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Clinical Benefit Analysis of a Phase I/II Study Using Lurbinectedin Combined with Ipilimumab and Nivolumab as First-Line Therapy for Advanced Soft Tissue Sarcoma (NCT05876715)

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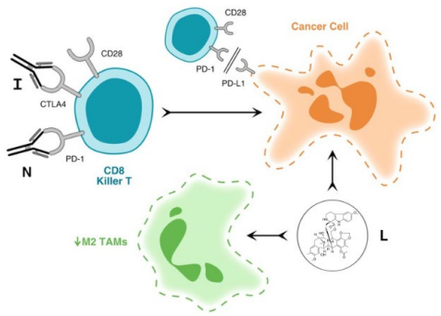
Background

The efficacy of **immune checkpoint inhibitors** (ICIs) increases when given as **first line therapy** for **sarcomas** and may have **synergistic** activity with **lurbinectedin**, a synthetic version of the marine alkaloid trabectedin, whose plausible mechanism of action is not only to **induce apoptosis** in cancer cells but also to **deplete growth promoting tumor-associated macrophages** in the tumor microenvironment. Here, we report the interim **clinical benefit analysis** of **lurbinectedin** combined with **ipilimumab** and **nivolumab** in previously treated and previously untreated **advanced soft tissue sarcoma** (STS).

Figure 1. Mechanism of Action



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

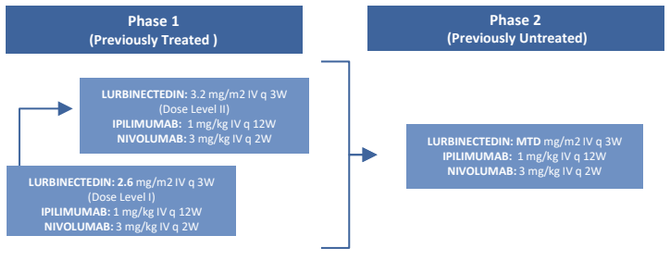
Ipilimumab (I) is a monoclonal antibody that binds to the CD8+ Killer T-Cell CTLA-4 receptor, a negative regulator of T cell activation. Via preventing CTLA-4 from outcompeting the CD28 receptor for B7 on Antigen Presenting Cells, ipilimumab allows CD28 to bind B7, resulting in CD28 pathway-mediated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

Patients & Methods

This is a **single-site dose-seeking Phase I/II** study. Up to **40 patients** with **advanced STS** will be enrolled. **Phase I** will enroll **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**.

Figure 2. Study Schema



Treatment Schedule

LURBINECTEDIN: 2.6 mg/m2 IV every 3 weeks (Dose Level I); if no DLT continue to: 3.2 mg/m2 IV every 3 weeks (Dose Level II); if no DLT = MTD
IPILIMUMAB: 1 mg/kg IV every 12 weeks
NIVOLUMAB: 3 mg/kg IV every 2 weeks

Patients & Methods

Key Inclusion Criteria

- **Adult** patients ≥ 18 years
- Confirmed pathologic diagnosis of **advanced STS**
- At least **one measurable target lesion** by **RECIST v1.1** of 1 cm
- **Previously treated** in Phase I; **previously untreated** in Phase II

Key Exclusion Criteria

- **Untreated CNS** disorder
- History of **autoimmune disease**
- **Prior immunotherapy** with PD1/PD-L1 and CTLA4 inhibitor
- **Uncontrolled systemic disease**

Interim Endpoints

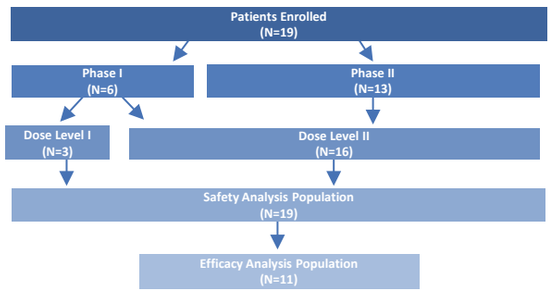
- **Clinical Benefit Rate** (CBR) defined by confirmed response of CR, PR, or SD by RECIST v1.1 via CT or MRI
- **Disease Control Rate** (DCR) defined by confirmed response of CR, PR, or SD by RECIST v1.1 via CT or MRI
- **Best Overall Response Rate** (BORR) defined by best overall response of CR or PR by RECIST v1.1 via CT or MRI

Analysis

Patients who received at least one dose of study drug are evaluable for safety. Patients who completed at least one treatment cycle and had a follow-up CT or MRI at week 12 are evaluable for efficacy. A modified **Simon 2-stage design** with Type I error rate = 0.1 and power = 0.8 is used for CBR analysis. Accordingly, a CBR ≥ 30% would warrant continuing the phase 2 part of the study.

Results

Figure 3. Patient Distribution



Safety Analysis

19 patients who received at least one dose of study drug were evaluable for safety. **No ≥ Grade 3 adverse events** were reported **during the DLT period**. **Eight of 19** patients (42%) **experienced ≥ Grade 3 TRAEs.** There were **no unexpected TRAEs nor Grade 5 TRAEs**.

TRAE Incidence (N=19)

n, (%)	≥Grade 3	Grade 3	Grade 4
Patients with ≥ 1 TRAE	8 (42%)	7 (37%)	2 (11%)
Lymphocyte count decrease	5 (26%)	4 (21%)	1 (5%)
White blood cell count decrease	2 (11%)	1 (5%)	1 (5%)
ANC decreased	2 (11%)	1 (5%)	1 (5%)
Platelet count decrease	1 (5%)	0 (0%)	1 (5%)
Anemia	1 (5%)	1 (5%)	0 (0%)
Flu-like symptoms	1 (5%)	1 (5%)	0 (0%)
Fatigue	1 (5%)	1 (5%)	0 (0%)

Results

Efficacy Analysis

11 patients who completed at least one treatment cycle and had a follow-up CT or MRI at week 12 were evaluable for efficacy.

Phase I

In Phase I, there were 5 efficacy evaluable patients, with 4/5 SD and 1/5 PD at week 12 (**80% CBR**; **80% DCR**), and a BOR of 5/5 SD (**0% BORR**).

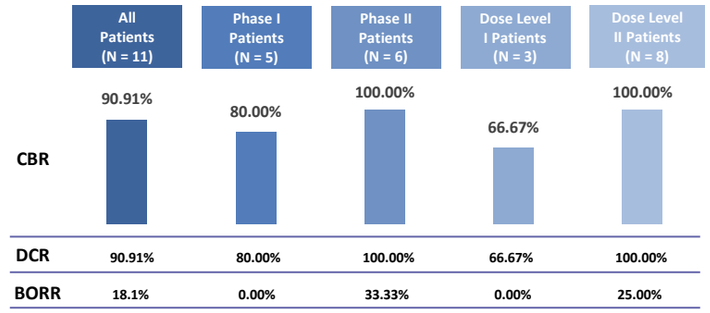
Phase II

In Phase II, there were 6 efficacy evaluable patients, with 1/6 CR and 5/6 SD at week 12 (**100% CBR**; **100% DCR**), and a BOR of 1/6 CR, 1/6 PR, and 4/6 SD (**33.3% BORR**).

Patient Responses (N=11)

Diagnosis	Phase	Dose Level	BOR	Confirmed Response
Angiosarcoma	II	II	SD	SD
Chondrosarcoma	II	II	SD	SD
Clear Cell Sarcoma	II	II	SD	SD
Desmoplastic Small Round Cell Tumor	I	I	SD	PD
Endometrial Stromal Sarcoma	I	II	SD	SD
Epithelioid Hemangioendothelioma	II	II	CR	CR
Myxofibrosarcoma	II	II	SD	SD
Synovial Sarcoma	I	II	SD	SD
Undifferentiated Pleomorphic Sarcoma	II	II	PR	SD
Undifferentiated Pleomorphic Sarcoma	I	I	SD	SD
Uterine Leiomyosarcoma	I	I	SD	SD

Figure 4. Response Outcomes



Conclusion

Taken together, the **interim results** of **lurbinectedin in combination with ipilimumab and nivolumab** for **advanced soft tissue sarcoma**, demonstrated a **100% CBR** (100% DCR and 33.33% BORR) for Phase II, with **manageable toxicity**, warranting **continuation of Phase II** of the study.

Author Information

Disclosure
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