A Phase 1/2 Trial of TH-302 and Dexamethasone with Bortezomib (TBorD) in Patients with Relapsed/Refractory Multiple Myeloma

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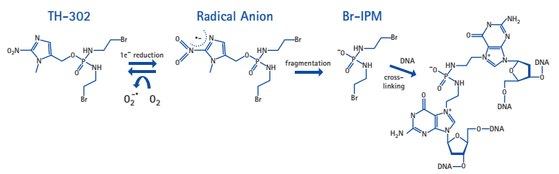
56th ASH Annual Meeting, Abstract Number: 2142

Introduction

- While alkylators, IMiDs, and proteasome inhibitors are current standard treatment for patients with multiple myeloma (MM), the presence of hypoxia in the diseased bone marrow (Colla et al., *Leukemia* 2010; Ghobrial et al., *Blood* 2012) presents a new therapeutic target for MM.
- TH-302 is an investigational 2-nitroimidazole prodrug of the DNA alkylator bromo-isophosphoramide (Br-IPM) designed to be selectively activated under hypoxic conditions (Figure 1).
- TH-302 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 TH-302 was combined with the proteasome inhibitor bortezomib (Hu et al., *Mol Cancer Ther* 2013).
- This phase 1/2 study (NCT01522872) is investigating TH-302 and dexamethasone with or without bortezomib in patients with relapsed/refractory MM.
- The maximum-tolerated dose (MTD) of TH-302 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).
- Initial results of the ongoing dose-escalation and dose-expansion of TH-302 plus bortezomib and dexamethasone ("TBorD") are presented.

Figure 1. TH-302 is a Nitroimidazole Prodrug of the Cytotoxin, Bromo-Isophosphoramide Mustard (Br-IPM)



Under normal oxygen conditions or normoxia, TH-302 is essentially inactive. In the presence of certain reductases and with hypoxic conditions, the nitroimidazole is reduced and Br-IPM is released to alkylate DNA, inducing intrastrand and interstrand crosslinks.

Study Objectives of TBorD Study Component

Primary

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

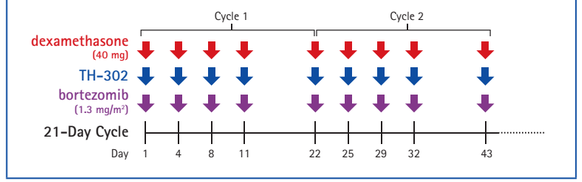
Secondary

- To assess the preliminary efficacy of TBorD

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 toxicity.
- Patients had measurable disease as defined by the International Myeloma Working Group (IMWG) Criteria (Durie et al, *Leukemia* 2006, Rajkumar et al, *Blood* 2010).
- Patients had ANC ≥1000/μL, platelet count ≥50,000/μL and creatinine clearance of ≥30 mL/min.
- A standard 3+3 dose escalation design was used with 40% dose increments of TH-302 starting at a 240 mg/m^2 and dose escalation up to the MTD established with TH-302 plus dexamethasone at 340 mg/m^2.
- TH-302 was administered IV with a fixed oral 40 mg dose of dexamethasone and a fixed IV or SC administration of bortezomib (1.3 mg/m^2) on days 1, 4, 8, and 11 of a 21-day cycle (Figure 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% alpha).
- If four or more patients of the first 11 patients at the MTD achieve partial response or better, enrollment will continue to 24 patients treated at the MTD.

Figure 2. Study Dosing Schedule



Results

A total of 18 patients with relapsed/refractory MM have been enrolled in the TBorD component of the study as of November 17, 2014. This report includes preliminary safety and efficacy analyses from 9 patients who initiated therapy prior to September 12, 2014, with presented analyses reflecting data in the clinical database as of November 25, 2014. The majority of patients (67%) had ECOG 1 performance status. Patients had received a median of 8 prior systemic therapy regimens (range: 4 – 11) including at least one regimen with bortezomib and one regimen with thalidomide/lenalidomide.

Table 1: Demographics

	TH-302 Dose 240 mg/m^2 (N = 3)	TH-302 Dose 340 mg/m^2 (N = 6)	Total (N = 9)
Male/Female	0/3	4/2	4/5
Age			
Median	56	64.5	57
Range	46 – 57	45 – 68	45 – 68
ECOG Status			
0	1 (33%)	1 (17%)	2 (22%)
1	1 (33%)	5 (83%)	6 (67%)
2	1 (33%)	0	1 (11%)

Table 2: Cancer History and Prior Cancer Therapy

	TH-302 Dose 240 mg/m^2 (N = 3)	TH-302 Dose 340 mg/m^2 (N = 6)*	Total (N = 9)*
Time from Diagnosis (years)			
Median	4.1	7.5	4.5
Range	2.6 – 4.5	3.1 – 30.7	2.6 – 30.7
Prior Number of Systemic Therapy Regimens Including Induction			
Median	6	8	8
Range	4 – 12	5 – 12	4 – 12
Prior bortezomib	3/3 (100%)	5/5 (100%)	8/8 (100%)
Prior carfilzomib	1/3 (33%)	3/5 (60%)	4/8 (50%)
Prior bortezomib and carfilzomib	1/3 (33%)	3/5 (60%)	4/8 (50%)
Prior lenalidomide or thalidomide	3/3 (100%)	5/5 (100%)	8/8 (100%)
Prior pomalidomide	2/3 (67%)	5/5 (100%)	7/8 (88%)
Prior lenalidomide/thalidomide and pomalidomide	2/3 (67%)	5/5 (100%)	7/8 (88%)
Prior alkylator	2/3 (67%)	5/5 (100%)	7/8 (88%)
Prior radiotherapy	3/3 (100%)	2/5 (40%)	5/8 (62%)
Prior transplant	2/3 (67%)	4/5 (80%)	6/8 (75%)

* Data missing on prior regimens for one patient in the 340 mg/m^2 dose cohort.

Table 3: Prior Systemic Therapy Regimens

Patient	349-001	348-002	182-002	217-024	217-025	217-026	217-028	349-002
TH-302 Dose	240 mg/m^2			340 mg/m^2				
Prior Therapies/Regimens 1	Rd	Rd	CYBORD	VRd	VTd	VTd	RV	VdDox
2	Vd	CYBORD + R	D	Rd	Vd	Rd	Vd	Mel + ASCT
3	RVd	VRd	Rd	Vd	CY + ASCT	CY + ASCT	RVd	RVd
4	Cfzd	MelVRd + ASCT	Mel + ASCT	Perifosine	RVd	Mel + ASCT	POMd	Rd
5		V	VdDox	CYBORD+T	CYBORD	POMd	Cfzd	CYd
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		CYCfzPOMd				
12		D		Dox				

V/BOR: Velcade; **R:** Revlimid; **D/d:** Dexamethasone; **CY:** Cytoxan; **T:** Thalidomide; **Pom:** Pomalidomide; **DCEP:** Dex, Cytoxan, Etoposide, Cisplatin; **Ben:** Bendamustane; **Cfz:** Carfilzomib; **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 TH-302 doses of 240 mg/m^2 or 340 mg/m^2. The MTD of TH-302 with dexamethasone had previously been established at 340 mg/m^2 and dose escalation above that dose of TH-302 with dexamethasone plus bortezomib was not allowed. Therefore, after 6 patients had been treated at 340 mg/m^2 without a DLT, the RP2D dose of TH-302 in TBorD was established at 340 mg/m^2.

Adverse Events

- Adverse events regardless of relationship to study drug occurring in more than two patients are provided in Table 4.
- Five serious adverse events (SAEs) were reported in 4 patients. One SAE of thrombocytopenia was considered related to TH-302. One SAE of epistaxis was considered unrelated to TH-302 and was reported in a patient who was platelet transfusion-dependent and had a platelet count of 33,000/μL.
- Skin toxicity, an AE of interest with TH-302, has been limited: one Grade 2 rash of the abdomen and groin resulting in treatment delay was reported at the 240 mg/m^2 dose of TH-302 and one Grade 2 skin lesion under the breast with no impact on treatment was reported at the 340 mg/m^2 dose of TH-302.
- There were no deaths related to study drug.

Table 4: Most Common Adverse Events Regardless of Relationship to Study Drug (occurring in 2 or more patients)

Adverse Event	TH-302 Dose 240 mg/m^2 All Grades (N = 3)	TH-302 Dose 340 mg/m^2 All Grades (N = 5)*	Total All Grades (N = 8)*	Total Grade 3/4 (N = 8)*
Hematologic				
Thrombocytopenia	1 (33%)	4 (80%)	5 (62%)	4 (50%)
Anemia	2 (67%)	3 (60%)	5 (62%)	2 (25%)
Lymphopenia	1 (33%)	1 (20%)	2 (25%)	2 (25%)
Neutropenia	0	2 (40%)	2 (25%)	1 (12%)
Non-Hematologic				
Fatigue	3 (100%)	2 (40%)	5 (62%)	1 (12%)
Nausea	2 (67%)	2 (40%)	4 (50%)	1 (12%)
Constipation	1 (33%)	2 (40%)	3 (38%)	0
Neuropathy Peripheral	2 (67%)	1 (20%)	3 (38%)	0
Abdominal Pain	0	2 (40%)	2 (25%)	1 (12%)
Back Pain	1 (33%)	1 (20%)	2 (25%)	0
Blood Creatinine Increased	1 (33%)	1 (20%)	2 (25%)	0
Contusion	0	2 (40%)	2 (25%)	0
Hyperglycemia	1 (33%)	1 (20%)	2 (25%)	0
Insomnia	2 (67%)	0	2 (25%)	0
Pyrexia	1 (33%)	1 (20%)	2 (25%)	0
Rectal Hemorrhage	1 (33%)	1 (20%)	2 (25%)	0
Vomiting	0	2 (40%)	2 (25%)	1 (12%)

* Data missing for one patient.

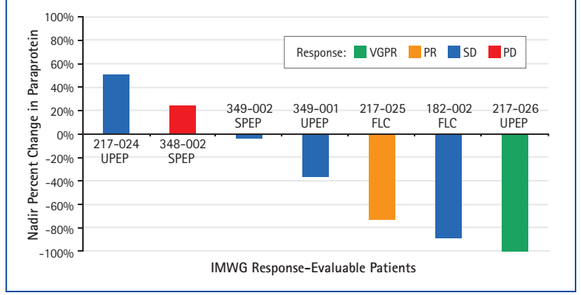
Efficacy and Maximum Change in Paraprotein

- IMWG responses are summarized in Table 5, and maximum changes in paraprotein are provided in Figure 3.
- IMWG partial responses [one partial response (PR) and one very good partial response (VGPR)] were reported in 2 of 7 (29%, 95% CI: 4% to 71%) evaluable patients in the entire group and 2 of 4 (50%, 95% CI: 7 to 93%) evaluable patients at the RP2D. Two of the patients treated at the RP2D were not evaluable for response. One of these two patients discontinued for reason of disease progression on Day 43. The other patient continues on study.
- The patients with PR and VGPR had both previously undergone two autologous transplantations and had received prior treatment with lenalidomide or thalidomide, pomalidomide, bortezomib, dexamethasone, and at least one alkylating agent.

Table 5: IMWG Overall Response

	TH-302 Dose 240 mg/m^2 (N = 3)	TH-302 Dose 340 mg/m^2 (N = 6)	Total (N = 9)
Number Evaluable	3	4	7
Very Good Partial Response (VGPR)	0	1 (25%)	1 (14%)
Partial Response (PR)	0	1 (25%)	1 (14%)
Stable Disease (SD)	2 (67%)	2 (50%)	4 (57%)
Progressive Disease (PD)	1 (33%)	0	1 (14%)

Figure 3. Nadir Percent Change in Paraprotein



SPEP: Serum paraprotein; **UPEP:** Urine paraprotein; **FLC:** Absolute difference in involved and uninvolved free light chain. One patient with >50 decrease in FLC had overall response of SD as plasmacytomas did not meet definition for PR.

Treatment Discontinuation

Five of 9 patients (56%) discontinued with progressive disease. Four patients, all in the 340 mg/m^2 treatment group, continue on study, including the patients with PR and VGPR, after 5 and 3 cycles, respectively. No patients discontinued due to an adverse event.

Conclusions

- TH-302 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 TH-302 doses of 240 or 340 mg/m^2 and the TH-302 RP2D was established at 340 mg/m^2.
- The most common adverse events were thrombocytopenia, anemia and fatigue.
- IMWG partial responses were observed in 2 of 7 (29%) evaluable patients including 2 of 4 (50%) at the RP2D in patients with extensive prior treatment with a median of 8 prior systemic therapy regimens.
- A total of up to 24 patients are scheduled to be treated in the RP2D expansion cohort.

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