A First-in-Man Phase 1 Study of TH-302, A Hypoxia-Activated Cytotoxic Prodrug (HAP)

Abstract # ENA-0175

Poster # 412

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ABSTRACT

Background: TH-302 is a 2-nitroimidazole prodrug of the DNA alkylator, bromo-isophosphoramide mustard (Br-IPM). Under normoxic conditions, TH-302 is relatively inactive but in hypoxic conditions and in the presence of certain reductases, TH-302 is reduced and Br-IPM is released. In xenograft models, TH-302 was active as a single agent and resulted in complete responses in combination with chemotherapy.

Materials and Methods: Eligible patients (pts) had ECOG ≤1, advanced or metastatic solid tumors, at least one target lesion by RECIST, and acceptable hematologic, liver and renal function. A modified accelerated titration design was used. TH-302 was administered intravenously over 30 minutes on Day 1, 8 and 15 of a 28-day cycle. CT scans were obtained after every 2 cycles. Detailed pharmacokinetic (PK) sampling was performed during Days 1 and 15. The objectives of this study were to determine the maximum tolerated dose and dose limiting toxicity (DLT) and to evaluate the safety, PK and anti-tumor activity of TH-302 in advanced solid tumors.

Results: Twenty pts have enrolled at 3 sites. Median age: 63. ECOG 0/1 in 11/9 pts. Primary tumor: prostate (6), colorectal (5), NSCLC (2), SCLC (2), other (5). Pts received 1-8 cycles (median 2; 1-22 doses) at 7.5-670 mg/m^2. All 20 pts have discontinued: progressive disease (PD; 11), clinically significant deterioration not meeting RECIST PD (4), PSA PD (3; SD by RECIST), pt decision (1) and adverse event (AE; 1; unrelated to TH-302). One DLT has occurred in the 20 pts: Herpes simplex virus perianal and rectal ulcers at 670 mg/m^2. The most common AEs are fatigue, nausea, vomiting and constipation. Seven pts have had skin or mucosal lesions including blisters and ulcers. Grade 2 neutropenia has occurred in 2 pts: 1 with pre-existing cyclic neutropenia treated at 7.5 mg/m^2 not considered due to TH-302 and 1 at 480 mg/m^2 due to TH-302. Two pts at 670 mg/m^2 developed grade 1 thrombocytopenia, 13 pts developed worsening or new lymphopenia and 6 pts had worsening or new anemia. One pt with SCLC treated at 480 mg/m^2 had an unconfirmed partial response and 10 had a best response of stable disease, one of whom (NSCLC; dose level 7.5 mg/m^2) had PET metabolic response with 35% and 36% declines in maximum SUV following cycles 2 and 4. Five pts had progressive disease and 4 were unevaluable. Cmax and AUC for TH-302 and Br-IPM increased linearly over the range of doses evaluated to date (7.5-670 mg/m2) with no accumulation at Day 15. Half-life ranged from 0.5-1h. The ratio of TH-302 to Br-IPM is higher than in rats or dogs but the Cmax and AUC for Br-IPM are similar to dogs at comparable doses.

INTRODUCTION

TH-302 is a nitroimidazole prodrug of the cytotoxin, bromo-isophosphoramide mustard (Br-IPM). Under normoxic conditions, TH-302 is inactive but 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.

Few normal cells ever reach severe hypoxia. In contrast, tumor cells often consist of large areas of highly hypoxic cells that are known to be resistant to chemotherapy and radiation treatment. As long as the prodrug is in areas of normoxia it remains intact and toxicity is minimized. Because TH-302 has been designed to be selectively activated in highly hypoxic regions, it is an attractive candidate for clinical development for solid tumors. In addition, preclinical data suggest that after activation, the active moiety may diffuse to areas outside the hypoxic region, demonstrating a "bystander" effect which may provide additional anti-tumor activity.

TH-302 was found to be significantly active as monotherapy and in combination with other chemotherapies in several xenograft mouse models including orthotopic and metastatic models. Preclinical toxicology studies in rats and dogs resulted in reversible hematologic and renal toxicity at the highest doses.

OBJECTIVES

Primary

•To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of TH-302 administered weekly x 3, repeated every 4 weeks in patients with advanced solid tumors

Secondary

•To establish the pharmacokinetics of intravenously administered TH-302

•To assess the anti-tumor activity of TH-302 as measured by objective response and duration of response

METHODS

Key inclusion criteria

•IRB approved informed consent

•Histological or cytological evidence of advanced and/or metastatic solid malignancy previously treated with one or more regimens of chemotherapy or for which no effective therapy is available

•Recovered from toxicities of prior therapy

•ECOG performance status 0 or 1

•Adequate organ function:

- •ANC ≥ 1500/μL, Platelets ≥ 100,000/μL, Hemoglobin ≥ 9 g/dL
- •Serum creatinine within normal limits and creatinine clearance ≥ 60 mL/min/1.73 m^2
- •Total bilirubin ≤ 1.5 x ULN, AST / ALT ≤ 2.5 x ULN or ≤ 5 x ULN if liver metastases

Key exclusion criteria

•Prior treatment with more than 3 myelosuppressive cytotoxic chemotherapy regimens

•Prior treatment with high dose chemotherapy

•Prior radiotherapy to more than 25% of the bone marrow

•Severe chronic obstructive pulmonary disease with hypoxemia or in the opinion of the investigator any physiological state leading to hypoxemia

Study Design

•Open-label, multicenter (3), dose-escalation study

•Modified acceleration titration design

- •100% dose escalations and cohort size 1-3 patients until first DLT or first grade 2 toxicity (excluding Grade 2 nausea, vomiting, diarrhea, alopecia and fatigue) that is clearly not related to disease progression, intercurrent illness, concomitant medications or other non-drug intervention
- •Then 20-40% dose escalations with 3-6 subjects per cohort

DLT definition

•Grade 3 or Grade 4 non-hematologic toxicity (including febrile neutropenia),

•Grade 3 or Grade 4 nausea, vomiting or diarrhea not able to be medically managed,

•Grade 4 neutropenia lasting > 5 days,

•Grade 4 thrombocytopenia (or any requirement for platelet transfusion),

•Grade 4 anemia (unexplained by the underlying disease),

•Any non-preexisting Grade 2 non-hematologic toxicity (excluding Grade 2 nausea, vomiting, diarrhea, alopecia and fatigue) which, in the judgment of the Investigator, medical monitor and sponsor, is considered a DLT,

•Any Grade 2 or higher non-hematologic toxicity that does not resolve to Grade 0 or 1 toxicity by the start of the next cycle which, in the judgment of the Investigator, medical monitor and sponsor, is considered a DLT,

•Inability to begin the next cycle of treatment within two weeks of the last dose due to unresolved toxicity.

MTD definition

•The highest dose level at which 0 or 1 of 6 subjects experiences a DLT

TH-302 administration

•Starting dose 7.5 mg/m^2

•Administered IV over 30 minutes (60 minutes for doses over 2000 mg) on Days 1, 8 and 15 of every 4-week cycle.

•Treatment for 6 cycles unless disease progression or unacceptable toxicity.

•Planned enrollment: Up to 48 patients; once MTD established, 6 additional patients will be enrolled at the MTD

•Response evaluated according to RECIST criteria after every 8 weeks of treatment

•Survival follow-up every 3 months

•Tumor markers (eg PSA, CEA, CA19-9, CA-125) every cycle.

Pharmacokinetic sampling

•Blood samples collected for analysis of TH-302 and Br-IPM (sampling times: pre-dose and up to 12.5 hours post-start of the infusion)

•Samples analyzed by a validated LC/MS/MS method

•Pharmacokinetic parameters computed from plasma drug concentrations using standard non-compartmental methods with WinNonlin v. 5.2

•Toxicity assessed using NCI-CTCAE version 3.0

RESULTS

20 patients have enrolled at 3 US sites from July 2007 to July 2008 and have initiated at least 1 cycle at doses from 7.5 to 670 mg/m2. Patient demographics and cancer history are summarized in Table 1. All 20 patients have discontinued from the study. Two patients completed all 6 cycles. Reasons for discontinuation were progressive disease (11), PSA progression (3) clinical deterioration without documentation of progression by RECIST (4), patient decision (1), adverse event (1).

Table 1: Patient characteristics and Cancer History (n = 20)

Sex (M / F)(N)	13/7
Age (yrs)	
Median	63
Range	31 - 77
ECOG (N)	
0	11
1	9
Prior systemic therapy (# regimens)	
1	1
2	5
3	6
>3	8
Tumor type (N)	
Prostate	6
Colorectal	5
NSCLC	2
SCLC	2
Other	5
Months since diagnosis of advanced/metastatic disease	
Median	28
Range	3 – 143

Safety

Study Drug Exposure and DLT

Study drug exposure is summarized in Table 2. The accelerated titration phase ended at 480 mg/m^2 after one patient developed grade 2 neutropenia during Cycle 1. Four subjects were enrolled at 7.5 mg/m^2 because of grade 2 neutropenia in the initial subject (a fourth subject replaced another subject who was not evaluable for DLT). Upon review, the grade 2 neutropenia was determined to be associated with cyclic neutropenia not related to study drug. One subject treated at 670 mg/m^2 developed grade 3 Herpes simplex virus (HSV) perianal and rectal ulcers that were considered related to study drug. Because of this DLT, the 670 mg/m^2 cohort is being expanded to 6 subjects. Median time on treatment is currently 2 cycles (8 weeks); range 1-8 cycles.

Table 2: Patient Dosing

Dose (mg/m^2)	Number of Patients	No. Cycles/Doses
7.5	4	1 - 8 / 1 – 22
15	1	2 / 6
30	2	4 - 6 / 12 – 18
60	2	1 - 4 / 3 – 12
120	3	2 / 4 – 6
240	2	1 - 4 / 3 – 12
480	3	2 - 4 / 6 – 12
670	3	2 - 3 / 4 - 9

Table 3: Most common adverse events regardless of relationship to study drug (all cycles)

Adverse event*	Number of Patients with an AE (%)					
	Dose (mg/m^2)					
	7.5-30 N=7	60-120 N=5	240 N=2	480 N=3	670 N=3	All N=20
Fatigue	3	1	1	2	1	8 (40%)
Nausea	2	2	0	2	1	7 (35%)
Vomiting	1	1	0	1	3	6 (30%)
Constipation	0	2	2	0	1	5 (25%)

* Coded with MedDRA

There has been one dose reduction for grade 3 hand-foot skin reaction considered to be study drug-related in a patient treated at 670 mg/m^2. Several patients have had dose delays for adverse events, two of which were considered study drug-related: peripheral neuropathy and HSV perianal, rectal and esophageal ulcers.

Deaths and Serious Adverse Events (SAE)

Three patients have died from progressive cancer and one from an SAE of obstructive pneumonia from 19 - 95 days after initiating therapy

Twelve SAEs have occurred in 9 patients including one event of HSV perianal and rectal ulcers that was considered study drug-related in a patient with diabetes treated at 670 mg/m^2

The remaining events were biliary obstruction, worsening back pain, increasing abdominal pain, constipation, obstructive pneumonia, worsening fatigue, empyema, dehydration, pulmonary embolism, E coli bacteremia and ischemic stroke

Other Adverse Events

Adverse events (AE) have been reported in all patients. AEs occurring in 4 or more subjects are summarized in Table 3. Severe (Grade 3/4/5) adverse events were reported in 10 patients. The most common study drug-related AEs were fatigue (6), nausea (5), dysgeusia (3), constipation (2) and vomiting (2). Standard anti-emetic prophylaxis for moderately emetogenic therapy (generally 5HT blocker and steroid) was recommended starting at 670 mg/m^2. One AE (biliary obstruction) led to study discontinuation.

Seven pts have had skin or mucosal adverse events including all 3 pts treated at 670 mg/m^2. Epidermis and intestinal mucosa are known to have hypoxic regions particularly if wounded. TH-302 may be activated in these regions resulting in local toxicity.

Hematologic Toxicity

Hematologic toxicity has been minimal to date (Table 4)

Grade 2 neutropenia has been reported in 2 patients: one treated at 7.5 mg/m^2 with a history of cyclic neutropenia and one treated at 480 mg/m^2 who developed grade 2 neutropenia at the end of Cycle 1 that recovered quickly allowing continued dosing

Grade 1 thrombocytopenia has occurred in 2 pts treated at 670 mg/m^2 at Cycles 2 and 3

Anemia and lymphopenia were present at baseline in 17 (85%; 14 grade 1, 3 grade 2) and 5 (25%; 2 grade 1, 3 grade 2) patients, respectively. Three patients have received darbepoetin.

Other Laboratory Data

There has been no evidence of renal or liver toxicity of TH-302 and no other consistent laboratory abnormalities

Table 4: Hematologic Toxicity (all cycles)

Maximum Grade*	0	1	2	3	4	All
Neutropenia N=20	18 (90%)	0 (0%)	2 (10%)	0 (0%)	0 (0%)	2 (10%)
Lymphopenia (N=20)	7 (35%)	1 (5%)	7 (35%)	4 (20%)	1 (5%)	13 (65%)
Thrombo-cytopenia N=20	18 (90%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	2 (10%)
Anemia N=20	1 (5%)	12 (60%)	6 (30%)	1 (5%)	0 (0%)	19 (100%)

* CTCAE v3.0

Pharmacokinetics

TH-302 and Br-IPM exhibit linear pharmacokinetics up to 670 mg/m^2 with half-lives of slightly less than 1 hour (Figure 1)

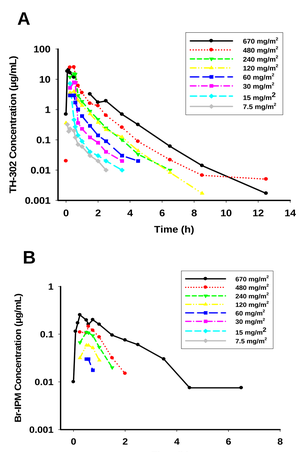
TH-302 has a large Vdss (26 L/m^2) and high clearance (36 L/h/m^2)

Once weekly dosing of TH-302 does not result in accumulation of TH-302 and Br-IPM

Plasma concentrations of Br-IPM are not detectable at doses less than 60 mg/m^2

Plasma Br-IPM concentrations are ~1% of TH-302 plasma concentrations

Figure 1. TH-302 (A) and Br-IPM (B) plasma concentrations by dose level



Preliminary Assessment of TH-302 Activity

•To date 16 patients have had at least one evaluable post-treatment tumor assessment.

•One patient with SCLC metastatic to liver treated at 480 mg/m^2 had a partial response (44% decrease in SLD of target lesions) at the end of Cycle 2 (Figure 2). LDH had decreased 72% and liver function tests had normalized. The Cycle 2 tumor assessment also showed a large empyema that required surgical intervention and a 22-day delay of Cycle 3 dosing. Confirmation CT scan one month after the Cycle 2 scan showed progressive disease.

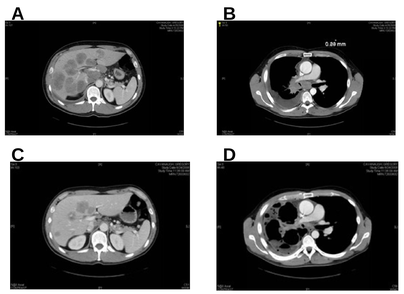
•10 patients have had a best response of stable disease lasting from 1.7+ to 7.3 months; these patients had prostate cancer (5), colorectal cancer (3), SCLC (1) and NSCLC (1).

•1 patient with NSCLC treated at 7.5 mg/m^2 had stable disease by RECIST and had a FDG-PET metabolic response with 35% and 36% declines in maximum SUV following cycles 2 and 4

•5 patients had a best response of progressive disease

•Of the 6 patients with prostate cancer, none had a PSA response (>50% decrease). However 2 subjects with early PSA progression had stable disease by RECIST criteria and remained on study for 4 and 6 cycles.

Figure 2. 39 yo male with small cell lung cancer metastatic to liver. Spiral CT scan of abdomen (A) and chest (B) at baseline and after 2 cycles of treatment (C and D; partial response). Note empyema in D.



CONCLUSIONS

•Based on preclinical toxicology and because preclinical data suggest that blood cell precursors in the bone marrow may be hypoxic, hematologic toxicity was expected to be dose-limiting; however hematologic toxicity has been minimal at doses up to 670 mg/m^2

•There is evidence that areas of the retina are hypoxic and thus may be susceptible to damage by a drug activated by hypoxia; however no retinal toxicity has been observed to date

•TH-302 may be causing skin and mucosal toxicity, possibly due to activation of TH-302 in areas of epithelium that are normally hypoxic

•Although only an exploratory endpoint in this Phase I trials, there is evidence of anti-tumor activity including activity at doses as low as 7.5 mg/m^2 (SD in NSCLC lasting 7.3 months) and an unconfirmed PR in a patient with SCLC treated at 480 mg/m^2

•These early efficacy data suggest that activated TH-302 (Br-IPM) may be diffusing into adjacent aerobic tumor regions producing a 'bystander' effect

•Extrapolations from preclinical pharmacokinetic data suggest that adequate plasma concentrations of TH-302 for efficacy were reached at 120 mg/m^2; however, it is likely that the local concentrations of the active Br-IPM are most important and the PK data show that the ratio of TH-302 to Br-IPM in the plasma is higher in humans than in rats and dogs

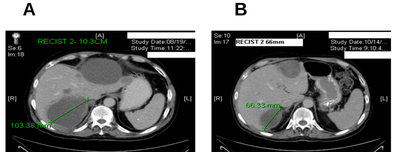
•The MTD for single agent TH-302 has not yet been reached and is at least 480 mg/m^2; enrollment in this trial is continuing

•Because TH-302 targets hypoxic cells, Phase I/2 studies in combination with chemotherapy that will target aerobic tumor cells have been initiated

ADDENDUM

After the data cutoff for this poster, 2 more patients were enrolled at 670 mg/m^2. One had a DLT of grade 3 mucositis leading to dehydration. With the second DLT in this cohort, the dose was de-escalated and the 480 mg/m^2 cohort is currently being expanded. The other additional patient at 670 mg/m^2 had a PR (unconfirmed) at the end of Cycle 2 (Figure 3) and continues on study.

Figure 3. 74 yo male with malignant melanoma metastatic to lung and liver. Spiral CT scan of abdomen at baseline (A) and after 2 cycles of treatment (B; partial response; 53% decrease in target lesion SLD).



We thank the patients who participated in this trial and the study coordinators, nurses, clinical research assistants and doctors who assisted with the research.