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

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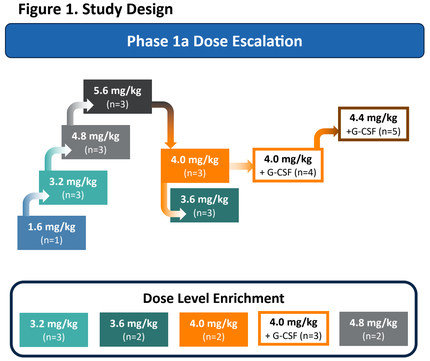
Background

- 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 endometrial carcinomas.[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]
- We report here the initial results from the First-in-Human (FIH) study CUSP06-1001, a Phase 1a/1b, open-label, multi-center dose escalation and expansion study in patients with platinum-refractory/resistant ovarian cancer (PROC), advanced RCC and other advanced CDH6-positive solid tumors.[3]

Methods

Figure 1. Study Design



- The ongoing study used an accelerated 3+3 design and includes patients with platinum-refractory/resistant ovarian cancer, advanced RCC, and other advanced CDH6-positive solid tumors.
- Prescreening for CDH6 expression was required for those patients with solid tumors other than OC or RCC. CUSP06 was administered IV every 21 days. The dose is capped at 100 kg body weight.

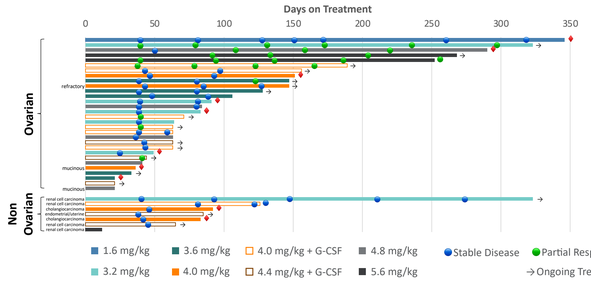
Table 1. Study Patient Demographics

	Total (n = 37)
Median age, yrs (range)	61.0 (38–79)
≥ 65 years	15 (40.5)
Sex, n (%)	
Female	34 (91.9)
Male	3 (8.1)
ECOG Status, n (%)	
0	12 (32.4)
1	25 (67.6)
Prior lines of therapy, median (range)	4.0 (1–9)
Ovarian Cancer	4.0 (1–9)
Tumor Types, n (%)	
Ovarian Cancer	30 (81.1)
Platinum-resistant	29 (96.7)
Platinum-refractory	1 (3.3)
Renal Cell Carcinoma	4 (10.8)
Cholangiocarcinoma	2 (5.4)
Endometrial Carcinoma	1 (2.7)
Prior Therapies in Ovarian Cancer	
Prior platinum	30 (100.0)
Prior taxane	30 (100.0)
Prior bevacizumab	23 (76.7)
Prior mirvetuximab	7 (23.3)

- As of May 13, 2025, data are available for 37 patients who received CUSP06 Q3W at doses ranging from 1.6 to 5.6 mg/kg. As neutropenia was frequent, cohorts exploring prophylactic G-CSF were added.
- DLTs observed were Grade 5 febrile neutropenia at 5.6 mg/kg and Grade 3 stomatitis at 4.4 mg/kg + G-CSF.
- Enrichment cohorts were opened at 3.2 mg/kg, 3.6 mg/kg, 4.0 mg/kg, 4.0 mg/kg +G-CSF, and 4.8 mg/kg.

Results

Figure 2. Treatment Duration and Response



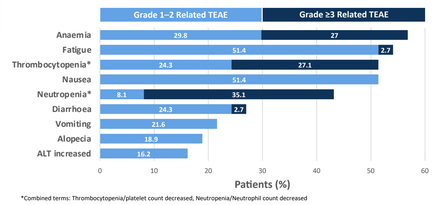
- Responses emerged mainly at the first scan (~6 weeks) and were durable.
- Six patients with PROC and one patient with renal cell carcinoma (RCC) received CUSP06 for more than six months

Safety

Table 2. Safety Summary

n (%)	Total (n = 37)
Any TEAE	37 (100.0)
Grade ≥3	22 (59.5)
Treatment-related TEAE	36 (97.3)
Grade ≥3	18 (48.6)
Any SAE	8 (21.6)
Grade ≥3	7 (18.9)
Treatment-related SAE	2 (5.4)
Grade ≥3	1 (2.7)
Dose modifications	
Drug discontinuation	3 (8.1)
Dose delay due to AE	12 (32.4)
Dose reduction due to AE	9 (24.3)

Figure 3. TRAEs of Any Grade Occurring in ≥15% of Patients



*Combined terms: Thrombocytopenia/platelet count decreased, Neutropenia/Neutrophil count decreased

- The most common Treatment-Related Adverse Events (TRAEs) were hematologic toxicities, fatigue, and nausea, which are consistent with the toxicity profile of the exatecan payload.
- The most frequent reasons for dose modifications were neutropenia, followed by thrombocytopenia and fatigue.
- Both prophylactic G-CSF cohorts had significantly reduced Gr3+ neutropenia (16.7% with N=12).
- Two Grade 5 events occurred: multiorgan failure at 4.8 mg/kg (deemed unrelated to the drug), and febrile neutropenia at 5.6 mg/kg (deemed drug-related).
- Three cases of pneumonitis (one Grade 1, two Grade 2) were reported, with one Grade 2 case adjudicated by an independent committee as Not ILD.
- No ocular toxicity was reported.

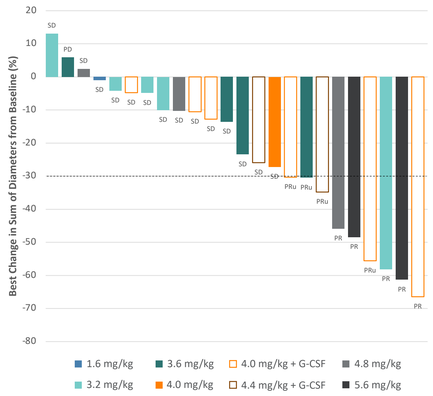
Efficacy

Table 3. Summary of Preliminary Efficacy in HGSOC

n (%)	Total (n = 25)
Best Response to CUSP06	
Partial Response	9 (36.0)
Stable Disease	14 (56.0)
Clinical Benefit Rate (CR+PR+SD)	23 (92.0)
Median Duration of Response, months (range)	NE* (0.2 – 9.4)

* Greater than 75% of patients have ongoing responses

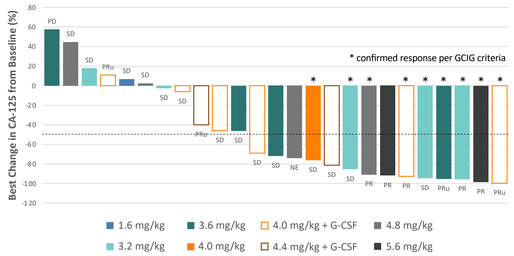
Figure 4. Best Overall Response in HGSOC



- In patients with platinum-resistant high-grade serous ovarian cancer (HGSOC), ORR was 36% (9/25, 5 confirmed and 4 unconfirmed PRs), and CBR was 92% (23/25).
  - Two patients previously treated with mirvetuximab had PRs with tumor reductions of 63.8% and 48.5%.
  - All patients with unconfirmed PRs remain on treatment, with the potential to confirm the response.
- ORR was 50% at both the 4.0 mg/kg + G-CSF and 4.4 mg/kg + G-CSF dose (3/6 and 1/2 patients respectively);
  - All responders in these cohorts remain on treatment.
  - The other ongoing patient at 4.4 mg/kg + G-CSF had a tumor reduction of 25.9%.
- Responses were seen in low and high-CDH6-expressing tumors.

CA-125 Assessment

Figure 5. Change from Baseline in CA-125 Levels in HGSOC



- HGSOC patients were included if they had a baseline CA-125 value and at least one post-baseline CA-125 measurement.
- Among the 20 patients evaluable using Gynecologic Cancer InterGroup (GCIG) criteria, 9 CA-125 responses were confirmed.[4]
- The corresponding best radiological response is denoted.

Conclusions

- CUSP06 showed a safety profile consistent with other TOP1-inhibitor ADCs, with manageable hematologic toxicities as the most common treatment-related adverse events.
- Promising efficacy was observed in patients with heavily pretreated platinum-resistant HGSOC without CDH6 pre-selection
  - ORR was 36% (9/25), including two responders who had previously received mirvetuximab treatment.
  - ORR reached 50% at both 4.0 mg/kg + G-CSF and 4.4 mg/kg + G-CSF (3/6 and 1/2 patients, respectively).
- CA-125 responses occurred in 45% of GCIG-evaluable HGSOC patients, further supporting clinical activity.
- Responses were seen across high and low CDH6 expression, suggesting broader potential in CDH6-positive solid tumors.
- These Phase 1a safety and efficacy results support continued evaluation of CUSP06 in platinum resistant HGSOC and other CDH6-positive tumors in Phase 1b expansion cohorts.

References and Acknowledgements

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