SGNLVA-005: Open-Label, Phase 2 Study of Ladiratuzumab Vedotin (LV) for Advanced Aerodigestive Tract Malignancies (Trial in Progress)

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Disease Background

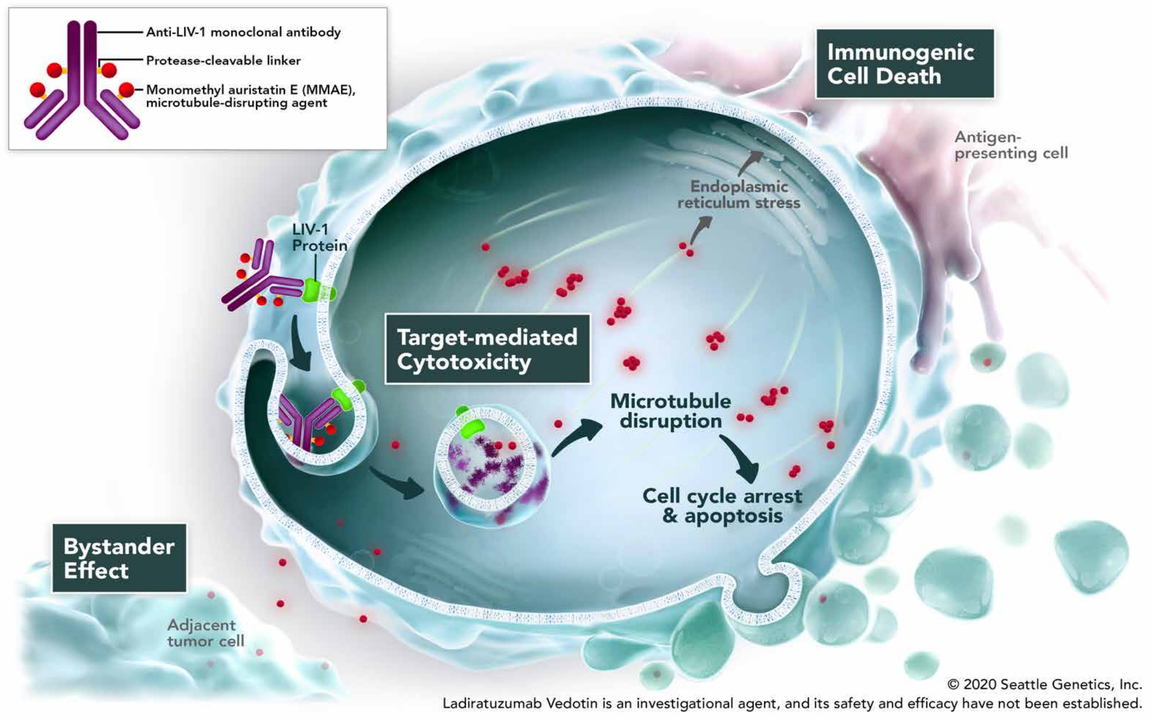
- Gastric cancer and esophageal cancer rank among the 10 most common cancers worldwide and are leading causes of cancer mortality worldwide.[1]
- Patients with metastatic gastric or esophageal cancer have poor outcomes; the 5-year relative survival rate is approximately 5% for each cancer.[2,3]
- While second-line chemotherapy, targeted therapies, and immunotherapies are potential treatment options, they are associated with modest responses and significant adverse events.
- There remains a high unmet need for patients in later lines of therapy.
- This phase 2 study (Study SGNLVA-005) is evaluating ladiratuzumab vedotin (LV) in patients with advanced upper aerodigestive tract malignancies.

LIV-1 Target

- LIV-1 is a transmembrane protein, zinc transporter, and downstream target of STAT3 whose expression can downregulate E-cadherin leading to epithelial-mesenchymal transition (EMT).[4,5]
- A moderate-to-high prevalence of LIV-1 expression has been detected in advanced upper aerodigestive tract malignancies.[6]
- LIV-1 expression has been linked with malignant progression to metastasis in breast cancer.[4]
- Treatment with LV, an investigational antibody-drug conjugate (ADC) that targets LIV-1-expressing cells, is associated with mitotic arrest, infiltration of macrophages, and upregulation of cytokine signaling,[7] which is in line with preclinical reports demonstrating that LV monotherapy causes immunogenic cell death (ICD).[8]

Ladiratuzumab Vedotin

- LV
  - Humanized IgG1 ADC
  - Conjugated to monomethyl auristatin E (MMAE)
  - Selectively binds to cells expressing LIV-1
- LV mediated delivery of MMAE drives antitumor activity through
  - Cytotoxic cell killing
  - Inducing ICD[8]



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

LV Monotherapy Background

Safety Summary[9]

- Results from an ongoing phase 1 study of LV monotherapy showed tolerability and manageable toxicity with antitumor activity in heavily pretreated patients with metastatic triple-negative breast cancer (mTNBC).
- The maximum tolerated dose was not reached during dose escalation, and there were no dose-limiting toxicities.
- The main toxicities associated with LV monotherapy were peripheral neuropathy and neutropenia.
- The recommended phase 2 dose of 2.5 mg/kg and maximum dose of 200 mg per cycle for LV monotherapy were identified.

Preliminary Efficacy[9]

- Interim results have shown clinically meaningful antitumor activity in heavily pretreated (median of 4 prior therapies) patients with mTNBC.
- Among 60 efficacy evaluable patients (LV 2.0–2.8 mg/kg), the objective response rate (confirmed/unconfirmed) was 25% (95% CI, 15–38) and the disease control rate was 58%.

References

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Study Design

- This ongoing, open-label, phase 2 study (NCT04032704) evaluating LV is enrolling adults with unresectable locally advanced or metastatic solid tumors, including gastric and gastroesophageal junction (GEJ) adenocarcinoma and esophageal squamous cell carcinoma.

Key Inclusion Criteria
- No more than 1 line of prior platinum-based chemotherapy for advanced disease
- Prior HER2-targeted therapy for patients with HER2 overexpression permitted
- Prior anti-PD(L)1 therapy permitted but not mandated

Gastric and GEJ adenocarcinoma

Esophageal squamous cell carcinoma

Small cell lung carcinoma; Non-small cell lung carcinoma-squamous; Non-small cell lung carcinoma-nonsquamous; Head and neck squamous cell carcinoma

Part A
LV q3wk*

Part B
LV q1wk*

Efficacy Endpoints

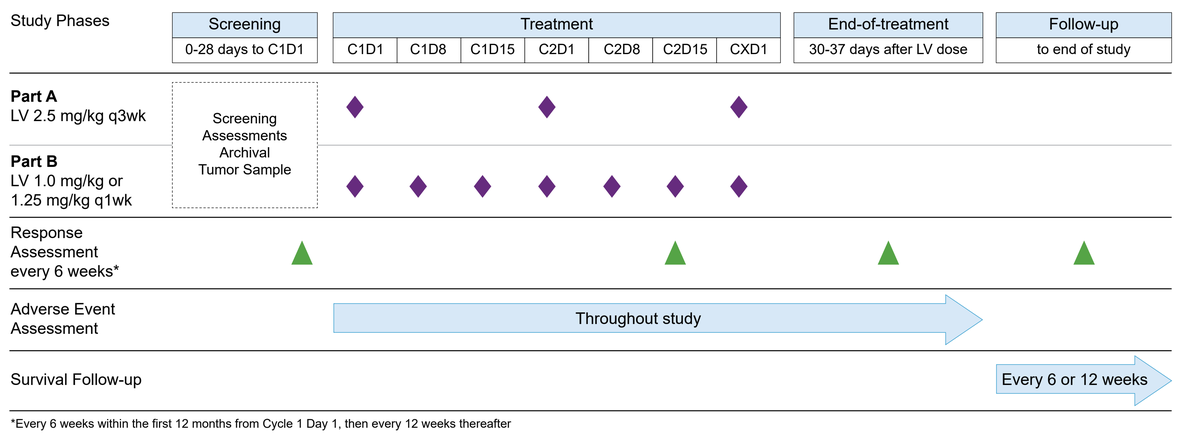
Primary
- Objective response rate

Secondary
- Disease control rate
- Duration of response
- Progression-free survival
- Overall survival

Accrue first 12 patients per cohort → Continue accrual if at least 2 out of 12 patients have a response → Accrue up to 30 patients per cohort

* q3wk: LV administered once every 3 weeks; q1wk: LV administered weekly

Treatment Schema



*Every 6 weeks within the first 12 months from Cycle 1 Day 1, then every 12 weeks thereafter

Key Inclusion Criteria

- Unresectable locally-advanced or metastatic solid tumors:
  - Gastric and GEJ adenocarcinoma
  - Esophageal squamous cell carcinoma
  - Small cell lung carcinoma
  - Non-small cell lung cancer (NSCLC)-squamous
  - NSCLC-nonsquamous
  - Head and neck squamous cell carcinoma
- Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Eastern Cooperative Oncology Group performance status score of 0 or 1
- No more than 1 line of prior platinum-based chemotherapy for advanced disease
- Prior anti-PD(L)1 therapy permitted
- Adequate hematologic, kidney, and liver function
- No pre-selection for LIV-1 expression

Key Exclusion Criteria

- Active concurrent malignancy or previous malignancy within the past 3 years
- Ongoing sensory or motor neuropathy ≥Grade 2
- Malignant CNS disease that has not been definitively treated

Objectives

Primary Objective
- Evaluate antitumor activity

Secondary Objectives
- Evaluate safety and tolerability
- Evaluate disease control rate
- Evaluate duration of response
- Evaluate progression-free survival
- Evaluate overall survival
- Assess pharmacokinetics

Response Assessments

- Response assessed per RECIST v1.1
- Response assessments performed every 6 weeks (±3 days) for the first 12 months, and every 12 weeks (±7 days) thereafter

Study Sites

- Global study with ongoing accrual at sites in the United States, Asia, Australia, and with anticipated sites in Europe

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