**BACKGROUND**

SM-88 is a novel anti-cancer regimen that consists of one investigational drug (DL-α-metyrosine), and three repurposed agents (methoxsalen, phenytoin, and sirolimus). It is hypothesized that all four agents, including both the D- and L-isomers of α-metyrosine contribute to the anti-cancer properties of SM-88. Both the D- and L-isomers are believed to differ in their anti-cancer properties with independent mechanisms of action.

**METHODS**

PK samples were collected from all subjects at baseline, 0.5, 1, 2, and 6 hours post-dose on Day 1 of Cycles 1 and 2.

Plasma concentrations of methoxsalen, phenytoin, and sirolimus were determined using a HPLC method with a fully validated method. The method was sensitive and specific for the analytes of interest.

PK parameters were calculated using standard non-compartmental methods in Phoenix WinNonlin version 8.1 or higher.

A full description of the Tymes-BPc study design is presented in a separate paper (J Clin Oncol 37, 2019; suppl abstr 6002).

**RESULTS**

**Table 1: Baseline Demographics and Characteristics**

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<td>Weight (kg)</td>
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<td>Race</td>
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**Table 2: Summary of PK Parameters of D,L-α-metyrosine**

- Approximately 80-100% accumulation observed between Cycles 1 and 2 based on Cmax and AUC. This is consistent with the dosing schedule and half-life.
- Based on T1/2 and AUC, exposure to D,L-α-metyrosine was approximately dose proportional between the 230 mg BID and 460 mg BID dose groups.
- T1/2 and half-life are consistent with previously published literature for oral metyrosine.

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

PK Parameters were determined using data combined from both dose groups.

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

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

- Following a single dose of DL-α-metyrosine, the proportion of the D isomer, as a percentage of total α-metyrosine, increases over the first 6 hours.
- By Cycle 2, when D,L-α-metyrosine dose was increased to 460 mg BID, the proportion of the D isomer is approximately 10%-15% at all time points examined.
- Data are available for 14 subjects in Cycle 1 and 11 subjects in Cycle 2.

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

**Figure 4: Correlation between the proportion of the D isomer at steady-state of α-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 CTCA is improved when the patient’s tumor is included (R2 = 0.68).

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

SM-88 was well tolerated with few grade 3 or 4 adverse events relative to the expected regimen and is appropriate for further study as a Phase II trial meeting (Poster G8; J Clin Oncol 37, 2019 (suppl 4; abstr 3101)).

**CONCLUSIONS**

- DL-α-metyrosine exhibits predictable pharmacokinetic properties.
- In both dose groups, D,L-α-metyrosine is rapidly absorbed and achieves steady state.
- DL-α-metyrosine is approximately dose proportional across both dose groups examined.
- DL-α-metyrosine is rapidly absorbed and achieves steady state.
- Concentration-time profiles of three adjacent components (methoxsalen, phenytoin, and sirolimus) were similar to each other.

Subjects treated with SM-88 are at low risk of experiencing adverse events related to the three adjacent components.

Mean methoxsalen Cmax is below the lower bound of the therapeutic range used in melanomas and long-acting PUVA (PDT) therapy, but some individuals may have higher levels.

All phenytoin levels observed in Tymes-BPc were less than 10% of the level of clinical concern (20 µg/mL), which is associated with myopathy.

All sirolimus levels observed in Tymes-BPc 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**

- Nork et al. Feasibility of SM-88 in PC: A phase II trial meeting (abstr G8), J Clin Oncol 37, 2019 (suppl 4; abstr 3101).
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