A Phase 1 Study of HWK-007, a Next-Generation, Protein Tyrosine Kinase 7 (PTK7)-Targeted Antibody–Drug Conjugate (ADC), in Patients with Advanced Solid Tumors

Manish R. Sharma[1]; Jennifer M. Segar[2]; Sheena Sahota[3]; Edward Spindler[4]; Aamena Chaudhry[4]; Ashwini B. Pai[4]; Margaret Dugan[4]; Alexander I. Spira[5]

[1]The START Center for Cancer Research – Midwest, Grand Rapids, MI, USA; [2]NEXT Houston, Houston, TX, USA; [3]NEXT Austin, Austin, TX, USA; [4]Whitehawk Therapeutics, Morristown, NJ, USA; [5]NEXT Virginia, Fairfax, VA, USA

Summary

» **HWK-007 is a next-generation ADC that targets PTK7, the overexpression of which contributes to metastasis, chemoresistance, and poor clinical outcomes in multiple tumor types**

» **HWK-007-101 (NCT07444814) is a multicenter, open-label, first-in-human, phase 1 study of HWK-007 monotherapy in patients with advanced or metastatic solid tumors known to be expressing PTK7**

– **The study consists of phase 1a (dose escalation) and phase 1b (dose expansion)**

– **Primary endpoints in phase 1a are safety, maximum tolerated dose, maximum administered dose, and recommended dose for expansion**

» **The study is enrolling adult patients with non-squamous epidermal growth factor receptor–wild-type non-small cell lung cancer, platinum-resistant ovarian cancer, or endometrial carcinoma**

– **Recruitment to the study is under way across the United States**

Background

» Protein tyrosine kinase 7 (PTK7) is a catalytically inactive receptor tyrosine kinase. Overexpression of PTK7 in cancer cells promotes tumor progression through several signaling pathways, and is associated with metastasis, chemoresistance, and poor clinical outcomes across multiple tumor types[1,2]

» PTK7 is known to have a wide expression profile in numerous malignancies, including in >80% of cases of non-small cell lung cancer (NSCLC), endometrial carcinoma, and ovarian cancer; expression remains high across disease stages and histologic subtypes.[1–3] This makes PTK7 a therapeutic target of interest across indications

– *PTK7* is the third most highly expressed marker across solid tumors and is expressed at levels comparable to several validated antibody–drug conjugate (ADC) targets[3]

– In NSCLC, *PTK7* expression is observed irrespective of epidermal growth factor receptor (*EGFR*) mutation status[3]

» Cofetuzumab pelidotin, a PTK7-targeting ADC with an auristatin payload, demonstrated clinical activity with objective response rates of ~16–27% in a first-in-human phase 1 study,[4] and 18% in a biomarker-selected NSCLC population with activity enriched in tumors with higher *PTK7* expression[5]; treatment was generally manageable, with predominantly low-grade adverse events and grade ≥3 neutropenia (~25%) as the most common severe toxicity, and no treatment-related deaths were reported[4,5]

– Despite evidence of target engagement and antitumor activity, further development of cofetuzumab pelidotin was discontinued

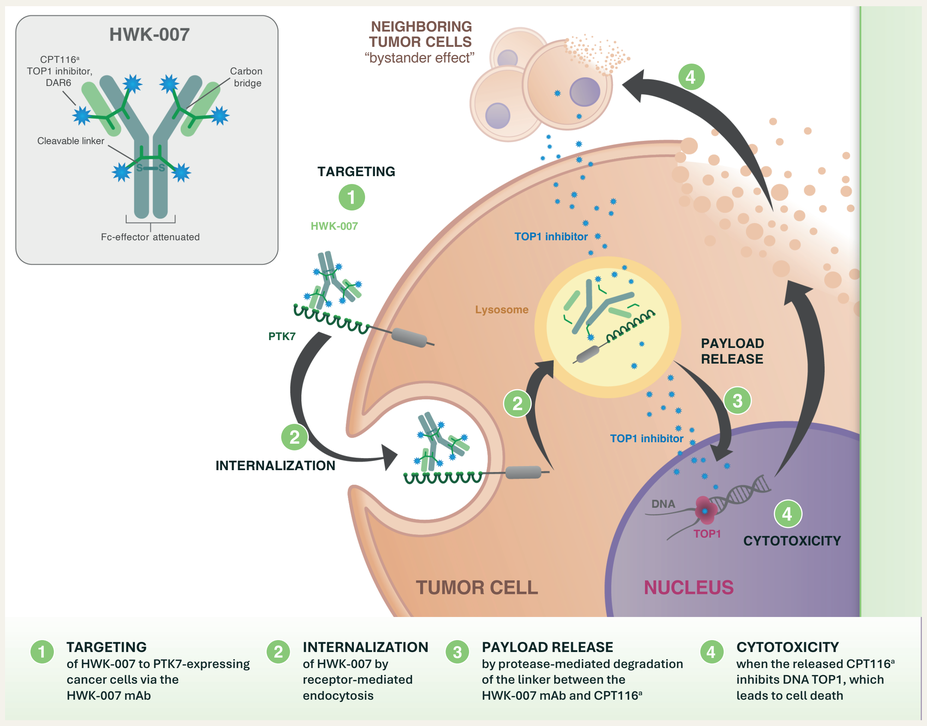
» HWK-007 is a next-generation, PTK7-targeting ADC comprising a high-affinity, anti-PTK7 monoclonal IgG1 antibody with attenuated Fc activity conjugated to a novel topoisomerase I inhibitor payload, CPT116, via carbon-bridge cysteine re-pairing (**Figure 1**)[6]

– HWK-007 leverages novel bioconjugation and linker-payload technologies to minimize off-target effects and increase therapeutic index compared with earlier PTK7-targeting ADCs[6]

» Preclinical studies have shown that HWK-007 demonstrates potent binding, internalization, induction of DNA damage, and bystander activity, which lead to cell death in a range of solid cancer cell lines[6]

» The first-in-human HWK-007-101 study will evaluate HWK-007 monotherapy in patients with advanced or metastatic solid tumors

FIGURE 1. HWK-007 Structure and Mechanism of Action[6]



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[a]CPT116 (an exatecan analog) is the payload.

DAR, drug-to-antibody ratio; **Fc**, fragment crystallizable; **mAb**, monoclonal antibody; **PTK7**, protein tyrosine kinase 7; **TOP1**, topoisomerase I.

Methods

» HWK-007-101 (NCT07444814) is a multicenter, open-label, single-arm, phase 1 study consisting of two stages: phase 1a (dose escalation) and phase 1b (dose expansion)

» The study is enrolling patients aged ≥18 years with advanced or metastatic solid tumors known to be expressing PTK7 (**Table 1**)

– Phase 1a is enrolling patients with non-squamous *EGFR*wt NSCLC, platinum-resistant ovarian cancer, or endometrial carcinoma

– In phase 1b, non-squamous *EGFR*wt NSCLC expansion cohort(s) will be opened, based on the safety, tolerability, pharmacokinetics, and preliminary antitumor data from phase 1a

TABLE 1. Key Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• ≥18 years of age	• Clinically active brain metastases, defined as untreated or symptomatic or requiring therapy with systemic corticosteroids or anticonvulsants to control associated symptoms
• ECOG PS 0 or 1	• History of pleural effusion or ascites requiring repeated drainage of fluid for symptomatic relief
Phase 1a: Dose-Escalation Cohorts	• Current requirement for parenteral nutrition
• Non-squamous *EGFR*wt NSCLC – Measurable disease per RECIST v1.1 – Prior treatment with platinum-based chemotherapy and a PD-(L)1 inhibitor, if eligible, and/or appropriate targeted therapy for an actionable gene alteration, if applicable	• Significant cardiovascular disease
• Platinum-resistant ovarian cancer – Non-target lesions per RECIST v1.1 and CA125 ≥2 × ULN are permitted (excludes backfill cohorts)	• Prolongation of QTcF ≥470 milliseconds
• Endometrial carcinoma – Measurable disease per RECIST v1.1 – Prior treatment with platinum-based chemotherapy and a PD-(L)1 inhibitor, if eligible	• Any history of pneumonitis/ILD; any requirement for oxygen treatment; or preexisting chronic lung condition requiring the use of corticosteroids within the past 6 months
Phase 1b: Dose-Expansion Cohorts	• Prior treatment with PTK7-targeted therapies or ADCs with a TOP1 inhibitor payload
• Non-squamous *EGFR*wt NSCLC	
• Additional tumor indications to be defined in a future amendment	

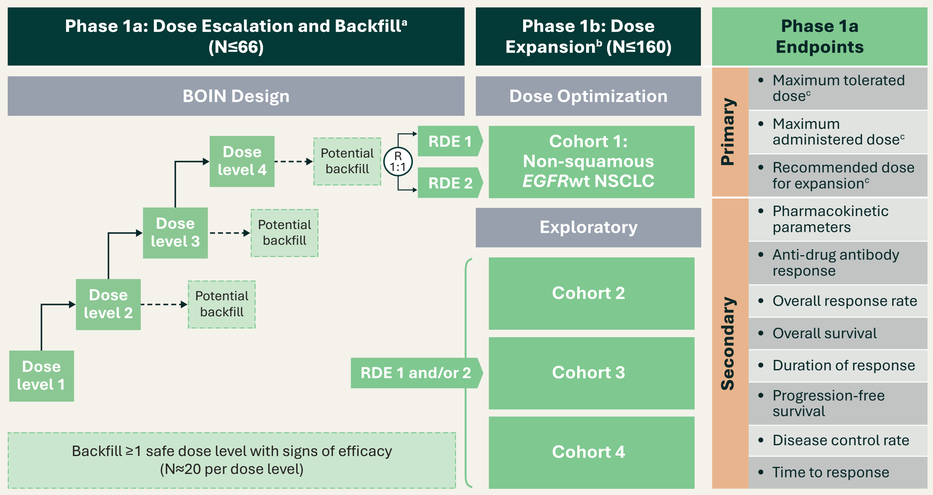
ADC, antibody–drug conjugate; **CA125**, cancer antigen 125; **ECOG PS**, Eastern Cooperative Oncology Group performance status; ***EGFR*wt**, epidermal growth factor receptor–wild-type; **ILD**, interstitial lung disease; **NSCLC**, non-small cell lung cancer; **PD-(L)1**, programmed death-(ligand) 1; **PTK7**, protein tyrosine kinase 7; **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.

» In phase 1a, patients are sequentially assigned to HWK-007 dose levels (administered as an intravenous infusion once every 3 weeks) using a Bayesian Optimal Interval design with a toxicity threshold of 25%, with potential backfill (**Figure 2**)

– Backfill cohorts are enriched for patients with *EGFR*wt NSCLC

» Primary endpoints in phase 1a are safety, maximum tolerated dose, maximum administered dose, and recommended dose for expansion

FIGURE 2. HWK-007-101 Study Schema



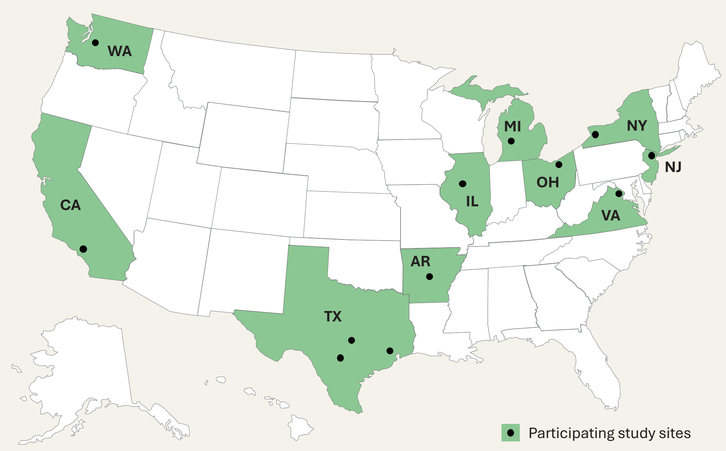
[a]Patients may be enrolled at intermediate dose levels, higher dose levels, and/or previously tested dose levels. Higher doses added in 2 mg/kg increments. [b]Four cohorts include up to two RDEs each, with 20 patients enrolled per RDE. Dose-expansion cohort indications will include additional tumor types of interest based on PTK7 target expression. [c]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; ***EGFR*wt**, epidermal growth factor receptor–wild-type; **NSCLC**, non-small cell lung cancer; **PTK7**, protein tyrosine kinase 7; **R**, randomization; **RDE**, recommended dose for expansion.

STUDY SITES

» Recruitment to the HWK-007-101 study is under way across the United States (**Figure 3**)

FIGURE 3. HWK-007-101 Study Sites



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Corresponding author: Manish R. Sharma (manish.sharma@startmidwest.com)

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