Phase 2/3 Study of SM-88 in Patients With Metastatic Pancreatic Cancer

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BACKGROUND

- **SM-88** (racemetyrosine, TYME Inc): a dysfunctional tyrosine derivative used with MPS (methoxsalen 10mg, phenytoin 50mg and sirolimus 0.5mg); SM-88 is an investigational compound that is not approved in any disease indication. SM-88 is believed to disrupt protein synthesis machinery, induce oxidative stress, and alter autophagy and immune function[1]
  - SM-88 was well tolerated with improvement in survival among select heavily pretreated PDAC patients who achieved stable disease (HR 0.08, p = 0.02)[2]
  - Circulating tumor cells (CTCs) have been shown to be prognostic in identifying a PDAC subgroup that may be more likely to benefit from SM-88. Preliminary radiomic analysis of the largest metastases at baseline correlated with baseline CTCs[3]

1)Therapeutic potential of targeting amino acid metabolism in pancreatic cancer. M. Fernandez-Zapico, D. W. Kim, P. Philip, A. Vandell, J. Eckard, R. Korn, G. Del Priore, D. Simeone. Cancer Res December 15 2019 (79) (24 Supplement) B15; **DOI:** 10.1158/1538-7445.PANCA19-B15

2)SM-88 therapy in high risk poor prognosis pancreatic cancer (PDAC). M. S. Noel, A. Wang-Gillam, A. J. Ocean, S. P. Chawla, V. Chung, G. Del Priore, and V. J. Picozzi. Journal of Clinical Oncology 2019 37:15_suppl, e15714-e15714

3)Phase II monotherapy efficacy of cancer metabolism targeting SM-88 in heavily pre-treated PDAC patients. A. Ocean, M. Noel, A. Wang-Gillam, S. Chawla, V. Chung, S. Pant, R. Korn, G. Del Priore, V. Picozzi. Annals of Oncology (2019) 30 (suppl_5): v253-v324. 10.1093/annonc/mdz247

METHODS

- Currently Enrolling: prospective open-label RCT (TYME-88-Panc Part 2, NCT03512756) after 2 prior lines for metastatic PDAC. **SM-88** vs. physician/patient choice chemotherapy **standard of care** (SOC capecitabine, or gemcitabine, or 5-FU)
- Preliminary analyses of randomized portion of the trial to evaluate potential role of SM-88 in metastatic PDAC through analysis of **CTCs** and **passively acquired biometrics data** from a wearable device with available data as of September 15, 2020
- CTCs (n=27 with available data): Isolated CTCs collected each cycle on Day 1, isolated, enumerated by flow cytometry using the epithelial cell surface marker Epi+ and cellular uptake of green fluorescent labeled CAM (GCAM+). A cell adhesion matrix (CAM) used to enrich CTCs and cells in clusters floating in the medium after 24-hour culture
  - Four phenotypic CTCs enumerated: Epi+, GCAM+, Epi+ floating fraction, GCAM+ floating fraction
- Biometrics (n=20 with available data): Passively acquired data, including total number of steps taken per day and heart rate, collected via wearable technology (Fitbit) worn continuously by subjects
  - Parameters examined by those who died early during the trial (within 3 months of Randomization) vs. those who did not
  - Following two global questions from EORTC QLQ-C30 analyzed for correlation with biometric parameters: Question 29 (Q29), "How would you rate your overall health during the past week?" and Question 30 (Q30), "How would you rate your overall quality of life during the past week?"

Study Identifier: NCT03512756

PIVOTAL — SM-88 used with MPS in Patients with Metastatic Adenocarcinoma of the Pancreas Whose Disease Has Progressed or Reoccurred

KEY ELIGIBILITY CRITERIA

- Histologically or cytologically confirmed pancreatic adenocarcinoma
- Received exactly two prior lines of systemic therapy
- Adequate organ function

DESIGN

SCREENING → Randomized 1:1 → SM-88 (N=~125) / Investigator-chosen Therapy (N=~125)

Treatment until unacceptable toxicity, disease progression or any treatment discontinuation criteria are met

ENDPOINT(S)

Primary: OS

Secondary*: PFS, CBR, and QoL

Key Exploratory Endpoints*: Biomarker analysis, including CTCs, and wearable device data

*Other secondary and exploratory endpoints will also be captured.

RESULTS

Table 1: **Demographics and Descriptive Characteristics (n=38)**

Age (yr), mean (range)	65 (48 – 86)
BMI, mean (range)	24.6 (18.8 – 38.7)
Female, n (%)	15 (39.5%)
Race, n (%)	
White	29 (76.3%)
Asian	6 (15.8%)
CA 19.9, mean (range)	23,678.2 (2.9 – 422,000.4)
Albumin (g/dL), mean (range)	3.8 (2.7 – 4.6)

- As of September 15, 2020:
  - 67 subjects consented
  - 38 subjects randomized and evaluable
- All subjects were randomized to either SM-88 (920 mg/day) or physician/patient choice chemotherapy
  - 52.6% (20/38) on SM-88
  - 47.4% (18/38) on SOC

*Only 1 Grade 3 AE that was possibly related was reported in the SM-88 arm

Table 2a: **Adverse Events by Relatedness**

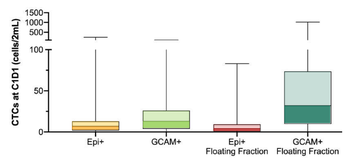
	SM-88	SOC
Possibly Related		
Grade 1 or 2	24 (23.76%)	12 (18.46%)
Grade 3	1 (0.01%)*	0 (0.00%)
Probably Related		
Grade 1 or 2	1 (0.01%)	10 (15.38%)
Grade 3	0 (0.00%)	3 (4.61%)
Related		
Grade 1 or 2	0 (0.00%)	6 (9.23%)
Grade 3	0 (0.00%)	2 (3.08%)

Table 2b: **Adverse Events By System Category**

	SM-88	SOC
Dermatologic	5 (19.2%)	5 (15.2%)
GI	7 (26.9%)	16 (48.5%)
LFTs	5 (19.2%)	1 (3.0%)
Pulmonary	2 (7.7%)	0 (0.0%)
Hematologic	2 (7.7%)	8 (24.2%)
Fatigue	2 (7.7%)	2 (6.1%)
Other	3 (11.5%)	1 (3.0%)
TOTAL	**26 (100.0%)**	**33 (100.0%)**

- Of treated subjects:
  - There were 166 AEs among 25 subjects of all those randomized (n=38)
    - Of those reporting any AE, 14 subjects (56.0%) were on SM-88 and 11 (44.0%) on SOC
  - Of all events, 10 (6.02%) were considered serious, and were reported among 4 subjects on SM-88 and 4 subjects on SOC
  - 25.7% (26/101) of AEs were deemed at least possibly related to SM-88; 50.8% (33/65) were deemed at least possibly related to SOC (p=0.001)
  - As shown in Tables 2a and 2b, all events deemed at least possibly related to SM-88 or SOC were Grade 1 or 2, except for: 4 hematologic events, 1 LFTs, and 1 other category (abdominal pain)

Figure 1: **Circulating Tumor Cells (CTCs) at Baseline**



- Four CTC subpopulation phenotypes defined by GCAM+, Epi+ and cluster status were enumerated and correlated to each other (r=0.03-0.71)
  - At least one CTC subpopulation was detected at baseline (mean 33.8 cells/2mL) in subjects with available data (n=27)
  - The longest metastatic lesion diameter at baseline correlated with baseline CTCs (r=0.55 for Epi+ cluster, p=0.05; r=0.52 for GCAM+cluster, p=0.07)
  - CTCs were successfully separated and enumerated at each subsequent cycle for further analyses

Figure 2: **Wearable Device Biometric Data**

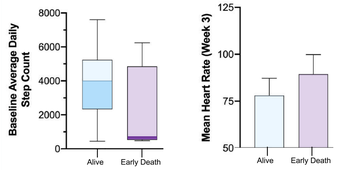
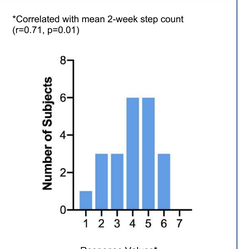


Figure 3: **EORTC QoL (Q30)**



- All subjects who received treatment were set up with a wearable device; 16 synchronized on C1D1; 20 had available data (synchronized within the first two weeks); 1 subject did not have the technical support available to feasibly collect data
- Median baseline daily step count during the first two weeks on treatment was 3993.8 (IQR: 2745.6 - 5078) for those alive (who did not experience early death) vs. 689.3 (IQR: 630.0-2083.6) among those who died early in evaluable subjects with available data (p=NS)
- Passively acquired mean heart rate during week 3 on trial was 89.3 (SD 10.5) among those who died early vs. 78.0 (SD 9.2) among those alive; medians were 87.0 for early deaths vs. 79.2 for alive (p=NS)
- Median baseline ECOG Performance Status was 1 for both groups
- Median Cycle 2 EORTC Q29 (overall health) score was 3 for early deaths vs. 4 for those alive; median Q30 (quality of life; QoL) score was 3 for early deaths vs. 4.5 for those alive
  - Mean steps during the first two weeks was correlated with EORTC Q30 responses (r=0.71, p=0.01)
- Median weight from Cycle 1 to 2 decreased by 2.5 lbs for early death vs. 0.5 lbs for alive

CONCLUSIONS

- In a preliminary exploratory analysis, mean daily step count during the first two weeks on treatment correlated with overall self-reported QoL
- Passively acquired biometrics from a wearable device can be collected for correlation with other clinical outcomes
- CTC collection and enumeration is also feasible for correlation with traditional trial outcomes
- Given that the longest lesion diameter is correlated with CTCs at baseline, additional radiologic feature analysis (e.g., radiomics) may be an important predictor of CTCs
- SM-88 was well tolerated with no treatment-related Grade 4 or 5 events

DISCUSSION

- Potentially, CTCs and/or biometric parameters may help predict clinical outcomes in patients with pancreatic cancer
- The significance of the four CTC subpopulation phenotypes warrant additional investigation
- Due to COVID-19, clinical trials are more reliant on methods of remote monitoring and data collection, including the use of telehealth tools, such as wearable devices for passively acquiring data. This trend may continue as trials move into the future. Further work will continue to explore the use of biometric data collected from wearable devices for association with clinically meaningful outcomes

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