SM-88 THERAPY IN HIGH-RISK POOR PROGNOSIS PANCREATIC CANCER

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INTRODUCTION

- TYME conducted a multi-center*, open-label, dose optimization randomized Phase II trial evaluating SM-88 in advanced Pancreatic Ductal Adenocarcinoma (PDAC).
- SM-88 is the lead investigational therapy in the TYME Cancer Metabolism Based Therapies (CMBTs™) platform. SM-88 is an oral modified dysfunctional tyrosine that is hypothesized to disrupt cancer cell metabolism.
- SM-88 has demonstrated encouraging efficacy and a well-tolerated safety profile in 15 different tumor types, including solid tumors and hematologic malignancies across four separate studies.

BACKGROUND

- Refractory PDAC has no established therapy. Previously reported survival for third line PDAC patients is approximately 2.0 – 2.5 months (JCO 37, 2019 supp 4; 226).
- SM-88 (D,L-alpha-metyrosine, racemetyrosine) is a novel oral therapy used with low doses of methoxsalen, phenytoin and sirolimus.
- Previous studies with SM-88 demonstrated safety and efficacy in compromised patients (JCO 37, 2019 supp 4; 200. JCO 37, 2019 supp 4; 310). We now report an update of the dose selection phase as of April 25, 2019 (NCT03512756).

METHODS

- Phase II trial of PDAC with radiographic PD, after at least 1 prior line and ECOG PS ≤2. Patients randomized to 460 or 920 mg/d of SM-88; all received methoxsalen 10 mg, phenytoin 50 mg and sirolimus 0.5 mg per day.
- 99 patients were consented for screening and 49 met criteria for randomization.
- 10 patients did not complete at least one cycle of SM-88 treatment (median 17 days; range 7 – 26 total time on treatment) and were considered not evaluable for efficacy as per protocol. One patient had unreported survival data.

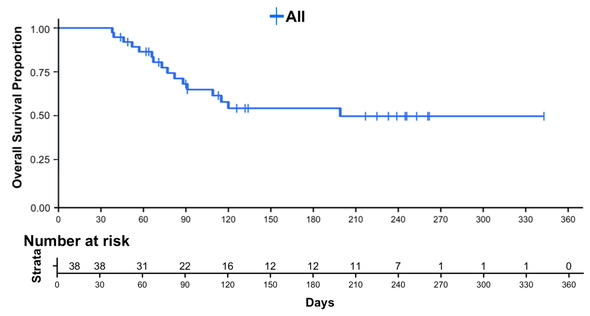
RESULTS

DEMOGRAPHICS	Intent to Treat (ITT) n=49	Evaluable n=38
Age, years ± SD	66.4 ± 10.5	66.6 ± 10.9
Gender, n (% female)	24 (49.0%)	18 (47.4%)
Body Mass Index, BMI ± SD	23.6 ± 4.4	23.5 ± 4.4
Race, n (%)		
White	44 (89.8%)	34 (89.5%)
Asian	2 (4.1%)	2 (5.3%)
Black or African American	3 (6.1%)	2 (5.3%)
Prior Radiotherapy, n (%)	12 (24.5%)	10 (26.3%)
Prior Surgery, n (%)	15 (30.6%)	13 (34.2%)
Prior Lines of Therapy, n (%)		
1	6 (12.2%)	5 (13.2%)
2	21 (42.9%)	16 (42.1%)
3	10 (20.4%)	7 (18.4%)
4+	10 (20.4%)	8 (21.1%)
Prior Therapy Type, n (%)		
Gemcitabine	39 (79.6%)	31 (81.6%)
Fluorouracil	40 (81.6%)	30 (78.9%)
Irinotecan	36 (73.5%)	26 (68.4%)
Platinums	37 (75.5%)	27 (71.1%)
Taxanes	31 (63.3%)	26 (68.4%)
Immunotherapy	6 (12.2%)	3 (7.9%)
Investigational agents	8 (16.3%)	5 (13.2%)
PARP inhibitors	2 (4.1%)	2 (5.3%)
Albumin, g/dL ± SD	3.8 ± 0.4	3.9 ± 0.4
CA-19.9, IU/mL (median, range)	2,674 (0.8 - ~700,000)	2,605 (0.8 - ~700,000)
NLR (neutrophil lymphocyte ratio) (median, range)	3.9 (0.9 - 13.3)	3.7 (0.9 - 11.8)
Alkaline Phosphatase, U/L ± SD	200.0 ± 145.3	204.4 ± 153.7
Circulating Tumor Cells (CTCs), count normalized to 4 mL volume ± SD	141.5 ± 138.3	144.6 ± 149.6

- Demographics and baseline characteristics were similar between the ITT and evaluable groups.
- More than 80% of patients received at least two prior lines of therapy.
- All patients had radiographic progressive disease.
- Before beginning SM-88, there were 22 disease-related SAEs during screening reported by 15 patients among the 99 screened, including six Grade 5 events. After beginning SM-88, two patients reported four Grade 3 – 4 SAEs (abdominal pain, arthralgia, and hypotension) reported to be at least possibly related.
- 94% of ITT subjects (46/49) experienced an aggregate of 365 AEs, with 63 of such AEs (17%) at least possibly related and 12 (19%) Grade 3 – 4.

OVERALL SURVIVAL

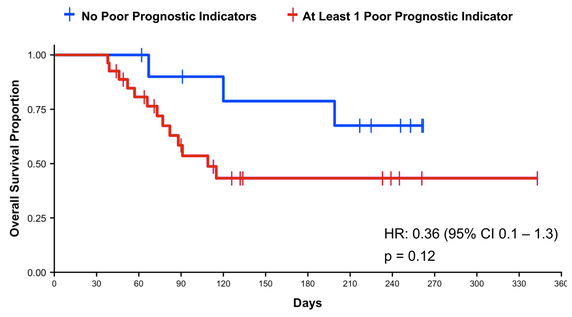
Evaluable (n=38) *Figure 1*



- The preliminary median Kaplan-Meier (KM) derived overall survival of the evaluable population is currently 6.4 months.
- The preliminary median KM derived overall survival of the ITT population is currently 3.6 months.

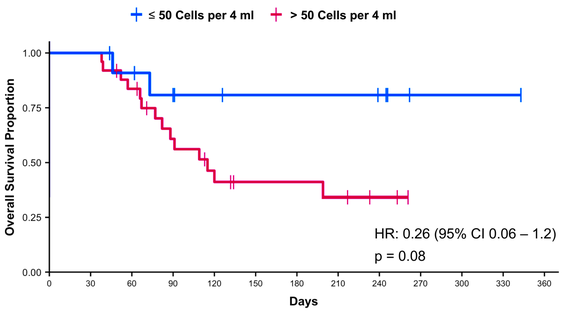
BASELINE PROGNOSTIC INDICATORS ASSOCIATED WITH SHORTENED SURVIVAL

Baseline Clinical Prognostic Indicators *Figure 2a*



- Poor prognostic indicators were defined as any of the following at baseline: > 2 prior lines, age > 75 y/o, or albumin < 3.5.
- Poor prognostic indicators at baseline trended toward reduced OS.

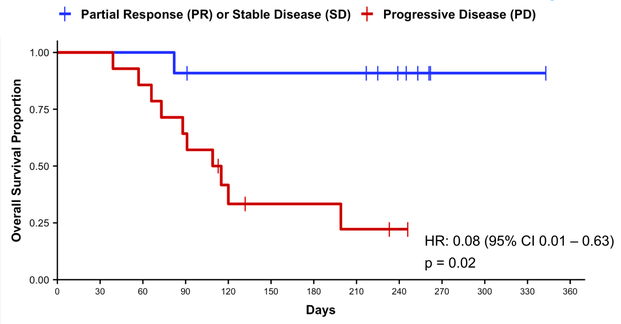
Baseline CTC Count as a Prognostic Indicator *Figure 2b*



- Patients with baseline CTCs ≤50 cells/4mL trended toward improved OS.
- Additional analysis with baseline CTCs ≤10 cells/4mL showed similar results.

SD/PR ASSOCIATED WITH GREATER SURVIVAL

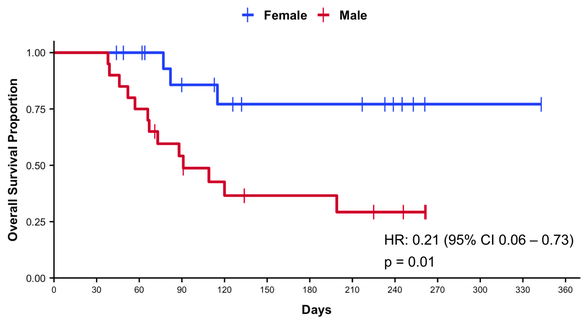
Disease Control *Figure 3*



- 44% (11/25) RECIST Clinical Benefit Rate (SD or PR).
- Patients who achieved at least SD by first assessment demonstrated statistically significant greater survival than PD patients.

FEMALES ACHIEVED GREATER SURVIVAL

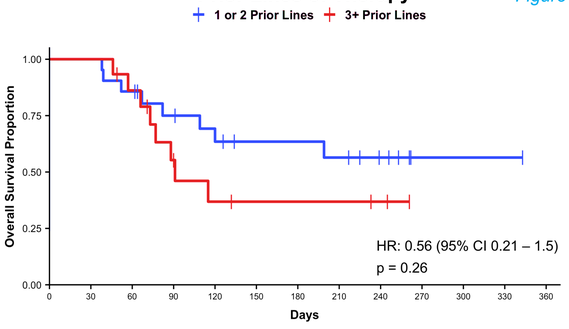
Gender *Figure 4*



- Females demonstrated improved survival vs. males.
- Currently evaluating potential covariates to better understand this observation.

3+ PRIOR LINES ASSOCIATED W/ REDUCED SURVIVAL

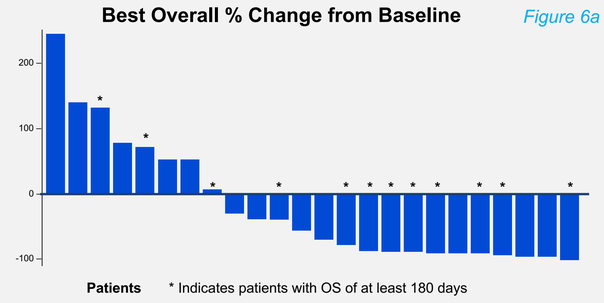
Prior Lines of Therapy *Figure 5*



- Patients with three or more prior lines of treatment demonstrated reduced OS.
- Future planned trials are focused on patients with one or two prior lines.

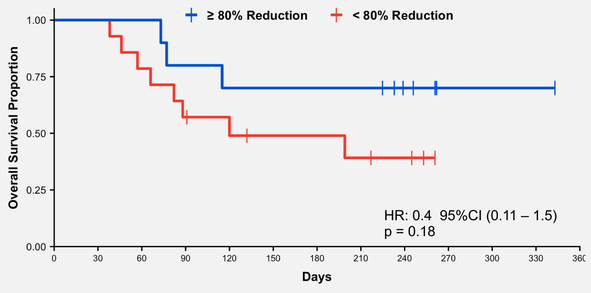
CIRCULATING TUMOR CELLS (CTCs) AND OVERALL SURVIVAL

Best Overall % Change from Baseline *Figure 6a*



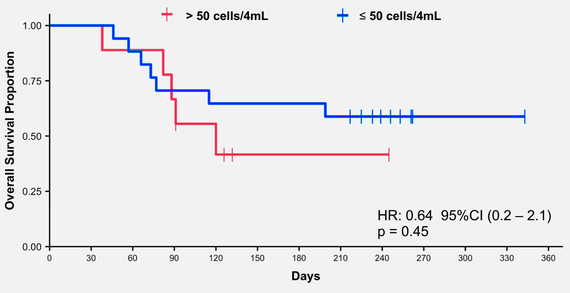
- The median percentage decrease of CTCs is 63%.
- 56.3% (9/16) patients with CTC decreases had OS of at least 180 days vs. 37.5% (3/8) of patients with CTC increases.

Best CTC Response by % Reduction (n=24) *Figure 6b*



- Patients who had at least an 80% CTC reduction trended towards greater survival.

Best CTC Response by Absolute Number *Figure 6c*



- Patients with ≤ 50 cells/4mL at nadir trended towards greater survival.

- The three longest survivors (261+, 262+, and 343+ days) had both a >80% reduction and <50 cells/4mL.

DISCUSSION

- SM-88 demonstrated encouraging survival trends. In addition, certain efficacy indicators correlated with greater OS, including achieving SD or better (CBR) and decreases in CTCs.
- Using a next generation CTC quantitation assay, 50 cells/4 mL represents the approximate equivalent of the lower limit of detection of previous generation assays (Transl Oncol 6, 2013).
- Baseline CTCs may be a useful predictive indicator of survival prognosis in advanced PDAC. Furthermore, decreases in CTC count during SM-88 therapy correlated with improved survival.
- Female patients achieved greater overall survival. This preliminary observation warrants further clinical investigation.
- Consistent with prior studies, SM-88 was well tolerated across all patient sub-types.
- In a previous study of patients with prostate cancer, SM-88 treatment was also associated with a reduction of CTC count (JCO 37, 2019 supp 7S; 83). This is now the second report showing that SM-88 is associated with CTC reduction.
- The 920 mg/day dose has been selected for further evaluation in anticipated future SM-88 pancreatic pivotal registrational trials.

CONCLUSIONS

- SM-88 OS trend is encouraging in this poor prognosis patient population.
- Several encouraging efficacy markers (reduction in CTCs; achieving SD or better) correlate with greater survival.
- Further investigation will be conducted into the prognostic indicators associated with longer survival.
- SM-88 was well tolerated.
- Further SM-88 pivotal trials in pancreatic cancer are planned as well as evaluation in other tumor types.

REFERENCES

- Manax et al. Designing clinical trials in 3L+ pancreatic cancer. J Clin Oncol 37, 2019 (suppl 4; abstr 226)
- Noel et al. Feasibility of SM-88 in PC after multiple prior lines and ECOG < 2 J Clin Oncol 37, 2019 (suppl 4; abstr 310)
- Noel et al. Phase II trial of SM-88 in patients with metastatic pancreatic cancer: Preliminary results of the first stage. J Clin Oncol 37, 2019 (suppl 4; abstr 200)
- Noel et al. Phase II pharmacokinetics of oral SM-88 in heavily pretreated advanced pancreatic ductal adenocarcinoma (PC). J Clin Oncol 37, 2019 (suppl 4; abstr 277)
- Gartrell et al. Evaluating non-hormonal therapy in a Phase II trial of SM-88 for rising PSA prostate cancer. J Clin Oncol 37, 2019 (suppl 7S; abstr 83)
- Harb et al. Mutational analysis of circulating tumor cells using a novel microfluidic collection device and qPCR assay. Transl Oncol 6(5): 528–538, 2013

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