TPS11599

Trial in Progress: A phase I/II study of safety/efficacy using lurbinectedin, combined with ipilimumab, and nivolumab for advanced soft tissue sarcomas (NCT05876715)

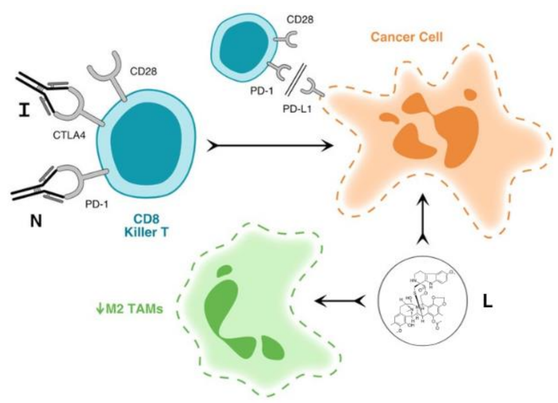
Samantha Jeffrey, Sant P. Chawla, Oliver Davidorf, Sarah Lande, Allyssa Lingad, Vanessa Xayasak, Jason Ballon, Ania M. Moradkhani, Ted Kim, Victoria S. Chua-Alcala, Neal Shiv Chawla, Erlinda Maria Gordon

Sarcoma Oncology Center, Santa Monica, CA 90403 USA

Background

Soft tissue sarcoma (STS) cells exhibit heightened immunogenicity during the early stages of the disease. Therefore, immunotherapies such as ipilimumab (ipi) and nivolumab (nivo), which enhance sustained T-cell activation by suppressing regulatory T cells, are potentially more effective when administered as first-line therapy in combination with lurbinectedin—a synthetic analog of the marine alkaloid trabectedin—that not only induces apoptosis in cancer cells and exposes tumor neoantigens for immune recognition but also depletes tumor-associated growth promoting macrophages, thereby restoring immune surveillance and potentially enhancing the efficacy of immunotherapy.

Figure 1.



Lurbinectedin (L) is a synthetic agent derived from trabectedin. Via inducing PD-L1 expression and depleting growth promoting Tumor Associated Macrophages (TAMs), Lurbinectedin sensitizes tumors to immune checkpoint inhibitor therapy

Ipilimumab (I) is a monoclonal antibody that binds to the CD8+ Killer T-Cell CTLA-4 receptor, a negative regulator of T cell activation. Via preventing CTLA-4 from outcompeting the CD28 receptor for B7 on Antigen Presenting Cells, Ipilimumab allows CD28 to bind B7, resulting in CD28 pathway-mediated positive T-cell costimulatory signals, ultimately allowing for T-cell activation.

Nivolumab (N) is a monoclonal antibody that binds to the CD8+ Killer T cell PD-1 receptor, a negative regulator of T-cell activation. Via blocking the interaction between PD-1 and PD-L1/L2 on Tumor Cells, Nivolumab prevents PD-1 pathway-mediated T-cell inhibition, ultimately allowing for T-cell activation.

Methods

This **Phase I/II** open-label single-site study will evaluate the safety and efficacy of **lurbinectedin** in combination with **ipilimumab** and **nivolumab** in patients with advanced STS. Up to **40 patients** with **advanced STS** will be treated. **Phase I** will include **6-12 previously treated** participants and will employ a standard **"cohort of 3"** design with a DLT window of 3 weeks to determine the Maximum Tolerated Dose (**MTD)**. In **Phase II**, an additional **28-34 previously untreated** participants will receive **lurbinectedin at the MTD** and **fixed doses of ipilimumab** and **nivolumab**.

Objectives

Primary
- **Evaluate MTD** of lurbinectedin in combination with fixed doses of ipilimumab and nivolumab

Secondary
- Evaluate **objective response rate (ORR)** by RECIST v1.1 via CT/MRI/PET q 6w until end of treatment (EOT)
- Determine **progression-free survival (PFS)**
- Determine **overall survival (OS)**

Exploratory
- Correlate response with amount of **ctDNA** via Signatera testing q 6w until EOT

Enrollment Criteria

Key Inclusion Criteria
- Confirmed pathologic diagnosis of locally advanced unresectable or metastatic **STS**
- At least **one measurable target lesion** by **RECIST v1.1** of 1 cm
- **≥ 18 years**
- **ECOG ≤ 1**
- Life expectancy of **≥ 3 months**
- Acceptable **hematological** status and **liver/renal** function
- **Previously treated** in Phase I; **previously untreated** in Phase II

Key Exclusion Criteria
- Untreated **CNS metastases**
- **Radiation** therapy, **targeted therapy**, other **antitumor treatment**, or **investigational drug** or **device study**, within **2 weeks** prior to study entry
- **Prior immunotherapy** with PD1/PD-L1 and CTLA4 inhibitor
- Current **pregnancy** or **breastfeeding**
- **Autoimmune disease**
- **Carcinomatous meningitis**
- Systemic **immunosuppression**
- **Skin rash** affecting > 25% of body surface area
- **Inflammatory bowel disease**

Treatment Schedule

Lurbinectedin
Phase I: Escalating doses per standard "cohort of three" design 2.6 mg/m2 (Dose Level I) - 3.2mg/m2 (Dose Level II) IV every 3 weeks
Phase II: Determined MTD

Ipilimumab
1 mg/kg IV every 12 weeks

Nivolumab
3 mg/kg IV every 2 weeks

Participants may continue treatment until significant **disease progression** or **unacceptable toxicity** occurs.

Analysis

Safety
The **Intention-To-Treat (ITT)** population (all patients who received at least one dose of study drug) will be used for **adverse event** analysis.

Efficacy
The **Intention-To-Treat (ITT)** population (all patients who received at least one dose of study drug) will be used for **OS** analysis. The **Modified Intention-To-Treat (mITT)** population (patients who completed the first two 3-week cycles and follow-up imaging) will be used for analysis of **PFS**.

PFS and OS will be estimated by **Kaplan Meier** method with two-sided 95% confidence interval.

Status

The study has **enrolled 40 patients. C**linical trial information: **NCT04535271**

Study Schema

Screening (D-14)
≥18 years
With Advanced Soft tissue sarcoma

Phase I

Drug	Route	Dose	Schedule
Lurbinectedin	IV	2.6-3.2 mg/m2	D1, q 3 weeks
Ipilimumab	IV	1 mg/kg	D14, q 12 weeks
Nivolumab	IV	3 mg/kg	D14, q 2 weeks

Safety Analysis
MTD Determination

Phase II

Drug	Route	Dose	Schedule
Lurbinectedin	IV	2.6-3.2 mg/m2	D1, q 3 weeks
Ipilimumab	IV	1 mg/kg	D14, q 12 weeks
Nivolumab	IV	3 mg/kg	D14, q 2 weeks

Efficacy Analysis
CT Scan or MRI q 6 weeks until EOT

End of Study (36 months)
Safety and Efficacy Analysis

Author Information

Disclosure
The authors declare no conflict of interest. This Investigator-Sponsored Trial (IST) is funded by Jazz Pharmaceuticals via a research grant.

Presenting Author
Samantha Jeffrey
Research Fellow, Sarcoma Oncology Center

Corresponding Author
Dr. Erlinda Gordon
Director, Gene and Cell Therapy/Immunotherapy, Sarcoma Oncology Center
egordon@sarcomaoncology.com

Presented at the 2026 American Society of Clinical Oncology (ASCO) Annual Meeting, May 29 – June 2. 2026, Chicago, IL, USA

Funded by a grant from Jazz Pharmaceuticals.

References: 1. Eisenhauer et al. RECIST v1.1, 2009; 2. NCI CTCAE vs 5.0; 3. Kaplan and Meier 1958; 4. Belgiovini et al. Brit J Cancer 2017; 5. Gordon et al., Cancers, 2023; 6.Kundu et al. Transl Lung Cancer Res 2021;10(11):4095-4105.