Phase 2 Study of Disitamab Vedotin in Patients With HER2-Expressing Non-Small Cell Lung Cancer (SGNDV-005; Trial in Progress)

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Summary

- For patients with NSCLC and HNSCC, 2L treatment options following disease progression are limited
- DV is an investigational HER2-directed ADC comprising a monoclonal antibody, disitamab, conjugated to MMAE via a protease-cleavable mc-vc linker
- SGNDV-005 is a phase 2 trial assessing DV monotherapy for the treatment of patients with previously treated, locally-advanced unresectable or metastatic HER2-expressing solid tumors
- Enrollment is currently ongoing in Australia, Canada, and the US, with additional sites planned in Germany, Italy, Japan, South Korea, Spain, and the UK

Abbreviations

1L, first line; 2L, second line; ADA, antidrug antibody; ADC, antibody-drug conjugate; AE, adverse event; AESI, AE of special interest; CNS, central nervous system; DCR, disease control rate; DOR, duration of response; DV, disitamab vedotin; IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; HNSCC, head and neck squamous cell carcinoma; la/mGC, locally advanced/metastatic gastric cancer; la/mGEJC, locally advanced/metastatic gastroesophageal junction cancer; la/mUC, locally advanced/metastatic urothelial cancer; MMAE, monomethyl auristatin E; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PD-(L)1, programmed ligand 1/cell death protein 1; PFS, progression-free survival; PK, pharmacokinetics; Q2W, every 2 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; TAb, total antibody

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Disclosures/COIs

- Jonathan W. Riess: Advisory boards: Amgen, Bayer, Beigene, Biodesix, Blueprint, BMS, Catalyst, Daiichi Sankyo, EMD Serono, Janssen, Jazz Pharmaceuticals, Merus NV, Regeneron, Roche/Genentech, Turning Point, Sanofi, Seagen; Consulting: Boehringer Ingelheim, Novartis; Travel: AstraZeneca, IO Biotech; Research grants (to institution): AnriVent, AstraZeneca, IO Biotech, Merck, Kinnate, Novartis, Novalent, Revolution Medicines, Summit, Seagen
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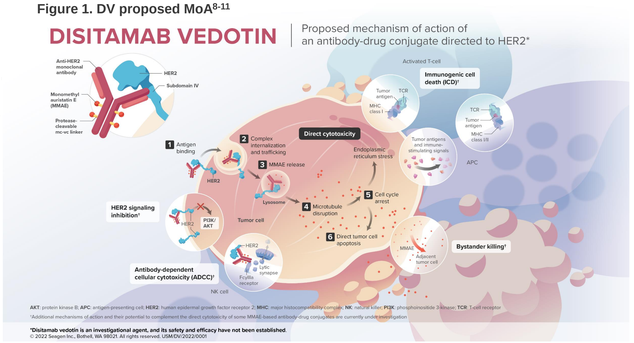
Background

- In NSCLC, immune checkpoint inhibitors, either as a monotherapy or in combination with chemotherapy, have emerged as the standard of care for 1L treatment of patients without actionable oncogenic gene mutations[1]
- For patients with unresectable or metastatic HNSCC, 1L treatment options include the immune checkpoint inhibitor pembrolizumab[2,3]
- Despite advances in 1L treatments, 2L+ treatment options for patients with HNSCC or NSCLC who progress remain limited[4,5]
- HER2 expression (defined as IHC ≥1+) has been reported across multiple tumor types, including HNSCC and NSCLC, and may be associated with poor outcomes[6]
- Disitamab vedotin (DV; RC48-ADC) is an investigational ADC comprising a fully humanized HER2-directed monoclonal antibody, disitamab, conjugated to MMAE via a protease-cleavable mc-vc linker[7]
- DV binds to a distinct epitope on HER2 and elicits antitumor activity through multimodal mechanisms of action, including MMAE-mediated direct cytotoxicity, bystander effect, and immunogenic cell death (**Figure 1**)[7-11]
- DV has previously demonstrated a clinically meaningful response in patients with HER2-expressing breast cancer, urothelial cancer, gastric or gastroesophageal junction cancers who had received ≥2 prior lines of systemic treatment, and is also conditionally approved in China for treatment of patients with HER2-positive la/mUC (defined as HER2 IHC 2+/3+) who had received prior platinum-based chemotherapy, and in HER2-positive la/mGC/GEJC (defined as HER2 IHC 2+/3+)[7,12-14]
  - These data support DV as an investigational therapy for patients with previously treated, advanced HNSCC and NSCLC
- SGNDV-005 (NCT06003231) is a phase 2 study investigating DV for 2L+ treatment of patients with previously treated, locally advanced unresectable or metastatic HER2-expressing solid tumors[15]
  - Cohorts 1 and 2 of the SGNDV-005 study include patients with metastatic or locally advanced unresectable HNSCC and NSCLC, respectively
  - The study designs of Cohorts 3 (ovarian cancer) and 4 (endometrial cancer) of SGNDV-005 have been previously presented and enrollment for both cohorts is complete (for HER2-expressing tumors)[16]

Figure 1. DV proposed MoA[8-11]



Eligibility criteria

Inclusion criteria

- Age ≥18 years
- Locally advanced unresectable or metastatic HER2-expressing (IHC 1+, 2+, or 3+) solid tumors

HNSCC cohort inclusion criteria (cohort 1)

- Pathologically documented HNSCC
- Unresectable locally advanced recurrent or metastatic stage disease
- Must have progressed after treatment with a platinum-based therapy
- Must have received no more than 1 line of cytotoxic chemotherapy for advanced disease
- May have received prior anti-PD(L)1 therapy

NSCLC cohort inclusion criteria (cohort 2)

- Pathologically documented NSCLC
- Unresectable locally advanced or metastatic stage disease
- Must have disease progression:
  - After treatment with a platinum-based therapy, or
  - Within 6 months of platinum-based adjuvant, neoadjuvant, or concomitant chemoradiotherapy for early or locally advanced stage disease
- Must have received prior anti-PD(L)1 therapy, unless contraindicated
- Must have received no more than 2 prior lines of cytotoxic chemotherapy for advanced disease

Exclusion criteria

- Prior treatment with an MMAE-containing agent
- Known hypersensitivity to any excipient contained in the drug formulation of DV
- Prior invasive malignancy within 2 years of the first dose of the study or any evidence of residual disease from a previously diagnosed malignancy
- Active untreated CNS or leptomeningeal metastasis
- Peripheral neuropathy grade ≥2

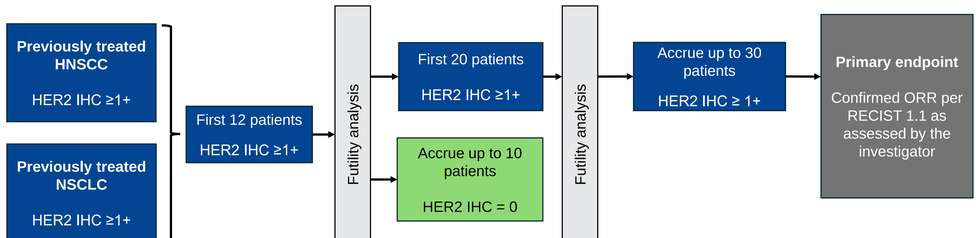
Objectives and endpoints

Primary objective	Corresponding endpoint
Evaluate the antitumor activity of DV in patients with previously treated, locally-advanced unresectable or metastatic HER2-expressing solid tumors	• Confirmed ORR per RECIST 1.1 as assessed by the investigator
Secondary objectives	**Corresponding endpoints**
Evaluate the safety and tolerability profile of DV	• Type, incidence, severity, seriousness, and relatedness of AEs, including AESIs • Type, incidence, and severity of laboratory abnormalities, as well as significant changes from baseline • Frequency of treatment interruptions, dose reductions, and treatment discontinuations due to AEs
Assess antitumor activity of DV per investigator assessment by other clinically relevant measures	• Confirmed DCR per RECIST 1.1 as assessed by the investigator • DOR per RECIST 1.1 as assessed by the investigator • PFS per RECIST 1.1 as assessed by the investigator • OS
Evaluate the PK of DV	• Select PK parameters of DV, TAb, and unconjugated MMAE
Evaluate the immunogenicity of DV	• Incidence of ADA against DV
Exploratory objective	**Corresponding endpoint**
Assess biomarkers in relation to response, toxicity, PD relationship, or resistance to DV	• Biomarkers of DV-mediated biological activity, resistance, and their potential associations with clinical outcome measures

Study design

- SGNDV-005 is a phase 2, multicohort, multicenter, open-label basket study assessing DV as a monotherapy in adults with previously treated, locally-advanced unresectable or metastatic HER2-expressing solid tumors (**Figure 2**)

Figure 2. SGNDV-005 phase 2 trial design (HNSCC and NSCLC cohorts)



Study treatment will continue until disease progression or unacceptable toxicity, pregnancy, death, withdrawal of consent, or termination of the study by the sponsor.
Initial disease assessment will occur at screening. After the screening disease assessment, tumor response assessments will occur Q6W for the first 72 weeks and Q12W after 72 weeks.

Enrollment sites