OPEN-LABEL, PHASE 2 STUDY OF LADIRATUZUMAB VEDOTIN (LV) FOR UNRESECTABLE LOCALLY ADVANCED OR METASTATIC SOLID TUMORS (SGNLVA-005, TRIAL IN PROGRESS)

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Background

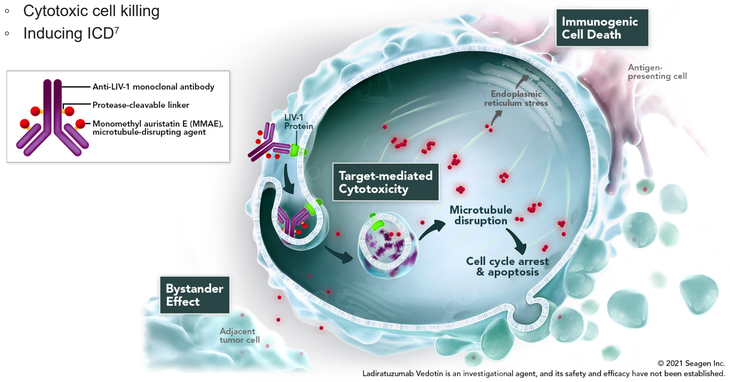
- Prostate cancer is the second most common cancer and the fifth leading cause of cancer mortality in men worldwide[1].
- Patients with metastatic, castration-resistant prostate cancer (mCRPC) and other advanced solid tumors generally have poor outcomes, with a 5-year relative survival rate of approximately 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 investigating SGN-LIV1A (or ladiratuzumab vedotin [LV]) monotherapy in patients with advanced solid tumors.

LIV-1 and Ladiratuzumab Vedotin

- Prostate cancer has been shown in clinical studies to be sensitive to tubulin-targeting chemotherapy (eg, docetaxel)[4,5].
- LIV-1 is a transmembrane protein highly expressed in prostate cancer and 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.
  - In preclinical studies, LV drives antitumor activity through cytotoxic cell killing and induction of immunogenic cell death (ICD)[7].
  - In clinical biomarker studies, LV induced immune activation in the tumor microenvironment[8].
- More frequent, fractionated dosing has improved the activity and/or safety of other ADCs[9,10].

LV Proposed Mechanism of Action

- LV[6]
  - Humanized IgG1 ADC
  - Selectively binds to cells expressing LIV-1
  - Conjugated to MMAE
- 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), LV (2.5 mg/kg every 3 weeks) was tolerable and active in heavily pretreated patients with metastatic breast cancer[11].
- The maximum tolerated dose was not reached during the completed dose escalation phase.
  - There were no dose-limiting toxicities.
- Commonly reported toxicities associated with LV monotherapy were peripheral neuropathy and neutropenia.
- Interim data indicate clinically meaningful antitumor activity in heavily pretreated (median of 4 prior therapies) patients with metastatic triple-negative breast cancer (mTNBC).
- In 60 efficacy evaluable mTNBC patients (LV 2.0–2.8 mg/kg):
  - Objective response rate (ORR) = 25% (95% confidence interval, 15–38)
  - Disease control rate = 58%

Study Design

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

Tumor Types
- mCRPC
- Squamous non-small cell lung cancer
- Head and neck squamous cell carcinoma
- Esophageal squamous cell carcinoma
- Melanoma

→ LV Q1W
1.25 mg/kg
(up to n=252 total) →

Primary Endpoint
- ORR per PCWG3 for mCRPC
- ORR per RECIST v1.1 for non-mCRPC tumors
- PSA response rate

Secondary Endpoints
- Safety
- DCR, DOR, PFS, OS

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; mCRPC = metastatic castration-resistant prostate cancer; OS = overall survival; PCWG3 = Prostate Cancer Clinical Trials Working Group 3; PFS = progression-free survival; PSA = prostate-specific antigen; Q1W = every week; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

Treatment Schema

- Patients are enrolled and receive LV administered as an intravenous infusion at 1.25 mg/kg every week.

Study Phases	Screening	Treatment							End-of-treatment	Follow-up
	0-28 days to C1D1	C1D1	C1D8	C1D15	C2D1	C2D8	C2D15	CXD1	30-37 days after LV dose	To end of study
1.25 mg/kg Q1W	Screening Assessments Archival Tumor Sample	◆	◆	◆	◆	◆	◆	◆		
Response Assessment*	all				PSA	RECIST v1.1**	PSA	ST/B	all	all
Adverse Event Assessment	Throughout study									
Survival Follow-up every 6 or 12 weeks										

* 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.
** Assessment of mCRPC according to PCWG3. 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.

Key Inclusion Criteria

- The study is enrolling previously treated patients with unresectable locally advanced or metastatic disease.
- mCRPC cohort
  - Patients must have metastatic castration-resistant disease and have received ≤1 prior line of 2nd generation androgen receptor-targeted therapy for metastatic castration-sensitive prostate cancer or mCRPC
  - 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
- Eastern Cooperative Oncology Group (ECOG) score of 0 or 1
- Adequate organ function
- No patient preselection based on tumor LIV-1 expression.

Key Exclusion Criteria

- mCRPC patients must not have
  - BCRA gene mutations
  - Prior cytotoxic chemotherapy in the metastatic mCRPC setting
  - Prior radioisotope therapy
  - Radiotherapy to ≥30% of bone marrow
- Active concurrent malignancy or previous malignancy within the past 3 years.
  - Exception: 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 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 DOR
- Evaluate PFS
- 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 mCRPC, investigator-determined confirmed PSA response rate in addition to ORR
- For non-mCRPC tumors, investigator-determined confirmed ORR as measured by RECIST v1.1

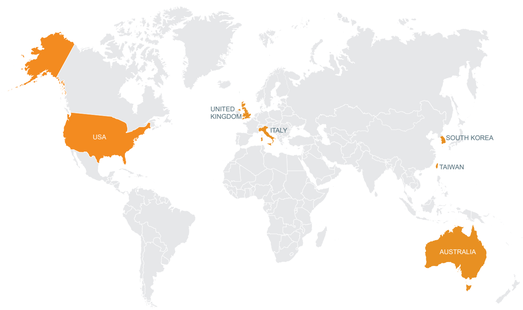
Secondary Endpoints
- Type, incidence, severity, seriousness, and relatedness of adverse events
- Investigator-determined DCR as measured by RECIST v1.1
- Investigator-determined DOR as measured by RECIST v1.1 for all tumors
- Investigator-determined PFS as measured by RECIST v1.1 for all tumors
- For 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.

Summary

- SGNLVA-005 (NCT04032704) is an ongoing, global, open-label, phase 2 study investigating LV monotherapy given once every week in previously treated patients with unresectable locally advanced solid tumors or metastatic disease.
- Study accrual is ongoing in the USA, UK, Italy, South Korea, Taiwan, and Australia.



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