A Phase 1 Study of TH-302, an Investigational Hypoxia-Targeted Drug, in Patients with Advanced Leukemias

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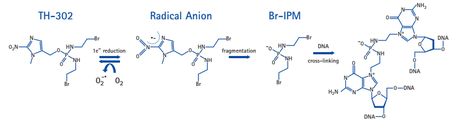
Introduction

Hypoxia promotes resistance to radiotherapy and chemotherapy in part through upregulation of HIF-1α. In bone marrow biopsies from newly diagnosed acute myelogenous leukemia (AML), HIF-1α was expressed (Deeb, *Leuk Res* 2011). Preclinical data in mice with acute lymphoblastic leukemia (ALL) have demonstrated marked expansion of hypoxia in areas of marrow leukemia infiltrates (Benito *et al., PLoS One* 2011). Increased levels of HIF-1α are often associated with increased tumor aggressiveness and therapeutic resistance (Semenza, *Nat Rev Cancer* 2003; Quintero, *Sur Oncol* 2004). TH-302 has exhibited specific hypoxia-dependent cytotoxicity when tested against primary ALL and AML samples *in vitro* (Benito *et al., ASH* 2012). Based on these findings, a Phase 1 study of TH-302 was designed for advanced leukemias.

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.

Objectives

Primary

- To determine the maximum tolerated dose, dose limiting toxicity, safety and tolerability of TH-302 in patients with acute leukemias, advanced phase chronic myelogenous leukemia (Arm A), high risk myelodysplastic syndromes (Arm A), advanced myelofibrosis (Arm A) or relapsed/refractory chronic lymphocytic leukemia (Arm A)

Secondary

- To determine the clinical activity of TH-302
- To evaluate the pharmacokinetics (PK) of TH-302 and Br-IPM

Exploratory

- To compare the safety and efficacy of TH-302 administered as a 30-60 minute infusion with TH-302 administered as a continuous infusion

Methods

Arm A: TH-302 administered over 30 - 60 minutes daily on days 1-5 of a 21 day cycle.

Arm B: TH-302 administered as continuous administration over 120 hours on days 1 - 5 of 21 day cycle.

Eligibility

- Age ≥18
- ECOG performance status ≤3
- Adequate renal and hepatic function
- Relapsed/refractory leukemia for which no standard therapy options are anticipated to result in a durable remission
  - Acute myelogenous leukemia (AML)
  - Acute lymphoblastic leukemia (ALL)
  - Chronic myelogenous leukemia (CML)
  - High-risk myelodysplastic syndrome (MDS)
  - Chronic lymphocytic leukemia (CLL)
  - Advanced myelofibrosis (MF)

Dose Limiting Toxicity: A dose-limiting toxicity (DLT) was defined as a clinically significant grade 3 or grade 4 adverse event or abnormal laboratory value assessed as attributed to TH-302 and unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first cycle of therapy with TH-302. Specific exceptions to this definition were outlined in the protocol.

Results

Patient characteristics, disease history and treatment history are summarized in Table 1. Patients had received a median of 5 prior therapies and 84% had received over 3 prior therapies.

Table 1. Patient Characteristics

Characteristic	Arm A: Daily IV TH-302 Administration (N = 38)	Arm B: Continuous TH-302 Administration (N = 11)	Total (N = 49)
Age			
Median	61.5	56	58
Range	24 – 76	23 – 73	23 – 76
Gender			
Male/Female	20/18	5/6	25/24
ECOG Performance Status			
0	0	1 (9%)	1 (2%)
1	25 (66%)	5 (45%)	30 (61%)
2	10 (26%)	5 (45%)	15 (31%)
3	3 (8%)	0	3 (6%)
Type of Leukemia			
AML	30 (79%)	9 (82%)	39 (80%)
ALL	7 (18%)	2 (18%)	9 (18%)
CML	1 (3%)	0	1 (2%)
Prior Stem Cell Transplant	12 (32%)	6 (55%)	18 (37%)
Number of Prior Systemic Therapies			
Median	5	5	5
Range	2 – 13	2 – 9	2 – 13
>3 Prior Therapies	33 (87%)	8 (73%)	41 (84%)

Daily dose level cohorts, study drug exposure and the frequency of DLTs are provided in Table 2. In Arm A, 2 of 4 patients treated at 550 mg/m^2 had DLTs of grade 3 esophagitis. The MTD in Arm A was established at a daily dose of 460 mg/m^2. In Arm B, 2 of 3 patients treated at 460 mg/m^2 had DLTs of grade 3 stomatitis and grade 3 hyperbilirubinemia. The MTD in Arm B was established at a daily dose of 330 mg/m^2.

Table 2: Study Drug Exposure

	Arm A: Daily IV TH-302 Administration (N = 38)	Arm B: Continuous TH-302 Administration (N = 11)	Total (N = 49)
Daily Dose Level			
120 mg/m^2	4 (11%)	0	4 (8%)
170 mg/m^2	4 (11%)	0	4 (8%)
240 mg/m^2	3 (8%)	0	3 (6%)
330 mg/m^2	3 (8%)	8 (73%)	11 (22%)
460 mg/m^2	20 (53%)	3 (27%)	23 (47%)
550 mg/m^2	4 (11%)	0	4 (8%)
Number of Cycles			
120 mg/m^2			
Median	1.5		1.5
Range	1 – 4		1 – 4
≥2	2 (25%)		2 (25)%
170 mg/m^2			
Median	1.5		1.5
Range	1 – 3		1 – 3
≥2	2 (50%)		2 (50%)
240 mg/m^2			
Median	1		1
Range	1 – 2		1 – 2
≥2	1 (33%)		1 (33%)
330 mg/m^2			
Median	1	1	1
Range	1 – 1	1 – 3	1 – 3
≥2	0 (0%)	3 (38%)	3 (27%)
460 mg/m^2			
Median	1	2	1
Range	1 – 4	1 – 2	1 – 4
≥2	3 (15%)	2 (67%)	5 (22%)
550 mg/m^2			
Median	1		1
Range	1 – 2		1 – 2
≥2	1 (25%)		1 (25%)
Dose Limiting Toxicity			
120 mg/m^2	0/4	NA	0/4
170 mg/m^2	0/4	NA	0/4
240 mg/m^2	0/3	NA	0/3
330 mg/m^2	0/3	2/8 (25%)	2/11 (18%)
460 mg/m^2	0/20	2/3 (67%)	1/23 (4%)
550 mg/m^2	2/4 (50%)	NA	1/4 (25%)

The most common non-hematological adverse events reported in over 15% of patients in either Arm A or Arm B are provided in Table 3. In general, the adverse event profiles were similar in Arm A and Arm B. Pneumonia and sepsis were more frequent in Arm B; urinary tract infections were more frequent in Arm A.

Table 3: Most Common Non-Hematologic Adverse Events (>15% of patients in either Arm)

	Arm A: Daily IV TH-302 Administration (N = 38)		Arm B: Continuous TH-302 Administration (N = 10*)	
Preferred Term	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Diarrhea	17 (44%)	2 (5%)	3 (30%)	1 (10%)
Fatigue	10 (26%)	2 (5%)	1 (10%)	0 (0%)
Peripheral Edema	9 (24%)	1 (3%)	2 (20%)	0 (0%)
Rash	9 (24%)	0 (0%)	3 (30%)	0 (0%)
Pneumonia	8 (21%)	7 (18%)	6 (60%)	4 (40%)
Urinary Tract Infection	7 (18%)	5 (13%)	0 (0%)	0 (0%)
Nausea	7 (18%)	1 (3%)	3 (30%)	1 (10%)
Headache	6 (16%)	2 (5%)	0 (0%)	0 (0%)
Stomatitis	5 (13%)	1 (3%)	3 (30%)	2 (20%)
Dermatitis Bullous	2 (5%)	0 (0%)	2 (20%)	0 (0%)
Sepsis	2 (5%)	2 (5%)	2 (20%)	2 (20%)
Mucosal Inflammation	1 (3%)	0 (0%)	2 (20%)	1 (10%)
Cough	0 (0%)	0 (0%)	2 (20%)	0 (20%)
Epistaxis	0 (0%)	0 (0%)	2 (20%)	0 (20%)
Multi-Organ Failure	0 (0%)	0 (0%)	2 (20%)	2 (20%)

* Adverse event data in clinical database on 07 November 2013; AE data was unavailable in database for one patient.

Serious Adverse Events

Forty-nine serious adverse events (SAEs) regardless of relationship to study drug were reported in 28 (57%) patients. SAEs occurring in more than two patients were pneumonia (n = 9), febrile neutropenia (n = 6), and sepsis (n = 3).

Eight SAEs related to study drug were reported in 5 patients. SAEs related to study drug were stomatitis (one patient with two events and one patient with a single event), mucosal inflammation and multi-organ failure in one patient, esophagitis in one patient, and esophagitis and dysphagia in one patient.

Efficacy

The majority of patients had rapid cytoreduction early in Cycle 1, which increased prior to initiating the next cycle. The median decrease in peripheral blasts was 67% and 12 patients had a clearing of all peripheral blasts; however, the decreases were generally transient with most patients experiencing disease progression prior to initiating Cycle 2. Two AML patients from Arm A who received 550 mg/m^2 had complete resolution of leukemia cutis. One AML patient at 550 mg/m^2 bolus TH-302 had a complete response with incomplete platelet recovery (CRp), and one AML patient at 440 mg/m^2 bolus TH-302 had a CR.

Table 4. Response Summary

	Arm A: Daily IV TH-302 Administration (N = 38)	Arm B: Continuous TH-302 Administration (N = 11)	Total (N = 49)
120 - 330 mg/m^2			
N	14	8	22
CR/CRi	0	0	0
PR	1 (7%)	0	1 (5%)
SD	4 (28%)	1 (13%)	5 (23%)
PD	9 (64%)	7 (88%)	16 (73%)
460 mg/m^2			
N	20	3	23
CR/CRi	1 (5%)	0	1 (4%)
PR	0	0	0
SD	4 (20%)	2 (67%)	6 (26%)
PD	14 (70%)	1 (33%)	15 (65%)
NA*	1 (5%)		1 (4%)
550 mg/m^2			
N	4	N/A	4
CR/CRi	1 (25%)		1 (25%)
PR	0		0
SD	1 (25%)		1 (25%)
PD	2 (50%)		2 (50%)

* NA = Not assessed.

Conclusions

- Utilizing a daily TH-302 dosing schedule on Days 1-5 of a 21 day cycle, the maximum tolerated dose was established at a daily dose of 460 mg/m^2
- Utilizing a continuous TH-302 dosing schedule over 120 hours on Days 1-5 of a 21 day cycle, the maximum tolerated dose was established at a daily dose of 330 mg/m^2
- The dose-limiting toxicity was primarily mucositis
- TH-302 demonstrated evidence of activity in this heavily pre-treated population with three objective responses, but the majority of cytoreductions were transient
- Further investigations including assessing TH-302 in combination with cytotoxic or demethylating agents are warranted

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