

A PHASE 1 STUDY OF DAILY ORAL TRC102 (METHOXYAMINE) TO ENHANCE THE THERAPEUTIC EFFECTS OF PEMETREXED IN PATIENTS WITH ADVANCED REFRACTORY CANCER

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INTRODUCTION

TRC102 (methoxyamine) is a small molecule inhibitor of base-excision repair (BER) that enhances the cytotoxicity of alkylator and antimetabolite chemotherapy and reverses chemotherapy resistance (Liu et al, 2002; Liu et al, 1999; Bulgar et al, 2006). TRC102 inhibits BER by binding apurinic (AP) sites produced by glycosylase removal of damaged DNA bases, thereby targeting them for cleavage by topoisomerase II and triggering apoptosis (Yan et al, 2007).

OBJECTIVES

- Evaluate the safety and tolerability of escalating doses of TRC102 in combination with pemetrexed in patients with advanced or metastatic solid cancers
- Evaluate pharmacokinetics, tumor response, and pharmacodynamics by AP site assay

METHODS

STUDY DESIGN

- Phase 1, first in human, open-label, dose escalation study conducted at 3 institutions in the United States
- Oral TRC102 was escalated in cohorts of 3-6 patients in combination with a standard dose of i.v. pemetrexed
- All patients received TRC102 alone, dosed daily on Days 1-4 of an initial 2 week cycle, followed by the combination of pemetrexed on Day 1 and TRC102 on Days 1-4 every 3 weeks thereafter
- In Cycle 3, the Day 1 TRC102 dose was held in order to obtain the AP site assay sample for pemetrexed alone

	Cycle 1 (2 Weeks)	Cycle 2 (3 Weeks)	Cycle 3 (3 Weeks)	Cycle 4+ (3 Weeks)
Oral TRC102 Dosing	Days 1-4	Days 1-4	Days 2-4	Days 1-4
Pemetrexed Dosing	None	Day 1	Day 1	Day 1

KEY INCLUSION CRITERIA

- Adults (age ≥ 18 years) with advanced or metastatic solid cancer for whom curative therapy is unavailable
- ECOG performance status of 0 or 1
- Adequate organ function

KEY EXCLUSION CRITERIA

- Receipt of cancer treatment within 4 weeks of study start
- History of primary or secondary brain tumors
- Significant pericardial, pleural or peritoneal effusions

REFERENCES

- Bulgar AD, Liu L, Kirkland EB, et al. Proc Amer Assoc Cancer Res 2006; Abstract #517.
- Liu L, Nakatsuru Y, Gerson SL. Clin Cancer Res 2002; 8:2985-99.
- Liu L, Taverna P, Whitacre CM, Chatterjee S, Gerson SL. Clin Cancer Res 1999; 5:2908-17.
- Yan L, Bulgar A, Miao Y, Mahajan V, Donze JR, Gerson SL, Liu L. Clin Cancer Res 2007; 13:1532-9.

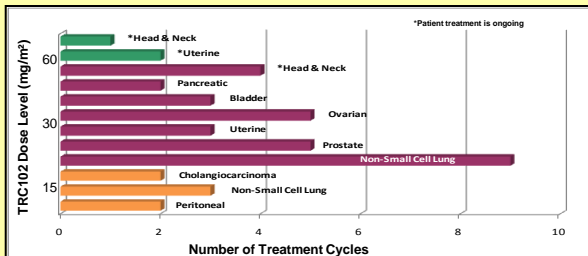
RESULTS

This is an interim analysis of an ongoing study; data have not been audited. A total of 12 patients have been enrolled and evaluated as part of this presentation.

Demographics

Characteristic	Number of Patients (n=12)
Median Age	69
Gender	Female: 8 Male: 4
Screening ECOG Performance Status	ECOG 0: 4 ECOG 1: 8
Number of Prior Regimens	Median: 2 Range: 1 to 6
Race	Caucasian: 10 Black/African American: 1 Hispanic/Latino: 1

Treatment Status



Pharmacokinetics

Clinical pharmacokinetic (PK) analyses of the first 2 cohorts indicate that:

- TRC102 plasma concentrations required for *in vivo* activity are achievable at 15 and 30 mg/m² with daily oral administration
- TRC102 exposure increased proportionally between 15 and 30 mg/m²
- TRC102 accumulated with daily dosing (Days 1-4), but did not accumulate between cycles
- Pemetrexed and TRC102 co-administration did not alter the PK of either compound

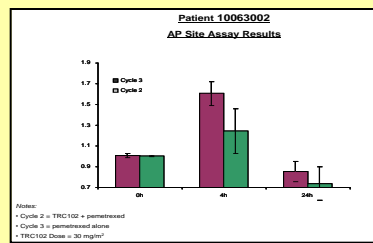
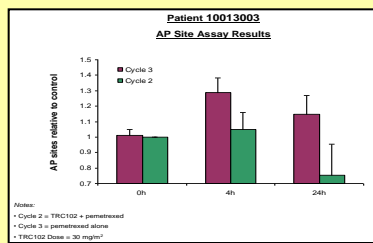
Dose (mg/m ²)	Cycle	Day	N	C-max* (ng/mL)	Half-life* (hr)	AUC* (hr-ng/mL)
15	1	1	4	20.5 (12.7 - 57.4)	35.7 (24.8 - 41.2)	291 (219 - 1132)
15	1	4	3	68.1 (27.0 - 129)	41.5 (36.0 - 52.2)	1136 (188 - 2580)
15	2	1	3	21.4 (12.7 - 56.0)	35.8 (5.6 - 55.4)	258 (126 - 1186)
30	1	1	6	43.9 (16.9 - 205.0)	21.8 (15.9 - 43.6)	716 (263 - 3462)
30	1	4	5	115.0 (29.2 - 282.0)	30.9 (26.5 - 59.4)	1829 (585 - 5230)
30	2	1	6	56.2 (14.2 - 137.0)	22.3 (12.6 - 52.5)	894 (222 - 2071)

*C-max, half-life and AUC are reported as median values with ranges in parentheses

Pharmacodynamics

Pharmacodynamic data are consistent with TRC102's ability to covalently bind pemetrexed-induced AP sites:

- During Cycle 3 Day 1, pemetrexed alone exposed AP sites
- During Cycle 2 Day 1, TRC102 bound to the AP sites that were exposed by pemetrexed, thereby preventing them from being detected in the AP site assay

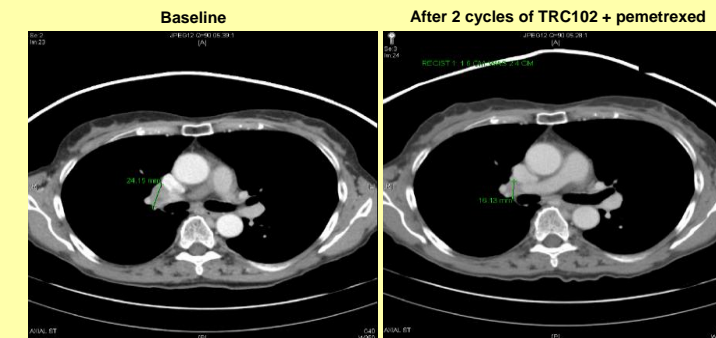


Efficacy

Efficacy data is available on the first 9 patients as follows:

- Ongoing partial response after 2 cycles of pemetrexed + 30 mg/m² TRC102 in a female patient with squamous cell cancer of the tonsil metastatic to the right lung and right hilum (prior therapies included radiation therapy, paclitaxel/cetuximab, and carboplatin/paclitaxel)
- Mixed response after 2 cycles of pemetrexed + 30 mg/m² TRC102 in a female patient with epithelial clear cell cancer of the ovary metastatic to the liver, who came off study in Cycle 6 for rising CA-125 (prior therapies included carboplatin/paclitaxel, cisplatin, and liposomal doxorubicin)
- Stable disease for 9 cycles of pemetrexed + 30 mg/m² TRC102 as 3rd line therapy for a male patient with metastatic squamous cell lung cancer

Partial Response - Right Hilar Metastasis



Safety

Preferred Term	N=12 Treated Patients		
	Grade 1	Grade 2	Grade 3
Anemia		2	2 (1=DLT)
Leukopenia			1
Neutropenia			3
Abdominal pain lower	1		
Diarrhea	1		
Nausea	1		
Retching	1		
Asthenia	1		
Fatigue	1	1	
Edema peripheral	1		
Pain		1	
Pyrexia	1		
Cellulitis		1	
Anorexia	2		
Dehydration		1	
Hypomagnesemia	1		
Insomnia	1		
Petechiae	1		
Pruritus	1		
Purpura	1		
Rash	1		

Preferred Term	N=12 Treated Patients			
	Grade	Grade 2	Grade 3	Grade 4
Anemia	1	3	3 (1=DLT)	
Leukopenia			1	
Neutropenia			4	1
Thrombocytopenia			1	

- No adverse events were attributed to TRC102 when dosed alone in Cycle 1
- One patient who received pemetrexed + 30 mg/m² TRC102 experienced Grade 3 anemia during Cycle 2 that was considered a dose-limiting toxicity, recovered after 2 units PRBCs and a 50% TRC102 dose-reduction, and remained on study through Cycle 5

Summary and Conclusions

- Daily oral TRC102 was well-tolerated at doses that achieved plasma levels associated with *in vivo* activity
- Pemetrexed and TRC102 co-administration did not alter the PK of either compound
- TRC102 accumulated with daily dosing in a manner consistent with its half-life >24 hours, but did not accumulate between cycles
- Pharmacodynamic data are consistent with the TRC102 mechanism of action
- There is early evidence of activity of the combination of pemetrexed + TRC102, including one partial response in a patient with refractory metastatic head and neck cancer
- Phase 2 studies are planned in multiple indications