Final Results From a Phase 1 Study of Oral TRC102 (Methoxyamine HCl), an Inhibitor of Base-Excision Repair, to Potentiate the Activity of Pemetrexed in Patients with Refractory Cancer

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Presentation Outline

- TRC102 mechanism of action
- Phase 1 study objectives
- Phase 1 study methods
- Phase 1 study results
- Summary and conclusions

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/apyrimidinic (AP) sites
- 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

Objectives

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

Methods

- 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

Methods

- 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

Methods

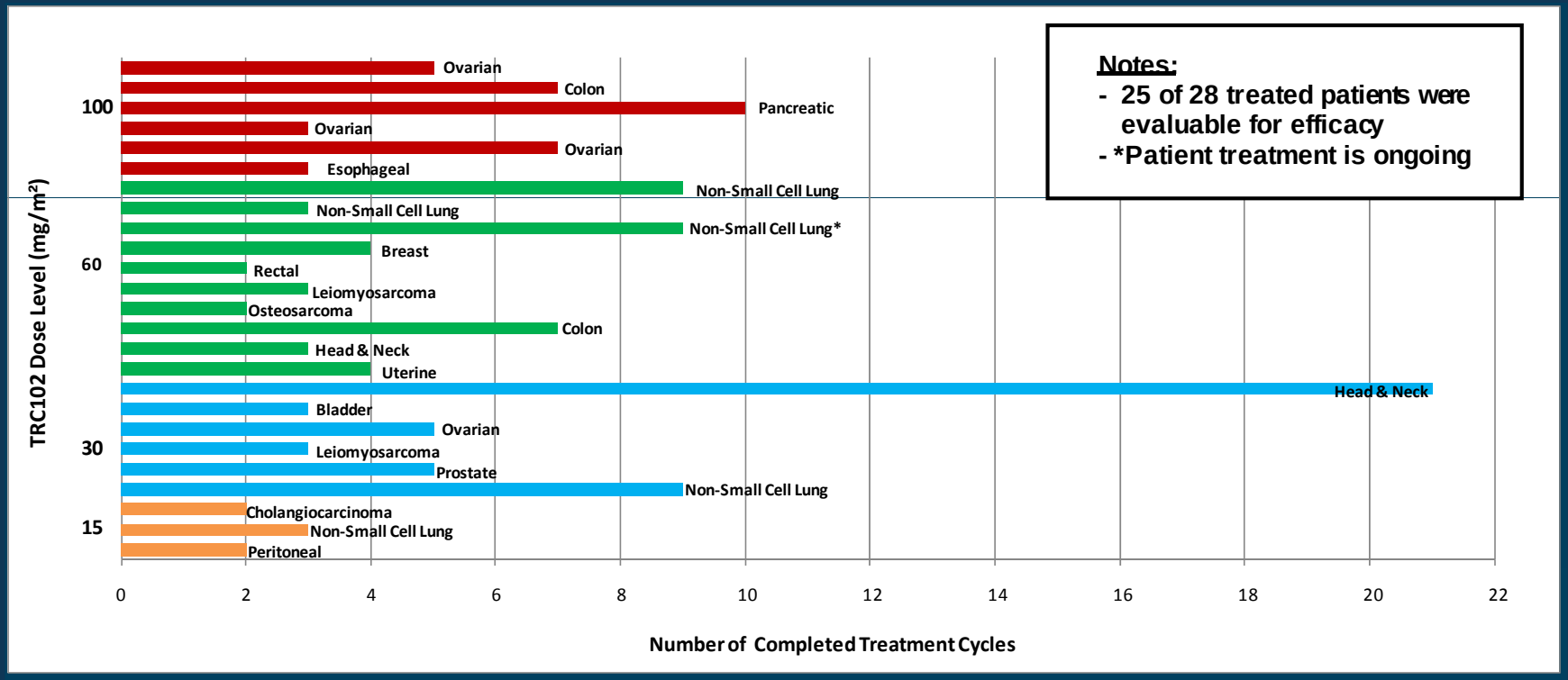
- All patients received TRC102 alone, dosed daily on Days 1-4 of an initial 2 week cycle, followed by the combination of pemetrexed on Day 1 and TRC102 on Days 1-4 every 3 weeks thereafter
- In Cycle 3, the Day 1 TRC102 dose was held in order to obtain the AP site assay sample after dosing with pemetrexed 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

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

Duration of Patient Treatment



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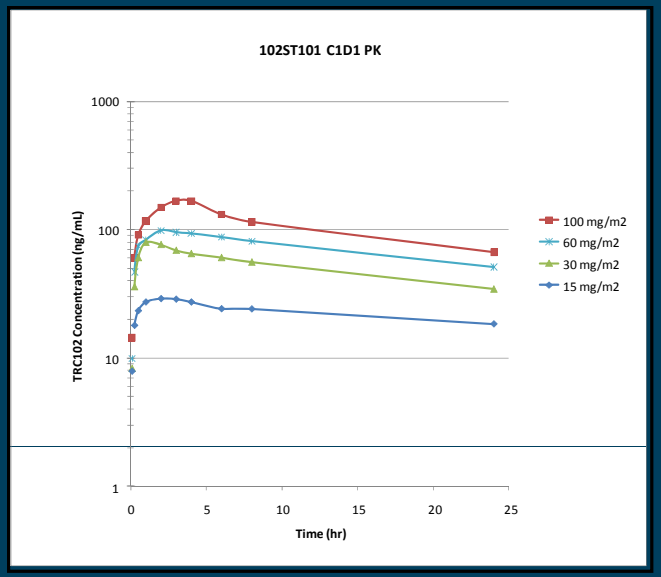
Pharmacokinetics

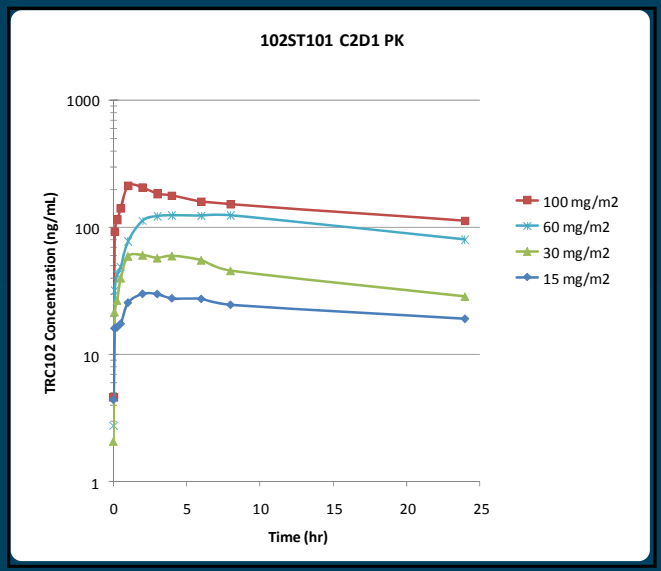
- TRC102 plasma levels required for *in vivo* activity (50 ng/mL) were achieved with daily oral administration in all 4 cohorts
- TRC102 accumulated with daily dosing (Days 1-4), but did not accumulate between cycles
- Pemetrexed and TRC102 coadministration did not alter the PK of either compound

Pharmacokinetics

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**





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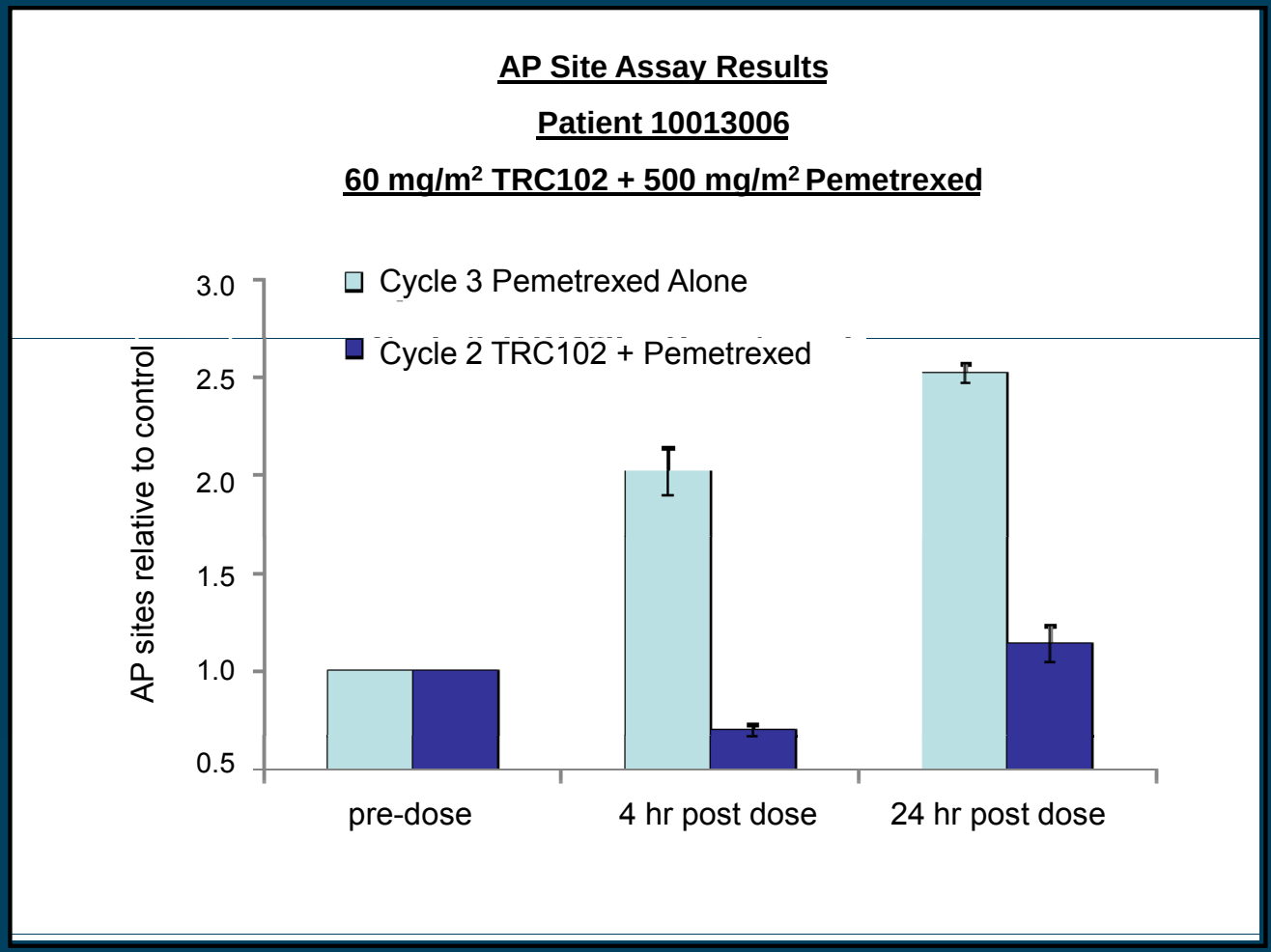
Pharmacodynamics – AP Site Assay

- Data confirmed TRC102's ability to covalently bind pemetrexed induced AP sites at all dose levels:
  - 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

TRC102 Dose	Number of Patients Evaluated	Positive	Negative
15 mg/m^2	1	1	0
30 mg/m^2	4	4	0
60 mg/m^2	3	3	0
100 mg/m^2	2	2	0

Pharmacodynamics AP-Site Assay



Efficacy

- 14 of 25 patients evaluable for efficacy (56%) had RECIST-defined partial response (PR) or stable disease (SD) including:
  - PR at 30 mg/m^2 TRC102 in a patient with metastatic squamous cell head and neck cancer who remained on study for 21 cycles (15 months)
  - SD at 30-60 mg/m^2 TRC102 in 4 of 5 NSCLC patients lasting up to 9 cycles (6 months)
  - One patient with lung adenocarcinoma had a 17% reduction in tumor burden at Cycle 5 (month 3) and treatment is ongoing in Cycle 9 (month 6)
  - SD at 100 mg/m^2 TRC102 in a patient with pancreatic cancer who remained on study for 10 cycles (7 months)

Efficacy

TRC102 Dose	Cancer Type	Prior Regimens	Response	Patient Status (N=25)
30 mg/m^2	Squamous cell cancer of the tonsil metastatic to the lung	2	Partial Response	Off study after 15 mo. of treatment due to RECIST defined progression
	Squamous cell lung cancer	2	Stable Disease	Off study after 6 mo. of treatement due to clinical progression
	Clear cell ovarian cancer	4	Stable Disease	Off study after 4 mo. of treatement due to clinical progression & rising CA-125
	Prostate cancer	7	Stable Disease	Off study after 3.5 mo. of treatment due to RECIST defined progression
60 mg/m^2	~~Lung adenocarcinoma~~	~~1~~	~~Stable Disease~~	~~Treatment is ongoing in Cycle 9 (mo. 6 of treatment)~~
	Squamous cell lung cancer	3	Stable Disease	Off study after 6 mo. of treatment due to RECIST defined progression
	Colon cancer	5	Stable Disease	Off study after 5 mo. of treatment due to clinical progression
	Breast cancer	11	Stable Disease	Off study after 3 mo. of treatment due to clinical progression
	Endometrial cancer	1	Stable Disease	Off study after 3 mo. of treatment due to patient withdrawal of consent
	Squamous cell lung cancer	6	Stable Disease	Off study after 2 mo. of treatment due to fatigue
100 mg/m^2	Pancreas cancer	1	Stable Disease	Off study after 7 mo. of treatment due to LFT elevation
	Colon cancer	4	Stable Disease	Off study after 5 mo. of treatment due to RECIST defined progression
	Clear cell ovarian cancer	8	Stable Disease	Off study after 5 mo. of treatment due to RECIST defined progression
	Ovarian cancer	3	Stable Disease	Off study after 3 mo. of treatment due to clinical progression

Safety – Non-Anemia Adverse Events

- The majority of possibly related adverse events were Grade 1 or 2
- TRC102-related adverse events > Grade 3 were not observed

TRC102 Possibly Related Events Ocurring in More than 1 Patient (N=28)*			
Preferred Term	**Grade 1**	**Grade 2**	**Grade 3**
Neutropenia		1	3
Fatigue	6	3	1
Nausea	3	3	
Vomiting		3	
Anorexia	6		
Mucosal inflammation	3		
Pruritus	3		
Pyrexia	3		
Rash	2		

*anemia excluded from this table

Safety – Frequency of Anemia

- Anemia was the only dose-limiting toxicity observed
- The maximum tolerated TRC102 dose was exceeded at 100 mg/m^2/day x 4 due to Grade 3 anemia in 50% of patients by end of Cycle 2 (month 2)
- Dose-limiting anemia was predicted by animal toxicology studies where extravascular hemolysis occurred at doses 20-fold higher than required for efficacy

Safety – Frequency of Anemia

Anemia by TRC102 Dose Level (N=28)				
TRC102 Dose	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
15 mg/m^2 (N=4)	1	2		
30 mg/m^2 (N=7)	4	1	2	
60 mg/m^2 (N=11)	1	6	3	1
100 mg/m^2 (N=6)		3	3	
TOTAL	**6**	**12**	**8**	**1**

Summary and Conclusions

- TRC102 was well-tolerated at 15, 30, and 60 mg/m^2/day on Days1-4 of a 21-day cycle, 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^2/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)

Summary and Conclusions

- 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

Summary and Conclusions

- RECIST-defined partial response and stable disease in refractory patients (including 4 of 5 NSCLC patients for up to 6 months) 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