CTC-based Efficacy of SM-88 Correlates with Overall Survival in Advanced Pancreatic Cancer

Marcus Smith Noel[1] Andrea Wang-Gillam[2] Allyson J. Ocean[3] Sant Chawla[4] Vincent Chung[5] Ron Korn[6] Giuseppe Del Priore[7] Vincent J. Picozzi[8]

[1]University of Rochester Wilmot Cancer Institute [2]Washington University in St. Louis [3]Weill Cornell Medical College [4]Sarcoma Oncology Center [5]City of Hope [6]Imaging Endpoints [7]TYME Inc. [8]Virginia Mason Medical Center

INTRODUCTION

- SM-88 (racemetyrosine) is an oral modified dysfunctional tyrosine hypothesized to disrupt cancer cell metabolism with encouraging efficacy and a well-tolerated safety profile in 15 different tumor types across four separate cohorts[1].
- SM-88 used with MPS (methoxsalen, phenytoin, and sirolimus) may work in part by its ability to reduce CTCs as demonstrated in advanced pancreatic ductal adenocarcinoma (PDAC)[2] and prostate cancer[3].
- We previously reported preliminary results of a randomized Phase II with SM-88 demonstrating safety and efficacy in compromised mostly third-line PDAC patients[1,3] (see Fig 1a) and that circulating tumor cells (CTCs) were associated with survival in PDAC[4].
- We now report on additional exploratory analyses of CTCs and typical disease parameters including prior treatment, responses, and drug levels.

BACKGROUND

- PDAC patients have difficulty tolerating 3 or more lines of chemotherapy that are largely ineffective and associated with severe toxicity.
- SM-88 has previously reported a favorable lack of toxicity across 4 patient cohorts[1-5].
- There is a need for additional therapies, as demonstrated by previously reported survival for third-line PDAC patients of approximately 2.0 – 2.5 months[6].
- As previously reported at ESMO GI 2019, patients treated with SM-88 achieved a 44% (11/25) RECIST Clinical Benefit Rate (SD or PR)[2,4,5].
  - Patients on SM-88 who achieved at least SD by first assessment demonstrated statistically significant greater survival than PD patients (HR=0.08, p=0.02).
  - The preliminary median Kaplan-Meier (KM) derived overall survival of the evaluable population as of April 2019 is 6.4 months.
  - The preliminary median KM determined overall survival as of April 2019 of the intention to treat (ITT) population is 3.6 months.
- SM-88 used with MPS may become an option for this patient group.

METHODS

- 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 CA19.9 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.
- CTC results using a highly sensitive 3rd generation microfluidic magnetic capture technique were available for 24 patients for at least one cycle beyond baseline[8].

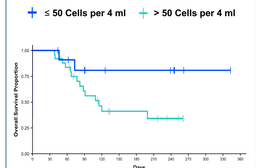
RESULTS

Table 1: **Demographics**

	Intent to Treat (ITT) n=49	Evaluable n=38	CTC Evaluable n=24
Age, years ± SD	66.4 ± 10.5	66.6 ± 10.9	64.9 ± 10.7
Gender, n (% female)	24 (49.0%)	18 (47.4%)	11 (45.8%)
Body Mass Index, BMI ± SD	23.6 ± 4.4	23.5 ± 4.4	23.7 ± 4.5
Race, n (%)			
White	44 (89.8%)	34 (89.5%)	22 (91.7%)
Asian	2 (4.1%)	2 (5.3%)	1 (4.2%)
Black or African American	3 (6.1%)	2 (5.3%)	1 (4.2%)
Prior Radiotherapy, n (%)	12 (24.5%)	10 (26.3%)	6 (25.0%)
Prior Surgery, n (%)	15 (30.6%)	13 (34.2%)	10 (41.7%)
Prior Lines of Therapy, n (%)			
1	6 (12.2%)	5 (13.2%)	3 (12.5%)
2	21 (42.9%)	16 (42.1%)	10 (41.7%)
3	10 (20.4%)	7 (18.4%)	4 (16.7%)
4+	10 (20.4%)	8 (21.1%)	7 (29.2%)
Prior Therapy Type, n (%)			
Gemcitabine	39 (79.6%)	31 (81.6%)	20 (83.3%)
Fluorouracil	40 (81.6%)	30 (78.9%)	21 (87.5%)
Irinotecan	36 (73.5%)	26 (68.4%)	18 (75.0%)
Platinums	37 (75.5%)	27 (71.1%)	20 (83.3%)
Taxanes	31 (63.3%)	26 (68.4%)	18 (75.0%)
Immunotherapy	6 (12.2%)	3 (7.9%)	3 (12.5%)
Investigational agents	8 (16.3%)	5 (13.2%)	2 (8.3%)
PARP inhibitors	2 (4.1%)	2 (5.3%)	1 (4.2%)
Albumin, g/dL ± SD	3.8 ± 0.4	3.9 ± 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)	1,981 (0.8 - ~700,000)
NLR (neutrophil lymphocyte ratio) (median, range)	3.9 (0.9 - 13.3)	3.7 (0.9 - 11.8)	3.7 (1.2 - 11.8)
Alkaline Phosphatase, U/L ± SD	200.0 ± 145.3	204.4 ± 153.7	164.4 ± 104.2
Circulating Tumor Cells (CTCs), count normalized to 4 mL volume ± SD	141.5 ± 138.3	144.6 ± 149.6	135.9 ± 162.8

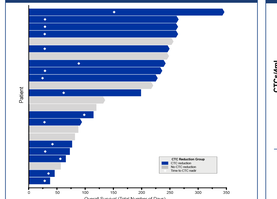
- Demographics and baseline characteristics were similar between the ITT, evaluable, and CTC evaluable groups.
- More than 80% of patients in Table 1 received at least two prior lines of therapy.
- All patients had radiographic progressive disease at enrollment.

Figure 1a: **Baseline CTC Count as a Prognostic Indicator**



- Patients with baseline CTCs ≤50 cells/4mL trended toward improved OS (HR=0.26, 95%CI 0.06-1.2, p=0.08).
- Additional analysis with baseline CTCs ≤10 cells/4mL showed similar results.
- Radiomic analysis of tumor texture on target lesions selected by Blinded Independent Centralized review correlated with CTC at baseline (r=0.59, p=0.007)[9,10].

Figure 1b: **Overall Survival by CTC Response (n=24)**



- Individuals who had a CTC reduction are represented in blue. Arrow heads indicate patients who were censored for survival.
- The occurrence of a CTC reduction appeared to be associated with an increase in survival.
- Of those patients whose overall survival extended past at least 6 months (180 days), 75.0% (n=9) experienced a reduction in CTC, while 25.0% (n=3) did not.

Figure 2: **Early CTC Trajectories by CTC Response Groups**

Figure 2a

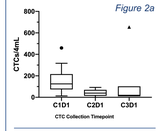
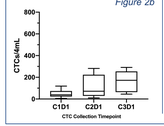


Figure 2b



- Of the 16 defined as achieving a CTC nadir on study: 56.3% (n=9) did so at Cycle 2; 18.8% (n=3) at Cycle 3; 6.3% (n=1) at Cycle 5; 6.3% (n=1) at End-of-Treatment; 12.5% (n=2) at the 28-day Follow-up visit.
- Within patients who experienced a CTC reduction, cell counts fell rapidly and appeared to hold steady over at least 2 cycles.
- CTC values were available for a limited number of patients at Cycle 3.
- Further analysis is needed to determine how CTCs respond over additional cycles.

Figure 3: **CTC Response as a Predictor of Survival in High Risk Groups**

OS By CTC Reduction in Patients with Progressive Disease

Figure 3a

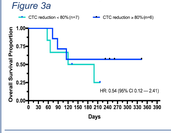
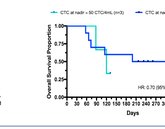


Figure 3b



OS By CTC Reduction in Patients with at Least 2 Prior Lines of Therapy

Figure 3c

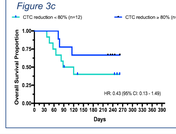
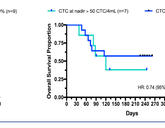


Figure 3d



- CTC reduction, whether defined as experiencing at least an 80% decrease, or achieving a minimum value of less than or equal to 50 cells/4mL, was associated with longer overall survival.
- Even among patients traditionally identified as being at relatively higher risk for worse outcomes (progressive disease in 3a and 3b; or having previously failed at least 2 lines of therapy in 3c and 3d), those with a reduction in CTC demonstrated longer overall survival.
- Future planned trials are focused on patients with one or two prior lines of therapy.

Figure 4: **SM-88 C_{max} and AUC_{0-6} Correlation with CTC Response (n=11)**

Figure 4a

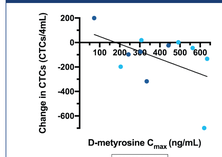


Figure 4b

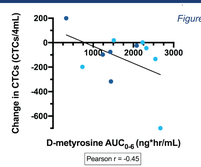


Figure 4c

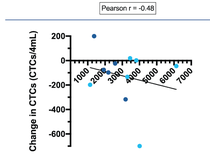
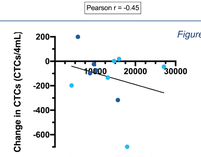


Figure 4d



- SM-88 is composed of D- and L-isomers, and the effects of each isomer on CTC response were investigated. These analyses included all 11 patients who had both CTC and PK data available[7].
- Steady state levels of D- and L-metyrosine C_{max} and AUC_{0-6} were correlated with changes in CTCs from baseline to nadir, with slightly stronger correlations for the D-metyrosine.
- One subject was excluded from this analysis due to ineligibility secondary to renal failure at screening (creatinine clearance <40).

Tables 2 and 3: **Key Hematologic and Serum Parameters by CTC Response**

Table 2: **Key descriptive and related prognostic factors between CTC response groups (n=24)**

		CTC Reduction (n=16)	No CTC Reduction (n=8)
Dose (n, %)	Higher (920)	8 (50.0%)	3 (37.5%)
	Lower (460)	8 (50.0%)	5 (62.5%)
RECIST Status (n, %)	SD or PR	5 (31.3%)	3 (37.5%)
	PD	8 (50.0%)	5 (62.5%)
	Unknown	3 (18.8%)	0 (0.0%)
Weight (median, IQR)	C1D1	154.0 (133.8 – 170.5)	156.8 (129.3 – 177.0)
	C2D1	156.0 (129.0 – 173.3)	158.1 (130.5 – 176.0)
	C3D1	156.9 (127.0 – 180.0)	145.9 (126.0 – 173.0)
Leptin (median, IQR)	C1D1	1.2 (0.9 – 4.7)	3.8 (2.4 – 13.3)
	C2D1	2.1 (0.9 – 4.2)	5.6 (2.2 – 12.9)
	C3D1	1.9 (1.3 – 4.2)	9.3 (3.4 – 17.6)
Albumin (median, IQR)	C1D1	3.9 (3.7 – 4.0)	3.8 (3.7 – 4.1)
	C2D1	3.9 (3.7 – 4.1)	3.8 (3.5 – 4.0)
	C3D1	3.8 (3.8 – 3.9)	3.7 (3.4 – 4.1)
CA 19.9 (median, IQR)	C1D1	2689.3 (276.4 – 19,294.8)	1286.2 (3.2 – 20,132.0)
	C2D1	3981.6 (334.9 – 37,805.8)	1732.1 (5.2 – 28,462.8)
	C3D1	779.0 (213.3 – 1447.6)	3337.0 (1677.5 – 20,482.2)
CEA (median, IQR)	C1D1	6.1 (4.6 – 29.1)	12.5 (2.0 – 78.2)
	C2D1	9.3 (5.3 – 34.6)	15.3 (2.6 – 78.9)
	C3D1	6.5 (4.5 – 13.2)	7.9 (4.8 – 39.4)

Table 3: **Key hematologic measures by CTC response groups (n=24)**

		CTC Reduction (n=16)	No CTC Reduction (n=8)
NLR (median, IQR)	C1D1	4.2 (2.6 – 7.7)	2.7 (2.2 – 3.9)
	C2D1	3.7 (2.4 – 5.6)	2.9 (2.2 – 5.4)
	C3D1	2.9 (2.2 – 4.0)	2.8 (2.0 – 3.7)
% Neutrophils (median, IQR)	C1D1	68.4 (60.2 – 78.7)	61.0 (55.8 – 69.0)
	C2D1	67.2 (61.1 – 74.1)	61.8 (58.2 – 71.1)
	C3D1	66.5 (57.6 – 70.6)	63.5 (58.8 – 65.5)
% Lymphocytes (median, IQR)	C1D1	15.6 (10.1 – 23.2)	21.8 (17.3 – 25.3)
	C2D1	18.0 (14.1 – 25.9)	20.3 (13.8 – 23.7)
	C3D1	21.8 (16.5 – 26.4)	22.0 (18.0 – 27.6)
Leukocytes (WBC) (median, IQR)	C1D1	5.9 (4.5 – 6.9)	4.8 (4.2 – 6.4)
	C2D1	5.1 (4.2 – 5.8)	5.2 (4.5 – 5.9)
	C3D1	5.1 (4.6 – 6.1)	4.9 (4.3 – 6.4)
% Monocytes (median, IQR)	C1D1	8.0 (7.8 – 10.3)	10.5 (9.8 – 12.3)
	C2D1	9.5 (8.0 – 12.3)	11.5 (6.8 – 12.3)
	C3D1	9.0 (9.0 – 11.3)	12.0 (8.0 – 12.0)

- Key hematologic measures were examined in both CTC response groups.
- In those with CTC reduction, NLR decreased overall from Cycle 1 to 3.
- CTC reductions were not associated with differences in other hematologic parameters, including: hematocrit; platelets; erythrocytes; MCV; % eosinophils.
- Weight and leptin remained stable in individuals who experienced CTC reductions.
- In patients who did not experience a CTC reduction, weight decreased, and leptin increased.
- While on treatment, 3 patients achieved a CA 19.9 reduction ≥80%, and 7 patients achieved a CEA reduction >20%; the total number of patients with either reduction was 9.
- These differences between groups were limited by small sample size and not statistically significant.

CONCLUSIONS

- Based on this analysis, patients reaching a certain threshold of CTCs appeared to have prolonged survival.
- CTC reductions while on SM-88 used with MPS, were associated with greater overall survival across numerous poor prognosis categories.
- Patients with progressive disease on trial had an increase in OS if their CTCs declined.
- CTC decline was correlated with the C_{max} and AUC_{0-6} of the D isomer and less so with the L isomer.

DISCUSSION

- Refractory heavily pretreated PDAC has no established therapy. Based on safety and efficacy, SM-88 used with MPS may have a role in this recalcitrant patient group.
- CTC reduction may be considered a potential tumor marker for patients treated for pancreatic cancer. Further exploration is needed, including additional radiomics analyses.

REFERENCES

1. Stiega et al.A first-in-human study of the novel metabolism-based anti-cancer agent SM-88 in subjects with advanced metastatic cancer. Invest New Drug 2019
2. 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)
3. 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)
4. 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)
5. Noel et al. Annals of Oncology 2019, Volume 30, Issue Supplement_4, July 2019, mdz155058
6. Manax et al. Designing clinical trials in 3L+ pancreatic cancer. J Clin Oncol 37, 2019 (suppl 4; abstr 226)
7. 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)
8. 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
9. Cozzi et al. Computed tomography based radiomic signature as predictive of survival and local control after stereotactic body radiation therapy in pancreatic carcinoma PLoS One. 2019; 14(1): e0210756
10. Korn, RL, Rahmanuddin S and Borazanci, E. (2019). Use of Precision Imaging in the Evaluation of Pancreas Cancer. In Nature, Precision Medicine in Cancer Therapy, Cancer Treatment and Research (Ed. D. D. Von Hoff and H. Han) pp. 209-236

*** OTHER PARTICIPATING INSTITUTIONS:**

H. Lee Moffitt Cancer Center – Florida
Karmanos Cancer Institute – Michigan
Ohio State University – Ohio
University Medical Center of New Orleans – Louisiana
New York Cancer and Blood Specialists – New York
Cancer Center of Central Connecticut – Connecticut

CORRESPONDING AUTHOR:
(e): Giuseppe.DelPriore@TymeInc.com
(ph): +1-917-634-6165