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

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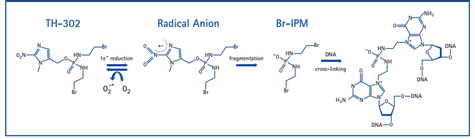
Introduction

TH-302 is a nitroimidazole prodrug of the cytotoxin, bromo-isophosphoramide mustard (Br-IPM). 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. Repair of TH-302-induced DNA damage is dependent on homologous recombination repair.

Figure 1. Chemical Structure and Mechanism of Activation of TH-302



1e⁻=one-electron; **Br-IPM**: bromo-isophosphoramide mustard. Adapted from Meng et al. 2012.[1]

Recently, hypoxia has been implicated in the etiology of hematological malignancies, including multiple myeloma (MM). Preclinically, there is a marked expansion of the hypoxic bone marrow areas in diseased mice.[2] Anti-tumor activity of TH-302 has been demonstrated in MM *in vitro* and *in vivo*, including *in vivo* synergism of TH-302 when combined with bortezomib.[3, 4, 5] A Phase 1/2 study (NCT01522872) is investigating TH-302 and dexamethasone with or without bortezomib in subjects with relapsed/refractory MM. We present results of the Phase 1 dose escalation portion of the study.

Objective

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

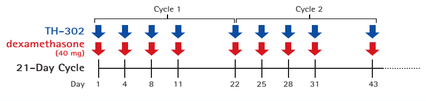
Secondary

- 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 PS ≤ 2, and acceptable hepatic, renal and hematologic function
- Patients must have had at least 2 prior therapies
- A standard 3+3 dose escalation design was used with a fixed oral 40 mg dose of dexamethasone and 40% dose increments of TH-302 starting at a 240 mg/m^2. TH-302 was administered IV with dexamethasone on days 1, 4, 8, and 11 of a 21-day cycle (Figure 2).

Figure 2. Study Dosing Schedule



Results

Thirteen patients initiated therapy: 8M/5F with a median age of 59 years (range: 53 – 86). These patients had received a median of 6 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. Demographics

	240 mg/m^2 (N=5)	340 mg/m^2 (N=6)	480 mg/m^2 (N=2)	Total (N=13)
Received Cycle 1 Day 1	5	6	2	13
Male/Female	3/2	4/2	1/1	8/5
Age				
Median	61	59	60	59
Range	53 – 78	54 – 86	57 – 63	53 – 86
ECOG Status				
0	1 (20%)	2 (33%)	1 (50%)	4 (31%)
1	3 (60%)	3 (50%)	1 (50%)	7 (54%)
2	1 (20%)	1 (17%)	0	2 (15%)

Table 2. Cancer History and Cancer Therapy

	240 mg/m^2 (N=5)	340 mg/m^2 (N=6)	480 mg/m^2 (N=2)	Total (N=13)
ISS Stage prior to Anti-Myeloma Treatment				
I	1 (20%)	1 (17%)	1 (50%)	3 (23%)
II	1 (20%)	3 (50%)	0	4 (31%)
III	1 (20%)	0	1 (50%)	2 (15%)
Unknown	2 (40%)	2 (33%)	0	4 (31%)
Time from diagnosis (mos)				
Median	67	52	48	55
Range	15 – 153	21 – 77	17 – 79	15 – 153
Prior Systemic Therapy				
Median	7	4	6.5	6
Range	5 – 8	3 – 11	3 – 10	3 – 11
Prior Proteasome Inhibitor	5 (100%)	6 (100%)	2 (100%)	13(100%)
Prior Imid	5 (100%)	6 (100%)	2 (100%)	13(100%)
Prior Alkylator	5 (100%)	6 (100%)	2 (100%)	13(100%)
Prior Radiotherapy	3 (60%)	1 (17%)	1 (50%)	5 (38%)
Prior Transplant	3 (60%)	4 (67%)	0 (0%)	7 (54%)

ISS=International Staging System

Dose Limiting Toxicity and Maximum Tolerated Dose

- No DLTs were reported during Cycle 1 at 240 mg/m^2 or 340 mg/m^2
- Two DLTs of Grade 3 stomatitis were reported during Cycle 1 at 480 mg/m^2
- MTD established at 340 mg/m^2

Preliminary Safety

The most common Grade 3/4 adverse events by treatment dose are shown in Table 3.

Table 3. Most Common[a] Grade 3/4 Adverse Events

Adverse Event	240 mg/m^2 (N=5)	340 mg/m^2 (N=6)	480 mg/m^2 (N=2)	Total (N=13)
Leukopenia	3 (60%)	2 (33%)	1 (50%)	6 (46%)
Thrombocytopenia	4 (80%)	1 (17%)	1 (50%)	6 (46%)
Anaemia	2 (40%)	1 (17%)	1 (50%)	4 (31%)
Neutropenia	3 (60%)	1 (17%)	0	4 (31%)
Hyperphosphataemia	0	2 (33%)	0	2 (15%)
Stomatitis	0	0	2 (100%)	2 (15%)

[a] >1 Patient

- Grade 3/4 TH-302 Related Non-Laboratory Adverse Events: Stomatitis (2), Abdominal pain (1), Diarrhoea (1), Fatigue (1), Rectal pain (1), Superventricular tachycardia (1)
- Serious Adverse Events: Thirteen SAEs occurred in 5 patients. SAEs occurring in more than one patient: pneumonia (3).

Preliminary Efficacy

Table 4. mIMWG Best Overall Response

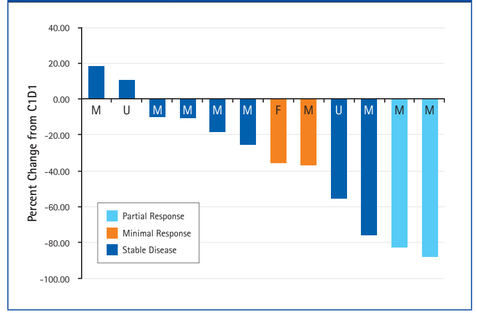
	240 mg/m^2 (N=5)	340 mg/m^2 (N=6)	480 mg/m^2 (N=2)	Total (N=13)
Number Evaluable	5	5[a]	2	12
SD	3 (60%)	3 (60%)	2 (100%)	8 (67%)
MR[b]	1 (20%)	1 (20%)	0	2 (17%)
PR	1 (20%)	1 (20%)	0	2 (17%)

mIMWG=modified International Myeloma Working Group; **SD**=stable disease; **MR**=minimal response; **PR**=partial response

[a] Excludes one patient who discontinued from study prior to completing Cycle 1

[b] Serum M-spike decrease >/=25%-<50%

Figure 3. Maximum Change in Paraprotein



M=Serum M-component; **U**=Urine M-component; **F**=Serum FLC

- 13 patients were dosed with a median of 5 cycles. 3 patients continue on study after 5, 15 and 16 cycles.
- Reasons for discontinuation were: disease progression (4), subject decision (2), clinical deterioration (2), adverse event (1), alternative therapy [transplant] (1)

Figure 4. Time on Study (months)

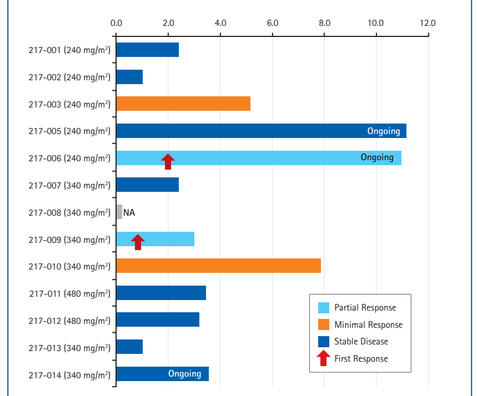
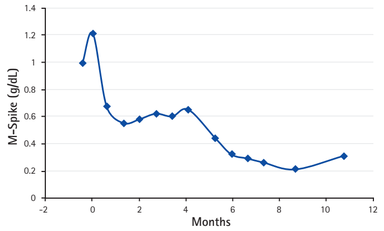


Figure 5. Case Report: M-Spike Response During Treatment

- Patient 217-006
- 78 Year old Female
- Diagnosed November 1, 2006
- 7 Prior Therapies (Prior proteasome inhibitor, prior IMiD, prior alkylator)
- Relapsed/Refractory Disease
- Patient received TH-302 (240 mg/m^2) and dexamethasone



IMiD=Immunomodulatory Drug

Conclusions

TH-302 can be administered at 340 mg/m^2 in combination with dexamethasone on a twice weekly schedule. Dose limiting mucositis was observed at higher doses. Initial clinical activity has been noted with a clinical benefit rate (PR+MR) of 33% in heavily pretreated multiple myeloma patients who are relapsed/refractory to both bortezomib and thalidomide/lenalidomide regimens.

References

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Acknowledgements

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Disclosures

TH-302 is currently under clinical investigation and has not been approved by any regulatory authority. Status: May 2013