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Phase 2 trial of TRC102 (methoxyamine HCl) with temozolomide (TMZ) in patients with granulosa cell ovarian cancer

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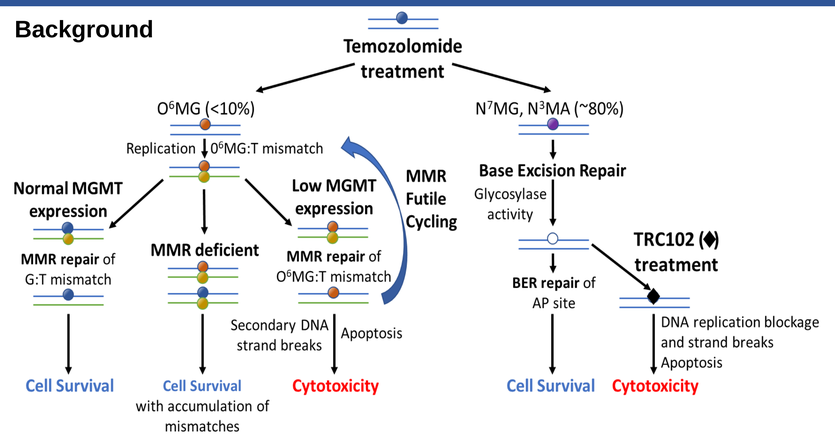
Background



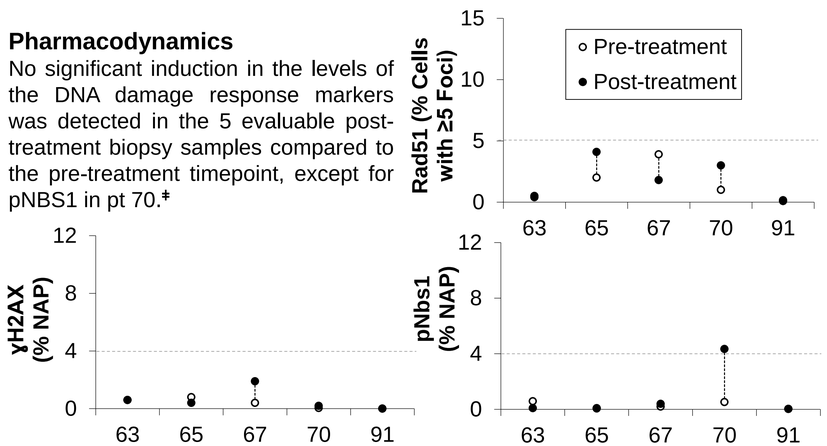
- TRC102 is a novel small molecule that binds to apurinic/apyrimidinic sites, inhibiting base excision repair (BER), which is implicated as a pathway of resistance to alkylating agents.
- The phase 1 trial of this combination reported 4 patients (pts) with partial response, two of which were of granulosa cell ovarian cancer (GCOC) histology.

Material and Methods

- Dosing: TRC102 at 125 mg (100 mg for BSA < 1.6) and TMZ at 150 mg/m^2 orally on day (D) 1-5 in 28-day cycle (C).
- Mandatory paired biopsies: C1D1 pretreatment and C1D4 3-4 hours after drug administration.
- Optional blood samples for circulating tumor cells (CTC): prior to treatment on C1D1, C1D4, D1 for subsequent cycles, and at progression.

Pharmacodynamics

No significant induction in the levels of the DNA damage response markers was detected in the 5 evaluable post-treatment biopsy samples compared to the pre-treatment timepoint, except for pNBS1 in pt 70.‡



Results

Characteristics	No. of Patients (n = 9)
Median Age (range)	53 (21-79)
Histology	
Adult Granulosa Cell Ovarian Cancer	7 (78%)
Juvenile Granulosa Cell Ovarian Cancer	2 (22%)
Race/Ethnicity	
White, not Hispanic	8 (89%)
Black or African-American, not Hispanic	1 (11%)
Median prior lines of therapy (range)	6 (3-9)

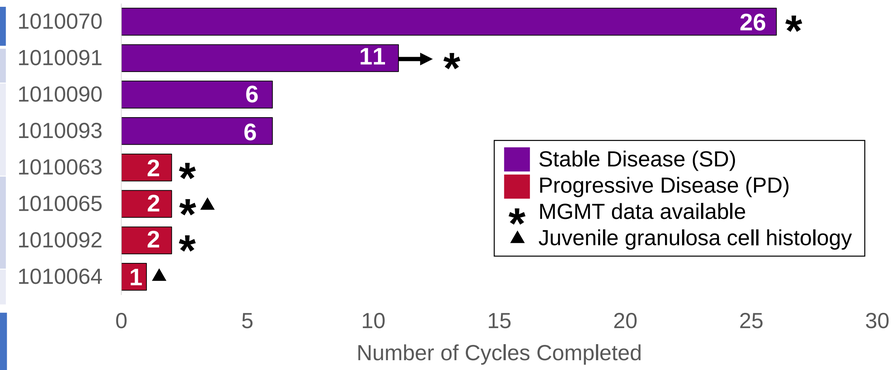
Treatment-related Adverse Events	Grade 1 n = 8	Grade 2 n = 4	Grade 3 n = 1
Nausea	6	1	0
Anemia	5	1	0
Fatigue	4	0	0
Emesis	3	1	1
Lymphopenia	2	1	0
Leukopenia	1	0	0
Neutropenia	1	1	0
Thrombocytopenia	1	0	0
Diarrhea	1	0	0
Hypomagnesemia	1	0	0
Alkaline phosphatase elevation	1	0	0
Headache	1	0	0
Back ache	0	1	0
Infusion site extravasation	0	1	0

No toxicity-related study discontinuations or deaths were reported.

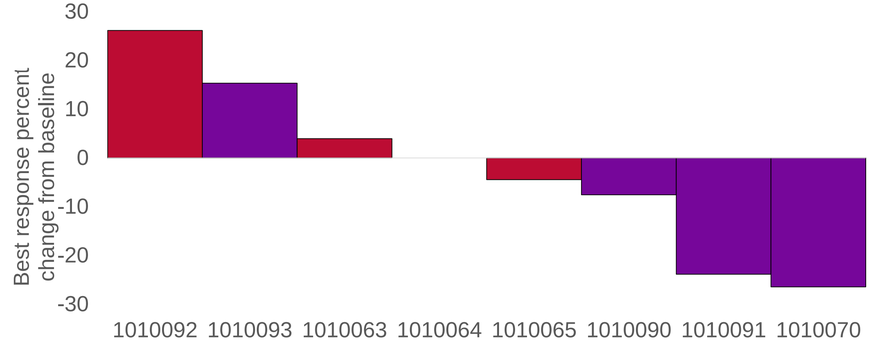
MGMT analysis

Patient ID	MGMT promoter	MGMT IHC	Best response
1010063	unmethylated	positive	PD
1010065	unmethylated	positive	PD
1010067	unmethylated	positive	not evaluable
1010070	unmethylated	positive	SD
1010091	unmethylated	positive	SD
1010092	unmethylated	positive	PD

All 6 pts had unmethylated MGMT, consistent with MGMT IHC positivity.



The median PFS for the 8 evaluable pts was 3.7 months. Four pts had stable disease (SD) as their best response. Of those with SD, one pt completed 26 Cs prior to progression, one pt completed 11 Cs as of data cut-off but continues on study. Five pts (and one not evaluable pt) had enough biopsy sample for MGMT data analyses.



Conclusions

- TRC102 combined with TMZ was well-tolerated.
- Durable disease control seen in 4 pts, which is promising in this heavily pre-treated GCOC cohort.
- MGMT analysis suggests that unmethylated MGMT status and protein expression does not preclude disease control with TRC102/TMZ combination therapy.
- Analysis of CTCs and biopsy samples are ongoing to further elucidate possible biomarkers of response.

‡ Biomarker effect level cutoff defined in *Wilsker DR, Barrett AM, Dull AB, Lawrence SM, Hollingshead MG, Chen A, Kummar S, Parchment RE, Doroshow JH, Kinders RJ. Evaluation of Pharmacodynamic Responses to Cancer Therapeutic Agents Using DNA Damage Markers. Clin Can Res 2019 May 15; 25(10):3084-3095*

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