TPS3166

# A Phase 1, First-in-Human Study of CUSP06, a Cadherin-6 (CDH6)-directed Antibody-Drug Conjugate, in Patients with Platinum-Refractory/Resistant Ovarian Cancer and Other Advanced Solid Tumors.

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## Background

- Cadherin-6 (CDH6) is a transmembrane glycoprotein involved in cancer metastasis and invasion expressed in various tumor types including ovarian cancer (OC), renal cell carcinoma (RCC), papillary thyroid cancer (PTC), cholangiocarcinoma (CCA), sarcoma, and uterine serous carcinoma (USC)[1]
- CUSP06 is an antibody-drug conjugate composed of a human IgG1 monoclonal antibody against CDH6 conjugated with a protease-cleavable linker, T1000, to exatecan, a topoisomerase I inhibitor payload
- In preclinical studies, CUSP06 showed CDH6-dependent cell growth inhibition in ovarian cancer cell lines; high CDH6-expressing ovarian and renal CDX and PDX models demonstrated tumor regression after treatment with CUSP06, as did low CDH6-expressing PDX models of other solid tumors[2]

## Figure 1. Expression of CDH6 Across Multiple Tumor Types

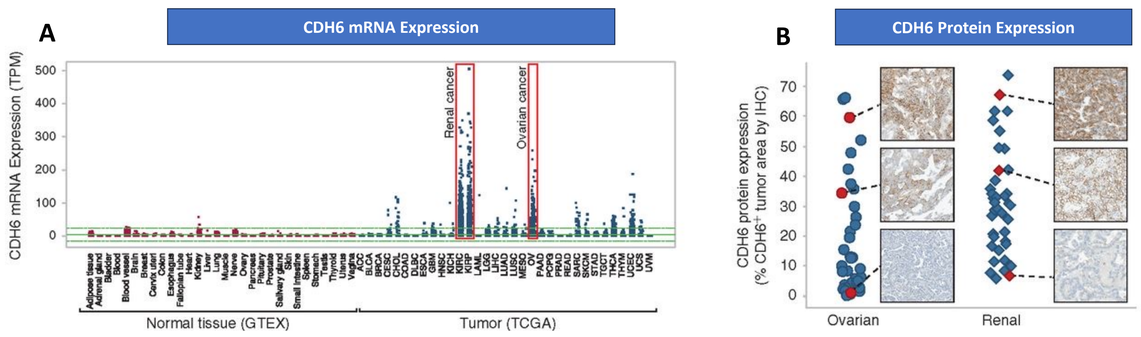
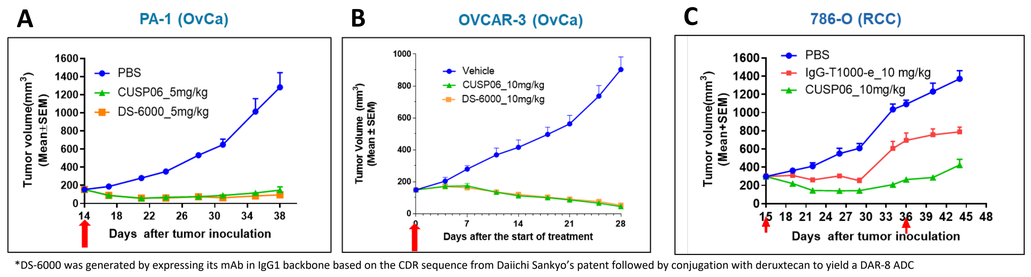



**Figure 1.** A, CDH6 expression in transcripts per million reads (TPM) across normal tissue (pink) and cancer tissue (blue) samples. Renal and ovarian cancers are highlighted (red box) indications featuring frequent CDH6 overexpression. B, CDH6 protein expression across clinical primary renal and ovarian cancer samples as assessed by IHC. Image analysis was performed to quantify each sample's percent CDH6-positive tumor area. Inlays show IHC on sections of representative samples. CDH6 positive OcCA patients ≥85%, CDH6 positive RCC patients ≥95%. Adapted from: Bialucha CU, et al. Cancer Discovery 2017

## Figure 2. Preclinical Activity of CUSP06 in Ovarian and RCC Models




*DS-6000 was generated by expressing its mAb in IgG1 backbone based on the CDR sequence from Daiichi Sankyo's patent followed by conjugation with deruxtecan to yield a DAR-8 ADC

**Figure 2.** CUSP06 exhibits potent in vivo efficacy in three CDH6 high cell line derived xenograft (CDX) models (A, ovarian cancer PA-1; B, ovarian cancer OVCAR-3; C, renal cell carcinoma 786-O). Adapted from: Lu W, et al. AACR 2023.

## Study Design and Objectives

- CUSP06-1001 trial (NCT06234423) is a Phase 1a/1b, open-label, multi-center dose escalation and expansion study to evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), recommended Phase 2 dose (RP2D), and preliminary efficacy of CUSP06 in patients with platinum-refractory/resistant ovarian cancer (PRROC), advanced RCC and other advanced CDH6-positive solid tumors
- CUSP06 will be administered intravenously once every 21 days
- CDH6 prescreening is required for tumor types other than platinum-refractory or -resistant ovarian cancer and renal cell carcinoma

### Phase 1a

- Follows a standard 3+3 dose escalation design with a single patient in cohort 1
- Includes up to 3 dose enrichment cohorts at doses that have demonstrated safety, each with a maximum of 18 patients

**Primary objectives**

- Characterize safety and tolerability of CUSP06
- Determine the Recommended Dose for Expansion

**Secondary objectives**

- Characterize the PK profile of CUSP06
- Evaluate preliminary efficacy of CUSP06 using RECIST v1.1 including overall response rate, disease control rate, clinical benefit rate, duration of response, time to progression, progression-free survival, and overall survival
- For patients with Platinum-Resistant or Refractory Ovarian cancer, determine the proportion of patients with a change from baseline CA-125 level ≥50% for at least 28 days
- Evaluate the immunogenicity of CUSP06

### Phase 1b

- Consists of 4 expansion cohorts including PRROC, RCC, and other CDH6+ tumor types to be enrolled according to Simon's 2-Stage design
- Cohort selection will be informed by data from Phase 1a
- Requires mandatory pre- and on-study biopsies

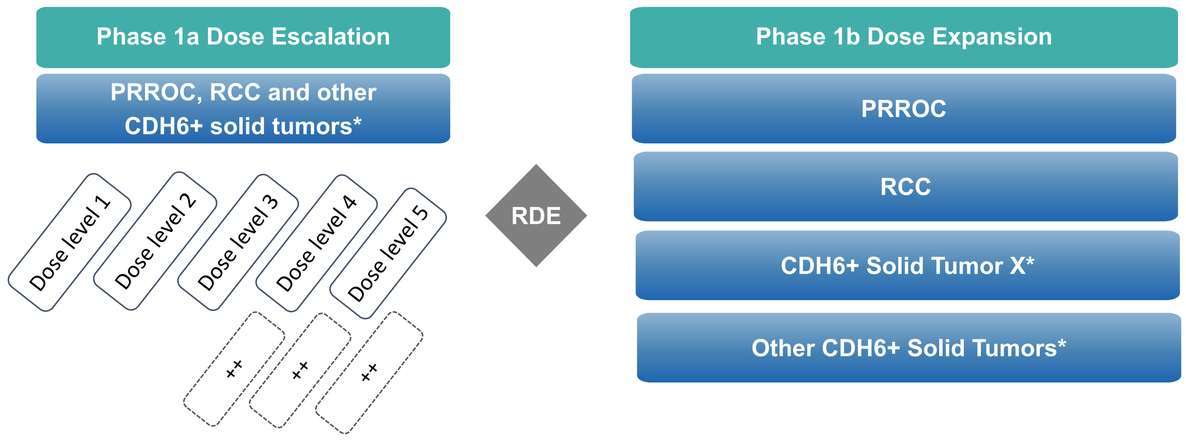
**Primary objectives**

- Evaluate preliminary efficacy of CUSP06 as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 using ORR
- Further characterize safety and tolerability of CUSP06

**Secondary objectives**

- Characterize the PK profile of CUSP06
- Evaluate preliminary efficacy of CUSP06 using RECIST v1.1 including disease control rate, clinical benefit rate, duration of response, time to progression, progression-free survival, and overall survival
- For patients with Platinum-Resistant or Refractory Ovarian cancer, determine the proportion of patients with a change from baseline CA-125 level ≥50% for at least 28 days
- Evaluate the immunogenicity of CUSP06

## Figure 3. Phase 1a/1b Study Design




**PRROC:** platinum-resistant/refractory ovarian cancer **RCC:** renal cell carcinoma

* Tumors other than PRROC and RCC require prescreening for Cadherin-6 expression
**++** Enrichment Cohorts

## Key Inclusion and Exclusion Criteria

### Key Inclusion Criteria

- Male or female patients, ≥18 years of age at the time of obtaining informed consent
- Patients with histologically or cytologically confirmed advanced solid tumors previously treated with standard of care systemic therapy, or for whom no standard therapy is available
  - platinum-refractory/resistant epithelial ovarian cancer
  - advanced renal cell carcinoma
  - other CDH6-positive solid tumors such as CCA, USC, PTC, and anaplastic thyroid cancer.
- Willingness to provide archival tumor tissue collected when available; if no archival tissue is available, willingness to undergo a pretreatment biopsy if medically feasible and safe
- For patients on Phase 1b dose expansion, willingness to undergo pre- and on-treatment biopsies if medically feasible and safe
- Measurable disease per RECIST 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and life expectancy of ≥12 weeks

### Key Exclusion Criteria

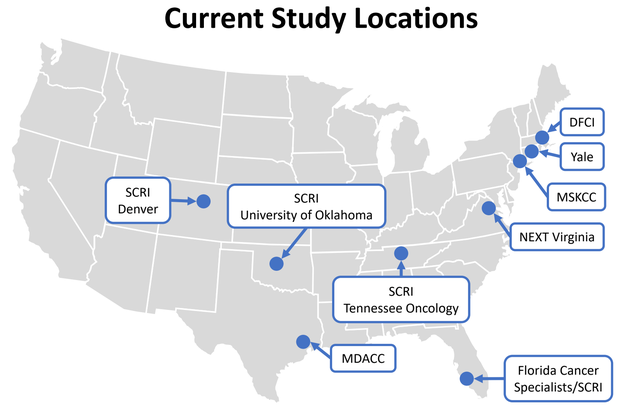
- Prior treatment with an ADC with a topoisomerase I (TOP1) payload
- Active or progressing brain metastases or evidence of leptomeningeal disease
- Major surgery within 4 weeks prior to first dose of study drug, or no recovery from side effects of such intervention
- Clinically significant lung disease requiring systemic corticosteroid treatment within the last 6 months
- Hepatic insufficiency manifesting as clinical jaundice, hepatic encephalopathy, and/or variceal bleed within 60 days prior to study entry
- History of liver transplant, significant cardiac disease, or thromboembolic/cerebrovascular events within 3 months prior to first dose of the study drug
- Prior allogeneic bone marrow transplantation
- Acute and/or clinically significant bacterial, fungal, or viral infection including hepatitis B (HBV), hepatitis C (HCV), known human immunodeficiency virus (HIV)
- Prior history of malignancy other than inclusion diagnosis within 3 years prior to first dose of the study drug

## Enrollment and Status

- The study is currently enrolling in Phase 1a in the United States
- Please contact Priya Marreddy for more information: priya.marreddy@oncusptx.com
- A digital copy of this poster is available below



**Current Study Locations**




* Note additional Ph1b sites will expand geographic footprint

## References

1. Bialucha CU, Collins SD, Li X, Saxena P, Zhang X, Dürr C, et al. Discovery and Optimization of HKT288, a Cadherin-6–Targeting ADC for the Treatment of Ovarian and Renal Cancers. Cancer Discovery 2017;7:1030–1045
2. Lu W, Shi J, Liu S-H, Covino N, Meng X, Slosberg ED. CUSP06/AMT-707, a new CDH6-targeting antibody-drug conjugate, demonstrates potent antitumor activity in preclinical models. AACR 2023, Abstract 6320.

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