Preliminary Safety and Efficacy of TH-302, an Investigational Hypoxia-Targeted Drug, and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

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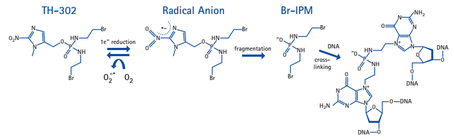
Introduction

- 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).
- A Phase 1/2 study (NCT01522872) is investigating TH-302 and dexamethasone with or without bortezomib in subjects with relapsed/refractory MM. Current results of the Phase 1 dose escalation and ongoing Phase 2 dose expansion at MTD component with TH-302 and dexamethasone 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

Primary

- To evaluate the safety and tolerability of TH-302 and dexamethasone.
- To identify the dose-limiting toxicities (DLTs) and determine the maximum tolerated dose (MTD) of TH-302 and dexamethasone.

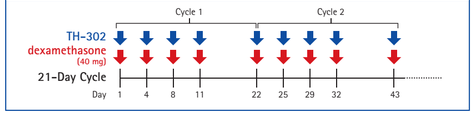
Secondary

- To assess the preliminary efficacy of TH-302 and dexamethasone.

Patients and Methods

- Eligible patients were diagnosed with relapsed/refractory MM, had ECOG performance status of 0-2 and acceptable hepatic, renal and hematologic function.
- Patients had received at least 2 prior therapies.
- A standard 3+3 dose escalation design was used with 40% dose increments of TH-302 starting at a 240 mg/m^2. TH-302 was administered IV with a fixed oral 40 mg dose of dexamethasone on days 1, 4, 8, and 11 of a 21-day cycle (Figure 2).
- If 1 or more patients of the first 9 patients treated at the MTD achieved partial response or better, enrollment was to be expanded to an additional 15 patients at the MTD.
- At the MTD, a Simon two-stage minimax design will be implemented to pursue a regimen with ≥25% response rate or discontinue if ≤5% (90% power, 10% alpha).

Figure 2. Study Dosing Schedule



Results

A total of 30 patients with relapsed/refractory MM have been enrolled in the study as of May 19, 2014. For this poster, safety and efficacy analyses are presented from 24 patients who initiated therapy prior to March 1, 2014, with presented analyses reflecting data in the clinical database as of May 19, 2014: 18 male and 6 female with a median age of 62.5 years (range: 53 – 86). Patients had received a median of 6.5 prior therapies (range: 3 – 13). Four of the twenty-four (4/24) patients had treatment ongoing as of the data cutoff on May 19, 2014.

Table 1: Demographics

	TH-302 Dose			
	240 mg/m^2 (N = 5)	340 mg/m^2 (N = 17)	480 mg/m^2 (N = 2)	Total (N = 24)
Male/Female	3/2	14/3	1/1	18/6
Age				
Median	61	65	60	62.5
Range	53 – 78	53 – 86	57 – 63	53 – 86
ECOG Status				
0	1 (20%)	6 (35%)	1 (50%)	8 (33%)
1	3 (60%)	9 (53%)	1 (50%)	13 (54%)
2	1 (20%)	2 (12%)		3 (13%)

Table 2: Cancer History and Prior Cancer Therapy

	TH-302 Dose			
	240 mg/m^2 (N = 5)	340 mg/m^2 (N = 17)	480 mg/m^2 (N = 2)	Total (N = 24)
ISS Stage prior to Anti-Myeloma Treatment				
I	1 (20%)	6 (35%)	1 (50%)	8 (33%)
II	1 (20%)	3 (18%)		4 (17%)
III	1 (20%)	4 (24%)	1 (50%)	6 (25%)
Unknown / Not Reported	2 (40%)	4 (24%)		6 (25%)
Time from diagnosis (mos)				
Median	67.5	54.6	47.9	54.6
Range	15.4 – 152.6	15.6 – 120.9	16.9 – 78.9	15.4 – 120.9
Prior Systemic Therapy				
Median	8	6	6.5	6.5
Range	5 – 9	3 – 13	3 – 10	3 – 13
Prior Bortezomib (Bort)	5 (100%)	17 (100%)	2 (100%)	24 (100%)
Prior Carfilzomib (CFZ)	0	9 (53%)	0	9 (38%)
Prior Bort and CFZ	0	9 (53%)	0	9 (38%)
Prior Lenalidomide (Len) or Thalidomide (Thal)	5 (100%)	17 (100%)	2 (100%)	24 (100%)
Prior Pomalidomide (Pom)	1 (20%)	6 (35%)	0	7 (29%)
Prior Len/Thal and Pom	1 (20%)	6 (35%)	0	7 (29%)
Prior Alkylator	5 (100%)	15 (88%)	2 (100%)	22 (92%)
Prior Radiotherapy	3 (60%)	7 (41%)	1 (50%)	11 (46%)
Prior Transplant	3 (60%)	11 (65%)	0	14 (58%)

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.
- Two DLTs of Grade 3 stomatitis were reported during Cycle 1 in the two patients treated at 480 mg/m^2.
- The MTD was established at 340 mg/m^2.

Table 3: Exposure

	TH-302 Dose			
	240 mg/m^2 (N = 5)	340 mg/m^2 (N = 17)	480 mg/m^2 (N = 2)	Total (N = 24)
Total Cycles				
Median	8	3	4.5	4
Range	2 – 19	1 – 12+	4 – 5	1 – 19
Months of Exposure				
Median	5.2	1.9	3.4	2.7
Range	1.0 – 14.2	0.3 – 10.6+	3.2 – 3.5	0.3 – 14.2

Adverse Events

- Grade 3/4 adverse events regardless of relationship to study drug occurring in more than two patients are provided in Table 4.
- Most common (>20%) adverse events related to study drug (all grades) are provided in Table 5.
- Seven serious adverse events related to TH-302 occurred in 5 patients: pneumonia (n=2), abdominal pain (n=1), cellulitis (n=1), proctalgia (n=1), pseudomonas sepsis (n=1), pyrexia (n=1).
- There were no deaths related to study drug.

Table 4: Most Common Grade 3/4 Adverse Events Regardless of Relationship to Study Drug (occurring in 2 or more patients)

	TH-302 Dose			
Adverse Event	240 mg/m^2 (N = 5)	340 mg/m^2 (N = 17)	480 mg/m^2 (N = 2)	Total (N = 24)
Hematologic				
Thrombocytopenia	4 (80%)	2 (12%)	1 (50%)	7 (29%)
Anaemia	2 (40%)	3 (18%)	1 (50%)	6 (25%)
Leukopenia	3 (60%)	2 (12%)	1 (50%)	6 (25%)
Neutropenia	3 (60%)	1 (6%)	0	4 (17%)
Nonhematologic				
Pneumonia	1 (20%)	1 (6%)	0	2 (8%)
Hyperphosphataemia	0	2 (12%)	0	2 (8%)
Stomatitis	0	0	2 (100%)	2 (8%)

Table 5: Most Common (>20%) Adverse Events related to TH-302

	Th-302 Dose							
	240 mg/m^2 (N=5)		340 mg/m^2 (N=17)		480 mg/m^2 (N=2)		Total (N=24)	
Adverse Event	Gr 3/4	All	Gr 3/4	All	Gr 3/4	All	Gr 3/4	All
Hematologic								
Leukopenia	3 (60%)	3 (60%)	2 (12%)	7 (41%)	1 (50%)	2 (100%)	6 (25%)	12 (50%)
Thrombo-cytopenia	4 (80%)	5 (100%)	2 (12%)	6 (35%)	1 (50%)	1 (50%)	7 (29%)	12 (50%)
Neutropenia	3 (60%)	4 (80%)	1 (6%)	5 (29%)	0	2 (100%)	4 (17%)	11 (46%)
Anaemia	2 (40%)	2 (40%)	2 (12%)	3 (18%)	1 (50%)	1 (50%)	5 (21%)	6 (25%)
Nonhematologic								
Nausea	0	3 (60%)	0	3 (18%)	0	1 (50%)	0	7 (29%)
Fatigue	1 (20%)	3 (60%)	0	3 (18%)	0	1 (50%)	1 (4%)	7 (29%)
Decreased Appetite	0	2 (40%)	0	2 (12%)	0	1 (50%)	0	5 (21%)
Diarrhoea	0	1 (20%)	1 (6%)	3 (18%)	0	1 (50%)	1 (4%)	5 (21%)
Hyperphos-phataemia	0	2 (40%)	2 (12%)	3 (18%)	0	0	2 (8%)	5 (21%)
Rash	0	0	0	4 (24%)	0	1 (50%)	0	5 (21%)

Efficacy and Maximum Change in Paraprotein

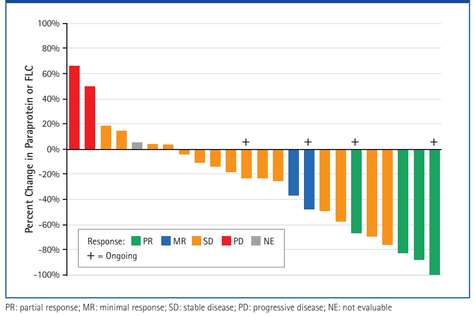
Best responses are summarized in Table 6, and maximum changes in paraprotein are provided in Figure 3. IMWG partial responses were observed in 4 of 23 (17%, 95% CI: 5% - 38%) evaluable subjects with a clinical benefit rate (PR+MR) of 26% (95% CI: 10% - 48%). The clinical benefit rate at MTD dose 340 mg/m^2 was 31%.

Table 6: IMWG Best Overall Response

	TH-302 Dose			
	240 mg/m^2 (N = 5)	340 mg/m^2 (N = 17)	480 mg/m^2 (N = 2)	Total (N = 24)
Number Evaluable	5	16**	2	23
Partial Response	1 (20%)	3 (19%)	0	4 (17%)
Minimal Response	0	2 (13%)	0	2 (9%)
Stable Disease	4 (80%)	9 (56%)	2 (100%)	15 (65%)
Progressive Disease	0	2 (13%)	0	2 (9%)
Clinical Benefit	1 (20%)	5 (31%)	0	6 (26%)

* Modified IMWG, Minimal Response (Serum M-spike decrease ≥25% – <50%).
** Excludes one patient who discontinued from study prior to completing Cycle 1.

Figure 3. Maximum Change in Paraprotein



PR: partial response; MR: minimal response; SD: stable disease; PD: progressive disease; NE: not evaluable

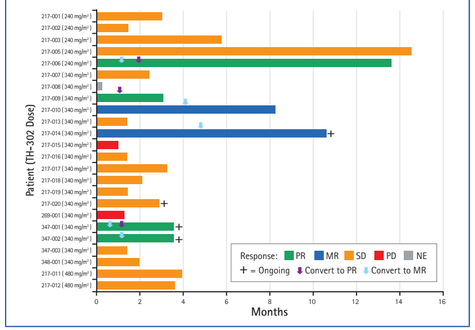
Treatment Discontinuation

The primary reason for discontinuing treatment is summarized in Table 6. Nine patients (38%) discontinued with progressive disease. One patient discontinued with an adverse event of fatigue and reduced appetite.

Table 7: Discontinuations

	TH-302 Dose			
	240 mg/m^2 (N = 5)	340 mg/m^2 (N = 17)	480 mg/m^2 (N = 2)	Total (N = 24)
Ongoing	0	4 (24%)	0	4 (17%)
Discontinued				
Clinical Deterioration	2 (40%)	0 (0%)	0	2 (8%)
Progressive Disease	3 (60%)	7 (41%)	1 (50%)	11 (46%)
Adverse Event	0	1 (6%)	0	1 (4%)
Alternative Therapy	0	1 (6%)	0	1 (4%)
Patient Decision	0	4 (24%)	1 (50%)	5 (21%)

Figure 4. Time on Study (months)



Conclusions

- TH-302 can be administered intravenously biweekly at 340 mg/m^2 in combination with dexamethasone administered orally at 40 mg on same day to patients with multiple myeloma.
- The most common (>20%) grade 3/4 TH-302 related adverse events were leukopenia, thrombocytopenia and anemia and the dose limiting toxicity at higher doses is oral mucositis.
- IMWG partial responses were observed in 4 of 23 (17%) evaluable patients with a clinical benefit rate (PR+MR) of 26% (95% CI: 10% - 48%) in patients with extensive prior treatment including a regimen with bortezomib and another regimen with thalidomide or lenalidomide.
- Objective responses have been observed in patients who failed multiple IMiDs (including pomalidomide) or multiple proteasome inhibitors (including carfilzomib).
- All 15 planned patients have initiated therapy in the TH-302 plus dexamethasone MTD expansion cohort.
- A TH-302 plus dexamethasone and bortezomib dose escalation and expansion arm will be initiated upon completion of the TH-302 plus dexamethasone MTD expansion cohort.

References

1. Colla et al. Low bone marrow oxygen tension and hypoxia-inducible factor-1α overexpression characterize patients with multiple myeloma: role on the transcriptional and proangiogenic profiles of CD138(+) cells. *Leukemia.* 2010 Nov;24(11):1967-70.
2. Ghobrial I et al. "Myeloma as a model for the process of metastasis: implications for therapy." *Blood.* 2012 Jul 5;120(1):20-30
3. Chesi et al. Drug response in a genetically engineered mouse model of multiple myeloma is predictive of clinical efficacy. *Blood.* 2012 Jul 12;120(2):376-85.
4. Hu J, et al. "Hypoxia activated prodrug TH-302 for the treatment of multiple myeloma." *Blood.* 2010 Sep 2;116(9):1524-7
5. Hu et al. Synergistic induction of apoptosis in multiple myeloma cells by bortezomib and hypoxia-activated prodrug TH-302, *in vivo* and *in vitro. Mol Cancer Ther.* 2013 Sep;12(9):1763-73

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Disclosures

DH and SK: Employees of Threshold Pharmaceuticals. All other authors have no potential conflicts of interest to disclose. TH-302 is currently under clinical investigation and has not been approved by any regulatory authority.

Status

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