Phase 1 Study Of TH-302, an Investigational Hypoxia-Targeted Drug, and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

Irene M. Ghobrial, MD[1], Jacob P. Laubach, MD[1], Noopur Raje, MD[2], Philippe Armand, MD, PhD[1], Robert L. Schlossman, MD[1], Erica N. Boswell, BS[1*], Courtney Hanlon[1*], Stacey Chuma, BSN[1*], Damian R. Handisides[3*], Stewart Kroll[3*], Kenneth C. Anderson, MD[1], Paul G. Richardson, MD[1]

[1]Jerome Lipper Multiple Myeloma Center, Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [2]Massachusetts General Hospital, Boston, MA; [3]Threshold Pharmaceuticals, South San Francisco, CA

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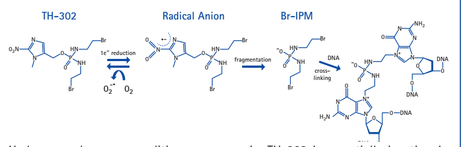
Introduction

- In multiple myeloma (MM) mouse models, diseased animals demonstrate a marked expansion of areas of hypoxia in the bone marrow (Ghobrial *et al., Blood* 2012), suggesting that hypoxia may be a therapeutically meaningful target in this disease
- TH-302 is an investigational 2-nitroimidazole prodrug of the DNA alkylator bromo-isophosphoramide (Br-IPM) designed to be selectively activated in hypoxia (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; results of the Phase 1 dose escalation 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.

Phase I 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

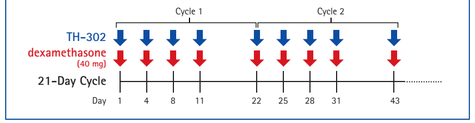
Secondary

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

Patients and Methods

- Eligible patients were diagnosed with relapsed 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
- 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).

Figure 2. Study Dosing Schedule



Dose-Limiting Toxicity

A dose-limiting toxicity (DLT) is defined as a clinically significant adverse event or abnormal laboratory value assessed as attributed to TH-302 (Part A) or either TH-302 or bortezomib (Part C) and unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first cycle of therapy, which meets any of the following criteria:

- Hematologic toxicity defined as: thrombocytopenia with platelets <10,000 on more than one occasion within first cycle despite transfusion. Grade 4 neutropenia for more than 5 days and/or results in neutropenic fever with elevated temperature (defined as ≥101 degrees F).
- Grade 3 or greater non-hematologic toxicity, considered by the investigator to be related to TH-302 or bortezomib, with the exception of nausea, diarrhea, or vomiting that did not receive maximal supportive care
- Inability to receive Day 1 dose for Cycle 2 by more than 3 weeks due to prolonged recovery due to a drug-related toxicity. A toxicity that would prohibit a subject from receiving Cycle 2 day 1 would include a subject experiencing one of the above two events

Pharmacokinetic Methods

Pharmacokinetic parameters for TH-302/ Br-IPM (Cycle 1, Day 1 and Cycle 1, Day 11) and bortezomib were computed:

- T_{max}: Time to maximum concentration
- C_{max}: Maximum peak observed concentration; observations are standardized by length of administration
- $T_{½}$: Half-life, computed as ln (2) divided by slope of linear regression of the log concentration versus time during the terminal phase
- AUC: Area under the concentration-time curve from 0 to infinity, computed using the linear trapezoidal rule as AUC to last observation plus extrapolation based on $T_{½}$ from last concentration time point

All calculations use the actual times and zero was substituted for concentrations below the quantification limit (BQL) of the assay.

Results

Fourteen (14) patients initiated therapy: 9 male and 5 female with a median age 60 years (range: 53 - 86). Patients had received a median of 6.5 prior therapies (range: 3 - 11) and all patients received a prior bortezomib-containing regimen, a prior lenalidomide / thalidomide-containing regimen and a prior alkylator-containing regimen.

Table 1: Cancer History and Prior Cancer Therapy

TH-302 Dose	240 mg/m^2 (N = 5)	340 mg/m^2 (N = 7)	480 mg/m^2 (N = 2)	Total (N = 14)
ISS Stage Prior to Anti-Myeloma Treatment				
I	1 (20%)	2 (29%)	1 (50%)	4 (29%)
II	1 (20%)	3 (43%)	0	4 (29%)
III	1 (20%)	1 (14%)	1 (50%)	3 (21%)
Unknown	2 (40%)	1 (14%)	0	3 (21%)
Time from Diagnosis (mos)				
Median	67	55	48	55
Range	15 – 153	21 – 77	17 – 79	15 – 153
Prior Systemic Therapy				
Median	7	4	6.5	6.5
Range	5 – 8	3 – 11	3 – 10	3 – 11
Prior Proteasome Inhibitor	5 (100%)	7 (100%)	2 (100%)	14 (100%)
Prior IMiD	5 (100%)	7 (100%)	2 (100%)	14 (100%)
Prior Alkylator	5 (100%)	7 (100%)	2 (100%)	14 (100%)
Prior Radiotherapy	3 (60%)	2 (29%)	1 (50%)	6 (43%)
Prior Transplant	3 (60%)	4 (57%)	0 (0%)	7 (50%)

Table 2: Demographics

TH-302 Dose	240 mg/m^2 (N = 5)	340 mg/m^2 (N = 7)	480 mg/m^2 (N = 2)	Total (N = 14)
Male/Female	3/2	5/2	1/1	9/5
Age				
Median	61	59	60	60
Range	53 – 78	54 – 86	57 – 63	53 – 86
ECOG Status				
0	1 (20%)	2 (29%)	1 (50%)	4 (29%)
1	3 (60%)	3 (43%)	1 (50%)	7 (50%)
2	1 (20%)	2 (29%)	0	3 (21%)

Dose Limiting Toxicity and Maximum Tolerated Dose

- 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 = 7)	480 mg/m^2 (N = 2)	Total (N = 14)
Total Cycles				
Median	8	4	4.5	4
Range	2 – 19	1 – 11	4 – 5	1 – 19
Months of Exposure				
Median	5.2	2.4	3.2	3
Range	1.0 – 14.1	0.2 – 7.9	3.2 -3.3	0.2 – 14.1

Pharmacokinetics

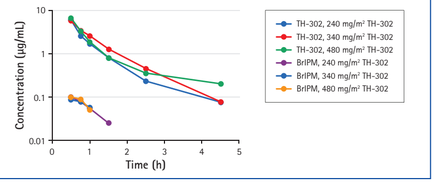
- The maximum concentrations of TH-302 and Br-IPM were at the end of infusion
- The terminal half-life was approximately 40 minutes across all dose groups for both TH-302 and Br-IPM
- Maximum concentration adjusted for length of administration (generally 30-60 minutes) and extrapolated AUC were roughly dose proportional although there was some overlap across dose groups reflecting the large coefficient of variation
- Circulating levels of Br-IPM were approximately 1 - 2% of circulating levels of the prodrug TH-302
- There was no apparent accumulation as Day 1 and Day 11 (data not shown) pharmacokinetic parameters were similar

Table 4: Pharmacokinetics

TH-302 Dose	240 mg/m^2			340 mg/m^2			480 mg/m^2		
PK Parameter	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
T_{max} (hour)	10	0.7	0.2	11	0.8	0.3	3	1.6	1
Adjusted C_{max} (ug/mL)	9	7.2	1.6	11	7.4	2.9	3	11.8	6.6
AUC (ug-hr/mL)	9	5	0.7	11	6.4	2.9	3	8.7	5
Half-Life (hr)	9	0.6	0.1	11	0.6	0.1	3	0.7	0.1

Note: N represents the number of administrations; the majority of patients had data following both Day 1 and Day 11.

Figure 3: TH-302 and Br-IPM Mean Concentrations from Time of Start of Infusion



Adverse Events

The most frequent adverse events grade 3/4/5 adverse events regardless of relationship to study drug are provided in Table 5. Cytopenias were the most commonly reported adverse events. There were no fatal adverse events.

Table 5: Most Common Grade 3/4/5 Adverse Events (occurring in 2 or more patients)

TH-302 Dose	240 mg/m^2 (N = 5)	340 mg/m^2 (N = 7)	480 mg/m^2 (N = 2)	Total (N = 14)
Thrombocytopenia	4 (80%)	2 (29%)	1 (50%)	7 (50%)
Leukopenia	3 (60%)	2 (29%)	1 (50%)	6 (43%)
Anaemia	2 (40%)	1 (14%)	1 (50%)	4 (29%)
Neutropenia	3 (60%)	1 (14%)	0	4 (29%)
Hyperphosphataemia	0	2 (29%)	0	2 (14%)
Stomatitis	0	0	2 (100%)	2 (14%)

Adverse events based on data through 15 November 2013.

Efficacy and Maximum Change in Paraprotein

Multiple myeloma is a disorder of the plasma cells, the blood cells that produce immunoglobulins. Myeloma cells overproduce within the marrow and generate excessive levels of abnormal immunoglobulins. These are referred to as M-protein or paraprotein and are measured and followed in the serum and urine. In some patients the myeloma only generates a free light chain (FLC) component of the immunoglobulin and in these patients the FLCs are measured and followed in the serum and urine. The International Myeloma Working Group (IMWG) consensus criteria for uniform reporting of clinical studies (Rajkumar *et al*, 2011) are utilized to classify the response to therapy. These criteria involve measures of serum and urine M-protein or FLC as well as other disease characteristics. Best responses are summarized in Table 6 and maximum changes in paraprotein are provided in Figure 3. IMWG responses were observed in 5 of 13 (38%; 95% CI: 14% to 68%) patients with with 2 partial responses (PRs) and 3 minimal responses (MRs).

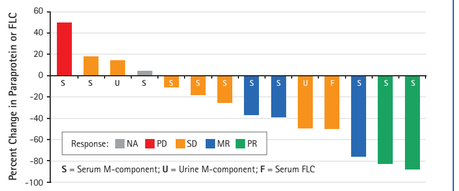
Table 6: IMWG Best Overall Response

TH-302 Dose	240 mg/m^2 (N = 5)	340 mg/m^2 (N = 7)	480 mg/m^2 (N = 2)	Total (N = 14)
Number Evaluable	5	6	2	13
Progressive Disease (PD)	0	1 (17%)	0	1 (8%)
Stable Disease (SD)	3 (60%)	2 (33%)	2 (100%)	7 (54%)
Minimal Response (MR)	1 (20%)	2 (33%)	0	3 (23%)
Partial Response (PR)	1 (20%)	1 (17%)	0	2 (15%)

* Modified IMWG, Minimal Response (Serum M-spike decrease ≥25% - <50%). Best response based on data through 08 November 2013.

Note: Excludes one patient who discontinued from study prior to completing Cycle 1.

Figure 4. Maximum Change in Paraprotein



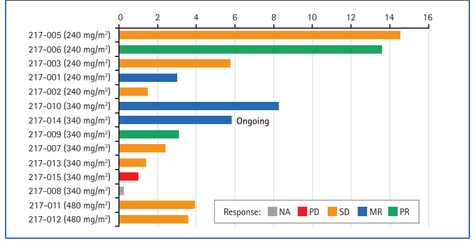
Treatment Discontinuation

The primary reason for discontinuing treatment is summarized in Table 7. Six patients (43%) 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 = 7)	480 mg/m^2 (N = 2)	Total (N = 14)
Ongoing	0	1 (14%)	0	1 (7%)
Discontinued				
Clinical Deterioration	2 (40%)	0	0	2 (14%)
Progressive Disease	3 (60%)	2 (29%)	1 (50%)	6 (43%)
Adverse Event	0	1 (14%)	0	1 (7%)
Alternative Therapy	0	1 (14%)	0	1 (7%)
Patient Decision	0	2 (29%)	1 (50%)	3 (21%)

Figure 5. 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 dose limiting toxicity at higher doses is oral mucositis
- IMWG responses were observed in 5 of 13 (38%; 95% CI: 14% to 68%) patients with 2 PRs and 3 MRs in patients with extensive prior treatment including a regimen with bortezomib and another regimen with thalidomide or lenalidomide

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