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# 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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## 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 (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 cancer
- 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

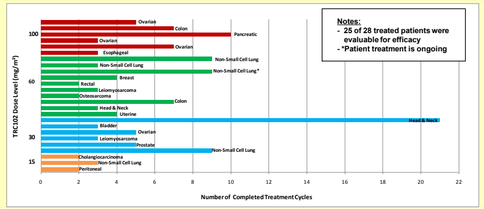

## RESULTS

One patient remains on study and the clinical database remains open; thus data included in this presentation have not been quality assured. 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<br>Female: 17 |
| Screening ECOG Performance Status | ECOG 0: 9<br>ECOG 1: 19 |
| Number of Prior Regimens | Median: 3<br>Range: 1 to 11 |
| Race | Caucasian: 23<br>Black or African American: 1<br>Hispanic or Latino: 3<br>Asian: 1 |

### Treatment Status



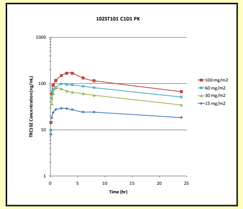

### Pharmacokinetics

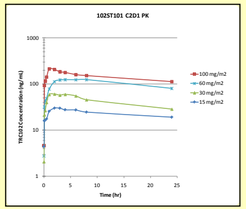
Clinical PK analyses up to the 100 mg/m² TRC102 dose level showed:

- 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/m² | 3 | 19.7 (12.7 - 57.4) | 37.3 (34.1 - 41.2) | 287 (219 - 1132) |
| 30 mg/m² | 6 | 64.3 (22.7 - 205.0) | 21.8 (15.9 - 25.5) | 1041 (263 - 3462) |
| 60 mg/m² | 3 | 119.0 (63.7 - 126.0) | 21.9 (17.6 - 29.9) | 1991 (1093 - 2161) |
| 100 mg/m² | 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/m² | 3 | 68.1 (27.0 - 129) | 41.5 (36.0 - 52.2) | 1136 (188 - 2580) |
| 30 mg/m² | 6 | 126.0 (73.2 - 282.0) | 30.9 (26.5 - 59.4) | 1960 (1158 - 5230) |
| 60 mg/m² | 3 | 327.0 (155.0 - 626.0) | 26.9 (25.8 - 44.8) | 5812 (2632 - 11075) |
| 100 mg/m² | 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/m² | 3 | 24.6 (18.2 - 56.0) | 34.3 (5.6 - 55.4) | 297 (126 - 1186) |
| 30 mg/m² | 6 | 57.4 (25.6 - 137.0) | 21.9 (12.6 - 43.3) | 943 (381 - 2071) |
| 60 mg/m² | 3 | 103.0 (93.6 - 239.0) | 26.7 (25.4 - 28.0) | 1654 (1332 - 4556) |
| 100 mg/m² | 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



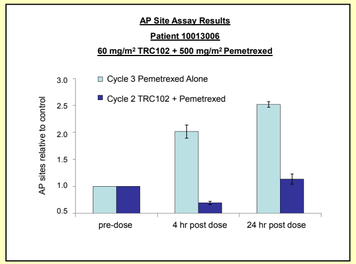




### Pharmacodynamics

Clinical PD data confirmed TRC102's ability to covalently bind pemetrexed induced AP sites 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/m² | 1 | 1 | 0 |
| 30 mg/m² | 4 | 4 | 0 |
| 60 mg/m² | 3 | 3 | 0 |
| 100 mg/m² | 2 | 2 | 0 |




### Efficacy

| TRC102 Dose | Cancer Type | Prior Regimens | Response | Patient Status (N=25) |
|---|---|---|---|---|
| 30 mg/m² | 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/m² | 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/m² | 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 |

**14 of 25 patients evaluable for efficacy (56%) had RECIST-defined partial response (PR) or stable disease (SD) including:**

- PR at 30 mg/m² 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/m² 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/m² TRC102 in a patient with pancreatic cancer who remained on study for 10 cycles (7 months)

### Safety

| 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 was excluded from this table

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

| Anemia by TRC102 Dose Level (N=28) | | | | |
|---|---|---|---|---|
| TRC102 Dose | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| 15 mg/m² (N=4) | 1 | 2 | | |
| 30 mg/m² (N=7) | 4 | 1 | 2 | |
| 60 mg/m² (N=11) | 1 | 6 | 3 | 1 |
| 100 mg/m² (N=6) | | 3 | 3 | |
| TOTAL | 6 | 12 | 8 | 1 |

- Anemia was the only dose-limiting toxicity observed
- The maximum tolerated TRC102 dose was exceeded at 100 mg/m²/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

### 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 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 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