Preliminary Safety and Efficacy of Evofosfamide (TH-302), an Investigational Hypoxia Activated Prodrug Combined with Bortezomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma (RR MM)

Jacob P Laubach MD[1,2], Noopur S Raje MD[3], Andrew J Yee MD[3], Philippe Armand MD PhD[1,2], Robert L Schlossman MD[1,2], Jacalyn Rosenblatt MD[2,4], Jacquelyn Hedlund MD[2,5], Michael Martin MD[2,6], Craig Reynolds MD[2,7], Kenneth H Shain MD PhD[8], Ira Zackon MD[2,9], Laura Stampleman MD[2,10], Erica N Boswell BS[1,2], Stacey Chuma BSN[1,2], Rebecca Liguori[1,2], Damian R Handisides[11], Stew Kroll[11], Kenneth C Anderson MD[1,2], Paul G Richardson MD[1,2], Irene M Ghobrial MD[1,2]

[1]Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [2]Blood Cancer Research Partnership, Boston, MA; [3]Massachusetts General Hospital, Boston, MA; [4]Beth Israel Deaconess, Boston, MA; [5]Maine Center For Cancer Medicine, Scarborough, ME; [6]The West Clinic, Memphis, TN; [7]Ocala Oncology Center, Ocala, FL; [8]Moffitt Cancer Center, Tampa, FL; [9]New York Oncology Hematology, Albany, NY; [10]Pacific Cancer Care, Salinas, CA; [11]Threshold Pharmaceuticals, South San Francisco, CA

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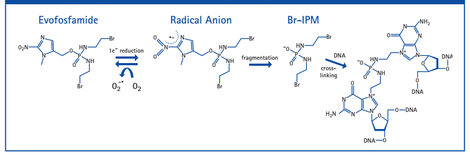
Contact: JacobP_Laubach@DFCI.Harvard.edu

Introduction

- The presence of hypoxia in the diseased bone marrow (Azab et al, *Blood* 2012, Colla et al., *Leukemia* 2010; Ghobrial et al., *Blood* 2012) presents a new therapeutic target for patients with multiple myeloma (MM).
- Evofosfamide (formerly TH-302) is an investigational 2-nitroimidazole hypoxia-activated prodrug of the DNA alkylator bromo-isophosphoramide mustard (Br-IPM). Evofosfamide is reduced at the nitroimidazole site of the prodrug by intracellular reductases, and when exposed to hypoxic conditions, releases Br-IPM.
- Evofosfamide exhibited activity in preclinical MM models *in vitro* and *in vivo* (Hu et al, *Blood* 2010; Chesi et al., *Blood* 2012), and *in vitro* synergism was seen when evofosfamide was combined with the proteasome inhibitor bortezomib (Hu et al., *Mol Cancer Ther* 2013).
- This phase 1/2 study (NCT01522872) is investigating evofosfamide and dexamethasone with or without bortezomib in patients with relapsed/refractory MM.
- The maximum-tolerated dose (MTD) of evofosfamide was previously established at 340 mg/m^2 in combination with dexamethasone (Ghobrial et al., *Blood* 2013). In a total of 24 patients treated at the MTD, objective responses were observed in 5/23 evaluable patients (three partial responses and two minimal responses).
- Data from the ongoing dose-escalation and dose-expansion of evofosfamide plus bortezomib and dexamethasone ("EBorD") are presented.

Figure 1. Evofosfamide is a Nitroimidazole Prodrug of the Cytotoxin, Bromo-Isophosphoramide Mustard (Br-IPM)



Study Objectives

Primary

- To evaluate the safety and tolerability of evofosfamide + bortezomib + dexamethasone (EBorD) in patients with relapsed/refractory MM.
- To identify the dose-limiting toxicities (DLTs) and determine the MTD of EBorD.
- To identify a recommended Phase 2 dose (RP2D) for EBorD.

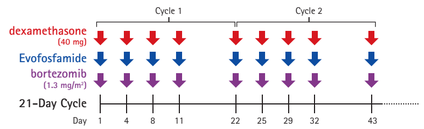
Secondary

- To assess the preliminary efficacy of EBorD.

Patients and Methods

- Eligible patients were diagnosed with relapsed and/or refractory MM, had ECOG performance status of 0-2, and acceptable hepatic, renal and hematologic function.
- Patients had received at least 2 prior therapies which included an immunomodulatory agent and a proteasome inhibitor.
- Patients receiving prior bortezomib could not have discontinued due to bortezomib toxicity.
- Patients had to have measurable disease as defined by the International Myeloma Working Group (IMWG) Criteria (Durie et al, *Leukemia* 2006, Rajkumar et al, *Blood* 2010); the criterion for measurable serum M-protein was set at ≥0.5 g/dL.
- Patients had to have ANC ≥1000/μL, platelet count ≥50,000/μL and creatinine clearance of ≥30 mL/min.
- Evofosfamide was administered IV with a fixed oral 40 mg dose of dexamethasone and a fixed IV of bortezomib (1.3 mg/m^2) on days 1, 4, 8, and 11 of a 21-day cycle or SC administration (Figure 2).
- A dose escalation design was used with evofosfamide starting at a 240 mg/m^2 and dose escalation up to the evofosfamide MTD established with evofosfamide plus dexamethasone at 340 mg/m^2.
- At the MTD, a Simon two-stage minimax design will be implemented to pursue a regimen with ≥50% response rate or discontinue if ≤25% (85% power, 10% one-sided alpha).
- If four or more patients of the first 11 patients achieve partial response or better, enrollment continued to 24 patients treated at the MTD. Enrollment was not halted between the two stages of the design.

Figure 2. Study Dosing Schedule



Results

A total of 25 patients with relapsed/refractory MM have been enrolled in the EBorD component of the study as of May 1, 2015. This report includes preliminary safety and efficacy analyses from 18 patients who initiated therapy prior to December 1, 2014, with presented analyses reflecting data in the clinical database as of May 2015. The majority of patients (67%) had ECOG 1 performance status. Patients had received a median of 8 prior systemic therapy regimens (range: 4 - 16) and all had received at least one regimen with bortezomib and one regimen with thalidomide/lenalidomide. Overall patients had received a median of 3 prior bortezomib-containing regimens (range: 1 - 7). In addition, 61% had received carfilzomib and 72% had received pomalidomide.

Table 1: Demographics

	Evofosfamide Dose		Total
	240 mg/m^2 (N = 4)	340 mg/m^2 (N = 14)	(N = 18)
Male/Female	1/3	9/5	10/8
Age			
Median	56.5	57.5	57
Range	46 – 63	45 – 68	45 – 68
ECOG Status			
0	1 (25%)	2 (14%)	3 (17%)
1	2 (50%)	10 (71%)	12 (67%)
2	1 (25%)	2 (14%)	3 (17%)

Table 2: Cancer History and Prior Cancer Therapy

	Evofosfamide Dose		Total
	240 mg/m^2 (N = 4)	340 mg/m^2 (N = 14)	(N = 18)
Time from Diagnosis (years)			
Median	4.3	5.2	4.4
Range	2.6 – 11.0	1.3 – 30.7	1.3 – 30.7
Prior Systemic Therapy			
Median	8	8	8
Range	4 – 12	4 – 16	4 – 16
Prior Bortezomib	4 (100%)	14 (100%)	18 (100%)
Median (range) Prior Bortezomib Regimens	3 (2 – 5)	3 (1 – 7)	3 (1 – 7)
Prior Carfilzomib	2 (50%)	9 (64%)	11 (61%)
Prior Bortezomib and Prior Carfilzomib	2 (50%)	9 (64%)	11 (61%)
Prior Lenalidomide or Thalidomide	4 (100%)	14 (100%)	18 (100%)
Prior Pomalidomide	2 (50%)	11 (79%)	13 (72%)
Prior Lenalidomide/ Thalidomide and Pomalidomide	2 (50%)	11 (79%)	13 (72%)
Prior Alkylator	3 (75%)	14 (100%)	17 (94%)
Prior Radiotherapy	3 (75%)	7 (50%)	10 (56%)
Prior Transplant	3 (75%)	10 (71%)	13 (72%)

Table 3: Prior Systemic Therapy Regimens

Patient		349-001	348-002	182-002	217-024	217-025	217-026	217-028	349-002	182-003
Evo Dose mg/m^2		240	240	240	340	340	340	340	340	340
Prior Therapies/Regimens	1	Rd	Rd	CYBORD	VRd	VTd	VTd	RV	VdDox	VRd
	2	Vd	CYBORD + R	D	Rd	Vd	Rd	Vd	Mel + ASCT	MEL + ASCT → CY
	3	RVd	VRd	Rd	Vd	CY + ASCT	CY+ ASCT	RVd	RVd	VincDoxDex
	4	Cfzd	MelVRd + ASCT	Mel + ASCT	Perifosine	RVd	Mel + ASCT	POMd	Rd	CYCfzD
	5		V	VdDox	CYBORD + T	CYBORD	POMd	Cfzd	CYd	POMd
	6		Rd	POMd	CYBORD + TDox	RVdDox		VBen	CYCfzD	
	7		CYCfzD		MelCY + ASCT	Mel + ASCT		CYBORD	CYCfzD + POM	
	8		POMdDox		VRd	VPOMd		V+DCEP	VdBen	
	9		V + DCEP		Dara					
	10		CD38 Ab		CfzPOMd					
	11		CisCYEtop		CYCPOMd					
	12		D		Dox					

Patient		182-004	182-005	217-029	217-030	217-031	217-032	217-033	217-034	347-004
Evo Dose mg/m^2		340	340	240	340	340	340	340	340	340
Prior Therapies/Regimens	1	Vd	Rd	Td	VRd	D	RVd	Vd	VRd	CYBORD
	2	VRd	MelVT	CYV	Mel + ASCT → R	Td	R	VRd	VPOMd	V
	3	Rd	Mel + ASCT	V	VRd	Mel + ASCT	Rd	CYBorD	CY	CYBORD
	4	VRd	MLN9708	KOS-953	CYCfzD	Vd	RVd	CY	Mel + ASCT	MEL + ASCT → R
	5	CYBORD + dox	CXCR4Ab + Rd	CC-5013 + RV	CY	MelVd	CYBORD	V	Vd	
	6	CfzRd	Vd	MEL + ASCT Oct 2006	POMVd	Rd	CYRd	CY	CfzARRY520	
	7	CY	CYCfzD	CP-751	CfzPOMd	VRd	DCEP			
	8	CfzPOMd	POMd	TANESPIMYCIN + V	DCEP	CYBORD	CfzPOMd			
	9			TANESPIMYCIN		R + Vorinostat				
	10			PRIX 93936		V + Vorinostat				
	11					Bend + V				
	12					T				
	13					Mel + T				
	14					DCEP				
	15					CfzD				
	16					VRd				

V/BOR: Velcade
R: Revlimid
D/d: Dexamethasone
CY: Cytoxan
T: Thalidomide
Pom: Pomalidomide
DCEP: Dex, Cytoxan, Etoposide, Cisplatin
Ben: Bendamustane
Cfz: Carfilzomib
Ben: Bendamustane
Dox: Doxil
Per: Perifosine
Mel: Melphalan
ASCT: Transplant

Dose Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD)

No DLTs were reported during Cycle 1 at evofosfamide doses of 240 mg/m^2 or 340 mg/m^2. The MTD of evofosfamide with dexamethasone had previously been established at 340 mg/m^2 and dose escalation above that dose of evofosfamide with dexamethasone plus bortezomib was not allowed. Therefore, after 6 patients had been treated at 340 mg/m^2 without a DLT, the dose expansion was initiated with an evofosfamide dose of 340 mg/m^2 and the RP2D of Evofosfamide in EBorD was established at 340 mg/m^2.

Adverse Events

- Adverse events regardless of relationship to study drug occurring in five or more patients are provided in Table 4.
- The most frequent adverse events were thrombocytopenia in 13 patients (72%) including platelet support in 9 patients (50%) and anemia in 10 patients (56%) including red blood cell support in 6 patients (33%).
- Eleven serious adverse events (SAEs) were reported in 9 patients. The only SAE occurring in more than one patient were two events of colitis. Neither event was considered related to study drug. Five SAEs were considered as related to evofosfamide: bronchiolitis, melena, pneumonia, thrombocytopenia and viral infection.
- Skin toxicity and mucosal toxicities were not dose limiting. Rash was reported in five patients; stomatitis, skin lesion, pruritus and skin hyperpigmentation were each reported in one patient; none of these were Grade 3 or higher.
- No patients discontinued treatment due to an adverse event.
- There were no deaths related to study drug.

Table 4: Most Common Adverse Events Regardless of Relationship to Study Drug (occurring in 5 or more patients)

	Evofosfamide Dose			
Adverse Event	240 mg/m^2 All Grades (N=4)	340 mg/m^2 All Grades (N=14)	Total All Grades (N=18)	Total Grade 3/4 (N=18)
Hematologic				
Thrombocytopenia/Platelet Count Decreased	2 (50%)	11 (79%)	13 (72%)	11 (61%)
Anemia	3 (75%)	7 (50%)	10 (56%)	6 (33%)
Neutropenia/Neutrophil Count Decreased	1 (25%)	6 (43%)	7 (39%)	4 (22%)
Non-Hematologic				
Nausea	2 (50%)	6 (43%)	8 (44%)	1 (6%)
Fatigue	3 (75%)	4 (29%)	7 (39%)	1 (6%)
Vomiting	0 (0%)	6 (43%)	6 (33%)	1 (6%)
Neuropathy Peripheral	3 (75%)	3 (17%)	6 (33%)	0 (0%)
Constipation	1 (25%)	4 (29%)	5 (28%)	0 (0%)
Rash	2 (50%)	3 (21%)	5 (28%)	0 (0%)

Efficacy and Maximum Change in Paraprotein

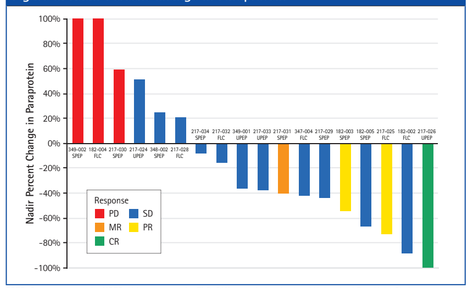
- IMWG responses are summarized in Table 5, and maximum changes in paraprotein are provided in Figure 3.
- IMWG partial responses [two partial responses (PR) and one complete response (CR)] were reported in 3 of 18 (17%, 95% CI: 4 to 41%) patients in the entire group and 3 of 14 (21%, 95% CI: 5 to 52%) patients at the RP2D with 4 of 14 (29%, 95% CI: 8% to 58%) achieving MR, PR or CR.
- The patients with PRs and CR had both previously undergone at least one autologous transplant and had received prior treatment with lenalidomide or thalidomide, pomalidomide, bortezomib, dexamethasone, and at least one alkylating agent.

Table 5: IMWG Best Overall Response

	Evofosfamide Dose		
	240 mg/m^2 (N = 4)	340 mg/m^2 (N = 14)	Total (N = 18)
Complete Response (CR)	0	1 (7%)	1 (6%)
Partial Response (PR)	0	2 (14%)	2 (11%)
Minimal Response (MR)	0 (0%)	1 (7%)	1 (7%)
Stable Disease (SD)	4 (100%)	7 (50%)	11 (61%)
Progressive Disease (PD)	0 (0%)	3 (21%)	3 (17%)

The nadir percent change from baseline in paraprotein and method of assessment are summarized in Figure 3.

Figure 3. Nadir Percent Change in Paraprotein

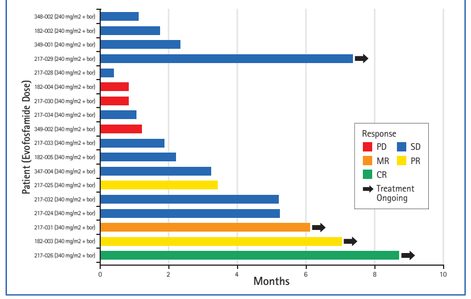


SPEP: Serum paraprotein; **UPEP:** Urine paraprotein; **FLC:** Difference in Involved and Uninvolved Free Light Chain.
Two patients with 100% had increases of 200% and 104%. IMWG requires responses be confirmed on two consecutive evaluations.

Time on Treatment

The time on treatment, defined as time from initial dose of evofosfamide to last dose of evofosfamide or bortezomib, for all patients is provided in Figure 4. Recall each cycle is 3 weeks.

Figure 4. Time on Treatment (months)



Treatment Discontinuation

Fourteen of 18 patients (78%) discontinued treatment, 12 patients (67%) with progressive disease and 2 patients (11%) for significant clinical deterioration. Four patients, including 3 in the 340 mg/m^2 treatment group, continue on study, including patients with PR and CR, after 10 and 12 cycles, respectively. No patients discontinued due to an adverse event.

Conclusions

- Evofosfamide can be administered intravenously biweekly in combination with dexamethasone administered orally at 40 mg and bortezomib (1.3 mg/m^2) on the same day to patients with heavily pre-treated multiple myeloma.
- No dose limiting toxicity was observed at evofosfamide doses of 240 or 340 mg/m^2 and the evofosfamide RP2D was established at 340 mg/m^2.
- The most common adverse events were thrombocytopenia and anemia. No patients discontinued due to an adverse event.
- IMWG responses (MR, PR or CR) were observed in 4 of 14 (29%) patients at the RP2D in patients with extensive prior treatment with a median of 8 prior systemic therapy regimens including a median of 3 prior bortezomib-containing regimens.

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Disclosures

DH and SK: Employees of Threshold Pharmaceuticals. All other authors have no potential conflicts of interest to disclose. Evofosfamide is currently under clinical investigation and has not been approved by any regulatory authority.

Status

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