9055

Phase I Study of TRC102 in Combination with Cisplatin and Pemetrexed in Patients with Advanced Solid Tumors / Phase II Study of TRC102 with Pemetrexed in Patients Refractory to Pemetrexed and Cisplatin or Carboplatin (NCI P9837) (COH CCSG, UM1CA186717)

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BACKGROUND

- Treatment options remain limited in malignant pleural mesothelioma refractory to pemetrexed +/- platinum. TRC102 (methoxyamine hydrochloride) is a novel biochemical inhibitor of the BER pathway
- Available data support the hypothesis that TRC102 bound DNA is a substrate for topoisomerase II, which cleaves TRC102-bound DNA sites to produce strand breaks in cancer cells that cause cellular apoptosis and enhance the cytotoxic effects of chemotherapy

METHODS

- **Arm A:** This arm was a Phase I trial to select a Recommended Phase 2 Dose (RP2D) of TRC102 in combination with Cisplatin and Pemetrexed in patients with advanced solid tumors
- **Arm B:** This arm was designed as the first stage of a two stage (Gehan) design trial of patients with mesothelioma who had progressed while being treated with or had recurred within 6 months of being treated with pemetrexed + cisplatin frontline

OBJECTIVES

PRIMARY OBJECTIVES

- **Arm A:** Determine the MTD, toxicities, assess preliminary safety and activity in an expansion cohort of chemotherapy-naïve advanced unresectable malignant mesothelioma patients, and describe responses
- **Arm B:** Detect activity of the combination of TRC 102 and pemetrexed

SECONDARY OBJECTIVES

- PKs, PDs, feasibility of establishing pleural and peritoneal effluent-derived cell lines for *in vitro* studies, and evaluate objective clinical responses

Table 1. Demographic and Clinical Characteristics

		Arm A (Phase I)	Arm B (Phase II)	All
Number of Patients Treated:		16	14	30
Median Age (range) yrs.:		68.5 (57-76)	74.5 (56-85)	70 (56-85)
Gender:				
	Female	5 (31%)	3 (21%)	8 (27%)
	Male	11 (69%)	11 (79%)	22 (73%)
Race:				
	Asian	2 (13%)	0 (0%)	2 (7%)
	Caucasian	13 (81%)	13 (93%)	26 (87%)
	Hispanic	1 (6%)	0 (0%)	1 (3%)
	Unknown	0 (0%)	1 (7%)	1 (3%)
Performance Status (ECOG)				
	0	8 (50%)	3 (21%)	11 (37%)
	1	8 (50%)	11 (79%)	19 (63%)
Primary Site:				
	Bladder	2 (13%)	0 (0%)	2 (7%)
	Chest	1 (6%)	0 (0%)	1 (3%)
	Left parotid gland	1 (6%)	0 (0%)	1 (3%)
	Lung	8 (50%)	8 (57%)	16 (53%)
	Mesothelioma	1 (6%)	0 (0%)	1 (3%)
	Parotid-left	1 (6%)	0 (0%)	1 (3%)
	Peritoneum	0 (0%)	3 (21%)	3 (10%)
	Pleura	0 (0%)	3 (21%)	3 (10%)
	Right parotid gland	1 (6%)	0 (0%)	1 (3%)
	Right posterior neck	1 (6%)	0 (0%)	1 (3%)

Table 2. Treatment Summary Table

Dose Level	Number pts. treated	Number pts. excluded from course one toxicity evaluation	Number pts. excluded from response evaluation	Number completed cycles median (range) (excluding ineligible pts. for response)	Number pts. with DLTs	DLT description	Best responses during therapy (all eligible pts. for response)
TAC 1A: TRC102 50 mg PO D1-4; Pemetrex 500 mg/m2 IV over 10 min D1; Cisplatin 60 mg/m2 IV over 30-60 min D1	3	0	0	6 (2 - 6)	0	---	SD - 2 PD - 1
TAC 2A: TRC102 75 mg PO D1-4; Pemetrex 500 mg/m2 IV over 10 min D1; Cisplatin 60 mg/m2 IV over 30-60 min D1	4	1*	0	2 (1 – 22)	0	---	PR - 1 PD - 3
TAC 3A: TRC102 100 mg PO D1-4; Pemetrex 500 mg/m2 IV over 10 min D1; Cisplatin 60 mg/m2 IV over 30-60 min D1	3	0	0	20 (10 – 25)	0	---	PR - 2 SD - 1
TAC 4A: TRC102 100 mg PO D1-4; Pemetrex 500 mg/m2 IV over 10 min D1; Cisplatin 75 mg/m2 IV over 30-60 min D1	6	1**	0	4.5 (3 – 12)	0	---	SD - 6
TAC 1B: TRC102 50mg PO on D1-4; Pemetrex 500mg/m2 IV over 10 min D1	14	NA	1***	4 (0 – 15)	0	---	PR – 1 UPR – 1**** SD – 8 PD – 3 NA - 1

*-Pt. 6 received only 68% of TRC 102.
**-Pt. 30 mistakenly dosed at 50mg/day TRC 102.
*** - Pt. 12 refused treatment prior to the end of course 1.
****-Pt. 18 first assessment on 9/18/18 was PR, progressed on next assessment 10/31/18.

Figure 1. Progression-free Survival

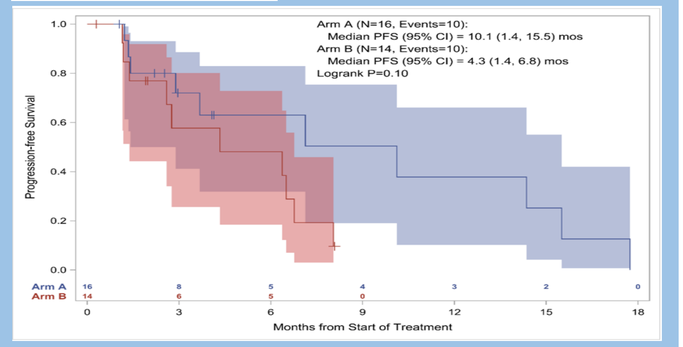

Figure 2. Overall Survival

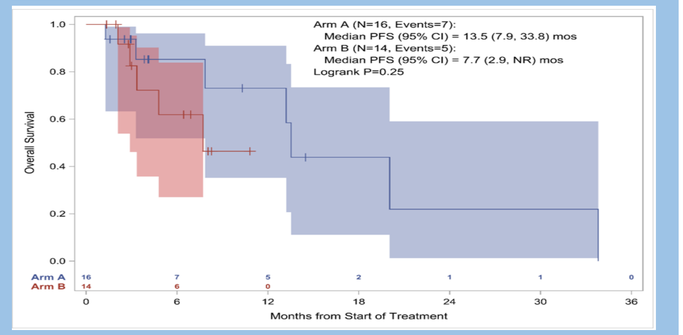

Table 3. Adverse Events Table

	Arm A - Phase I N=16						Arm B – Phase II N=14					
	Course 1			Subsequent Courses			Course 1			Subsequent Courses		
Adverse Event*	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Neutrophil count decreased	2 (13%)	---	---	2 (13%)	1 (6%)	---	1 (7%)	---	---	2 (14%)	1 (7%	1 (7%)
Platelet count decreased	---	---	---	1 (6%)	---	1 (6%)	---	---	---	1 (7%)	---	---
Lymphocyte count decreased	2 (13%)	1 (6%)	---	3 (19%)	4 (25%)	---	3 (21%)	---	---	3 (21%)	4 (29%)	---
Anemia	2 (13%)	---	---	7 (44%)	2 (13%)	---	2 (14%)	---	---	6 (43%)	1 (7%)	---
White blood cell decreased	2 (13%)	1 (6%)	---	3 (19%)	1 (6%)	---	1 (7%)	2 (14%)	---	3 (21%)	1 (7%)	---
Fatigue	3 (19%)	---	---	4 (25%)	1 (6%)	---	1 (7%)	---	---	1 (7%)	1 (7%)	---
Hypophosphatemia	---	1 (6%)	---	1 (6%)	1 (6%)	---	1 (7%)	---	---	2 (14%)	---	---
Nausea\Vomiting	2 (13%)	---	---	1 (6%)	1 (6%)	---	---	---	---	---	---	---
Blood bilirubin increased	---	---	---	---	1 (6%)	---	---	---	---	---	---	---
Febrile neutropenia	---	---	---	---	1 (6%)	---	---	---	---	---	---	---
Hypertension	---	---	---	---	1 (6%)	---	---	---	---	---	---	---
CD4 lymphocytes decreased	---	---	---	---	---	---	---	1 (7%)	---	---	---	---
Hyponatremia	---	---	---	---	---	---	---	---	---	---	1 (7%)	---
Hypoalbuminemia	---	---	---	---	---	---	2 (14%)	---	---	2 (14%)	---	---

* Grade 2 and above adverse events related to treatment with at least two patients experiencing a grade 2 or one patient experiencing a grade 3 or higher.

RESULTS

- In **Arm A** dose escalation, 16 pts (11M/5F) were treated; 9 evaluable through 3 TRC102 dose levels (50, 75, and 100 mg/day, PO), with CDDP 60 mg/m^2 and pemetrexed 500 mg/m^2 (levels 1- 3); and 5 evaluable at TRC102 100 mg/day PO, CDDP 75 mg/m^2, pemetrexed 500 mg/m^2 (level 4). Cycles were every 21 days. There were no DLT's, establishing level 4 as the RP2D. The only grade 4 treatment-related AE was thrombocytopenia on cycle 22 (level 2) . Cycle 1 grade 3 AEs were 1 hypophosphatemia (level 1), 1 leukopenia (level 2) and 1 lymphopenia (level 4). There were 3 PRs (all parotid salivary gland tumors). Median PFS (95%CI) = 10.1% (1.4 – 15.5) mos
- **Arm B** was designed as the first stage of a two stage Gehan design trial of patients with mesothelioma who had progressed on or recurred within 6 months of pemetrexed + platinum frontline treatment. 14 pts were treated with TRC102 50 mg/day D1-4 and pemetrexed 500 mg/m^2 every 21 days. There were 2 PRs (both in epithelioid cancer of which 1 was confirmed), meeting the pre-specified criteria for continued interest (>0/14). Median PFS (95% CI) was 4.3 (1.4 - 6.8) mos. 8 pts had stable disease for at least 1 cycle (4 stable at cycles 6, 10, 12 and 12). There were 1 grade 4 neutropenia, 4 grade 3 lymphopenia, 2 grade 3 leukopenia and 1 grade 3 for each of the following – anemia, neutropenia, fatigue, hyponatremia and CD4 lymphocytes decreased

CONCLUSION

- TRC102 in combination with CDDP and pemetrexed exhibited antitumor activity, particularly in salivary gland tumors
- TRC102 has a tolerable safety profile
- The combination of TRC102 and pemetrexed demonstrated activity in malignant mesothelioma that progressed on prior pemetrexed
- Additional studies are warranted to confirm preliminary signals of activity