

# RESULTS FROM A PHASE 1 STUDY OF THE SAFETY OF ORAL TRC102, A NOVEL 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

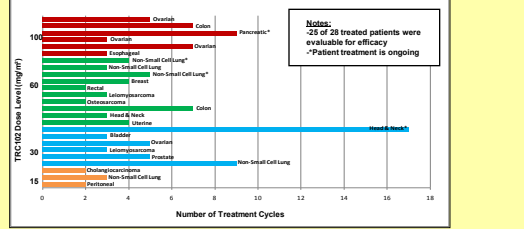
## RESULTS

This is an interim analysis of an ongoing study; data have not been audited. A total of 28 patients have been enrolled and evaluated as part of this presentation.

### Demographics

Characteristics	Number of Patients (n= 28)
Median Age	61
Gender	Male: 11 Female: 17
Screening ECOG Performance Status	ECOG 0: 9 ECOG 1: 19
Number of Prior Regimens	Median: 3 Range: 1 to 11
Race	Caucasian: 23 Black or African American: 1 Hispanic or Latino: 3 Asian: 1

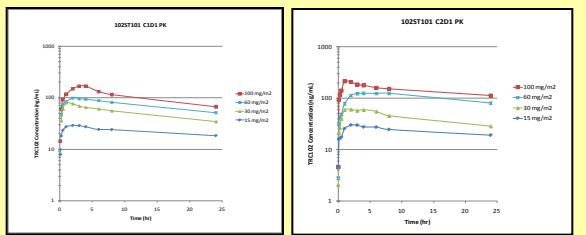
### Treatment Status



### 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

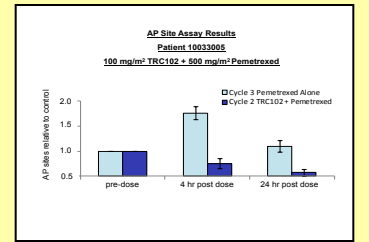
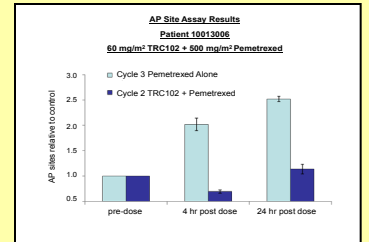
Cycle	Day	N	Cmax (ng/mL)	Half-life (hr)	AUC (hr·ng/mL)
Cycle 1 Day 1	15 mg/m <sup>2</sup>	3	19.7 (12.7 - 57.4)	37.3 (34.1 - 41.2)	287 (219 - 1132)
	30 mg/m <sup>2</sup>	6	64.3 (22.7 - 205.0)	21.8 (15.9 - 29.5)	1041 (263 - 3462)
	60 mg/m <sup>2</sup>	3	119.0 (63.7 - 126.0)	21.9 (17.6 - 29.9)	1991 (1093 - 2161)
	100 mg/m <sup>2</sup>	5	152.0 (83.5 - 417)	26.8 (14.1 - 44.0)	2312 (987 - 5331)
	Cycle 1 Day 4	15 mg/m <sup>2</sup>	3	68.1 (27.0 - 129)	41.5 (36.0 - 52.2)
30 mg/m <sup>2</sup>		6	126.0 (73.2 - 282.0)	30.9 (26.5 - 59.4)	1960 (1158 - 5230)
60 mg/m <sup>2</sup>		3	327.0 (155.0 - 626.0)	26.9 (25.8 - 44.8)	5812 (2632 - 11075)
100 mg/m <sup>2</sup>		5	247.0 (148.0 - 435.0)	25.0 (16.4 - 36.6)	3105 (2066 - 7969)
Cycle 2 Day 1		15 mg/m <sup>2</sup>	3	24.6 (18.2 - 56.0)	34.3 (5.6 - 55.4)
	30 mg/m <sup>2</sup>	6	57.4 (25.6 - 137.0)	21.9 (12.6 - 43.3)	943 (381 - 2071)
	60 mg/m <sup>2</sup>	3	103.0 (93.6 - 239.0)	26.7 (25.4 - 28.0)	1654 (1332 - 4556)
	100 mg/m <sup>2</sup>	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 <sup>2</sup> )	Cancer Type	Number of Prior Regimens	Response Assessment	Patient Status (N=25)
30	Squamous cell cancer of the tonsil metastatic to the lung	2	Partial Response	Treatment is ongoing in Cycle 18
	Squamous cell lung cancer	2	Stable Disease	Off study in Cycle 9 due to clinical progression
	Clear cell ovarian cancer	4	Stable Disease	Off study in Cycle 6 due to clinical progression & rising CA-125
	Prostate cancer	7	Stable Disease	Off study in Cycle 5 due to RECIST defined progression
60	Colon cancer	5	Stable Disease	Off study in Cycle 7 due to clinical progression
	Lung adenocarcinoma	1	Stable Disease	Treatment is ongoing in Cycle 5
	Squamous cell lung cancer	6	Stable Disease	Off study in Cycle 3 due to fatigue
	Squamous cell lung cancer	3	Stable Disease	Treatment is ongoing in Cycle 6
	Breast cancer	11	Stable Disease	Off study in Cycle 4 due to clinical progression
	Endometrial cancer	1	Stable Disease	Off study in Cycle 4 due to patient withdrawal of consent

TRC102 Dose (mg/m <sup>2</sup> )	Cancer Type	Number of Prior Regimens	Response Assessment	Patient Status (N=25)
100	Pancreas cancer	1	Stable Disease	Treatment is ongoing in Cycle 10
	Colon cancer	4	Stable Disease	Off study in Cycle 7 due to RECIST defined progression
	Clear cell ovarian cancer	8	Stable Disease	Off study in Cycle 7 due to RECIST defined progression
	Ovarian cancer	3	Stable Disease	Off study in Cycle 5 due to clinical progression

- 56% of 25 patients evaluable for efficacy had RECIST-defined partial response (PR) or stable disease (SD) including:**
- PR at 30 mg/m<sup>2</sup> in a patient with squamous cell head and neck cancer who remains on study at Cycle 18
  - SD at 30 mg/m<sup>2</sup> in a patient with squamous cell lung cancer who remained on study for 9 cycles
  - SD at 60 mg/m<sup>2</sup> in a patient with squamous cell lung cancer who had a 17% reduction in tumor burden and remains on study at Cycle 5
  - SD at 100 mg/m<sup>2</sup> in a patient with pancreatic cancer who remains on study at Cycle 10 with SD

### Safety

Preferred Term	Grade 1	Grade 2	Grade 3
Fatigue	6	2	1
Anorexia	5		
Nausea	2	3	
Neutropenia			3
Vomiting		3	
Mucosal inflammation	3		
Pruritus	3		
Diarrhea	1		1
Pyrexia	2		
Rash	2		

- \*anemia was excluded from this table
- The majority of possibly related adverse events were Grade 1 or 2
  - TRC102-related adverse events > Grade 3 were not observed

### Summary and Conclusions

- TRC102 was well-tolerated at 15, 30, and 60 mg/m<sup>2</sup>/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/m<sup>2</sup>/day x 4 days due to Grade 3 anemia in 50% of patients (extravascular hemolysis was 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, including non-small cell lung cancer