Complete Phase 1B Study of TH-302 in Combination with Gemcitabine, Docetaxel or Pemetrexed

Mitesh Borad[1], Jeffrey R Infante[2], Alain C Mita[3], E. Gabriela Chiorean[4], Gordana Vlahovic[5], Andrew Armstrong[5], Anne Traynor[6], William Schelman[6], Virginia K Langmuir[7], Clarence Eng[7], Stew Kroll[7], John Curd[7].

[1]Mayo Clinic Cancer Center-Arizona, Scottsdale, AZ, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]University of Texas Health Science Center, San Antonio, TX, USA; [4]Indiana University Simon Cancer Center, Indianapolis, IN, USA; [5]Duke University Medical Center, Durham, NC, USA; [6]University of Wisconsin Paul P Carbone Comprehensive Cancer Center, Madison, WI, USA; [7]Threshold Pharmaceuticals, Redwood City, CA, USA.

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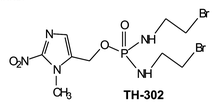
Introduction

TH-302 is a hypoxia-activated prodrug (HAP) 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, creating intrastrand and inter-strand crosslinks.



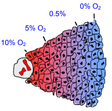
TH-302

TH-302 has been designed to be selectively activated in the highly hypoxic regions characteristic of 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/m^2 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

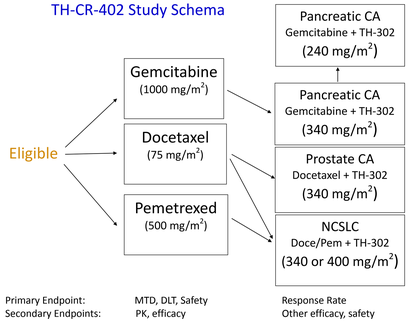
Primary
- To determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of TH-302 when used in combination with 1) gemcitabine or 2) docetaxel or 3) pemetrexed in subjects with advanced solid tumors
- To assess the safety of TH-302 in combination with 1) gemcitabine or 2) docetaxel 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
- 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

TH-CR-402 Study Schema



Dose Escalation: Classic Phase 1 3+3 dose escalation design. Initial weekly TH-302 dose of 240 mg/m^2 up to maximum monotherapy dose of 575 mg/m^2. MTD defined as highest dose level at which 0 or 1 of 6 patients experienced 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, 12-36 additional patients were enrolled at the MTD in specific indications
- gemcitabine: first-line pancreatic cancer (2 doses)
- docetaxel: second/third-line NSCLC and first-line castrate-resistant prostate cancer
- pemetrexed: second/third-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

Demographics

Table 1: Patient characteristics and Cancer History (n = 160)

	TH-302 + gemcitabine N= 71	TH-302 + docetaxel N= 51	TH-302 + pemetrexed N= 38	Total N= 160
Sex (F/M) (N)	**38/33**	**36/15**	**20/18**	**94/66**
Age (years)				
Median	**62**	**63**	**61**	**62**
Range	**41-83**	**39-76**	**22-86**	**22-86**
ECOG (N)				
0/1	**49/22**	**22/29**	**24/14**	**95/65**
No. of prior systemic therapies				
0/1/2/ >3	**47/7/8/9**	**1/23/10/17**	**1/16/10/11**	**49/46/28/37**
Tumor type (N)				
Pancreas	**48**	**1**	**3**	**52**
NSCLC	**4**	**19**	**18**	**41**
Prostate	**0**	**15**	**0**	**15**
Biliary	**4**	**0**	**1**	**5**
Colorectal	**0**	**1**	**4**	**5**
Neuroendocrine	**2**	**2**	**1**	**5**
Anal	**2**	**1**	**1**	**4**
Head/Neck	**1**	**2**	**1**	**4**
Esophageal	**1**	**1**	**1**	**3**
Melanoma	**0**	**3**	**0**	**3**
Ovarian	**3**	**0**	**0**	**3**
Renal	**0**	**1**	**2**	**3**
Unknown Primary	**1**	**0**	**2**	**3**
Other (HCC, Mesothelioma, Sarcoma, Bladder, Breast, Cervical, Gall Bladder, SCLC, Skin SCC, Thyroid, Ureteral)	**5**	**5**	**4**	**14**
Months since diagnosis of advanced/metastatic disease				
Median	**1.3**	**6.5**	**10.6**	**5.4**
Range	**0-49**	**0.5-170.9**	**0.8-88.5**	**0-170.9**
Metastatic sites (inc. multiple sites)				
Liver	**38**	**17**	**14**	**69**
Lung	**16**	**16**	**16**	**48**
Lymph	**27**	**29**	**17**	**73**
Other site (s)	**21**	**33**	**22**	**76**

135 patients have discontinued from the study and 25 patients continue on study after receiving 3 to 20 cycles. Reasons for discontinuation were progressive disease (67), patient decision (22), clinical deterioration without documentation of progression by RECIST (13), adverse event (12), physician decision (13), study completion (4), death (1), and for other reasons (4).

Safety

Table 2: DLTs and Study Drug Exposure

Dose (mg/m^2)	No. of Patients	No. DLT Evaluable	No. of DLTs	% with DLT	Dose Limiting Toxicities
Gemcitabine					
240	25	19	2	11%	Grd 3 ALT; Grd 3 Fatigue
340	27	17	1	6%	Grd 4 Thrombocytopenia
400	6	5	2	40%	Grd 4 Thrombocytopenia (2 patients)
480	7	5	2	40%	Grd 4 Thrombocytopenia; Grd 3 Proctalgia
575	6	5	2	40%	Grd 4 Thrombocytopenia; Grd 3 Esophagitis
Docetaxel					
240	8	7	1	14%	Febrile neutropenia
340	33	28	3	11%	Febrile neutropenia; Grd 2 Rash; Grd 3 Rash
400	3	3	2	67%	Febrile neutropenia; Grd 3 Pneumonia
480	7	6	2	33%	Grd 4 Neutropenia (2 patients)
Pemetrexed					
240	5	3	0	0%	
340	7	7	0	0%	
400	10	9	1	11%	Grd 3 Hyponatremia
480	9	6	1	17%	Grd 3 Oral candidiasis
575	7	6	2	33%	Grd 3 Infusion reaction; Grd 3 Stomatitis/Grd 4 Thrombocytopenia
Total	160	126	21	17%	

Deaths: There were no deaths clearly related to study drug. Seventy-three patients have died, 63 from progressive cancer, three from SAEs considered unrelated to study drug and seven from other causes including one patient with liver abscess (considered related to study drug), biliary obstruction and a biliary stent who died with progressive disease as the primary cause of death. The investigator could not exclude the possibility that the liver abscess contributed to the death.

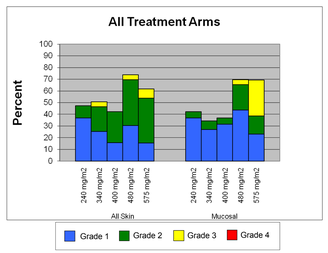
SAEs: One hundred twelve serious adverse events (SAEs) have been reported in 65 (41%) patients. Thirty-five of these SAEs in 27 (17%) patients have been reported as related to TH-302. Related SAEs that were reported in more than one patient were: febrile neutropenia (7 pts: 6 docetaxel arm, 1 pemetrexed arm), anemia (3 pts: one pt in each arm), stomatitis (3 pts: 2 pemetrexed arm, 1 gemcitabine arm), dehydration (2 pts: 1 docetaxel arm, 1 pemetrexed arm) and pancytopenia (2 pts: 1 gemcitabine arm, 1 pemetrexed arm).

AEs: AEs have been reported in all patients. The majority (83%) were grade 1 or grade 2. Fatigue, nausea, stomatitis, dysgeusia and vomiting have been the most commonly reported study drug related AEs (Table 3). Nausea and vomiting were noted with TH-302 monotherapy and standard anti-emetic prophylaxis for moderately emetogenic therapy (generally 5HT blocker and steroid) is recommended .

Table 3: Non-laboratory AEs Related to TH-302

Adverse Event	Number of Patients with an AE (%)			
	TH-302 + Gem	TH-302 + Doc	TH-302 + Pem	Total
	N= 66	N= 46	N=35	N=147
Fatigue	24 (33.8%)	23 (45.1%)	14 (36.8%)	61 (38.1%)
Nausea	27 (38.0%)	14 (27.5%)	13 (34.2%)	54 (33.8%)
Stomatitis	21 (29.6%)	15 (29.4%)	16 (42.1%)	52 (32.5%)
Dysgeusia	22 (31.0%)	15 (29.4%)	6 (15.8%)	43 (26.9%)
Vomiting	11 (15.5%)	11 (21.6%)	9 (23.7%)	31 (19.4%)
Diarrhoea	9 (12.7%)	14 (27.5%)	6 (15.8%)	29 (18.1%)
Anorexia	12 (16.9%)	11 (21.6%)	5 (13.2%)	28 (17.5%)

Figure 4: Skin and Mucosal Adverse Events

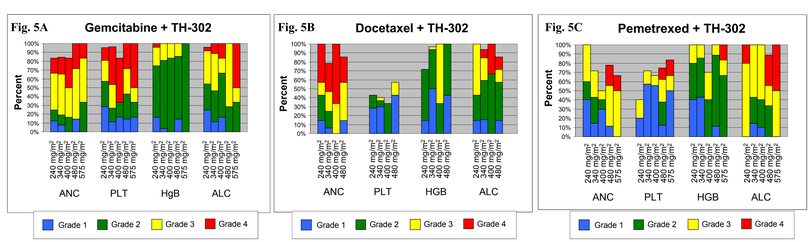


SKIN AND MUCOSAL TOXICITY

Skin and mucosal toxicities were dose limiting in the monotherapy study of TH-302. The skin and mucosal events in the current study are summarized by dose (38, 67, 19, 23 and 13 pts at TH-302 doses of 240, 340, 400, 480 and 575 mg/m^2) in Figure 4. The incidence and severity of the skin and mucosal toxicities increased with TH-302 dose. As shown, the majority of these toxicities were grade 1 or grade 2.

HEMATOLOGICAL TOXICITY

Hematologic toxicity was similar across the TH-302 dose levels from 240 mg/m^2 to 575 mg/m^2 (Figure 5A to Figure 5C) with an apparent increase in severity with TH-302 dose in the pemetrexed arm. Anemia and lymphopenia were often present at baseline with some worsening on the combination therapy. Hematologic toxicity has been dose limiting in each of the three arms. Based on hematologic toxicity in labels, the hematologic toxicity in combination with TH-302 has been greater than would be expected for the single agents.



Other Laboratory Data: There has been no evidence of renal or liver toxicity of TH-302 and no other consistent laboratory abnormalities.

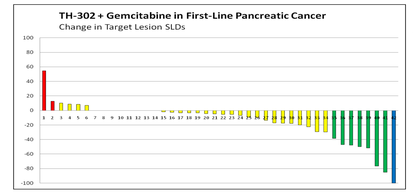
Efficacy

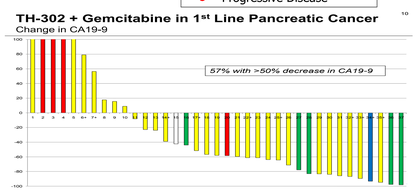
	TH-302 + gemcitabine	TH-302 + docetaxel	TH-302 + pemetrexed	Total
No Assessment	7	7	4	18
Best Response N	**64**	**44**	**34**	**142**
Complete Response	1 (1.6%)	0 (0%)	0 (0%)	1 (0.7%)
Partial Response	13 (20.3%)	6 (13.6%)	11 (32.4%)	30 (21.1%)
Stable Disease	40 (62.5%)	27 (61.4%)	12 (35.3%)	79 (55.6%)
Progressive disease	10 (15.6%)	11 (25.0%)	11 (32.4%)	32 (22.5%)

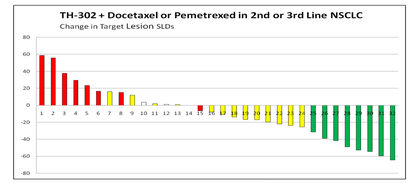
	TH-302 (mg/m^2) + gemcitabine					TH-302 + docetaxel				TH-302 + pemetrexed				
	240	340	400	480	575	240	340	400	480	240	340	400	480	575
Pancreatic	♦(13) ●(3)	■(1) ■(5) ♦(14) ●		■ ♦(3)	■ ♦			♦					■ ●	♦
NSCLC	●		●		■	♦	■(2) ♦(7) ●(7)			■(3)	■ ♦	■(2) ♦(4) ●(2)		♦ ●
Prostate							■(2) ♦(7) ●		■ ♦(2)					
Sarcoma		♦											●	
Anal			♦(2)			■					■			
Esophageal	■												●	
HCC											●		■	
Neuroendocrine	■		♦			♦							♦	
Ovarian	■ ●													
Renal									●				■	■
Thyroid					■									
Other	♦	♦(2) ●		■ ♦	♦ ●	♦(2)	♦(2) ●	♦	♦(3)	♦ ●	♦(2) ●		●(2)	♦

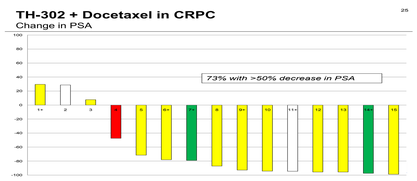
Other tumor types include: ampullary, bile duct, breast, colorectal, head/neck, melanoma, mesothelioma, parotid, SCLC, skin, urachal, urethral, unknown primary

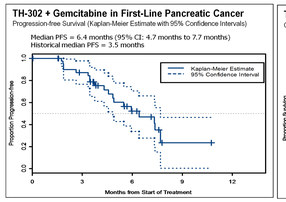
■/■ Complete/Partial Response
♦ Stable Disease
● Progressive Disease

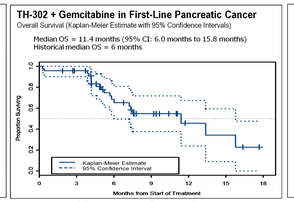


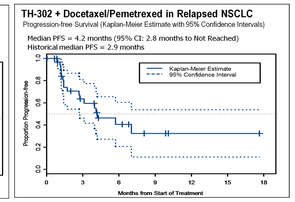












Conclusions

The MTDs were established as follows:

- TH-302 plus gemcitabine – 340 mg/m^2
- TH-302 plus docetaxel – 340 mg/m^2
- TH-302 plus pemetrexed – 480 mg/m^2

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.

Skin and mucosal toxicity were common, increased with TH-302 dose, and well-managed at the MTDs.

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

Higher response rates and longer progression-free survival than would be expected with single agent chemotherapy are evident in each combination. These suggest that the hypoxia penetration and activation of TH-302 may complement standard chemotherapy in some solid tumors.

The safety and activity provide rationale for comparing TH-302 plus gemcitabine versus gemcitabine in a recently initiated randomized Phase 2 trial (NCT01144455).