Phase II Monotherapy Efficacy of Cancer Metabolism Targeting SM-88 in Heavily Pre-Treated PDAC Patients

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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) 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).

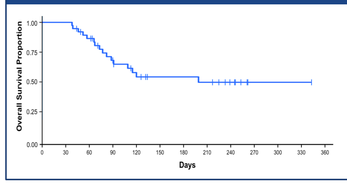
RESULTS

Table 1: **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+	41 (83.7%)	31 (81.6%)
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

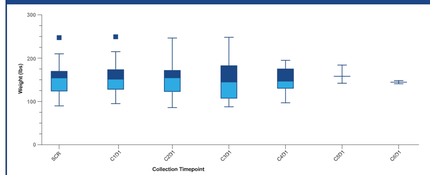
- Demographics and baseline characteristics were similar between the ITT and evaluable groups.
- More than 80% of patients received at least two prior lines of therapy.
- All patients had radiographic progressive disease at baseline.

Figure 1: **OVERALL SURVIVAL (n=38)**



- The preliminary median Kaplan-Meier (KM) derived overall survival (OS) 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.

Figure 2: **WEIGHT ON SM-88**



- 94.4% (34/36)[1] of patients' weight remained within 10% of baseline.
- 38.9% (14/36)[1] of patients gained weight after one cycle of SM-88.

[1]Two patients did not report weight.

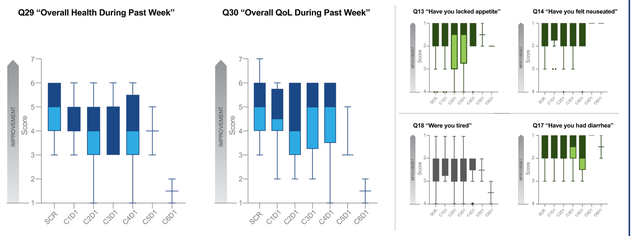
Table 2: **TUMOR TEXTURE AND CTCs**

VARIABLE		CIRCULATING TUMOR CELLS		% CHANGE CTC		OVERALL SURVIVAL	
		PEARSON COEFFICIENT	P-VALUE	PEARSON COEFFICIENT	P-VALUE	PEARSON COEFFICIENT	P-VALUE
Largest Lesion Metastasis							
Mean (mean, Std. Dev.)	(5.48, 12.89)	0.586	**0.007**	-0.256	0.277	0.025	0.916
Std. Dev.	(6.43, 11.89)	0.226	0.339	-0.084	0.725	0.666	**0.001**
Mean Positive Pixel (MPP) Value	(50.31, 13.49)	0.544	**0.013**	-0.196	0.407	0.483	**0.031**
Skewness	(0.09, 0.42)	-0.046	0.846	0.06	0.801	-0.357	0.122
Kurtosis	(3.41, 0.68)	-0.451	**0.046**	0.521	**0.019**	-0.341	0.141

- Radiomic analysis of tumor texture correlated with CTCs at baseline (r=0.59, p=0.007*).
- In addition, tumor texture was closely associated with the percentage change in CTCs on treatment (p=0.019*) and OS (Logrank p=0.001*).

*unadjusted p

Figure 3: **GLOBAL ASSESSMENT OF HEALTH AND QUALITY OF LIFE (QOL)***



*One patient did not have any available values to contribute to this analysis.

- Generally, patients maintained QOL and global EORTC questionnaire health scores throughout their treatment with SM-88.
- Patients reported generally low levels of GI-related symptoms (decreased appetite; nausea; vomiting; diarrhea), which are commonly reported while on chemotherapy-based treatments. There were no significant increases in symptom levels from baseline while on SM-88.
- Scores for specific pain- and fatigue-related questions showed that patients reported generally low levels of symptoms.

Table 3: **ADVERSE EVENTS (AEs)**

SERIOUS ADVERSE EVENTS[1]

Grade	Unrelated: Before Starting SM-88	Unrelated: On SM-88	At Least Possibly Related: On SM-88
1 / 2	3	4	0
3 / 4	13	29	4
5	6	3	0
Total	22	36	4

[1] Reported by number of events

	Unrelated	At Least Possibly Related	Total n=38
Treatment Emergent Adverse Events (TEAEs) Occurring In At Least 10% Of Patients[2]			
Abdominal Pain	13	2	**15 (39.5%)**
Fatigue	6	5	**11 (28.9%)**
Constipation	8	1	**9 (23.7%)**
Nausea	6	3	**9 (23.7%)**
Anorexia	8	0	**8 (21.1%)**
Diarrhea	5	2	**7 (18.4%)**
Vomiting	3	4	**7 (18.4%)**
Dyspnea	5	1	**6 (15.8%)**
Hypoalbuminemia	4	1	**5 (13.2%)**
Summary of Grade 3 – 4 TEAEs by Prior Line[2]			
Grade 3-4 TEAEs with 1 Prior Line	1	0	**1 (5.6%)**
Grade 3-4 TEAEs with 2 Prior Lines	5	2	**7 (38.9%)**
Grade 3-4 TEAEs with ≥ 3 Prior Lines	7	3	**10 (55.6%)**

[2] Reported by number of patients

- 37/38 (97.4%) patients reported any TEAE, with 32/37 (86.5%) reporting more than one event, and 18/37 (48.6%) reporting any Grade 3 – 4 events.
- TEAEs were not different between the 230mg BID and 460mg BID groups.
- No deaths (Grade 5 events) were related to SM-88, and the majority of these events (6/9, 66.7%) occurred before starting SM-88.
- 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 separate Grade 3 – 4 SAEs (abdominal pain; arthralgia; and hypotension) reported to be at least possibly related to SM-88.

METHOD

- Randomized phase II of 460mg vs 920mg per day of SM-88 in patients with radiographic PD, at least 1 prior line, and ECOG PS ≤2. All patients also received MPS (methoxsalen 10 mg, phenytoin 50 mg, and sirolimus 0.5 mg per day). There was no restriction on the size, number, or site of metastases nor baseline CA-19.9 or CTCs (NCT03512756).
- 99 patients were consented for screening and 49 met criteria for randomization (the ITT population).
- As of April 25, 2019, 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 the dose finding protocol. One additional patient had unreported survival data.
- Radiomics were performed on largest lesions at baseline selected by blinded independent central review with an SSF2 (spatial scale filtration) based on the methods of Weiss et al., 2014.

CONCLUSIONS

- SM-88 OS trend is encouraging in this poor prognosis patient population.
- Several encouraging efficacy markers correlate with greater survival.
- Radiomics found an association with SM-88 use, baseline tumor characteristics, CTC response, and OS.
- Further investigation will be conducted into the prognostic indicators associated with longer survival.
- SM-88 was well tolerated in this patient population.
- Further SM-88 pivotal trials in pancreatic cancer are planned as well as evaluation in other tumor types.

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.
- The 920 mg/day dose has been selected for further evaluation in anticipated future SM-88 pancreatic pivotal registrational trials.
- Overall stability of weight in this population is of note, as patients with pancreatic cancer typically experience noticeable, but unintentional, weight loss, which is a clinically meaningful indicator of poor prognosis (Hendifar et al., 2018; Nemer et al., 2017).
- Adverse events on SM-88 were reported less frequently overall than those commonly observed on other therapies for pancreatic cancer (Wang-Gillam et al., 2016).
- Although exploratory, radiomics could potentially identify patients who may be more likely to benefit from SM-88 used with MPS. Additional prospective trials are needed to confirm this hypothesis.

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