PHASE 2 CLINICAL STUDY EVALUATING THE EFFICACY AND SAFETY OF DISITAMAB VEDOTIN WITH OR WITHOUT PEMBROLIZUMAB IN PATIENTS WITH HER2-EXPRESSING UROTHELIAL CARCINOMA (RC48G001, TRIAL IN PROGRESS)

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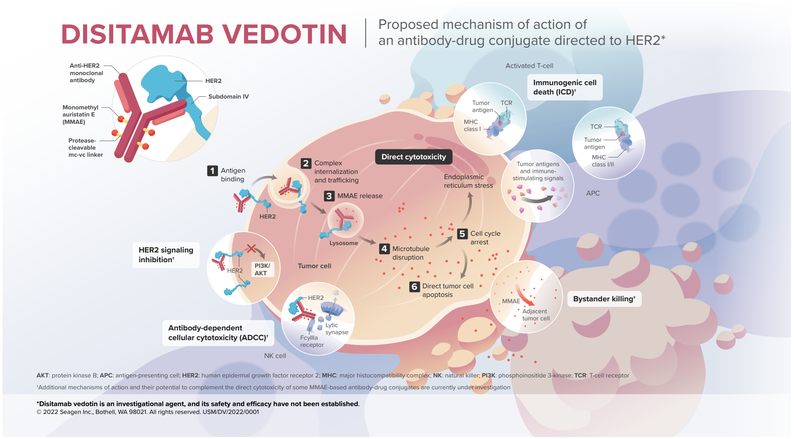
Background and Rationale

- Metastatic urothelial carcinoma (mUC) is an aggressive malignancy with 5-year survival rates of <5%
  The current standard of care, cisplatin-based 1L chemotherapy, can be difficult for many patients to tolerate[1,2]
  - In recent years, immunotherapy and antibody-drug conjugates (ADCs) have changed the later-line treatment of mUC[3]
- Overexpression of human epidermal growth factor receptor 2 (HER2) has been associated with poor outcomes in locally advanced and metastatic UC (la/mUC)[4]
- Disitamab vedotin (DV) is a HER2-directed ADC that elicits antitumor activity through proposed multimodal mechanisms of action including direct cytotoxicity, bystander effect, and immunogenic cell death (ICD)[5]
  - DV comprises a fully humanized immunoglobulin G1 monoclonal antibody (disitamab), the clinically validated microtubule-disrupting agent monomethyl auristatin E (MMAE) which induces apoptosis, and a protease-cleavable mc-vc linker that attaches MMAE to disitamab and enables preferential release of MMAE within target cells[6]
  - MMAE released from disitamab vedotin can induce ICD, which promotes activation and recruitment of immune cells to tumors to elicit antitumor activity[6]
- The capacity of DV to induce ICD supports the rationale for its combination with immunotherapy agents[7]
  - Preclinical data in xenograft mouse models show combining DV with immunotherapy enhances antitumor immunity and primes the immune system to mount a memory T-cell response[7]
- DV has been conditionally approved in LA/mUC and gastric cancer in China and was granted Breakthrough Therapy designation by the FDA for post-platinum treatment of HER2-expressing LA/mUC[8]
- RC48G001 (NCT04879329) is a phase 2, multicohort, open-label, multicenter trial to evaluate the antitumor activity, safety, and PK of DV monotherapy, and DV with pembrolizumab, in patients with HER2-expressing la/mUC

Proposed Mechanism of Action of Disitamab Vedotin



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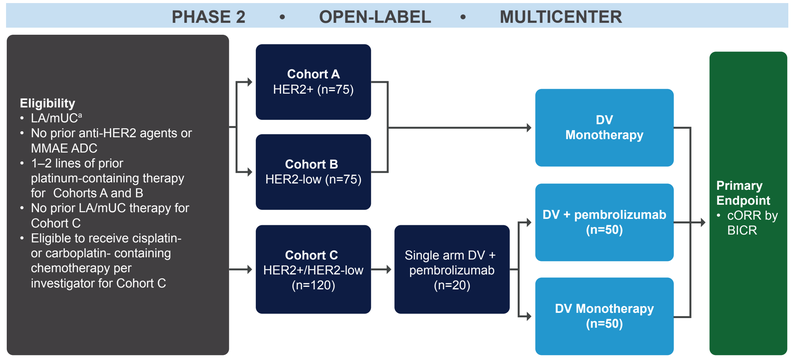
Study Design



[a]Histologically-confirmed, including UC originating from the renal pelvis, ureters, bladder, or urethra.

Study Treatment

- Cohort A will evaluate DV as a monotherapy for HER2-positive tumors (IV, Q2W)
- Cohort B will evaluate DV as a monotherapy for HER2-low tumors (IV, Q2W)
- Cohort C will evaluate DV (IV, Q2W) ± pembrolizumab (IV, day 1 of each 6-week cycle) for treatment-naïve HER2-positive and HER2-low tumors

Objectives and Endpoints

Primary Objectives

- Evaluate the efficacy of DV ± pembrolizumab
  - cORR per RECIST v1.1, assessed by BICR

Secondary Objectives

- Evaluate the efficacy of DV ± pembrolizumab as measured by DOR, PFS, DCR, and OS
  - cORR per RECIST v1.1, assessed by investigator
  - cDOR, PFS, and DCR (cCR, cPR, and SD) per RECIST v1.1, assessed by BICR and investigator
  - OS
  - Incidence of AEs, dose alterations, laboratory and ECG abnormalities, ADAs
  - Change from baseline LVEF
  - PK parameters (AUC, C_{max}, T_{max}, C_{trough})
- Evaluate the safety and tolerability of DV ± pembrolizumab
- Investigate the PK characteristics of DV ± pembrolizumab, free MMAE, and total amount of antibody
- Investigate the PK characteristics of pembrolizumab when administered in combination with DV
- Evaluate the immunogenicity of DV ± pembrolizumab
- Evaluate the immunogenicity of pembrolizumab when administered in combination with DV

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All authors met the ICMJE criteria for authorship.

Assessments

- Tumor response assessments will be performed according to RECIST v1.1
- cORR and DCR per RECIST v1.1 by BICR and investigator assessment will be evaluated in the Response Evaluable analysis set; corresponding 95% CI using the Clopper-Pearson method will be presented
- Blood samples will be collected for PK and ADA analysis and will be summarized using descriptive statistics
- For Cohorts A and B, the patient reported outcomes will be assessed
- Safety assessments will include monitoring and recording of AEs (including SAEs), concomitant medication, changes in laboratory test results and vital signs, ECOG PS, ECGs, and cardiac ejection fraction results. AE severity will be graded using CTCAE v5.0

Eligibility Criteria

Key Inclusion Criteria

- Histologically-confirmed, locally advanced, unresectable or metastatic urothelial cancer, including UC originating from the renal pelvis, ureters, bladder, or urethra
- HER2-expression status determined by central laboratory to be IHC 1+, 2+, or 3+, in the provided tumor sample

Cohorts A and B only

- Patients must have received only 1 or 2 lines of prior systemic treatment for LA/mUC, including 1 line of platinum-containing chemotherapy (neoadjuvant or adjuvant systemic chemotherapy with or without a PD-L1 inhibitor, with progression within 12 months of completing last dose, is considered a line of prior therapy)
- Radiographically documented disease progression during or after the most recent line of therapy for LA/mUC
- ECOG PS of 0 or 1

Cohort C only

- No prior systemic therapy for LA/mUC (neoadjuvant or adjuvant systemic chemotherapy with or without a PD-L1 inhibitor, with progression after 12 months of completing last dose, is allowed)
- Must be platinum eligible
- ECOG PS of 0, 1, or 2

Key Exclusion Criteria

- Known hypersensitivity to DV or pembrolizumab (Cohort C only)
- Prior antitumor treatment with 2 weeks of study start
- Toxicity from previous treatment that has not returned to grades 0 or 1 (exception: alopecia)
- Prior MMAE-based ADC or HER2-directed therapy
- Peripheral sensory or motor neuropathy ≥ grade 2
- Other malignant tumors within 3 years of treatment except the following:
  - Treated prostate cancer (treated with definitive intent) ≥1 year prior to treatment start
  - Malignancies that can be cured following treatment

Summary

- HER2 is overexpressed in multiple tumor types, including UC, and may be associated with poor outcomes; a targeted therapeutic approach has the potential to benefit patients with HER2-expressing tumors
- Disitamab vedotin (DV) is a HER2-directed ADC that elicits antitumor activity through proposed multimodal mechanisms of action
  - The capacity of disitamab vedotin to induce ICD, which promotes activation and recruitment of immune cells to tumors to elicit antitumor activity, supports the rationale for its combination with immunotherapy agents
- The RC48G001 trial is a phase 2 multicohort, open-label multicenter trial to evaluate the antitumor activity, safety, and PK of DV alone, and in combination with pembrolizumab, in patients with HER2-expressing la/mUC
- Enrollment is ongoing in North America and planned in Europe, Latin America, Asia-Pacific, and Israel

Abbreviations

1L, first-line; ADA, anti-drug antibody; ADC, antibody-drug conjugate; AE, adverse event; AUC, area under the concentration-time curve; BICR, blinded independent central review; cCR, confirmed complete response; cDOR, confirmed duration of response; C_{max}, maximum concentration; cORR, confirmed objective response rate; cPR, confirmed partial response; CTCAE, common terminology for adverse events; C_{trough}, trough concentration; DCR, disease control rate; DOR, duration of response; DV, disitamab vedotin; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GPP3, Good Publication Practice; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; ICMJE, International Committee of Medical Journal Editors; IHC, immunohistochemistry; IV, intravenous; LA/mUC, locally advanced unresectable or metastatic urothelial carcinoma; LVEF, left ventricular ejection fraction; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; MOA, mechanism of action; mUC, metastatic urothelial carcinoma; OS, overall survival; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetics; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse events; SD, stable disease; T_{max}, time to maximum concentration; UC, urothelial carcinoma.

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