Evofosfamide combined with gemcitabine/nab-paclitaxel in patients with previously untreated locally advanced or metastatic pancreatic adenocarcinoma (PAC): results of a phase I trial.

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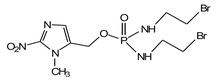
BACKGROUND

Evofosfamide (TH-302) is a nitroimidazole prodrug of the cytotoxin, bromo-isophosphoramide mustard (Br-IPM). Under normoxic conditions, evofosfamide is essentially inactive. In hypoxic conditions and in the presence of certain reductases, the nitroimidazole is preferentially reduced and Br-IPM is released to alkylate DNA, inducing intrastrand and interstrand crosslinks.

Figure 1: Structure of Evofosfamide



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 pro-drug, evofosfamide, is in areas of normoxia, it is designed to remain intact and toxicity is minimized; while in hypoxic regions in solid tumors, evofosfamide is preferentially activated.

Evofosfamide was investigated in Hs766t and MIA PaCa-2 models; enhanced tumor growth delay was observed when adding evofosfamide to nab-paclitaxel plus gemcitabine. The weight loss observed with nab-paclitaxel and gemcitabine was not increased by the addition of evofosfamide in these 2 models.

An open-label, randomized, phase II trial (NCT01144455) of 2 dose levels of evofosfamide (240 and 340 mg/m^2) in combination with gemcitabine versus gemcitabine alone and a Phase III trial (NCT01746979) of evofosfamide (340 mg/m^2) in combination with gemcitabine versus gemcitabine plus placebo were conducted in subjects with advanced pancreatic adenocarcinoma. Improvements in progression-free survival (PFS) were reported in each study. A Phase III study (NCT00844649) of nab-paclitaxel plus gemcitabine compared to gemcitabine demonstrated a significant improvement in overall survival (OS). The current study was designed to establish a treatment regimen for combining evofosfamide with nab-paclitaxel plus gemcitabine and to explore the safety and anti-tumor activity of the triplet combination.

METHODS

Primary Objectives

- To evaluate the safety and tolerability, define the maximum tolerated dose (MTD), and determine the recommended Phase 2 dose (RP2D) of evofosfamide in combination with gemcitabine and nab-paclitaxel in previously untreated subjects with locally advanced unresectable or metastatic pancreatic adenocarcinoma.

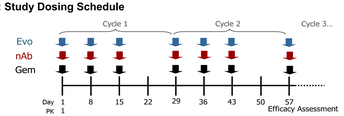
Secondary Objectives

- To describe and evaluate different doses of evofosfamide in combination with gemcitabine and nab-paclitaxel in terms of dose limiting toxicities (DLTs), occurrence, type, and severity grades according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 of treatment-emergent adverse events (TEAEs), SAEs, deaths, and laboratory investigations.
- To explore the antitumor activity of evofosfamide in combination with gemcitabine and nab-paclitaxel according to RECIST 1.1 criteria by objective overall response, duration of response, PFS and OS.
- To evaluate levels of carbohydrate antigen 19-9 (CA19-9), a tumor marker for pancreatic carcinoma.
- To explore the effect of evofosfamide in combination with gemcitabine and nab-paclitaxel on tumor metabolic activity using [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) scans according to the European Organization for Research and Treatment of Cancer (EORTC) criteria (cohort expansion at MTD only).
- To explore the pharmacokinetic (PK) profile of evofosfamide and Br-IPM in plasma of advanced pancreatic cancer subjects receiving gemcitabine and nab-paclitaxel and investigate the drug interaction between evofosfamide and nab-paclitaxel.

Study Design

- An open-label dose escalation trial was designed to assess the safety and tolerability, and to define the MTD/RP2D of evofosfamide combined with gemcitabine and nab-paclitaxel.
- Evofosfamide was administered by IV infusion over 30 - 60 minutes on Day 1, Day 8 and Day 15 of a 28-day cycle. Doses were fixed within a dose cohort. The initial cohort received 170 mg/m^2.
- Gemcitabine (800 mg/m^2), 80% of approved dose was administered as an IV infusion on Day 1, Day 8 and Day 15 two - four hours after evofosfamide administration.
- Nab-paclitaxel (100 mg/m^2), 80% of approved dose was administered as an IV infusion on Day 1, Day 8 and Day 15 two - four hours after evofosfamide administration.
- With some protocol-defined exceptions/refinements, a DLT was defined as febrile neutropenia or grade 4 neutropenia lasting more than 5 days, grade 4 thrombocytopenia lasting more than 7 days or grade 3 with associated bleeding, grade 3 or higher non-hematologic toxicity despite supportive care or an adverse event resulting in treatment interruption for greater than 3 weeks.

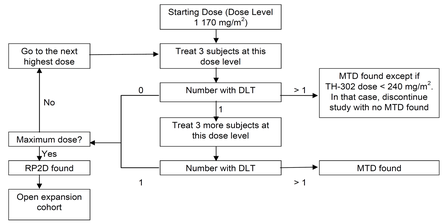
Figure 2: Study Dosing Schedule



Study Design

- A standard 3 + 3 dose escalation design (Figure 3) was utilized with fixed doses of gemcitabine and nab-paclitaxel and escalating mg/m^2 doses of evofosfamide (170, 240 and 340)

Figure 3: Dose escalation scheme



RESULTS

- 19 patients with metastatic or locally advanced pancreatic adenocarcinoma were enrolled between March 2014 and November 2015.
- The study was closed to enrollment in December 2015 as part of a broader change in the scope of evofosfamide development. At that point 2 patients had been treated in the expansion cohort.
- Data are pooled across the dose escalation and dose expansion cohorts for all analyses.
- Efficacy data and safety data are reported through the final study data cutoff date of 24 May 2016.
- Demographic and baseline disease characteristics are provided in Table 1.

Table 1: Demographics and Baseline Characteristics

Event Term	170mg/m^2 N=7	240mg/m^2 N=3	340mg/m^2 N=9	Total N=19
Median age, years (range)	62 (50-67)	61 (55-78)	66 (52-77)	62 (50-78)
Male/Female, n (%)	3/4 (43%/57%)	1/2 (33%/67%)	5/4 (56%/44%)	9/10 (47%/53%)
Extent of Disease				
Metastatic	6 (66.7%)	3 (100%)	8 (88.9%)	17 (89.5%)
Locally Advanced	1 (33.3%)	0 (0.0%	1 (11.1%)	2 (10.5%)
Diagnosis of Metastatic Dis	(N=6)	(N=1)	(N=7)	(N=14)
Median	0.9	1.3	1.1	1.0
Range	0.1—1.1	1.3—1.3	0.4—2.3	0.1—2.3
ECOG PS				
0	2 (28.6%)	2 (66.7%)	3 (33.3%)	7 (36.8%)
1	5 (71.4%)	1 (33.3%)	6 (66.7%)	12 (63.2%)
Site of Primary				
Body of Pancreas	1 (14.3%)	0 (0.0%)	3 (33.3%)	4 (21.1%)
Head of Pancreas	4 (57.1%)	2 (66.7%)	4 (44.4%)	10 (52.6%)
Tail of Pancreas	2 (28.6%)	1 (33.3%)	2 (22.2%)	5 (26.3%)
Albumin (g/dL)				
<3.5 g/dL	2 (28.6%)	0 (0.0%)	0 (0.0%)	2 (10.5%)
≥3.5 g/dL	5 (71.4%)	3 (100%)	9 (100%)	17 (89.5%)
Hemoglobin (g/dL)				
<12 g/dL	3 (42.9%)	1 (33.3%)	2 (22.2%)	6 (31.6%)
≥12 g/dL	4 (57.1%)	2 (66.7%)	7 (77.8%)	13 (68.4%)

SAFETY

Drug Exposure

- Study drug exposure is provided in Table 2. The median number of cycles received was greatest in the lower two dose cohorts. The median number of cycles received was 6 overall.
- For evofosfamide exposure data displayed individually for all patients refer to Figure 4.

Table 2: Study Drug Exposure

Dose Level	170mg/m^2 N=7	240mg/m^2 N=3	340mg/m^2 N=9	Total N=19
Number of Cycles				
1-2	2 (28.6%)	0 (0.0%)	1 (11.1%)	3 (15.8%)
3-4	1 (14.3%)	1 (33.3%)	3 (33.3%)	5 (26.3%)
5-6	0 (0.0%)	0 (0.0%)	3 (33.3%)	3 (15.8%)
7-12	2 (28.6%)	1 (33.3%)	2 (22.2%)	5 (26.3%)
>12	2 (28.6%)	1 (33.3%)	0 (0.0%)	3 (15.8%)
Median (range)	8 (1 - 27)	8 (4 - 15)	6 (1 - 11)	6 (1 - 27)

SAFETY (continued)

DLTs and MTD

- One DLT of grade 3/4 hematologic toxicity was reported in the 170 mg/m^2 cohort.
- No other DLTs were reported in any of the cohorts
- The MTD of evofosfamide was established at 340 mg/m^2.

Adverse Events

- The most frequently reported adverse events regardless of relationship to study drug occurring in >40% of patients are reported in Table 3.
- Hematological adverse events were the most frequent with no clear dependency on evofosfamide dose. One patient (5.3%) was reported with febrile neutropenia.
- Non-hematologic AEs of fatigue (73.7%), nausea (68.4%) and rash (63.2%) were common.

Table 3: Most Frequent (>40%) AEs Regardless of Relationship to Study Drug

Event Term	170mg/m^2 N=7	240mg/m^2 N=3	340mg/m^2 N=9	Total N=19
Thrombocytopenia	5 (71.4%)	3 (100%)	7 (77.8%)	15 (78.9%)
Neutropenia	6 (85.7%)	3 (100%)	5 (55.6%)	14 (73.7%)
Fatigue	4 (57.1%)	3 (100%)	7 (77.8%)	14 (73.7%)
Anemia	4 (57.1%)	3 (100%)	6 (66.7%)	13 (68.4%)
Nausea	5 (71.4%)	2 (66.7%)	6 (66.7%)	13 (68.4%)
Alopecia	4 (57.1%)	3 (100%)	5 (55.6%)	12 (63.2%)
Rash	3 (42.9%)	3 (100%)	6 (66.7%)	12 (63.2%)
Decreased appetite	5 (71.4%)	1 (33.3%)	3 (33.3%)	9 (47.4%)
Peripheral sensory neuropathy	4 (57.1%)	3 (100%)	2 (22.2%)	9 (47.4%)
Diarrhoea	3 (42.9%)	1 (33.3%)	5 (55.6%)	9 (47.4%)
Vomiting	3 (42.9%)	1 (33.3%)	5 (55.6%)	9 (47.4%)
Chills	2 (28.6%)	2 (66.7%)	4 (44.4%)	8 (42.1%)
Constipation	5 (71.4%)	1 (33.3%)	2 (22.2%)	8 (42.1%)
Leukopenia	2 (28.6%)	2 (66.7%)	4 (44.4%)	8 (42.1%)
Oedema peripheral	4 (57.1%)	2 (66.7%)	2 (22.2%)	8 (42.1%)
Pyrexia	3 (42.9%)	1 (33.3%)	4 (44.4%)	8 (42.1%)

- The most frequently reported Grade 3/4/5 adverse events regardless of relationship to study drug occurring in >40% of patients are reported in Table 4.
- Hematological AEs were the most frequent with no clear dependency on evofosfamide dose
- Bile duct obstruction and sepsis were the only Grade 3/4/5 non-hematologic AE reported in 3 or more patients.

Table 4: Most Frequent (>15%) Grade 3, 4, and 5 AEs Regardless of Relationship to Study Drug

Event Term	170mg/m^2 N=7	240mg/m^2 N=3	340mg/m^2 N=9	Total N=19
Neutropenia/ANC decreased	5 (71.4%)	2 (66.7%)	7 (77.8%)	14 (73.7%)
Leucopenia/WBC decreased	3 (42.9%)	2 (66.7%)	4 (44.4%)	9 (47.4%)
Thrombocytopenia	4 (57.1%)	1 (33.3%)	3 (33.3%)	8 (42.1%)
Bile Duct Obstruction	2 (28.6%)	0 (0.0%)	1 (11.1%)	3 (15.8%)
Pancytopenia	2 (28.6%)	0 (0.0%)	1 (11.1%)	3 (15.8%)
Sepsis	1 (14.3%)	0 (0.0%)	2 (22.2%)	3 (15.8%)

- AEs resulting in drug withdrawal of any of the three study drugs are reported in Table 5.
- Five patients discontinued all treatment due to an adverse event: 1 patient in 170 mg/m^2 cohort: sepsis; 3 patients in 240 mg/m^2 cohort: peripheral sensory neuropathy, peripheral sensory neuropathy and rash, pneumonia; 1 patient in 340 mg/m^2 cohort:: retroperitoneal hemorrhage.
- Four of the AEs leading to study drug withdrawal were considered related to study drug:(1 patient in 170 mg/m^2 cohort: sepsis; 3 patients in 240 mg/m^2 cohort: peripheral sensory neuropathy, rash, pneumonia.

Table 5: AEs leading to treatment discontinuation

Event Term	170mg/m^2 N=7	240mg/m^2 N=3	340mg/m^2 N=9	Total N=19
Any AE	1 (14.3%)	3 (100.0%)	1 (11.1%)	5 (26.3%)
Pneumonia	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (5.3%)
Sepsis	1 (14.3%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
Peripheral sensory neuropathy	0 (0.0%)	2 (66.7%)	0 (0.0%)	2 (10.5%)
Retroperitoneal Hemorrhage	0 (0.0%)	0 (0.0%)	1 (11.1%)	1 (5.3%)
Rash	0 (0.0%)	1 (33.3%)	0 (0.0%)	1 (5.3%)

Deaths, SAEs

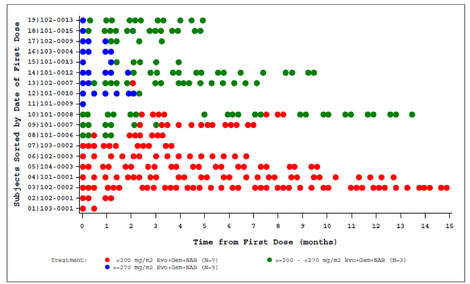
- Ten patients had deaths reported: 6 due to progressive disease, 2 of unknown cause and 2 due to adverse events (a case of sepsis in the 170 mg/m^2 cohort considered related to study drug and a case of retroperitoneal hemorrhage in the 340 mg/m^2 cohort considered unrelated to study drug).
- 29 SAEs were reported in 7 (36.8%) of 19 subjects. Sepsis was reported in 3 patients.
- 15 SAEs considered related to study drugs were reported in 5 (26.3%) of 19 subjects. Related SAEs reported in 2 subjects were pneumonia, sepsis and pancytopenia.

Efficacy

Time on Study

- Time on treatment (months) and evofosfamide dose administered as measured by time from first dose are displayed in Figure 4.
- Dose reduction of evofosfamide was common at the two higher dose levels.

Figure 4: Time on Treatment



RECIST 1.1 Response

- RECIST 1.1 best response and confirmed response are provided in Table 6.
- No complete responses were reported; 7 patients had confirmed PRs and 3 other patients had unconfirmed PRs. The best response rate was 52.6%. The confirmed response rate was 36.8%.
- The disease control rate (stable disease or better) was 84.2%.

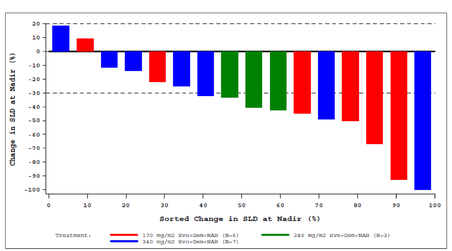
Table 6: Response

Response Category	170 mg/m^2 N=7	240 mg/m^2 N=3	340 mg/m^2 N=9	Total N=19
Best Response	4 (57.1%)	3 (100.0%)	3 (33.3%)	10 (52.6%)
Confirmed Response	4 (57.1%)	2 (66.7%)	1[C] (11.1%)	7 (36.8%)
Stable Disease or Better	5 (71.4%)	3 (100.0%)	8 (88.9%)	16 (84.2%)
Progressive Disease	2 (28.6%)[A]	0 (0.0%)	1 (11.1%)[B]	3 (15.8%)

[A]Includes one patient who discontinued study (death due to AE) prior to a response assessment.
[B]Includes one patient who discontinued study (patient decision) prior to a response assessment.
[C]One patient with PR is awaiting PR confirmation at time of study termination.

- The percent change in the sum of diameters of the RECIST 1.1 target lesions from baseline to nadir are provided in Figure 5.
- Three subjects are not included in the plot (two discontinued prior to first response assessment and one patient did not have measurable disease).

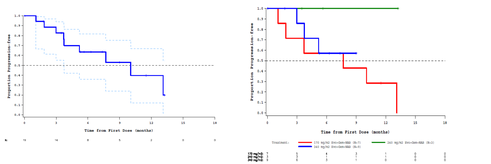
Figure 5: Waterfall Plot of Nadir Sum of Diameters of Target Lesions



Progression-free Survival

- Kaplan-Meier figures for PFS are plotted for all patients and by dose group in Figure 6.
- The median PFS was 10.1 (95% CI: 3.7 to Not Reached) months.

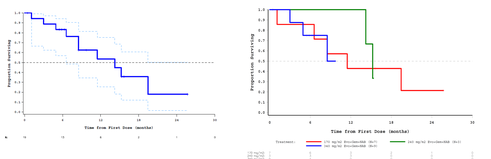
Figure 6: Progression-free Survival



Overall Survival

- Kaplan-Meier figures for OS are plotted for all patients and by dose group in Figure 7.
- The median OS was 14.2 (95% CI: 8.5 to 19.4) months.

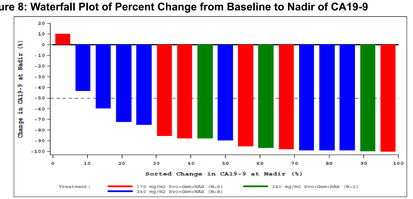
Figure 7: Overall Survival



CA19-9

- The percent changes in CA19-9 from baseline to nadir are provided in Figure 8.
- Two subjects are not included in the plot; both discontinued prior to first CA19-9 assessment.
- 12 of 17 (71%) nadir values were >80% decreased from baseline CA19-9 and 9 of 17 (53%) nadir values were greater than 90% decreased from baseline CA19-9.

Figure 8: Waterfall Plot of Percent Change from Baseline to Nadir of CA19-9



CONCLUSIONS

- The MTD of evofosfamide was established at 340 mg/m^2 when combined with weekly gemcitabine 800 mg/m^2 and nab-paclitaxel 100 mg/m^2.
- The best response rate was 52.6% and confirmed response rate was 36.8%.
- The primary toxicity was hematologic which resulted in dose reductions but not treatment termination.
- The regimen was well tolerated with the median number of cycles received of 6.
- There was one death due to sepsis reported as related to study drugs.
- No new safety signals were reported.

ACKNOWLEDGMENTS

- We want to thank the patients, families, investigators and investigative site staff for their participation and generosity.