**INTRODUCTION**

- D/L-alpha-metrosine (SM-88, metrosdinone) has displayed broad anticancer activity in patients across 15 different tumor types. While amino acid metabolism has been reviewed in oncology settings for decades, SM-88 offers a potential novel therapeutic approach to selectively disrupt cancer cells.

- A comprehensive in vitro and in vivo experimental program is undertaken to elucidate the mechanism of action and further characterize the anti-cancer effects of SM-88.

**METHODS**

- In all in vitro cell line experiments, and the Pan02 xenograft model, the SM-88 methyl-ester (SM-88 ME) was used, which has the same active moiety as SM-88 but with improved solubility characteristics. The SM-88 ME form was used in the HCT-116 xenograft experiment.

- Autophagy: Changes in LC3B and p62 expression were investigated using standard Western blot techniques.

- ROS Induction: Following treatment with SM-88, ROS induction was assessed using the CellROX® (Thermo Fisher) flow cytometry assay. Cells for ROS/autophagy cell selection was based on data obtained from negative controls.

- HCT-116 Xenograft: Female athymic nude mice were implanted subcutaneously with HCT-116 cells. Once tumors reached 50-100 mm3 tumor size, mice were treated with either vehicle alone, 81 mg/kg/day SM-88, 162 mg/kg/day SM-88, or 324 mg/kg/day SM-88 administered orally (n = 10 per group).

- Pan02 Xenograft Study: C57BL/6 mice were treated with either vehicle alone, 25 mg/kg/day SM-88 via intraperitoneal (IP) injection, or 75 mg/kg/day SM-88 (324 mg/kg/day SM-88 IP) (n = 10 per group). Treatments began on Day 0. On Day 4, Pan02 tumors from each treatment group were removed and processed for histology.

- Tumor Necrosis Profiling: On Day 24, Pan02 tumors from the randomly selected mice per treatment arm were processed for immunohistochemistry by flow cytometry using a 16 color myeloid and lymphocyte panel following standard protocols.

**RESULTS**

**CONCLUSIONS**

- The importance of amino acid metabolism in cancer has gained greater awareness over the past decade; however, potential therapeutic approaches in this arena remain limited.

- SM-88 has been dosed in over 180 cancer patient clinical trials and has shown encouraging toxicity and safety findings to date.

- Early data indicate that SM-88 may promote increases in ROS generation and alterations in autophagy in certain cancer cell lines (Pan02 pancreatic cancer).

- Potential immunomodulatory effects of SM-88, including alterations in macrophage polarization and other key tumor immune cells (CD4+ and CD8+) are being examined.

**REFERENCES**


- Pan02 Subcutaneous Xenograft Model

- Excised Pan02 tumors (Day 34) from the subcutaneous xenograft model are shown in Figure 2b.

- Dose dependent increases in LC3B and p62 expression were observed in Pan02 and PANC1 cells.

- Potential immunomodulatory effects of SM-88, including alterations in macrophage polarization and other key tumor immune cells (CD4+ and CD8+) are being examined.

- In vitro effects on apoptosis, viability, reactive oxygen species induction, autophagy, migration and invasion, cell cycle changes, and protein synthesis are being investigated.

**DISCUSSION AND FUTURE DIRECTIONS**

- SM-88 has demonstrated encouraging efficacy in 15 different tumor types. This may be due to the effects of SM-88 on cancer through multiple mechanisms, including immune modulation, alterations in autophagy and ROS induction.

- Alterations in autophagy have been associated with increased MCT1 expression in pancreatic cancer (Yamamoto et al., 2020). We are deepening our experimental understanding of the impact of SM-88 on autophagy/lysophagy, as well as any chemotherapeutic changes that might be related to these changes including MCT1 expression.

- We are continuing to explore the immune modulatory effects observed in these preliminary experiments.

- Based on these and other ongoing experiments, we are beginning to explore SM-88 combinations with chemotherapies, targeted agents, or immune-oncology therapies.

- We are continuing to explore these and other effects of SM-88, as well as potential biomarkers of SM-88 sensitization, through experiments on human organoids, and metabolic and gene expression analyses.

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