A Phase II Trial of TRC102 (methoxyamine HCl) in Combination with Temozolomide in Patients with Relapsed Metastatic Colorectal Carcinoma

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Background

The base excision repair (BER) pathway has been shown to play a major role in promoting resistance to both alkylating agents and antimetabolites. The agent TRC102 acts through a novel mechanism to inhibit BER and has shown chemopotentiation in murine models of human cancer, suggesting that TRC102 may enhance the activity of alkylating and antimetabolite chemotherapy in patients [1]. Published studies indicate that TRC102 has the ability to interrupt the process of BER by binding to apurinic/apyrimidinic (AP) sites produced during the initial step of BER (Figure 1) [1, 2]. TRC102-bound AP sites are not substrates for apurinic/apyrimidinic endonuclease (APE), which performs an essential step in BER.

TRC102 has been shown to potentiate DNA damage caused alkylating agent temozolomide (TMZ) [3, 4]. The available data indicate that treatment of cancer cells with TMZ produces N7-methylguanine and N3-methyladenine DNA adducts that activate BER to generate AP sites within double-stranded DNA.

We have previously conducted a phase 1 trial of TRC102 in combination with TMZ in patients with relapsed solid tumors and lymphomas that demonstrated anemia to be the major dose-limiting toxicity of this combination and determined the recommended phase II dose (RP2D) to be 125 mg TRC102 + 150 mg/m^2 TMZ (PO, D1-5 of 28-day cycles).

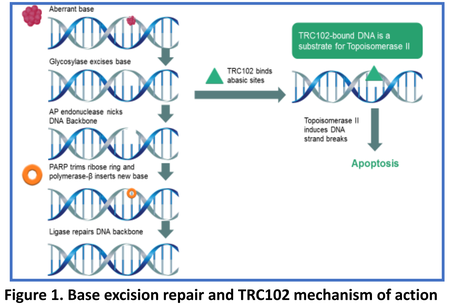
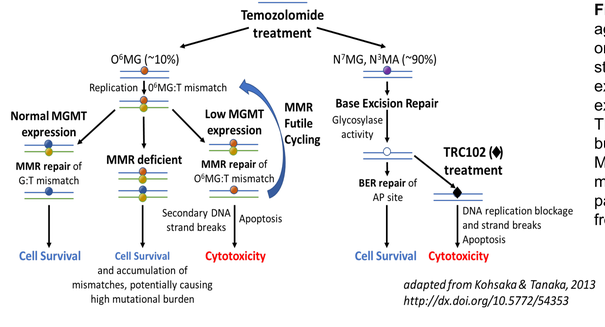


Figure 1. Base excision repair and TRC102 mechanism of action

Based on responses seen in the phase I trial (including a patient with colorectal carcinoma [CRC] who experienced a 70% response by RECIST and no progression after 17 months off-treatment), a Simon 2-stage design phase II trial of this combination is currently underway based on objective responses documented during the phase I portion of the study in patients with CRC, non-small cell lung cancer, and granulosa cell ovarian cancer.



adapted from Kohsaka & Tanaka, 2013 http://dx.doi.org/10.5772/54353

Figure 2. TMZ single agent activity is dependent on tumor MGMT and MMR status. TRC102 is expected to halt base excision repair of some TMZ-produced adducts, but assessing tumor MGMT and MMR status may still help to identify patients who could benefit from this combination.

Phase II Objectives

Primary Objective:
- To explore the response rate of the combination of TRC102 and TMZ in patients with CRC, NSCLC, and granulosa cell ovarian cancer

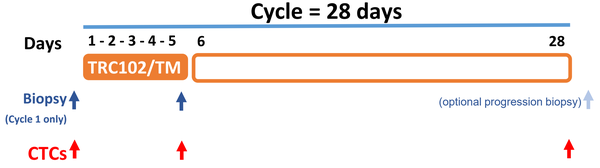
Secondary Objective:
- Explore the progression free survival rate of the combination of TRC102 and TMZ in patients with CRC, NSCLC, and granulosa cell ovarian cancer

Exploratory Objectives:
- Investigate tumor genomic and transcriptomic alterations potentially associated with sensitivity and/or the development of resistance to TRC102 and TMZ.
- Determine the effects of the study treatment on the level of histone γH2AX in circulating tumor cells (CTCs) and tumor and correlate the γH2AX response in tumor and CTCs

CRC Cohort Schema and Trial Design

Main eligibility criteria:
- histologically confirmed colorectal adenocarcinoma that has progressed on at least two lines of therapy
- ECOG ≤ 2
- normal organ function

Main exclusion criteria:
- MSI-high CRC not previously treated with immunotherapy
- symptomatic CNS metastases or carcinomatous meningitis
- pregnant or nursing women
- unstable medical illness
- HIV+ on protease inhibitors



Patients on three separate phase II cohorts (CRC, NSCLC, or granulosa cell ovarian cancer) each receive one of two dose levels:
- patients with a BSA ≥1.6 m^2 will receive the RP2D of 125 mg TRC 102 and 150 mg/m^2 TMZ po daily on days 1-5 (DL6)
- patients with a BSA <1.6 m^2 will receive 100 mg TRC 102 and 150 mg/m^2 TMZ po daily on days 1-5 (DL5)

CRC Cohort Results

Patient characteristics

Characteristic (n = 16)		
Age:	median (range)	64 (46-80)
Gender:	male female	11 (52%) 5 (48%)
Lines of Pretreatment:	median (range)	6 (3-14)
ECOG Performance Status:	1	16
Histology:	colon rectal	13 3

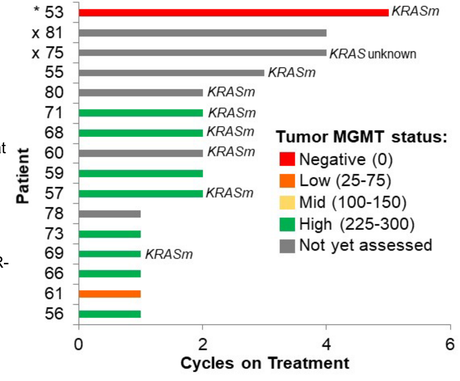
Common adverse events

Adverse event (grade 3/4)	Frequency
Thrombocytopenia	2 (12.5%)
Hemolysis	1 (6.3%)
Diarrhea	1 (6.3%)

No patients discontinued the protocol because of toxicity and only 1 patient required dose reduction for thrombocytopenia.

Patient Outcomes

Figure 3. Patients with a best response of stable disease are noted with "x"; partial response is noted with an asterisk (*).
- Tumor MGMT status was assessed by IHC; patients 56 and 66 had prior tumor MGMT promoter methylation analyses that matched the IHC outcome.
- *KRAS* status was known for all but one patient; mutations in *KRAS* are noted as "*KRASm*" and a lack of marking indicates patients with wildtype *KRAS*.
- Patients 53 and 61 were found to be MMR-proficient by IHC assessment of MLH1, MSH2, MSH6, and PMS2.



Summary

- Despite a promising phase I result from a patient with CRC, the phase II study of combined TRC102 and TMZ treatment in patients with metastatic colon or rectal adenocarcinoma displayed an ORR of 6%.
- MGMT expression by IHC, and DNA damage repair biomarker analysis are ongoing.
- Non-small cell lung cancer and granulosa cell ovarian phase II cohorts with this combination are ongoing.

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