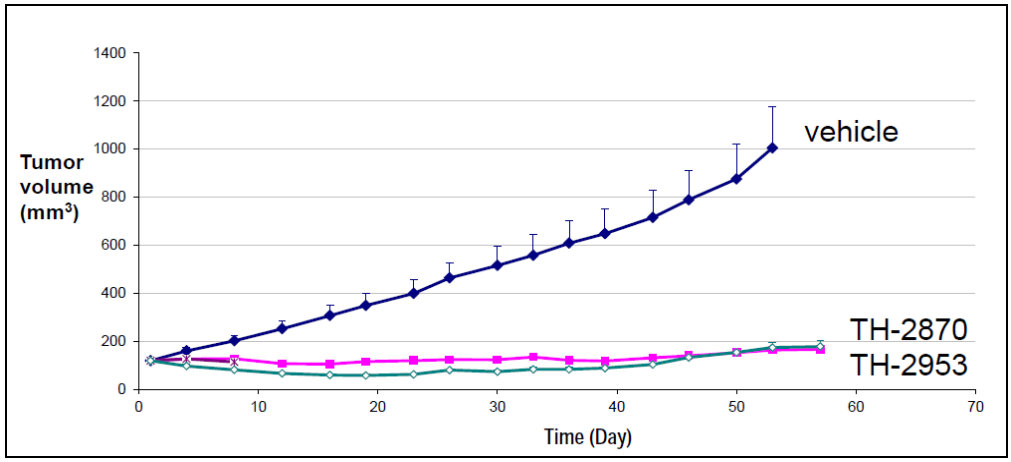
We think TH-302 has a **blockbuster potential** for Threshold considering its broad anticancer activity and favorable safety profile.

New Prodrugs Provides Sustainable Growth

In addition to TH-302, Threshold is also developing **new prodrugs** for targeted cancer therapy.

Through the study of TH-302, either alone or in combination, Threshold has better understood the mechanism of action of anti-hypoxic therapy for cancers. Based on this experience and its expertise in selectively designing cancer microenvironment based prodrugs, Threshold is developing new prodrug agents targeting **other aspects of tumor microenvironment**.

Current focus is on tumor microenvironment induced enzyme expression. The Company has identified two **lead compounds** of new prodrugs: **TH-2953** and **TH-2870**. In addition to promising **in vitro** anti-cancer activities, both drug candidates have demonstrated significant in vivo anti-cancer efficacy. In a non-small cell lung cancer xenograft mouse model below, TH-2870 and TH-2953 showed significant anti-tumor efficacy.



Additional preclinical study is underway.

We think the development of new candidates will provide the Company long term growth beyond TH-302.

Strong Balance Sheet

As of March 31, 2014, Threshold had $86.4 million in cash, cash equivalents and marketable securities.

Threshold has a collaboration agreement with Merck KGaA worth **total of $550 million** in terms of upfront and milestone payments. To date Threshold has received upfront and milestone payments of $110 million. The Company can earn additional potential milestone payments of up to $440 million, comprised of $100 million in development and regulatory milestones and $340 million in sales-based milestones.

We welcome this non-dilutive financing which benefits all of its shareholders. We estimate current cash balance combined with the potential payment from Merck KGaA could last into 2016 when the Company's TH-302 could be approved for soft tissue sarcoma.

Experienced Management Team

Harold E. "Barry" Selick, Ph.D.
Chief Executive Officer
Harold E. "Barry" Selick, Ph.D. joined Threshold as Chief Executive Officer in June 2002. Between June 2002 and July 2007, Dr. Selick was a Venture Partner of Sofinnova Ventures, Inc., a venture capital firm. From January 1999 to April 2002, he was Chief Executive Officer of Camitro Corporation, a biotechnology company. From 1992 to 1999, he was at Affymax Research Institute, the drug discovery technology development center for Glaxo Wellcome plc, most recently as Vice President of Research. Prior to working at Affymax he held scientific positions at Protein Design Labs, Inc. and Anergen, Inc. As a staff scientist at Protein Design Labs, he co-invented the technology underlying the creation of fully humanized antibody therapeutics and applied that to PDL's first product, Zenapax, which was developed and commercialized by Roche for treating kidney transplant rejection. Dr. Selick received his B.S. and Ph.D. from the University of Pennsylvania and was a Damon Runyon-Walter Winchell Cancer Fund Fellow and an American Cancer Society Senior Fellow at the University of California, San Francisco.

Joel A. Fernandes
Vice President of Finance and Controller
Joel Fernandes was appointed Threshold's Vice President, Finance and Controller in May 2011 having held roles of increasing responsibility in finance and accounting since joining the company in 2006. Prior to joining Threshold, Mr. Fernandes served as Associate Director of Finance at Theravance Inc., Senior Manager of Corporate Finance at KLA-Tencor, and Assistant Controller of ALZA Corporation. Mr. Fernandes holds a CPA and a Masters in Accountancy from Manchester College, Indiana.

Tillman Pearce, M.D.
Chief Medical Officer
Tillman Pearce, M.D. joined Threshold as Chief Medical Officer in February 2012. From April 2007 until March 2011, Dr. Pearce served as Chief Medical Officer at KaloBios Pharmaceuticals, Inc. Dr. Pearce has approximately 15 years of experience in the biopharmaceutical industry in both Europe and the United States. Prior to joining KaloBios, he was at Protein Design Labs in Paris, France, where he held the position Senior Director, Clinical Research and directed their European office. Between 1997 and 2002, Dr. Pearce was Medical Director at Sanofi-Synthelabo, S.A. in Paris, France, in their Oncology Business Unit. Prior to that, he held the position of Director, Clinical Research at Novartis Pharma AG in Basle, Switzerland. Dr. Pearce received his M.D. from the Medical College of Georgia and is board-certified in both internal medicine and hematology.

Stewart M. Kroll
Senior Vice President of Clinical Operations and Biostatistics
Stewart Kroll was appointed Threshold's Senior Vice President, Clinical Operations and Biostatistics in May 2011. Previously, he served as Threshold's Vice President, Biostatistics and Clinical Operations since March 2007. Mr. Kroll joined the company as Director, Biostatistics in January 2005. Prior to joining Threshold, Mr. Kroll served as Senior Director of Biostatistics at Corixa Corporation and held positions of increasing responsibility, most recently as Director of Biostatistics at Coulter Pharmaceuticals. Mr. Kroll holds a B.A. and M.A. in Mathematical Statistics from UC Berkeley.

Mark D. Matteucci, Ph.D.
Senior Vice President of Discovery Research
Mark Matteucci, Ph.D., joined Threshold as Vice President of Discovery in August 2002. From 1999 to 2002, he provided medicinal chemistry consultation to several biotechnology companies including Threshold. From 1988 to 1999, he was the Director of Bioorganic Chemistry at Gilead Sciences, Inc. where he was the first scientist hired and established that company's research program in nucleic acid targeting. He built and led an interdisciplinary team of 20 scientists and was a key player in establishing a well funded scientific collaboration between Gilead and Glaxo. During his time at Gilead, he established himself as an intellectual leader in the field of nucleic acids targeting with over 50 publications and 30 patents in the area and numerous invited presentations at international meetings. Prior to joining Gilead Sciences, Dr. Matteucci was a scientist at Genentech, Inc. There, he modernized the oligonucleotide synthesis efforts and invented the H phosphonate method of DNA synthesis. He received his B.S. from the Massachusetts Institute of Technology and Ph.D. from the University of Colorado where he co-invented the DNA synthesis technology which is the foundation of the modern "gene machine".

Nipun Davar, Ph.D., MBA
Vice President of Pharmaceutical Development and Manufacturing
Nipun Davar, Ph.D., joined Threshold as Vice President of Pharmaceutical Development and Manufacturing in October 2011. Dr. Davar has more than 17 years of product development experience in the pharmaceutical industry. Prior to Threshold, Dr. Davar was Vice President of Pharmaceutical Sciences at Transcept Pharmaceuticals where he led the CMC function and pharmaceutical development of Intermezzo® (low dose sublingual zolpidem) for the treatment of middle of the night insomnia. Prior to Transcept, Dr. Davar held various leadership positions at ALZA, most recently as Senior Director and Research Fellow, where he led multidisciplinary teams responsible for the approval of Jurnista® (OROS hydromorphone) in Europe and Invega® (OROS paliperidone) in the U.S. He has 11 issued or pending patent applications and multiple publications in the area of drug delivery and product development. Dr. Davar holds a Ph.D. in Pharmaceutical Sciences from the University of Maryland and an MBA from the Wharton School at the University of Pennsylvania.

Eric D. Malek, MBA
Vice President of Corporate Development
Eric Malek joined Threshold as Vice President, Corporate Development in 2010. Prior to joining Threshold, he led corporate development at BiPar Sciences where he initiated the partnering effort that led to BiPar's acquisition by Sanofi-Aventis. Prior to BiPar, Mr. Malek was Vice President, Corporate Development at Allos Therapeutics, where he led the acquisition and product planning efforts for FOLOTYN®, indicated for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma. Before Allos, Mr. Malek held business development positions at Gilead Sciences, NeXstar Pharmaceuticals and Ilex Oncology as well as research positions at Janssen Pharmaceuticals. Mr. Malek holds a B.A. in Biochemistry from the University of Arizona and an M.B.A. from the University of Michigan.

Robert L. Simon
Senior Vice President of Regulatory Affairs and Quality Assurance
Robert Simon joined Threshold as Senior Vice President of Regulatory Affairs and Quality Assurance in April 2012. Mr. Simon has more than 31 years of pharmaceutical drug development experience ranging from chemical development and manufacturing to global regulatory affairs. Prior to joining Threshold, Mr. Simon was most recently a Corporate Officer and Executive Vice President of Pharmaceutical Development at OSI Pharmaceuticals (acquired by Astellas Pharmaceuticals) where he joined as Vice President of Regulatory Affairs and CMC. During his tenure at OSI, Mr. Simon was instrumental in the registration of Tarceva® (erlotinib) in second/third line NSCLC and pancreatic cancer. Prior to OSI, Mr. Simon was Vice President of Global Regulatory Affairs at Gilead Sciences and was involved in the successful registration of Viread® (tenofovir) for the treatment of HIV-1 infection. Prior to Gilead, Mr. Simon held various positions at Bristol Myers-Squibb most recently as Vice President of CMC. During his tenure at BMS, Mr. Simon built a strong CMC Regulatory Affairs organization, which was instrumental in the registration of numerous new molecular entities in several therapeutic areas including oncology, anti-

infective, anti-viral, CNS and cardiovascular. He led the project for the first and only Environmental Assessment report required by FDA for the registration of Taxol® (paclitaxel). Prior to BMS, Mr. Simon held positions in regulatory affairs and chemistry at Syntex Pharmaceuticals. Mr. Simon began his career as a research and development chemist at the former Stanford Research Institute (SRI International) where he worked on a number of government and private programs. He received his introduction to pharmaceuticals through an NIH grant to evaluate novel volatile anesthetics. Mr. Simon received his B.S. degree in chemistry from California State University at San Jose.

Charles P. Hart, Ph.D.
Vice President of Biology
Charles Hart, Ph.D., was appointed Threshold's Vice President, Biology in 2008. He joined the company as Senior Director, Biology in 2004. Dr. Hart is responsible for in vitro and in vivo preclinical translational studies. Prior to joining Threshold, Dr. Hart was Senior Director, Biology at Galileo Pharmaceuticals, Director of Drug Discovery at Signature Bioscience, and a Research Unit Director at Affymax (a Glaxo company). Dr. Hart holds an A.B. from UC Berkeley, an M.S. from Stanford University, and a Ph.D. in Molecular Biology and Genetics from Yale University. Dr. Hart completed a postdoctoral fellowship at the University of Strasbourg, France.

Laura G. Hansen, Ph.D.
Senior Director of Corporate Communications
Laura Hansen, Ph.D., joined Threshold in August 2012 as Senior Director, Corporate Communications. Dr. Hansen has more than 13 years of experience in corporate communications and investor relations in the biotechnology industry. Prior to joining Threshold, she was Director, Corporate Communications at FibroGen, Inc., a privately held, development-stage biotechnology company. Prior to FibroGen, she was Director, Corporate Communications and Investor Relations at Corvas International, Inc. (acquired by Dendreon Corporation). Dr. Hansen began her communications career at Susan E. Atkins + Associates (acquired by Porter Novelli), an investor and public relations agency focused solely on the biotechnology industry. She holds a B.S. in Zoology and Ph.D. in Biological Sciences from the University of Texas at Austin.

VALUATION AND RECOMMENDATION

We are initiating coverage of Threshold (THLD) with an Outperform rating. Our 12-month price target is $9.50. Our call is based on the Company's strong fundamentals.

Threshold is a late development stage biopharmaceutical company focused on developing and commercializing **hypoxia based therapeutics** for cancer treatment based on its **prodrug platform technology**.

The Company's lead drug candidate is **TH-302**, a prodrug which can be taken by cancer cells and released in the microenvironment of tumor hypoxia. Th-302 is in a series of clinical trials targeting a variety of cancer indications either alone or in combination with other cancer therapeutics. The most advanced are two ongoing **Phase III clinical trials** for soft tissue sarcoma and for pancreatic cancer, respectively.

The Phase III trial of TH-302 in combination of doxorubicin has completed the target enrollment of **620 patients** with advanced soft tissue sarcoma. An interim efficacy and safety analysis is currently projected to be conducted after the required number of events are reached in **mid-2014**. Since the analyses themselves typically take anywhere from 6-12 weeks to complete, we are projecting the analysis should be completed **mid-late third quarter of 2014**. The number of events required to trigger the primary efficacy analysis is projected to occur **in mid-2015**. We estimate TH-302 could be approved by the FDA in **late 2016 or early 2017**.

The Phase III trial of TH-302 in combination with gemcitabine in pancreatic cancer patients is ongoing.

In addition to the two Phase III trials, Th-302 is in more than 10 Phase I/II clinical trials targeting different cancer indications.

Threshold has a collaboration agreement with Merck KGaA to co-develop TH-302 worth **total of $550 million** in terms of upfront and milestone payments. This agreement is a major de-risk factor for Threshold in our view. This non-dilutive financing not only boosts Threshold's balance sheet, but more importantly validates its technology and clinical programs.

In addition to TH-302, Threshold is also developing **second generation** candidates for tumor microenvironment targeted therapy for cancers. These early stage candidates provide sustainable growth for the Company.

In terms of valuation, we think Threshold shares are undervalued at current market price. Currently, Threshold shares are trading at about $3.60 per share, which values Threshold at $212 million in terms of market cap based on 59 million outstanding shares. We think this is a discount compared to its peers. Threshold is a late development stage company with its lead candidate TH-302 to be approved in as early as in late 2016. According to our financial model, we estimate Threshold will become profitable in fiscal 2018 with EPS of $0.27 based on $110 million in revenue. Revenue will grow to $170 million in 2019 with an EPS of $0.83. We think it's appropriate to use 35 x P/E multiple to valuate Threshold. If we use 35 x P/E ratio and EPS of $0.83 for 2019, discounted at 25% for 5 years, we come up with our price target of $9.50 per share. Our price target values Threshold at $560 million in market cap which we think is appropriate.

But keep in mind the **risks** associated with our price target. We assume that TH-302 will be approved by the FDA in late 2016 or early 2017. There are still some **clinical** and **regulatory** hurdles to overcome by Threshold. If TH-302 fails to be approved or is delayed for approval by the FDA, the share price could drop dramatically.

Even if TH-302 is approved by the FDA, there is still commercialization risk for Threshold since the Company has no experience in product commercialization.

Another risk we would like to remind investors is that the broad market fluctuation also has impact on the Company's share price. But overall we think Threshold is a risk/award opportunity for investors with a long term investment horizon.

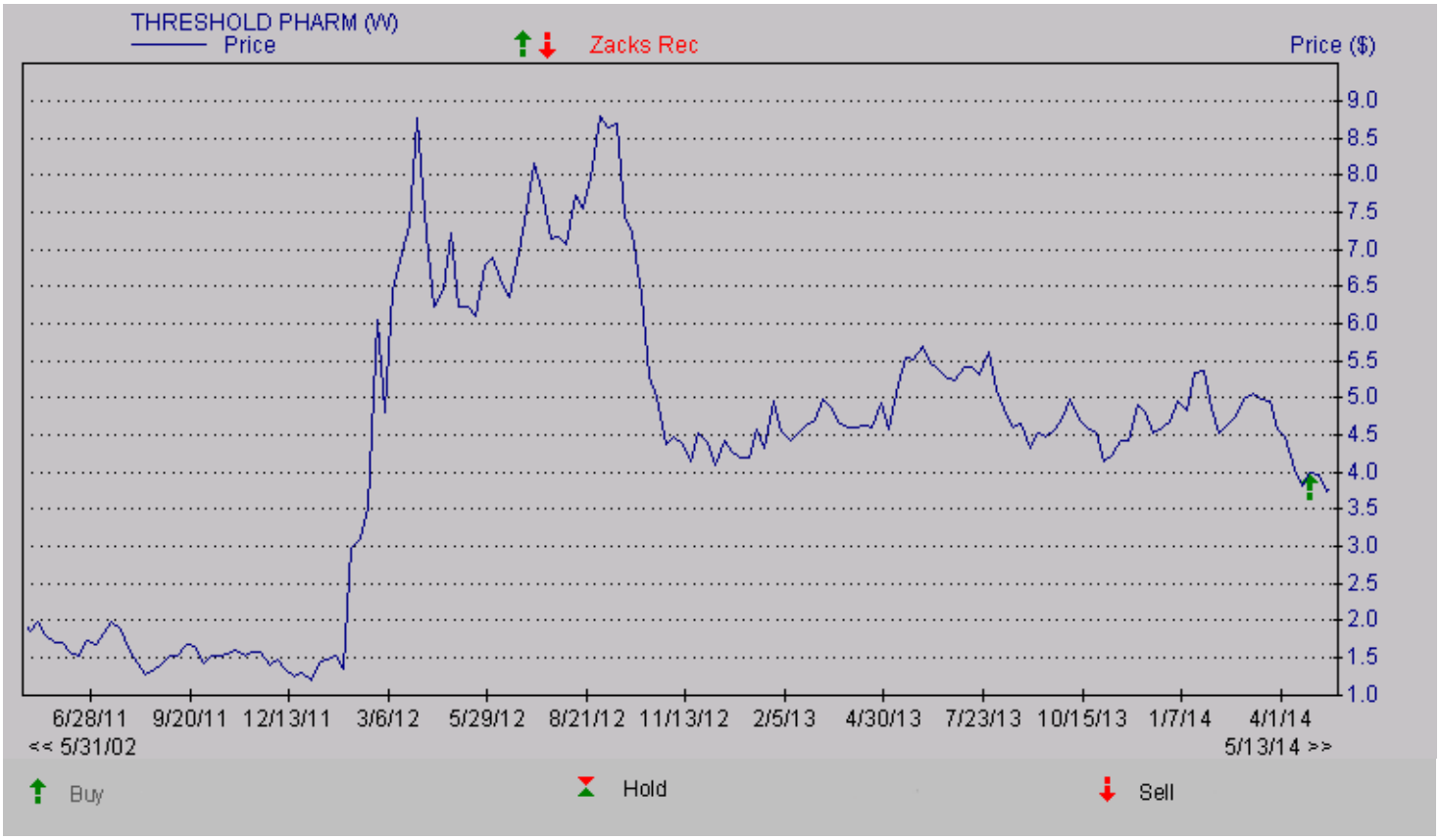
PROJECTED INCOME STATEMENT

	2012 (Dec)	2013A (Dec)	2014E (Dec)					2015E (Dec)	2016E (Dec)	2017E (Dec)	2018E (Dec)	2019E (Dec)
$ in million except per share data	FYA	FYA	Q1A	Q2E	Q3E	Q4E	FYE	FYE	FYE	FYE	FYE	FYE
Collaboration revenue	$5.87	$12.50	$3.68	$3.70	$3.85	$4.00	$15.23	$18.50	$22.00	$25.00	$35.00	$45.00
Product revenue	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$5.00	$35.00	$75.00	$125.00
Total Revenues	**$5.87**	**$12.50**	**$3.68**	**$3.70**	**$3.85**	**$4.00**	**$15.23**	**$18.50**	**$27.00**	**$60.00**	**$110.00**	**$170.00**
YOY Growth	-	113.0%	26.0%	16.4%	21.0%	24.5%	21.9%	21.5%	45.9%	122.2%	83.3%	54.5%
CoGS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.75	5.25	11.25	18.75
Gross Income	**$5.87**	**$12.50**	**$3.68**	**$3.70**	**$3.85**	**$4.00**	**$15.23**	**$18.50**	**$26.25**	**$54.75**	**$98.75**	**$151.25**
Gross Margin	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	97.2%	91.3%	89.8%	89.0%
R&D	$18.79	$29.33	$9.65	$9.70	$10.00	$10.50	$39.85	$45.00	$50.00	$55.00	$60.00	$65.00
% R&D	320.2%	234.8%	262.2%	262.2%	259.7%	262.5%	261.7%	243.2%	185.2%	91.7%	54.5%	38.2%
SG&A	$7.08	$9.19	$2.63	$2.65	$2.70	$2.75	$10.73	$12.50	$14.00	$16.00	$18.00	$20.00
%SG&A	121%	74%	72%	72%	70%	69%	70%	68%	52%	27%	16%	12%
Other	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Operating Income	**($20.0)**	**($26.0)**	**($8.6)**	**($8.7)**	**($8.9)**	**($9.3)**	**($35.4)**	**($39.0)**	**($37.8)**	**($16.3)**	**$20.8**	**$66.3**
Operating Margin	-	-	-	-	-	-	-	-	-	-	-	38.97%
Other Net	($51.1)	($2.2)	$1.5	($0.2)	($0.2)	($0.2)	$0.9	$0.0	$0.0	$0.0	$0.0	$0.0
Pre-Tax Income	**($71.1)**	**($28.2)**	**($7.1)**	**($8.9)**	**($9.1)**	**($9.5)**	**($34.5)**	**($39.0)**	**($37.8)**	**($16.3)**	**$20.8**	**$66.3**
Income taxes(benefit)	$0.0	$0.2	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	-	-	-	-	-	-	-	-	-	-	-	-
Reported Net Income	**($71.1)**	**($28.4)**	**($7.1)**	**($8.9)**	**($9.1)**	**($9.5)**	**($34.5)**	**($39.0)**	**($37.8)**	**($16.3)**	**$20.8**	**$66.3**
YOY Growth	-	-	-	-	-	-	-	-	-	-	-	-
Net Margin	-	-	-	-	-	-	-	-	-			
Diluted Shares Out	54.2	57.8	61.3	61.5	62.5	63.0	62.1	68.0	70.0	75.0	78.0	80.0
Reported EPS	**($1.31)**	**($0.49)**	**($0.12)**	**($0.14)**	**($0.14)**	**($0.15)**	**($0.56)**	**($0.57)**	**($0.54)**	**($0.22)**	**$0.27**	**$0.83**
One time charge	*$51.14*	*$2.19*	*($1.50)*	*$0.00*	*$0.00*	*$0.00*	*($1.50)*	*$0.00*	*$0.00*	*$0.00*	*$0.00*	*$0.00*
Non GAAP Net Income	**($20.0)**	**($26.2)**	**($8.6)**	**($8.9)**	**($9.1)**	**($9.5)**	**($36.0)**	**($39.0)**	**($37.8)**	**($16.3)**	**$20.8**	**$66.3**
Non GAAP EPS	**($0.37)**	**($0.45)**	**($0.14)**	**($0.14)**	**($0.14)**	**($0.15)**	**($0.58)**	**($0.57)**	**($0.54)**	**($0.22)**	**$0.27**	**$0.83**

Source: company filings and Zacks estimates

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HISTORICAL ZACKS RECOMMENDATIONS



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The current distribution is as follows: Buy/Outperform- 16.8%, Hold/Neutral- 75.5%, Sell/Underperform – 6.7%. Data is as of midnight on the business day immediately prior to this publication.