Phase I Trial of the Base – Excision Repair Blocker Methoxyamine (TRC-102) Combined with Fludarabine in Relapsed/Refractory Lymphoid Malignancies

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Background

Methoxyamine (TRC-102) is a first-in-class inhibitor of base excision repair (BER)
It covalently binds to the DNA abasic site generated by DNA-glycosylase-mediated removal of incorporated fludarabine. *In vitro* and animal studies demonstrated that methoxyamine augments the cytotoxicity of fludarabine against CLL cells but not normal bone marrow cells

Study Objectives

1. Determine the safety and tolerability of escalating doses of IV TRC102 in combination with Fludarabine
2. Find the MTD of IV methoxyamine combined with fludarabine
3. Study the pharmacokinetic and pharmacodynamic properties of a single IV dose of methoxyamine combined with Fludarabine

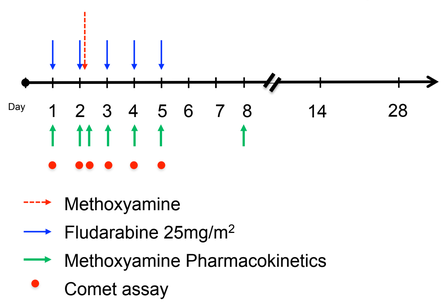
Design

Methoxyamine dose was escalated according to 3 + 3 design (Table 1)

TABLE 1: Dose escalation schema

Dose Level	Fludarabine(mg/m²/day)	TRC102 (mg/m²)
1	25	15
2	25	30
3	25	60
4	25	90
5	25	120

Figure 1: Treatment plan and laboratory studies



Results

TABLE 2: Patient Characteristics

Number of patients	20
Age (y), median (range)	64 (45-82)
Male / Female	12 / 8
Previous treatment lines, median (range)	3 (1 – 6)
Prior fludarabine	8
Diagnosis	
CLL	10
Follicular Lymphoma	3
DLBCL	3
Plasma cell myeloma	2
Mantle cell lymphoma	1
Anaplastic cell lymphoma	1

Toxicity:
- 20 patients enrolled
- 1 subject had DLT on dose level 5
- The MTD was not reached

TABLE 3: Toxicities

Hematologic toxicity	
Grade 3 - 4	
Lymphopenia	68%
Neutropenia	63%
Anemia	42%
Thrombocytopenia	26%
Grade 1 - 2	
Decreased haptoglobin	26%
Hemolysis (DAT negative)	5%
Non hematologic toxicity	
Grade 3 – 4	
Pneumonia	15%
Hyperuricemia	5%
Diarrhea	5%
Elevated AST	5%
Grade 1 - 2	
Fatigue	84%
Nausea	68%
Hypocalcemia	58%
Anorexia	53%
Constipation	43%

Table 5: Response to treatment (histology)

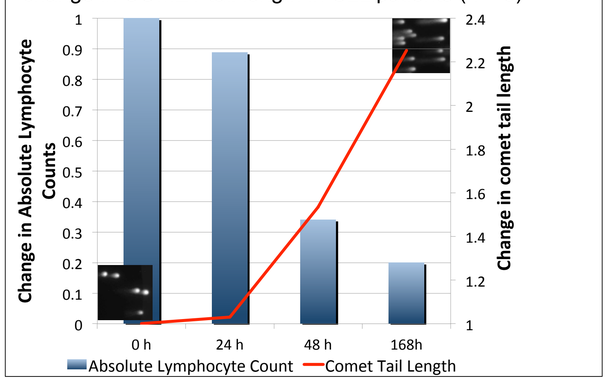
CR	PR	SD	PD
0	4	9	7
	CLL (2) FL (2)	CLL (7) DLBCL (1) FL (1)	CLL (1) DLBCL (2) MCL (1) PCM (2) ALCL (1)

Table 4: Methoxyamine pharmacokinetic analysis

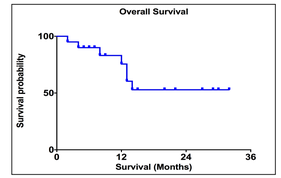
MX Dose (mg/m2)	Half Life (hrs.)	Cmax (ng/mL)	AUCinf (h*ng/mL)	Cl (mL/h/m2)
15	41	13	692	22062
30	42	19	1044	32241
60	45	37.5	2502	29014
90	46	100	6560	16035
120	45	100	6358	27067

Pharmacodynamic studies:
- Single and double strand DNA breaks measured with alkaline COMET assay
- Decrease in ALC correlated directly with COMET tail length increase at 48 hours after methoxyamine. (Pearson Correlation 0.91, R^2 0.8995; p = 0.001).

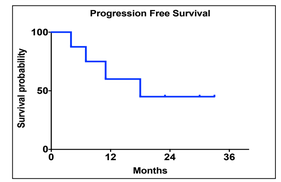
Figure 1: Decrease in absolute lymphocyte count and change in COMET tail length in CLL patients (n = 8)



Survival:
- Median follow up 16 months
- 1 year OS 75%



- PR and SD patients
- 1 year PFS 60%



Conclusions

- The combination of fludarabine and methoxyamine is well tolerated
- Combination results in PR and SD in patients previously treated with fludarabine
- The maximum tolerated dose was not reached and 120mg/m² is the RP2D
- Hematologic toxicity is the most frequent
- Non hematologic toxicity is tolerable
- Fludarabine and Methoxyamine cause DNA damage
  - Measured by COMET assay
  - Decrease in circulating CLL cells correlated with DNA damage

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CONFLICT OF INTEREST DISCLOSURES: Gerson , Tracon Pharmaceuticals, Patent and Royalties.