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Phase II Trial of TRC102 (methoxyamine HCl) in Combination with Temozolomide (TMZ) in Patients with Advanced Non-Small Cell Lung Cancer

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I have no financial relationships to disclose.

I will discuss investigational use in my presentation

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Preclinical Background

- TRC102 inhibits the base excision repair (BER) pathway through binding to DNA abasic sites
  - BER is a resistance mechanisms to alkylators

- Preclinical cell line and xenograft models demonstrated TRC102 synergy with alkylating agents
  - Synergy of TRC102 + TMZ demonstrated *in vivo* in human colon cancer xenografts in nude mice Liu et al. Clin Cancer Res. 2002 Sep;8(9):2985-91.

Clinical Background

- TRC102 + TMZ phase 1 part completed
- 52 patients with a variety of solid tumors
- Combination well-tolerated with acceptable toxicity profile
- MTD and RP2D determined
- Partial response in colon cancer (n=1), NSCLC-squam (n=1), granulosa cell ovarian tumor (n=2)
- Correlative studies revealed induction of Rad51 signal indicating DDR response
- Analysis of tumor biopsy from a colon cancer patient with PR revealed MGMT methylation

Methods

- Single arm open label – metastatic NSCLC expansion cohort
- Pts treated at RP2D
  - 125 mg TRC102 (100 mg for BSA < 1.6) and 150 mg/m2 TMZ on D1-5 of a 28-day cycle
- Imaging (CT) evaluation every 2 cycles
- CTC analysis at baseline and every 2 cycles
- 2-stage design
  - futility defined as < 2 responses in first 16 pts

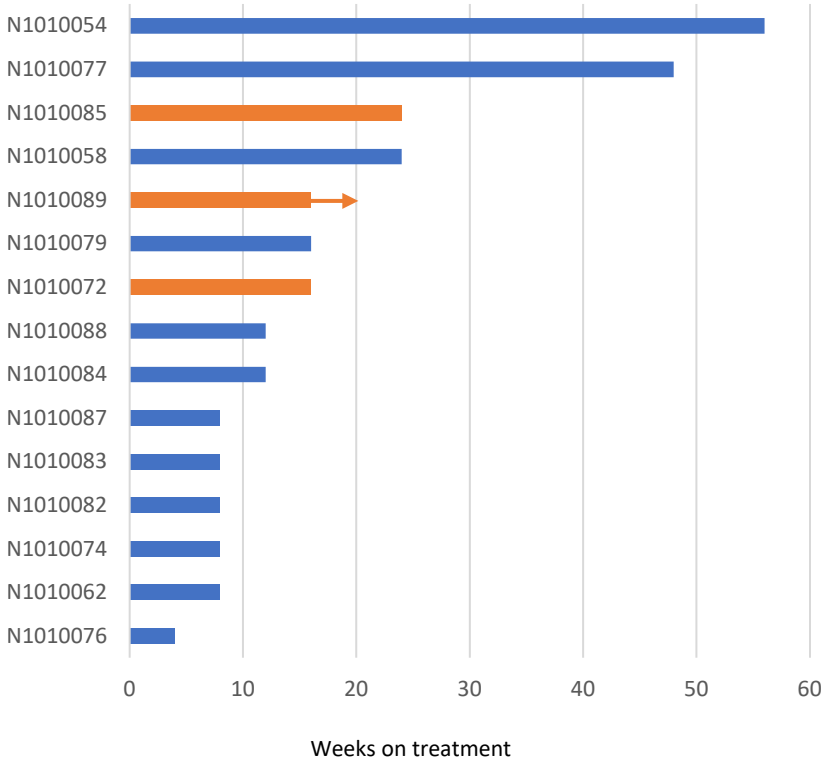
Patient Characteristics

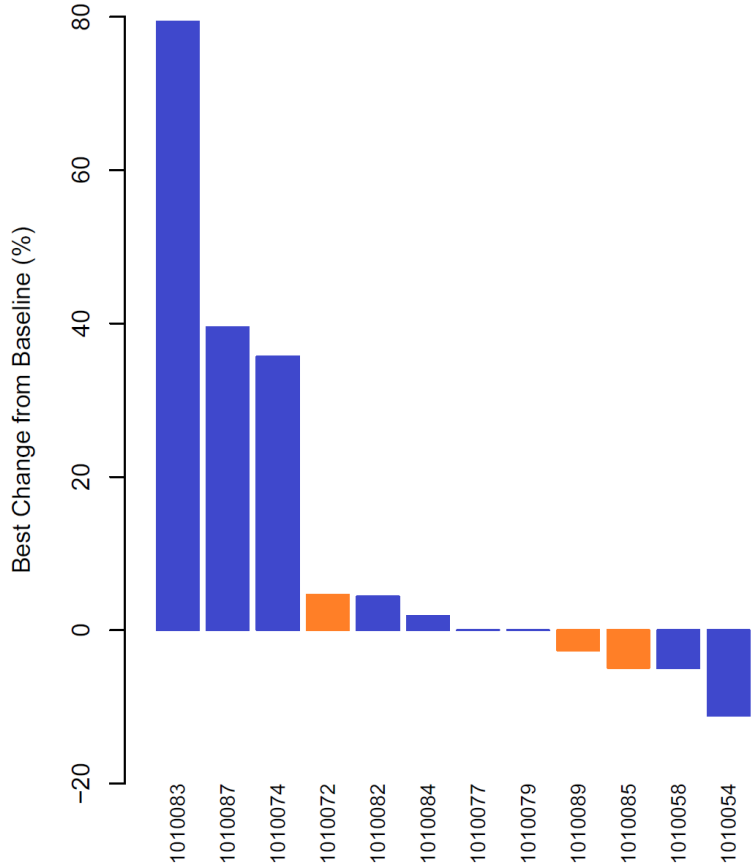
Number of treated patent	16
Gender	12 men, 4 women
Ethnicity/race	1 Hispanic, 3 Asian, 2 Black/African American, and 10 Caucasian
Histology	12 adenocarcinoma, 3 squamous cell carcinoma (15 pts evaluable)
Median age	69
Median number of prior lines of therapy	3 Nearly all pts (15) previously received anti-PD-(L)1

Results

- Median number of treatment cycles: 3 (range 1-14)
- 12 pts had at least one radiographic assessment of response
- 3 pts experienced clinical progression before first imaging evaluation
- 9 pts had stable disease as best response
  - Median duration of 12 weeks (range 8-56 wks)
  - 4 pts experienced prolonged SD > 6 cycles (24 wks)
- No objective responses (PR/CR) per RECIST 1.1
- Grade 3 TRAEs include lymphopenia (4) and anemia (1).

Time on Study





Adenocarcinoma

Squamous cell carcinoma

Molecular Characteristics of Tumors

Patient	Pathogenic mutations
1010054*	SMAD4
1010058*	PIK3CA, KRAS
1010062	IDH1 missense
1010074	NGS not performed – EGFR/ALK WT
1010072* (squamous)	NGS not performed
1010076	NGS not performed – EGFR/ALK/ROS1 WT
1010077*	NF1, STK11
1010079*	NGS not performed – EGFR/ALK/ROS1 WT
1010082	EGFR, TP53
1010083	KRAS, TP53, EP300, EML4, MAX, U2AF1, SMC3
1010084*	GNAS, MSI stable, TMB 4
1010085* (squamous)	NGS not performed
1010087	FGFR3 amp, MSI stable, TMB 7
1010088*	EGFR, SMAD4, CTNNB1, CDK4 amp, CSF3R amp, MDM2 amp, MYCL1 amp, MSI stable, TMB 5
1010089* (squamous)	PIK3CA amp, TP53, MSI stable, TMB 3

* Denotes patients with stable disease on first radiographic evaluation

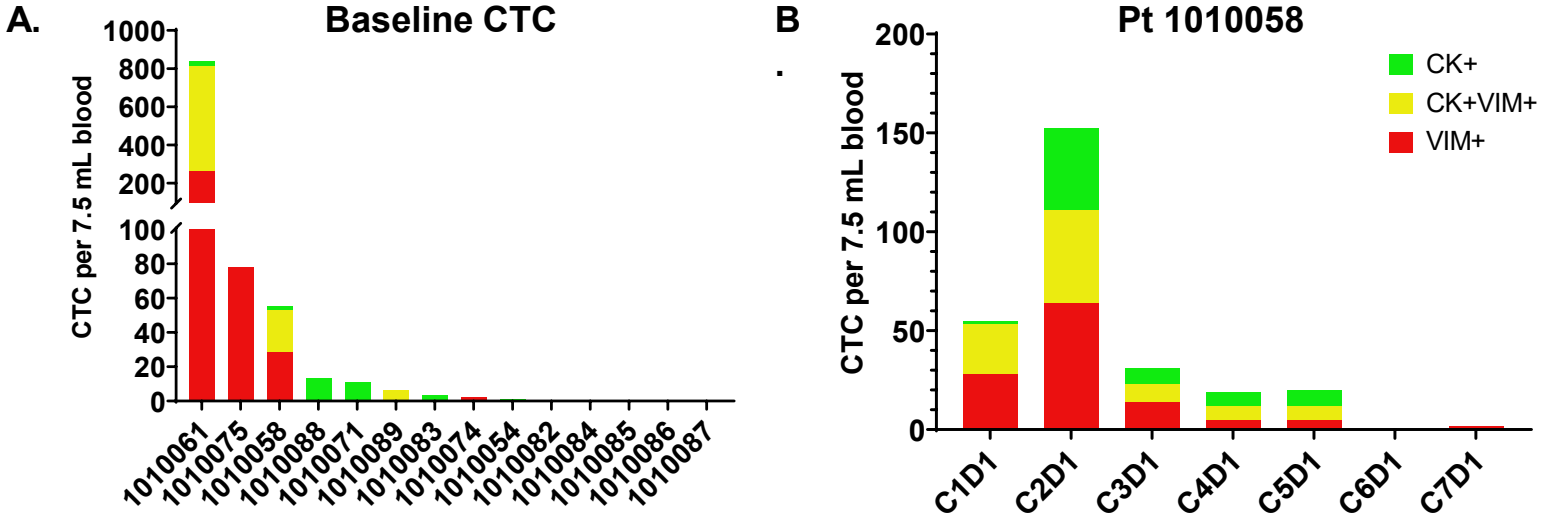
Adverse Events

	Number of Patients with Grade 2 AE	Number of Patients with Grade 3 AE
Anemia	1	1
Blood bilirubin increased	2	0
Dysphagia	1	0
Fatigue	1	0
Lymphocyte count decreased	4	4
Nausea	2	0
Thrush	1	0
Vomiting	1	0
White blood cell decreased	1	0

Correlative Studies

- Blood specimens for circulating tumor cell (CTC) analysis were collected at baseline and at the start of each cycle to assess the effects of the study treatment on the number of CTCs and the levels of epithelial-mesenchymal transition (EMT).
- Cells were stained with antibodies targeting the tumor marker MUC1 and pan-leukocyte marker CD45 (for exclusion), as well as pan-cytokeratin and vimentin to detect EMT.
- 88% (14/16) of patients were evaluable at baseline for CTCs, and CTCs were detected in 64% (9/14) of evaluable patients (median: 11 CTC per 7.5 mL blood, range: 1–837).
- Presence of both epithelial (CK+) and mesenchymal (VIM+) phenotypes was observed in most patients. No treatment-induced shift in EMT phenotype was observed.
- No biopsies were collected for this cohort.

Correlative Studies – CTC analysis



CTC analysis of the NSCLC cohort. CTCs were enriched from blood specimens using the antibody-independent ApoStream technology, and were detected using a validated, quantitative immunofluorescence assay.[1] **A.** Number of $MUC1^{+}CD45^{-}$ CTC per 7.5mL blood at baseline in 14 evaluable patients. EMT phenotype was measured using pan-cytokeratin (CK) to detect epithelial cells and vimentin (VIM) to detect mesenchymal cells. **B.** Time course of longitudinal blood sampling for patient 1010058 shows a consistent EMT phenotype during the study treatment. Blank values indicate zero CTCs were detected.

1. Balasubramanian P, Kinders RJ, Kummar S, Gupta V, Hasegawa D, et al. (2017) Antibody-independent capture of circulating tumor cells of non-epithelial origin with the ApoStream® system. PLOS ONE 12(4): e0175414. https://doi.org/10.1371/journal.pone.0175414

Conclusion

- TRC102 with TMZ well tolerated at RP2D
- Although no PR/CR, majority of treated pts derived clinical benefit
- All pts with squamous histology had disease control
  - heavily pretreated & ICI-refractory
- reasonable option for pts with limited second line options
- reliable markers crucially needed

Special thanks to

Patients and their families