Phase I clinical trial of temozolomide and methoxyamine (TRC-102) in patients with advanced solid tumors

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Background

- Temozolomide (TMZ) is an alkylating agent used in the treatment of glioblastoma multiforme, melanoma and pancreatic neuroendocrine tumors.
- Temozolomide acts by generating DNA adducts that are repaired by direct DNA and base excision repair mechanisms.
- Methoxyamine (MX, TRC-102) is a small molecule that acts by binding to apurinic and apyrimidinic sites after removal of N^3-methyladenine and N^7-methylguanine, inhibiting site recognition of apurinic/apyrimidinic (AP) endonuclease.
- Preclinical models in human tumor xenografts demonstrate that MX potentiates TMZ by inhibiting the base excision repair component of temozolomide induced DNA damage.

Objectives

- We conducted a phase I study to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of intravenous methoxyamine when administered with oral temozolomide.

Methods

Eligibility Criteria

- Histologically confirmed solid tumor with progression on standard therapy and not amenable to further surgical, radiation therapy or chemotherapeutic treatments
- At least 3 weeks since prior chemotherapy (6 weeks for mitomycin-C and nitrosoureas) or radiation therapy with recovery to ≤ grade 1 treatment related toxicities per CTCAE version 3.0
- Age ≥ 18 years
- ECOG performance status of ≤ 2
- Life expectancy of ≥ 12 weeks
- Normal organ and marrow function
- Able to understand and provide written informed consent
- No central nervous system involvement
- Prior temozolomide therapy permitted

Dose Levels

Dose Level	Temozolomide (mg/m^2/day) x 5 days	Methoxyamine (mg/m^2) x 1
Level -1	100	15
Level 1	150	15
Level 2	150	30
Level 3	150	60
Level 4	150	90
Level 5	150	120
Level 6	150	150
Level 7	200	150

Administration Schedule

Dose Levels 1-3 (DLT period of 42 days during cycle 1)

Cycle 1

	D1	D2	D3	D4	D5		D38	D39	D40	D41	D42
MX				X			X				
TMZ	X						X	X	X	X	X

Subsequent cycles (cycle length 28 days)

	Day 1	Day 2	Day 3	Day 4	Day 5
MX	X				
TMZ	X	X	X	X	X

Dose Levels 4-7 (DLT period of 28 days, cycle length 28 days)

	Day 1	Day 2	Day 3	Day 4	Day 5
MX	X				
TMZ	X	X	X	X	X

- Methoxyamine administered as a single one hour infusion.
- Temozolomide administered orally once daily—within 5 minutes of methoxyamine infusion where appropriate.
- Standard 3+3 dose escalation strategy used.
- Blood collected for pharmacokinetic analysis and Comet assay.

Results

Patient Baseline Characteristics

	Number of patients (%) (n=38)
Gender	
Male	17 (45)
Female	21 (55)
Race	
White	31 (82)
African American	6 (16)
Asian	1 (2)
Primary Site of Disease	
Colorectal	11 (29)
Lung	6 (16)
Pancreas	4 (11)
Head and neck	4 (11)
Soft tissue	3 (8)
Neuroendocrine	3 (8)
Melanoma	1 (2)
Breast	1 (2)
Ovarian	1 (2)
Cholangiocarcinoma	1 (2)
Gastroesophageal junction	1 (2)
Endometrial	1 (2)
Unknown primary	1 (2)

Median age: 59.5 years (38-76)
Median number of cycles received: 2.9 (1-13)

Dose Limiting Toxicities

- DLT period 42 days for dose levels 1-3, 28 days for DL 4-7.
- DLT—any grade 3 non-heme (MX related), grade 4 non-heme or grade 4 neutropenia, anemia, thrombocytopenia >7 days felt due to MX or MX+TMZ during the DLT period.
- Grade 3 psychosis/grade 4 confusion at DL1, cohort expanded.
- Grade 3 allergic reaction at DL1, cohort suspended.
  - Allergic reaction deemed unrelated to study drug, 10 pts assessed at DL1.
- No dose defining DLTs observed through DL7, MTD not reached.
- No further escalation as pk and pharmacodynamics optimized.

Adverse Events for all Cycles

Adverse Event	Toxicity Grade: Number (%), n=38 1-2	3	4
Hematologic			
ALT, SGPT	3 (8)		
AST, SGOT	3 (8)		
Creatinine	2 (5)		
Hemoglobin	18 (47)	1 (3)	
INR		1 (3)	
Leukocytes	2 (5)	1 (3)	
Lymphopenia	7 (18)	2 (5)	
Neutrophils	2 (5)	1 (3)	
Platelets	7 (18)		2 (5)
Non-hematologic			
Allergic reaction	1 (3)	1 (3)	
Anorexia	6 (16)		
Confusion			1 (3)
Constipation	4 (11)	1 (3)	
Diarrhea	2 (5)		
Dyspnea	2 (5)		
Fatigue	9 (24)	2 (5)	
Hot flashes	2 (5)		
Mucositis (oral)	2 (5)		
Nausea	9 (24)		
Neurology-paranoia		1 (3)	
Pain-headache	2 (5)		
Psychosis	1	1 (3)	
Weight loss	2 (5)		

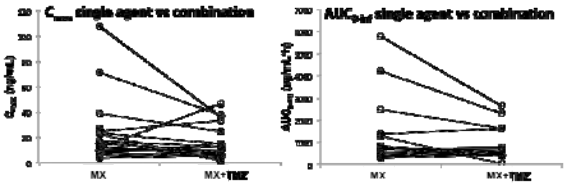
All grade 3/4 AEs and grade 1/2 AEs seen in ≥ 5% of patients

Response to Therapy

- Partial response (8 months) in 1 patient with a pancreatic neuroendocrine tumor.
- Prolonged stable disease
  - Ovarian cancer (12.5 months)
  - Pancreatic neuroendocrine tumor (9 months)
  - Small bowel neuroendocrine tumor (5.5 months)
  - Non-small cell lung cancer (5.5 months)
  - Pancreatic adenocarcinoma (4 months)

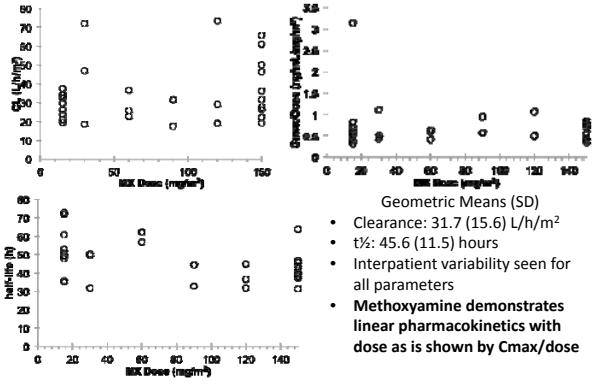
Pharmacokinetics

Quantification of methoxyamine determined using a LC-MS/MS method from human plasma.



- Pharmacokinetics of methoxyamine are not affected by the co-administration of temozolomide as assessed by Wilcoxon paired testing.

Methoxyamine Pharmacokinetic Parameters



Geometric Means (SD)

- Clearance: 31.7 (15.6) L/h/m^2
- t½: 45.6 (11.5) hours
- Interpatient variability seen for all parameters
- **Methoxyamine demonstrates linear pharmacokinetics with dose as is shown by Cmax/dose**

Conclusions

- Methoxyamine 150 mg/m^2 intravenously may be safely administered with Temozolomide 200 mg/m^2 orally with minimal toxicity and is the recommended phase II dose.
- Pharmacokinetics of methoxyamine are not affected by the concomitant administration of temozolomide.
- Evidence of antitumor activity was observed, particularly in ovarian cancer and neuroendocrine tumors.
- A cohort of patients with central nervous system involvement is currently ongoing.
- NCI-CTEP sponsored phase I and II studies using oral MX are ongoing.
- Further studies assessing this drug combination are warranted.

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