A dual phase I/II study of TH-302 and bevacizumab in resectable recurrent glioblastoma following single-agent bevacizumab failure

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Introduction

Glioblastoma (GBM) remains an incurable malignancy with poor survival despite resection and chemoradiation. Initially, when GBM recurs, the standard salvage therapy is recombinant human monoclonal anti-VEGF antibody bevacizumab, which offers a median progression free survival (PFS) of 4.2 months. Limited data suggest marginally improved survival outcomes as well for those who continue on a third line salvage regimen containing bevacizumab, despite failure of single-agent bevacizumab.

Hypoxic necrotic foci with pseudopalisading tumor cells are hallmarks of GBM. Antiangiogenic treatment has been shown in some studies to reduce perfusion and increase hypoxia in the tumor microenvironment. Hypoxia promotes more aggressive and invasive tumor phenotypes and has been associated with resistance to radiation and chemotherapies, as well as poor patient survival. Thus, given the hypoxic nature of GBM and exacerbation of hypoxia by bevacizumab, the use of agents that have specific activity in the hypoxic tumor environment may be of benefit in patients who have failed single-agent bevacizumab therapy.

TH-302 Profile

TH-302 is a hypoxia-activated prodrug that, when activated, releases the bis-alkylating agent Br-IPM. *In vivo*, this drug has shown to potentiate, the anti-tumor efficacy of other antiangiogenic agents. It is not a substrate for common efflux pumps or key cytochrome P450 enzymes. It is activated by a process that involves a one electron reduction to generate a radical anion prodrug (RP). Under normoxic conditions TH-302 remains inert and intact as a prodrug but when exposed to severe hypoxic conditions (<0.5% O2), the RP can fragment, and release Br-IPM which can then act as a DNA crosslinking agent (Figure 1 below).

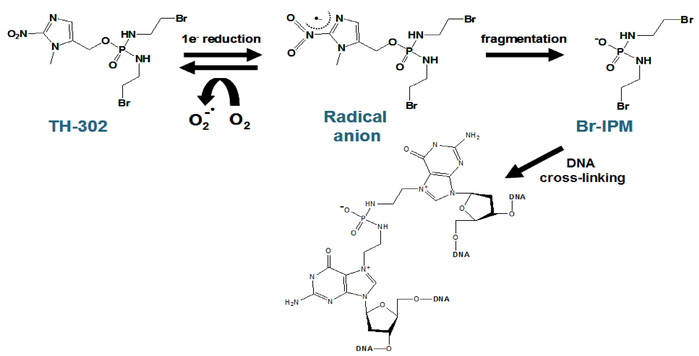


Figure 1. Hypoxia-Activated Drug TH-302. Mechansim of prodrug activation and action of released toxin on DNA.

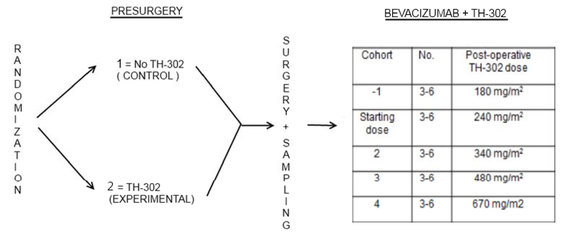
Study Objectives

Primary Objectives are:
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 in patients with glioblastoma undergoing surgery
To assess the safety of TH-302 in combination with bevacizumab for patients with glioblastoma
To determine the MTD and DLT(s) of TH-302 in combination with bevacizumab

Secondary Objectives are:
To determine the progression-free survival after debulking craniotomy for patients treated with combination bevacizumab and TH-302 following recurrence on single agent bevacizumab

Study Design

Single center, dose-escalation, prospective study with randomized in a 2 to 1 ratio to TH-302 single dose of 575 mg/m^2 versus placebo administered pre-operatively, followed by postoperative combination therapy of bevacizumab at 10 mg/m^2 every 2 weeks and TH-302 dose escalated 240-480 mg/m^2 (depending on dose escalation cohort) every 2 weeks (4 week cycle) until disease progression. Resected tumor tissue was evaluated for hypoxia induced pimonidazole (PIMO) adducts, endogenous CAIX staining, DNA damage by γH2AX, apoptosis by TUNEL, and MGMT expression. Hypoxic fraction (HF) was evaluated as the percentage of PIMO (or CAIX)-positive area in the whole tumor sample.



Cohort	No.	Post-operative TH-302 dose
-1	3-6	180 mg/m^2
Starting dose	3-6	240 mg/m^2
2	3-6	340 mg/m^2
3	3-6	480 mg/m^2
4	3-6	670 mg/m2

Figure 2. Design schema for presurgical dosing, followed by dose escalation.

Results

- 12 patients have been enrolled and underwent craniotomy, 4 receiving placebo prior to surgery and 8 receiving TH-302.
- 8 patients went on to post-surgical treatment with bevacizumab and TH-302 under dose escalation.
- 2 patients withdrew consent after surgery, and 2 failed to recover sufficiently to meet ongoing eligibility criteria.
- No DLTs occurred at 240mg/m^2 or 340mg/m^2; the third cohort at 480mg/m^2 is ongoing.
- No grade 3 or 4 adverse events (AEs) were reported at 240 mg/m2; one grade 3 (skin ulceration) and no grade 4 AEs were reported at 340 mg/m^2 to date. The primary TH-302 related toxicities were mucosal which have been managed conservatively.
- Extensive areas of hypoxia were observed by immunohistochemistry in surgical specimens (Figure 3 and 4a) and there was a strong concordance between both exogenous (pimonidazole) and endogeous (CAIX) markers of hypoxia (Figure 4 b) in serial sections.
- 6 patients were evaluable for response, with 1 unconfirmed partial response (Figure 5) and 4 demonstrating stable disease (Figure 6 and Table 1) .
- The longest disease stabilization is currently ongoing at 9.1 months and receiving cycle 10 (Figure 7).

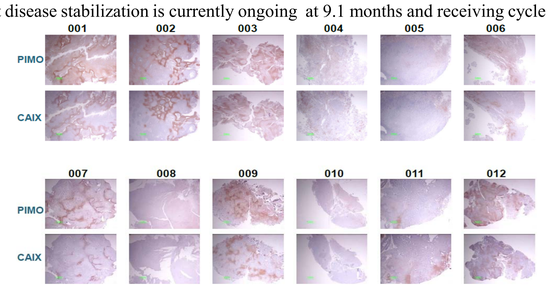


Figure 3. IHC of surgical specimens for pimonidazole and CAIX

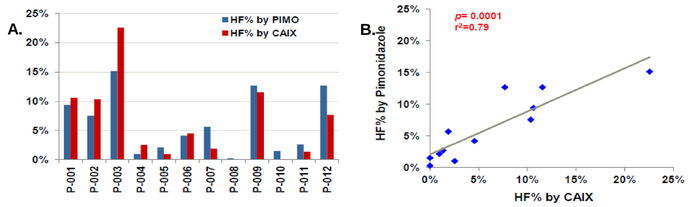


Figure 4. Quantification of hypoxic fraction by Image ProPlus (**A**) and scatterplot with R^2 and p-value of null hypothesis of no correlation (**B**).

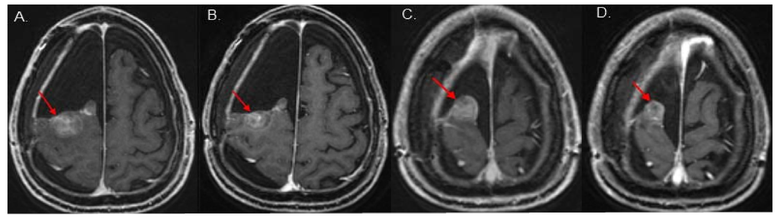


Figure 5. MRI response in a patient who progressed rapidly on 3 prior therapies, including bevacizumab. A. Primary lesion, day -1. B. Primary lesion, day 56. C. Satellite lesion, day -1. D. Satellite lesion, day 56.

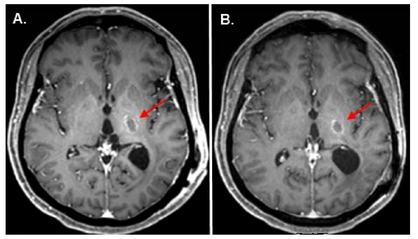


Figure 6. MRI demonstrating an unresectable lesion in the left thalamus progressing on bevacizumab at C1D0 (A) and after 10 cycles of TH-302 (340mg/m^2) with bevacizumab (B).

Patients Evaluable for Response (N=6)	Median	Range
Age (years)	48.5	(43-70)
# Prior therapies	**3**	**(2-4)**
TTP-1st line chemo-RT (days)	307.5	(81-435)
TTP-1st bevacizumab regimen (days)	**89.5**	**(24-206)**
TTP on TH-302 (days)	128*&	(59-275+)
Overall survival (days)	**175*&**	**(65-275+)**
Stable disease	4	
Unconfirmed Partial response	**1**	

Table 1. Patients' progression times for this study and prior treatments. *ongoing; &TTP and OS was defined from the post-surgical C1D0 MRI target lesion, not presurgical MRI

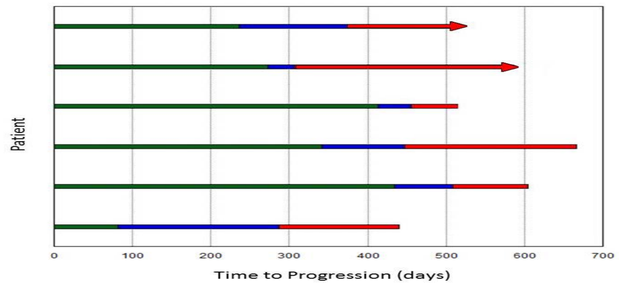


Figure 7. Time to progression by therapy for the 6 patients on the first two cohorts. Closed bars indicate off study. Arrows indicate ongoing. Green=TMZ+XRT; Blue=Bev; Red=TH302+Bev

Conclusions

- TH-302 has shown a manageable toxicity profile when used in combination with bevacizumab, with no dose limiting toxicities observed at doses up to 340mg/m^2. Most toxicity was mild and involved the mucosa, and was managed with conservative measures. Dose escalation is ongoing.
- Extensive tumor hypoxia was observed in resected specimens using both exogenous and endogenous markers. This may allow hypoxia identification based on an endogenous marker.
- Median TTP of TH-302 plus bevacizumab for the first two cohorts was 128+ days , which is longer than the TTP these same patients experienced on their 1st bevacizumab regimen, significantly longer than the reported 37.5 days for a second bevacizumab regimen historical control, and suggests clinical activity of TH-302 plus bevacizumab in recurrent glioblastoma after bevacizumab failure.
- The high degree of concordance between both markers of hypoxia suggests either may be suitable for future clinical study, and merit further investigation for predictive potential.

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