Phase 1b trial of camsirubicin, a novel doxorubicin analog, with concomitant pegfilgrastim for advanced soft tissue sarcoma to identify a new maximum tolerated dose/recommended phase 2 dose.

Monopar Therapeutics

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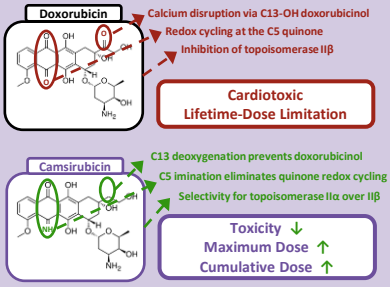
Background

Doxorubicin: Vital, but Toxic

Doxorubicin (Dox) is one of the most widely used cancer therapies, administered to > 1.2 million patients annually. It is FDA-approved for 14 different cancers, including first-line monotherapy for advanced soft-tissue sarcoma (ASTS). However, its risk of irreversible, life-threatening cardiotoxicity stops its use once a lifetime cumulative dose is reached in ~4-6 months.

Mechanisms of doxorubicin cardiotoxicity are understood to cover 3 different pathways.



Camsirubicin: Engineered to be Non-Cardiotoxic

In response to Dox's limitations, Camsirubicin HCl, a novel doxorubicin analogue, was created via chemical modification to mitigate cardiotoxicity while retaining antitumor activity.

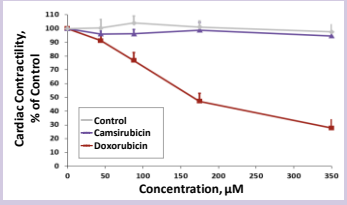
Increasing Maximum Tolerated Dose (MTD) via Pegfilgrastim

The prior Phase 1 dose-escalating trial suggested a Phase 2 dose of 265 mg/m^2 due to concerns of acute neutropenia. By administering pegfilgrastim with camsirubicin to address neutropenia toxicity, our Phase 1b study in ASTS patients seeks to determine a higher MTD for future studies.

Preclinical Trials

Dose Effect on Cardiac Contractility

Doxorubicin vs Camsirubicin



Unlike doxorubicin, camsirubicin shows no cardiotoxicity at increased concentrations in a rabbit atrial model.

Prior Phase 2 (265 mg/m^2)

LVEF Measurements over Camsirubicin Treatment

		Screening	Final Visit
LVEF (%)	Mean	61.8	58.4
	Median	61.0	60.0

		mg/m^2
Camsirubicin Cumulative Dose	Mean	1,486
	Median	530
	Max	5,300

n = 22

Average LVEF showed no significant decline vs baseline.

No patient experienced irreversible cardiotoxicity.[a]

20 Maximum # of cycles received with camsirubicin; Dox max is 8 cycles.

38% 6-month progression-free survival; Dox achieves 25-45% in ASTS patients.

[a] Four patients experienced LVEF decreases >10% from baseline but changes were transient, returning to normal during study treatment or prior to final safety visit.

Study Design, Status, & Demographics

Study Design *Phase 1b open-label, dose-escalation, **3+3 design***

Screening *(28 days)* → **Intervention Period** *(6 cycles of 21 days, with extension up to 16 cycles)* → **EoT Safety Visit** *(with 1-Yr Long-Term Follow-Up)*

Dosing Schedule

Camsirubicin + Pegfilgrastim *(starting at 265 mg/m^2 with 25% escalation)* *(to prevent neutropenia)* → DLT → **MTD/ RP2D** → **6 Patient Expansion** at RP2D

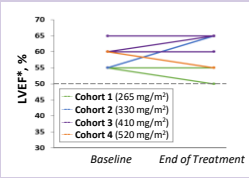
DLT = Dose-Limiting Toxicity, MTD = Maximum Tolerated Dose, RP2D = Recommended Phase 2 Dose, EoT = End of Treatment

Trial is ongoing and has advanced to the 4th cohort without any dose-limiting toxicity.

Demographics	n = 11
Median Age in Years [Min, Max]	49 [26, 81]
Sex (Female, Male)	8, 3
ECOG Score (0, 1)	0, 11
Tumor at Baseline (Localized, Locally Advanced, Metastatic)	1, 5, 5

Safety: LVEF Trends

LVEF Trends across Dose-Escalating Cohorts[b]



**LVEF readings can vary ~5-10%*

No drug-related cardiotoxicity observed up to current dose level of 520 mg/m^2 per cycle.

[b] Two patients excluded from graph: one patient died before their end of treatment visit due to COVID-19; one patient died from a sepsis-related event (not drug-related).

Clinical Outcomes: Disease Status

Expected Response & Disease Outcomes across Tumor Types

Patient	Dose (mg/m^2)	Diagnosis/ Tumor Type	Expected Anthracycline Treatment Response[c]	Stable Disease[d] (SD) vs Progressive Disease (PD)
1.1	265	Dedifferentiated Liposarcoma	UNLIKELY	SD
1.2	265	Undifferentiated Uterine Sarcoma	LIKELY	SD
1.3	265	Undifferentiated Pleomorphic Sarcoma	*Limited Data Available*	PD
2.1	330	Angiosarcoma	LIKELY	SD
2.2	330	Myxoid Liposarcoma	LIKELY	SD
2.3	330	Malignant PEComa	UNLIKELY	PD
3.1	410	Malignant Solitary Fibrous Tumor	UNLIKELY	PD
3.2	410	Malignant Peripheral Nerve Sheath Tumor	UNLIKELY	PD
3.3	410	Dedifferentiated Liposarcoma	UNLIKELY	PD
4.1	520	Undifferentiated Pleomorphic Sarcoma	*Limited Data Available*	SD[e]
4.2	520	Mesenchymal Chondrosarcoma	UNLIKELY	SD

Patients achieving stable disease on camsirubicin are similar to those who are likely to respond to anthracyclines.

[c] Includes partial and complete response rates; studies are heterogeneous including anthracycline- or doxorubicin-based regimens; "likely" is defined as > 25% expected anthracycline treatment response.

[d] SD is defined as stable tumor size on repeat CT scan (at 12 weeks); four patients with SD discontinued treatment due to non-study drug reasons.

[e] Patient had SD at 6-week scan but died from COVID-19 prior to 12-week scan.

Conclusions & Next Steps

SAFETY **No evidence** in this Phase 1b of **drug-related clinical cardiotoxicity**.

CLINICAL OUTCOMES Even with medically complex patients (i.e., 100% ECOG 1) and challenging patient mix (e.g., no leiomyosarcoma patients), **50% of patients had SD.**

CONTINUE ESCALATION Current Phase 1b dose level of 520 mg/m^2 is **~2x the prior Phase 2 dose.** MTD/RP2D has not been reached; trial is **still escalating**.

Citations: