Pharmacokinetics of intratumoral tigilanol tiglate in soft tissue sarcoma: data from a Phase IIa clinical trial (NCT05755113)

Nichita Kulkarni, Duan G. Li, Shanie Shemla, Charlotte E. Ariyan, Shannan Dickinson, Aimee Crago, George Li, Narasimhan P. Agaram, Sandra D'Angelo, Robert G. Maki, Samuel Singer, William D. Tap, Ciara M. Kelly, Edmund K. Bartlett

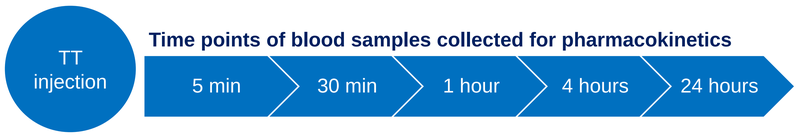
Memorial Sloan Kettering Cancer Center

Background and Objectives

- Tigilanol tiglate (TT) is an epoxytigliane diterpene small molecule that induces tumor cell necrosis and tumor vascular disruption and has shown promising activity in multiple tumor types as an intratumoral agent
- In vitro studies demonstrate dose and concentration dependent cell death in tumors and cell lines treated with TT
- In a Phase I, dose escalation study, TT was well-tolerated and demonstrated clinical response in 9 tumor types
- Pharmacokinetics from Phase I data demonstrated median half-life of 3.64h, with dose proportional increase of systemic TT concentration
- We analyzed pharmacokinetics data from a Phase II study of preliminary efficacy of TT in advanced and/or metastatic soft tissue sarcomas

Methods

- Single center, single arm, open label, pilot Phase II study
- Adults with advanced and/or metastatic STS with tumours accessible for injection
- Lesion volume measured by ultrasound (±CT or MRI) at multiple timepoints
- TT dose: 0.5 mg per 1.0 cm^3 tumor, max dose 3.6 mg/m^2 body surface area (BSA)



- **Primary endpoint**: Ablation of tumors or segments of tumors
  - Observing response in ≥ 20% of patients was predefined as promising
- **Secondary endpoints**: Adverse events; pharmacokinetic assessments
- **Exploratory endpoints**: Tumor microenvironment change in blood and tumor samples

Results

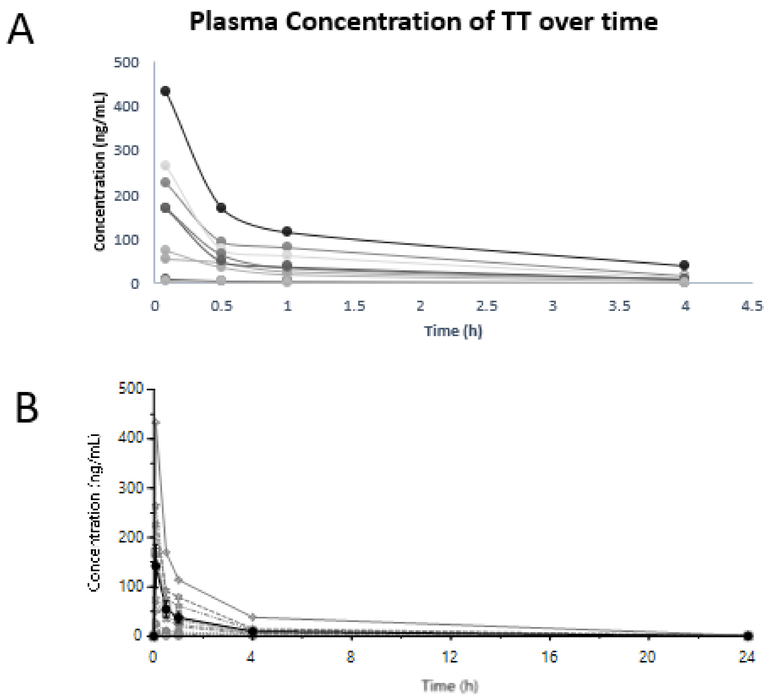


Figure 1: *Plasma concentration of TT over time with individual curves representing each patient enrolled in trial. TT concentration was determined from blood samples collected at 5 minutes, 30 minutes, 1 hour, 4 hours (A) and 24 hours post treatment (B).*

- Total tumor volume ranged from 1.3 cm^3 – 77.16 cm^3
- Mean half-life of TT was **2 hours**
- Cmax and AUC were normalized to total dose administered
  - Dose normalized Cmax ranged from **4.09-55.51 ng/mL/mg**
  - Dose normalized AUC ranged from **4.83-77.44 hr*ng/mL/mg**
- AUC and Cmax were significantly associated with total TT dose (p=0.05 and 0.03) and total size of injected tumors (p=0.05 and 0.03)
- For 6 out of 9 patients, **>90% of TT was eliminated by 4 hours**
- All patients had 84% or more of the drug eliminated by 4 hours

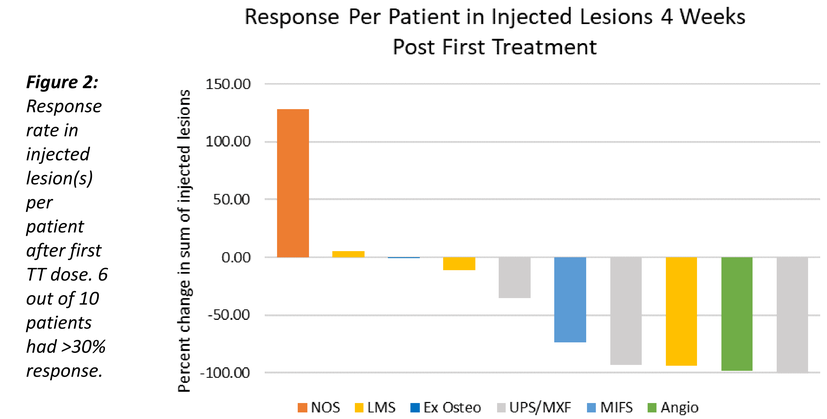
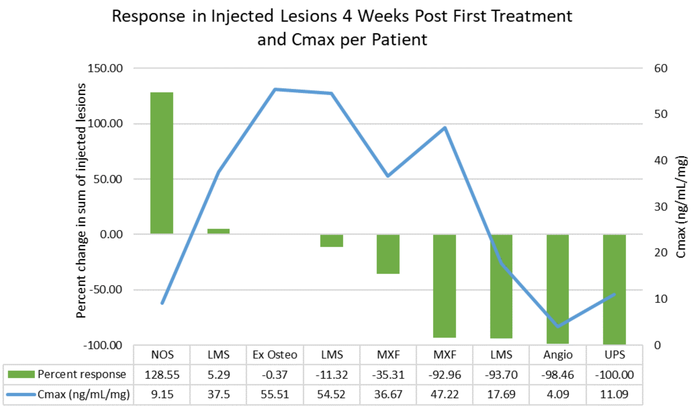


Figure 2: *Response rate in injected lesion(s) per patient after first TT dose. 6 out of 10 patients had >30% response.*



	NOS	LMS	Ex Osteo	LMS	MXF	MXF	LMS	Angio	UPS
Percent response	128.55	5.29	-0.37	-11.32	-35.31	-92.96	-93.70	-98.46	-100.00
Cmax (ng/mL/mg)	9.15	37.5	55.51	54.52	36.67	47.22	17.69	4.09	11.09

Figure 3: *Response rate in injected lesion(s) after first TT dose and dose normalized Cmax per patient demonstrate no association.*

Discussion

- TT demonstrates rapid systemic clearance after intratumoral injections in patients with STS
- Measurable concentrations of TT observable in all patients from 5 min to 4 hours after dosing; 4 patients had small but observable concentrations at 24 hours after dosing
- Given short half-life of TT, more frequent dosing of TT to be explored in trial expansion cohort, opening for enrolment shortly

References & Disclosures

- Panizza et al. 2019 EBioMedicine; Cullen et al.2021 Scientific Reports; Cullen et al. 2024 Journal of Immunotherapy of Cancer

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Corresponding author: kulkarn1@mskcc.org