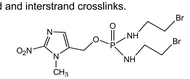
TH-302, A TUMOR SELECTIVE HYPOXIA-ACTIVATED PRODRUG, IN GASTROINTESTINAL CANCERS

M. J. Borad[1], A. C. Mita[2], E. G. Chiorean[3], J. R. Infante[4], V. K. Langmuir[5], C. Eng[5], S. Kroll[5], J. G. Curd[5]

[1]Mayo Clinic, Scottsdale, AZ; [2]Institute for Drug Development, Cancer Therapy and Research Center at the University of Texas Health Sciences Center San Antonio, San Antonio, TX; [3]Indiana University Simon Cancer Center, Indianapolis, IN; [4]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN; [5]Threshold Pharmaceuticals, Redwood City, CA; Threshold Pharmaceuticals, Redwood City

Introduction

TH-302 is a nitroimidazole prodrug of the cytotoxin, bromo-isophosphoramide mustard (Br-IPM). Under normoxic conditions, TH-302 is essentially 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, tumors 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, TH-302, is in areas of normoxia, it is designed to remain intact and toxicity is minimized. Because TH-302 has been designed to be selectively activated in these highly hypoxic regions, it is an attractive candidate for clinical development for solid tumors. In preclinical studies, the combination of TH-302 with a range of chemotherapies demonstrated significantly greater antitumor activity than single agent chemotherapy.

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 outside the hypoxic zone. In a Phase I monotherapy study, TH-302 showed activity as a single-agent with a maximum tolerated dose (MTD) of 575 mg/m^2 weekly, skin and mucosal dose limiting toxicity (DLT) and the absence of significant myelosuppression. Partial responses were reported in patients with metastatic melanoma and SCLC.

As TH-302 is designed to selectively target the hypoxic regions of solid tumors, the current study investigates the combination of TH-302 with chemotherapy which is effective in the normoxic regions of tumors. This complementary approach is designed to fully target solid tumors. This poster summarizes the current results in gastrointestinal malignancies.

Study Design

Three separate arms enroll independently:

Arm A: Gemcitabine plus TH-302
Arm B: Docetaxel plus TH-302
Arm C: Pemetrexed plus TH-302

- Initial TH-302 dose in each arm of 240 mg/m^2
- Escalate each arm independently in 20-40% increments up to maximum weekly monotherapy dose of 575 mg/m^2

MTD definition and Phase 2 dose
- Highest dose level at which 0 or 1 of 6 subjects experiences a DLT
- Phase 2 dose may be any dose at or below the MTD

TH-302 administration
- Administered IV over 30-60 minutes on Days 1, 8 and 15 of every 4-week gemcitabine cycle and on Days 1 and 8 of every 3-week docetaxel or pemetrexed cycle
- TH-302 is administered prior to chemotherapy

Chemotherapy administration
- Chemotherapy is administered at full dose on the standard schedule for each of the chemotherapies
- Chemotherapy administration is initiated 2 hours after the completion of the TH-302 administration

Once MTD established
- 12 additional patients will be enrolled at the MTD or lower dose to determine a recommended Phase 2 dose in:
  - Gemcitabine: first-line pancreatic cancer
  - Docetaxel: second-line NSCLC and first-line castrate-resistant prostate cancer
  - Pemetrexed: second-line NSCLC

Patient Assessments
- Response evaluated according to RECIST criteria after every even cycle
- Tumor markers (CEA, CA19-9) every cycle

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 (dose escalation)
- Recovered from toxicities of prior therapy
- ECOG performance status 0 or 1
- Evaluable by RECIST (at least one target or non-target lesion)
- Adequate hematologic function: ANC ≥ 1500/mL, Platelets ≥ 100,000/mL, Hemoglobin ≥ 9 g/dL
- Serum creatinine ≤ ULN
- Adequate liver function with chemotherapy dependent levels for total bilirubin, AST and ALT.

Key Exclusion Criteria

- Prior treatment with chemotherapy utilized in combination
- Prior treatment with more than 3 myelosuppressive cytotoxic chemotherapy regimens
- Symptomatic brain, leptomeningeal or epidural metastases (unless previously treated and well controlled for at least 3 months)
- 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

Demographics

Efficacy and safety of TH-302 and full dose chemotherapy are reported for the 43 patients with gastrointestinal (GI) tumors who were enrolled prior to 12 Nov 2009.

Table 1: Patient characteristics and Cancer History (n = 43)

	TH-302 + Gemcitabine	TH-302 + Docetaxel	TH-302 + Pemetrexed	Total
	N=24	N=6	N=13	N=43
Sex (F / M)(N)	12/12	4/2	8/5	24/19
Age (yrs)				
Median	62	58	55	60
Range	51 - 80	50 - 72	42 - 86	42 - 86
ECOG (N)				
0	15	4	6	25
1	8	2	7	17
No. of prior systemic therapies				
0	21	1	1	23
1	2	2	5	9
2	0	1	3	4
≥3	1	2	4	7
Tumor type (N)				
Pancreas	18	1	3	22
Colorectal	0	1	4	5
Bile Duct	3	0	1	4
Neuroendocrine	1	2	1	4
Esophageal	1	1	1	3
Anal	0	1	1	2
HCC	0	0	2	2
Ampullary	1	0	0	1
Months since diagnosis of advanced/ metastatic disease				
Median	1.1	7.9	8.9	4.6
Range	0.4 – 49.0	4.7 – 20.3	0.8 – 88.5	0.4 – 88.5
Metastatic Sites (may be multiple sites)				
Liver	12 (50%)	1 (17%)	8 (62%)	22 (51%)
Lung	7 (29%)	1 (17%)	6 (46%)	14 (33%)
Lymph	7 (29%)	3 (50%)	4 (31%)	14 (33%)
Other site(s)	5 (21%)	4 (67%)	5 (38%)	14 (33%)

Status

Seven patients completed 6 cycles and 12 other patients continue on study receiving therapy. Twenty-four patients discontinued from the study prior to Cycle 6. Reasons for discontinuation were progressive disease (9), subject decision (7), clinical deterioration without documentation of progression by RECIST (3), adverse event (3) and physician decision (2).

Study Drug Exposure and DLTS

Study drug exposure is summarized. The median time on treatment is 3 cycles; range 1-15+ cycles.

Table 2: Study Drug Exposure and DLTs

Dose (mg/m^2)	No. of Patients	DLTs	Median Cycles (Range)	Ongoing
TH-302 + Gemcitabine				
240	3		11 (4-15+)	1
340	14	2 (Grade 3 Pain associated with perineal skin rash)	3 (1-6+)	7
480	5	1 (Grade 4 thrombocytopenia)	3 (2-6)	0
575	2	1 (Grade 3 Esophagitis)	5 (3-7+)	1
TH-302 + Docetaxel				
240	4	1 (febrile neutropenia)	2 (1-8)	0
400	1	1 (infection with Grade 4 neutropenia)	3+	1
480	1	None	8+	1
TH-302 + Pemetrexed				
240	2	None	2 (2-2)	0
340	4	None	5 (2-10)	2
480	5	None	6 (1-10)	1
575	2	1 (Grade 4 thrombocytopenia and Grade 3 oral mucositis)	3 (2-3)	0

Adverse Events

Adverse events (AE) have been reported in 40 patients with evaluable AE data. AEs occurring in at least 35% of patients are summarized in Table 3 (skin and mucosal AEs are discussed separately. Nausea, fatigue, constipation and vomiting have been the most commonly reported AEs. Nausea and vomiting were noted with TH-302 monotherapy and standard antiemetic prophylaxis for moderately emetogenic therapy (generally 5HT blocker and steroid) was recommended at doses >240 mg/m^2.

Table 3: Non-laboratory adverse events regardless of relationship to study drug occurring in ≥35% of subjects (all cycles)

Adverse event*	Number of Patients with an AE (%)			
	TH-302 + Gemcitabine	TH-302 + Docetaxel	TH-302 + Pemetrexed	Total
	N=22	N=6	N=12	N=40
Fatigue	15 (68)	3 (50)	7 (58)	25 (62)
Nausea	15 (68)	3 (50)	5 (42)	23 (58)
Constipation	10 (45)	2 (33)	5 (42)	17 (42)
Vomiting	9 (41)	2 (33)	4 (33)	15 (38)
Alopecia	9 (41)	2 (33)	3 (25)	14 (35)
Anorexia	7 (32)	2 (33)	5 (42)	14 (35)
Dysgeusia	11 (50)	2 (33)	1 (8)	14 (35)

* Coded with MedDRA

Approximately half of the adverse events were considered related to TH-302 study drug (Table 4). The majority (86%) of these were grade 1 or grade 2.

Table 4: Non-laboratory adverse events related to TH-302 occurring in ≥20% of subjects (all cycles)

Adverse event*	Number of Patients with an AE (%)			
	TH-302 + Gemcitabine	TH-302 + Docetaxel	TH-302 + Pemetrexed	Total
	N=22	N=6	N=12	N=40
Fatigue	8 (36)	1 (17)	5 (42)	14 (35)
Nausea	8 (36)	2 (33)	3 (25)	13 (32)
Dysgeusia	8 (36)	2 (33)	1 (8)	11 (28)
Vomiting	5 (23)	1 (17)	2 (17)	8 (20)

* Coded with MedDRA

Serious Adverse Events

Twenty-seven serious adverse events (SAEs) have been reported in 17 patients. Eleven of these events in 10 patients have been reported as related to TH-302. These 11 events were:

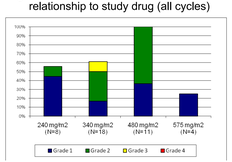
- Gemcitabine arm - liver abscess, pancytopenia, esophagitis, oral mucositis, vomiting, skin ulcer and pain due to perineal rash
- Docetaxel arm – febrile neutropenia and infection (pneumonia) with grade 4 ANC
- Pemetrexed arm – stomatitis

Deaths

There were no deaths clearly related to study drug. Twelve patients have died, 11 from progressive cancer. One of these patients with liver abscess considered related to study drug, biliary obstruction and a biliary stent died with progressive disease as the primary cause of death. The investigator could not exclude the possibility that the liver abscess contributed to her death. One other patient died from unknown causes.

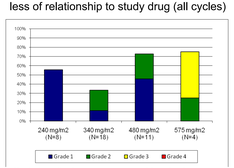
Skin and mucosal adverse events were dose limiting in the monotherapy study of TH-302. These events were reversible and the severity of the skin and mucosal toxicities increased with TH-302 dose. The majority of these were grade 1 or grade 2.

Figure 1: Skin adverse events* regardless of relationship to study drug (all cycles)



* Includes all adverse events considered to be skin; Coded with MedDRA

Figure 2: Mucosal adverse events* regardless of relationship to study drug (all cycles)



* Includes all adverse events considered to be mucosal; Coded with MedDRA

Hematologic Toxicity

Hematologic toxicity has been evident across TH-302 dose levels without a major change in toxicity level from 240 mg/m^2 to 575 mg/m^2 (Figure 3). Anemia and lymphopenia were often present at baseline with some worsening on the combination therapy. Hematologic toxicity has been a DLT in each of the three arms. Based on hematologic toxicity reported in the chemotherapy labels the hematologic toxicity has been greater than would be expected for single agent gemcitabine and single agent pemetrexed but not for single agent docetaxel although febrile neutropenia is more common in this arm and prophylactic G-CSF may be indicated.

Figure 3: Grade 3/4 Hematologic Toxicity by TH-302 Dose

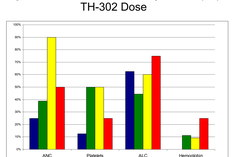
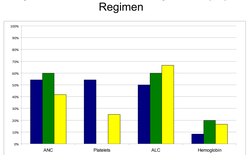


Figure 4: Grade 3/4 Hematologic Toxicity by Regimen



Other Laboratory Data: There has been no evidence of increased renal or liver toxicity with the addition of TH-302 to chemotherapy and no other consistent laboratory abnormalities.

Preliminary Assessment of TH-302 Activity

38 patients had at least one evaluable post-treatment tumor assessment (Table 5 and Figure 5) and 12 patients (32%) had a partial response (PR) as the best response assessment. An additional 22 patients (58%) had stable disease. Four patients (11%) had progressive disease. Partial responses have been noted across TH-302 dose levels, across combination chemotherapies and across indications.

Table 5: Best Response by RECIST*

	N	Partial Response	Stable Disease	Partial Response or Stable Disease
Pancreatic	20	7 (35%)	12 (60%)	19 (95%)
Colorectal	5	0	4 (80%)	4 (80%)
Neuroendocrine	3	1 (33%)	2 (67%)	3 (100%)
Bile Duct	3	0	3 (100%)	3 (100%)
Esophageal	2	1 (50%)	0	1 (50%)
Anal	2	2 (100%)	0	2 (100%)
HCC	2	1 (50%)	0	1 (50%)
Ampullary	1	0	1 (100%)	1 (100%)
Total	**38**	**12 (32%)**	**22 (58%)**	**34 (89%)**

*Five patients not assessed for tumor response (clinical deterioration – 2, adverse event - 2, patient decision – 1)

Figure 5: Best Response by Indication and Treatment

	TH-302 + Gemcitabine				TH-302 + Docetaxel				TH-302 + Pemetrexed			
	240 mg/m^2	340 mg/m^2	480 mg/m^2	575 mg/m^2	240 mg/m^2	400 mg/m^2	480 mg/m^2		240 mg/m^2	340 mg/m^2	480 mg/m^2	575 mg/m^2
Bile Duct	SD	SD-2										
Esophageal	PR										PD	
Pancreatic		PR-4 SD-7	PR SD-3	PR PD		SD					SD	PR
Ampullary			SD									
Neuroendocrine	PR				SD						SD	
Colorectal							SD	SD	PD	SD-2		
Anal					PR					PR		
HCC										PD	PR	

Figure 6: Waterfall Plot all Patients (N=38):
First-line Pancreatic Ca Patients Treated with TH-302 plus Gemcitabine in Blue (N=17)

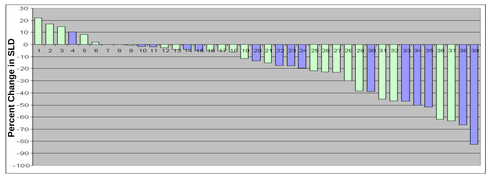
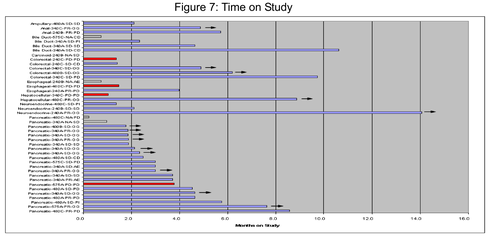


Figure 7: Time on Study



Tumor Biomarkers

Change in CA19-9: 18 of the 22 patients with pancreatic cancer enrolled with an elevated CA19-9. Follow-up assessments are available for 14 of the 18 patients. Of the 14 patients, 6 patients (43%) had a greater than 50% decrease in CA19-9; 7 patients (50%) had a decrease in CA19-9 between -24% and -42%; 1 patient had an increase.

Conclusions

1) TH-302 can be safely combined with full dose gemcitabine, docetaxel and pemetrexed.

2) The primary dose limiting toxicities have been hematologic. While the contribution of TH-302 to the hematologic toxicity is not identifiable, greater hematologic toxicity than would be expected with single agent chemotherapy is evident, especially in the gemcitabine and pemetrexed arms

3) Skin and mucosal toxicity related to TH-302 are common. The majority are grade 1 or grade 2 with an increase in severity with increasing dose of TH-302.

4) The addition of TH-302 to standard chemotherapies does not appear to enhance the toxicity in other body systems.

5) Higher response rates in GI cancers than would be expected with single agent chemotherapy are evident. This is most notable in the 20 patients assessed with pancreatic cancer, in which best response was 35% partial response and 60% stable disease.

6) Further investigations and additional follow-up will better define the therapeutic benefit of TH-302 in combination with chemotherapy in GI cancer.