Efficacy analysis of ZW191 by folate receptor α (FRα) expression level in a phase 1 study

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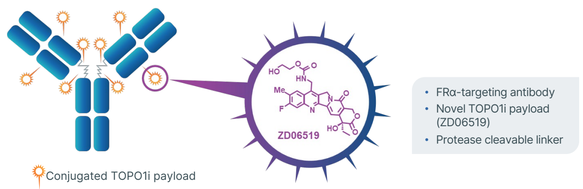
BACKGROUND

- Folate receptor alpha (FRα) is a clinically validated therapeutic target highly expressed in ovarian cancer (OC), endometrial cancer (EC), and non-small cell lung cancer (NSCLC), with limited expression in normal tissue[1-3]
- Currently available treatments lack significant activity toward lower FRα-expressing tumours; hence, there is a need for treatment with efficacy in both low and high FRα-expressing tumours[4]
- ZW191 is composed of a novel FRα-targeting antibody conjugated to a novel topoisomerase 1 inhibitor payload (ZD06519) with a protease cleavable linker (**Figure 1**)[4]
- ZWI-ZW191-101 (NCT06555744) is an ongoing, phase 1, open-label, 2-part, global study evaluating safety, tolerability, pharmacokinetics, and anti-tumour activity of ZW191 in participants with advanced solid tumours[5]
- In part 1 dose escalation, ZW191 showed promising activity, with a confirmed objective response rate (cORR) of 61% and 57% in participants with platinum-resistant ovarian cancer (PROC) and EC, respectively, across doses 6.4–9.6 mg/kg[6]
- Here, we report efficacy data by FRα expression levels from part 1 (data cutoff: 9 March 2026)

Figure 1. Schematic of ZW191 ADC



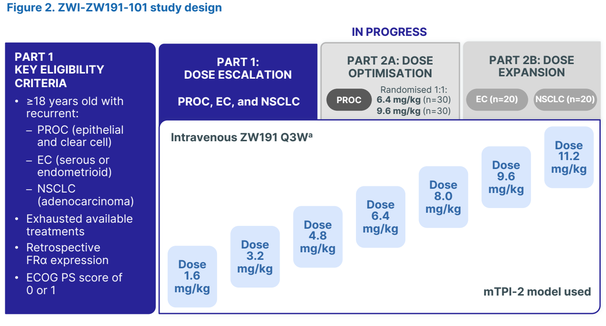
ZW191 has a drug-to-antibody ratio of ~8.[4]

ADC: antibody-drug conjugate; FRα: folate receptor alpha; TOPO1i: topoisomerase 1 inhibitor.

METHODS

- Part 1 dose escalation of ZWI-ZW191-101 is shown in **Figure 2**
  - Participants received intravenous ZW191 every 3 weeks until disease progression or unacceptable toxicity
- FRα expression was assessed by immunohistochemistry using archival or newly collected formalin-fixed, paraffin-embedded biopsies with the VENTANA® FOLR1 (FOLR1-2.1) assay
  - The PS2+ score was defined as the percentage of cells with 2+/3+ staining and categorised as FRα-negative (<75%) or FRα-positive (≥75%)
- Part 1 endpoints included safety, tolerability, and anti-tumour activity (Response Evaluation Criteria in Solid Tumors, version 1.1)

Figure 2. ZWI-ZW191-101 study design



[a]21-day dose-limiting toxicities evaluation period. CT/MRI testing every 6 weeks (first 4 assessments) or every 9 weeks timed from Cycle 1 Day 1. Safety follow-up was 30 days post last dose of ZW191; survival follow-up was every 3 months from last dose of ZW191 for up to 2 years.
CT: computed tomography; EC: endometrial cancer; ECOG PS: Eastern Cooperative Oncology Group performance status; FRα: folate receptor alpha; MRI: magnetic resonance imaging; mTPI-2: modified toxicity probability interval version 2 (keyboard design); NSCLC: non-small cell lung cancer; PROC: platinum-resistant ovarian cancer; Q3W: every 3 weeks.

RESULTS

- Analyses of part 1 dose escalation data with a median follow-up time of 7 months are reported (data cutoff: 9 March 2026)

Demographics and baseline characteristics

- A total of 51 participants (49 female, 2 male; **Table 1**) received ZW191 across 7 dose levels: 1.6 mg/kg (n=3), 3.2 mg/kg (n=3), 4.8 mg/kg (n=6), 6.4 mg/kg (n=12), 8.0 mg/kg (n=12), 9.6 mg/kg (n=12), and 11.2 mg/kg (n=3)
- Of the 51 participants, 19 (37%) were continuing on ZW191 treatment as of data cutoff
  - The most common reason for discontinuation was due to disease progression (n=21)
- All PROC and EC participants (n=46) received platinum and taxane as prior therapy lines (**Table 1**). Among NSCLC participants (n=5), all received platinum and 4 (80%) received taxane as prior therapy lines
- Among PROC participants (n=35), 15 were FRα-positive (PS2+ score ≥75%), 19 were FRα-negative (PS2+ score <75%), and 1 was not evaluated; all EC (n=11) and NSCLC (n=5) participants were FRα-negative
  - Baseline demographics were comparable in PROC participants across FRα expression levels

Table 1. Baseline participant and disease characteristics

Overall population	Total (N=51)
Female, n (%)	49 (96)
Median age (range), years	60 (35-79)
Race, n (%)	
Asian	35 (69)
White	13 (25)
Black or African American	1 (2)
Other/not reported	2 (4)
Baseline ECOG PS, n (%)	
0	25 (49)
1	26 (51)
Cancer type, n (%)	
Ovarian	35 (69)
Endometrial	11 (22)
Non-small cell lung	5 (10)
Median prior lines of therapy (range)	3 (1-9)
Prior therapy in PROC and endometrial cancer	**n=46**
Platinum and taxane, n (%)	46 (100)
PROC	**n=35**
Bevacizumab	29 (83)
PARP inhibitor	23 (66)
Mirvetuximab	2 (6)
Endometrial cancer	**n=11**
Checkpoint inhibitors	10 (91)

ECOG PS: Eastern Cooperative Oncology Group performance status; PARP: poly-ADP ribose polymerase; PROC: platinum-resistant ovarian cancer.

Anti-tumour activity of ZW191 in PROC and EC participants

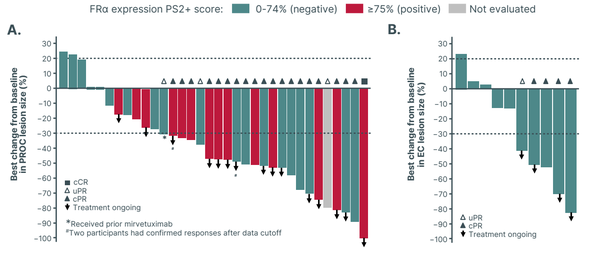
- 34 participants with PROC and 10 participants with EC were response-evaluable (≥1 postbaseline scan)
- Responses were observed in tumours with both FRα-positive and FRα-negative expression (**Figures 3-5**)
  - PROC participants with FRα-positive expression showed strong activity of 78.6% cORR, and participants who were FRα-negative showed promising activity of 47.4% cORR (**Table 2**)
  - EC participants with FRα-negative expression showed promising activity of 40.0% cORR
- The median duration of response across PROC and EC participants (n=22) was not reached (NR; 95% confidence interval [CI]: 4.2 months, NR)
- Median progression-free survival across PROC and EC participants (n=46) was 7.6 months (95% CI: 5.5, NR)

Table 2. Efficacy for response-evaluable PROC and EC participants

PROC[a]	FRα-positive (n=14)	FRα-negative (n=19)
cORR,[b] % (95% CI)	78.6% (49.2, 95.3)	47.4% (24.4, 71.1)
DCR, % (95% CI)	100.0% (76.8, 100.0)	89.5% (66.9, 98.7)
mTTR, months (range)	1.6 (1.2-4.2)	1.5 (1.2-5.7)
Endometrial cancer	**FRα-negative (n=10)**
cORR, % (95% CI)	40.0% (12.2, 73.8)
DCR, % (95% CI)	80.0% (44.4, 97.5)
mTTR, months (range)	1.2 (1.2-1.4)

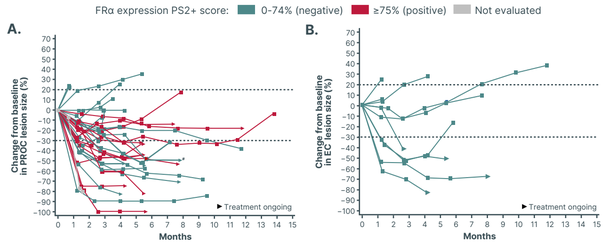
[a]One of 34 response-evaluable PROC participants was not evaluated for FRα expression. [b]Two participants had confirmed responses after data cutoff.
CI: confidence interval; cORR: confirmed objective response rate; DCR: disease control rate; EC: endometrial cancer; FRα: folate receptor alpha; mTTR: median time to response; PROC: platinum-resistant ovarian cancer.

Figure 3. Best percent change in target lesion size from baseline in response-evaluable participants with (A) platinum-resistant ovarian cancer and (B) endometrial cancer



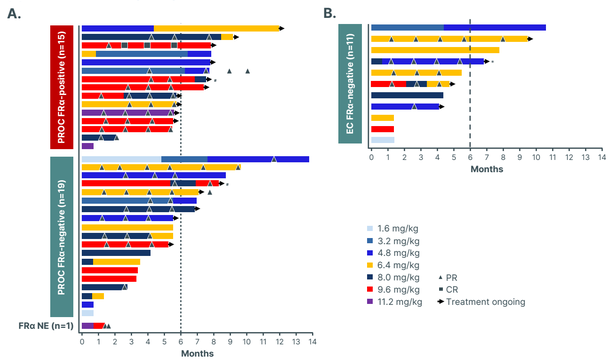
As of data cutoff, 34 participants with platinum-resistant ovarian cancer (A) and 10 with endometrial cancer (B) were response-evaluable and were included in the efficacy analysis. Response was based on RECIST v1.1 (response and progression defined as –30% and +20% change from baseline, respectively). PS2+ score was defined as the percentage of cells with 2+/3+ staining and categorised as FRα-negative (<75%) or FRα-positive (≥75%).
cCR: confirmed complete response; cPR: confirmed partial response; EC: endometrial cancer; FRα: folate receptor alpha; PROC: platinum-resistant ovarian cancer; RECIST v1.1: Response Evaluation Criteria in Solid Tumors, version 1.1; uPR: unconfirmed partial response.

Figure 4. Percent change in target lesion size from baseline in response-evaluable participants with (A) platinum-resistant ovarian cancer and (B) endometrial cancer



*Two participants had confirmed responses after data cutoff.
As of data cutoff, 34 participants with platinum-resistant ovarian cancer (A) and 10 with endometrial cancer (B) were response-evaluable and were included in the efficacy analysis. Response based on RECIST v1.1 (response and progression defined as –30% and +20% change from baseline, respectively). PS2+ score was defined as the percentage of cells with 2+/3+ staining and categorised as FRα-negative (<75%) or FRα-positive (≥75%).
EC: endometrial cancer; FRα: folate receptor alpha; PROC: platinum-resistant ovarian cancer; RECIST v1.1: Response Evaluation Criteria in Solid Tumors, version 1.1.

Figure 5. Duration of treatment and overall response for (A) platinum-resistant ovarian cancer and (B) endometrial cancer participants

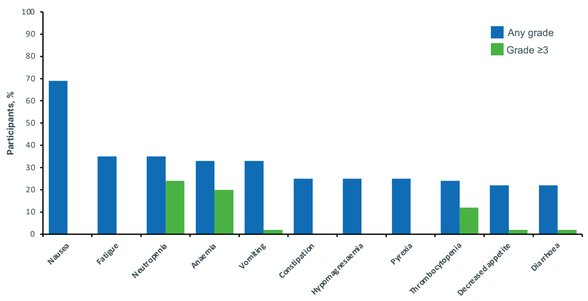


*Two participants had confirmed responses after data cutoff.
*Dose de-escalation from 8.0 mg/kg to 4.0 mg/kg.
CR: complete response; EC: endometrial cancer; FRα: folate receptor alpha; NE: not evaluated; PROC: platinum-resistant ovarian cancer; PR: partial response.

Safety and tolerability of ZW191

- Treatment-emergent adverse events (TEAEs) occurred in 50 participants (98%); the most common (≥20%) TEAEs are summarised in **Figure 6**
- 28 participants (55%) reported Grade ≥3 TEAEs; the most common were neutropenia (n=12), anaemia (n=10), and thrombocytopenia (n=6)
- 18 participants (35%) reported serious TEAEs
- TEAEs leading to dose reductions and discontinuations were reported in 9 (18%) and 10 (20%) participants, respectively
- Two participants had dose-limiting toxicities at doses 6.4 mg/kg and 11.2 mg/kg

Figure 6. TEAEs of any grade occurring in ≥20% of participants



TEAE: treatment-emergent adverse event.

CONCLUSIONS

- ZW191 demonstrated compelling efficacy in both FRα-positive (≥75%) and FRα-negative (<75%) cancers
  - cORR in PROC participants with FRα-positive and FRα-negative cancers was 78.6% and 47.4%, respectively
  - cORR in EC participants with FRα-negative cancers was 40.0%
  - Median duration of response was not reached
  - Median progression-free survival (95% CI) was 7.6 months (5.5, not reached)
- ZW191 demonstrated a broad therapeutic window and encouraging efficacy in both FRα-expression positive and negative tumours, justifying further investigation as monotherapy and/or in combination with other therapy
  - Part 2a dose optimisation is ongoing at dose levels 6.4 mg/kg and 9.6 mg/kg

References

1. Köbel M, et al. *Br J Cancer.* 2014;111(12):2297-2307. **2.** O'Shannessy DJ, et al. *Oncotarget.* 2012;3(4):414-425. **3.** Senol S, et al. *Int J Clin Exp Pathol.* 2015;8(5):5633-5641. **4.** Lawn S, et al. Poster. Presented at: AACR. 2024 (abstract #1862). **5.** ClinicalTrials.gov. A study of ZW191 in participants with solid tumors. NCT06555744. Updated 6 March 2026. Accessed 30 April 2026. https://clinicaltrials.gov/study/NCT06555744. **6.** LoRusso P, et al. Oral presentation. Presented at: AACR. 2026 (#CT306).

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