Phase 1 Study of TH-302, a Hypoxia Activated Cytotoxic Prodrug, in Subjects with Advanced Leukemias

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Background

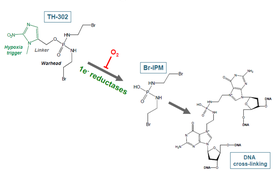
Progression of leukemia is associated with wide-spread hypoxia in the bone marrow (BM) microenvironment (Benito et al, PlosOne 2011). Hypoxia promotes resistance to radiation and chemotherapy in part through upregulation of HIF-1α. Increased levels of HIF-1α are often associated with increased tumor aggressiveness and therapeutic resistance (Semenza, Nat Rev Cancer 2003, Quintero, Sur. Oncol 2004). In BM biopsies from newly diagnosed AML, HIF-1α was expressed (Hu, Mod Path 2012).

TH-302

TH-302 is a nitroimidazole prodrug of the cytotoxin, bromo-isophosphoramide mustard (Br-IPM). **Figure 1**

Under normal oxygen conditions or normoxia, TH-302 is essentially inactive. In hypoxic conditions and in the presence of certain reductases, the nitroimidazole is reduced and Br-IPM is released to alkylate DNA, inducing intrastrand and interstrand crosslinks. The repair of the TH-302 DNA damage is dependent on homologous recombination repair.

Figure 1



In vitro, TH-302 exhibited potent activity in several leukemia cell lines including pre-B ALL (REH, NALM6), AML (OCI-AML3, MOLM-13, KG-1) and CML (KBM5).

Exposure to TH-302 for 6 hours at 1% 0_2 followed by 48 hours cell culture at 21% 0_2 yielded IC_{50}s that ranged from 0.04μM to 2.3μM.

In vivo, TH-302 exhibited specific hypoxia-dependent cytotoxicity when tested against primary ALL and AML models.

Methods

Key Inclusion/Exclusion Criteria:

- Age ≥18
- ECOG performance status ≤3
- Adequate renal 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)

Standard 3+3 dose escalation design with 40% dose increments.
TH-302 was administered over 30-60 minutes on days 1-5 of a 21 day cycle.

Primary objective to determine maximum tolerated dose (MTD).
Secondary objectives to determine pharmacokinetic profile and preliminary efficacy

Patient Characteristics

Characteristic	Total (N=38)
Age Median (range)	61.5 (24 - 76)
Gender Male/Female	20 (53%) / 18 (47%)
ECOG Performance Status 1/2/3	24 (63%) / 10 (26%) / 4 (11%)
Type of Leukemia AML ALL (B-cell/T-cell) CML	 30 (79%) 7 (18%) (3/4) 1 (3%)
Prior Stem Cell Transplant	13 (34%)
Prior Systemic Therapy Median (range) >3 Prior	 6 (2 - 10) 33 (87%)

Study Drug Exposure

Dose Level (mg/m^2)	Number of Subjects	Dosing Summary	Number of Cycles
120	4	3 of 4 evaluable. No DLTs.	1: n=2 2: n=1 4: n=1
170	4	3 of 4 evaluable. No DLTs.	1: n=1 2: n=1 3: n=1
240	3	3 of 3 evaluable. No DLTs.	1: n=2 2: n=1
330	3	3 of 3 evaluable. No DLTs.	1: n=2 2: n=1
460	7	6 of 7 evaluable. No DLTs.	1: n=7
550	4	3 of 4 evaluable. **2 of 3 DLT**. DLTs both esophagitis.	1: n=3 2: n=1
460	13	Efficacy expansion cohort No DLTs.	1: n=10 2: n=1 4: n=2 (1 ongoing)

Dose Escalation:
Maximum tolerated dose established at 460 mg/m^2 on days 1-5 of 21 day cycle.

Dose Expansion:
13 subjects (10 evaluable for response) were treated at 460 mg/m^2 in the dose expansion cohort

Adverse Events

Most common Non-hematologic Adverse Events (>15% of subjects)

Preferred Term	120-330 mg/m^2 (N=14)	460 mg/m^2 (N=20)	550 mg/m^2 (N=4)
Diarrhea	2 (14%)	11 (55%)	2 (50%)
Fatigue	4 (29%)	5 (25%)	0 (0%)
Peripheral edema	3 (21%)	5 (25%)	1 (25%)
Urinary tract infection	3 (21%)	4 (20%)	0 (0%)
Nausea	2 (14%)	3 (15%)	1 (25%)

Grade 3/4 Adverse Events Related to TH-302

- 222-016 (460 mg/m^2) grade 3 Fatigue
- 222-024 (550 mg/m^2) grade 3 dysphagia and grade 3 esophagitis
- 222-025 (550 mg/m^2) grade 3 esophagitis
- 222-036 (460 mg/m^2) grade 3 mucositis

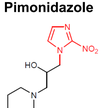
Serious Adverse Events Regardless of Relationship to Study Drug
Serious adverse events occurring in more than one subject: pneumonia (n=2), fungal pneumonia (n=2), sepsis (n=2), hypotension (n=2) and esophagitis (n=2)

Hypoxia Assessment

Pimonidazole is an exogenous marker of hypoxia

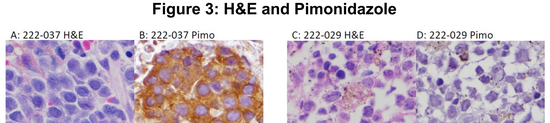
- Pimonidazole **(Figure 2)** and TH-302 **(Figure 1)** have similar physical chemical properties.
- Pimonidazole and TH-302 have the same "trigger" for hypoxia: 2-nitroimidazole.
- Pimonidazole and TH-302 have similar oxygen concentration dependence.

Figure 2: Pimonidazole



- A separate consent was required for the administration of pimonidazole prior to routine bone marrow biopsy. Limited samples were obtained as most subjects had already had a bone marrow biopsy prior to time of enrollment.

Figure 3: H&E and Pimonidazole



222-037: Positive for Pimonidazole
Eventual response of CR (Figure 4).

222-029: Negative for Pimonidazole
No response to treatment.

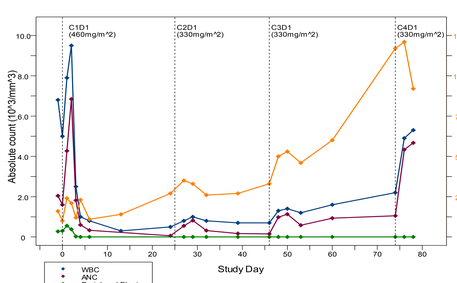
Efficacy

Best Response

TH-302 Cohort (mg/m^2)	Number of Evaluable Subjects	Best Response
120	4	SD: n=2, PD: n=2
170	4	PR: n=1, SD: n=1, PD: n=2
240	3	SD: n=1, PD: n=2
330	3	PD: n=3
460	19	CR: n=1, SD: n=2, PD: n=16
550	4	CRp: n=1, SD: n=1, PD: n=2

Leukemia cutis:
Two subjects treated at the 550 mg/m^2 cohort presented with leukemia cutis. In both cases the subjects experienced complete resolution of their leukemia cutis.

Figure 4: Subject 222-037, a 67 year old male with M1 AML previously treated with 4 prior regimens. Bone marrow blast 6% at baseline, 16% at end of cycle 1 and 0% at end of cycle 3. Platelet and ANC recovery resulted in CR. Treatment with TH-302 ongoing.



Conclusions

- Utilizing a daily TH-302 dosing schedule on Days 1-5 of a 21 day cycle
  - The maximum tolerated dose was established at 460 mg/m^2
  - The dose limiting toxicity was mucositis
- TH-302 demonstrated evidence of activity in this heavily pre-treated population
- Further investigations including assessing TH-302 in combination are warranted

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We thank the patients, families and investigative site personnel for their participation.

ASCO Annual '12 Meeting