FPN 1779TiP

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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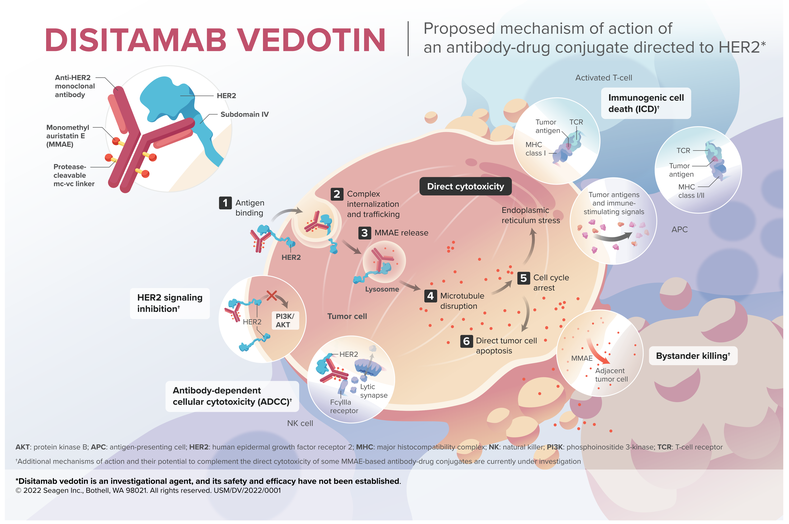
Background and Rationale

- Metastatic urothelial carcinoma (mUC) is an aggressive malignancy with 5-year survival rates of <5%[1] The current standard of care, cisplatin-based 1L chemotherapy, cannot be tolerated by many patients[2] There is a strong need for improved 1L and later lines of therapy
- HER2 is part of the human epidermal growth factor receptor family and is expressed on multiple tumor types, including UC. Overexpression of HER2 may be associated with poor outcomes[3] and no HER2-directed therapies are currently approved for UC in the US and EU
- Disitamab vedotin (DV) is a HER2-directed ADC that elicits antitumor activity through proposed multimodal MOAs including direct cytotoxicity, bystander effect, and immunogenic cell death. DV has previously shown promising efficacy in combination with PD-1 inhibition in patients with mUC[4]
- 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[5]
- RC48G001 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

Disitamab Vedotin Proposed Mechanism of Action



AKT: protein kinase B; **APC**: antigen-presenting cell; **HER2**: human epidermal growth factor receptor 2; **MHC**: major histocompatibility complex; **NK**: natural killer; **PI3K**: phosphoinositide 3-kinase; **TCR**: T-cell receptor

†Additional mechanisms of action and their potential to complement the direct cytotoxicity of some MMAE-based antibody-drug conjugates are currently under investigation

***Disitamab vedotin is an investigational agent, and its safety and efficacy have not been established.**

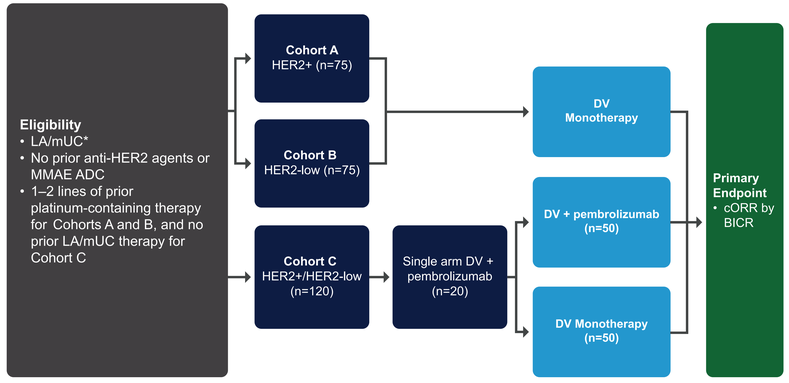
Study Treatment

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

Study Design

PHASE 2 • OPEN-LABEL • MULTICENTER



ADC: antibody-drug conjugate; **BICR:** blinded independent central review; **cORR:** confirmed objective response rate; **DV:** disotimab vedotin; **HER2:** human epidermal growth factor receptor 2; **LA/mUC:** locally advanced unresectable or metastatic urothelial carcinoma; **MMAE:** monomethyl auristatin E

†Histologically-confirmed, including UC originating from the renal pelvis, ureters, bladder, or urethra

Objectives and Endpoints

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

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Disclosures

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Eligibility

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-(L)1 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-(L)1 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 within 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

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

Summary

- HER2 is overexpressed in multiple tumor types, including UC, and may be associated with poor outcomes. No HER2-directed therapies have been approved in the US and EU for LA/mUC, and novel treatment options are urgently needed for this disease
- Disitamab vedotin is a novel, investigational ADC comprised of a HER2-directed mAb conjugated to MMAE that elicits antitumor activity through proposed MOAs including MMAE-directed cytotoxicity, bystander effect, and immunogenic cell death
- 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

1L: first-line; **ADA:** antidrug 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; **EU:** European Union; **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-(L)1:** 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; **US:** United States