A Multi-arm Phase IB Study of TH-302 in Combination with Gemcitabine, Docetaxel or Pemetrexed

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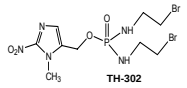
Poster 134

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.



TH-302

TH-302 has been designed to be selectively activated in these highly hypoxic regions and is an attractive candidate for clinical development for solid tumors.

In a Phase I monotherapy study, TH-302 showed activity as a single-agent with a maximum tolerated dose (MTD) of 575 mg/m² weekly, skin and mucosal dose limiting toxicity (DLT) and the absence of significant myelosuppression.

As TH-302 is designed to selectively target the hypoxic regions of solid tumors, the current study investigates the combination of TH-302 with another therapy that is effective in the normoxic regions of tumors. This complementary approach is designed to fully target solid tumors.

Chemotherapy:

- Targets the rapidly dividing cells in close proximity to the vasculature

HAP TH-302:

-Relative inactive in normoxic cells

-Designed to penetrate into the hypoxic compartment where it is selectively activated

OBJECTIVES

Primary

- To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of TH-302 when used in combination with 1) Gemcitabine or 2) Docetaxel or 3) Pemetrexed in subjects with advanced solid tumors
- To assess the safety of TH-302 in combination with 1) Gemcitabine or 2) Docetaxel or 3) Pemetrexed
- Dose expansion subjects: To make a preliminary assessment of the efficacy of TH-302 in combination with 1) Gemcitabine or 2) Docetaxel or 3) Pemetrexed as determined by response rate, duration of response, and progression-free survival in subjects with 1) pancreatic cancer, 2) castrate-resistant prostate cancer or NSCLC or 3) NSCLC treated at the chosen Phase 2 dose

Secondary

- To determine whether there is any pharmacokinetic interaction of TH-302 with gemcitabine, docetaxel or pemetrexed used in combination

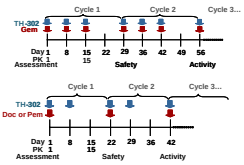
KEY ELIGIBILITY – Dose Escalation

- 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
- Evaluable by RECIST (at least one target or nontarget lesion)
- Adequate organ function:
  - ANC ≥ 1500/μL, Platelets ≥ 100,000/μL, Hemoglobin ≥ 9 g/dL
  - Serum creatinine ≤ ULN
  - Adequate liver function with chemotherapy dependent levels for total bilirubin, AST and ALT.
- No Prior treatment with chemotherapy utilized in combination
- No Prior treatment with more than 3 myelosuppressive cytotoxic chemotherapy regimens
- No symptomatic brain, leptomeningeal or epidural metastases (unless previously treated and well controlled for at least 3 months)

STUDY DESIGN

Complete Phase 1B - Three separate arms enroll independently:

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



Open-label, multicenter (8), dose-escalation Phase 1 and dose-expansion Phase 2 study

Dose Escalation: Classic Phase 1 3+3 dose escalation design. Initial dose in each arm of 240 mg/m² up to maximum weekly monotherapy dose of 575 mg/m². MTD defined as highest dose level at which 0 or 1 of 6 patients experiences a DLT. Phase 2 dose may be any dose at or below the MTD

TH-302 administered IV over 30 - 60 minutes 2 hours prior to chemotherapy

Chemotherapy administered at **full dose** on the **standard schedule** for each of the chemotherapies.

Treatment for 6 cycles unless disease progression or unacceptable toxicity

Once MTD established, 12 additional patients will be enrolled at the MTD in specific indications

- •Gemcitabine: first-line pancreatic cancer
- •Docetaxel: second-line NSCLC and first-line castrate-resistant prostate cancer
- •Pemetrexed: second-line NSCLC

Response evaluated according to RECIST criteria
Tumor markers (eg PSA, CEA, CA19-9, CA-125) every cycle
Pharmacokinetic sampling for TH-302, Br-IPM and chemotherapy
Toxicity assessed using NCI-CTCAE version 3.0

STATUS

29 patients have discontinued from the study and 21 patients continue on study after receiving 2 to 11 cycles. Reasons for discontinuation were progressive disease (15), patient decision (4), clinical deterioration without documentation of progression by RECIST (4), adverse event (3), physician decision (3).

Table 1: Patient characteristics and Cancer History (n = 50)

	TH-302 + Gemcitabine N=16	TH-302 + Docetaxel N=13	TH-302 + Pemetrexed N=21	Total N=50
Sex (F / M)(N)	7/9	6/7	10/11	23/27
Age (yrs)				
Median	58.5	61	62	61
Range	41 - 74	39 - 74	42 - 81	39 - 81
ECOG (N)				
0/1	11/ 5	9/4	12/9	32/18
No. of prior systemic therapies				
0/1/2/ >3	6/3/4/3	1/2/4/6	0/7/7/7	7/12/15/16
Tumor type (N)				
Colorectal	0	0	3	3
Esophageal	1	1	1	3
Prostate	0	2	0	2
NSCLC	2	2	6	10
Ovarian	3	0	0	3
Pancreas	4	0	2	6
Neuroendocrine	1	1	1	3
Cholangiocarcinoma, HCC, melanoma, TCC, carcinoma, sarcoma, unknown (2 subjects each)	3	2	7	12
Other (1 subject each)	2	5	1	8
Months since diagnosis of advanced/metastatic disease				
Median	6.6	16.8	12.3	11.8
Range	0.4 – 49.0	1.6 – 170.8	1.6 – 88.5	0.4 – 170.8
Metastatic Sites (inc. multiple sites)				
Liver	4 (44%)	3 (23%)	9 (43%)	19 (38%)
Lung	6 (38%)	6 (46%)	8 (38%)	20 (40%)
Lymph	10 (62%)	6 (46%)	8 (38%)	24 (48%)
Other site(s)	6 (38%)	12 (92%)	7 (33%)	25 (50%)

STUDY DRUG EXPOSURE and DLTs

Table 2: DLTS and Study Drug Exposure

Dose (mg/m²)	No. of Patients	No. DLT Evaluable	DLTs (description)	Median Cycles (Range)	No. Ongoing
Gemcitabine					
240	7	6	1 (grade 3 ALT elevation)	4 (1-11+)	3
340	6	3	0	3 (2-7)	4
480	7	5	2 (grade 3 pain/fatigue;grade 4 thrombocytopenia)	4 (2-6+)	6
575	6	5	2 (grade 3 esophagitis;grade 4 thrombocytopenia)	2 (1-3+)	6
Docetaxel					
240	7	7	1 (febrile neutropenia)	4 (1-10+)	1
340	6	5	0	1 (1-8+)	4
480	7	6	2 (grade 4 neutropenia)	3 (2-6+)	6
Pemetrexed					
240	5	3	0	10 (2-16)	1
340	5	5	0	2 (2-8+)	4
480	9	6	1 (grade 3 oral candidiasis)	2 (1-6+)	3
575	7	6	1 (grade 3 oral mucositis/grade 4 thrombocytopenia)	3 (1-4+)	3

SAFETY

Deaths: There were no deaths clearly related to study drug. Eleven patients have died, 9 from progressive cancer, one from an SAE of bowel perforation unrelated to study drug and one from unknown causes. A patient 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.

SAEs: Twenty-eight serious adverse events (SAEs) have been reported in 18 patients. Nine of these events in 8 patients have been reported as related to TH-302. These nine events were: gemcitabine arm - liver abscess, pancytopenia and pyrexia; docetaxel – febrile neutropenia (3 cases in 2 patients); pemetrexed – oral candidiasis, febrile neutropenia and pancytopenia.

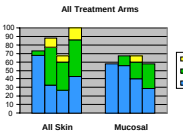
AEs: AEs have been reported in all patients. Nausea, fatigue, constipation and vomiting have been the most commonly reported AEs. Nausea and vomiting were noted with TH-302 monotherapy and standard anti-emetic prophylaxis for moderately emetogenic therapy (generally 5HT blocker and steroid) was recommended at doses >240 mg/m².

Approximately half of the adverse events were considered related to TH-302 study drug (Table 3). The majority (83%) were grade 1 or grade 2.

Table 3: AEs Related to TH-302

Adverse event*	Number of Patients with an AE (%)			
	TH-302 + Gem	TH-302 + Doc	TH-302 + Pem	Total
	N=16	N=13	N=21	N=50
Nausea	9 (56)	6 (46)	8 (38)	23 (46)
Fatigue	6 (38)	6 (46)	9 (43)	21 (42)
Stomatitis	4 (25)	4 (31)	8 (38)	16 (32)
Vomiting	5 (31)	3 (23)	5 (24)	13 (26)
Dysgeusia	6 (38)	4 (31)	3 (14)	13 (26)
Rash	5 (31)	1 (8)	5 (24)	11 (22)
Diarrhea	3 (19)	4 (31)	3 (14)	10 (20)

Figure 4: Skin and Mucosal Adverse Events

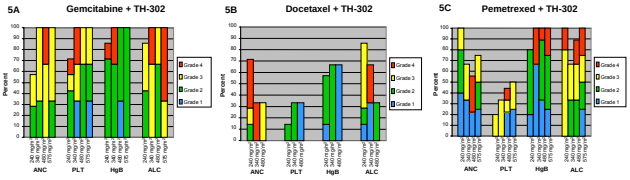


SKIN AND MUCOSAL TOXICITY

Skin and mucosal toxicities were dose limiting in the monotherapy study of TH-302. These events are summarized in Figure 4. The severity of the skin and mucosal toxicities increased with TH-302 dose. The majority of these were grade 1 or grade 2.

HEMATOLOGICAL TOXICITY

Hematologic toxicity across TH-302 dose levels without a major change in toxicity from 240 mg/m² to 575 mg/m² (Figure 5A to Figure 5C). 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 in labels, it has been greater than would be expected for single agent gemcitabine and pemetrexed but not for single agent docetaxel.



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 across 240 mg/m² to 575 mg/m² in combination.
- TH-302 has a large volume distribution and rapid plasma clearance. The terminal half-life is slightly less than 1 hour.
- Plasma Br-IPM concentrations are ~1% of TH-302 plasma concentrations.
- There does not appear to be any Interaction of TH-302 with standard chemotherapy. The pharmacokinetics of each of the chemotherapies has been consistent with that reported in the literature.

		Reported	TH-302 Dose 240 mg/m2	TH-302 Dose 340 mg/m2	TH-302 Dose Any
Gemcitabine	AUC (ug*h/mL)	8.77-18.4	6.70 (3.09)	12.9 (2.62)	8.03 (3.92)
	Cmax (ug/mL)	10-24.5	9.64 (5.58)	25.1 (7.67)	13.1 (8.84)
	T1/2 (hours)	0.233 - 1.42	0.270 (0.0546)	0.234 (0.0802)	0.262 (0.0593)
dFdU	AUC (ug*h/mL)	104 - 325	288 (67.5)	297 (72.8)	290 (66.6)
	Cmax (ug/mL)	26.3 - 54.7	29.8 (7.85)	25.2 (7.78)	28.7 (7.84)
	T1/2 (hours)	3.7 - 19.0	11.6 (3.49)	14.9 (3.71)	12.3 (3.69)
Docetaxel	AUC (ug*h/mL)	2.8 - 3.7	2.12 (1.41)	3.23 (1.96)	2.37 (1.49)
	Cmax (ug/mL)	1.18 - 3.53	1.15 (1.01)	1.62 (0.326)	1.26 (0.905)
	T1/2 (hours)	13.2 - 15.9	13.3 (3.22)	7.02 (3.68)	11.9 (4.13)
Pemetrexed	AUC (ug*h/mL)	122 - 197	233 (56.7)	171 (41.9)	238 (145)
	Cmax (ug/mL)	72.2 - 131	129 (22.4)	122 (21.5)	117 (24.5)
	T1/2 (hours)	3.15 - 4.4	2.10 (0.332)	2.19 (0.168)	2.66 (1.78)

EFFICACY

45 patients had at least one evaluable post-treatment tumor assessment (Table 6 and Figure 6) and 12 patients (27%) had a partial response (PR) at a response assessment. Partial responses have been noted across TH-302 dose levels, across combination chemotherapies and across indications.

	TH-302 + Gemcitabine				TH-302 + Docetaxel			TH-302 + Pemetrexed			
	240 mg/m²	340 mg/m²	480 mg/m²	575 mg/m²	240 mg/m²	340 mg/m²	480 mg/m²	240 mg/m²	340 mg/m²	480 mg/m²	575 mg/m²
Bile Duct	SD	SD									
Ovarian	PD PR										
Esophageal	PR									PD	
Pancreatic		PR	SD PR	SD						SD	
NSCLC	PD			PR	SD	PR		PR PR	SD	SD		SD PD
Prostate							SD				
Ampullary			SD								
Neuroendocrine	SD				SD					SD	
S.T. Sarcoma		SD								PD	
Colorectal								SD PD	SD		
Anal					PR						
Urachal					SD						
Urethral					PD						
Breast					SD						
Melanoma						SD PD					
HCC										SD	
Unknown 1 *										PD PD	
Thyroid				PR							
TCC										PR	PR
Parotid											SD
Renal							PD				

	TH-302 + Gemcitabine	TH-302 + Docetaxel	TH-302 + Pemetrexed	Total
No assessment*	1	2	2	5
Best Response N	**15**	**11**	**19**	**45**
Partial response	6 (40%)	2 (18%)	4 (21)%	12 (27%)
Stable disease*	7 (47%)	6 (55%)	9 (47%)	22 (49%)
Progressive disease	2 (13%)	3 (27%)	6 (32%)	11 (24%)

Figure 7A. Time on Study – All Patients (N=50)

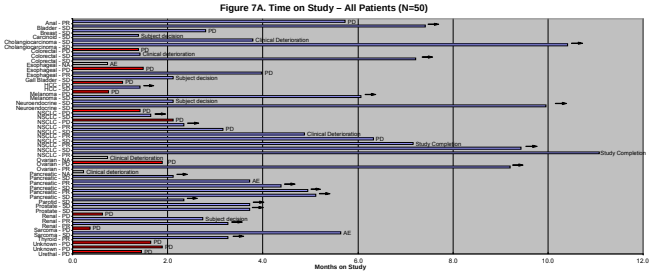


Figure 7B. Time on Study – First Line Pancreatic

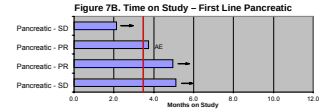
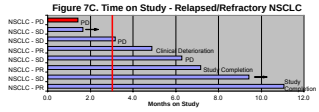
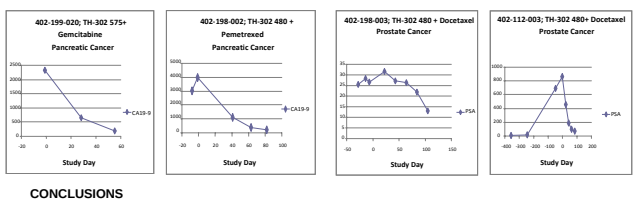


Figure 7C. Time on Study - Relapsed/Refractory NSCLC



Pancreatic Cancer: 2 subjects enrolled with highly elevated CA19-9 have had >90% decreases from baseline CA19-9.

Prostate Cancer: 2 subjects enrolled have had >50% decreases from baseline PSA.



CONCLUSIONS

The MTDs have been established as follows:

- •TH-302 plus Gemcitabine – anticipate 340 mg/m²
- •TH-302 plus Docetaxel – 340 mg/m²
- •TH-302 plus Pemetrexed – 480 mg/m²

The primary dose limiting toxicities have been hematologic. While the contribution of TH-302 to the hematologic toxicity is confounded with the concomitant chemotherapy, greater hematologic toxicity than would be expected with single agent chemotherapy is evident in the gemcitabine and pemetrexed arms

Skin and mucosal toxicity are common at doses above 240 mg/m². The mechanism is unknown but may be due to activation of TH-302 in areas of epithelium that are normally hypoxic

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

Higher response rates than would be expected with single agent chemotherapy are evident. Multiple responses in pancreatic cancer, NSCLC and transitional cell cancers have been reported

Dose expansion at the MTD has been initiated in both the docetaxel and pemetrexed arms

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