Oral SM-88 plus MPS: An effective yet less toxic treatment option in second-line advanced pancreatic cancer? Final Phase II/III study results.

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BACKGROUND

- Patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) have poor prognoses.[1,2]
- SM-88 Regimen, which comprises oral SM-88 (racemetyrosine) plus 10 mg methoxsalen, 50 mg phenytoin, and 0.5 mg sirolimus (MPS), has previously shown clinical activity in mPDAC.[3] Oral SM-88 (racemetyrosine; D,L-alpha-metyrosine) is a dysfunctional derivative of tyrosine intended to be non-functional for protein synthesis and comprises an equal proportion of the D- and L- stereoisomers of alpha metyrosine.
- In prior first-in-human (FIH)/compassionate use studies of pts with mPDAC (n=10), 4 pts treated in the 2nd line, 2 of whom had a RECIST-based improvement, had a trend towards better OS than the 5/10 pts who were treated in a higher line.[3]
- This trial explored 2 doses of SM-88 in patients with mPDAC who were pretreated with at least one line of chemotherapy.
- We report the final results (ORR, DCR, mOS, mPFS) of our multicenter, prospective open-label phase II portion (TYME-88-Panc Part 1, NCT03512756) of SM-88 Regimen in pts with mPDAC who had received at least one prior line of therapy. We compared response, survival, and AE data for patients treated at these 2 different oral SM-88 doses.

METHODS

- Key Eligibility Criteria: ≥ 18 years of age with histologically confirmed PDAC; adequate organ function; evidence of measurable metastatic disease using RECIST v1.1; progression on one or more prior lines of therapy; ECOG performance status of ≤ 2; last treatment was completed at least 30 days before the first dose of SM-88.
- Study Treatment: Oral SM-88 was given at doses of 460 mg or 920 mg daily, divided in a BID (twice a day) administration, together with fixed once-daily oral dosing of MPS (methoxsalen, 10 mg; phenytoin, 50 mg; sirolimus, 0.5 mg; SM-88 used with MPS is called “SM-88 Regimen”). All dosing was daily and continuous, administered in consecutive 28-day cycles. Treatment was continued until disease progression (PD) and/or unacceptable toxicity and/or withdrawal of consent.
- Study Design: Patients were randomized (1:1) to either 460 mg or 920 mg of SM-88 daily. Scans were conducted on the last day of Cycles 2, 4, 6, etc. Patients were followed in the clinic up to 28 days after treatment cessation and then at 3-month intervals via phone or in-person to assess survival. On signs of radiologic progression, petition could be granted to continue treatment until progression was confirmed on subsequent imaging analysis, provided there was a clinical benefit, and no other approved therapeutic intervention was available.
- Primary Endpoint: objective response rate (ORR; CR + PR) as defined by modified RECIST version 1.1 under blinded independent central review.
- Secondary Endpoints included median overall survival (mOS) and median progression-free survival (mPFS; time from randomization until disease progression or death by any cause). Disease control rate (DCR; SD + CR + PR), quality of life (QOL), and safety were also followed.

RESULTS

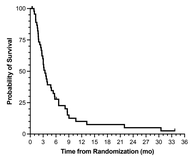
Table 1: Baseline Characteristics

	Intent-to-Treat (ITT), n=49	Evaluable, n=37
Age, years ± SD	66.9 ± 10.4	66.9 ± 10.6
Gender, female, n (%)	24 (49.0%)	17 (45.9%)
ECOG Performance Status/Score at Screening		
0, n (%)	15 (30.6%)	12 (32.4%)
1, n (%)	33 (67.4%)	25 (67.6%)
2, n (%)	1 (2.0%)	0 (0.0%)
Body Mass Index ± SD	23.6 ± 4.4	23.5 ± 4.3
Race, n (%)		
White	44 (89.8%)	34 (91.9%)
Black or African American	3 (6.1%)	2 (5.4%)
Asian	2 (4.1%)	1 (2.7%)
Prior Radiotherapy, n (%)	15 (30.6%)	12 (32.4%)
Prior Surgery, n (%)	19 (38.8%)	16 (43.2%)
Prior Lines of Therapy, n (%)		
1	7 (14.3%)	5 (13.5%)
2	24 (49.0%)	18 (48.6%)
3	10 (20.4%)	9 (24.3%)
4+	8 (16.3%)	5 (13.5%)

- 49 subjects were randomized to either 460 mg (n = 26) or 920 mg (n = 23) SM-88 plus MPS daily (ITT population).
- 37 pts were deemed evaluable after completing at least one 28-day cycle of treatment (min 23 days on treatment).
- In terms of previous treatments, the study population was heterogeneous; the majority of pts (32/37 = 86.5%) had failed at least 2 prior lines of therapy.

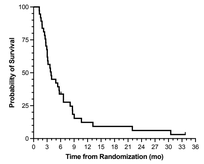
Figure 1: Overall and Stratified OS

A. OS for all ITT Patients (n=49)



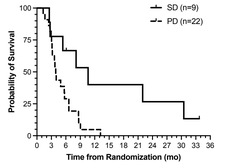
- DCR, mOS, and mPFS did not differ significantly between dose levels.
- mOS for all 49 ITT pts was 3.4 months (95% CI: 2.7 – 4.9).

B. OS for all Evaluable Patients (n=37)



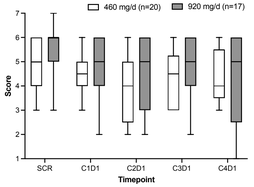
- mOS for the 37 Evaluable pts was 3.9 months (95% CI: 3.0 – 5.7).

C. All Patient OS by SD vs. PD



- Stable Disease (SD) was attained in 9/37 pts (DCR, 24.3%); there were no Complete or Partial Responses (CR/PRs).
- OS was significantly higher for pts with SD vs. PD (any line; mOS: 10.6 months vs. 3.9 months; p=0.01).

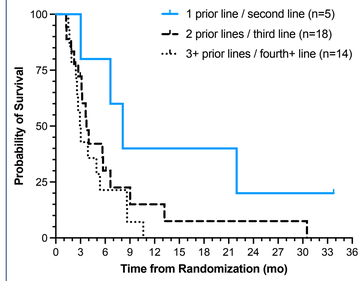
Figure 2: Quality of Life (QOL)



- QOL, as measured by the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) Question 30, was maintained and trended in favor of 920 mg.

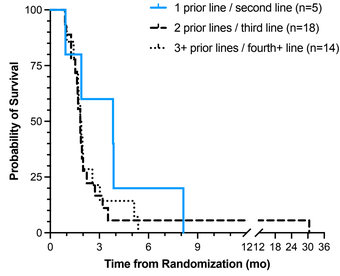
Figure 3: Stratified OS and PFS

A. Patient OS by prior line of therapy



- OS trended higher for those treated in the second line vs. ≥ third line.
- For pts treated in 2nd line, mOS was 8.1 months.
- For pts in ≥ third line, mOS was 3.7 months.

B. Patient PFS by prior line of therapy



- Similarly, there was a trend toward greater patient PFS with fewer prior lines of therapy:
  - 1 prior line, 3.8 months (95% CI: 0.9 – not reached)
  - 2 prior lines,1.8 months (95% CI: 1.5 - 2.0)
  - 3 or more prior lines, 1.9 months (95% CI: 1.4 - 2.6; log-rank P = 0.44).

Table 2: Treatment-Emergent SAEs (Safety Population, n=48)

	460 mg/day (N=25)		920 mg/day (N=23)			
	n	%	n	%		
Any Grade 3 or 4 event	14	56.0	13	56.5		
Grade 3	11	44.0	9	39.1		
Grade 4	3*	12.0	4*	17.4		
	Grade 3		Grade 4		Grade 3		Grade 4	
	n	%	n	%	n	%	n	%
Abdominal pain	1	4.0	0	0.0	6	26.1	0	0.0
Anemia	2	8.0	0	0.0	3	13.0	0	0.0
Thromboembolic event**	2	8.0	1	4.0	1	4.3	1	4.3
Ascites	1	4.0	0	0.0	1	4.3	0	0.0
Increased bilirubin	1	4.0	1	4.0	0	0.0	0	0.0
Sepsis	0	0.0	0	0.0	0	0.0	2	8.7
Cholangitis	0	0.0	0	0.0	1	4.3	1	4.3
Hyponatremia	1	4.0	0	0.0	2	8.7	0	0.0
Pleural effusion	1	4.0	0	0.0	1	4.3	0	0.0
Biliary obstruction	1	4.0	0	0.0	1	4.3	0	0.0
Arthralgia	1	4.0	0	0.0	1	4.3	0	0.0
Hypotension	0	0.0	0	0.0	1	4.3	1	4.3

n, number of subjects

*Subjects who reported both Grade 3 and 4 events are included only in the Grade 4 row.

**Thromboembolic events included the following: pulmonary embolism (n=2); deep vein thrombosis (n=1); portal vein thrombosis (n=1); thromboembolic event, not otherwise specified (n=1).

- Treatment-emergent serious adverse events (Grades 3 and 4) reported among treated subjects (safety population, n=48) with event frequency > 1, and of all relatedness categories, displayed by SM-88 dose.
- SM-88 Regimen was well tolerated: only a single patient (2.1%, 1/48) had events considered related to study treatment. These were abdominal pain (Grade 3) and hypotension (Grade 4), all of which later resolved.
- 85.2% of subjects reporting any of the events (23/27) had AEs deemed not related to SM-88 Regimen.

Table 3: Published 2nd Line mOS

Therapy	Reference	mOS (mo)	N
nanoliposomal-IRI + fluorouracil and folinic acid (FDA-approved)	Wang-Gillam et al. 2016 (NAPOLI-1)	6.1	117
5-FU/LV	Oettle et al. 2014 (CONKO); Gill et al. 2016 (PANCREOX)	3.3; 9.9	84; 54
OFF (FOLFOX)	Oettle et al. 2014 (CONKO)	5.9	76
mFOLFOX6	Gill et al. 2016 (PANCREOX)	6.1	54
mFOLFIRI.3	Yoo et al. 2009	4.2	31
docetaxel + capecitabine	Katopodis et al. 2011	6.3	31
gemcitabine + nab-paclitaxel	Mita et al. 2019	7.6	30
eryaspase + chemotherapy	Hammel et al. 2020	6.0	95

mOS published in previous 2nd line studies in the PDAC population ranged from 3.3 to 9.9 mo.

DISCUSSION

- SD was attained in 9/37 patients (DCR, 24.3%); no CR or PR was observed.
- For the patients treated in the 2nd line (n=5/37), the mOS was 8.1 months and mPFS was 3.8 months; these were similar to published data in 2nd line in this mPDAC population.
- Also, SM-88 Regimen exhibited far fewer Grade 3 and 4 AEs compared to other published cytotoxic regimens in the 2nd line.
- Quality of life was maintained on treatment and trended in favor of 920 mg/day.
- DCR, OS, and PFS did not differ significantly between 460 and 920 mg/day.

CONCLUSIONS

- In mPDAC, currently approved 1st line treatments provide an OS advantage, while those approved in 2nd line give pts a PFS advantage. However, these treatments are associated with severe toxicity. In 3rd line and beyond, there are no FDA-approved therapies.
- For the subset of patients treated in the 2nd line (n=5/37), the mOS and mPFS were on par with published results from various randomized Phase II and III trials in 2nd line for mPDAC (Table 3).
- SM-88 Regimen has a favorable safety profile and quality of life effects. The mOS for patients treated in 2nd line with SM-88 Regimen is encouraging.
- These data suggest that this regimen should be explored in the 2nd line treatment of patients with mPDAC.

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