Phase 1/2 Study of Investigational Hypoxia-Targeted Drug, TH-302, and Bevacizumab in Recurrent Glioblastoma Following Bevacizumab Failure

Andrew Brenner MD PhD[1], Jessica Sun MD PhD[2], John Floyd MD[1], Charles Hart PhD[2], Clarence Eng[2], Stew Kroll[2], Lisa Fichtel MD[3], Aleksandra Gruslova PhD[1], Alessia Lodi PhD[4], Stefano Tiziani PhD[4]

[1]Cancer Therapy & Research Center at UT Health Science Center, San Antonio, TX, USA; [2]Threshold Pharmaceuticals, Inc., South San Francisco, CA, USA; [3]South Texas Accelerated Research and Therapeutics (START), San Antonio, TX, USA; [4]University of Texas at Austin, Austin, TX, USA

Introduction

Bevacizumab-Refractory Glioblastoma

- The Phase 2 randomized BRAIN trial led to conditional FDA approval of bevacizumab (bev) for recurrent glioblastoma (GBM) based on objective response rate in the USA[1]:
  - 25.9% objective response rate; 4.2 months median duration of response.
- No standard therapeutic regimen has been established for patients who become refractory to bev.
- Despite second-line bev failure, third-line salvage therapy is often another bev-containing regimen:
  - Progression usually occurs within one to two months[2-4].
- A significant unmet medical need exists for bev-refractory patients with advanced GBM.

Targeting Tumor Hypoxia in GBM

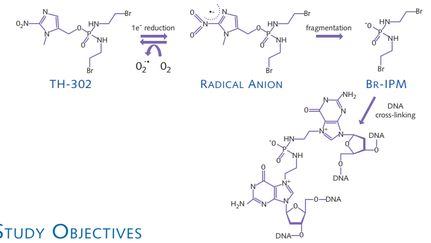
- Hypoxic necrotic foci with pseudopalisading tumor cells are hallmarks of GBM[5].
- Greater hypoxic burden has been associated with poorer outcomes in GBM[6].
- Antiangiogenic treatment with agents such as bev has been shown in some preclinical studies to reduce perfusion and increase hypoxia in the tumor microenvironment[7].
- The use of agents that have specific activity in the hypoxic tumor microenvironment may be of benefit in patients who have failed single-agent bev therapy.

Phase 1/2 Trial of TH-302 Plus Bev

- A Phase 1/2 trial (NCT01403610) is evaluating the safety and efficacy of the investigational hypoxia-activated prodrug TH-302 in combination with bev in patients with recurrent GBM following single-agent bev failure.
- The Phase 2 portion is enrolling, and interim results are presented.

TH-302 Hypoxia-Activated Prodrug

- TH-302 is a hypoxia-activated prodrug that, when activated in hypoxic conditions (<0.5% O_2), releases the bis-alkylating agent bromo-isophosphoramide mustard (Br-IPM), which can then act as a DNA crosslinking agent. *In vivo*, TH-302 has shown to potentiate the anti-tumor efficacy of other antiangiogenic agents.



TH-302 | Radical Anion | Br-IPM

Study Objectives

Primary Objectives

- To determine the extent by which TH-302 is able to penetrate the blood brain barrier and affect tumor tissue.
- To assess the safety of single dose TH-302 administered to patients with GBM prior to surgery.
- To assess the safety of TH-302 in combination with bev in patients with GBM.
- To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of TH-302 in combination with bev in patients with GBM.

Secondary Objective

- To determine the progression-free survival (PFS) for patients with GBM treated with combination bev and TH-302 following recurrence on single agent bev.

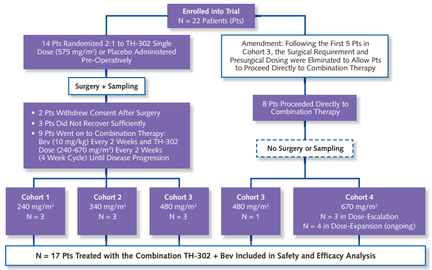
Study Design

Phase 1: Single center, dose-escalation, prospective study with randomization in a 2 to 1 ratio to TH-302 single dose of 575 mg/m² versus placebo administered pre-operatively (cohorts 1-3 only), followed by postoperative combination therapy of bev at 10 mg/kg every 2 weeks and TH-302 dose escalated 240-670 mg/m² (depending on dose cohort) every 2 weeks (4 week cycle) until disease progression. Tumor assessments are performed after every even cycle during treatment. Following the first 5 patients in cohort 3, the surgical requirement and presurgical dosing were eliminated to allow patients to proceed directly to combination therapy. Tumor response to therapy was assessed according to the Response Assessment in Neuro-oncology (RANO) criteria. Resected tumor tissue was evaluated for hypoxia. Hypoxic fraction (HF) was evaluated as the percentage of pimonidazole or CAIX-positive area in the whole tumor sample. Identification and quantification of endogenous and exogenous serum metabolites was performed by combining high-resolution magnetic resonance spectroscopy (MRS) and ultrahigh pressure liquid chromatography/mass spectrometry (UHPLC-MS). **Phase 2:** Expansion at MTD.

Results

Results are presented for all patients receiving the postoperative combination therapy regardless their pre-surgery randomization:

- All patients had histologically confirmed GBM.
- 22 patients have been enrolled with 14 randomized in cohort 1, cohort 2 or cohort 3, and an additional 8 proceeding directly to combination therapy.
- 2 patients withdrew consent after surgery, and 3 failed to recover sufficiently to meet ongoing eligibility criteria. Therefore, 9 of the 14 randomized patients received combination therapy of TH-302 plus bev, and 17 overall including the 8 patients without surgery.
- All of the 14 pre-surgical patients had partial resections.



Baseline Characteristics

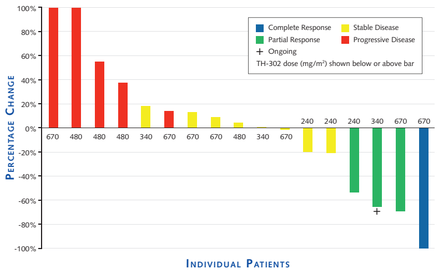
	TH-302 Dose (mg/m²)				
	240 (n=3)	340 (n=3)	480 (n=4)	670 (n=7)	Total (n=17)
Age, Median (range)	56 (43-70)	47 (44-51)	50 (35-58)	61 (42-67)	55 (35-70)
Male, n (%)	2 (67%)	1 (33%)	1 (25%)	5 (71%)	9 (53%)
ECOG Performance Status 0 1 2	 0 3 (100%) 0	 0 3 (100%) 0	 1 (25%) 3 (75%) 0	 2 (29%) 4 (57%) 1 (14%)	 3 (18%) 13 (76%) 1 (6%)
Prior Therapies, Median	2	3	3	2.5	3
Months to Progression on Chemo/ Radiation, Median (range)	11 (2.7 -14)	9 (7.8 – 14)	9.8 (4.5 – 20)	5.4 (2.4 – 14)	9.8 (2.4 – 20)
Months to Progression on Single-Agent bev, Median (range)	3.4 (2.4 – 6.4)	1.4 (1.1 – 4.8)	2.3 (1.2 – 5.5)	3.7 (0.9 – 8.9)	2.4 (0.9 – 8.9)
Median Months from Progression on bev to First Dose TH-302	1.1	3.3	1.2	0.5	1
Steroids at Study Entry, n (%)	1 (33%)	2 (67%)	0 (0%)	4 (57%)	7 (41%)

Safety

- The primary TH-302-related toxicities were mucosal:
  - Rectal/anal mucositis in 1 of 4 patients at 480 mg/m² (Gr 2) and 6 of 7 patients at 670 mg/m² (all Gr 1 or 2).
  - Limited oral mucositis was observed.
- Three Grade 3 AEs; no Grade 4 AEs:
  - Skin ulceration (second cycle) at 340 mg/m².
  - Oral mucositis (first cycle) at 670 mg/m².
  - Thrombocytopenia (third cycle) at 670 mg/m².

Change in Tumor Volume

Tumor volumes are calculated as the sum of products of perpendicular diameters of all measurable enhancing lesions. Maximum change from baseline is shown.



Best Objective Response

- All 17 patients were evaluable for response according to Response Assessment in Neuro-oncology (RANO) criteria.
- As best responses, one patient achieved a complete response (CR) and three patients achieved a partial response (PR) for an objective response rate of 24%.

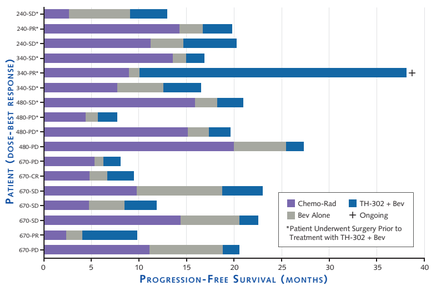
TH-302 Dose (mg/m²)	CR	PR	SD	PD	Total
240	0	1	2	0	3
340	0	1	2	0	3
480	0	0	1	3	4
670	1	1	3	2	7
Total	1	3	8	5	17

CR=complete response; **PR**=partial response; **SD**=stable disease; **PD**=progressive disease

Progression-Free Survival and Overall Survival

	Median, Months (95% CI)	4-Month Rate (95% CI)	6-Month Rate (95% CI)
PFS	3.1 (2.0 – 4.0)	26% (4% - 47%)	13% (0% - 33%)
OS	4.9 (3.5 – 7.2)	57% (32% - 81%)	38% (14% - 61%)

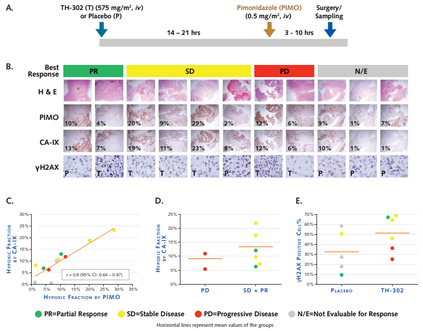
Progression-Free Survival on Prior Therapeutic Regimens and TH-302 Plus Bev



Correlative Studies

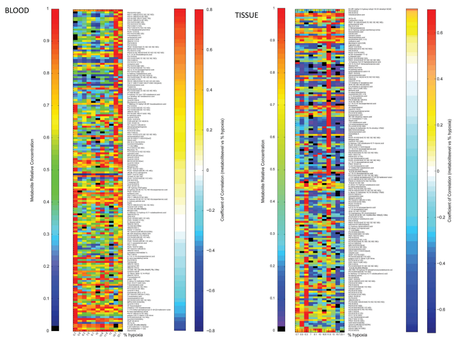
Immunohistochemistry

- The study design on sampling for biomarker investigation is shown in (A).
- Representative images of H&E histology staining, pimonidazole, CAIX and γH2AX immunostainings in individual GBM patients (B).
- There was a strong concordance between both exogenous (pimonidazole) and endogenous (CAIX) markers of hypoxia in serial sections (C).
- Tumors tended to have a higher hypoxic fraction in patients with a best response of PR or SD as compared with patients who had a best response of PD (D).
- Patients treated with a single dose of TH-302 prior to surgery tended to have higher levels of γH2AX positive cells (indicative of DNA damage) compared with patients who received placebo prior to the surgery (E).
- Patients treated with a single dose of TH-302 prior to surgery with higher levels of γH2AX positive cells tended to have better outcome compared with patients with lower levels of γH2AX positive cells (E).



Metabolomic Profiling

- Identification and quantification of endogenous blood and tissue metabolites was performed by combining high-resolution magnetic resonance spectroscopy and ultrahigh pressure liquid chromatography/mass spectrometry.
- Metabolomic profiles differed with degree of tumor hypoxia (CA-IX), particularly in blood vs. tissue.



Summary

In Patients with Bevacizumab-Refractory Recurrent Glioblastoma:

- TH-302 has a manageable safety profile when used in combination with bev:
  - MTD established at 670 mg/m² TH-302 every 2 weeks
  - Most adverse effects were Grade 1 or Grade 2 involving the mucosa
- Early signals of activity (N=17 evaluable patients) were observed:
  - 24% objective response rate (1 CR, 3 PR)
  - Median PFS 3.1 mos in bev/TH-302 combination
    - Longer than median PFS 2.4 mos on first bev regimen in same patients
    - Longer than the historically reported median PFS of 1 to 2 months following administration of a second bev regimen[2-4]
  - 26% PFS rate at 4 months
- Correlative studies show metabolomic profile varies with degree of tumor hypoxia, and hypoxic burden may be associated with treatment response
- Dose expansion at TH-302 670 mg/m² and bevacizumab is ongoing

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Disclosures

JS, CH, CE, SK: Employees of Threshold Pharmaceuticals. All other authors have no potential conflicts of interest to disclose. TH-302 is currently under clinical investigation and has not been approved by any regulatory authority.

Status

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