

A PHASE 1 STUDY OF ORAL TRC102 (METHOXYAMINE HYDROCHLORIDE), AN INHIBITOR OF BASE-EXCISION REPAIR, TO POTENTIATE THE THERAPEUTIC EFFECTS OF PEMETREXED IN PATIENTS WITH ADVANCED REFRACTORY CANCER

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INTRODUCTION

TRC102 is a small molecule inhibitor of base-excision repair (BER) that is highly water soluble and nearly completely bioavailable after oral administration. TRC102 potentiates the cytotoxicity of alkylator and antimetabolite chemotherapy and reverses chemotherapy resistance by rapidly and covalently binding to chemotherapy-induced apurinic/pyrimidinic (AP) sites (Liu 1999, Liu 2002, Bulgar 2006). TRC102-bound DNA is no longer a substrate for BER enzymes and is instead cleaved by topoisomerase II, resulting in double-strand DNA breaks that trigger apoptosis (Yan 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, pharmacodynamics (by AP site assay), and tumor response

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 standard dose 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 after dosing with 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 was 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

- Liu, Clinical Cancer Research 1999; 5:2908-17
- Liu, Clinical Cancer Research 2002; 8:2985-99
- Bulgar, Proceedings of AACR 2006; Abstract #517
- Yan, Clinical Cancer Research 2007; 13:1532-9

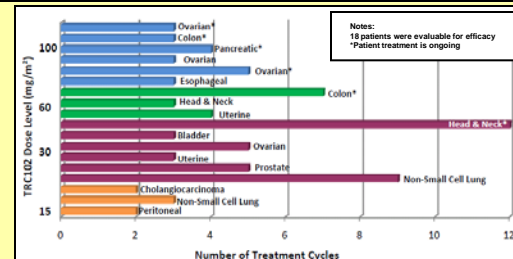
RESULTS

This is an interim analysis of an ongoing study; data have not been audited. A total of 20 patients have been enrolled and evaluated as part of this presentation.

Demographics

Characteristics	Number of Patients (n= 20)
Median Age	61
Gender	Male: 9 Female: 11
Screening ECOG	ECOG 0: 7
Performance Status	ECOG 1: 13
Number of Prior Regimens	Median: 2 Range: 1 to 8
Race	Caucasian: 17 Black or African American: 1 Hispanic or Latino: 2

Treatment Status

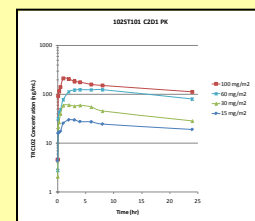
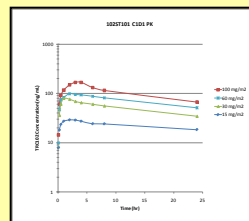


Pharmacokinetics

Clinical PK analyses of the 4 cohorts showed that:

- TRC102 plasma levels required for *in vivo* activity (50 ng/mL) were achieved with daily oral administration in all 4 cohorts
- 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

Cycle 1 Day 1	N	Cmax (ng/mL)	Half-life (hr)	AUC (hr-ng/mL)
15 mg/m ²	3	19.7 (12.7 - 57.4)	37.3 (34.1 - 41.2)	287 (219 - 1132)
30 mg/m ²	6	64.3 (22.7 - 205.0)	21.8 (15.9 - 25.5)	1041 (263 - 3462)
60 mg/m ²	3	119.0 (63.7 - 126.0)	21.9 (17.6 - 29.9)	1991 (1093 - 2161)
100 mg/m ²	5	152.0 (83.5 - 417)	26.8 (14.1 - 44.0)	2312 (987 - 5331)
Cycle 1 Day 4	N	Cmax (ng/mL)	Half-life (hr)	AUC (hr-ng/mL)
15 mg/m ²	3	68.1 (27.0 - 129)	41.5 (36.0 - 52.2)	1136 (188 - 2580)
30 mg/m ²	6	126.0 (73.2 - 282.0)	30.9 (26.5 - 59.4)	1960 (1158 - 5230)
60 mg/m ²	3	327.0 (155.0 - 626.0)	26.9 (25.8 - 44.8)	5812 (2632 - 11075)
100 mg/m ²	5	247.0 (148.0 - 435.0)	25.0 (16.4 - 36.6)	3105 (2066 - 7969)
Cycle 2 Day 1	N	Cmax (ng/mL)	Half-life (hr)	AUC (hr-ng/mL)
15 mg/m ²	3	24.6 (18.2 - 56.0)	34.3 (5.6 - 55.4)	297 (126 - 1186)
30 mg/m ²	6	57.4 (25.6 - 137.0)	21.9 (12.6 - 43.3)	943 (381 - 2071)
60 mg/m ²	3	103.0 (93.6 - 239.0)	26.7 (25.4 - 28.0)	1654 (1332 - 4556)
100 mg/m ²	5	225.0 (74.9 - 385.0)	37.0 (25.3 - 45.5)	3697 (940 - 6176)

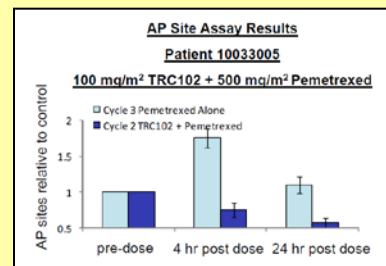
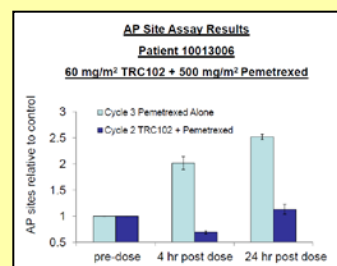


*Cmax, half-life and AUC are reported as median values with ranges in parentheses

Pharmacodynamics

Clinical PD data confirmed TRC102's ability to covalently bind pemetrexed-induced AP sites:

- During Cycle 2 Day 1, TRC102 bound to pemetrexed-induced AP sites, thereby preventing them from being detected in the AP site assay
- During Cycle 3 Day 1 (in the absence of TRC102), pemetrexed-induced AP sites were detected by the AP site assay

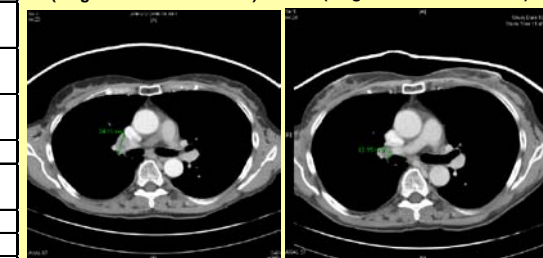


Efficacy

TRC102 Dose (mg/m ²)	Efficacy	Cancer Type	Patient Status
30	Partial Response	Squamous cell cancer of tonsil metastatic to right lung & right hilum	Treatment is ongoing in Cycle 12
	Stable Disease	Metastatic squamous cell lung cancer	Off study in Cycle 9 due to clinical progression
	Stable Disease	Clear cell of the ovary	Off study in Cycle 6 due to clinical progression & rising CA-125
60	Stable Disease	Metastatic prostate	Off study in Cycle 5 due to RECIST defined progression
	Stable Disease	Colon cancer	Treatment is ongoing in Cycle 7
	Stable Disease	Uterine adenocarcinoma	Off study in Cycle 4 due to patient withdrawal of consent
100	Stable Disease	Pancreatic carcinoma	Treatment is ongoing in Cycle 4
	Stable Disease	Colon cancer	Treatment is ongoing in Cycle 4
	Stable Disease	Clear cell of the ovary	Treatment is ongoing in Cycle 5

Partial Response - Right Hilar Metastasis

Baseline (longest diameter = 24 mm) After 11 Cycles (longest diameter = 12 mm)



Safety – Possibly TRC102 Related Events

System Organ Class Term	Preferred Term	Grade 1	Grade 2	Grade 3	
Blood and lymphatic system disorders	Anemia		3	4	
	Hemolysis		1		
	Leukopenia			1	
	Neutropenia			3	
	Abdominal pain lower	1			
Gastrointestinal disorders	Diarrhea			1	
	Dyspepsia		1		
	Nausea	2	1		
	Retching	1			
	Vomiting	1	1		
	General disorders and administration site conditions	Asthenia	1		
		Fatigue	5	1	
Mucosal inflammation		1			
Edema peripheral		1			
Pain				1	
Pyrexia		2			

System Organ Class Term	Preferred Term	Grade 1	Grade 2	Grade 3
Infections and infestations	Cellulitis			1
	Anorexia	4		
Metabolism and nutrition disorders	Dehydration		1	
	Hypokalemia	1		
	Hypomagnesemia	1		
Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain			1
Psychiatric disorders	Insomnia	1		
Skin and subcutaneous tissue disorders	Petechiae	1		
	Pruritus	2		
	Purpura	1		
	Rash	2		

- Possibly TRC102-related adverse events > Grade 3 were not observed
- Dose-limiting Grade 3 hemolytic anemia occurred in 3 of 6 patients at 100 mg/m²/day x 4, including 1 patient during Cycle 1 (TRC102 alone) and 2 patients during Cycle 2 (TRC102 + pemetrexed)
- Dose-limiting hemolytic anemia was also observed after similar TRC102 exposure in animal toxicity studies (at plasma levels 20-fold higher than those required for efficacy in preclinical models)

Summary and Conclusions

- TRC102 was well-tolerated at 15, 30, and 60 mg/m²/day x 4 days, and these doses achieved plasma levels associated with *in vivo* activity in preclinical models (Cmax > 50 ng/mL)
- The maximum tolerated dose of TRC102 was exceeded at 100 mg/m²/day x 4 days due to Grade 3 hemolytic anemia in 50% of patients (hemolytic anemia was also observed in animal toxicology studies at doses 20-fold higher than those required for efficacy)
- TRC102 accumulated with daily dosing in a manner consistent with its half-life >24 hours, but did not accumulate between cycles
- Pemetrexed and TRC102 co-administration did not alter the PK of either compound
- RECIST-defined partial response and extended stable disease in refractory patients were consistent with PD data confirming TRC102's ability to bind pemetrexed-induced AP sites, prevent base-excision repair, and selectively induce double-strand DNA breaks and cancer cell apoptosis
- Phase 2 studies are planned in multiple indications