Phase I trial of TRC102 (methoxyamine HCl) with temozolomide (TMZ) in patients with solid tumors and lymphomas

R.S. Meehan[1], G. O'Sullivan Coyne[1], S. Kummar[2], J. Collins[1], L. Anderson[1], J. Zlott[1], L. Juwara[3], N. Takebe[1], R. Piekarz[1], H. Streicher[1], E. Sharon[1], B. Conley[1], L. Rubinstein[1], D. Wilsker[3], A. Dull[3], K. Ferry-Galow[3], R. Kinders[3], R. Parchment[3], J.H. Doroshow[1], A.P. Chen[1]

[1]National Cancer Institute, Division of Cancer Treatment and Diagnosis, Bethesda, MD [2]Dept. of Medicine–Oncology, Stanford, Palo Alto, CA [3]Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc., Frederick, MD

Background

Among the various mechanisms by which resistance to chemotherapy can develop, the base excision repair (BER) pathway has been shown to play a major role in promoting resistance to both alkylating and antimetabolite chemotherapy. 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 [1, 2]. TRC102-bound AP sites are not substrates for apurinic/apyrimidinic endonuclease (APE), which performs an essential step in BER; they are, however, substrates for topoisomerase II (topo II). *In vitro* studies of cancer cells that contain high levels of topo II indicate that TRC102 effectively potentiates the activity of chemotherapy.

The ability of TRC102 to potentiate chemotherapy was initially demonstrated using the alkylating agent temozolomide (TMZ) [3, 4]. Collectively, the available data indicate that treatment of cancer cells with temozolomide produces N7-methylguanine and N3-methyladenine DNA adducts that activate BER to generate AP sites within double-stranded DNA.

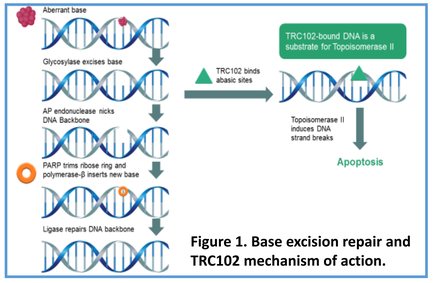


Figure 1. Base excision repair and TRC102 mechanism of action.

We conducted a phase 1 trial of TRC102 in combination with TMZ in patients with refractory colorectal carcinoma (CRC), non-small cell lung cancer (NSCLC), and granulosa cell ovarian cancer (GCOV). After the recommended Phase 2 Dose was defined as Dose Level (DL) 6 (TRC102 125mg, TMZ 150mg/m^2 D1-5), 15 additional pts were accrued to the expansion cohort from 9/2015 to 11/2016. A total of 52 pts were enrolled on the trial.

Objectives

Primary Objectives

- Establish the safety, tolerability, and maximum tolerated dose (MTD) of oral TRC102 in combination with oral TMZ in patients with refractory solid tumors.
- Evaluate the pharmacokinetic (PK) profile of oral TRC102 when administered in combination with TMZ.
- Explore the response rate as defined by RECIST 1.1 of this combination in patients with CRC, NSCLC, and GCOV.

Secondary Objectives

- 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.
- Determine the effects of the study treatment on the levels of cleaved caspase 3, epithelial mesenchymal transition, and APE in tumor and CTCs.
- Explore mechanisms of resistance to the study drug combination.
- Determine and characterize the effects of study treatment on erythrocytes and characterize the clinical presentation of hemolysis observed in earlier study subjects.
- Explore the progression-free survival rate of this combination in patients with CRC, NSCLC, and GCOV.

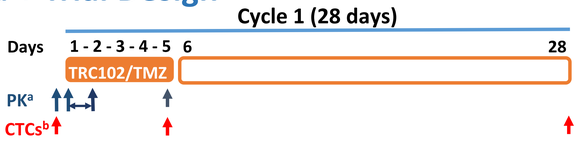
Study Schema + Trial Design

Main eligibility criteria:

- solid tumor patients whose disease has progressed on standard therapy
- ECOG ≤ 2
- normal organ function

Main exclusion criteria:

- symptomatic CNS metastases or carcinomatous meningitis
- pregnant or nursing women
- unstable medical illness
- HIV+ on protease inhibitors



Tumor Biopsies collected at baseline (before drug administration), cycle 1 day 5 (3-4 hrs after drug), and at disease progression[c].

[a]Blood samples for PK analyses (optional) will be collected in cycle 1 (C1) only prior to drug administration and 1, 2, 3, 4, 8, 12, and 24 hours post-dose, and 1x day 5 prior to dose (expansion phase only).

[b]Blood samples for CTCs (optional) will be collected from all pts at the following time points: C1 prior to treatment; C1 day 1, 8 hrs after drug; C1 day 5 before drug (expansion phase only); C2 day 1 before drug; day 1 of all subsequent cycles before drug, and at time of disease progression.

[c]Biopsies optional in escalation phase and mandatory in expansion phase (optional at disease progression).

Preliminary Results

Characteristic (n = 52)		
Age	median (range)	59 (38-83)
Gender	male	27 (52%)
	female	25 (48%)
Histology	colon	14
	ovary	6
	liver (HCC/cholangiocarcinoma)	4
	breast	3
	misc. (solid tumor NOS)	25

Total No. of Adverse Events (occurring in >5% of pts)	Grade 3	Grade 4
Anemia	9	1
Lymphopenia	7	1
Decreased WBC	3	-
Thrombocytopenia	3	3
Decreased ANC	2	3
Hemolysis	2	-

Figure 2. Patient characteristics and adverse event profile for all patients on the trial (escalation + expansion cohorts). Note that anemia was the dose-limiting toxicity during escalation.

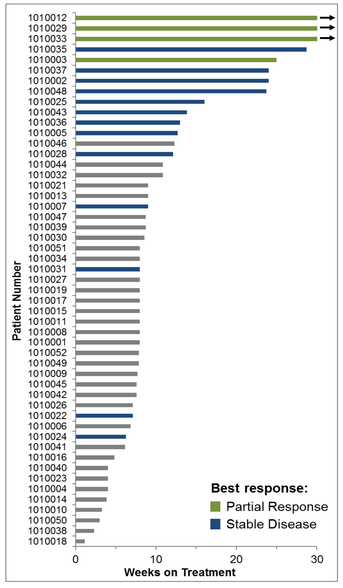


Figure 3 (right). Swimmer plot showing duration of therapy for all patients on the trial. Best response of PR or SD is indicated. Patients marked with an arrow continued on therapy after 30 weeks.

Radiological and Correlative Outcomes

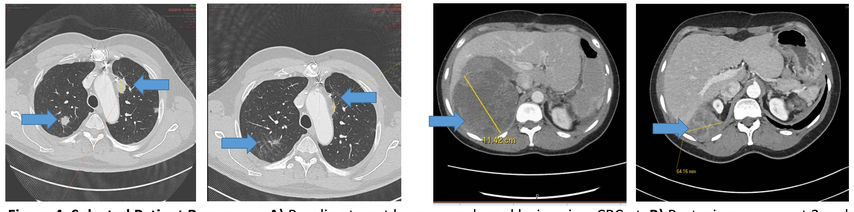


Figure 4. Selected Patient Responses. A) Baseline target lung parenchymal lesions in a CRC pt. **B)** Restaging scans post 2 cycles of therapy. **C)** Baseline target extra(hepatic)capsular lesion in a GCOV pt. **D)** Restaging scans post 14 cycles of therapy.

A.

Patient	Diagnosis	γH2AX response (mean % NAP)	pNbs1 response (mean % NAP)	Rad51 response (% cells ≥ 5 foci)
1010038	Colorectal	Pre: 7.7 Post: 3.9	Pre: 0.75 Post: 0.85	Pre: 0.4 Post: 0.7
1010041	Colorectal	Pre: 4.7 Post: 5.2	Pre: 1.7 Post: 1.8	**Pre: 2.0** **Post: 10.6** **(5-fold)**
1010044	Colon	**Pre: 0.4** **Post: 14.1**	Pre: 0.9 Post: 3.5	**Pre: 0.5** **Post: 7.1** **(14-fold)**
1010050	Colon	Pre: 0.8 Post: 2.9	**Pre: 4.9** **Post: 10.2**	**Pre: 5.6** **Post: 16.0** **(3-fold)**
1010051	Colon	Pre: 3.3 Post: 1.8	**Pre: 1.3** **Post: 11.3**	**Pre: 0.5** **Post: 17.0** **(34-fold)**

B.

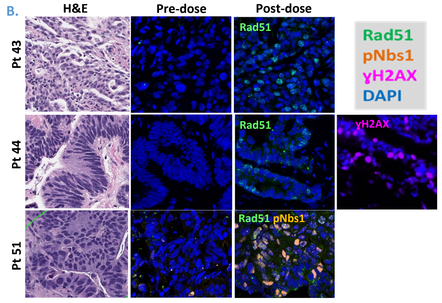


Figure 5. DDR Marker Analysis. A) The Pharmacodynamic Assay Development and Implementation Section (PADIS) at Frederick National Laboratory for Cancer Research (FNLCR) has validated an immunofluorescent assay (IFA) for DNA damage response (DDR) markers. This panel reports findings for CRC patients based on analysis of pre- and post-treatment liver biopsy specimens. Signal is quantified as % nuclear area positive (NAP). DDR response was noted in 4 of 5 pts. **B)** Representative IFA of DDR markers for various patients on study. DAPI nuclear staining (blue) is also shown.

Summary + Future Directions

- TRC102 inhibits BER and prevents DNA repair that occurs in response to TMZ therapy.
- The side effect profile of this combination is manageable, with anemia as the dose-limiting toxicity.
- The recommended phase 2 dose is 125 mg TRC102 and 150 mg/m2 TMZ, days 1-5 q 28 days.
- The combination is active, with 4 PRs + 13 SDs noted during the escalation and expansion cohorts.
- DDR markers were induced in 4 of 5 paired colon biopsies, indicating DNA damage following treatment.
- A phase 2 trial of patients with colon cancer, NSCLC, and GCOV is currently accruing.

References

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2. Yan, L., et al., Combined Treatment with Temozolomide and Methoxyamine: Blocking Apurinic/Pyrimidinic Site Repair Coupled with Targeting Topoisomerase IIβ. Clinical Cancer Research, 2007. 13(5): p. 1532-1539.
3. Liu, L., Y. Nakatsuru, and S.L. Gerson, Base Excision Repair as a Therapeutic Target in Colon Cancer. Clinical Cancer Research, 2002. 8(9): p. 2985-2991.
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