Poster
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Design of a First-in-Human Multicentre Open-Label Study of ZW191, a Folate Receptor α–Targeting Antibody-Drug Conjugate Utilising a Novel TOPOIi Payload, in Participants With Advanced Solid Tumours: ZWI-ZW191-101

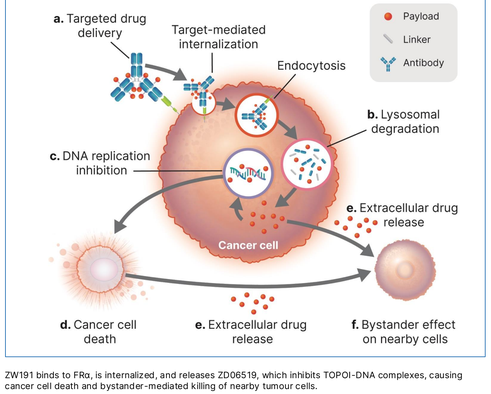
David Sommerhalder,[1] Alexander I. Spira,[2] Tarek Meniawy,[3] Kosei Hasegawa,[4] David Shao Peng Tan,[5] Daniel SW Tan,[6] Byoung-Gie Kim,[7] Nick Pavlakis,[8] Kenichi Harano,[9] Jae-Weon Kim,[10] Jung-Yun Lee,[11] Myong Cheol Lim,[12] Patricia LoRusso,[13] David M. O'Malley,[14] Kathleen Moore,[15] Pranshul Chauhan,[16] Akira Kojima,[16] Syed Raza,[16] Noboru Yamamoto[12]

[1]NEXT Oncology, San Antonio, TX, US; [2]NEXT Oncology, Fairfax, VA, US; [3]Linear Clinical Research and the University of Western Australia, Nedlands, WA, Australia; [4]Saitama Medical University International Medical Center, Hidaka, Saitama, Japan; [5]National University Cancer Institute, Singapore; [6]National Cancer Centre, Singapore; [7]Samsung Medical, Sangkyunkwan University, Seoul, Republic of Korea; [8]University of Sydney, Northern Clinical School, Sydney, Australia; [9]National Cancer Center Hospital East, Kashiwa, Chiba, Japan; [10]Seoul National University Hospital, Seoul, Republic of Korea; [11]Yonsei Cancer Center and Severance Hospital, Seoul, Republic of Korea; [12]National Cancer Center Hospital, Tokyo, Japan; [13]Yale Cancer Center, New Haven, CT, US; [14]The Ohio State University and James Comprehensive Cancer Center, Columbus, OH, US; [15]University of Oklahoma, Oklahoma City, OK, US; [16]Zymeworks Inc., Vancouver, BC, Canada

BACKGROUND

- Folate receptor alpha (FRα) is highly expressed in multiple epithelial tumours but has limited expression in normal tissue[1-3]
- ZW191 is an antibody-drug conjugate (ADC) composed of a novel fully humanized IgG1 FRα-targeting monoclonal antibody covalently conjugated to a novel camptothecin-derived topoisomerase I inhibitor (TOPOIi) payload, ZD06519, with a drug-to-antibody ratio of 8 and a linker that includes a maleimidocaproyl anchor and a glycine-glycine-phenylalanine-glycine (GGFG)-aminomethyl protease–cleavable sequence[4]
- Preclinical studies of ZW191 showed strong specific binding to FRα across broad expression profiles, enhanced internalization, intracellular release of bystander-active payload, significant tumour growth inhibition in spheroid and patient-derived xenograft (PDX) cancer models, a favourable pharmacokinetic (PK) profile, and good tolerability at exposure levels above those projected to be efficacious[4]
- ZW191 has shown preclinical efficacy across multiple tumour types, including FRα-high/mid/low ovarian cancer (OC), non-small cell lung cancer (NSCLC), endometrial cancer (EC), and triple-negative breast cancer, and is well tolerated, with a highest nonseverely toxic dose (HNSTD) of 60 mg/kg in nonhuman primates.[4] The completed good laboratory practice (GLP) toxicology studies of ZW191 and ZD06519 support the first-in-human starting dose of 1.6 mg/kg administered once every 3 weeks (Q3W) via intravenous infusion
- This is an ongoing, first-in-human, phase 1 study (ZWI-ZW191-101) to evaluate the safety, tolerability, and antitumour activity of ZW191 in participants with advanced OC, EC, or nonsquamous NSCLC

Mechanism of Action of ZW191 ADC



ZW191 binds to FRα, is internalized, and releases ZD06519, which inhibits TOPOI-DNA complexes, causing cancer cell death and bystander-mediated killing of nearby tumour cells.

METHODS

Key Eligibility Criteria

Inclusion Criteria

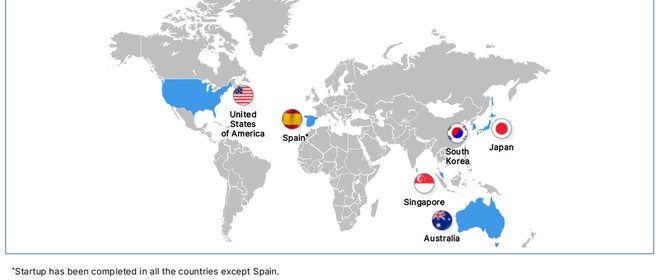
- Adults ≥18 years of age with OC (epithelial), EC, or nonsquamous NSCLC
- Pathologically or cytologically confirmed diagnosis of cancers with evidence of locally advanced (unresectable), recurrent, and/or metastatic disease
- Measurable disease per Response Evaluation Criteria in Solid Tumours v1.1
- Eastern Cooperative Oncology Group performance score of 0 or 1
- Adequate cardiac (left ventricular ejection fraction ≥50% as determined by echocardiogram or multigated acquisition scan), neurologic, pulmonary, and other organ function as per protocol
- Participants who have exhausted available treatment options, cannot tolerate or refuse available standard of care (SOC), or are not suitable for available SOC systemic therapies known to confer clinical benefit
- For Part 2, participants must have received ≥1 but ≤5 prior lines of documented systemic therapy
- For Part 2, in the OC cohort, participants will be eligible independent of FRα status. For the endometrial and NSCLC cohorts, only those participants positive for FRα expression by prospective testing will be eligible

Exclusion Criteria

- Has received prior TOPOIi ADC treatment
- Known additional malignancy that is progressing or requires active treatment or may interfere with study endpoints
- History of hypersensitivity or contraindications to any active substance/ingredient of ZW191
- Acute or chronic uncontrolled renal, pancreatic, or liver disease
- Severe chronic or active infections (including known active SARS-CoV-2 infection) requiring systemic therapy, including antibacterial, antifungal, or antiviral therapy

Participating Regions of Study: ZWI-ZW191-101

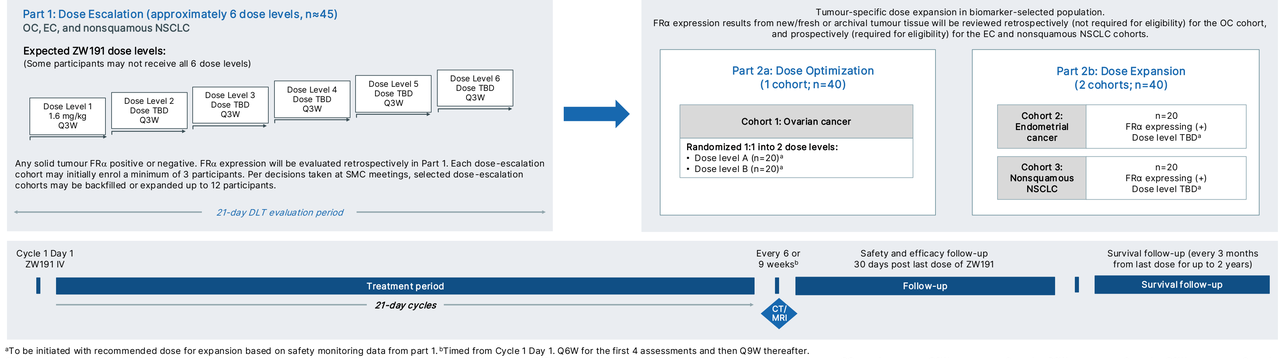
ZWI-ZW191-101 is a global study with 27 sites across multiple regions, including North America, Europe, and the Asia-Pacific, and is actively enroling patients into Part 1



*Startup has been completed in all the countries except Spain.

Study Design

ZWI-ZW191-101 is a first-in-human multicentre open-label phase 1 study of ZW191 in participants with advanced solid tumours (NCT06555744; EudraCT: 2024-512299-37-00)



[a]To be initiated with recommended dose for expansion based on safety monitoring data from part 1. [b]Timed from Cycle 1 Day 1. Q6W for the first 4 assessments and then Q9W thereafter.
CT: computed tomography; DLT: dose-limiting toxicity; EC: endometrial cancer; FRα: folate receptor alpha; IV: intravenous; MRI: magnetic resonance imaging; NSCLC: non-small cell lung cancer; OC: ovarian cancer; Q3W: once every 3 weeks; Q6W: once every 6 weeks; Q9W: once every 9 weeks; SMC: safety monitoring committee; TBD: to be determined.

This study comprises 2 parts:

- Part 1 is dose escalation to identify the maximum tolerated dose (using the modified toxicity probability interval design) of ZW191 in approximately 6 dose levels in participants with OC, EC, or NSCLC
- Participants will receive ZW191 intravenously, once every 3 weeks (21-day cycles)
- Dose level 1 is 1.6 mg/kg, increasing based on safety and tolerability to identify recommended dose level(s) for Part 2
- Part 2a is dose optimization in participants with OC, and Part 2b is dose expansion in FRα-expressing participants with EC or nonsquamous NSCLC

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
Secondary	• Serum or plasma concentrations of ZW191 • PK parameters (C_{max}, t_{max}, AUC, $t_{1/2}$, λ_z, CL, V_d) • Presence of ADAs • BOR, DOR, DCR, cORR, CBR • PFS, OS

Part 2: Dose Optimization/Dose Expansion	
Primary	• cORR • Frequency and severity of AEs, AESIs, and clinical lab abnormalities • Frequency of SAEs and deaths • Frequency of dose reductions
Secondary	• Serum or plasma concentrations and PK parameters of ZW191 • Presence of ADAs • DOR, DCR, CBR, BOR • PFS, OS

λ_z: terminal elimination rate constant; ADA: antidrug antibody; AEs: adverse events; AESIs: adverse events of special interest; AUC: area under the concentration-time curve; BOR: best overall response; CBR: clinical benefit rate; 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

- ZWI-ZW191-101 (NCT06555744; EudraCT: 2024-512299-37-00) is evaluating the safety, tolerability, PK, and antitumour activity of ZW191 in participants with advanced OC, EC, or NSCLC
- Enrolment for Part 1 of the study (dose escalation) is ongoing in the US, Japan, South Korea, Singapore, and Australia

References

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Presenter Email: Kathleen-Moore@ouhsc.edu

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