Final results of a phase I study of TH-302, a hypoxia-activated cytotoxic prodrug (HAP)

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Abstract # 2573

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I: INTRODUCTION

•TH-302 is a nitroimidazole prodrug of the cytotoxin, bromoisophosphoramide mustard (Br-IPM).
•Under normoxic conditions, TH-302 is essentially inactive but in hypoxic conditions, the nitroimidazole is reduced and Br-IPM is released to alkylate DNA.
•Tumors often consist of large areas of highly hypoxic cells known to be resistant to chemotherapy and radiation.
•TH-302 has been designed to be selectively activated in highly hypoxic regions that are unlikely to occur in normal tissues
•Preclinical data suggest that the active moiety may diffuse to areas outside the hypoxic region, a "bystander" effect that may provide additional anti-tumor activity.
• TH-302 has demonstrated activity as monotherapy and in combination with other chemotherapies in numerous orthotopic and ectopic xenograft mouse models.
•Preclinical toxicology studies in rats and dogs resulted in reversible hematologic and renal toxicities at the highest doses.

II: OBJECTIVES

Primary

•Determine the MTD & DLT of TH-302 administered weekly x3, repeated every 4 weeks in patients with advanced solid tumors

Secondary

•Establish the PK of intravenously administered TH-302
•Assess the anti-tumor activity of TH-302

III: METHODS

Key inclusion criteria

•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
•ECOG performance status 0 or 1; Adequate organ function

Key exclusion criteria

•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 DLT or grade 2 toxicity (excluding Grade 2 nausea, vomiting, diarrhea, alopecia and fatigue)
  •After first DLT or grade 2 study drug related toxicity, 20-40% dose escalations with 3-6 subjects per cohort
•MTD definition
  •The highest dose level at which 0 or 1 of 6 subjects experiences a DLT

Procedures/Assessments

•TH-302 starting dose 7.5 mg/m^2 administered IV over 30 minutes (60 minutes if >2000 mg) on Days 1, 8 and 15 of every 28-day cycle.
•Planned enrollment: Up to 48 patients

Procedures/Assessments (cont'd)

•Response evaluated according to RECIST criteria after every 8 weeks of treatment
•Tumor markers, if appropriate, every cycle
•PK sampling for analysis of TH-302 and Br-IPM
  •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

IV: RESULTS

•31 patients enrolled at 3 US sites from July 2007 to January 2009
•Median age 64y (range 31-79); ECOG 0/1: 18/13
•Prior systemic therapies: median of 3; 28 pts received ≥2
•Tumor types: Colorectal (9), prostate (8), SCLC (3), NSCLC (2), head and neck (2), other (7: pancreas, esophagus, breast, hepatocellular, melanoma, sarcoma, unknown)

Safety

Study Drug Exposure and DLT (Table 1)

•Accelerated titration ended at 480 mg/m^2 after one patient developed grade 2 neutropenia during Cycle 1.
•Two of 5 patients treated at 670 mg/m^2 developed DLT: grade 3 Herpes simplex virus (HSV) perianal/rectal ulcers; grade 3 oral mucositis with dehydration. The cohort at 480 mg/m^2 was then expanded to 6 patients with no DLT.
•An intermediate dose of 575 mg/m^2 was then evaluated and 1 of 6 subjects had a DLT (grade 3 urethritis).
•The MTD was determined to be 575 mg/m^2.
•Median time on treatment was 2 cycles (8 weeks); range 1-8 cycles

Adverse Events (AEs; Tables 2 and 3)

•No study drug-related deaths
•Nausea and vomiting increased with dose. Standard anti-emetic prophylaxis for moderately emetogenic therapy (generally 5HT blocker and steroid) was recommended at doses >240 mg/m^2
•Skin and mucosal AEs (Table 3): incidence and severity increased with dose; dose reductions or delays due to skin/mucosal toxicity occurred only at 575 and 670 mg/m^2.
•Severe (Grade 3/4/5) AEs were reported in 17 (55%) patients.
•Severe AEs related to study drug were HSV perianal and rectal ulcers with rectal pain, dehydration due to mucositis, hand-foot syndrome, urethritis, nausea and vomiting (1 case each, all grade 3). Two patients discontinued from the study for an AE (biliary obstruction and a buttock ulcer in a diabetic patient).

Hematologic Toxicity (Table 4)

•Hematologic toxicity has been minimal
•Grade 2 neutropenia was 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
•Grade 2 thrombocytopenia has occurred in 1 patient at 575 mg/m^2
•Worsening anemia and lymphopenia grade occurred in 14 (45%) and 20 (65%) patients, respectively and was more common at higher doses.

Table 1: Patient Dosing

Dose (mg/m^2)	No. of Patients	Median No. Cycles (Range)
7.5	4	2.5 (1 – 8)
15	1	2 (NA)
30	2	5 (4 – 6)
60	2	2.5 (1 – 4)
120	3	2 (2 – 2)
240	2	2.5 (1 – 4)
480	6	3 (1 – 4)
575	6	2.5 (1 – 4)
670	5	2 (2 – 3)

Table 2: Common adverse events (all cycles)

	Number of Patients with an AE (%) By Dose in mg/m^2					
AE*	7.5-240 N=14	480 N=6	575 N=6	670 N=5	All N=31	Gr 3/4 N=31
Nausea	4 (29)	4 (67)	4 (67)	4 (80)	16 (52%)	1 (3.2%)
Fatigue	5 (36)	4 (67)	1 (17)	3 (60)	13 (42%)	3 (9.7%)
Vomiting	2 (14)	1 (17)	3 (50)	5 (100)	11 (35%)	1 (3.2%)
Constipation	4 (29)	1 (17)	1 (17)	3 (60)	9 (29%)	0
Diarrhea	2 (14)	1 (17)	2 (33)	2 (40)	7 (23%)	0
Back pain	3 (21)	0	0	3 (60)	6 (19%)	1 (3.2%)
Dyspnoea	2 (14)	2 (33)	1 (17)	1 (20)	6 (19%)	1 (3.2%)

* Coded with MedDRA

Table 3: Skin and Mucosa Adverse Events (all cycles)

	Number of Patients with an AE by Dose (%)				
AE*	7.5-240 N=14	480 N=6	575 N=6	670 N=5	All N=31
Skin	1 (7)	4 (67)	5 (83)	5 (100)	15 (48%)
Gr 3/4	0	0	0	2 (40)	2 (6%)
Mucosa	1 (7)	3 (50)	4 (67)	2 (40)	10 (32%)
Gr 3/4	0	0	1 (17)	2 (40)	3 (10%)

* Includes all AEs considered to be skin or mucosal

Table 4: Hematologic Toxicity (all cycles; N=31)

Maximum Grade*	0	1	2	3	4	All
Neutropenia	25 (81%)	4 (13%)	2 (6%)	0 (0%)	0 (0%)	6 (19%)
Lymphopenia	9 (29%)	1 (3%)	12 (39%)	8 (26%)	1 (3%)	22 (71%)
Thrombocytopenia	25 (81%)	5 (16%)	1 (3%)	0 (0%)	0 (0%)	6 (19%)
Anemia	1 (3%)	17 (55%)	12 (39%)	1 (3%)	0 (0%)	30 (97%)

* CTCAE v3.0

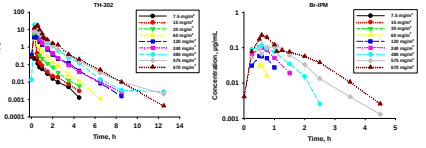
Other Laboratory Data

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

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 rapid clearance and the volume of distribution approximates total body water
•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 and Br-IPM plasma concentrations by dose level (Days 1 and 15 combined)



Preliminary Assessment of TH-302 Activity

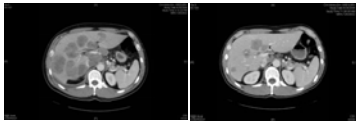
•27 patients had at least one evaluable post-treatment tumor assessment (Table 5) and 2 patients had a partial response (PR; unconfirmed):
  •A patient with SCLC metastatic to liver treated at 480 mg/m^2 had a PR (44% decrease in SLD of target lesions) at the end of Cycle 2 (Figure 2). A large empyema required surgical intervention and a 22-day delay of dosing. Confirmation CT scan showed progressive disease.
  •A patient with malignant melanoma treated at 670 mg/m^2 had an unconfirmed PR at the end of Cycle 2 but discontinued after a seizure due to unrecognized brain metastases.
•Both patients with a PR had elevated LDH at baseline that normalized on treatment (72 and 75% reductions)
•7 patients had SD lasting >3 months (2 patients each with prostate, colorectal and SCLC and 1 with NSCLC)
•Median progression-free survival: 3.7 months (95% CI: 1.8 – 3.8)

Table 5: Best Response by RECIST

Best Response	N (%)
Partial response	2 (6%)
Stable disease	16 (52%)
Progressive disease	9 (29%)

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

A B



V: CONCLUSIONS

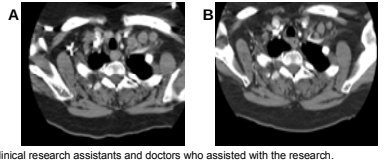
•The MTD for weekly single agent TH-302 is 575 mg/m^2
•Mucosal toxicity was dose-limiting. Skin and mucosal toxicity are common at doses above 240 mg/m^2. The mechanism is unknown but may be due to activation of TH-302 in areas of epithelium that are normally hypoxic
•Hematologic and renal toxicity were expected to be dose-limiting; however hematologic toxicity has been minimal and renal toxicity has not occurred at doses up to 670 mg/m^2
•Areas of the retina may be hypoxic but no retinal toxicity has been observed to date
•There is evidence of anti-tumor activity at doses as low as 7.5 mg/m^2 (SD in NSCLC lasting 7.3 months) including two unconfirmed PRs in patients with SCLC and malignant melanoma treated at 480 and 670 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
•Phase I studies of TH-302 in combination with chemotherapy that preferentially targets aerobic tumor cells have been initiated

VI: ADDENDUM

Enrollment expansion at the MTD is ongoing. Nine patients have enrolled and one additional DLT has been reported (grade 3 cheilitis). Three patients have had a tumor assessment; one patient with SCLC has had a 49% decrease in the sum of longest diameters at the end of Cycle 2 (Figure 3).

Figure 3. 61 yo female with SCLC treated with 3 prior chemotherapy regimens. Spiral CT scan of the neck at baseline (A) and end of Cycle 2 (B) showing decreases in bilateral supraclavicular lymphadenopathy.

A B



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