

Phase II Pharmacokinetics of Oral SM-88 in Heavily Pre-Treated Advanced Pancreatic Ductal Adenocarcinoma (PC)

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BACKGROUND

- SM-88 is a novel anti-cancer regimen that consists of one investigational drug (D,L-alpha-metyrosine), and three repurposed agents (methoxsalen, phenytoin, and sirolimus).
- It is hypothesized that all four agents, including both the D- and L- isomers of alpha-metyrosine contribute to the anti-cancer properties of SM-88. Both the D- and L- isomers are believed to be distinct drugs with independent mechanisms of action.
- Tyme-88-Panc (NCT# 03512756) is a 2 Part randomized, open-label Phase II study of the SM-88 regimen in subjects with metastatic pancreatic adenocarcinoma who have had at least 1 prior line of chemotherapy, with an Eastern Cooperative Oncology Group (ECOG) score ≤ 2 .
- In Part 1, subjects were randomized to receive one of two D,L-alpha-metyrosine oral dosing regimens, 230 mg BID, or 460 mg BID.
- The oral doses of methoxsalen (10 mg QD), phenytoin (50 mg QD), and sirolimus (0.5 mg QD), administered were the same regardless of randomization.
- The present study describes the pharmacokinetics (PK) of all four components of the SM-88 regimen for subjects in Part 1 of the study, during the first two cycles of therapy.

METHODS

- PK samples were collected from all subjects at predose (0), 0.5, 1, 2, 4, and 6 hours post-dose on Day 1 of Cycles 1 and 2.
- Plasma concentrations of methoxsalen, phenytoin, and both the D- and L- isomers of alpha-metyrosine, were determined using a fit-for-purpose MS/MS bioanalytical assay.
- Whole blood concentrations of sirolimus were determined using a fit-for-purpose MS/MS bioanalytical assay.
- PK parameters were calculated using standard non-compartmental methods in Phoenix WinNonlin version 8.1 or higher.
- A full description of the Tyme-88-Panc study design is presented on A16 poster (J Clin Oncol 37, 2019 (suppl 4; abstr 200)).

Table 1: Baseline Demographics and Characteristics

There were no meaningful differences observed between dose levels.

	230 mg BID	460 mg BID
N	19	19
Age, years \pm SD	65.4 \pm 10.4	68.0 \pm 11.7
Sex, n (%)		
Male	12 (63.2%)	10 (52.6%)
Female	7 (36.8%)	9 (47.4%)
Weight, kg \pm SD	70.3 \pm 16.4	70.2 \pm 13.0
Body Mass Index, \pm SD	23.4 \pm 4.6	25.0 \pm 4.8
Race, n (%)		
White	18 (94.7%)	18 (94.7%)
Black	1 (5.3%)	0 (0.0%)
Asian	0 (0.0%)	1 (5.3%)
CrCL, mL/min \pm SD	89.4 \pm 22.5	83.5 \pm 23.9

Figure 1: Mean Concentration-time Profiles of D,L-alpha-metyrosine

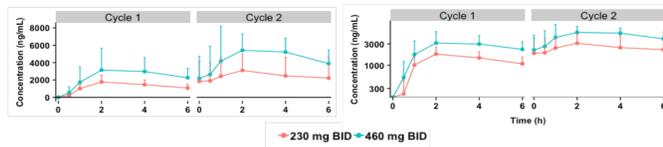
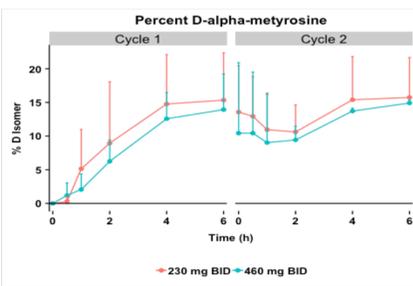


Figure 2: Proportion of the D Isomer of Alpha-metyrosine Present in the Plasma Over Time



- Following a single dose of D,L-alpha-metyrosine, the proportion of the D-isomer, as a percentage of total alpha-metyrosine, increases over the first 4 hours.
- By Cycle 2, when D,L-alpha-metyrosine has reached steady state, the proportion of the D-isomer is approximately 10-15% at all time points examined.
- D-isomer data was available for 14 subjects in Cycle 1, and 11 subjects in Cycle 2.

RESULTS

Table 2: Summary of PK Parameters of D,L-alpha-metyrosine

- Approximately ~80-100% accumulation observed between Cycles 1 and 2 based on C_{max} and AUC. This is consistent with the dosing schedule and half-life.
- Based on C_{max} and AUC, exposure to D,L-alpha-metyrosine was approximately dose proportional between the 230 and 460 mg BID doses.
- T_{max} and half-life are consistent with previously published literature for L-alpha-metyrosine.

	Cycle 1		Cycle 2	
	230 mg BID	460 mg BID	230 mg BID	460 mg BID
C_{max} (ng/mL)	1911 (746)	3698 (2069)	3313 (2241)	6550 (3037)
Mean (SD)	n = 14	n = 15	n = 8	n = 4
T_{max} (h)	2 (1 - 4)	4 (2 - 6)	2 (2 - 6)	3 (1 - 4)
Median (Range)	n = 14	n = 15	n = 8	n = 4
AUC ₀₋₆ (ng*h/mL)	7511 (2663)	14493 (8904)	15538 (13334)	28005 (14928)
Mean (SD)	n = 14	n = 15	n = 8	n = 4
$t_{1/2}$ (h)	3.2 (2.2 - 8.1)	3.4 (2.7 - 6.0)	9.1 (1.8 - 13.8)	4.1 (3.0 - 12.2)
Median (Range)	n = 8	n = 7	n = 4	n = 4

Table 3: Summary of PK Parameters of Methoxsalen, Phenytoin, and Sirolimus

	Methoxsalen		Phenytoin		Sirolimus	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2
C_{max} (ng/mL)	38.0 (35.4)	49.0 (46.4)	475 (201)	741 (283)	2.3 (1.0)	3.3 (1.8)
Mean (SD)	n = 29	n = 12	n = 29	n = 12	n = 14	n = 6
T_{max} (h)	1 (0.5 - 4)	0.5 (0 - 2)	4 (1 - 6)	4 (0.5 - 6)	2 (1 - 4)	2 (0.5 - 4)
Median (Range)	n = 29	n = 12	n = 29	n = 12	n = 14	n = 6
AUC ₀₋₆ (ng*h/mL)	54.8 (52.6)	78.3 (80.2)	1840 (746)	3243 (1061)	9.9 (3.9)	16.0 (7.7)
Mean (SD)	n = 29	n = 12	n = 29	n = 12	n = 13	n = 6
$t_{1/2}$ (h)	1.4 (0.4 - 2.8)	1.4 (1.0 - 3.9)	11.9 (7.4 - 17.8)	10.5 (5.1 - 15.9)	6.3 (3.5 - 14.7)	24.0 (10.9 - 86.8)
Median (Range)	n = 24	n = 10	n = 5	n = 8	n = 5	n = 4

Figure 3: Mean Concentration-time Profiles of Methoxsalen, Phenytoin, and Sirolimus

- Doses of methoxsalen, phenytoin, and sirolimus, were the same for both D,L-alpha-metyrosine dose groups.
- There was no difference in the PK of methoxsalen, phenytoin, and sirolimus, if examined based on D,L-alpha-metyrosine dose group (data not shown).
- Plots show data combined from both dose groups.

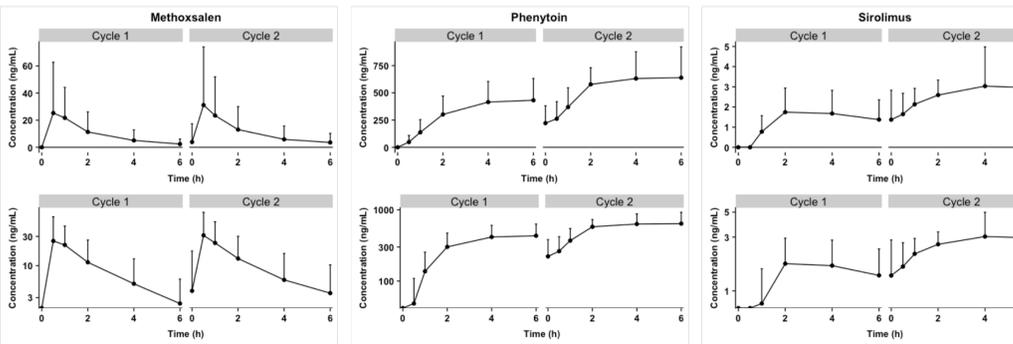
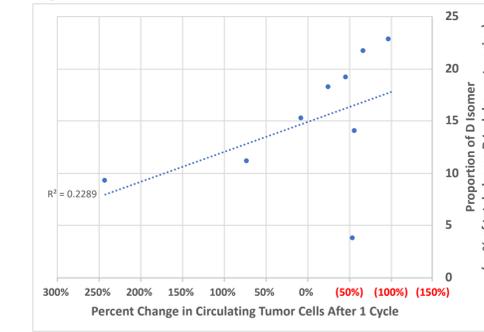
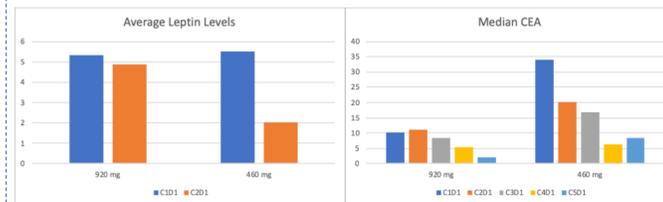


Figure 4: Correlation between the proportion of the D-isomer at steady state of alpha-metyrosine and the best overall reduction in circulating tumor cells.



The strength of the correlation between the proportion of the D-isomer and reduction in circulating CTCs improves when the potential outlier is excluded ($R^2 = 0.7081$).

Figure 5: Correlation of D,L-alpha-metyrosine total daily dose and changes in plasma leptin and CEA.



SAFETY

SM-88 was well tolerated with few grade 3 or 4 adverse events related to the regimen and is reported in detail elsewhere at this meeting (Poster G8; J Clin Oncol 37, 2019 (suppl 4; abstr 310))

CONCLUSIONS

- D,L-alpha-metyrosine exhibits predictable pharmacokinetic properties.
 - In both dose groups, D,L-alpha-metyrosine is rapidly absorbed and achieves steady state.
 - D,L-alpha-metyrosine is approximately dose proportional across both doses examined.
 - The D isomer of alpha-metyrosine accounts for approximately 10-15% of the total concentration present at steady state.
- Concentration-time profiles of three adjuvant components (methoxsalen, phenytoin, and sirolimus) were similar to expectations based on previous literature.
- Subjects treated with SM-88 are at low risk of experiencing adverse events related to the three adjuvant components.
 - Mean methoxsalen C_{max} is below the lower bound of the therapeutic range used in methoxsalen and long wave UVA (PUVA) therapy, but some individuals may have higher levels.
 - All phenytoin levels observed in Tyme-88-Panc were less than 10% the level of clinical concern (20 μ g/mL which is associated with nystagmus).
 - All sirolimus levels observed in Tyme-88-Panc were substantially below concentrations associated with greater risk of adverse events (>15-18 ng/mL).
- Overall, SM-88 is safe and well tolerated in subjects with metastatic pancreatic adenocarcinoma.

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)

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