Phase 1/2 Study of TH-302, Investigational Hypoxia-Activated Prodrug, and Bevacizumab in Patients with Bevacizumab-Refractory Recurrent Glioblastoma

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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, continuation of bev in combination with another antineoplastic agent is regularly considered for salvage therapy:
  - 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

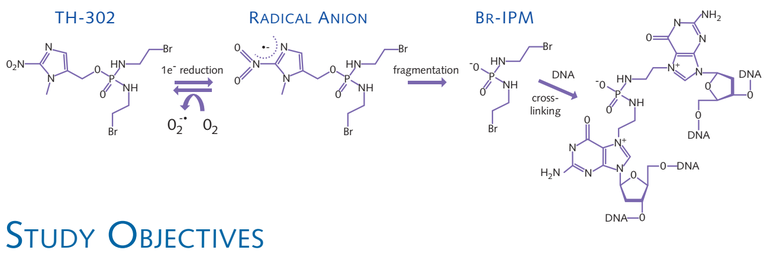
- Hypoxic necrotic foci with pseudopalisading tumor cells are hallmarks of GBM[5].
- Greater hypoxic burden has been associated with poorer outcomes in GBM[6].
- Antiangiogenic treatment with agents such as bev has been shown in some preclinical studies to reduce perfusion and increase hypoxia in the 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 trial is fully enrolled; 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.



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.

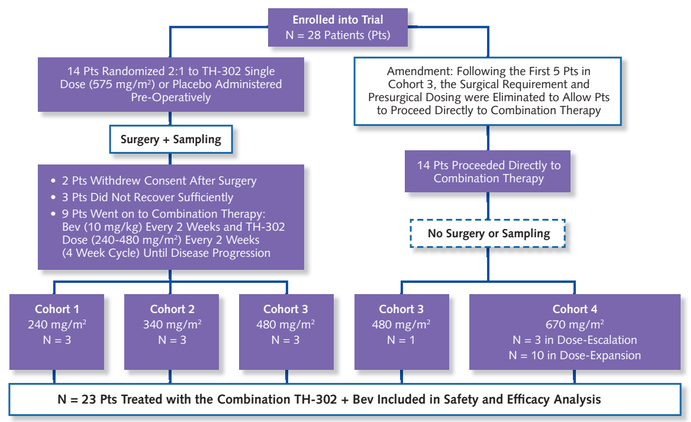
Study Design

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.
- 28 patients were enrolled with 14 randomized in cohort 1, cohort 2 or cohort 3, and an additional 14 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 23 overall including the 14 patients without surgery.
- All of the 14 pre-surgical patients had partial resections.



Baseline Characteristics

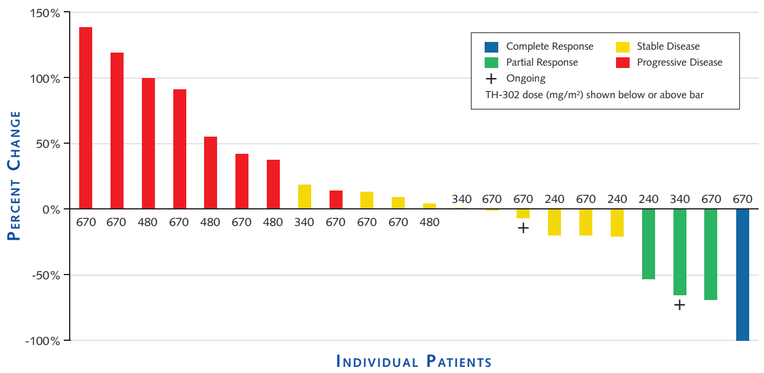
	TH-302 Dose (mg/m²)				
	240 (n=3)	340 (n=3)	480 (n=4)	670 (n=13)	Total (n=23)
Age, Median (range)	56 (43 – 70)	47 (44 – 51)	50 (35 – 58)	61 (42 – 74)	56 (35 – 74)
Male, n (%)	2 (67%)	1 (33%)	1 (25%)	10 (77%)	14 (61%)
ECOG, (%)					
0	0	0	1 (25%)	3 (23%)	4 (17%)
1	3 (100%)	3 (100%)	3 (75%)	7 (54%)	16 (70%)
2	0	0	0	3 (23%)	3 (13%)
Prior Therapies (median)	2	3	3	2	3
Months to Progression on Chemo/Radiation, Median (range)	11.3 (2.7 -14)	9 (7.8 – 14)	15.6 (4.5 – 20)	4.5 (1.8 – 14)	6.6 (1.8 – 20)
Months to Progression on Single-Agent bev, Median (range)	3.5 (2.5 – 6.5)	1.4 (1.1 – 4.9)	2.3 (1.3 – 5.5)	4.1 (1.0 – 9.0)	3.7 (1.0 – 9.0)
Median Months from Progression on bev to First Dose TH-302	1.2	3.3	1.0	0.6	0.8
Steroids at Study Entry n (%)	1 (33%)	2 (67%)	0 (0%)	9 (69%)	12 (52%)

Safety

- The primary TH-302-related toxicities were mucosal:
  - Rectal/anal mucositis in 1 of 4 patients at 480 mg/m² (Gr 2) and 13 of 13 patients at 670 mg/m² (all Gr 1 or 2).
  - Oral mucositis was less frequent.
- 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 Size

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



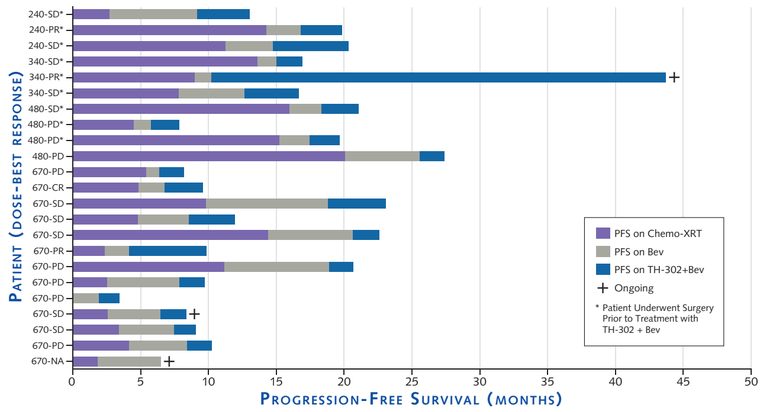
Best Objective Response

- 22 of the 23 patients were evaluable for response according to Response Assessment in Neuro-oncology (RANO) criteria.
- In a total of 22 patients, best responses included one complete response (CR; 670 mg/m²) and three partial responses (PR; 240, 340, 670 mg/m²) for a response rate of 18%, and ten stable disease (SD) assessments for a clinical benefit rate of 64%; eight patients had progressive disease (PD).

Progression-Free Survival and Overall Survival

	Median, Months (95% CI)	4-Month Rate (95% CI)	6-Month Rate (95% CI)
PFS	2.8 (1.9 – 3.9)	22% (3.2% – 41%)	11% (0% – 29.3%)
OS	4.6 (3.4 – 6.2)	55% (33% – 77%)	33% (12% – 55%)

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

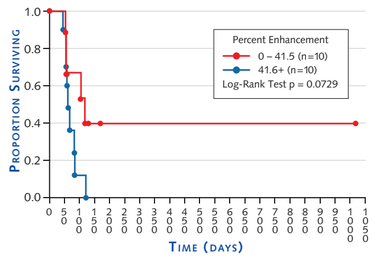


Volumetric Studies

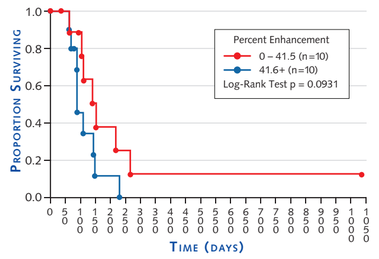
- Total tumor volume and percent enhancing region for each patient for whom data were available are shown in table below. Exploratory analyses were conducted.
- An exploratory analysis of PFS and OS stratified by percent enhancement at the median value is presented below using the Kaplan-Meier method. Separation of the survival curves suggests trends that percent enhancement may be prognostic for progression-free survival and overall survival. These results are consistent with those found using a Cox proportional hazards model.
- Tumor volume was not identified as a significant prognostic factor for either PFS or OS.

Patient Number	Dose (mg/m²)	Tumor Volume	% Enhancing	Best Response
1	240	102.17	0	SD
2	240	NA	NA	PR
3	240	157	33.12	SD
4	340	353.51	72.28	SD
5	340	1.71	0	PR
9	340	154.05	65.16	SD
10	480	11.75	42.05	SD
12	480	46.17	59.23	PD
14	480	NA	89	PD
15	480	6.22	38.26	PD
16	670	18.14	41.79	PD
17	670	89.54	48.96	CR
18	670	57.19	33.92	SD
19	670	84.08	30.28	SD
20	670	33.45	67.46	SD
21	670	NA	NA	PR
22	670	211.61	8.23	PD
23	670	72.06	5.21	PD
24	670	82.44	77.36	PD
25	670	30.9	32.29	SD
26	670	NA	NA	SD
27	670	62	87.42	PD
28	670	42.57	41.11	NA

Progression-Free Survival



Overall Survival



Summary

In Patients with Bevacizumab-Refractory Recurrent Glioblastoma:

- TH-302 has a manageable safety profile when used in combination with bev:
  - Recommended Phase 2 dose 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=22 evaluable patients) were observed:
  - 18% objective response rate (1 CR, 3 PR).
  - Median PFS 2.8 mos in bev/TH-302 combination.
  - Longer than the historically reported median PFS of 1 to 2 months following administration of a second bev regimen[2-4].
  - Some patients with large tumor volumes at the beginning of TH-302/bev therapy achieved stable disease as best response.
- Exploratory analyses suggest trends towards increased PFS and OS for patients whose tumors showed greater percent non-enhancement at the beginning of treatment with TH-302/bev.
- A Phase 2 Investigator-Sponsored trial will investigate 670 mg/m² TH-302 in combination with bev in up to 33 patients with recurrent GBM following bev failure.

References: **1.** Friedman HS, et al. *J Clin Oncol 27*:4733-4740, 2009. **2.** Quant EC, et al. *Neuro-Oncology 11*:550–555, 2009. **3.** Iwamoto FM, et al. *Neurology 73*:1200-1206, 2009. **4.** Reardon DA, et al. *Cancer 117(23)*:5351-5358, 2011. **5.** Rong Y et al. *Neuropathol Exp Neurol*:529-39, 2006. **6.** Spence AM, *Clin Cancer Res 14(9)*:2623-30, 2008. **7.** Rapisarda A, et al. *Mol Cancer Ther* 8:1867-1877, 2009.

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