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ORIGINAL REPORT

Randomized Phase II Trial of Gemcitabine Plus TH-302 Versus Gemcitabine in Patients With Advanced Pancreatic Cancer

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
TH-302 is an investigational hypoxia-activated prodrug that releases the DNA alkylator bromoisophosphoramide mustard in hypoxic settings. This phase II study (NCT01144455) evaluated gemcitabine plus TH-302 in patients with previously untreated, locally advanced or metastatic pancreatic cancer.

Patients and Methods
Patients were randomly assigned 1:1:1 to gemcitabine (1,000 mg/m^2), gemcitabine plus TH-302 240 mg/m^2 (G+T240), or gemcitabine plus TH-302 340 mg/m^2 (G+T340). Randomized crossover after progression on gemcitabine was allowed. The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS), tumor response, CA 19-9 response, and safety.

Results
Two hundred fourteen patients (77% with metastatic disease) were enrolled between June 2010 and July 2011. PFS was significantly longer with gemcitabine plus TH-302 (pooled combination arms) compared with gemcitabine alone (median PFS, 5.6 *v* 3.6 months, respectively; hazard ratio, 0.61; 95% CI, 0.43 to 0.87; $P = .005$; median PFS for metastatic disease, 5.1 *v* 3.4 months, respectively). Median PFS times for G+T240 and G+T340 were 5.6 and 6.0 months, respectively. Tumor response was 12%, 17%, and 26% in the gemcitabine, G+T240, and G+T340 arms, respectively (G+T340 *v* gemcitabine, $P = .04$). CA 19-9 decrease was greater with G+T340 versus gemcitabine (−5,398 *v* −549 U/mL, respectively; $P = .008$). Median OS times for gemcitabine, G+T240, and G+T340 were 6.9, 8.7, and 9.2 months, respectively (P = not significant). The most common adverse events (AEs) were fatigue, nausea, and peripheral edema (frequencies similar across arms). Skin and mucosal toxicities (2% grade 3) and myelosuppression (55% grade 3 or 4) were the most common TH-302–related AEs but were not associated with treatment discontinuation.

Conclusion
PFS, tumor response, and CA 19-9 response were significantly improved with G+TH-302. G+T340 is being investigated further in the phase III MAESTRO study (NCT01746979).

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INTRODUCTION

Pancreatic cancer is among the most lethal solid tumors, with a 5-year survival rate of approximately 5% in all stages of disease and a median survival of only 6 to 12 months in metastatic disease.[1] The pivotal study for gemcitabine demonstrated improvement in clinical benefit response and overall survival (OS).[2] The subsequent approval of erlotinib in combination with gemcitabine provided modest incremental improvements in OS compared with gemcitabine alone (6.24 *v* 5.91 months, respectively) with increased toxicity.[3] A notable advance in treatment of advanced pancreatic cancer was reported with the combination regimen of fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX), demonstrating significant improvements in outcome compared with single-agent gemcitabine (median progression-free survival [PFS], 6.4 *v* 3.3 months, respectively; median OS, 11.1 *v* 6.8 months, respectively).[4] Although confirmatory studies have not been reported, this was the first phase III study to

demonstrate an increase in median OS of more than 2 months. FOLFIRINOX was associated with significant increases in hematologic and nonhematologic toxicity, including GI toxicity and neuropathy, which may limit its applicability. In 2013, a phase III study comparing nanoparticle albumin-bound (nab) –paclitaxel plus gemcitabine to single-agent gemcitabine demonstrated significant improvement in survival (median PFS, 5.5 *v* 3.7 months, respectively; median OS, 8.5 *v* 6.7 months, respectively), establishing it as a current standard of care for gemcitabine-based therapy.[5] The most common severe adverse events (AEs) associated with the combination were neutropenia, fatigue, and neuropathy.

Tumor hypoxia has been associated with a worsened prognosis in a wide array of tumor types.[6] Whereas conventional anticancer therapies typically target actively dividing cells near the vasculature, they are believed to poorly penetrate hypoxic regions.[7] Because cells in hypoxic regions are relatively quiescent, they also tend to be refractory to agents targeting rapidly proliferating cells.[7-10] Novel therapeutics that specifically target the resistant hypoxic zones may provide additional antitumor activity and clinical benefit when combined with conventional treatments.[10,11]

TH-302 (Threshold Pharmaceuticals, South San Francisco, CA, and Merck KGaA, Darmstadt, Germany) is a hypoxia-activated, cytotoxic prodrug with a 2-nitroimidazole component designed to release the DNA cross-linker bromo-isophosphoramide mustard (Br-IPM) when reduced by intracellular reductases in the setting of severe hypoxia.[12] Once released, Br-IPM may also diffuse to adjacent cells in normoxic regions of the tumor and thus act via a bystander effect as a cytotoxic agent outside of the hypoxic activation zone.[13]

TH-302 has shown preclinical and clinical activity in a variety of solid tumors including pancreatic cancer.[14-16] In a phase I/II clinical study (NCT00743379) of solid tumors investigating TH-302 doses of 240 to 575 mg/m^2 on days 1, 8, and 15 of a 28-day cycle, the recommended phase II dose of the combination of gemcitabine 1,000 mg/m^2 with TH-302 was established at 340 mg/m^2.[16] Dose-limiting hematologic and mucosal toxicities were more frequent at 340 than 240 mg/m^2, and further TH-302 dose exploration was indicated. An overall response rate of 21%, per RECIST version 1.0, and a median PFS time of 5.9 months were observed in 46 patients with advanced pancreatic cancer.[16]

The current open-label, multicenter, randomized phase II trial with a planned crossover was designed to assess the benefit of adding TH-302 to single-agent gemcitabine, the standard of care at the time the study was conducted, as systemic therapy in patients with previously untreated advanced pancreatic cancer.

PATIENTS AND METHODS

Patients

Eligible patients were older than 18 years of age, had cytologic/histologically confirmed locally advanced/metastatic pancreatic cancer, had not received prior systemic therapy, and had measurable disease by RECIST version 1.1, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and acceptable liver, renal, and hematologic status. Complete criteria are provided in the Data Supplement. The study protocol was approved by the institutional review board at each study site, and all patients provided written informed consent.

Random Assignment and Masking

This was an open-label study with 1:1:1 random assignment to gemcitabine alone, gemcitabine plus TH-302 240 mg/m^2 (G+T240), or gemcitabine plus TH-302 340 mg/m^2 (G+T340). Random assignment was stratified by extent of disease (locally advanced *v* metastatic). Fifteen patients randomly

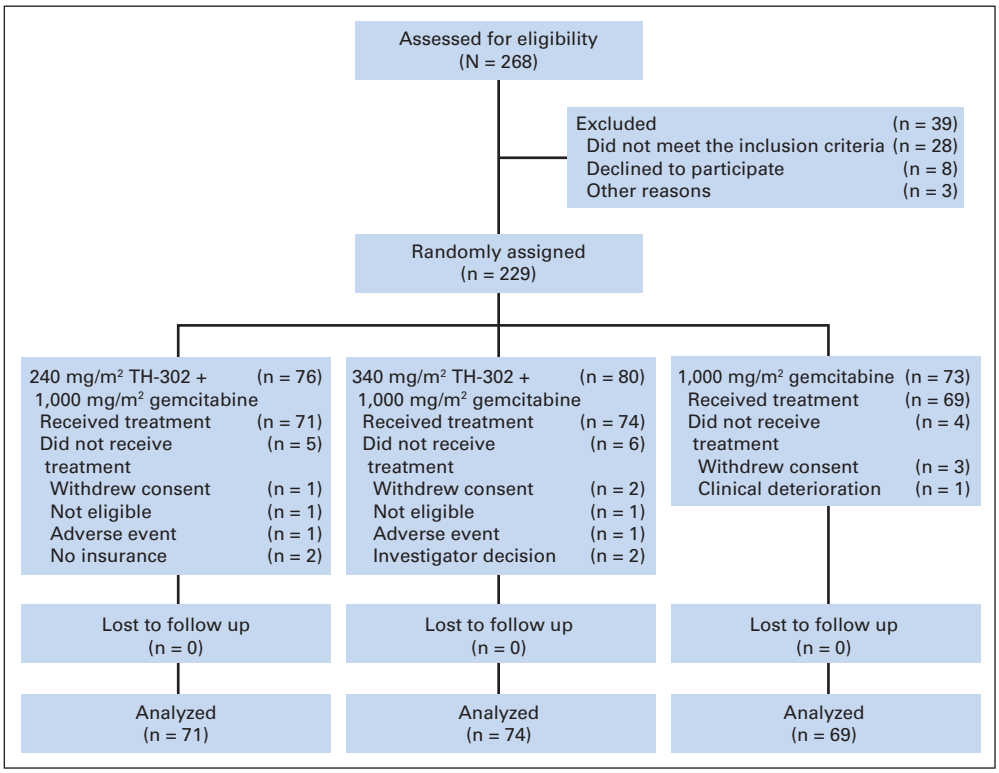

Fig 1. CONSORT diagram showing patient flow through the study.

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assigned but not treated were excluded from the analyses (Fig 1). Patients randomly assigned to gemcitabine alone whose disease progressed and who met eligibility criteria were allowed to cross over and be randomly assigned to G+T240 or G+T340.

Procedures

On days 1, 8, and 15 of each 28-day cycle, patients assigned to combination therapy received TH-302 infused intravenously (IV) over 30 to 60 minutes, followed 2 hours later by a 30-minute IV infusion of gemcitabine 1,000 mg/m^2. Patients assigned to gemcitabine alone received 1,000 mg/m^2 infused IV over 30 minutes. Hemoglobin ≥ 9 g/dL, platelets ≥ 100,000/μL, and absolute neutrophil count ≥ 1,500/μL were required for full dosing at the start of each cycle. Modifications to the TH-302 dose were permitted in accordance with protocol-specified algorithms provided in the Data Supplement. Modifications to the gemcitabine dose were permitted in accordance with the manufacturer's product labeling. Patients who had not experienced disease progression after six cycles and who experienced no unacceptable toxicity could continue their assigned therapy in each treatment arm at the discretion of the investigator and medical monitor. Tumor assessments were performed locally every 8 weeks. Plasma samples for measurement of TH-302 and Br-IPM were analyzed using a validated liquid chromatography/tandem mass spectrometry method.

Statistical Analysis

The primary efficacy outcome measure was PFS, which was defined as the interval from treatment initiation to first occurrence of progressive disease or death from any cause within 56 days of the last tumor assessment. The primary PFS log-rank test analysis required 144 events and had 80% power to detect a 50% improvement in PFS, comparing the pooled combination treatment arms with the gemcitabine-alone arm using a two-sided log-rank test with α set at 20% appropriate for phase II screening trial.[17] OS, including 6- and 12-month survival rates, was a secondary efficacy end point; no formal statistical power analysis was performed for OS because the crossover option in the gemcitabine-alone treatment arm confounded the analysis. PFS and OS were analyzed with no adjustment for crossover using Kaplan-Meier and log-rank procedures. The primary PFS treatment analysis is reported using the protocol-specified primary analysis conducted in February 2012; all other analyses, including updated PFS, are based on data through November 2013.

Other secondary efficacy outcome measures included objective response rate, which was defined by RECIST version 1.1 (confirmed and unconfirmed); response duration (time from first response to progression); CA 19-9 response (> 50% decline from baseline CA 19-9); and changes in ECOG performance status, visual analog scale (VAS) pain score (scale of 0 [no pain] to 100 [worst possible pain]), and serum CA 19-9. A Cochran-Mantel-Haenszel test stratified by extent of disease was used to compare response across treatment groups. Changes from baseline in ECOG, VAS pain, and CA 19-9 within treatment groups and across treatment groups were analyzed by analysis of variance. Statistical significance was assessed at a two-sided level of 20%. Analyses were conducted for both pooled data across the combination arms and individual treatment arms for all end points. Univariable and multivariable models were performed to compare PFS and OS across subgroups. The log-rank test was used to compare subgroups in the univariable models, and a stepwise Cox regression model was used for the multivariable analyses. The following covariates were analyzed: sex (male or female), age (≥ or < 65 years), ECOG performance status (0 or 1), months from initial diagnosis (< or ≥ 1 month), metastatic disease (yes or no), presence of liver metastases (yes or no), site of primary tumor in pancreas head (yes or no), prior radiotherapy

Table 1. Patient Demographics and Disease Characteristics at Baseline

Characteristic	Gemcitabine Alone (n = 69)		Gemcitabine + TH-302: TH-302 240 mg/m^2 (n = 71)		Gemcitabine + TH-302: TH-302 340 mg/m^2 (n = 74)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	67		63		65	
Range	41-83		41-81		29-86	
Male sex, %		58		62		57
ECOG performance status*						
0	24	35	35	49	26	36
1	45	65	36	51	46	64
CA 19-9 level, U/mL†						
Median	1,291		2,464		2,391	
Range	37 to > 42,500		55 to > 42,500		45 to > 42,500	
Albumin < 3.5 g/dL	35	51	23	32	25	34
Hemoglobin < 12 g/dL	26	38	26	37	24	32
Time from diagnosis, months						
Median	1.1		1.1		1.2	
Range	0.4-94.0		0.3-21.4		0.3-221.2	
Locally advanced disease	15	22	15	21	20	27
Metastatic disease	54	78	56	79	54	73
Prior radiotherapy	6	9	5	7	5	7
Site of primary pancreatic tumor involves head	42	61	39	55	44	59
Metastatic sites						
Liver	46	67	47	66	42	57
Lung	11	16	10	14	15	20

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Baseline data available for 69, 71, and 72 patients in the gemcitabine-alone, gemcitabine + TH-302 240 mg/m^2, and gemcitabine + TH-302 340 mg/m^2 treatment arms, respectively. Percentages are calculated based on the total number of patients with available data.
†Data available for 55, 54, and 58 patients with elevated baseline CA 19-9 in the gemcitabine-alone, gemcitabine + TH-302 240 mg/m^2, and gemcitabine + TH-302 340 mg/m^2 treatment arms, respectively. Normal CA 19-9 levels are ≤ 35 U/mL.

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(yes or no), albumin (< or ≥ 3.5 g/dL), and hemoglobin (< or ≥ 12 g/dL). For the forward-selection Cox model, the significance level to enter the model was $P = .15$, and the level to stay was $P = .05$; sex and age were fixed factors. No multiplicity adjustments were performed. The US National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 was used to grade AE toxicity.

RESULTS

Between June 2010 and July 2011, 214 patients were enrolled and treated at 45 investigative sites in the United States (Fig 1). Treatment groups were balanced for patient demographic and disease characteristics at baseline (Table 1).

The extent of exposure to study treatment was dependent on treatment, with a median of four, five, and six cycles and 32%, 45%, and 54% of patients receiving ≥ six cycles in the gemcitabine-alone, G+T240, and G+T340 arms, respectively. After progression, 26 patients (38%) crossed over from the gemcitabine-alone arm and were randomly assigned to TH-302 240 mg/m^2 (n = 14) or 340 mg/m^2 (n = 12).

The protocol-specified primary end point of PFS was significantly prolonged in the pooled combination arms compared with gemcitabine alone (median PFS, 5.6 *v* 3.6 months, respectively; hazard ratio [HR], 0.61; 95% CI, 0.43 to 0.87; $P = .005$). This was similar in the updated data, with an HR of 0.63 (95% CI, 0.45 to 0.88; $P = .005$). Each of the individual TH-302 arms also had significantly prolonged median PFS compared with the single-agent gemcitabine arm (G+T240: 5.6 months; $P = .040$; HR, 0.66; 95% CI, 0.45 to 0.98; G+T340: 6.0 months; $P = .008$; HR, 0.59; 95% CI, 0.40 to 0.87; Fig 2A). Fifty-three patients were censored from the PFS analysis, including 47 patients who died a median of 4.7 months (range, 1.9 to 24.1 months) after last tumor assessment. Subgroup analyses favored the combination treatment over gemcitabine alone for all analyzed subgroups (see forest plot in Data Supplement), including sex, age (≥ or < 65 years), ECOG performance status (0 or 1), metastatic or locally advanced cancer, time since diagnosis (≥ or < 1 month), liver metastases (present or absent), site of primary tumor (pancreas, head, or other), prior radiotherapy (yes or no), serum albumin level (≥ or < 3.5 g/dL), and hemoglobin (≥ or < 12 g/dL). The HR was most pronounced in patients with poor prognostic characteristics, including anemia (hemoglobin < 12 g/dL), hypoalbuminemia (albumin < 3.5 g/dL), and poorer performance status (ECOG performance status of 1). In the gemcitabine-alone versus the pooled combination arms, the median PFS was 3.4 versus 5.1 months (HR, 0.59; 95% CI, 0.41 to 0.86), respectively, for metastatic disease and 6.2 versus 9.0 months (HR, 0.82; 95% CI, 0.36 to 1.89), respectively, for locally advanced disease. In multivariable analysis, the HR for TH-302 after adjusting for age, ECOG performance status, metastatic disease and sites, and sex was unchanged at 0.61 (95% CI, 0.43 to 0.85).

Objective best (unconfirmed or confirmed) response (complete response plus partial response) was observed in 12 (17%) of 71 patients treated with G+T240 and 19 (26%) of 74 patients treated with G+T340 compared with eight (12%) of 69 patients in the gemcitabine-alone arm (Table 2). Disease control (complete response, partial response, and stable disease) was observed in 53 (75%) of 71 and 56 (76%) of 74 patients treated with G+T240 and G+T340, respectively, compared with 46 (67%) of 69 patients in the gemcitabine-alone arm.

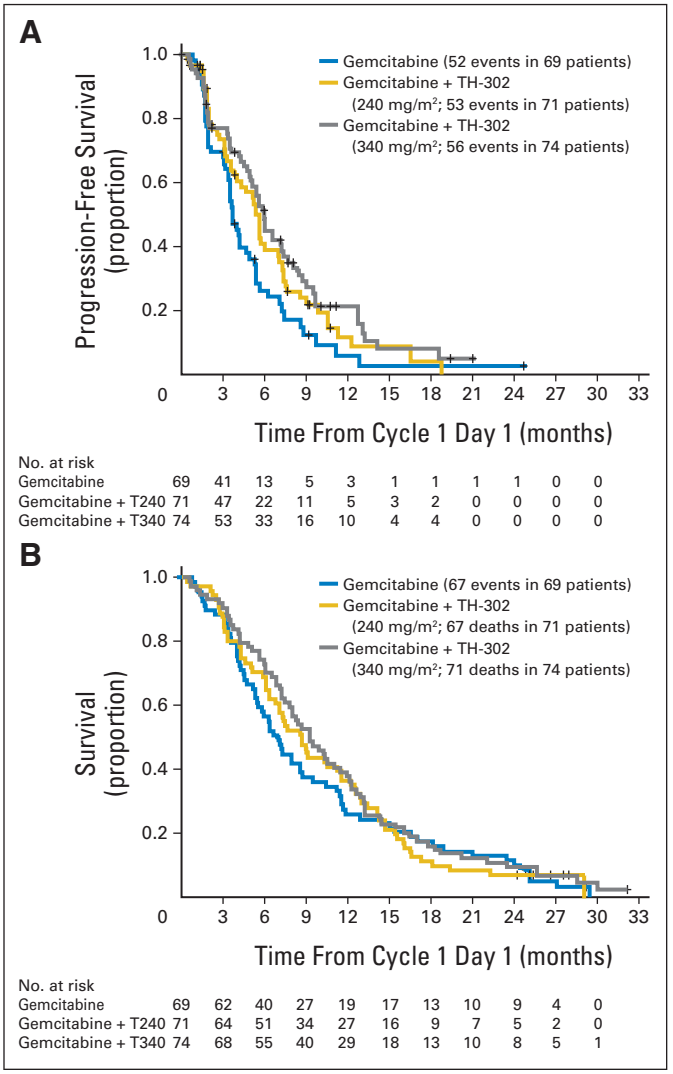

Fig 2. (A) Progression-free survival and (B) overall survival by treatment group in patients with advanced pancreatic cancer.

Median OS time was longer in the combination arms than in the gemcitabine-alone arm (Table 2); median OS was 8.7 months with G+T240 ($P = .77$; HR, 0.95; 95% CI, 0.67 to 1.34) and 9.2 months with G+T340 ($P = .39$; HR, 0.86; 95% CI, 0.61 to 1.21) compared with 6.9 months with gemcitabine alone (Fig 2B). The differences between treatment groups were not statistically significant and remained unchanged with multivariable covariate adjustments. The median OS was 7.6 months for metastatic disease and 13.1 months for locally advanced disease with the combinations compared with 6.3 and 15.0 months, respectively, with gemcitabine alone. The OS rate at 6 months was 57% in the gemcitabine-alone arm compared with 69% with G+T240 ($P = .12$) and 73% with G+T340 ($P = .04$). The OS at 12 months was 26% in the gemcitabine-alone arm compared with 37% ($P = .18$) and 38% ($P = .13$) in the G+T240 and G+T340 combination arms, respectively. For the pooled combination arms, the OS was 71% at 6 months ($P = .04$) and 37% at 12 months ($P = .09$).

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Table 2. Maximum RECIST Response, CA 19-9 Response, and OS

Response	Gemcitabine Alone (n = 69)		G+T240 (n = 71)		G+T340 (n = 74)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
RECIST best tumor response						
Overall response rate (CR + PR)	8	12	12	17	19	26*
CR	0	0	0	0	2	3
PR	8	12	12	17	17	23
SD	38	55	41	58	37	50
DCR (CR + PR + SD)	46	67	53	75	56	76
CA 19-9 parameters†						
No. of patients	50		50		53	
Nadir change, U/mL						
Mean	−549		−3857		−5398*	
Range	−17,870-8490		−42,051-18,866		−40,108-13,968	
Decrease						
> 20%	34	68	37	73	47	89
> 50%	26	52	26	51	37	70‡
> 90%	8	16	13	25	17	32
Time to response, months						
Median	1.8		0.9		0.9	
Range	0.9-5.6		0.8-2.8		0.7-4.6	
OS						
Median, months	6.9		8.7		9.2	
6-month OS, %	57		69‡		73*	
95% CI	44 to 67		57 to 78		61 to 82	
12-month OS, %	26		37‡		38‡	
95% CI	16 to 37		26 to 48		27 to 49	

Abbreviations: CR, complete response; DCR, disease control rate; G+T240, gemcitabine plus TH-302 240 mg/m^2; G+T340, gemcitabine plus TH-302 340 mg/m^2; OS, overall survival; PR, partial response; SD, stable disease.
*$P < .05$ compared with gemcitabine-alone group.
†Based on patients with baseline assessment above upper limit of normal and at least one postbaseline CA 19-9 assessment.
‡$P < .20$ compared with gemcitabine-alone group.

Twenty-six patients who were initially randomly assigned to gemcitabine alone crossed over after disease progression and were randomly assigned to G+T240 (n = 14) or G+T340 (n = 12). Median PFS after crossover was 1.8 months in the G+T240 arm and 2.8 months in the G+T340 arm ($P = .16$). Median OS after crossover was 2.6 months in the G+T240 arm compared with 12.2 months in the G+T340 arm ($P = .004$).

Results for the CA 19-9 tumor marker are listed in Table 2. Both combination treatment arms achieved a tumor marker response at a median of 0.9 months compared with 1.8 months in the gemcitabine monotherapy arm. The G+T340 combination arm had the greatest mean nadir change from baseline in CA 19-9 (−5,398 U/mL), which was significantly different from that of the gemcitabine-alone arm (−549 U/mL; $P = .008$); the G+T240 combination arm was intermediate at −3,857 U/mL. Nearly one third of patients receiving G+T340 (17 of 53 patients; 32%) had a CA 19-9 decrease exceeding 90% of baseline value, as did 25% of patients who received G+T240 (13 of 51 patients). Only eight (16%) of 50 patients in the gemcitabine-alone arm achieved a decrease of this magnitude.

The median VAS pain assessment scores were 24, 22, and 23 at baseline, and 12, 5, and 3 at lowest assessment, with median change from baseline of −12, −7.5, and −9.0, in the gemcitabine-alone, G+T240, and G+T340 arms, respectively.

The most frequent nonlaboratory AEs are listed in Table 3. Fatigue was the most common AE in all treatment arms. Rash and stomatitis occurred more frequently in the combination treatment arms; however, grade 3 rash was rare (n = 3), and all events of stomatitis were grade 1 or 2. Hematologic AEs were also more frequent in the combination arms and were dependent on TH-302 dose. Treatment-emergent grade 3 or 4 thrombocytopenia was reported in 12% of patients in the gemcitabine-alone arm compared with 30% and 55% of patients in the G+T240 and G+T340 arms, respectively. No patients discontinued study treatment because of thrombocytopenia-associated bleeding. Treatment-emergent grade 3 or 4 neutropenia was observed in 17% of patients receiving gemcitabine monotherapy compared with 34% and 43% of patients in the G+T240 and G+T340 arms, respectively, and 0%, 2.8%, and 5.4% of patients, respectively, experienced grade 3 or 4 febrile neutropenia. No patients discontinued the study because of febrile neutropenia. There were no findings suggestive of cardiac, hepatic, or renal toxicity.

Nineteen percent of patients (13 of 69 patients) in the gemcitabine-alone arm discontinued therapy because of AEs compared with 15% of patients (11 of 71 patients) and 14% of patients (10 of 74 patients) in the G+T240 and G+T340 arms, respectively. Gemcitabine dose reductions during the first six cycles occurred in 42%, 51%, and 72% of patients in the gemcitabine-alone, G+T240, and G+T340 arms, respectively.

TH-302 and Br-IPM pharmacokinetics were dose proportional for the two TH-302 dose groups, and Br-IPM concentrations were approximately 2% of TH-302 concentrations. Terminal half-lives

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Table 3. Most Frequent Adverse Events (regardless of relationship to study drug)

	Gemcitabine Alone (n = 69)				G+T240 (n = 71)				G+T340* (n = 74)			
	All Grades		Grade 3/4		All Grades		Grade 3/4		All Grades		Grade 3/4	
Adverse Event	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Fatigue	29	42	3	4	43	61	6	8	41	55	3	4
Anemia	30	43	20	29	37	52	24	34	39	53	32	43
Thrombocytopenia	20	29	8	12	36	51	21	30	44	59	41	55
Peripheral edema	27	39	3	4	26	37	0	0	31	42	0	0
Nausea	27	39	4	6	28	39	7	10	34	46	4	5
Constipation	22	32	1	1	25	35	2	3	25	34	0	0
Abdominal pain†	22	32	4	6	31	44	6	8	28	38	9	12
Neutropenia	15	22	12	17	27	38	24	34	32	43	32	43
Vomiting	21	30	2	3	17	24	4	6	28	38	6	8
Pyrexia	17	25	0	0	20	28	1	1	19	26	2	3
Diarrhea	17	25	2	3	20	28	2	3	27	36	3	4
Decreased appetite	16	23	1	1	18	25	4	6	26	35	3	4
Any rash‡	12	17	1	1	30	42	1	1	37	50	2	3
Stomatitis	5	7	0	0	13	18	0	0	27	36	0	0

Abbreviations: G+T240, gemcitabine plus TH-302 240 mg/m^2; G+T340, gemcitabine plus TH-302 340 mg/m^2.
*One patient in the G+T340 arm died as a consequence of an adverse event (suicide) that was considered to be possibly related to treatment.
†Any adverse event, including the term abdominal pain.
‡Any adverse event, including the term rash.

for both TH-302 dose groups and both TH-302 and Br-IPM were 0.7 hours.

DISCUSSION

Hypoxic regions of the tumor play a critical role in tumor progression, development of aggressive tumor phenotypes, and resistance to chemotherapy and radiotherapy and contribute significantly to ultimate treatment failure.[6,8] Multiple investigational agents have been designed to target tumor hypoxia for the treatment of cancer[11,18]; however, none have yet received regulatory approval.

In the current study, the combination of gemcitabine and TH-302 significantly improved PFS when compared with gemcitabine alone in patients with locally advanced or metastatic pancreatic carcinoma (5.6 months with G+T240 combination therapy and 6.0 months with G+T340 combination therapy *v* 3.6 months with gemcitabine alone). Other secondary end points, such as objective tumor response rate, CA 19-9 response, and OS rates at 6 and 12 months, met protocol-defined statistical significance with a $P < .20$ in favor of the combination therapy arm receiving G+T340 compared with the gemcitabine-alone arm. In fact, all end points, except for OS, had $P < .05$, which indicates that this combination should be studied in an appropriately sized phase III study. OS was not significantly different across arms using the log-rank test, which provides a global comparison of survival curves. This result may be partially attributable to the study not being designed to compare OS, which would require a large sample size as well as disallowing the control arm patients from crossing over to one of the TH-302 combination arms after disease progression. The absolute increase in median PFS of 2.0 and 2.4 months for G+T240 and G+T340, respectively, was mirrored by increases in median OS of 1.8 and 2.3 months, respectively, compared with the gemcitabine control arm. Significant improvements in survival were also present at 6 and 12 months in both combination arms and the pooled combination arm compared with gemcitabine alone. With additional time, the survival curves crossed, which may reflect the effects of subsequent therapy, including crossover.

Although the timing of response assessments did not differ across treatment groups, consistent with the absence of early assessment biases, the open-label investigator-assessed outcomes have the potential to introduce investigator bias. Nevertheless, the concordance between the laboratory-derived CA 19-9 decreases and both tumor response and PFS measures is supportive evidence against any overt investigator bias. In addition, inclusion of patients with locally advanced and metastatic disease could introduce unintended bias; the randomized design stratified for extent of disease to minimize this.

The combination of gemcitabine and TH-302 was tolerated. Consistent with previous early-phase studies of TH-302 in patients with solid tumors, skin toxicity, mucosal toxicity, and enhanced myelosuppression were the most commonly reported AEs related to TH-302.[19] These AEs were manageable, as evidenced by no increase in treatment discontinuation in patients treated with TH-302 compared with those treated with gemcitabine alone.

The efficacy and safety results from this randomized phase II study of hypoxia-activated TH-302 are encouraging. However, no methods for verifying the presence or measuring the extent of tumor hypoxia are currently validated for clinical studies. A number of positron emission tomography imaging agents are being investigated as potential identifiers of tumor hypoxia.[20,21]

On the basis of the findings in this phase II study, a global phase III clinical trial (MAESTRO; NCT01746979) comparing gemcitabine plus TH-302 at 340 mg/m^2 versus gemcitabine plus placebo was initiated. If successful, the combination of gemcitabine plus TH-302 has the potential to provide an alternative regimen to the current standard-of-care regimens, gemcitabine plus nab-paclitaxel and FOLFIRINOX, particularly given the limited neuropathy of gemcitabine plus TH-302. Given preclinical data exhibiting improved preclinical efficacy

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of triple-combination gemcitabine, nab-paclitaxel, and TH-302 versus gemcitabine and nab-paclitaxel, a phase IB/II study combining gemcitabine plus nab-paclitaxel with TH-302 (NCT02047500) was also initiated to continue to investigate optimizing gemcitabine-based pancreatic cancer therapies.[22]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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GLOSSARY TERMS

hypoxia: oxygen concentration below normal physiologic limits in a specific tissue.

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