A Phase 1 Study of HWK-016, a Next-Generation, Mucin 16 (MUC16)-Directed Antibody–Drug Conjugate, in Patients with Advanced Solid Tumors

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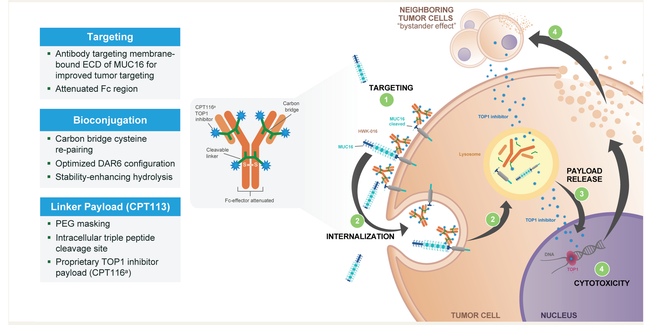
Summary

- **HWK-016 is a next-generation antibody–drug conjugate that targets the non-shed extracellular domain of MUC16, the overexpression of which facilitates tumor cell proliferation, metastasis, and immune evasion in cancer. The shed portion is the well-known biomarker CA125**
- **HWK-016-101 (NCT07470853) is a multicenter, open-label, first-in-human, phase 1 study of HWK-016 in patients with advanced or metastatic ovarian or endometrial tumors**
  - **The study comprises part A (HWK-016 monotherapy) and part B (HWK-016 plus bevacizumab combination therapy)**
  - **Each part consists of phase 1a (dose escalation) and phase 1b (dose expansion)**
  - **Primary endpoints in phase 1a are maximum tolerated dose, maximum administered dose, and recommended dose for expansion (RDE); in phase 1b, the primary endpoint is safety and tolerability at the recommended RDE(s)**
- **The study is enrolling adult patients with ovarian cancer or endometrial carcinoma to part A; it will enroll patients with ovarian cancer only to part B**
  - **Recruitment to the study is under way across the United States**

Background

- MUC16 is a cell-surface glycoprotein that is involved in tumor cell proliferation, metastasis, and immune evasion in cancer[1,2]
  - MUC16 is proteolytically cleaved to form the well-known serum biomarker cancer antigen 125 (CA125), which is shed into the bloodstream. The non-shed extracellular domain of MUC16 remains on the tumor cell surface[1,2]
- *MUC16* expression is higher in tumor versus normal tissue. Analyses have shown robust concordance between *MUC16* mRNA expression and protein abundance in both ovarian cancer and endometrial carcinoma[3,4]
- *MUC16* is overexpressed in several tumor types, including approximately 80% of ovarian cancers[2] and >90% of high-grade endometrial carcinomas[5]
  - *MUC16* is expressed in serous and non-serous histological subtypes of ovarian cancer[3] and in the most common subtypes of endometrial carcinoma (serous adenocarcinoma and endometrioid adenocarcinoma)[4]
  - In ovarian cancer, *MUC16* expression remains high irrespective of platinum-sensitivity status and is 3- to >100-fold higher than that of clinically validated and emerging antibody–drug conjugate (ADC) targets, including *SLC34A2* (NaPi2b; 3-fold), *PTK7* (4-fold), *ERBB2* (HER2; 4-fold), *FOLR1* (FRα; 4-fold), *TACSTD2* (TROP2; 5-fold), *VTCN1* (B7-H4; 15-fold), *CDH6* (15-fold), and *CLDN6* (126-fold)[6]
  - In endometrial carcinoma, *MUC16* expression is uniformly high irrespective of disease stage and is up to 5-fold higher than that of other ADC targets in development[4]
- Previous MUC16-directed ADCs targeted the shed portion of MUC16 and demonstrated response rates of 14%–42% in patients with high *MUC16* expression;[7,8] however, these ADCs bound serum CA125, potentially creating an antigen sink, limiting tumor access, and necessitating higher dosing to overcome target-mediated drug disposition[7–10]
- HWK-016 is an investigational, next generation ADC that selectively binds to the non-shed extracellular domain of MUC16. It comprises a monoclonal antibody conjugated to a novel topoisomerase I inhibitor via a stable, cleavable linker that enhances intracellular delivery and limits systemic exposure (**Figure 1**)[11]
- In preclinical studies, HWK-016 has demonstrated potent binding, internalization, and reduced cancer cell viability. Its activity is minimally affected by the addition of high levels of exogenous CA125[11]
  - HWK-016 has also shown robust antitumor activity—including bystander activity—in preclinical models of ovarian cancer[11]
- The first-in-human HWK-016-101 study will evaluate HWK-016 in patients with advanced or metastatic ovarian cancer or endometrial carcinoma

FIGURE 1. HWK-016 Structure and Mechanism of Action[11]



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ᵃCPT116 (an exatecan analog) is the payload.
DAR, drug-to-antibody ratio; **ECD**, extracellular domain; **Fc**, fragment crystallizable; **MUC16**, mucin 16; **PEG**, polyethylene glycol; **TOP1**, topoisomerase I.

Methods

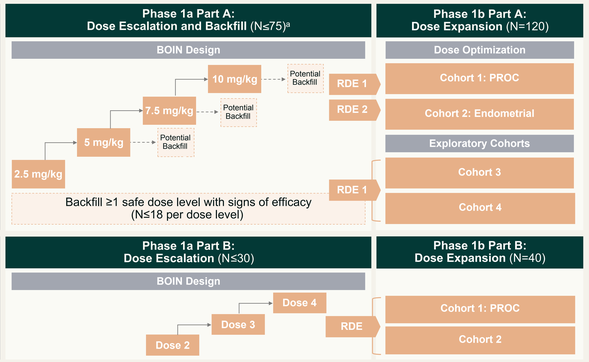
- HWK-016-101 (NCT07470853) is a multicenter, open-label, single-arm, first-in-human, phase 1 study evaluating HWK-016 as monotherapy (part A) and in combination with bevacizumab (part B)
  - Each part consists of two stages: phase 1a (dose escalation) and phase 1b (dose expansion)
- The study is enrolling patients aged ≥18 years with ovarian cancer or endometrial carcinoma (**Table 1**)
  - Part A includes those with ovarian cancer or endometrial carcinoma
  - Part B includes those with ovarian cancer only
- In phase 1a of each part, patients are sequentially assigned to HWK-016 dose levels, administered as an intravenous infusion once every 3 weeks (plus bevacizumab 15 mg/kg in part B only) using a Bayesian Optimal Interval design and a toxicity threshold of 25%, with potential backfill in part A (**Figure 2**)
- Primary endpoints in phase 1a (parts A and B) are maximum tolerated dose, maximum administered dose, and recommended dose for expansion (RDE); in phase 1b (parts A and B), the primary endpoint is safety and tolerability at the recommended RDE(s)

TABLE 1. Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• ≥18 years of age	• Prior treatment with MUC16-directed therapy or an ADC with a TOP1 inhibitor payload (excluded for Part A, but allowed for Part B)
• ECOG PS 0 or 1	
• Advanced or metastatic disease	
• Measurable disease per RECIST v1.1	
Part A: HWK-016 Monotherapy[a]	• History of pleural effusion or ascites requiring repeated drainage of fluid for symptomatic relief
• Ovarian cancer (epithelial, fallopian tube, or primary peritoneal carcinoma) – Platinum-resistant disease – CA125 ≥2 × ULN – Non-target lesions per RECIST v1.1 with CA125 ≥2 × ULN are permitted in phase 1a only – Prior standard-of-care therapy – No prior treatment with a TOP1 inhibitor-containing ADC	• History of small or large bowel obstruction requiring surgery within the past 90 days
	• Current requirement for parenteral nutrition
• Endometrial carcinoma – All histologic subtypes – Prior platinum-based chemotherapy and PD-(L)1 inhibitor therapy, unless contraindicated – No prior treatment with a TOP1 inhibitor-containing ADC	• Major surgery within 28 days, minor procedures within 24 hours prior to first dose, or lack of sufficient recovery • Significant cardiac disease within 6 months prior to first dose; QTcF >470 milliseconds (based on average of triplicate ECGs); thromboembolic or cerebrovascular events within 6 months prior to first dose
Part B: HWK-016 plus Bevacizumab Combination Therapy	
• Ovarian cancer (epithelial, fallopian tube, or primary peritoneal carcinoma) – Same as for part A, except that prior treatment with a TOP1 inhibitor-containing ADC is permitted	• History of pneumonitis/ILD; oxygen requirement treatment or chronic lung condition requiring corticosteroids within past 6 months

[a]In part A only, prior bevacizumab is required for backfill (phase 1a) and phase 1b cohorts.
ADC, antibody–drug conjugate; **CA125**, cancer antigen 125; **ECG**, electrocardiogram; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ILD**, interstitial lung disease; **MUC16**, mucin 16; **PD-(L)1**, programmed death-(ligand) 1; **QTcF**, QT interval corrected for heart rate using Fridericia's formula; **RECIST v1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **TOP1**, topoisomerase I; **ULN**, upper limit of normal.

FIGURE 2. HWK-016-101 Study Schema and Endpoints



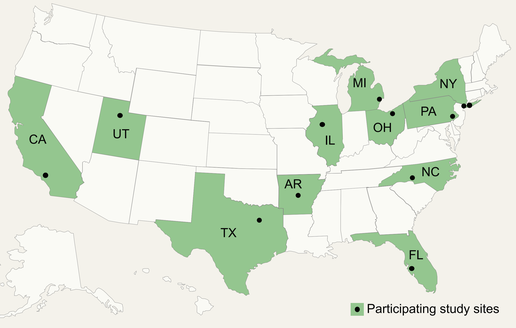
Endpoints	
Primary	**Secondary**
In Phase 1a • Maximum tolerated dose[b] • Maximum administered dose[b] • RDE[b]	**In Phase 1a and at the Selected RDE(s) in Phase 1b** • Pharmacokinetic parameters • Anti-drug antibody response • Overall response rate • Overall survival • Duration of response • Progression-free survival • Disease control rate • Time to response
In Phase 1b • Safety and tolerability at the selected RDE(s)	

[a]Additional participants may be enrolled at intermediate dose levels, higher dose levels, alternative dosing schedules, and/or previously tested dose levels. [b]Measured at the end of Cycle 1 (21-day cycle) by incidence and severity of adverse events, incidence of dose-limiting toxicities, and incidence of serious adverse events.
BOIN, Bayesian Optimal Interval; **PROC**, platinum-resistant ovarian cancer; **RDE**, recommended dose for expansion.

STUDY SITES

- Recruitment to the HWK-016-101 study is under way across the United States (**Figure 3**)

FIGURE 3. HWK-016-101 Study Sites



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For disclosures of co-authors, please refer to the abstract.