TH-302 + gemcitabine (G+T) vs gemcitabine (G) in patients with previously untreated advanced pancreatic cancer

David P. Ryan,[1] Shantan G. Reddy,[2] Nathan Bahary,[3] Hope Elizabeth Uronis,[4] Darren Sigal,[5] Allen Lee Cohn,[6] William R. Schelman,[7] Joe Stephenson Jr,[8] Clarence Eng,[9] Mitesh J. Borad[10]

[1]Massachusetts General Hospital, Boston, MA, USA; [2]Louisiana State University Health Sciences Center Shreveport, Shreveport, LA, USA; [3]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [4]Duke University Medical Center, Durham, NC, USA; [5]Scripps Clinic, La Jolla, CA, USA; [6]Rocky Mountain Cancer Center, LLP, Denver, CO, USA; [7]University of Wisconsin Carbone Cancer Center, Madison, WI, USA; [8]Institute for Translational Oncology Research, Greenville, SC, USA; [9]Threshold Pharmaceuticals, South San Francisco, CA, USA; [10]Mayo Clinic, Scottsdale, AZ, USA

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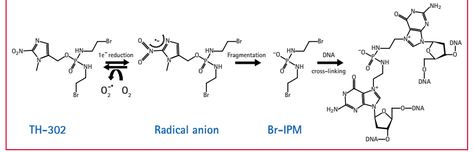
Introduction

- Most solid tumors have significant areas of hypoxia that limit the efficacy of antitumor agents.[1]
- TH-302 is a hypoxia-targeted cytotoxic prodrug with a 2-nitroimidazole component designed to release the DNA crosslinker bromo-isophosphoramide mustard when reduced in severe hypoxia (**Figure 1**).[2]
- In hypoxic xenograft models of pancreatic cancer, TH-302 enhanced the efficacy of gemcitabine.[3]
- In a Phase I/II study TH-302 in combination with gemcitabine was well tolerated and showed promising antitumor activity as first-line treatment in patients with pancreatic cancer compared with results of previous studies of gemcitabine monotherapy.[4]
- The present randomized Phase II study assessed the benefit of the addition of TH-302 to gemcitabine compared with standard gemcitabine dose as first-line therapy of patients with previously untreated advanced pancreatic cancer.

Figure 1. Chemical structure and mechanism of activation of TH-302



1e⁻, one-electron; Br-IPM, bromo-isophosphoramide mustard.
Adapted from Meng et al. 2012.[2]

Objectives

Primary objectives

- To compare progression-free survival (PFS) between patients treated with gemcitabine plus TH-302 and gemcitabine alone, and to determine the safety profile of gemcitabine plus TH-302.

Secondary objectives

- To determine overall survival (OS), response rates, cancer antigen (CA) 19-9 changes/response, and similar endpoints following crossover (comparing the two TH-302 arms post-crossover).

Methods

Study design and treatment

- This was an open-label, multicenter, randomized, Phase II study (NCT01144455) of two dose levels of TH-302 in combination with gemcitabine vs gemcitabine alone.
- Patients were stratified according to their disease stage (unresectable locally advanced vs distant metastases) and randomized 1:1:1 to gemcitabine 1,000 mg/m^2 plus TH-302 240 mg/m^2 (G+T240), gemcitabine 1,000 mg/m^2 plus TH-302 340 mg/m^2 (G+T340), or gemcitabine 1,000 mg/m^2 alone (G; **Figure 2**).
- The treatments were administered intravenously in sequential 30- to 60-minute infusions (TH-302 followed by gemcitabine) on days 1, 8, and 15 of a 28-day cycle.
- Unless patients experienced progressive disease (PD) or unacceptable toxicity, they could continue to receive treatment beyond 6 cycles if considered clinically beneficial.
- Patients initially randomized to G alone could cross-over after PD and be randomized to one of the two G+T arms.

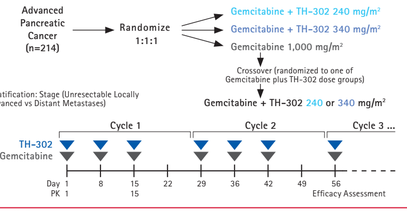
Patient eligibility

- Key eligibility criteria included histologically or cytologically confirmed locally advanced or metastatic pancreatic ductal adenocarcinoma, measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and a bilirubin level of ≤ 1.5 times upper limit of normal.

Outcome measures

- PFS and OS (both calculated from day 1 of cycle 1) were assessed using Kaplan–Meier methodology.
- PFS was measured from treatment start to first occurrence of PD or death from any cause.
- Response to treatment and PD were assessed according to RECIST version 1.1.
- Changes in CA 19-9 were assessed using analysis of variance.
- Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Figure 2. Study design



PK, pharmacokinetics.

Statistical analyses

- The following statistical considerations were made:
  - PFS (primary efficacy endpoint): 80% power to detect 50% improvement in PFS with one-sided alpha of 10%
  - OS (secondary efficacy endpoint): no formal statistical power analysis was performed because the crossover contribution confounds OS analysis
  - Sample size for primary efficacy analysis: 200 patients were required to obtain 144 events
- Updated results are presented; data cut-off date was September 2012.

Results

Patients and treatment

- A total of 214 patients were treated. Median age was 65 years (range: 29–86) and 126 (59%) patients were male.
- ECOG performance status was 0 in 38% of patients and 1 in 62% of patients. Overall, 76% and 24% of patients had Stage IV and Stage IIIB disease at baseline, respectively.
- Patient baseline characteristics and demographics according to treatment assignment are presented in **Table 1**.
- 32, 45, and 55% of patients in the G, G+T240, and G+T340 arms, respectively, received at least 6 treatment cycles.
- **Table 2** summarizes the exposure to treatment across groups.

Table 1. Baseline patient demographics and disease characteristics

Characteristics	G n=69	G+T240 n=71	G+T340 n=74
Median age, years (range)	67 (41–83)	63 (41–81)	65 (29–86)
Male, %	58	62	57
ECOG PS, n (%)*			
0	20 (30)	31 (45)	28 (39)
1	47 (70)	38 (55)	43 (61)
Median CA 19-9 level, U/mL (range)†	1,291 (37–>42,500)	2,575 (55–>42,500)	2,391 (45–>42,500)
Hemoglobin <12 g/L, n (%)	25 (37)	26 (37)	24 (32)
Median time from diagnosis, months (range)	1.1 (0.4–68.7)	1.1 (0.3–21.4)	1.2 (0.3–221.2)
Unresectable locally advanced disease, n (%)	14 (20)	17 (24)	20 (27)
Site of primary pancreatic tumor involves head, n (%)	41 (59)	40 (56)	44 (59)
Metastatic sites			
Liver, n (%)	46 (67)	44 (62)	42 (57)
Lung, n (%)	10 (14)	11 (15)	15 (20)

*Data available for 67, 69, and 71 patients in the G, G+T240, and G+T340 groups, respectively. Percentages calculated based on the total number of patients with available data.
†Data available for 55, 53, and 58 patients in the G, G+T240, and G+T340 groups, respectively. Normal CA 19-9 levels are 35 U/mL or less.
CA, cancer antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; G, gemcitabine 1,000 mg/m^2; G+T240, gemcitabine 1,000 mg/m^2 + TH-302 240 mg/m^2; G+T340, gemcitabine 1,000 mg/m^2 + TH-302 340 mg/m^2.

Table 2: Exposure to treatment

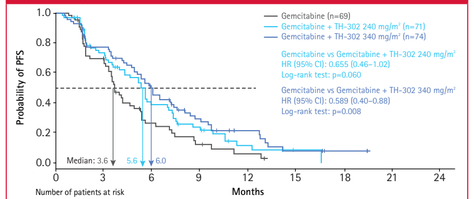
Characteristics	G n=69	G+T240 n=71	G+T340 n=74
No. of cycles received, n (%)			
1	69 (100)	71 (100)	74 (100)
2	60 (87)	67 (94)	66 (89)
3	44 (64)	49 (69)	55 (74)
4	41 (59)	44 (62)	50 (68)
5	26 (38)	36 (51)	48 (65)
6	22 (32)	32 (45)	41 (55)
7	11 (16)	21 (30)	27 (36)
8	11 (16)	18 (25)	27 (36)
≥9	7 (10)	12 (17)	20 (27)
Mean no. of cycles (range)	4.5 (1–16)	5.5 (1–17)	6.4 (1–21)
Mean cumulative gemcitabine dose intensity at the end of cycle 6, % (range)	88 (60–101)	81 (36–100)	72 (38–101)
Patients on ongoing treatment, n (%)	1 (1)	1 (1)	2 (3)

G, gemcitabine 1,000 mg/m^2; G+T240, gemcitabine 1,000 mg/m^2 + TH-302 240 mg/m^2; G+T340, gemcitabine 1,000 mg/m^2 + TH-302 340 mg/m^2.

PFS, response to treatment, and OS

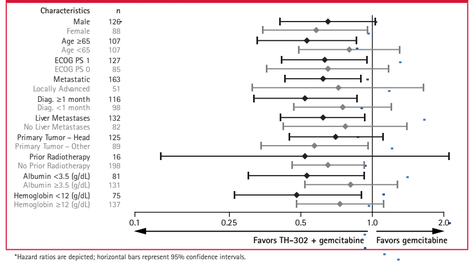
- Median PFS was significantly prolonged in the G+T arms vs the G arm (**Figure 3**; 5.6 months with G+T240 [p=0.060] and 6.0 months with G+T340 [p=0.008] vs 3.6 months with G).
- A subgroup analysis of PFS according to patients' baseline demographics and disease characteristics favored gemcitabine + TH-302 over gemcitabine alone for all analyzed variables (**Figure 4**).

Figure 3: Progression-free survival



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Figure 4. Subgroup analysis of progression-free survival*



*Hazard ratios are depicted; horizontal bars represent 95% confidence intervals.
ECOG PS, Eastern Cooperative Oncology Group performance status.

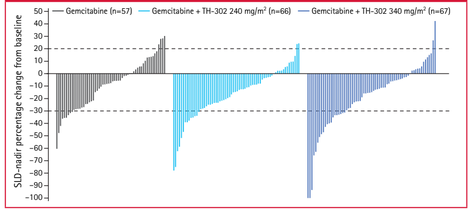
- CA19-9 responses according to treatment arms are shown in **Table 3**.
- Objective best (unconfirmed) response (complete response [CR] plus partial response [PR]) was observed in 10% of patients in the G arm vs 17% and 26% in the G+T240 and G+T340 arms, respectively (p=0.220 for G+T240 and p=0.021 for G+T340 vs G). **Figure 5** shows a waterfall plot of the tumor shrinkage observed.
- Disease control (CR, PR, plus stable disease) was observed in 67, 75, and 76% of patients treated with G, G+T240, and G+T340, respectively.
- Median OS for G, G+T240, and G+T340 was 6.9, 8.7, and 9.2 months, respectively; the differences between treatment groups were not significant (**Figure 6**).
- Rates of 6-month survival were 57, 69, and 73% in the G, G+T240, and G+T340 arms, respectively (p=0.123 for G+T240 and p=0.037 for G+T340 vs G). 12-month survival rates were 26% in the G arm vs 37% in the G+T240 arm (p=0.178) and 38% in the G+T340 arm (p=0.130).
- A total of 14 and 12 patients who were initially randomized to G crossed over to G+T240 and G+T340, respectively.
  - Median post-crossover PFS was 1.8 months with G+T240 vs 2.9 months with G+T340 (p=0.13)
  - Median post-crossover OS was 2.6 months with G+T240 vs 13.4 months with G+T340 (p=0.010)

Table 3. Maximum CA19-9 decrease and response*

Characteristics	G n=50	G+T240 n=50	G+T340 n=53
Mean CA 19-9 nadir change, U/mL (range)	-523 (-17,870–8,490)	-3,909 (-42,051–18,866)	-5,385† (-40,108–13,968)
CA 19-9 decrease, n (%)			
>20%	34 (68)	36 (72)	47 (89)
>50%	26 (52)	25 (50)	37 (70)
>90%	8 (16)	12 (24)	17 (32)
Median time to CA 19-9 response, months (range)	1.8 (0.9–5.6)	0.9 (0.8–2.8)	0.9 (0.7–4.6)

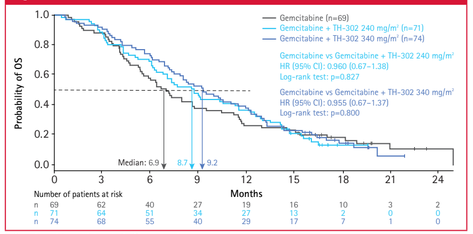
*Based on patients with baseline assessment > upper limit of normal and at least one post-baseline CA19-9 assessment.
†p=0.008 in a two-sample t-test of change from baseline with log-transformed data.
CA, cancer antigen; G, gemcitabine 1,000 mg/m^2; G+T240, gemcitabine 1,000 mg/m^2 + TH-302 240 mg/m^2; G+T340, gemcitabine 1,000 mg/m^2 + TH-302 340 mg/m^2.

Figure 5. Tumor shrinkage in patients with post-baseline tumor measurement



SLD, sum of longest diameter.

Figure 6. Overall survival



CI, confidence interval; HR, hazard ratio; OS, overall survival.

Safety

- Non-laboratory adverse events (AEs) are reported in **Table 4**. Rash and stomatitis occurred more frequently in the G+T arms. However, only 3 patients experienced Grade 3 rash and all reported events of stomatitis were of Grade 1/2.
- Treatment-emergent Grade 3/4 thrombocytopenia was reported in 10, 28, and 57% in the G, G+T240, and G+T340 arms, respectively. No patients discontinued study treatment due to bleeding as a consequence of low platelet counts.
- Treatment-emergent Grade 3/4 neutropenia was observed in 16, 32, and 42% of patients treated with G, G+T240, and G+T340, respectively, and 0, 1.4 and 5.4% of patients, respectively, experienced Grade 3/4 febrile neutropenia. No patients discontinued the study because of febrile neutropenia.
- AEs leading to discontinuation were observed in 16% of patients in the G arm, in 17% of patients in the G+T240 arm, and in 12% of patients in the G+T340 arm. One patient died due to an AE (suicide) considered as possibly related to treatment.

Table 4. Most frequent non-laboratory AEs (regardless of relationship to study drug)

	G n=69		G+T240 n=71		G+T340 n=74	
Patients with AEs, n (%)	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Fatigue	30 (43)	3 (4)	43 (61)	6 (8)	40 (54)	3 (4)
Peripheral edema	28 (41)	3 (4)	25 (35)	0	29 (39)	0
Nausea	25 (36)	4 (6)	28 (39)	7 (10)	35 (47)	4 (5)
Constipation	22 (32)	1 (1)	25 (35)	1 (1)	25 (34)	0
Abdominal pain	20 (29)	4 (6)	27 (38)	6 (8)	27 (36)	9 (12)
Vomiting	20 (29)	2 (3)	16 (23)	4 (6)	27 (36)	6 (8)
Decreased appetite	16 (23)	1 (1)	18 (25)	4 (6)	24 (32)	3 (4)
Pyrexia	16 (23)	0	19 (27)	1 (1)	21 (28)	2 (3)
Diarrhea	15 (22)	2 (3)	19 (27)	2 (3)	28 (38)	3 (4)
Any rash*	11 (16)	0	30 (42)	1 (1)	35 (47)	2 (3)
Stomatitis	5 (7)	0	13 (18)	0	31 (42)	0

*Includes all AEs including the term "rash".
AE, adverse event; G, gemcitabine 1,000 mg/m^2; G+T240, gemcitabine 1,000 mg/m^2+TH-302 240 mg/m^2; G+T340, gemcitabine 1,000 mg/m^2+TH-302 340 mg/m^2.

Conclusions

- PFS, the primary study endpoint, was significantly improved in patients treated with the combination of gemcitabine plus TH-302 compared with gemcitabine alone.
- A consistent dose effect was evident in terms of improved PFS, increased objective response rate, and decreased CA 19-9 levels in the G+T340 arm compared with the G+T240 and the gemcitabine-alone arms.
- OS was not significantly different across treatment arms. This may be at least partially explained by control arm patients with PD crossing over to one of the G+T treatment arms. The 6- and 12-month survival rates were higher in the G+T arms compared to G alone.
- Skin or mucosal toxicity and myelosuppression were the most commonly reported TH-302-related AEs. These AEs were manageable. There was no increase in treatment discontinuation compared with gemcitabine alone.
- Based on the encouraging findings from this Phase II study, a Phase III study of TH-302 at 340 mg/m^2 combined with gemcitabine was initiated in patients with locally advanced, unresectable, and metastatic adenocarcinoma of the pancreas.

References

1. Minchinton AI, Tannock IF. Nat Rev Cancer 2006;6:583-92.
2. Duan JX, et al. J Med Chem 2008;51:2412-20.
3. Liu Q, et al. Cancer Chemother Pharmacol 2012;69:1487-98.
4. Borad MJ, et al. J Clin Oncol 2011;29(Suppl 4): Abstract 265.
5. Meng F, et al. Mol Cancer Ther 2012;11:740-51.

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Acknowledgments

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Disclosures

DPR: member of a data and safety monitoring board for Merck Serono. **CE:** employee of Threshold Pharmaceuticals. All other authors have no potential conflicts of interest to disclose.
TH-302 is currently under clinical investigation and has not been approved by any regulatory authority. Status: January 2013.