#2789

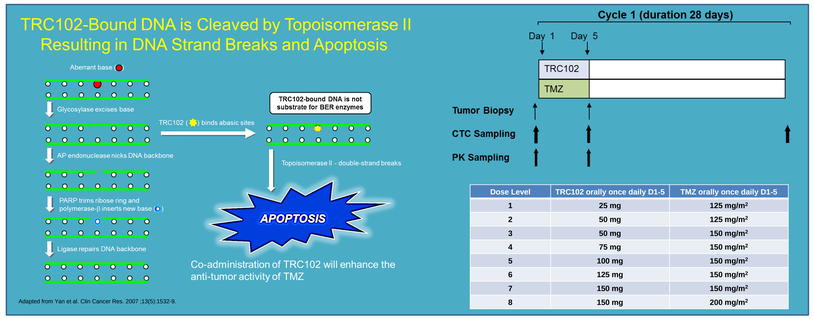
Phase I Trial of TRC102 (methoxyamine HCl) in Combination with Temozolomide in Patients with Relapsed Solid Tumors

Woondong Jeong[1], Khanh Do[1], Alice Chen[1], Jennifer Zlott[1], Lamin Juwara[2], Yvonne Horneffer[1], Lihua Wang[2], Priya Balasubramanian[2], Larry Anderson[1], Elad Sharon[1], Howard Streicher[1], Richard Piekarz[1], Barbara Conley[1], Jerry Collins[1], James Doroshow[1], Shivaani Kummar[1]

[1]Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland 20892,
[2]Leidos Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, Maryland 21702

Introduction

- Base excision repair (BER), one of the pathways of DNA damage repair, has been implicated in chemoresistance.
- TRC102 is small molecule amine that covalently binds to abasic sites generated by BER, resulting in DNA strand breaks and apoptosis; therefore, co-administration of TRC102 is anticipated to enhance the antitumor activity of temozolomide (TMZ).
- TRC102 has been shown to act through a novel mechanism to inhibit BER, causing DNA strand breaks and potentiating the antitumor activity of TMZ in preclinical models.
- 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).



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

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 on 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 criteria

Eligibility

- Adults with histologically confirmed solid tumors that have progressed on standard therapy known to prolong survival or for which no standard treatment options exist
- Performance status ECOG 0-2
- Adequate organ function

This trial was conducted under an NCI-sponsored IND with approval from the NCI Institutional Review Board. Protocol design and conduct followed all applicable regulations, guidances, and local policies.

Study Design

- This is an open-label Phase I trial; traditional 3+3 design.
- Oral TRC102 and oral TMZ are administered daily, days 1-5, in 28-day cycles
- Once the MTD is established, 6 additional patients will be enrolled at the MTD to further evaluate that dose 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 6 additional patients enrolled to further evaluate PD endpoints.

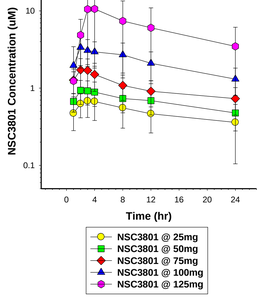
Patient Characteristics

No. of Patients	27
Age (median)	59
Range	39 - 78
Race	
Caucasian	19
African American	5
Asian	2
Hispanic	1
Tumor Sites	
GI	9
H&N	4
Lung	4
Breast	3
GYN	5
Soft tissue sarcoma	2
No. Prior lines Chemotherapy (median)	3.5
Range	1-9

First enrollment: 7/16/2013
Data cut off: 3/31/2015

Accrual is ongoing; 27 patients have been enrolled:
3 patients are still on study
1 patient enrolled but withdrew prior to receiving treatment and is not evaluable

Pharmacokinetics/Pharmacodynamics



- There is no pharmacokinetic interaction with TMZ; the pharmacokinetics of combination TMZ and TRC102 (NSC 3801) are similar to those of both drugs as single agents
- The drug level (Cmax) required for preclinical activity (50 ng/mL; 0.6 µM) was achieved with the 25 mg dose of TRC102
- $T_{1/2}$ ~26 hr
- CTC analysis for evidence of DNA damage response is ongoing

TRC102	Tmax	Cmax	T1/2
25 mg	3 hr	58 ng/mL	27.1 hr
50 mg	2 hr	78 ng/mL	25.2 hr
75 mg	2 hr	217 ng/mL	25.9 hr

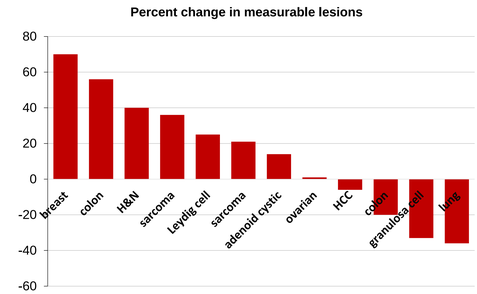
Drug-related Adverse Events

Adverse Event	Number		
	Grade 2	Grade 3	Grade 4
Neutrophil count decreased		1	1
Platelet count decreased			1
Lymphocyte count decreased	5	1	
Anemia	2	1	
White blood cell decreased	1	1	
Hypophosphatemia		1	
Fatigue	2		
Alkaline phosphatase increased	2		
Vomiting	1		
Hemolysis	1		
Creatinine increased	1		

Worst grade of toxicity per patient is reported

Response

Observed clinical activity

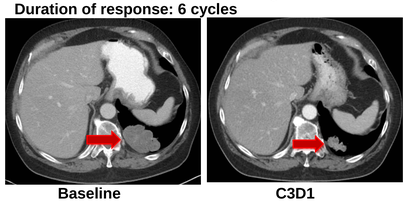


Durations of response for 2 PRs: 6 and 14 cycles
Durations of response for 3 SDs: 3, 4, and 6 cycles

Partial Response

65 year-old male with squamous NSCLC
Cisplatin/etoposide/RT; carboplatin/paclitaxel; carboplatin/gemcitabine; Vinorelbine

DL1:TRC102 25 mg and TMZ 125 mg/m²
Duration of response: 6 cycles

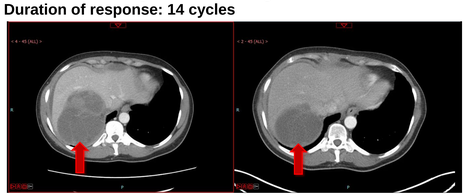


Baseline C3D1

Partial Response

51 year-old female with ovarian granulosa cell carcinoma
BEP; carboplatin/etoposide; leuprolide; paclitaxel; P1 trial of Z-endoxifen; P1 trial of pazopanib + ARQ197

DL3: TRC102 50 mg and TMZ 150 mg/m²
Duration of response: 14 cycles

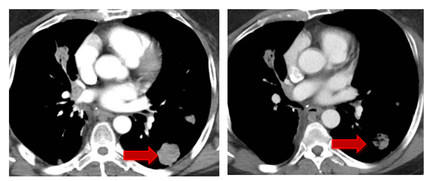


Baseline C3D1

Stable disease (20% decrease)

58 year-old male with KRAS-mutant colon cancer
FOLFOX/Bev; Capecitabine; IFL; Bev/5-FU; P2 trial of sorafenib + cetuximab; P1 trial of weekly LMP400

DL2: TRC102 50 mg + TMZ 125 mg/m²



Baseline C3D1

Conclusions

- The combination of TRC102 with TMZ has been well tolerated to date up to dose level 5 (100 mg + 150 mg/m²)
- The MTD has not yet been reached; accrual is ongoing
- Pharmacokinetic data showed that all dose levels of TRC102 reached Cmax >50 ng/mL required for the activity observed in preclinical models
- Co-administration of TMZ with TRC102 did not alter the pharmacokinetics of either compound
- Two patients had partial responses (lasting 6 and 14 cycles) and 3 had stable disease (lasting 3, 4, and 6 cycles, respectively), consistent with clinical benefit in this refractory population
- Paired tumor biopsies to assess the DNA damage response and apoptosis are planned in an expansion cohort at the MTD

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