Design of a First-in-Human Multicenter Open-Label Study of ZW171, a Mesothelin x CD3–Targeting Bispecific T Cell Engager, in Participants With Advanced Solid Tumors: ZWI-ZW171-101

Melissa Johnson,[1] John T. Hamm,[2] Fiona Thistlethwaite,[3] Myung-Ju Ahn,[4] Erin L. Schenk,[5] Diana Hanna,[6] Anna Minchom,[7] Jason Luke,[8] Byoung Chul Cho,[9] Dong-Wan Kim,[10] Rebecca Kristeleit,[11] Dmitriy Zamarin,[12] Catherine Davidson,[13] Joseph Woolery,[14] Pranshul Chauhan,[14] Martin Wermke[15]

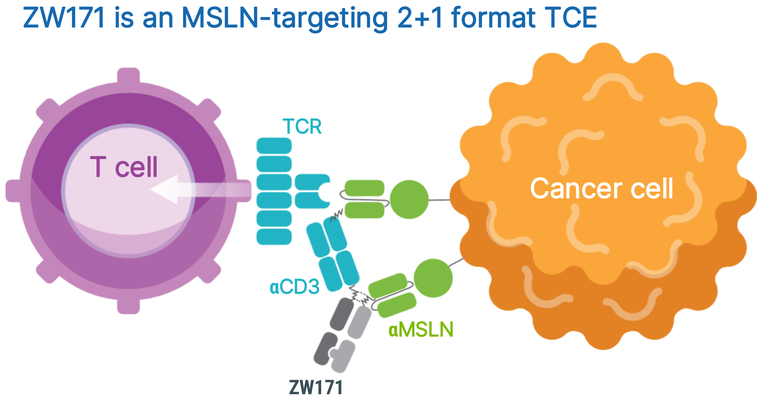
[1]Sarah Cannon Research Institute, Nashville, TN, US; [2]Norton Cancer Institute, Louisville, KY, US; [3]The Christie NHS Foundation Trust and The University of Manchester, Manchester, UK; [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [5]University of Colorado Anschutz Medical Center, Aurora, CO, US; [6]USC Norris Comprehensive Cancer Center, Los Angeles, CA, US; [7]Royal Marsden Hospital, Sutton, UK; [8]UPMC Hillman Cancer Center, Pittsburgh, PA, US; [9]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [10]Seoul National University Hospital, Seoul, South Korea; [11]Guy's and St. Thomas' NHS Foundation Trust and Comprehensive Cancer Centre, King's College London, London, UK; [12]Mount Sinai, New York, NY, US; [13]Belfast Health and Social Care Trust, Belfast, Ireland; [14]Zymeworks Inc., Vancouver, BC, Canada; [15]Technische Universität Dresden, NCT/UCC Early Clinical Trial Unit, Dresden, Germany

Poster: 473b

BACKGROUND

- Mesothelin (MSLN) is a glycosylphosphatidylinositol-linked membrane glycoprotein overexpressed in multiple solid tumors, such as ovarian, lung, pancreatic, and mesothelioma,[1] making it a promising target for cancer treatments, including T cell engagers (TCEs)
- Although MSLN-targeting agents have shown early clinical activity, improved therapies with better safety and efficacy are still needed[2]
- ZW171 is a humanized trivalent bispecific TCE antibody in a 2+1 format, targeting a threshold level of MSLN expression with 2 binding sites and the CD3ε receptor on T cells with 1 binding site[3]
- The 2+1 TCE format of ZW171 facilitates avidity-driven tumor cell binding, stimulates MSLN-dependent T cell activation, and limits on-target, off-tumor toxicities[4]
- Preclinical studies of ZW171 demonstrated favorable pharmacology, pharmacokinetics (PK), and toxicology. In the pivotal good laboratory practice (GLP) study, ZW171 was well tolerated in cynomolgus monkeys up to a maximum dose tested of 50 mg/kg, demonstrating the potential of ZW171 to target MSLN-expressing tumors while limiting on-target, off-tumor adverse effects by sparing healthy tissues with low MSLN expression[4]
- This ongoing first-in-human phase 1 study (ZWI-ZW171-101) evaluates the safety, tolerability, PK, and antitumor activity of ZW171 in participants with advanced solid tumors

ZW171 is an MSLN-targeting 2+1 format TCE



Bivalent binding to MSLN via dual engagement of single-chain variable fragment and monovalent binding to CD3ε via Fab arm.
MSLN, mesothelin; TCR, T cell receptor.

METHODS

Key Eligibility Criteria

Inclusion Criteria

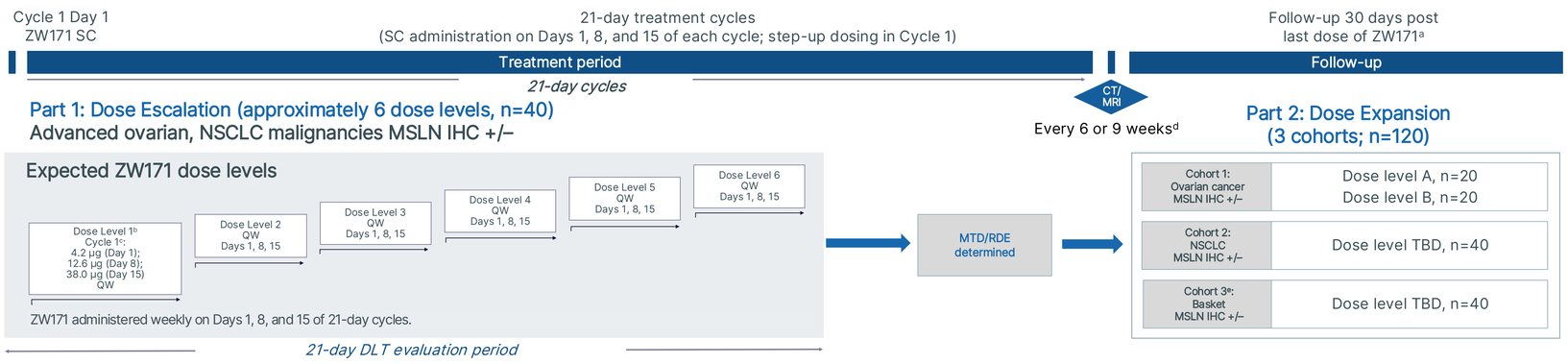
- Adults ≥18 years of age with ovarian cancer (OC), non-small cell lung cancer (NSCLC), or other MSLN-expressing cancers
- Pathologically confirmed diagnosis of cancers with evidence of locally advanced (unresectable) and/or metastatic disease
- Participants may be MSLN immunohistochemistry +/–, for which MSLN expression will be evaluated retrospectively
- Cancer refractory to all available standard of care treatments
- Eastern Cooperative Oncology Group performance score of 0 or 1
- Measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1
- Adequate cardiac (left ventricular ejection fraction ≥50% as determined by echocardiogram or multigated acquisition scan), neurologic, pulmonary, and other organ function

Exclusion Criteria

- Known additional malignancy that is progressing or that has required active treatment
- History of hypersensitivity or contraindications to any active substance/ingredient of ZW171
- Ongoing, clinically significant toxicity (grade ≥2) associated with prior cancer therapies
- Acute or chronic uncontrolled renal, pancreatic, or liver disease
- Active or recurrent clinically significant autoimmune disease requiring systemic high-dose corticosteroids or immunosuppressive drugs
- Severe chronic or active infections requiring systemic therapy, including antibacterial, antifungal, or antiviral therapy

Study Design

ZWI-ZW171-101 is an ongoing first-in-human multicenter open-label phase 1 study of ZW171 in participants with advanced solid tumors (NCT06523803; EudraCT: 2024-511119-11)



[a]Additional survival follow-up (collected every 3 months from EOT). [b]Dose level 1 is determined by QSP-based MABEL approach.[4] [c]For cycles ≥2, dose level 1 will be 38 µg onD1, 8, and 15. [d]Timed from Cycle 1, Day 1. Every 6 weeks for the first 4 cycles and then every 9 weeks thereafter. [e]Cohort 3 (basket cohort) may include, but is not limited to, pancreatic adenocarcinoma, malignant mesothelioma (pleural or peritoneal with epithelioid histology), and endometrial (serous or endometrioid) and gastrointestinal adenocarcinomas. Cohort to open after Cohorts 1 and 2.
Part 2 will be conducted using the RDE(s), which depend on the MTD and/or MAD and are used with an intent to determine the OBD of ZW171 in Part 2. Efficacy will be assessed once every 6 weeks for the first 4 cycles and once every 9 weeks thereafter, using CT or MRI scans. Study conduct will follow RECIST version 1.1.
CT, computed tomography; DLT, dose-limiting toxicity; EOT, end of treatment; IHC, immunohistochemistry; MABEL, minimal anticipated biological effect level; MAD, maximum administered dose; MRI, magnetic resonance imaging; MSLN, mesothelin; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; OBD, optimal biologic dose; QSP, quantitative systems pharmacology; QW, once every week; RDE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumours; SC, subcutaneous; TBD, to be determined.

This study comprises 2 parts:

- Part 1 is dose escalation to identify the maximum tolerated dose (using modified toxicity probability interval design) of ZW171 in approximately 6 dose levels in participants with OC or NSCLC
- Participants will receive subcutaneous ZW171 monotherapy weekly on Days 1, 8, and 15 of 3-week (21-day) cycles
- A 2-step-up dosing approach is used; ZW171 step-up doses are administered on Cycle 1 Day 1 and Day 8, followed by the target dose on Day 15
- Dose level 1, determined by quantitative systems pharmacology (QSP)–based minimal anticipated biological effect level (MABEL) approach,[4] starting with 4.2 µg (Day 1), 12.6 µg (Day 8), and 38.0 µg (Day 15), using step-up dosing in Cycle 1. Dose levels 2 and above are determined by the data from the prior dose and prespecified rules within the protocol
- Part 2 is dose expansion in participants with OC, NSCLC, and other MSLN-expressing cancers including, but not limited to, pancreatic, mesothelioma, endometrial, and gastrointestinal
- Intrapatient dose escalation may be allowed after completing the dose-limiting toxicity (DLT) period and 4 cycles at their assigned dose levels
- Backfill enrollment will be allowed for selected dose-level cohorts

Endpoints

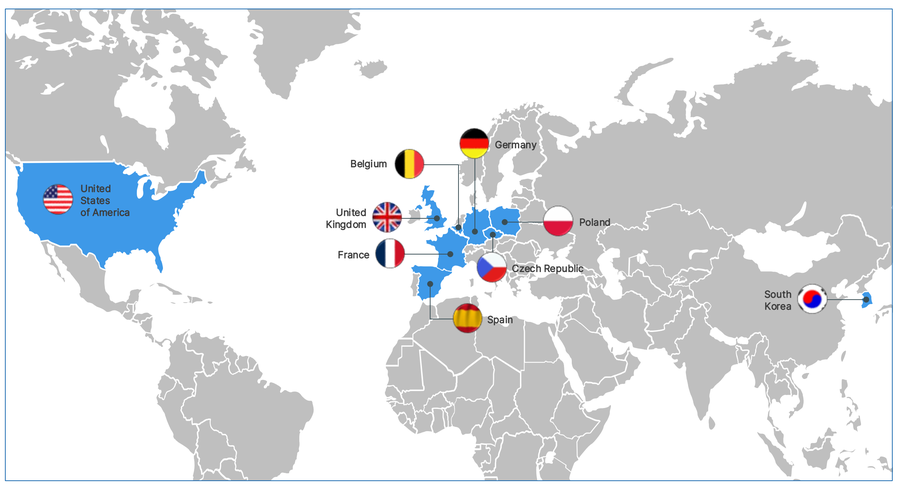
Part 1 Dose Escalation	
Primary	• Frequency of DLTs • Frequency and severity of AEs, clinical lab abnormalities, CRS, and neurotoxicity, including ICANS • Frequency of SAEs and deaths • Frequency of dose reductions of ZW171 • Frequency of treatment discontinuations due to AEs
Secondary	• Serum concentrations of ZW171 • PK parameters (C_{max}, T_{max}, AUC, $t_{1/2}$, λz, CL, V_d) • Presence of ADAs • cORR

Part 2 Dose Expansion	
Primary	• cORR • Frequency and severity of AEs, clinical lab abnormalities, CRS, and neurotoxicity, including ICANS • Frequency of SAEs and deaths • Frequency of dose reductions of ZW171 • Frequency of treatment discontinuations due to AEs
Secondary	• Serum concentrations and PK parameters of ZW171 • Presence of ADAs • DOR • DCR • PFS • OS

ADAs, anti-drug antibodies; AEs, adverse events; AUC, area under the concentration-time curve; CL, clearance; C_{max}, maximum observed serum and/or plasma concentration; cORR, confirmed objective response rate; CRS, cytokine release syndrome; DCR, disease control rate; DLTs, dose-limiting toxicities; DOR, duration of response; ICANS, immune effector cell–associated neurotoxicity syndrome; λz, terminal elimination rate constant; 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.

Participating Regions of Study ZWI-ZW171-101

ZWI-ZW171-101 is a global study with sites across multiple regions, including North America, Europe, and Asia-Pacific, and is actively enrolling participants



SUMMARY

- ZWI-ZW171-101 (NCT06523803; EudraCT: 2024-511119-11) is evaluating the safety, tolerability, PK, and antitumor activity of ZW171 in participants with unresectable MSLN-expressing OC, NSCLC, or other MSLN-expressing cancers
- Enrollment for Part 1 (dose escalation) of the study is ongoing in the US, UK, Germany, and South Korea
- Part 2 (dose expansion) will include additional countries such as Spain, France, Czech Republic, Poland, and Belgium

References

1. Morello A, et al. *Cancer Discov*. 2016;6:133-146. **2.** Faust J, et al. *Cancers (Basel)*. 2022;14(6):1550. **3.** Afacan N, et al. Poster presented at: Society for Immunotherapy of Cancer (SITC) 39th Annual Meeting, November 6-10, 2024; Houston, TX. Abstract #1062. **4.** Afacan N, et al. Poster presented at: SITC 38th Annual Meeting, November 1-5, 2023; San Diego, CA. Abstract #2942.

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Presenter Email: melissa.johnson@scri.com

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