Open-Label, Phase 2 Study of Ladiratuzumab Vedotin (LV) for Castration Resistant Prostate Cancer

(SGNLVA-005, Trial in Progress)

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Disease Background

- Prostate Cancer is the second most common cancer and the fifth leading cause of cancer mortality in men worldwide[1].
- Patients with metastatic Castration Resistant Prostate Cancer (mCRPC) and other advanced solid tumors generally have poor outcomes; the 5-year relative survival rate for distant stage prostate cancer is approximately 30%[2].
- While post-2nd generation anti-androgen receptor chemotherapy and immunotherapies are potential treatment options, they are associated with modest responses and significant adverse events[3].
- There remains a high unmet need for patients in later lines of therapy.
- SGNLVA-005 (NCT04032704) is an open-label, phase 2 study evaluating SGN-LIV1A (or ladiratuzumab vedotin [LV]) monotherapy in patients with advanced solid tumors.
- The study is currently evaluating the safety and efficacy of weekly LV dosing.

LIV-1 and Ladiratuzumab Vedotin (LV)

- Prostate Cancer has been shown in clinical studies to be sensitive to tubulin-targeting chemotherapy with drugs such as docetaxel[4,5].
- LIV-1 is a transmembrane protein highly expressed in prostate cancer as well as showing expression in a variety of other cancer types[6].
- LV is a novel investigational humanized Immunoglobulin G1 (IgG1) antibody-drug conjugate (ADC) directed against LIV-1[6].
- LV mediates delivery of monomethyl auristatin E (MMAE), a potent microtubule disrupting agent. Preclinical studies have shown LV drives antitumor activity through cytotoxic cell killing and induction of immunogenic cell death (ICD)[7]. Clinical biomarker studies also showed that LV induced immune activation in the tumor microenvironment[8].
- In a phase 1 study, LV was tolerable and active in heavily pretreated patients with metastatic breast cancer at a recommended dose of 2.5 mg/kg every 21 days[9].
- More frequent, fractionated dosing has improved the activity and/or safety of other ADCs[10,11].

LV Proposed Mechanism of Action

- LV[6]
  - Humanized IgG1 ADC
  - Conjugated to MMAE
  - Selectively binds to cells expressing LIV-1
- LV-mediated delivery of MMAE drives antitumor activity through
  - Cytotoxic cell killing
  - Inducing ICD[7]

Ladiratuzumab Vedotin is an investigational agent, and its safety and efficacy have not been established.

Safety and Efficacy of LV Monotherapy Given on a 3-week Cycle

- In a phase 1 study (SGNLVA-001) with LV given on an every 3-week cycle, LV was tolerable and active in heavily pretreated patients with metastatic breast cancer at a recommended dose of 2.5 mg/kg[9].
- The maximum tolerated dose was not reached during the completed dose escalation phase, and there were no dose-limiting toxicities.
- The main toxicities associated with LV monotherapy were peripheral neuropathy and neutropenia.
- Interim results have shown clinically meaningful antitumor activity in heavily pretreated (median of 4 prior therapies) patients with metastatic triple-negative breast cancer.
- Among 60 efficacy evaluable patients (LV 2.0–2.8 mg/kg), the objective response rate was 25% (95% confidence interval, 15–38) and the disease control rate was 58%.

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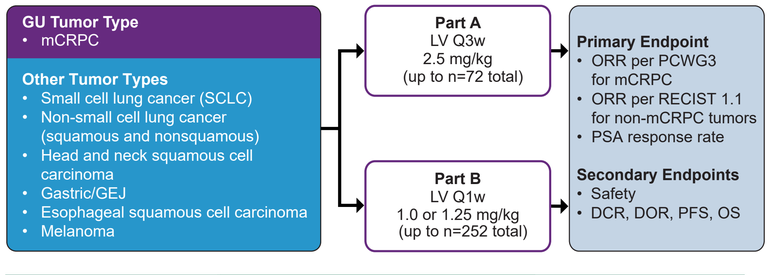
Study Design

- SGNLVA-005 (NCT04032704) is an ongoing, global, open-label, phase 2 study evaluating LV monotherapy in patients with advanced solid tumors.

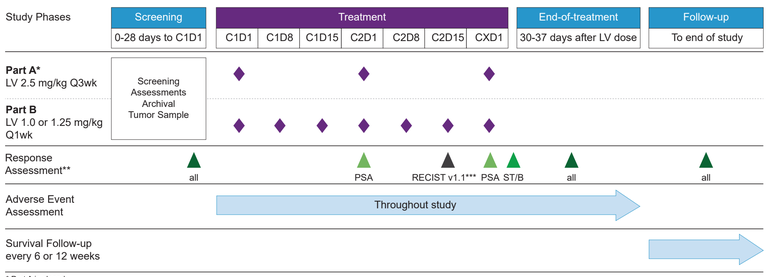


Accrue first 12 patients per cohort → Continue accrual if tolerability is demonstrated and interim analysis for futility is passed → Accrue up to 30 patients per cohort

DCR = disease control rate; DOR = duration of response; GEJ = gastroesophageal junction; GU = genitourinary; OS = overall survival; ORR = objective response rate; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PFS = progression free survival; PSA = prostate-specific antigen; Q1w = every 1 week; Q3w = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

Treatment Schema

- Patients with mCRPC are enrolled in Part B and will receive LV administered as an intravenous infusion at 1.25 mg/kg every 1 week.



* Part A is closed
** For mCRPC patients, PSA will be assessed every 3 weeks. Soft tissue tumor assessment and bone scans (ST/B) will be assessed every 8 weeks for the first 24 weeks, then every 12 weeks thereafter.
*** For all other tumors, assessment according to RECIST v1.1 every 6 weeks within the first 12 months from Cycle 1 Day 1 (C1D1), then every 12 weeks thereafter.

Eligibility

- The study is enrolling previously treated patients with unresectable locally advanced or metastatic disease.
- For the mCRPC cohort, patients must have metastatic castration-resistant disease and have received no more than 1 prior line of 2nd generation androgen receptor-targeted therapy for metastatic castration-sensitive prostate cancer or mCRPC.
- For the mCRPC cohort, patients with measurable and non-measurable disease according to PCWG3 are eligible if the protocol-defined criteria are met.
  - Patients with non-measurable disease must have documented rising PSA levels or appearance of new lesion according to PCWG3.
- For all other cohorts, patients must have measurable disease per RECIST v1.1.
- All patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1, and adequate organ function.
- Patients are not preselected based on tumor LIV-1 expression.

Key Exclusion Criteria

- mCRPC patients must not have BRCA gene mutations, prior cytotoxic chemotherapy in the metastatic mCRPC setting, prior radioisotope therapy, or radiotherapy to ≥30% of bone marrow.
- Active concurrent malignancy or previous malignancy within the past 3 years. Exceptions are malignancies with a negligible risk of metastasis or death (eg, 5-year OS ≥90%).
- Any anticancer therapy within 3 weeks of starting study treatment.
- Known active central nervous system (CNS) lesions (including leptomeningeal metastasis) that have not been definitively treated.
- Ongoing sensory or motor neuropathy ≥Grade 2.

Objectives

Primary Objective

- Evaluate antitumor activity of LV

Secondary Objectives

- Evaluate safety and tolerability of LV
- Evaluate stability and control of disease
- Evaluate durability of response
- Evaluate progression-free survival
- Evaluate survival of patients treated with LV
- Evaluate pharmacokinetics (PK) of LV
- Evaluate Immunogenicity of LV

Endpoints

Primary Endpoints

- For mCRPC, investigator-determined confirmed ORR as measured by PCWG3
- For non-mCRPC tumors, investigator-determined confirmed ORR as measured by RECIST v1.1
- For mCRPC, investigator-determined confirmed PSA response rate in addition to ORR

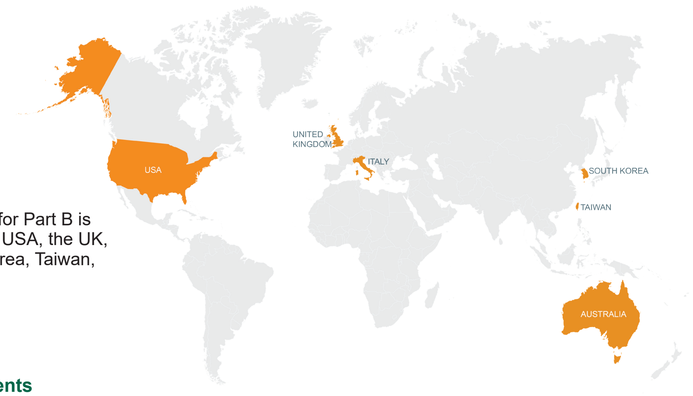
Secondary Endpoints

- Type, incidence, severity, seriousness, and relatedness of adverse events
- Investigator-determined DCR as measured by RECIST v1.1
- Investigator-determined DOR as measured by RECIST v1.1 for all tumors
- Investigator-determined PFS as measured by RECIST v1.1 for all tumors
- For the mCRPC cohort, investigator determined PSA-PFS
- OS
- Selected PK parameters for LV, total antibody, and MMAE
- Incidence of antitherapeutic antibodies to LV

Response Assessments

- For mCRPC patients, soft tissue tumor assessment by computed tomography or magnetic resonance imaging scan (CT/MRI) and bone scans according to PCWG3 (modified RECIST v1.1 criteria specific to prostate cancer).
- PSA response rate will be assessed per PCWG3.
- For non-mCRPC cohorts, tumors will be assessed according to RECIST v1.1.

Study Sites



- Study accrual for Part B is ongoing in the USA, the UK, Italy, South Korea, Taiwan, and Australia.

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