**INTRODUCTION**

TYME-18 is a combination of two agents administered intra-tumorally to induce tumor regression without injuring adjacent tissue. The surfactant component (proprietary combination solubilization system) causes cancer cell death to local toxicity by increasing cell membrane permeability. Sulfonic Acid Component: naturally occurring acid that is cytostatic at high concentrations within the tumor but is rapidly broken down in the bloodstream when released systemically. Sulfonic acids are lipid-solubilizers, and thus can disrupt cell membranes, especially in the presence of the penetration enhancers used here.

The sulfonic acid component is approved for human use in dermatological studies, and TYME’s proprietary solvent system is designed to enhance penetration of the sulfonic acid into the tumor. Reducing the integrity of the cancer cell can disrupt normal function, promoting cell capture and exposure to the toxic tumor microenvironment.

In many non-metastatic cancers, resection is the primary curative treatment. However, many patients possess lesions located in traditionally challenging locations (i.e., head/neck, pancreas), or those involving impingement on vital structures that make resection or radiotherapy, difficult or impossible.

A safe and effective intra-tumor therapy would have utility for treating unresistant or inoperable primary or metastatic tumors or where standard radiotherapeutic options may be considered higher risk.

The intra-tumor injection is designed to selectively kill cancer through disrupting intracellularly toxic compounds, while maintaining safety for healthy tissues, as displayed in the hypothesized MDA below.

**PRELIMINARY DEVELOPMENT AND DOSE OPTIMIZATION**

To date, several preliminary studies have been conducted to explore the potential anti-cancer effects of TYME-18. A preliminary proof-of-concept study was performed to evaluate the antitumor effect of TYME-18 in BALB/c mice bearing CT26 tumors (data not shown).

Treatment with TYME-18 significantly inhibited CT26 tumor growth in BALB/c mice, compared with control (saline) p<0.01, at least of tumor volumes at treatment Day 15.

4 of 7 (57.1%) mice in the control group reached the pre-specified maximum allowed tumor volume, compared with 1 of 8 (12.5%) in the TYME-18 treated group (p=0.11). In an initial dose optimization study, various dosages and administration frequencies of TYME-18 were tested (data not shown).

**RESULTS**

To investigate the effects of the individual components of TYME-18 tumor growth, an in vivo xenograft model was used using the murine colon cell line CT26 (Figure 1, Tables 1 and 2).

A minor reduction in tumor cell mass was observed in response to the surfactant component, with the tumors reduced by ~16× mean growth in the control compared with ~16× mean growth in the surfactant component alone.

Six intra-tumoral injections were administered at 3-day intervals.

Measurements were taken every 3 days. Animals were sacrificed when tumors reached 2000 mm³ or at the end of the study.

**CONCLUSIONS**

TYME-18 has been studied in three preclinical mouse xenograft studies, each with encouraging efficacy.

The current studies were aimed to establish proof of concept, optimize dosing and treatment schedule, and confirm findings.

In the component effect study, TYME-18 inhibited tumor growth in CT26 tumors, established tumors growing completely, compared with 16× mean growth in the control treatment.

While not a primary focus, no local or systemic toxicities were reported in rodents administered TYME-18.

TYME-18 has demonstrated encouraging initial efficacy and warrants additional study.

**DISCUSSION**

Local administration of TYME-18 led to significant tumor regression compared to rapid growth observed in control treatments. Sulfonic acids (similar to the one used in TYME-18), are recognized as important regulators of energy metabolism. Through effects on FXR, LXR, PPARδ, and PPARγ, sulfonic acids regulate important changes in energy metabolism including insulin utilization, insulin receptor sensitivity, and transcription of the genes that mediate glucose and lipid metabolism, as well as various immune effects; all of which may contribute to potential anti-cancer effects (Di Ciaula 2017).

Unfortunately, many cancer patients present with unacceptable measures that could benefit from a well-tolerated, localized treatment. Additional treatment approaches are needed to optimally address these cases, either as standalone treatment, or as an adjunct to other local therapies, such as stereotactic radiotherapy, ablative or other such treatments.

Further studies may better define the optimal dosing frequency, route and concentration for specific clinical use.

**REFERENCES**