# TH-302, A TUMOR-SELECTIVE HYPOXIA-ACTIVATED PRODRUG, COMPLEMENTS THE CLINICAL BENEFITS OF GEMCITABINE IN FIRST LINE PANCREATIC CANCER

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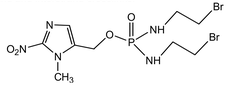
## Introduction

TH-302 is a nitroimidazole prodrug of the cytotoxin, bromo-isophosphoramide mustard (Br-IPM). Under normoxic conditions, TH-302 is essentially inactive. 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.



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 prodrug, TH-302, is in areas of normoxia, it is designed to remain intact and toxicity is minimized. Because TH-302 has been designed to be selectively activated in these highly hypoxic regions, it is an attractive candidate for clinical development for solid tumors. In preclinical studies, the combination of TH-302 with a range of chemotherapies demonstrated significantly greater antitumor activity than single agent chemotherapy.

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. Partial responses were reported in patients with metastatic melanoma, small cell lung cancer and squamous cell carcinoma of the head and neck.

As TH-302 is designed to selectively target the hypoxic regions of solid tumors, the current study investigates the combination of TH-302 with gemcitabine which is effective in the normoxic regions of tumors. This complementary approach is designed to fully target solid tumors. This poster summarizes the current results in first line pancreatic adenocarcinomas.

## Study Design

Study Design
This data is part of a larger complete Phase 1/2 study (TH-CR-402) in which TH-302 was combined with three different chemotherapies to evaluate the DLTs, MTD and preliminary efficacy. Data from 47 first-line pancreatic patients treated with TH-302 in combination with gemcitabine were evaluated for the purposes of this poster.

Three separate arms enrolled independently:

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

- Initial TH-302 dose was 240 mg/m$^2$
- Each arm was escalated independently in 20-40% increments up to maximum weekly monotherapy dose of 575 mg/m$^2$

MTD definition and Phase 2 dose
- Highest dose level at which 0 or 1 of 6 subjects experiences a DLT
- Phase 2 dose may be any dose at or below the MTD

TH-302 administration
- Administered IV over 30-60 minutes on Days 1, 8 and 15 of every 4-week gemcitabine cycle

Gemcitabine administration
- Gemcitabine is administered at full dose on the standard schedule
- Gemcitabine administration is initiated 2 hours after the completion of the TH-302 administration

Once MTD established
- 36 additional patients were enrolled at the MTD or lower dose to determine a recommended Phase 2 dose in first-line pancreatic cancer

Patient Assessments
- Response was evaluated by RECIST 1.0 criteria after every even cycle
- CA19-9 tumor marker was measured every cycle
- Toxicity was assessed every visit using NCI-CTCAE version 3.0

## Key Inclusion Criteria

- IRB approved informed consent
- Locally advanced unresectable or metastatic pancreatic ductal adenocarcinoma proven by histology or cytology previously untreated with chemotherapy other than radiosensitizing doses of 5-FU
- Recovered from toxicities of prior therapy
- ECOG performance status 0 or 1
- Evaluable by RECIST (at least one target or non-target lesion)
- Adequate hematologic function: ANC ≥ 1500/mL, Platelets ≥ 100,000/mL, Hemoglobin ≥ 9 g/dL
- Serum creatinine ≤ ULN
- Adequate liver function with chemotherapy dependent levels for total bilirubin, AST and ALT.

## Key Exclusion Criteria

- Prior treatment with gemcitabine
- Prior treatment with more than 3 myelosuppressive cytotoxic chemotherapy regimens
- Symptomatic brain, leptomeningeal or epidural metastases (unless previously treated and well controlled for at least 3 months)
- Prior radiotherapy to more than 25% of the bone marrow
- Severe chronic obstructive pulmonary disease with hypoxemia or in the opinion of the investigator any physiological state leading to hypoxemia

## Demographics

Forty-seven subjects with previously untreated locally advanced unresectable or metastatic pancreatic adenocarcinoma were enrolled at 9 investigational sites between December 2008 and May 2010.

**Table 1: Patient Characteristics and Cancer History (N=47)**

| TH-302 Dose | 240 mg/m$^2$ | 340 mg/m$^2$ | 480-575 mg/m$^2$ | Total |
|---|---|---|---|---|
| | N=18 | N=23 | N=6 | N=47 |
| Sex (F / M) (N) | 9/9 | 13/10 | 3/3 | 25/22 |
| Age (yrs) | | | | |
| Median | 62 | 64 | 67 | 64 |
| Range | 49 - 83 | 41 - 79 | 57 - 80 | 41 - 83 |
| ECOG (N) | | | | |
| 0 | 5 | 13 | 4 | 22 |
| 1 | 13 | 10 | 2 | 25 |
| Any Metastases | | | | |
| Yes | 12 (67%) | 20 (87%) | 4 (67%) | 36 (77%) |
| No | 6 (33%) | 3 (13%) | 2 (33%) | 11 (23%) |
| Months since diagnosis of advanced/metastatic disease | | | | |
| Median | 1.0 | 0.7 | 0.9 | 0.9 |
| Range | 0.2 – 7.4 | 0.0 – 3.6 | 0.6 – 1.2 | 0.0 – 7.4 |
| Metastatic Sites (may be multiple sites) | | | | |
| Liver | 9 (50%) | 15 (65%) | 2 (33%) | 26 (55%) |
| Lung | 3 (17%) | 7 (30%) | 1 (17%) | 11 (23%) |
| Lymph | 2 (11%) | 9 (39%) | 2 (33%) | 13 (28%) |
| Peritoneum | 3 (17%) | 2 (9%) | 0 (0%) | 5 (11%) |
| Other site(s) | 2 (11%) | 3 (13%) | 0 (0%) | 5 (11%) |

## Study Drug Exposure

Study drug exposure is summarized (Table 2). The median time on treatment was 4 cycles; range 1-14+ cycles. Twenty patients completed 6 cycles and 8 other patients continue on study receiving therapy. The MTD was established to be 340 mg/m$^2$.

**Table 2: Study Drug Exposure**

| TH-302 Dose | 240 mg/m$^2$ | 340 mg/m$^2$ | 480-575 mg/m$^2$ | Total |
|---|---|---|---|---|
| | N=18 | N=23 | N=6 | N=47 |
| Number of Cycles | | | | |
| Median | 4.5 | 4 | 4.5 | 4 |
| Range | 1 - 11+ | 1 - 14+ | 3 - 6 | 1 - 14+ |
| Received 6 or more Cycles | 8 (44%) | 10 (43%) | 2 (33%) | 20 (43%) |

## Serious Adverse Events

Forty-nine serious adverse events (SAEs) have been reported in 26 patients. Twelve of these events in 10 patients have been reported as related to TH-302. These 12 events were single events of anaemia, liver abscess, pancytopenia, oesophagitis, stomatitis, vomiting, skin ulcer, haematuria and pyrexia and two events of genital pain and genital rash in one patient.

## Deaths

There were 30 deaths on-study including 26 deaths due to progressive disease. There were four deaths for other reasons: Klebsiella liver abscess considered related to study drug in the setting of progressive disease, cerebral infarct considered unrelated to study drug, myocardial infarction considered unrelated to study drug and Klebsiella sepsis secondary to bacterial peritonitis six months after study discontinuation.

## Adverse Events

Adverse events (AE) were reported in all 47 patients. AEs occurring in at least 20% of patients are summarized in Table 3. Fatigue, nausea, rash and constipation were the most commonly reported AEs. Nausea and vomiting were noted with TH-302 monotherapy and standard antiemetic prophylaxis for moderately emetogenic therapy (generally 5HT blocker and steroid) was implemented.

**Table 3: Non-laboratory adverse events regardless of relationship to study drug**

| Adverse event* | Number of Patients with an AE (%) | | | |
|---|---|---|---|---|
| TH-302 Dose | 240 mg/m$^2$ | 340 mg/m$^2$ | 480-575 mg/m$^2$ | Total |
| | N=18 | N=23 | N=6 | N=47 |
| Fatigue | 12 (67) | 14 (61) | 4 (67) | 30 (64) |
| Nausea | 6 (33) | 15 (65) | 4 (67) | 25 (53) |
| Rash** | 7 (39) | 13 (57) | 3 (50) | 23 (49) |
| Constipation | 6 (33) | 10 (43) | 5 (83) | 21 (45) |
| Diarrhoea | 7 (39) | 10 (43) | 2 (33) | 19 (40) |
| Dysgeusia | 5 (28) | 10 (43) | 3 (50) | 18 (38) |
| Alopecia | 5 (28) | 7 (30) | 4 (67) | 16 (34) |
| Vomiting | 4 (22) | 8 (35) | 3 (50) | 15 (32) |
| Stomatitis | 2 (11) | 8 (35) | 4 (67) | 14 (30) |
| Anorexia | 3 (17) | 6 (26) | 2 (33) | 11 (23) |
| Dyspnoea | 2 (11) | 4 (17) | 5 (83) | 11 (23) |
| Pyrexia | 1 (6) | 7 (30) | 2 (33) | 10 (21) |

* Coded with MedDRA; ** Preferred term includes the term "rash".

Less than half of the adverse events were considered related to TH-302 study drug (Table 4). The majority of the non-laboratory adverse events (95%) were grade 1 or grade 2.

**Table 4: Non-laboratory adverse events related to TH-302 occurring in ≥15% of subjects**

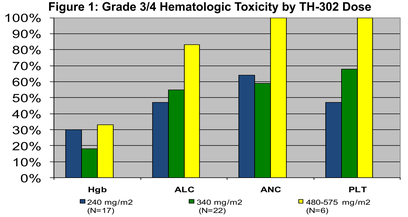
| Adverse event* | Number of Patients with an AE (%) | | | |
|---|---|---|---|---|
| TH-302 Dose | 240 mg/m$^2$ | 340 mg/m$^2$ | 480-575 mg/m$^2$ | Total |
| | N=18 | N=23 | N=6 | N=47 |
| Rash** | 7 (39) | 12 (52) | 3 (50) | 22 (47) |
| Fatigue | 8 (44) | 7 (30) | 2 (33) | 17 (36) |
| Dysgeusia | 5 (28) | 9 (39) | 3 (50) | 17 (36) |
| Nausea | 3 (17) | 9 (39) | 2 (33) | 14 (30) |
| Stomatitis | 2 (11) | 7 (30) | 4 (67) | 13 (28) |

* Coded with MedDRA; ** Preferred term includes the term "rash".

## Hematologic Toxicity

Hematologic toxicity has been evident across TH-302 dose levels with moderate evidence of a TH-302 dose dependent effect (Figure 1). Anemia and lymphopenia were often present at baseline with some worsening on the combination therapy. Hematologic toxicity, primarily thrombocytopenia, has been greater than would be expected for single agent gemcitabine.

**Figure 1: Grade 3/4 Hematologic Toxicity by TH-302 Dose**




## RECIST Best Response

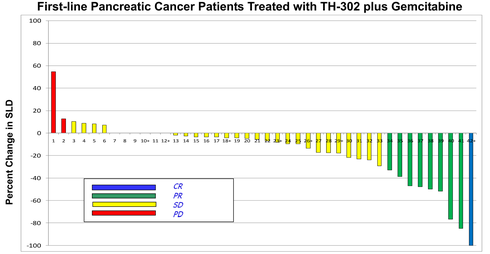
Forty-three patients had at least one evaluable post-treatment tumor assessment (Table 5) and nine patients (21%) had a complete response (CR) or partial response (PR) as the best response assessment. An additional 30 patients (70%) had stable disease (Figure 2). Four patients (9%) had progressive disease.

**Table 5: Best Response by RECIST***

| TH-302 Dose | Number of Patients Evaluable for Response (%) | | | |
|---|---|---|---|---|
| | 240 mg/m$^2$ | 340 mg/m$^2$ | 480-575 mg/m$^2$ | Total |
| | N=16 | N=21 | N=6 | N=43 |
| Complete Response | 0 (0%) | 1 (5%) | 0 (0%) | 1 (2%) |
| Partial Response | 0 (0%) | 6 (29%) | 2 (33%) | 8 (19%) |
| Stable Disease | 13 (81%) | 13 (62%) | 4 (67%) | 30 (70%) |
| Progressive Disease | 3 (19%) | 1 (5%) | 0 (0%) | 4 (9%) |

*Four patients not assessed for tumor response (patient decision – 2, adverse event - 1, clinical deterioration – 1)

**Figure 2: Waterfall Plot (N=42*):**
**First-line Pancreatic Cancer Patients Treated with TH-302 plus Gemcitabine**

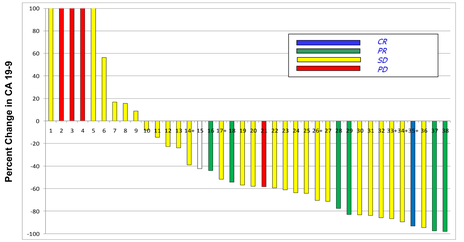



*One patient had stable disease based on non-target lesions only.

## CA19-9 Biomarker

Change in CA19-9: 41 of the 47 patients with pancreatic cancer enrolled with an elevated CA19-9. Follow-up assessments are available for 38 of the 41 patients. Of the 38 patients, 22 patients (58%) had a greater than 50% decrease in CA19-9; 13 patients (34%) had a decrease in CA19-9 greater than 70%.

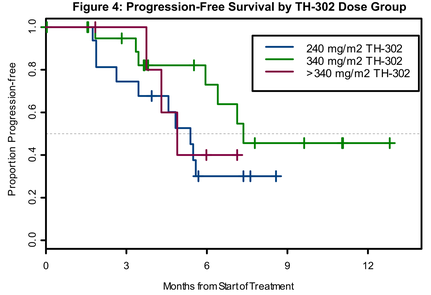
**Figure 3: Waterfall Plot (N=38):**
**First-line Pancreatic Cancer Patients Treated with TH-302 plus Gemcitabine**




## Progression-Free Survival

The median PFS for the 47 subjects was 5.95 months (95% CI: 4.83 months to not reached). Kaplan Meier curves are provided by TH-302 dose group in Figure 4. The median PFS across dose groups ranged from 4.9 months to 7.5 months.

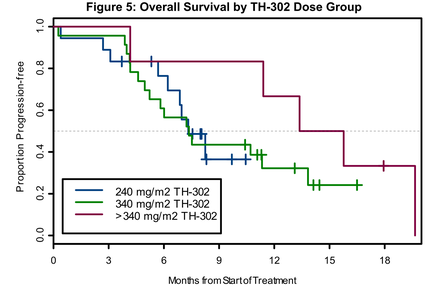
**Figure 4: Progression-Free Survival by TH-302 Dose Group**




## Overall Survival

The median overall survival was 8.5 months (95% CI: 6.9 months to 13.4 months). Kaplan Meier curves are provided by TH-302 dose group in Figure 5. The median OS across dose groups ranged from 7.3 months to 14.6 months.

**Figure 5: Overall Survival by TH-302 Dose Group**




## Conclusions

- TH-302 can be safely combined with full dose gemcitabine.
- The primary dose limiting toxicity was hematologic. While the contribution of TH-302 to the hematologic toxicity was not identifiable, greater hematologic toxicity than would be expected with single agent chemotherapy is evident.
- Rash and stomatitis are the most common TH-302 related toxicities and are rarely dose limiting.
- Higher response rates, longer PFS and longer OS are observed with TH-302 plus gemcitabine than have been reported with single agent gemcitabine in subjects with first-line pancreatic adenocarcinoma.
- A randomized Phase 2 study (NCT01144455) is actively enrolling subjects to better define the contribution of TH-302 in the combination regimen. The study has a planned enrollment of 165 subjects and is open in over 50 sites in the US.

We thank the patients, families and investigative site personnel for their participation.