Phase II Trial of SM-88 in Patients with Metastatic Pancreatic Cancer: Preliminary Results of the 1st Stage

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BACKGROUND

- Pancreatic cancer remains a clinically challenging disease with an 80% mortality rate within 12 months of initial diagnosis (ACS Estimates). Recent clinical trials have shown median overall survival of four to six months with single digit RECIST response rates in the second-line setting. (Conroy et al. 2011; NAPOLI-1[1,2])
- The standard of care remains toxic chemotherapy regimens (FOLFIRINOX or gemcitabine with nab-paclitaxel) with grade 3 or greater toxicity in over 50%[3].
- Currently, there are no FDA approved treatments specifically indicated for third-line metastatic pancreatic adenocarcinoma patients. Neither ASCO nor NCCN guidelines recommend any treatment for third-line pancreatic cancer patients.
- SM-88 is a novel anti-cancer regimen that consists of one investigational agent (D,L-alpha-metyrosine {D/L}), and three repurposed drugs (methoxsalen, phenytoin, and sirolimus).
- It is hypothesized that all four, including both the D/L isomers contribute to the anti-cancer properties of SM-88. Both the D/L isomers are believed to be distinct drugs with independent mechanisms of action.

TRIAL DESIGN

- Tyme-88-Panc (NCT# 03512756) is a 2 Part randomized, open-label Phase II of SM-88 in progressive metastatic pancreatic adenocarcinoma with at least 1 prior line of chemotherapy, and an Eastern Cooperative Oncology Group (ECOG) score ≤ 2.
- In Part 1, subjects were randomized to receive one of two D,L-alpha-metyrosine oral dosing regimens, 230 mg BID, or 460 mg BID.
- The oral doses of methoxsalen (10 mg QD), phenytoin (50 mg QD), and sirolimus (0.5 mg QD), were the same regardless of randomization.
- The present study describes the efficacy results from randomized Part 1 of Tyme-88-Panc.
- Pharmacokinetic data are presented on poster board E15 (J Clin Oncol 37, 2019 (suppl 4; abstr 277)
- Additional safety data is on poster board G8 (J Clin Oncol 37, 2019 (suppl 4; abstr 310)

METHODS

- Survival status is ongoing but reported here only as of Dec 31, 2018. KM curves were generated using standard methods. Subjects were censored if they were lost to follow up for any reason.
- CT imaging was performed at baseline and repeated every other cycle.
- Tumor response was determined according to RECIST 1.1 by BICR and the local investigator/PI separately.
- Blood samples, including for circulating tumor cell (CTC) analysis were collected at baseline, and at the start of each cycle.

ENROLLMENT & EVALUABLE SUBJECTS

- 85 subjects were consented for screening and 38 met criteria for randomization.
- 10 subjects did not complete at least one Cycle of SM-88 treatment (median 17 days; range 7 – 26 days total treatment), and were excluded from subsequent efficacy analyses per protocol.
- The present analysis includes data from the 28 evaluable subjects unless otherwise stated.

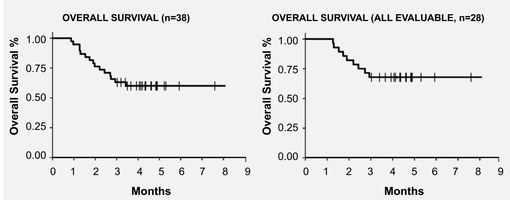
RESULTS

Demographics and Baseline Characteristics

The table below summarizes demographics and baseline characteristics for the 28 evaluable subjects.

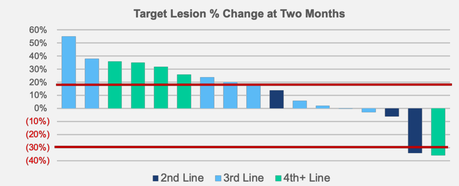
Age, years ± SD	66.9 ± 11.5
Sex, n (% female)	10 (35.7%)
Weight, kg ± SD	69.8 ± 15.1
Body Mass Index, BMI ± SD	24.1 ± 4.7
Race, n (%)	
White	27 (96.4%)
Asian	1 (3.6%)
Stage at Diagnosis	
1	1 (3.6%)
2	10 (35.7%)
3	8 (28.6%)
4	9 (32.1%)
Prior Radiotherapy, n (%)	8 (28.6%)
Prior Surgery, n (%)	11 (39.3%)
Prior Lines of Therapy, n (%)	
1	4 (14.3%)
2	14 (50.0%)
3	4 (14.3%)
4+	6 (21.4%)
Prior Therapy Type, (%)	
Gemcitabine	89.3%
Fluorouracil	85.7%
Irinotecan	67.9%
Platinum	71.4%
Immunotherapy	10.7%
Investigational agents	14.3%
PARP inhibitors	3.6%
Albumin	3.94 ± 0.36
CA-19.9, IU/mL (median, range)	2,562 (1.2 – 700,000)
NLR (neutrophil lymphocyte ratio) (median, range)	3.56 (1.4 – 13.2)
Alkaline Phosphatase, U/L ± SD	172 ± 148

Figure 1: Overall Survival Following Treatment with SM-88 for ITT and Evaluable Subjects



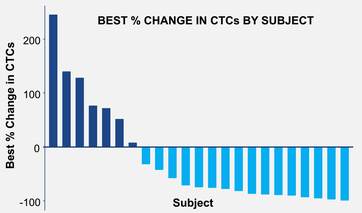
- As of Jan 6th, 2019, 67.8% (19 of 28) evaluable subjects remain alive at a median follow up of 4.3 months (range 1.3 to 8.3 months).
- No subjects were lost to follow up.

Figure 2: Best Percent Change in Target Lesion Measurement Following 2 Months of Treatment with SM-88



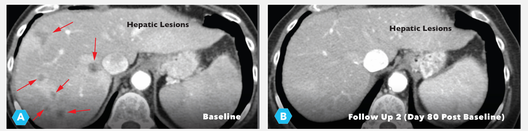
- 47.1% (8/17) of subjects achieved a clinical benefit (stable disease (7) or partial response (1)).
- 63.7% (7/11) of evaluable subjects with PERCIST reads achieved PET SD or greater SUV response.
- 11 subjects were not included as 2 month imaging data was not yet available.
- Two subjects with stable target lesions were deemed progressive disease based on non-target lesion growth or new lesions.
- Best percent change from baseline in the sum of longest diameters of target lesion determined by BICR or Investigator for 17 subjects.

Figure 3: Circulating Tumor Cell Response Following Treatment with SM-88



- 70% of subjects experienced a greater than 30% decline in CTC count that was maintained for at least one cycle.
- Median CTC decrease (best response) of 73% (range -100% to 242%).
- 96.5% of subjects had CTCs detectable at baseline (evaluable subject's median 105, range 6-712 CTCs/4mls).
- 9 patients had either a CA-19.9 or CEA decrease.
  - 2/3 with CA-19.9 reductions also had a CEA decrease
  - 2/8 with CEA reductions also had a CA-19.9 decrease

Figure 4: Representative Case Study

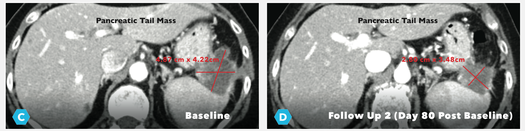


Hepatic Lesions Resolved

Background: 61 year old female with stage IV PDAC. Hx of GA with Indoximod, FOLFIRINOX, and Pembrolizumab.

SM-88 Therapy: Monotherapy in the fourth line setting.

Tumor Marker Results: CA-19.9 decreased 90% after three months of therapy. Panel A shows several hepatic lesions at baseline that improve by the second follow up scan (Panel B). Similarly, Panel C and D demonstrate a reduction in a peripancreatic lymph node.



Tumor Mass Decreased By 31%

SAFETY

A detailed description of Tyme-88-Panc safety data can be found on poster board G8 (J Clin Oncol 37, 2019 (suppl 4; abstr 310). There was 1 related grade 4 hypotension. There was no significant deterioration of PRO by EORTC questionnaires.

REFERENCES

1. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. Conroy et al., NEJM, 2011 364 (19).
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3. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. Von Hoff DD, et al. N Engl J Med. 2013
4. Prospective comparison of invasive circulating tumor cells (iCTCs) vs PSA and mPFS in prostate cancer (PC) treated with SM-88. Journal of Clinical Oncology 36(15_suppl):e24072-e24072 · May 2018
5. Phase II pharmacokinetics of oral SM-88 in heavily pretreated advanced pancreatic ductal adenocarcinoma (PC). J Clin Oncol 37, 2019 (suppl 4; abstr 277)

CONCLUSIONS

- 68% of subjects were still alive at a median of 4.3 months of follow up
  - Based on a literature review of 21 studies, the estimated survival of a subject entering a third-line trial is approximately 2 months (ASCO GI poster C22 J Clin Oncol 37, 2019 (suppl 4; abstr 226)).
- Clinical benefit rate (SD and PR) of 47% has been observed to date
  - The response rate observed in second-line trials typically is usually <10%. In third-line trials, no responses are typically observed.
- CTCs, an early indicator of disease status, decreased in most patients may predict future clinical benefit.
  - The CTC response observed in Tyme-88-Panc was similar to that seen in the SM-88 Phase 1b/II prostate cancer trial.[4,5]
- Despite approximately 85% of subjects having had 2 or more prior lines of therapy, SM-88 was safe and well-tolerated in heavily pretreated patients with pancreatic cancer.

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