A Phase 1, First-in-Human, Multicenter Study of ZW251, a Novel Glypican-3 (GPC3)-Targeted Antibody-Drug Conjugate (ADC), in Participants With Hepatocellular Carcinoma (HCC)

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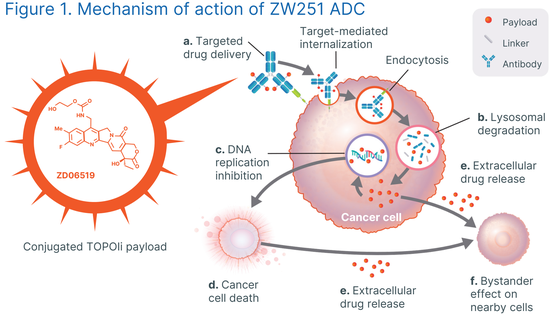
BACKGROUND

- In advanced hepatocellular carcinoma (HCC), unmet treatment needs persist due to limited durable response rates and poor overall survival following disease progression on systemic therapies[1]
- Glypican-3 (GPC3) is highly expressed in HCC and in select solid tumors, with limited expression in normal tissues, making it an attractive therapeutic target[2,3]
- ZW251 is a novel GPC3-targeted antibody-drug conjugate (ADC) composed of a humanized IgG1 antibody covalently linked to ZD06519, a camptothecin derivative topoisomerase I inhibitor (TOPOIi) payload, with a protease cleavable linker and an average drug-to-antibody ratio of 4[4,5] (**Figure 1**)

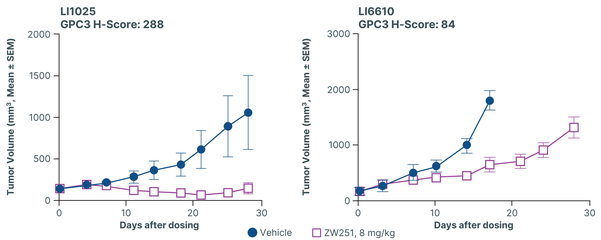
Figure 1. Mechanism of action of ZW251 ADC



ADC: antibody-drug conjugate; GPC3, glypican-3; TOPOIi: topoisomerase I inhibitor.

- ZW251 has shown strong specific binding to GPC3-expressing cancer cells, enhanced internalization into target cells, and intracellular release of bystander-active payload, resulting in tumor killing[4,5]
- ZW251 has also shown broad antitumor activity in nonclinical efficacy studies in mice across a large panel of cell-derived xenograft and patient-derived xenograft liver cancer models with a range of low to high GPC3 expression levels[4,5] (**Figure 2**)

Figure 2. Antitumor activity of ZW251 against patient-derived xenografts expressing high and low GPC3



GPC3: glypican-3; SEM: standard error of mean.

- In the good laboratory practice toxicology study in nonhuman primates, no hematologic toxicity was observed at 50 mg/kg. At the highest non-severely toxic dose (HNSTD) of 100 mg/kg, white blood cell parameters remained unchanged, while mild, transient decreases in red-cell mass and platelet counts were observed and fully resolved during the recovery period. No biochemical or histopathologic evidence of hepatic or pulmonary injury was identified at the HNSTD

METHODS

Key Eligibility Criteria

Inclusion Criteria

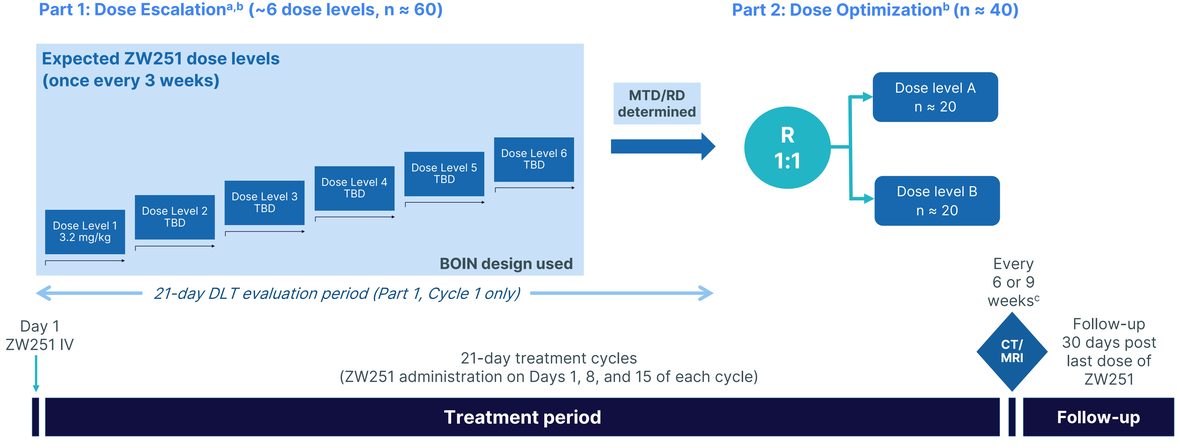
- Adults with histologically or radiographically confirmed metastatic HCC (ineligible for transplant and locoregional therapies) with Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 measurable lesions
- For Part 1 (Dose Escalation): Progressed after ≥1 first-line therapy, or intolerant to, or refused treatment with, approved and available immunotherapy or tyrosine kinase inhibitors
- For Part 2 (Dose Optimization): Progressed on ≥1 prior regimen, including approved PD-(L)1 inhibitors
- Child-Pugh Class A liver function
- Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 and adequate organ function
- Fresh biopsy, if available, or archival formalin-fixed paraffin embedded tumor tissue sample for retrospective GPC3 expression assessment

Exclusion Criteria

- Participants with main portal vein tumor invasion and evidence of active hepatic decompensation
- Gastrointestinal bleeding (eg, esophageal varices or ulcer bleeding) within 3 months
- History of hepatic encephalopathy within the past 6 months
- Inadequate pulmonary function, severe pleural effusion requiring >1 thoracocentesis, history of clinically significant interstitial lung disease (ILD), pneumonitis (including radiation pneumonitis), noninfectious pulmonary toxicity, or severe dyspnea requiring active treatment

Study Design

ZWI-ZW251-101 is an ongoing, open-label, phase 1 study of ZW251 in participants with HCC (NCT07164313; EudraCT: 2025-523088-39)



[a]In Part 1, adolescent participants (age ≥12 years) may be enrolled in backfill cohorts at dose levels that have been deemed to be safe and demonstrate preliminary antitumor activity based on SMC recommendation. [b]GPC3-expression will be evaluated retrospectively in Parts 1 and 2. [c]Timed from Cycle 1, Day 1. Every 6 weeks for the first 4 assessments and then every 9 weeks thereafter.
BOIN: Bayesian optimal interval; CT: computed tomography; DLT: dose-limiting toxicity; IV: intravenous; MRI: magnetic resonance imaging; MTD: maximum tolerated dose; n: number of participants; R: randomized; RD: recommended dose; TBD: to be determined.

This study comprises 2 parts:

- Part 1 (Dose Escalation) will use a dose-escalation design to identify the maximum tolerated dose and recommended doses (RDs) for Part 2. Approximately 60 participants will receive ZW251 intravenously every 3 weeks across ~6 dose levels, starting at 3.2 mg/kg
- In Part 2 (Dose Optimization), approximately 40 adults with advanced HCC will be randomized 1:1 to receive 1 of 2 dose levels selected from Part 1 to further evaluate the safety and antitumor activity of the RDs

Endpoints

Part 1: Dose Escalation

Primary	• Frequency and severity of DLTs, AEs, AESIs, and clinical lab abnormalities • Frequency of SAEs and deaths • Frequency of dose reductions and treatment discontinuations of ZW251
Secondary	• Serum or plasma concentrations of ZW251 • PK parameters of ZW251 (C_{max}, t_{max}, AUC, $t_{1/2}$, λ_z, CL, V_d) • Presence of ADAs • BOR, DOR, DCR, cORR • PFS

Part 2: Dose Optimization

Primary	• cORR • Frequency and severity of AEs, AESIs, and clinical lab abnormalities • Frequency of SAEs and deaths • Frequency of dose reductions and treatment discontinuations of ZW251
Secondary	• Serum or plasma concentrations of ZW251 • PK parameters of ZW251 (C_{max}, t_{max}, AUC, $t_{1/2}$, λ_z, CL, V_d) • Presence of ADAs • DOR, DCR, BOR • PFS, OS

λ_z: terminal elimination rate constant; ADAs: anti-drug antibodies; AEs: adverse events; AESIs: adverse events of special interest; AUC: area under the concentration-time curve; BOR: best overall response; CL: clearance; C_{max}: maximum observed serum and/or plasma concentration; cORR: confirmed objective response rate; DCR: disease control rate; DLTs: dose-limiting toxicities; DOR: duration of response; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetic; SAEs: serious adverse events; t_{max}: time to maximum observed serum and/or plasma concentration; $t_{1/2}$: apparent elimination half-life; V_d: volume of distribution.

SUMMARY

- The strong antitumor activity in preclinical studies, with no evidence of hepatic and pulmonary toxicity, and limited hematologic findings, suggests that ZW251 is a potential best-in-class GPC3 targeting ADC
- ZWI-ZW251-101 is evaluating the safety, tolerability, pharmacokinetics, and antitumor activity of ZW251 in participants with advanced solid tumors, including advanced HCC
- The study is currently enrolling in the US, Europe, and Asia-Pacific regions

References: 1. Philippi Z, et al. *Int J Mol Sci.* 2025;26(11):5994. **2.** Wang L, et al. *Oncotarget.* 2016;7(27):42150-42158. **3.** Shih TC, et al. *Liver Res.* 2020;4(4):168-172. **4.** Madera L, et al. Poster presented at: EORTC-NCI-AACR (ENA) 36th Symposium, October 23-25, 2024; Barcelona, Spain. Abstract #177. **5.** Madera L, et al. Poster presented at: American Association for Cancer Research (AACR) Annual Meeting, April 14-19, 2023; Orlando, FL. Abstract #2658

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