Phase I Trial of TRC102 (methoxyamine HCL) in Combination with Temozolomide in Patients with Relapsed Solid Tumors

#2556

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Introduction

- Base excision repair (BER), one of the pathways of DNA damage repair, has been implicated in chemoresistance.
- TRC102 is a small molecule amine that covalently binds to abasic sites generated by BER, resulting in DNA strand breaks and apoptosis; therefore, co-adminstraion of TRC102 is anticipated to enhance the antitumor activity of temozolomide (TMZ), which methylates DNA at N-7 and O-6 positions of guanine.
- We conducted a phase 1 trial of TRC102 in combination with TMZ to determine the safety, tolerability, and maximum tolerated dose (MTD) of the combination (Clinicaltrials.gov identifier: NCT01851369)
- First enrollment: 7/16/2013. Data cut off for this report was 8/24/2015 and includes only pts on the escalation phase.

Objectives

- To establish the safety, tolerability and MTD of oral TRC102 in combination with oral TMZ in patients with refractory solid tumors.
- Evaluate the pharmacokinetic (PK) profile of oral TRC102 in combination with TMZ.
- Determine and correlate the effects of study treatment to the level of histone γH2AX (indicative of response to DNA damage) in circulating tumor cells (CTCs) and tumor.
- Determine the effects of the study treatment on the levels of cleaved caspase 3 and Ki-67 in tumor
- Evaluate antitumor responses as determined by RECIST.

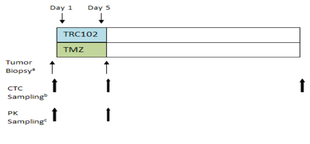
Eligibility

- Study participants must have histologically confirmed solid tumors that have progressed on standard therapy or for which no standard treatment options exist
- No major surgery, radiation, or chemotherapy within 4 weeks prior to entering the study
- Adequate organ function

Study Design

- This is an open-label Phase I trial; traditional 3+3 design.
- Oral TRC102 and oral TMZ will be administered daily, days 1-5 in 28-day cycles
- Once the MTD is established, up to 15 additional patients will be enrolled at the MTD to further evaluate MTD for PK and PD endpoints for evidence of DNA damage and apoptosis.
- During the escalation phase, tumor biopsies will be optional. During the expansion phase, (once MTD is reached), mandatory paired tumor biopsies will be pursued in the 15 additional patients enrolled to further evaluate PD endpoints.

Dose Level (DL)	TRC102 orally once daily D1-5	TMZ orally once daily D1-5
1	25mg	125 mg/m²
2	50mg	125 mg/m²
3	50mg	150 mg/m²
4	75mg	150 mg/m²
5	100mg	150 mg/m²
6	125mg	150 mg/m²
7	150mg	150 mg/m²
8	150mg	200 mg/m²



Patient Characteristics

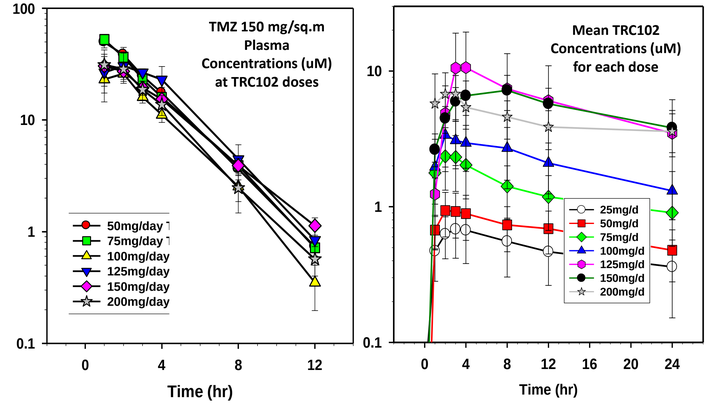
No. of Patients	34
Age (median)	60
Range	39-78
Race	
Caucasian	24
African American	6
Asian	2
Hispanic	2
Tumor Sites	
GI	11
H&N	4
Lung	7
Breast	3
GYN	6
Other	3
Prior Lines of chemotherapy, N	
Median	3.5
Range	1-9

Adverse Events

Adverse Event	Grade 2	Grade 3	Grade 4
Neutrophil count decreased	1	3	2
Platelet count decreased	2	1	2
Lymphocyte count decreased	6	5	
Anemia	9	3	1
Hypophosphatemia	2	2	
Fatigue	3	1	
Hypophosphatemia		1	
Hemolysis	1	1	1
Alkaline Phosphatase	4		
Vomiting	2		
Hyperbilirubinemia	3	1	

*only highest grade reported per patient

Pharmacokinetics/Pharmacodynamics



- TMZ: Plasma concentrations are independent of TRC102 dose (left graph)
- TRC102: T1/2 ~26 hours for oral TRC102, and plasma concentrations increase with dose (right graph)
- Pharmacokinetics TMZ and TRC102 in combination are similar to those reported for each of drug as a single agent
- CTC analysis for evidence of DNA damage response is ongoing

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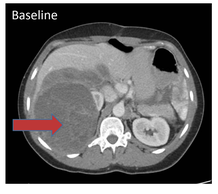
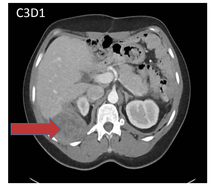
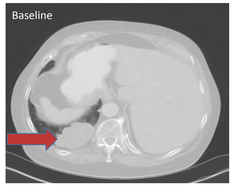
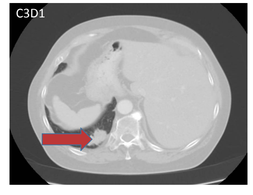
Response



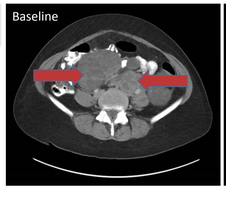


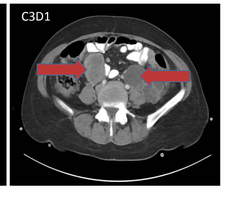
Ovarian Cancer- Dose Level 3
53 year old female with ovarian carcinoma:
BEO; carboplatin/etoposide; leuprolide; paclitaxel; P1 trial of z-endoxifen; P1 trial of pazopanib + ARQ197
Duration of response: 18 months



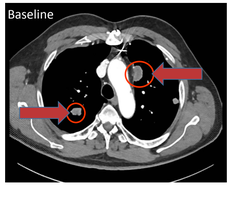


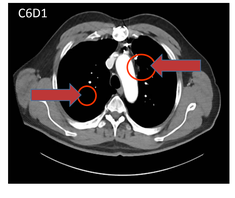
NSCLC- Dose Level 1
65 year old male with squamous NSCLC: Cisplatin/etoposide/RT; carboplatin/paclitaxel; carboplatin/gemcitabine; vinorelbine
Duration of response: 5 months





Ovarian Cancer- Dose Level 7
52 year old female with ovarian carcinoma:
Carboplatin/paclitaxel; Lupron; bevacizumab; arimidex; oral Cytoxan
Duration of response: 8 months





Colon caner- Dose Level 7
69 year old male with KRAS+ colon carcinoma:
FOLFOX; FOLFIRI
Duration of response: 8 months

Conclusions

- The escalation phase completed accrual between August 2013 and August 2015
- The MTD was reached at DL7 (TRC102 150mg PO D1-5 TMZ 150mg/m2 PO D1-5)
- The DLTs at DL8 was found to be due to hematologic toxicities, including hemolysis
- A total of 34 patients were enrolled on study, of which 4 had partial response (PR) in NSCLC, ovarian, and colon carcinoma, with one further unconfirmed PR in colon removed due to concurrent illness, 9 had stable disease (SD)
- The expansion phase is in progress and MGMT status and PD for DNA damage and apoptosis are ongoing
- With an ORR of 12% in this phase I trial, this combination appears to be active with manageable toxicities. The combination warrants further investigation.

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