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Phase II Study of TRC102 in Combination with Temozolomide for Recurrent Glioblastoma

A Protocol of the Adult Brain Tumor Consortium (ABTC)

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1.0 OBJECTIVES

Primary Objectives

Arm 1

- To estimate the efficacy of TRC102 and temozolomide, as measured by response rate, in bevacizumab naïve glioblastoma

Arm 2 (opens only if Arm 1 meets efficacy criteria)

- To estimate the efficacy of TRC102 and temozolomide, as measured by response rate, in bevacizumab refractory glioblastoma

Secondary Objectives

1. Evaluate the toxicities of oral TRC102 and temozolomide in this patient population
2. Estimate the efficacy of TRC102 and temozolomide, as measured by progression-free survival, progression-free survival at 6 months and overall survival, in bevacizumab naïve glioblastoma
3. Estimate the efficacy of TRC102 and temozolomide, as measured by progression-free survival in bevacizumab refractory glioblastoma

Exploratory Objective

- Assess the tissue correlates of methylpurine DNA-glycosylase (MPG) and topoisomerase II α (Topo II α), and O⁶-methylguanine DNA methyltransferase (MGMT) status, with response, PFS, and overall survival

2.0 BACKGROUND AND RATIONALE

2.1 Glioblastoma

Although the recent addition of temozolomide (TMZ) to radiation therapy for the treatment of glioblastoma (GBM) has resulted in improved outcomes, the estimated 2-year survival with maximal therapy remains only 27% (Stupp 2005, Stupp 2009). Almost all GBMs progress, with a median time to progression of approximately 7 months. The prognosis is very poor for patients who have progressive/recurrent GBM. There is currently no standard therapy for recurrence. Salvage chemotherapies are largely ineffective, with progression-free survival at 6 months (PFS6) rates of 10-15%. Bevacizumab therapy at recurrence is associated with a high response rate, but not significantly increased survival. Survival after failure of bevacizumab administered for GBM recurrence is very poor with a median survival of 4-6 months and PFS 6 of 0 (Reardon 2012). Hence, new therapies for recurrent GBM are urgently needed.

2.2 TRC102

An NCI phase I study of TRC102 and temozolomide in relapsed solid tumors and lymphomas evaluated the safety of the combination of TRC102 and temozolomide (P9483, NCT01851369). Based on this dose escalation trial, the recommended doses for the phase II study are 150mg/m² for temozolomide and 150mg flat dose for TRC102. No dose limiting toxicity was seen at 150mg/m² of temozolomide and a TRC102 dose of 150mg administered days 1-5 of a 28-day cycle (personal communication, Naoko Takebe). We propose to evaluate efficacy of TRC102 at 150mg flat dose combined with TMZ 150mg/m² in a phase II trial of recurrent GBM.

We hypothesize that oral TRC102 can be safely administered with TMZ and that it will potentiate DNA damage caused by TMZ, resulting in increased tumor response and improved survival as compared with historic controls. A dose escalation trial of intravenous TRC102 in combination with TMZ has been performed in relapsed systemic and central nervous system tumors at Case Comprehensive Cancer Center. A variety of dose-intense schedules of TMZ at recurrence have been evaluated. As compared with the standard 5 days every 28 days schedule, the dose- intense regimens have not shown greater efficacy and are associated with increased incidence and severity of lymphocytopenia (Weller 2013.). Therefore, we selected the standard schedule of TMZ.

We hypothesize that biologic markers obtained in tumor tissue collected at the time of tumor progression will correlate with treatment response. N-methylpurine DNA glycosylase (MPG) overexpression, together with inhibition of base excision repair (BER), sensitizes glioma cells to TMZ (Tang 2011). As an exploratory aim, we propose to determine expression of MPG by IHC in resected tumor tissue from initial diagnosis, and correlate this with treatment response, a design similar to the study of Weeks et al (Weeks 2013) in which expression of uracil-DNA glycosylase in lung cancer was found to correlate with pemetrexed response. Because overexpression of topoisomerase 2a

(topo2a) correlates with increased sensitivity to the TRC102 potentiation of cytotoxicity of DNA damaging agents, we propose to determine expression of topo2a in resected tumor tissue and correlate its expression with treatment response. O⁶-methylguanine DNA methyltransferase (MGMT) is a strong predictor of response to TMZ. MGMT methylation status will be collected to correlate response with TMZ, independent of TRC102 co-administration.

Resistance to TMZ

A major obstacle to effective treatment with TMZ in GBM is the presence of elaborate mechanisms of DNA repair. For instance, TMZ forms O⁶-methylguanine (O⁶mG), 7-methylguanine (N⁷mG), and 3-methyladenine (N³mA) DNA adducts that are repaired by at least two mechanisms. The O⁶mG DNA adduct, a cytotoxic and genotoxic lesion, is repaired by MGMT. MGMT activity is a major mechanism of resistance to methylating agents. In contrast, cell death caused by O⁶mG adducts is promoted by mismatch repair (MMR) system, such that deficiency in MMR is associated with pronounced resistance to methylating agents. N⁷mG and N³mA DNA adducts are removed by the BER pathway (Liu 1999, Liu 2002).

Base excision repair (BER) pathway

BER is an important drug resistant factor because it recognizes a variety of substrates and has the ability to rapidly and efficiently repair N⁷mG and N³mA DNA adducts. BER is the major pathway that protects cells against the potentially harmful effects of spontaneously and chemically occurring DNA damage, including (i) inappropriate bases; (ii) abasic sites that are formed by enzyme-catalyzed, spontaneous or chemical-induced base release; and (iii) DNA single strand breaks produced during the processing of damaged DNA. Efficient BER minimizes the impact of these lesions in normal and tumor cells. Thus, when BER is disrupted, these abundant N-methylated DNA adducts and intermediates generated in the repair process become highly cytotoxic. Most importantly, BER disruption is able to bypass other resistance factors such as MMR defects and high MGMT activity.

Base excision repair efficiently repairs DNA bases through a series of enzymatic steps, starting with the action of a glycosylase to excise the damaged base. TRC102 interrupts this process because TRC102 binds to the apurinic site created through the action of the glycosylase, thereby interrupting normal repair. As well, TRC102 bound DNA is a substrate for topo IIa which results in DNA strand breaks that then trigger cellular apoptosis.

Introduction to TRC102

TRC102 (NSC-3801), a biochemical inhibitor of the BER pathway developed and studied by investigators from Case Comprehensive Cancer Center (CCCC), Cleveland Ohio, reverses TMZ resistance in preclinical models at doses that are well tolerated. The ability of TRC102 to interrupt the BER pathway was demonstrated *in vitro* (Yan 2007).

Pharmacology studies demonstrated its ability to inhibit BER induced by treatment with alkylating agents, including TMZ, and anti-metabolite chemotherapy. When administered with TMZ, TRC102 covalently binds to apurinic/apyrimidinic (AP) sites generated by DNA glycosylase, in an attempt to replace DNA bases damaged by TMZ. TRC102-bound AP sites are refractory to the catalytic activity of the apurinic/apyrimidinic endonuclease (APE), leading to the interruption of BER.

Available data support the hypothesis that TRC102-bound DNA is a substrate for topo II, which cleaves TRC102-bound DNA sites to produce strand breaks in cancer cells that cause cellular apoptosis.

As a result, TRC102 is able to potentiate the activity of TMZ (and other chemotherapeutics that activate the BER pathway) in cancer cells that express high levels of topo II (both *in vitro* and *in vivo*), without increasing toxicity in non-cancer cells (i.e., bone marrow cells) that express low levels of topo II.

Activity of TRC102 in Combination with Alkylating Chemotherapy

The ability of TRC102 to potentiate chemotherapy was initially demonstrated using TMZ (Li 1999, Liu 2002, Taverna 2001). Collectively, the available data indicate that treatment of cancer cells with TMZ produced N⁷-methylguanine and N³-methyladenine DNA adducts that activated BER to generate AP sites within double-stranded DNA. TRC102 bound covalently to AP sites to form structurally modified AP sites that were then resistant to the repair activity of APE. The persistence of these lesions led to cell death through the generation of DNA strand breaks.

The lethal toxicity induced by TMZ combined with TRC102 appears to be mediated through the poisoning effect of topo II. While TRC102-bound AP sites are refractory to the catalytic activity of APE (indicating their ability to block BER), they are cleaved by purified topo II or nuclear extracts from tumor cells expressing high levels of topo II, suggesting that TRC102-bound AP sites stimulate topo II-mediated DNA cleavage .

Furthermore, cells treated with TMZ and TRC102 demonstrate increased expression of topo II and increased formation of γ -H2AX foci (a marker of DNA double strand breaks) that co-localizes with up-regulated topo II. The cleavage of TRC102-bound AP sites by topo II also explains the ability of TRC102 to potentiate the effects of TMZ in cancer cells (that have high levels of topo II) compared to normal cells (which have low levels of topo II). For example, *in vitro* addition of TRC102 effectively sensitized tumor cells, but not bone marrow cells, to the effects of TMZ

Several preclinical studies have demonstrated improved therapeutic efficacy of alkylating agents by blocking BER with TRC102. *In vivo* studies have shown that TRC102 potentiates the antitumor effect of TMZ in human tumor xenografts in nude mice. Mice carrying SW480 tumor (AGT expressing, MMR wt and p53 mutant) that were resistant to treatment with TMZ alone had cessation of tumor growth lasting 50 ± 13 days and very slow regrowth when treated with TRC102 (2 mg/kg) plus TMZ (120 mg/kg), yielding tumor growth delays of 70 ± 14 days ($p < 0.002$) compared with untreated tumors. Tumor

regression following treatment with TMZ and TRC102 treatment reflected DNA strand breaks and a significant increase in tumor apoptosis. Therefore, TRC102 inhibition of DNA BER is a promising strategy to sensitize tumor cells to therapeutic alkylating agents.

In the first in human phase I clinical trial, TRC102 was administered as a 5-day intravenous continuous infusion based on animal data. Dosing started at 15 mg/m² TRC102 daily for 5 days and plasma samples were collected and analyzed for TRC102 using validated methods. Pharmacokinetic parameters were derived using a single compartment intravenous infusion model and plasma TRC102 concentrations from 5 patients across 15 dosing cycles. Pharmacokinetic studies demonstrated an unexpected prolonged half-life of TRC102, estimated to be 45 hours (range: 32.1 - 68.8 hours) which represents a 10-fold increase when compared to the TRC102 half-life observed in dogs ($t_{1/2}$ = 4.5 hours) and a 143-fold increase when compared to the half-life observed in rats ($t_{1/2}$ = 19 min). The volume of distribution (Vss) was estimated to be 1,437 L and the clearance (CL) was estimated to be 22.47 L/h. The C_{max} (across all patients) was 41.4 ng/mL. Individual pharmacokinetic exposures and derived PK parameters demonstrated very little intra- and interpatient variability. (Savvides (a) abstract) The protocol was therefore revised with TRC102 administered as one hour continuous infusion. The average half-life of TRC102 at this schedule was 55.04 hours (range: 12.2 - 100.3 hours, n = 20), statistically not different from half-life of TRC102 administered as a five-day continuous infusion (Savvides (b) abstract).

Subsequently PK of the oral formulation of TRC102 was assessed in a phase I study of TRC102 and pemetrexed in advanced solid tumors. TRC102 was administered as monotherapy on days 1 to 4 of a two-week cycle. Plasma for PK parameters was collected prior to dosing and 5, 15, and 30 minutes, and one, 2, 3, 4, 6, 8, and 24 hours following the first and fourth doses of TRC102. The overall mean half-life of 28 hours was unchanged with increasing doses or cycle and the exposure increased proportionally with dose. The target AUC was exceeded in all patients who received at least 4 doses of TRC102. TRC102 accumulated with daily dosing. The target C_{max} of 50 ng/mL for in vivo activity was achieved by the fourth daily dose in 2 of 3 patients at 15 mg/M²/day and in all patients receiving 30 mg/M²/day and higher doses. The variability and PKs between patients were significantly influenced by both gender and baseline serum creatinine (Gordon 2012).

Pharmacodynamic markers, including analysis of AP sites measured on DNA extracted from patients' mononuclear cells (PBMCs) as well as DNA strand break determined by comet assay at multiple time points were obtained in the Phase I clinical trial of TRC102 and TMZ. PD results, performed on 22 patients, showed that administration of the combination of TMZ and TRC102 resulted in 10-40% reduction in detectable AP sites. Comet assay results, performed on 20 patients revealed that the combination of TMZ and TRC102 2 to 3-fold higher levels of DNA strand breaks compared to TMZ alone (Savvides (a) abstract).

In several preclinical studies of human tumor xenografts in nude mice, improved therapeutic efficacy of TMZ by blocking BER with TRC102 has been demonstrated. Mice carrying SW480 colon cancer tumors (MGMT-expressing, MMR wt and p53 mutant) treated with TRC102 (2 mg/kg) plus TMZ (120 mg/kg) had cessation of tumor growth lasting 50 ± 13 days and very slow regrowth, yielding tumor growth delays of 70 ± 14 days ($p < 0.002$) compared with untreated tumors. Importantly, a survival benefit from TMZ combined with TRC102 has been demonstrated in CD133+ GBM stem cell orthotopic xenografts in mice. Combination therapy significantly ($p < .001$) increased the median survival (not reached after 230 days, with 65% survival at this time point) as compared with MX alone (79 days) and saline controls (75 days). Survival after the combination treatment was also significantly (< 0.01) better than TMZ alone (120 days) (Figure 1, unpublished data courtesy, Andrew Sloan, University Hospital-Case Medical Center, Cleveland, Ohio).

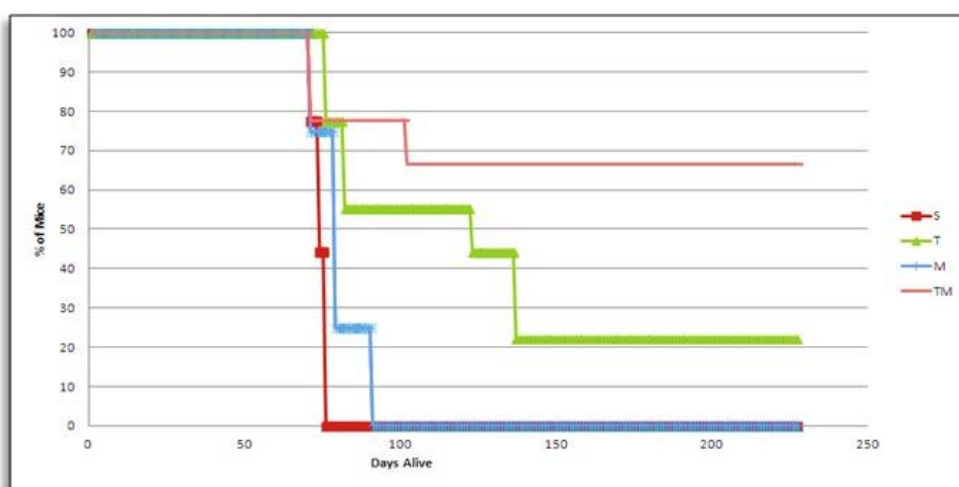


Figure 1. Survival of CD 133+ GBM CW 357 orthotopic xenografts receiving varying treatments: S= saline (control), T=TMZ (75 mg/kg), M = TRC102 alone, TM = TMZ + TRC102.

The first in human Phase I trial of intravenous TRC102 and TMZ is ongoing at CCCC in relapsed solid tumor patients (Arm A) and in relapsed CNS tumor (primary and metastatic) patients (Arm B) (Principal Investigator Lisa Rogers). The escalation dose of TMZ in Arm A is from 100 to 200 mg/m²/day in combination with TRC102 dose escalation from 15 to 150 mg/ m²/day, each given days 1-5 every 28 days. The current Arm A cohort is dosed at 200mg/m²/day TMZ and 150 mg/ m²/day TRC102). The Arm B design and doses are identical, except that TMZ dose escalation begins at 75 mg/ m²/day (Table 1). The Arm B cohort is currently dosed at 150mg/m² of TMZ and 120mg/ m² of TRC102. Of note, these studies employ the intravenous formulation of TRC102, not the oral formulation as proposed in this protocol.

Early results of this trial were presented at AACR in 2012 (Savvides (b) abstract). In Arm A, grade 3 psychoses at 15mg/m² TRC102 occurred in a patient with Parkinson disease on increasing opioid doses. A grade 3 allergic reaction classified as an idiosyncratic event

resulted in further expansion to 10 evaluable patients, with no additional DLTs observed. No DLTs have been observed in Arm B. The best response in Arm B is partial response in one patient with GBM and stable disease in head/neck squamous cell brain metastasis, off treatment for 24 months.

2.3 Rationale

TRC102 reverses TMZ resistance in preclinical models at doses that are well tolerated. When administered with TMZ, TRC102 covalently binds to apurinic/apyrimidinic (AP) sites which are generated by DNA glycosylase in an attempt to replace DNA bases damaged by TMZ. TRC102-bound AP sites are refractory to the catalytic activity of the apurinic/apyrimidinic endonuclease (APE), leading to the interruption of BER. Moreover, TRC102-bound DNA causes topoisomerase II dependent DNA strand breaks that induce apoptosis. TRC102 is selective for rapidly dividing cancer cells as these cells express higher levels of topoisomerase II compared with normal cells. Therefore we propose a trial of TMZ and TRC102 in patients with recurrent GBM who have failed prior TMZ.

3.0 PATIENT ELIGIBILITY CRITERIA

3.1 Patient Sample

Sample Size:

Arm 1: 31 bevacizumab-naïve patients

Arm 2: 35 bevacizumab-refractory patients

Accrual Rate:

4-5 patients per month

Gender:

Male and female

Age:

Patients must be at least 18 years of age.

Race:

Minorities will be actively recruited. No exclusion to this study will be based on race or ethnicity.

3.2 Eligibility Criteria

1. Patients must have histologically confirmed glioblastoma that is progressive or recurrent following radiation therapy and temozolomide.
2. Tumor MGMT methylation status must be available. Results of routinely used methods for MGMT methylation testing (e.g. MSPCR or quantitative PCR) are acceptable.
3. Arm 1 patients must have measurable (defined by at least 1 cm x 1 cm) contrast-enhancing disease by MRI imaging within 21 days of starting treatment.
4. Patients must be able to undergo MRI of the brain with gadolinium. Patients must be maintained on a stable or decreasing dose of corticosteroid regimen (no increase for 5 days) prior to this baseline MRI.

5. Arm 1 patients must be in first recurrence of glioblastoma following radiation therapy and temozolomide.
Arm 2 patients may have an unlimited number of prior therapy regimens but may not have received prior antiangiogenesis therapy except for bevacizumab (patients may not have received aflibercept, ramucirumab, cediranib, cabozantinib, or XL184).
6. Arm 1 patients must have not received bevacizumab previously.
Arm 2 patients must have progressed/recurred on bevacizumab as the most recent regimen. Patients on Arm 2 should continue on bevacizumab as clinically necessary to control brain edema.
7. Patients must have a tumor tissue form indicating availability of archived tissue from initial resection at diagnosis of glioblastoma completed and signed by a pathologist. See Section [9.5.1](#). Availability of tissue is not a requirement for study participation.
8. Patients must have recovered from severe toxicity of prior therapy. The following intervals from previous treatments are required to be eligible:
 - 12 weeks from the completion of radiation
 - 6 weeks from a nitrosourea chemotherapy
 - 3 weeks from a non-nitrosourea chemotherapy
 - 4 weeks from any investigational (not FDA-approved) agents
 - 2 weeks from administration of a non-cytotoxic, FDA-approved agent (e.g., erlotinib, hydroxychloroquine, etc.)
9. Patients must be 18 years of age or older.
10. Patients must have a Karnofsky Performance Status $\geq 60\%$ (i.e. the patient must be able to care for himself/herself with occasional help from others).
11. Patients must have the following organ and marrow function:

Absolute neutrophil count	$\geq 1,500/\text{mcL}$
Platelets	$\geq 100,000/\text{mcL}$
Hemoglobin	$\geq 9 \text{ g/dL}$
Total bilirubin	\leq institutional upper limit of normal
AST (SGOT)/ALT (SGPT)	$\leq 4 \times$ institutional upper limit of normal
Creatinine	\leq institutional upper limit of normal
	OR
Creatinine clearance	$\geq 60 \text{ ml/min/1.73m}^2$ for patients with creatinine levels above institutional normal
APTT or PTT	$\leq 1.5 \times$ institutional upper limit of normal
12. Patients must be able to provide written informed consent.

13. Women of childbearing potential must have a negative serum pregnancy test prior to study start. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and through 30 days after the last dose of study drug. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and through 30 days after the last dose of study drug.
14. Patients must have no concurrent malignancy except curatively treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix, breast, or bladder. Patients with prior malignancies must be disease-free for \geq five years.
15. Patients must be able to swallow capsules.

3.3 Ineligibility Criteria

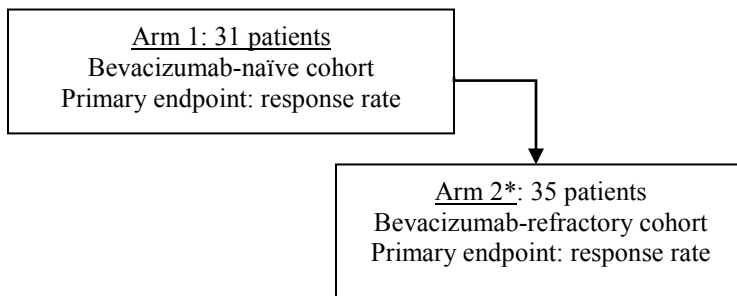
1. Patients receiving any other investigational agents are ineligible.
2. Patient must not have known sensitivity to TRC102 or any formulation excipients.
3. Patients on enzyme-inducing anti-epileptic drugs (EIAED) are not eligible for treatment on this protocol. Patients may be on non-enzyme inducing anti-epileptic drugs or not be taking any anti-epileptic drugs. Patients previously treated with EIAED may be enrolled if they have been off the EIAED for 10 days or more prior to the first dose of TRC102.
4. Patients must not be on any anticoagulation.
5. Patient must not have prior gastrointestinal (GI) surgery or GI disease that might interfere with the absorption of TRC102.
6. Patients who have not recovered to $<$ CTCAE grade 2 toxicities related to prior therapy are ineligible.
7. Patients must not have active brain metastases from a systemic solid tumor.
8. Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, clinically significant cardiac disease, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements, are ineligible.

9. Pregnant women are excluded from this study because TRC102 has potential for teratogenic or abortifacients effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with TRC102, breastfeeding should be discontinued if the mother is treated with TRC102.
10. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with TRC102. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

4.0 TREATMENT PLAN

This is a Phase II, open-label, multicenter study of TRC102 in patients with recurrent glioblastoma. All subjects must have had histological confirmation of glioblastoma by either biopsy or resection that is progressive or recurrent following radiation therapy + temozolomide.

This phase II trial will be performed in 2 sequential arms: the first arm of bevacizumab-naïve patients and the second arm of bevacizumab-failure patients.



** Arm 2 (bevacizumab refractory cohort) will only activate if Arm 1 (bevacizumab-naïve cohort) meets the statistical criteria of efficacy. See Section [11.0](#), Statistical Considerations.*

4.1 Treatment Schema

Arm 1: Bevacizumab-naïve patients

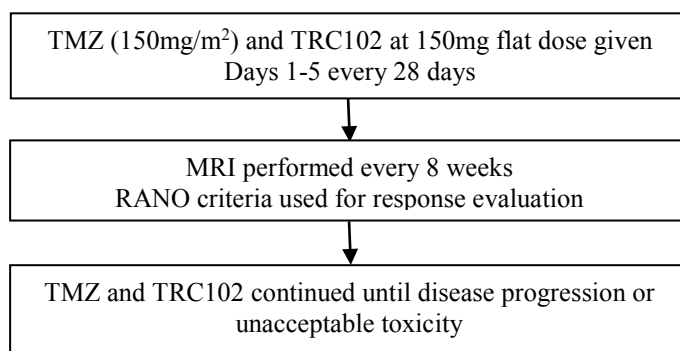
Arm 1 will estimate the efficacy of TRC102 and temozolomide (TMZ), as measured by response rate, in bevacizumab-naïve glioblastoma (patients may not have received prior treatment with bevacizumab).

Arm 2: bevacizumab-refractory patients

(This arm will only activate if Arm 1 meets the statistical criteria of efficacy as defined in Section [11.0](#))

Arm 2 will estimate the efficacy of TRC102 and TMZ, as measured by response rate, in bevacizumab-refractory glioblastoma (patients must have progressed/recurred following prior treatment with bevacizumab but should continue receiving bevacizumab as clinically indicated).

All patients will receive the maximum tolerated dose of oral TRC102 as determined in the NCI phase I trial, 150mg flat dose, combined with temozolomide 150mg/m² on days 1-5 every 28 days. The dose of temozolomide will remain at 150 mg/m² throughout the study.



TRC102 and TMZ are being given together as a combined treatment. If for any reason a patient is permanently taken off TRC102 or TMZ the patient will be off treatment.

An MRI will be performed prior to every odd-numbered cycle (every 8 weeks).

Patients will continue receiving TRC102 and TMZ until they meet the criteria for disease progression or other criteria for going off treatment (Section [10.0](#)). All patients will be followed for survival.

4.2 Treatment Requirements

All eligible patients who consent to this study must have a baseline (post-operative, if surgery is applicable) pre-treatment MRI. This baseline scan must be done within 21 days prior to the initiation of treatment.

Prior to every cycle patients must have:

- 1) ANC \geq 1500/ μ l and platelets \geq 100,000 / μ l.
AND
- 2) All toxicities recovered to \leq grade 1 [or tolerable grade 2 for non-hematologic toxicity] or \leq baseline.

4.3 Drug Administration

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Treatment will be administered on an outpatient basis. Patients will be provided with medication diaries and instructed in their use. Patients will be instructed to bring all unused medication and their diaries to each study visit for assessment of compliance.

4.3.1 TRC102 Administration

TRC102 will be administered on an outpatient basis once daily as an oral dose of 150mg flat dose given for 5 consecutive days every 4 weeks. Patients should take the dose approximately the same time each day, in the morning, at the same time as the temozolomide dose.

Drug should be taken on an empty stomach, 1 hour before a meal or 2 hours after a meal. Take with 8 ounces of water. Capsules should be swallowed whole, do not chew or crush.

If a patient misses or vomits a dose, he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed or vomited doses should not be made up. A dose will be considered missed, and should not be made up, if more than 6 hours have passed from the time the dose is normally taken.

4.3.2 Temozolomide Administration

Temozolomide will be administered orally once a day for 5 consecutive days and repeated every 28 days. The dose will be 150 mg/m²/day.

The dose administered will be determined using the body surface area (BSA) calculated at the beginning of each cycle. The BSA will be calculated from the height obtained at the baseline evaluation and from the weight obtained at the most recent pre-odd-numbered cycle evaluation before each 5-day TMZ treatment. Prior to each 5-day treatment with temozolomide a complete blood count (CBC) has to be obtained (within -5 days prior to dosing). The start of all 5-day TMZ treatments will be scheduled every 4 weeks (28 days, +3 days) after the first daily dose of temozolomide of the preceding 5-day treatment.

If liver function tests (alkaline phosphatase, total bilirubin, SGOT, SGPT) are abnormal, the decision to initiate temozolomide treatment should carefully consider the benefits and risks for the individual patient. For patients with significant liver function abnormalities, the benefits and risks of continuing treatment should be carefully considered.

Blood counts will be evaluated weekly. Within -5 days prior to the first dose of each 5-day TMZ treatment, the patient must have an ANC \geq 1500/ul and platelet count \geq 100,000/ul. On Day 1 of each cycle (within -5 days) all **non-hematological** toxicity grades 3 or 4 (except for alopecia, nausea and vomiting), related at least possibly to TMZ must have resolved (CTCAE grade \leq 1 [or tolerable grade 2]). If toxicity persists, treatment should be delayed by one week for up to 3 consecutive weeks and directions for dose reduction should be followed (see Section 5.2). If after 3 weeks of delay all toxicity has still not resolved then any further adjuvant treatment with temozolomide should be stopped (patient is off treatment).

For this study of the combination treatment of temozolomide and TRC102, the dose of temozolomide will remain at 150mg/m² for the duration of the study and not escalate to 200 mg/m². If during the first cycle the patient experiences **platelets < 50,000/ul and/or**

ANC < 1000/ul and/or a non-hematologic toxicity \geq grade 3 then patient should follow directions for dose reduction in Section [5.2](#).

Capsules of temozolomide are available in 5, 20, 100, 140, 180, 250 mg strengths. The daily dose will be rounded to the nearest 10 mg. The exact dose administered should be recorded in the CRF. Each daily dose should be given with the least number of capsules.

Temozolomide should be taken at the same time as TRC102 capsules on an empty stomach, 1 hour before a meal or 2 hours after a meal. Take with 8 ounces of water. Patients should be told to swallow the whole capsules in rapid succession without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. Missed doses should not be made up. A dose will be considered missed, and should not be made up, if more than 6 hours have passed from the time the dose is normally taken.

Antiemetic prophylaxis with a 5-HT₃-antagonist is strongly recommended.

4.4 General Concomitant Medication and Supportive Care Guidelines

Prohibited Concomitant Medication During Study

Patients may receive other medications that the investigator deems to be medically necessary, with the specific exception of non-protocol specified chemotherapy, radiotherapy, anti-neoplastic biological therapy or other investigational agents. Patients who require the use of any of the aforementioned treatments for clinical management should be removed from the study.

Anticoagulants

Patients may not be on anticoagulation at study start but may be treated with anticoagulation therapy for medical reasons that occur on study.

Corticosteroids

Postoperatively, corticosteroids should be tapered to a stable dose as determined by the clinical status of the patient. The lowest required steroid dose should be maintained throughout the duration of the study in order to eliminate steroid effects as a confounding variable in the interpretation of serial brain imaging studies. Corticosteroid doses can be tapered as clinically indicated if the patient appears to be responding to therapy as judged by serial scans. Corticosteroid dose may, of course, be increased in the event of clinical deterioration or at the discretion of the attending physician. In the event of suspected clinical deterioration, repeat brain imaging is recommended.

Anticonvulsants

No data exist regarding the interaction of TRC102 with enzyme-inducing anti-epileptic drugs (EIAEDs). For this study, patients may **not** be on EIAEDs; patients who require anti-epileptic drugs (AED) may be on non-enzyme inducing anti-epileptic drugs (NEIAED). If a patient on this study protocol needs to have an AED started or needs to have a second AED added then only NEIAED should be used. There must be a ≥ 10 day period from discontinuation of an EIAED and initiation of therapy. In the event that an enzyme-inducing anti-epileptic drug must be used for a patient on study the patient will be removed from the protocol.

Herbal and Non-Traditional Medications

No data exist regarding the interaction of TRC102 with commonly used herbal or non-traditional medications. Patients should be instructed not to use such medications while receiving TRC102 therapy.

5.0 DOSING DELAYS/DOSE MODIFICATION FOR TOXICITY

Clinically significant adverse events or abnormal laboratory values assessed as unrelated to disease progression, intercurrent illness, or concomitant medications require dose delay and dose modification. Such toxicities must have an attribution of possible, probable, or definite to TRC102 or temozolomide (see Section [9.2.2](#)).

In general, if toxicity occurs that is attributed to only one of the agents, only that agent should be dose-reduced/modified. The dose of the other agent can be maintained at the same level. If multiple toxicities occur, dose modification decisions should be based on the most severe toxicity.

Because the protocol is designed to look at the effects of a combination treatment of TRC102 with TMZ, if either TRC102 or TMZ is permanently discontinued, the patient will be off treatment.

For patients experiencing toxicity meeting the criteria below, the attributed drug(s) will be stopped. If the patient recovers (\leq grade 1 [or tolerable grade 2 for non-hematologic toxicity] or \leq baseline) a dose reduction is required for subsequent doses. Skipped doses will not be made up. If there is any question or confusion concerning a toxicity, the treating site should contact the ABTC Central Office to determine patient's toxicity status. The ABTC Central Office, with the Study Chair, will make the final decision.

- Hematological toxicities will require dose modification if any of the following occur and complete blood counts and differentials were obtained according to the mandated schedule (CBC, differential, and platelets drawn twice a week until the $ANC \geq 1500/mm^3$ and platelets $\geq 100,000/mm^3$): grade 3 or 4 lymphopenia will not be considered a toxicity requiring dose modification.

- ANC of $< 500/mm^3$.

- Platelets < 25,000/mm³.
- Febrile neutropenia
- Any hematological toxicity that prevents administration of > 80% of the planned TRC102 and temozolomide doses

➤ Non-hematological toxicities will require dose modification if any of the following occur:

- Grades 3-4 severity (except nausea, vomiting, and diarrhea without sufficient prophylaxis; except alopecia; except grade 3 hyperglycemia; except grade 3 electrolyte disturbances that are asymptomatic and that respond to replacement therapy; and except grade 3 neurologic toxicity responding within two weeks to steroids, anticonvulsants, or electrolyte correction. A subject's first episode of deep venous thrombosis (DVT) or pulmonary embolism (PE) will not require dose modification.)

ANY TOXICITY (AS DEFINED ABOVE) CAUSING DELAY IN TREATMENT OF OVER 21 DAYS IN THE START OF A CYCLE WOULD RESULT IN TAKING THE PATIENT OFF TREATMENT.

5.1 Dose Modification for TRC102

The dose levels and the general approach to TRC102 dose modification on this trial are shown below. Adverse events (AEs) should be treated with the appropriate maximum supportive care, and dose reductions should be clearly recorded on the case report form.

Dose reductions are required for any clinically significant toxicity as defined above. Dosing will stop until the toxicity has resolved to ≤ grade 1 (or tolerable grade 2 for non-hematologic toxicity) or ≤ baseline. The maximum length of time that TRC102 can be held is 21 days. If treatment-related toxicity is not resolved in ≤ 21 days, the patient will be removed from treatment. After resolution, when dose reduction is permitted, the dose of TRC102 will be modified as stipulated below, with a maximum of 2 dose reductions. If there is any question, the ABTC Central Office and the Study Chair should be contacted.

Dose Reduction Table for TRC102

Dose Level	TRC102
Starting dose	150mg flat dose
First dose reduction	125mg flat dose
Second dose reduction	100mg flat dose

5.2 Dose Modification for Temozolomide

Clinically significant toxicities having an attribution to TMZ of possible, probable or definite will result in the following TMZ dose modifications. Dosing is based on toxicity during the prior treatment cycle. If multiple toxicities are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single toxicity.

Blood counts will be evaluated weekly. Within -5 days prior to first dose of each 5-day TMZ treatment the patient must have an ANC $\geq 1500/\text{ul}$ and platelet count $\geq 100,000/\text{ul}$. On Day 1 of each cycle (within -5 days) all **non-hematological** toxicity grade 3 or 4 (except for alopecia, nausea and vomiting) must have resolved (CTCAE grade ≤ 1 [or tolerable grade 2]). If toxicity persists, treatment should be delayed by one week for up to 3 consecutive weeks. If after 3 weeks of delay all toxicity has still not resolved then any further treatment with temozolomide should be stopped (patient is off treatment).

Dose reductions: If any non-hematological toxicity observed during the most recent pre-cycle evaluation was CTCAE **Grade** > 2 (except for alopecia, nausea and vomiting) **and/or** if **platelets** $< 50,000/\text{ul}$ **and/or** **ANC** $< 1000/\text{ul}$, then the dose should be reduced by one dose level (see table below). For patients who would require dose reductions to a dose level $< 100\text{mg}/\text{m}^2/\text{day}$, temozolomide will be **stopped**. Also, if any of the same non-hematological **Grade 3 toxicity recurs** (except for alopecia, nausea and vomiting) after reduction for that toxicity, then temozolomide will be **stopped** (patient is off treatment).

Temozolomide Dose Reduction Table

Dose Level	TMZ Dose mg/m^2
starting dose	150
first dose reduction	100
second dose reduction	off treatment

- If any non-hematological toxicity observed was CTCAE **Grade 4** (except for alopecia, nausea and vomiting) then adjuvant temozolomide treatment should be **stopped** (patient is off treatment).

Subsequent 5-day TMZ treatments: Any dose reductions of temozolomide will be determined according to (1) non-hematological toxicity during the preceding treatment cycle, as well as (2) the worst ANC and platelets toxicity. No dose escalation should be attempted. The same dose reductions as for the second 5-day TMZ treatment should be applied.

5.3 Major Events

Major Events are non-treatment-related grade 3 and 4 hematologic and non-hematologic toxicities. Treatment should be delayed for major events if TRC102 may further complicate the non-treatment-related event. If a major event requires a delay of treatment, treatment must be delayed until toxicity is resolved (\leq grade 1 [or tolerable grade 2 for non-hematologic toxicity] or \leq baseline). If toxicity is not resolved in ≤ 28 days, the

patient will be removed from treatment. The ABTC Central Office should be consulted if you are not clear on whether to continue or delay treatment.

5.4 Use of Hematologic Growth Factors

No growth factors (G-CSF or GM-CSF) are to be used prophylactically in this protocol. Clinicians caring for patients on this protocol are permitted to use these growth factors to provide optimal care for patients with severe neutropenia in accordance with the ASCO guidelines, (JCO, 12, 1994: pp2471-2508). If these growth factors are used in the acute setting of neutropenia and infection (documented or suspected), they will not be utilized prophylactically in subsequent cycles and they will not subsequently be used in lieu of dose reduction of (study agent).

5.5 Toxicity Criteria

All toxicities will be described and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (<http://ctep.cancer.gov>). See also Section [9.2.2](#), Recording of Adverse Events.

6.0 PHARMACEUTICAL INFORMATION

6.1 TRC102

Chemical Name: Methoxyamine hydrochloride

Other Names: Methoxyamine HCl

Classification: Biochemical inhibitor of the BER pathway

Molecular Formula: $\text{CH}_3\text{ONH}_2\cdot\text{HCl}$

M.W.: 83.52 Daltons

Approximate Solubility: At ambient temperature, TRC102 is freely soluble in water, sparingly in ethanol (70mg/mL), and slightly in DMSO (140mg/mL).

Mode of Action: TRC102 has the ability to interrupt the process of base excision repair (BER) by binding to apurinic/apyrimidinic sites produced during the initial step of the BER pathway. These sites are substrates for topoisomerase II (topo II); an enzyme that cleaves damaged DNA. TRC102 has demonstrated the ability to potentiate the activity of the alkylating agents temozolomide and carmustine, and antimetabolite agents fludarabine and pemetrexed, in murine models of human cancer. Therefore, TRC102 may be able to potentiate the activity of alkylating and antimetabolite chemotherapy in patients.

Description: TRC102, a white, crystalline solid, is the hydrochloride salt of methoxyamine.

How Supplied: TRC102 is supplied by IriSys, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. The white, opaque, size 2, hard gelatin capsules contain 25 mg of Methoxyamine HCl powder, microcrystalline cellulose, croscopovidone, sodium starch glycolate, colloidal silicon dioxide, and talc. Each HDPE bottle with child-resistant screw cap contains 30 capsules.

Storage: Store bottles of TRC102 at refrigerated temperature (2-8°C).

Stability: Shelf life surveillance of the intact bottles is ongoing.

Route of Administration: Oral

Method of Administration: Capsules are taken in the morning after patients have fasted for at least two hours. Take with 8 ounces of water. Capsules should be swallowed whole, do not chew or crush. Patients should refrain from eating or drinking for one hour following TRC102 dosing.

Availability

TRC102 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

TRC102 is provided to the NCI under a Collaborative Agreement between the pharmaceutical collaborator and the DCTD, NCI (see Section [14.0](#)).

6.1.1 Agent Ordering and Agent Accountability

TRC102 may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (<https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jsp>). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (<https://eapps-ctep.nci.nih.gov/iam/>) and the maintenance of an “active” account status and a “current” password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

6.1.2 Agent Inventory Records

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Oral Drug Accountability Record Form (Oral DARF). (See the NCI Investigator’s Handbook for Procedures for Drug Accountability and Storage.)

6.2 Temozolomide

Generic name: Temozolomide

Commercial name: Temodar®

Chemical name: 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8 carboxamide

Classification	Antineoplastic agent, alkylating
Molecular Formula:	C ₆ H ₆ N ₆ O ₂
Molecular Weight:	194.15
Mechanism of Action:	Temozolomide is not directly active but undergoes rapid non-enzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O ⁶ and N ⁷ positions of guanine.
Appearance:	White to light tan/light pink powder
Melting point:	Decomposes at 206°C
How Supplied:	Commercially available
Stability:	The molecule is stable at acidic pH (<5), and labile at pH >7, hence TEMODAR can be administered orally. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH. The product label recommends Storage at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
Half life:	Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours

Packaging, Dispensing and Storage

TEMODAR Capsules are available in 5-mg, 20-mg, 100-mg, 140-mg, 180-mg, and 250-mg strengths. The capsules contain a white capsule body with a color cap and the colors vary based on the dosage strength. The 5-mg, 20-mg, 100-mg, 140-mg, and 180-mg capsule strengths are available in 5-count and 14-count packages. The 250-mg capsule strength is available in a 5-count package. The product label recommends Storage at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Labeling of the packages containing the capsules will be done in accordance with the local procedures (as required by law). According to the dosing the hospital pharmacist delivers the temozolomide dosage for a complete cycle to the subject.

7.0 PROCEDURES FOR PATIENT ENTRY ON STUDY

This study is supported by the NCI Cancer Trials Support Unit (CTSU) Regulatory Office and uses the Oncology Patient Enrollment Network (OPEN).

Site Registration Requirements – IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at <https://www.ctsus.org> and clicking on the RSS tab.

Site registration documents and a CTSU Transmittal Sheet (on CTSU website) must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone – 1-866-651-CTSU
Fax – 215-569-0206
CTSURegulatory@ctsus.coccg.org (for submission of regulatory materials only)

Patient Registration:

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). All site staff will use OPEN. OPEN is a web-based registration system available to users 9 a.m. to 4:30 p.m. Eastern Time. The system can be accessed by entering credentials at <https://www.ctsus.org> and clicking on the OPEN tab, or by entering credentials at the OPEN portal URL <https://open.ctsus.org>.

Prior to discussing protocol entry with the patient, site staff must check the ABTC website (abtconsortium.org) for protocol status and slot availability.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for credentialing in the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role (or equivalent) on the relevant Group or CTSU roster.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Upon completion of the registration process in OPEN, sites should contact the ABTC Central Office to confirm the patient's registration.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (<https://open.ctsu.org>). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.0 RESPONSE ASSESSMENT / SAFETY AND QUALITY ASSURANCE

8.1 Criteria for Response Assessment

Subjects with measurable disease will be assessed by the RANO (radiographic assessment in neuro-oncology) criteria (Wen 2010). For the purposes of this study, subjects should be re-evaluated at the end of every 2 cycles (approximately every 8 weeks) with a contrast-enhanced cranial MRI scan. The response will be determined as outlined in the RANO criteria below.

Measurable disease. Bidimensionally, contrast-enhancing, measurable lesions with clearly defined margins by MRI scan, with a minimal diameter of 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are too many measurable lesions to measure at each evaluation, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered non-measurable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

Complete Response (requires all of the following):

- a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
- b) No new lesions.
- c) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
- d) Subjects must be off corticosteroids (or on physiologic replacement doses only).
- e) Stable or improved non-enhancing (T2/FLAIR) lesions.
- f) Stable or improved clinically.

Note: Subjects with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial Response (requires all of the following):

- a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
- b) No progression of non-measurable disease.
- c) No new lesions.
- d) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
- e) The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
- f) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
- g) Stable or improved clinically.

Note: Subjects with non-measurable disease cannot have a partial response. The best response possible is stable disease.

Stable Disease (requires all of the following):

- a) Does not qualify for CR, PR, or progression.
- b) The designation of stable disease requires a minimum of 4-week duration.
- c) All measurable and non-measurable sites must be assessed using the same techniques as baseline.
- d) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
- e) Stable clinically.

Progressive Disease (defined by any of the following):

- a) $\geq 25\%$ increase in sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids.*
- b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of

- therapy,* not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).
- c) Any new lesion.
 - d) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose. The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decrease in 20% of KPS or from any baseline to 50% or less be considered, unless attributable to comorbid events.
 - e) Failure to return for evaluation due to death or deteriorating condition.
 - f) Clear progression of non-measurable disease.

* Stable doses of corticosteroids include patients not on corticosteroids.

8.2 Assessment of Response

Assessment of response will begin with the MRI performed just prior to *every odd-numbered* treatment cycle. If during any scheduled MRI, the subject has a Complete Response or Partial Response, the MRI should be repeated prior to the next cycle. All scans are to be compared to the smallest measurement scan to date. The subject will then return to the every odd-numbered cycle schedule. This is required to confirm the duration of response. Subjects will be classified as responders if they have a minimum duration of response for 4 weeks at any time after the first cycle of TRC102. MRI scans of subjects showing tumor response will be centrally reviewed by a neuroradiologist who will independently assess tumor size and compute percent tumor regression.

8.3 Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry, regular measurement of vital signs, and the performance of physical/neurological examinations.

8.4 Quality Assurance

Neuropathology: The neuropathologic diagnosis of glioblastoma will be made at the respective institution. If any question arises regarding the accuracy of the neuropathologic diagnosis, slides (and pathological blocks, if necessary) will be reviewed by the central review pathologist. For protocols with “response” as an outcome, all patients with a documented complete response or partial response will have representative pathology slides undergo central review.

Neuroradiology: MRI scans of patients showing tumor response will be centrally reviewed by a neuroradiologist who will independently assess tumor size and compute percent tumor regression.

Neuro-oncology: The local investigator at the participating institution will communicate to the ABTC Central Office any unexpected neurological effects such as change in seizure frequency, alteration in neuromuscular function, alteration in cognitive function, or fluctuations in serum anticonvulsant drug levels.

Adherence to protocol therapy: Screening/baseline source documentation will be submitted/uploaded into CTEP's iMedidata Rave system and will be reviewed by the ABTC Central Office. As a quality assurance measure for the treatment delivered on this protocol, primary patient records may be reviewed. The records to be examined will be selected retrospectively and at random; complete records must therefore be maintained on each patient treated on the protocol. These records should include primary documentation (e.g., laboratory report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.), which confirm that:

- The patient met each eligibility criterion.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given; any reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (MRI scan, lab reports, dated notes on measurements and clinical assessment, as appropriate).
- NCI Drug Accountability Records were maintained for this protocol.

9.0 MONITORING OF PATIENTS

9.1 Table of Required Observations

Arms 1 & 2 (28-Day Cycles)

	Baseline	Days 1-5 of every cycle	Weekly During Cycle 1	Weekly During All Cycles	Pre-Odd Cycles (cycles 3+)	Pre- Even Cycles	Off Treatment	30 Days post-last dose
TRC102		6						
Temozolomide		7						
Glucocorticoids Dose Evaluation	1				5		8	
AE Evaluation	1		12		5	5	8,10	11
MRI	1				5		8	
H&P/Neuro Exam	1				5	5	8	
KPS	1				5	5	8	
Vital Signs	1,2		12		2,5	2,5	2,8	
CBC, Diff, Platelets	1			9,12	5,9	5,9	8,9	
Serum Chemistry	1,3		12		3,5	3,5	3,8	
APTT or PTT	1							
Serum Pregnancy Test	1,4							
Archived Tumor Tissue	13							

- 1– All baseline measurements must be done within minus 21 calendar days of treatment administration unless otherwise specified.
- 2– Including blood pressure, respiratory rate, heart rate, temperature, weight, height: height is required at baseline only; weight is required at pre-odd cycle evaluations only.
- 3– Including albumin, alkaline phosphatase, total bilirubin, calcium, creatinine, magnesium, phosphorus, potassium, SGOT, SGPT, sodium.
- 4– For women of child-bearing potential.
- 5– Within minus 5 calendar days of cycle start.
- 6– TRC102 is administered orally on Days 1-5 of each 28-day cycle (see Section [4.3.1](#)). Patients are required to keep a medication diary.
- 7– Temozolomide is administered orally on Days 1-5 of each 28-day cycle (see Section [4.3.2](#)). Patients are required to keep a medication diary.
- 8– Evaluations done within +7 days of off treatment date unless indicated: do not repeat: if MRI within minus 14 days of off-treatment date; if H&P/neuro, KPS, labs within minus 5 days of off-treatment date.
- 9– If ANC < 1500 or plts < 100,000, CBCs/differentials will be repeated twice a week until counts are recovered (ANC ≥1500 or plts ≥100,000) per protocol. If counts are recovered (ANC ≥1500 or plts ≥100,000) on day of scheduled drawing do not repeat until next protocol schedule day
- 10– Adverse Events must be followed for at least 30 days from last dose of TRC102.
- 11– Perform within +14 days of the 30-day post-last dose date.
- 12– ± 1 day
- 13– Unstained slides from initial resection at diagnosis of glioblastoma, if available (see Section [9.5.1](#))

9.2 Adverse Events: Lists and Reporting Requirements

Patients will be evaluated for toxicity if they have received at least one dose of TRC102 or temozolomide.

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 9.2.1, below) and the characteristics of an observed AE (Section [9.2.2](#)) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

Adverse Events will be collected for at least 30 days following the last dose of study drug.

All adverse events must be reported to the ABTC Central Office and the NCI in the manner described and per the requirements of the investigative site's Institutional Review Board.

Adverse events will be entered into CTEP's Medidata Rave database by the investigative site in a timely manner. See Section [12.0](#) – Records to be Kept.

9.2.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPR)

9.2.1.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Methoxyamine hydrochloride (TRC102, NSC 3801)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Methoxyamine hydrochloride (TRC102).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 1.0, February 8, 2013¹

Adverse Events with Possible Relationship to Methoxyamine hydrochloride (TRC102) (CTCAE 4.0 Term)		Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	<i>Anemia (Gr 2)</i>
GASTROINTESTINAL DISORDERS		
	Diarrhea	<i>Diarrhea (Gr 1)</i>
	Mucositis oral	<i>Mucositis oral (Gr 1)</i>
	Nausea	<i>Nausea (Gr 2)</i>
	Vomiting	<i>Vomiting (Gr 2)</i>
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Fatigue	<i>Fatigue (Gr 2)</i>
	Fever	<i>Fever (Gr 1)</i>
INVESTIGATIONS		
	Blood bilirubin increased	<i>Blood bilirubin increased Gr 1)</i>
	Haptoglobin decreased	<i>Haptoglobin decreased (Gr 1)</i>
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	<i>Anorexia (Gr 1)</i>
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Pruritus	<i>Pruritus (Gr 1)</i>
	Rash maculo-papular	<i>Rash maculo-papular (Gr 1)</i>

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Also reported on methoxyamine hydrochloride (TRC102) trials but with the relationship to methoxyamine hydrochloride (TRC102) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Hemolysis

GASTROINTESTINAL DISORDERS - Constipation

IMMUNE SYSTEM DISORDERS – Allergic reaction

INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Creatinine increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Hypocalcemia

NERVOUS SYSTEM DISORDERS - Dysgeusia

PSYCHIATRIC DISORDERS – Psychosis

RESPIRATORY, THORACIC, & MEDIASTINAL DISORDERS - Dyspnea

VASCULAR DISORDERS - Thromboembolic event

Animal Data: The following toxicities have been observed in animal studies with methoxyamine hydrochloride (TRC102):

Dogs:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - bone marrow hypercellularity; epididymal cellular debris; small thymus

GASTROINTESTINAL DISORDERS - abnormal excreta

INVESTIGATIONS – increased reticulocytes, lymphocytes increased

NERVOUS SYSTEM DISORDERS - convulsions; tremors

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - seminiferous tubule degeneration

Rats:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - enlarged or swollen spleens; increased spleen weight

INVESTIGATIONS - increased monocytes; increased reticulocytes; lymphocytes increased

Note: Methoxyamine hydrochloride (TRC102) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.2.1.2 Adverse Event List for Temozolomide

Known potential toxicities of temozolomide are hematological toxicities (leucopenia, lymphopenia, thrombocytopenia, and anemia), renal insufficiency, nausea and vomiting, liver enzyme abnormalities, lethargy, rash, headache, alopecia, constipation, fatigue/malaise, anorexia, hyperglycemia and diarrhea are known toxicities. Recently, cases of hepatic injury, including fatal hepatic failure, have been observed in patients enrolled in clinical studies utilizing the agent temozolomide. In addition, it was noted that liver toxicity may occur several weeks or more after initiation of treatment or after temozolomide discontinuation. Refer to the package insert for additional information on adverse events observed to date.

Rats given temozolomide in recent multidose toxicity studies have developed adenocarcinoma of the breast, fibrosarcomas, malignant Schwannomas (a variant of fibrosarcoma), keratoacanthomas and basal cell adenomas. Similar studies conducted in dogs did not reveal any similar findings. The significance of this finding for humans is not known presently.

Temozolomide is potentially mutagenic and should be handled with appropriate precautions by both staff and subjects. Subjects with known or suspected hypersensitivity to temozolomide should not be treated with temozolomide. There are no data available on the effect or management of temozolomide overdose.

Additional information is available in the temozolomide package insert (www.temodar.com).

9.2.2 Adverse Event Characteristics

Definition - Adverse Event (AE)

Adverse event is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Recording of Adverse Events - ABTC AE Form

- The investigator will monitor each patient closely for the development of adverse events and record all such events on the ABTC AE Case Report Form. Each single sign or symptom must be reported separately.
- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). You must use one of the CTCAE criteria to define your event.

Adverse events not included in the CTCAE should be reported under “Other” within the appropriate category and graded 1 to 5 according to the general grade definitions - mild, moderate, severe, life-threatening, fatal or disabling - as provided in the CTCAE or the CTCAE Manual. New adverse events may be submitted to the CTEP Help Desk at ncictcaehelp@mail.nih.gov for annual evaluation by the CTCAE Change Management Committee.

- **For expedited reporting purposes only:** AEs for TRC102 that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section [9.2.1.1](#)) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
- **Attribution of the AE:** The investigator will be asked to document his/her opinion of the relationship of the event to study medication as follows:
 - *Unrelated* – The AE is clearly not related to the investigational agent(s).
 - *Unlikely* – The AE is doubtfully related to the investigational agent(s).
 - *Possible* – The AE may be related to the investigational agent(s).
 - *Probable* – The AE is most likely related to the investigational agent(s).
 - *Definite* – The AE is clearly related to the investigational agent(s).
- All adverse events should be followed up in accordance with good medical practice. Abnormalities of laboratory events which, in the opinion of the investigator, constitute adverse events (even if not serious) should be followed.

9.3 Serious Adverse Events and Expedited Adverse Event Reporting

9.3.1 Definition – Serious Adverse Event (SAE)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours

- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3.2 Expedited Adverse Event Reporting

➤ Use CTEP-AERS Web Application and Document on ABTC AE Form

- All SAEs must be documented on both the ABTC AE form and using the CTEP-AERS Web Application within 24 hours of learning of the event.
- Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP web site (<https://eapps-ctep.nci.nih.gov/ctepaers>). The reporting procedures to be followed are presented in the “NCI Guidelines for Investigators: Adverse Event Reporting Requirements” which can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

- CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) of the Adult Brain Tumor Consortium (ABTC), the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.
- The ABTC Central Office is responsible for submitting to the CTSU documentation of AEs that they deem reportable for posting on the CTSU protocol web page and inclusion on the CTSU bi-monthly broadcast.
- Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 “Neoplasms benign, malignant and unspecified (including cysts and polyps) - Other (Progressive Disease)”** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention^{1,2}

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- “24-Hour; 5 Calendar Days” - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

²For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above

applies after this reporting period.

Effective Date: May 5, 2011

9.3.3 Other Reporting

Any Serious Adverse Event, as described in Section [9.3.1](#), including death due to any cause, which occurs during this study must be **reported immediately (within 24 hours)** to the ABTC Central Office.

A phone call must be made to:

SERENA DESIDERI

ABTC DATA COORDINATOR

OFFICE: 410-614-4400

FAX: 410-614-9335

OR JOY FISHER, ABTC MANAGER: 410-955-3657 / 410-599-4610

These events also must be reported by the investigator to the appropriate Institutional Review Board (IRB).

Patients who are removed from study due to adverse events should be followed until the adverse event has resolved or stabilized. Copies of relevant documentation, such as laboratory reports, should be kept with the patient's study records.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

9.4 Routine Adverse Event and Data Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

This study will be monitored by the Clinical Data Update System (CDUS). The ABTC Central Office is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the principal investigator for review.

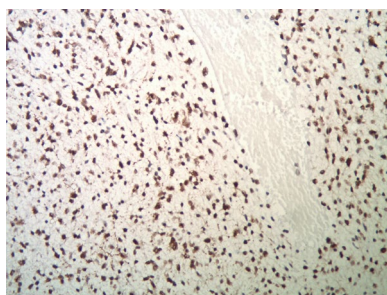
Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

9.5 Exploratory Correlative Studies

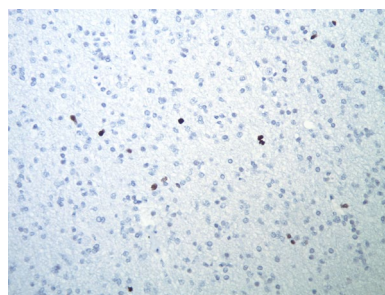
9.5.1 Immunohistochemical Detection of Topoisomerase II α and MPG on Archived Tumor Samples

Formalin fixed, paraffin embedded pretreatment tumor specimens will be stained with antibodies to methylpurine DNA-glycosylase (MPG) and topoisomerase II α (Topo II α) in the IHC lab of the Tissue Resources Core of the Case Comprehensive Cancer Center, under the direction of Dr. Dawn Dawson. The IHC Core has extensive experience in method development and validation of IHC for use as correlative markers in clinical trials. The relevant antibodies have been identified and methods developed for the targets.

IHC results will be determined by a combination of the percentage of tumor cell staining and the intensity of tumor cell staining. These results will be correlated between the responders and non-responders in the trial.



Methyl Purine DNA-Glycosylase
(Abcam#ab55461)



Topoisomerase II α
(BioCare#API3045AA)

Figure 1: Immunohistochemical staining of clinical GBM specimens. Archived GBM specimens were identified, slides were cut, antigen retrieval was performed and slides stained with the indicated primary antibodies and HRP conjugated anti-mouse secondary antibodies and DAB detection performed in a Nemesis IHC Autostainer.

Sample Packaging and Shipping

Archived tumor tissue from the initial resection at diagnosis of glioblastoma (pre-treatment) will be collected from patients when sufficient tissue is available. At the time of registration, prior to beginning treatment, a tumor tissue form indicating availability

will need to be completed and signed by a pathologist. This form provides written documentation of the availability of tissue for this study and the pathologist's agreement to send it as described below. A minimum of 10 unstained slides will be requested. The associated pathology report from the institution of collection should be shipped with the slides.

Ship slides and associated pathology report to:

John Pink, PhD
Scientific Director, Translational Research Core Facility
Case Comprehensive Cancer Center
2103 Cornell Road
Wolstein Research Building 3529
Cleveland, OH 44106-7285
Office: 216-368-5420
Lab: 216-368-1141
Email: jrp16@case.edu

10.0 OFF TREATMENT/OFF STUDY CRITERIA

Each subject has the right to withdraw from the study at any time without prejudice. The investigator may discontinue any subject's participation for any reason, including adverse event or failure to comply with the protocol (as judged by the investigator such as compliance below 80%, failure to maintain appointments, etc.).

Should a subject withdraw from the study, the reason must be stated on the case report form, and a final evaluation of the subject should be performed.

Patients who go off treatment must be followed for adverse events (AEs) for at least 30 days from the last dose of TRC102.

10.1 Off Treatment Criteria

1. **Disease Progression:** Remove patient from protocol therapy at the time progressive disease is documented. Disease progression is defined as: Progressive neurologic abnormalities not explained by causes unrelated to tumor progression (e.g. anticonvulsant or corticosteroid toxicity, electrolyte abnormalities, hyperglycemia, etc.) or a greater than 25% increase in the measurement of the tumor by MRI scan. If neurologic status deteriorates, on a stable or increasing dose of steroids, or if new lesions appear on serial MRI, further study treatment will be discontinued.
2. **Adverse Event:**
 - Intercurrent illness that prevents further administration of treatment
 - Patients who experience unacceptable toxicity. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of

the adverse event.

3. Patient Withdrawal: Patient's refusal to continue treatment: in this event, document the reason for withdrawal.
4. Non Compliance: Failure to comply with protocol (as judged by the investigator such as compliance below 80%, failure to maintain appointments, etc.)
5. Physician Decision: If at any time the treating physician feels constraints of this protocol are detrimental to the patient's health remove the patient from protocol therapy.
6. Protocol Defined Delay:
 - Patients who experience a treatment-related toxicity causing a delay in treatment >21 days
 - Delay in protocol >28 days for major events or other non-treatment related delays
 - Patients who require >2 dose reductions
 - If either TRC102 or temozolomide is permanently discontinued, patient will be off treatment.
 - Patients who must be put on an enzyme-inducing anti-epileptic drug (EIAED) during the study
7. Death

10.2 Off Study Criteria

Patients will only be off study at the time of death. All patients will be followed for survival every 2 months for the first two years from the off treatment date; after 2 years, patients will be followed every 6 months until death. Survival status may be obtained by phone call, clinic visit, or medical records (e.g. physician notes/laboratory results of clinic or hospital visit). Please note that additional survival status reports will be required twice yearly for ABTC Central Office reporting.

11.0 STATISTICAL CONSIDERATIONS

Primary Objectives

Arm 1

Objective response

Arm 2

Objective response

Secondary Objectives

1. Toxicity and safety of the combination TMZ and TRC102
2. Progression-free survival, progression-free survival at 6 months, and overall survival

Exploratory Objective

Correlation of MPG, topo II α , and MGMT with response, PFS, and overall survival

Sample size justification for primary endpoints:

Arm1: The Arm 1 study is to test the hypothesis that the combination treatment of TMZ and TRC102 will achieve 30% radiographic response rate (PR+CR) in patients with first recurrence of glioblastoma. A 2-stage design (minimax design) would discriminate between true response rates of no more than 13% and at least 30%. Maximum trial size would be set at 31 evaluable patients. If at least 7 responses (at least 22.5%) were observed among the 31 evaluable patients, this regimen would be considered worthy of further testing in this disease. If no more than 2 responses (no more than 10.5%) were observed among the initial 19 patients, the study would be terminated early and declared negative. This design yields at least 85% power to detect a true response rate of at least 30%. It yields at least .90 probability of a negative result if the true response rate is no more than 13%, with at least .54 probability of early negative stopping.

The Arm 2 study for bevacizumab-refractory patients is warranted only if the Arm 1 study meets its efficacy criteria. Arm 2 will not open without prior discussion between ABTC and CTEP.

Arm2: Arm 2 is a single arm study to test the hypothesis of clinical benefit of 30% radiographic response rate (PR+CR) for patients who had multiple numbers of prior therapies and are bevacizumab refractory, who are treated with TMZ and TRC102, and who continue bevacizumab. A safety run with 6 patients will be conducted prior to hypothesis testing in Arm 2. The expected DLT rate is $\leq 33\%$. If more than 2 patients experience dose limiting toxicity (DLT) associated with this regimen, Arm 2 will not be pursued further for safety reasons. If 2 or fewer patients experience DLT, Arm 2 will be

conducted using Simon's two-stage design. The 6 patients who were treated in the initial safe run will be counted as part of the first stage patients in the two-stage design.

Using Simon's two-stage design, if at least 7 responses (at least 20%) were observed among the 35 evaluable patients, this regimen could be considered worthy of further testing in this disease. If no more than 2 responses (no more than 11%) were observed among the initial 18 patients, the study would be terminated early and declared negative. This design yields at least 90% power to detect a true response rate of at least 30% from a null of 10% at an alpha level of 0.05 (one-sided). It yields 73% probability of early stopping if the true response rate is 10%.

All secondary and exploratory objective outcomes will be analyzed using standard descriptive statistical methods. Potential statistical comparisons are considered exploratory.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	0
Asian	2	2	0	0	4
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	2	3	0	0	5
White	15	22	2	3	42
More Than One Race	0	0	0	0	0
Total	19	27	2	3	51

12.0 RECORDS TO BE KEPT

Data collection for this study will be done exclusively through CTEP's Medidata Rave.

Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in the Regulatory Support System (RSS). To access iMedidata/Rave the site user must have an active CTEP IAM account (<https://eapps-ctep.nci.nih.gov/iam>). In addition, site users that are a member of the ABTC must have the Rave CRA role in RSS at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive an invitation from iMedidata to activate their account. If you have any questions please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

- All data are due within 14 days of evaluation time point. Please see Section [9.1](#) for evaluation time points.
- Serious Adverse Events, PHONE IMMEDIATELY, SEE SECTION [9.3](#)

13.0 REFERENCES

Ang C, Guiot MC, Ramanakumar AV, Roberge D, Kavan P. Clinical significance of molecular biomarkers in glioblastoma. *Can J Neurol Sci* 2010;37:625-30.

Batchelor TT, Mulholland P, Neyns B, et al. Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. *J Clin Oncol* 2013;31:3212-8.

Gordon MS, Rosen LS, Mendelson D, et al. A phase 1 study of TRC102, an inhibitor of base excision repair, and pemetrexed in patients with advanced solid tumors. *Invest New Drugs* 2013;31:714-23.

Liu L, Taverna P, Whitacre CM, Chatterjee S, Gerson SL. Pharmacologic disruption of base excision repair sensitizes mismatch repair-deficient and -proficient colon cancer cells to methylating agents. *Clin Cancer Res* 1999;5:2908-17.

Liu L, Nakatsuru Y, Gerson SL. Base excision repair as a therapeutic target in colon cancer. *Clin Cancer Res* 2002;8:2985-91.

Montaldi AP, Sakamoto-Hojo ET. Methoxyamine sensitizes the resistant glioblastoma T98G cell line to the alkylating agent temozolomide. *Clin Exp Med* 2013;13:279-88.

Savvides PS, Xu Y, Liu L, et al. Phase 1 clinical trial of the base-excision repair inhibitor Methoxyamine-HCl (TRC102; MX) in combination with Temozolomide (TMZ) in patients with solid tumors Cancer Research 2012;72

Reardon DA, Herndon JE, 2nd, Peters KB, et al. Bevacizumab continuation beyond initial bevacizumab progression among recurrent glioblastoma patients. Br J Cancer 2012;107:1481-7.

Savvides P, Xu Y, Liu L, et al. Pharmacokinetic profile of the base-excision repair inhibitor methoxyamine-HCl (TRC102; MX) given as an one-hour intravenous infusion with temozolomide (TMZ) in the first-in-human phase I clinical trial. ASCO Meeting Abstracts 2010;28:e13662.

Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987-96.

Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459-66.

Tang JB, Svilar D, Trivedi RN, et al. N-methylpurine DNA glycosylase and DNA polymerase beta modulate BER inhibitor potentiation of glioma cells to temozolomide. Neuro Oncol 2011;13:471-86.

Taverna P, Liu L, Hwang HS, Hanson AJ, Kinsella TJ, Gerson SL. Methoxyamine potentiates DNA single strand breaks and double strand breaks induced by temozolomide in colon cancer cells. Mutat Res 2001;485:269-81.

Weeks LD, Fu P, Gerson SL. Uracil-DNA glycosylase expression determines human lung cancer cell sensitivity to pemetrexed. Mol Cancer Ther 2013;12:2248-60.

Weller M, Cloughesy T, Perry JR, Wick W. Standards of care for treatment of recurrent glioblastoma--are we there yet? Neuro Oncol 2013;15:4-27.

Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. Apr 10 2010;28(11):1963-1972.

Wick W, Puduvalli VK, Chamberlain MC, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. J Clin Oncol 2010;28:1168-74.

Yan L, Bulgar A, Miao Y, et al. Combined treatment with temozolomide and methoxyamine: blocking apurinic/pyrimidinic site repair coupled with targeting topoisomerase IIalpha. Clin Cancer Res

Yang S, Savvides P, Liu L, Gerson SL, Xu Y. Development and validation of an LC-MS/MS method for pharmacokinetic study of methoxyamine in phase I clinical trial. J Chromatogr B Analyt Technol Biomed Life Sci 2012;901:25-33.

14.0 COLLABORATIVE AGREEMENTS LANGUAGE

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as “Collaborator(s)”) and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator” (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient’s family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: <http://ctep.cancer.gov>.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
 - a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
 - b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
 - c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).

Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

15.0 ETHICAL AND LEGAL CONSIDERATIONS

This study will be conducted in accordance with the Declaration of Helsinki and in compliance with all applicable laws and regulations of the locale where the study is conducted.

It is the responsibility of the investigator that the patient is made aware and consent is given that personal information may be scrutinized during audits by competent authorities and properly authorized persons, but that personal information will be treated as strictly confidential and not be publicly available. The investigator is responsible for the retention of the patient log and patient records.

APPENDIX I – PATIENT MEDICATION DIARIES**TRC102 DIARY** (TRC102 on Days 1- 5 every 28 days)**Patient Name** _____ (*initials acceptable*) **Patient Study ID** _____**Cycle #** _____**INSTRUCTIONS TO THE PATIENT:**

1. You will take **TRC102** _____ **mg on Days 1- 5 of every 28-day cycle.**
Take TRC102 in the morning at the same time as your temozolomide capsules, on an empty stomach, 1 hour before a meal or 2 hours after. Take with 8 ounces of water. Capsules should be swallowed whole, do not chew or crush.
2. Record the date and the time you took the TRC102 dose.
Record missed or skipped dose(s).
3. Bring this form and any remaining TRC102 when you return for each appointment.

Week	Day	Date	Time of dose	# of 25 mg capsules		Week	Day	Date	
1	1					3	15	(no dose)	–
	2						16	(no dose)	–
	3						17	(no dose)	–
	4						18	(no dose)	–
	5						19	(no dose)	–
	6	(no dose)	–	–			20	(no dose)	–
	7	(no dose)	–	–			21	(no dose)	–
2	8	(no dose)	–	–		4	22	(no dose)	–
	9	(no dose)	–	–			23	(no dose)	–
	10	(no dose)	–	–			24	(no dose)	–
	11	(no dose)	–	–			25	(no dose)	–
	12	(no dose)	–	–			26	(no dose)	–
	13	(no dose)	–	–			27	(no dose)	–
	14	(no dose)	–	–			28	(no dose)	–

Patient's Signature _____**Date** _____**Nurse's Signature** _____**Date** _____

TEMOZOLOMIDE DIARY (Temozolomide on Days 1- 5 every 28 days)**Patient Name** _____ (*initials acceptable*) **Patient Study ID** _____**Cycle #** _____**INSTRUCTIONS TO THE PATIENT:**

- You will take **Temozolomide (TMZ)** _____ **mg on Days 1- 5 of every 28-day cycle.**
Take the TMZ capsules in the morning at the same time as your TRC102 capsules, on an empty stomach, 1 hour before a meal or 2 hours after.
Take with 8 ounces of water. Capsules should be swallowed whole, do not chew or crush.
Dose: take ____ 5 mg capsules, ____ 20 mg capsules, ____ 100 mg capsules, ____ 140 mg capsules, ____ 180 mg capsules, and ____ 250 mg capsules.
- Record the date, the time you took the capsules, and the number of capsules of each size that you took.
Record missed or skipped dose(s).
- Bring this form and your bottles of TMZ capsules when you return for each appointment.

Week	Day	Date	Time of dose	# of TMZ capsules							Week	Day	Date	
				5 mg	20 mg	100 mg	140 mg	180 mg	250 mg					
1	1										3	15	(no dose)	—
	2											16	(no dose)	—
	3											17	(no dose)	—
	4											18	(no dose)	—
	5											19	(no dose)	—
	6	(no dose)	—									20	(no dose)	—
	7	(no dose)	—									21	(no dose)	—
2	8	(no dose)	—								4	22	(no dose)	—
	9	(no dose)	—									23	(no dose)	—
	10	(no dose)	—									24	(no dose)	—
	11	(no dose)	—									25	(no dose)	—
	12	(no dose)	—									26	(no dose)	—
	13	(no dose)	—									27	(no dose)	—
	14	(no dose)	—									28	(no dose)	—

Patient's Signature _____**Date** _____**Nurse's Signature** _____**Date** _____