**Phase II Monotherapy Efficacy of Cancer Metabolism Targeting SM-88 in Heavily-Treated PDAC Patients**

**INTRODUCTION**

- TYMÉ conducted a multi-center, open-label, dose optimization randomized Phase II trial evaluating SM-88 in advanced Pancreatic Ductal Adenocarcinoma (PDAC).

- SM-88 is the lead investigational therapy in the TYMÉ Cancer Metabolism Based Therapies (CBT)TM platform. SM-88 is an oral modified dysfunctional tyrosine that is hypothesized to disrupt cancer cell metabolism.

- SM-88 has demonstrated encouraging efficacy and a well-tolerated safety profile in 15 different tumor types, including solid tumors and hematologic malignancies across four separate studies.

**BACKGROUND**

- Refractory PDAC has no established therapy.

- Previous reported survival for third-line treatments is approximately 2.0 months (JCO 2017; 30: 2045-2055).

- SM-88 (L-L-α-methyl-L-tyrosine, racemetyrosine) is a novel oral therapy used with low doses of different inhibitors, including achieving SD or better (CBR) and compared to previous tumor types.

- Previous studies with SM-88 have demonstrated safety and efficacy in compromised patients (JCO 2017; 30: 2045-2055).

**METHOD**

- Randomized Phase II of 450mg vs 900mg per day of SM-88 in patients with radiographic PD, at least 1 prior line, and ECOG 0-2. All patients also received MPS (metronomic 10mg/kg once weekly, and 5-methyl-cytosine 0.5 mg/kg once weekly). There was no restriction on the size, number, or site of metastases nor baseline CA-19-9 or CTCA (studies). 96 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: 2 - 26 total time on treatment) and were considered evaluable for efficacy as per the three finding protocol. One additional patient had unreported survival data.

- Radiomics were performed on largest lesions at baseline selected by blinded independent central review with an SSF2 (spatial scale filtration) based on the methods of Weiss et al., 2014.

**RESULTS**

- **SM-88 OS trend is encouraging in this poor prognosis patient population.** Several encouraging efficacy markers correlate with greater survival.

- Radiomics found an association with SM-88 use, baseline tumor characteristics, CTC response, and OS. Further investigation will be conducted into the prognostic indicators associated with longer survival.

- **SM-88 demonstrated encouraging survival trends.** In addition, certain efficacy indicators correlated with greater OS, including achieving SD or better (CBR) and decreases in CTCs.

- The 920 mg/dl dose has been selected for evaluation in anticipated future Phase III randomized pivotal trials.

**CONCLUSIONS**

- **SM-88 demonstrated encouraging survival trends.** In addition, certain efficacy indicators correlated with greater OS, including achieving SD or better (CBR) and decreases in CTCs.

- Overall stability of weight in this population is of note, as patients with pancreatic cancer typically experience noticeable, but unintentional, weight loss, which is clinically meaningful indicator of poor prognosis (Hendrief et al., 2018; Namer et al., 2017).

**DISCUSSION**

- Adverse events on SM-88 were reported less frequently overall than those commonly observed on other therapies for pancreatic cancer (Wang-Gillam et al., 2016).

- Although exploratory, radiomics could potentially identify patients who are more likely to benefit from SM-88 used with MPS. Additional prospective trials are needed to confirm this hypothesis.