Preliminary Results From a Phase 1 First-in-Human Multicenter Open-Label Study of ZW191, a Folate Receptor α–Targeting Antibody-Drug Conjugate, in Participants With Advanced Solid Tumors

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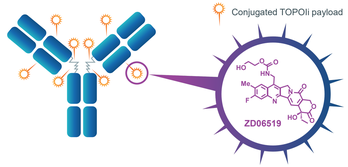
INTRODUCTION

- 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]
- ZW191 is composed of a FRα-targeting antibody conjugated to a novel topoisomerase I inhibitor (TOPOli) payload (ZD06519) with a protease cleavable linker[4] (**Figure 1**)
- ZW191's antibody selectively binds to a distinct epitope of FRα and was chosen for high levels of internalization and tumor penetration in nonclinical models
- Nonclinical studies of ZW191 showed[4]:
  - Intracellular release of bystander-active payload
  - Superior payload delivery over other antibodies from FRα-targeting antibody-drug conjugates
  - Anti-tumor activity in FRα-high/mid/low OC, EC, and NSCLC xenograft models
  - Favorable safety and pharmacokinetic (PK) profile
  - Good tolerability at exposure levels above those predicted to be efficacious (highest non–severely toxic dose of 60 mg/kg in nonhuman primates)

Figure 1: Schematic of ZW191



FRα-targeting antibody conjugated to TOPOli payload using a cleavable peptide linker. ZW191 has an average drug-to-antibody ratio of 8.[4]

FRα, folate receptor alpha; TOPOli, topoisomerase I inhibitor.

Mechanism of Action

- ZW191 binds specifically to the extracellular domain of FRα, expressed on tumor cells
- ZW191 undergoes internalization followed by lysosomal degradation, releasing the ZD06519 payload, causing cell cycle arrest and death of the FRα-positive cells[4]
  - Bystander-mediated killing from extracellular release of payload after cell death can target both FRα-positive and FRα-negative tumor cells

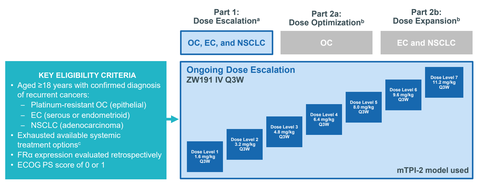
OBJECTIVES

- ZWI-ZW191-101 (NCT06555744) is an ongoing, 2-part, global, open-label, phase 1 study evaluating safety, tolerability, pharmacokinetics, and anti-tumor activity of ZW191 in participants with advanced solid tumors[5]
- We report the preliminary results from dose-escalation Part 1 of the study

METHODS

- Participants received intravenous (IV) ZW191 every 3 weeks (Q3W) until disease progression or unacceptable toxicity (**Figure 2**)
- Dose escalation is based on the modified toxicity probability interval version 2 (mTPI-2) design
- Participants who had exhausted available systemic treatment options (including prior platinum-based chemotherapy, checkpoint inhibitors, and other biomarker-directed therapies) were recruited regardless of FRα expression
- FRα expression was measured by immunohistochemistry on archival or newly collected formalin-fixed, paraffin-embedded biopsies with the VENTANA® FOLR1 (FOLR1-2.1) assay
- H-score was calculated as [1x % 1 intensity] + [2x % 2 intensity] + [3x % 3 intensity]. Categorization: low/negative 0-74, intermediate 75-199, and high 200-300
- Primary endpoints of Part 1 are to characterize safety and tolerability and to determine maximum tolerated dose (MTD) and recommended dose(s) for expansion; key secondary endpoints include PK, anti-drug antibodies, and anti-tumor activity (Response Evaluation Criteria in Solid Tumors, version 1.1)

Figure 2. ZWI-ZW191-101 study design



[a]21-day DLT 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. [b]To be initiated with recommended doses for optimization based on safety data from Part 1. [c]No limits on the number of prior treatments received.

CT, computed tomography; DLT, dose-limiting toxicity; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor alpha; IV, intravenous; MRI, magnetic resonance imaging; mTPI-2, modified toxicity probability interval version 2 (keyboard design); NSCLC, non-small cell lung cancer; OC, ovarian cancer; Q3W, once every 3 weeks.

RESULTS

- Analyses of Part 1 dose escalation data are presented as of 10 Sept 2025 data cutoff

Participant Disposition

- 41 participants (40 female, 1 male) were treated with ZW191 across 7 dose levels (Q3W): 1.6 mg/kg (n=3), 3.2 mg/kg (n=3), 4.8 mg/kg (n=4), 6.4 mg/kg (n=10), 8.0 mg/kg (n=11), 9.6 mg/kg (n=8), and 11.2 mg/kg (n=2); **Table 1**
  - Enrollment at dose 11.2 mg/kg was ongoing at time of data cutoff
  - Participants were backfilled into dose levels with acceptable toxicity
- 41 participants underwent safety analysis
- 27 participants were response-evaluable (≥1 post-baseline scan)
- Of the 41 participants, 35 (85%) were continuing on ZW191 treatment as of data cutoff; 6 (15%) participants had discontinued due to disease progression
- All participants received platinum and taxane as prior therapy lines; 3 out of 4 NSCLC participants and 8 out of 8 EC participants received checkpoint inhibitors

Table 1. Baseline participant and disease characteristics

ZW191	1.6 mg/kg (n=3)	3.2 mg/kg (n=3)	4.8 mg/kg (n=4)	6.4 mg/kg (n=10)	8.0 mg/kg (n=11)	9.6 mg/kg (n=8)	11.2 mg/kg (n=2)	Total (n=41)
Median age (range), years	62 (58-68)	64 (59-73)	59 (35-62)	59 (48-79)	58 (52-68)	62 (40-74)	60 (55-65)	59 (35-79)
Ongoing treatment, n (%)	1 (33)	2 (67)	3 (75)	9 (90)	10 (91)	8 (100)	2 (100)	35 (85)
Race, n (%)								
Asian	1 (33)	1 (33)	4 (100)	8 (80)	7 (64)	8 (100)	1 (50)	30 (73)
White	2 (67)	1 (33)	0	2 (20)	4 (36)	0	1 (50)	10 (24)
Not reported	0	1 (33)	0	0	0	0	0	1 (2)
Baseline ECOG PS, n (%)								
0	1 (33)	1 (33)	2 (50)	5 (50)	4 (36)	6 (75)	1 (50)	20 (49)
1	2 (67)	2 (67)	2 (50)	5 (50)	7 (64)	2 (25)	1 (50)	21 (51)
Cancer type, n (%)								
Ovarian	2 (67)	2 (67)	4 (100)	5 (50)	7 (64)	7 (88)	2 (100)	29 (71)
Endometrial	1 (33)	1 (33)	0	3 (30)	2 (18)	1 (13)	0	8 (20)
Non-small cell lung	0	0	0	2 (20)	2 (18)	0	0	4 (10)
Median number of prior lines of therapy (range)	2 (1-4)	3 (2-4)	4 (3-7)	4 (2-7)	3 (2-9)	4 (2-6)	7 (7-7)	3 (1-9)
Number of prior lines of therapy, n (%)								
1-2	2 (67)	1 (33)	0	1 (10)	4 (36)	3 (38)	0	11 (27)
3-4	1 (33)	2 (67)	3 (75)	5 (50)	3 (27)	1 (13)	0	15 (37)
≥5	0	0	1 (25)	4 (40)	4 (36)	4 (50)	2 (100)	15 (37)
Prior lines of therapy (ovarian cancer), n (%)								
Platinum	2 (100)	2 (100)	4 (100)	5 (100)	7 (100)	7 (100)	2 (100)	29 (100)
Taxane	2 (100)	2 (100)	4 (100)	5 (100)	7 (100)	7 (100)	2 (100)	29 (100)
Bevacizumab	2 (100)	2 (100)	3 (75)	4 (80)	7 (100)	4 (57)	2 (100)	24 (83)
PARP inhibitor	1 (50)	0	2 (50)	2 (40)	7 (100)	6 (86)	2 (100)	20 (69)
Mirvetuximab	0	0	0	0	1 (14)	0	1 (50)	2 (7)

ECOG PS, Eastern Cooperative Oncology Group performance status; PARP, poly-ADP ribose polymerase.

Safety

- MTD has not been identified, and escalation is ongoing
- Treatment-related safety results are summarized in **Table 2**
- No serious treatment-related adverse events (TRAEs), discontinuations due to AEs, or deaths were reported
- The most common (≥15%) TRAEs are summarized in **Table 3**
- Seven (17%) participants reported Grade ≥3 TRAEs; the most common were anemia (n=4; 10%), neutropenia (n=2; 5%), and thrombocytopenia (n=2; 5%)
- Within the population evaluable for dose-limiting toxicities (DLTs; n=25), 1 DLT was reported at the 6.4 mg/kg dose (Grade 3 anemia) with no DLTs at other dose levels; DLT evaluation for participants at 11.2 mg/kg is ongoing

Table 2. ZW191-related safety summary

ZW191 TRAE, n (%)	1.6 mg/kg (n=3)	3.2 mg/kg (n=3)	4.8 mg/kg (n=4)	6.4 mg/kg (n=10)	8.0 mg/kg (n=11)	9.6 mg/kg (n=8)	11.2 mg/kg (n=2)	Total (n=41)
Any TRAE	1 (33)	3 (100)	3 (75)	8 (80)	10 (91)	6 (75)	2 (100)	33 (80)
Grade ≥3 TRAE	0	1 (33)	0	1 (10)	4 (36)	1 (13)	0	7 (17)
TRAE leading to dose interruption	0	2 (67)	0	0	1 (9)	0	0	3 (7)
TRAE leading to dose reduction	0	0	0	1 (10)	1 (9)	0	0	2 (5)
DLT events (n=25)[a]	**0**	**0**	**0**	**1 (20)[b]**	**0**	**0**	**0**	**1 (4)[b]**

[a]Backfilled participants are not included in the DLT evaluable set.
[b]Percentages calculated based on the number of participants in the DLT evaluable set (n=5 at dose 6.4 mg/kg; n=25 total).
DLT, dose-limiting toxicity; TRAE, treatment-related adverse event.

Table 3. TRAEs of any grade occurring in ≥15% of participants

ZW191 TRAEs, n (%)	1.6 mg/kg (n=3)		3.2 mg/kg (n=3)		4.8 mg/kg (n=4)		6.4 mg/kg (n=10)		8.0 mg/kg (n=11)		9.6 mg/kg (n=8)		11.2 mg/kg (n=2)		Total (n=41)	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Any TRAE	1 (33)	0	3 (100)	1 (33)	3 (75)	0	8 (80)	1 (10)	10 (91)	4 (36)	6 (75)	1 (13)	2 (100)	0	33 (80)	7 (17)
Nausea	0	0	2 (67)	0	2 (50)	0	6 (60)	0	7 (64)	0	5 (63)	0	2 (100)	0	24 (59)	0
Fatigue	1 (33)	0	2 (67)	0	1 (25)	0	1 (10)	0	3 (27)	0	1 (13)	0	0	0	9 (22)	0
Anemia	0	0	0	0	0	0	2 (20)	1 (10)	4 (36)	3 (27)	1 (13)	0	0	0	7 (17)	4 (10)
Diarrhea	1 (33)	0	1 (33)	0	0	0	1 (10)	0	4 (36)	0	0	0	0	0	7 (17)	0
Vomiting	0	0	0	0	1 (25)	0	3 (30)	0	1 (9)	0	2 (25)	0	0	0	7 (17)	0
Alopecia	1 (33)	0	0	0	0	0	2 (20)	0	2 (18)	0	1 (13)	0	0	0	6 (15)	0

All Grade ≥3 events were Grade 3 except for one Grade 4 TRAE at dose level 8.0 mg/kg.
TRAE, treatment-related adverse event.

Anti-Tumor Activity

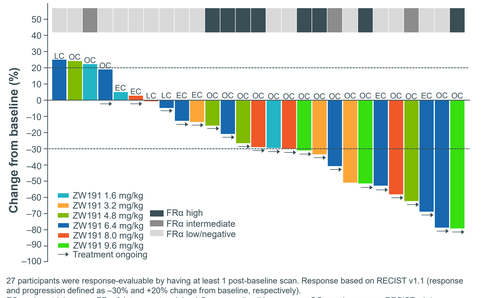
- Responses were observed beginning at the 3.2 mg/kg dose (**Figures 3-5**)
- For all response-evaluable participants (n=27) across dose levels, objective response rate (ORR) was 44%; across doses of 6.4 mg/kg to 9.6 mg/kg, ORR was 53%
- For response-evaluable gynecological cancer participants (n=24) across dose levels, ORR was 50% (**Table 4**); across doses of 6.4 mg/kg to 9.6 mg/kg, ORR was 64%
- Responses were observed in tumors with low/negative levels of FRα expression

Table 4. Preliminary efficacy for response-evaluable gynecological cancer participants

ZW191 best response	1.6 mg/kg (n=3)	3.2 mg/kg (n=3)	4.8 mg/kg (n=4)	6.4 mg/kg (n=7)	8.0 mg/kg (n=4)	9.6 mg/kg (n=3)	6.4-9.6 mg/kg (n=14)	Total (n=24)
PR, n (%)[a]	0	2 (67)	1 (25)	4 (57)	2 (50)	3 (100)	9 (64)	12 (50)
cPR, n (%)	0	2 (67)	1 (25)	3 (43)	1 (25)	0	4 (29)	7 (29)
SD, n (%)	1 (33)	1 (33)	2 (50)	3 (43)	2 (50)	0	5 (36)	9 (38)
PD, n (%)	2 (67)	0	1 (25)	0	0	0	0	3 (13)

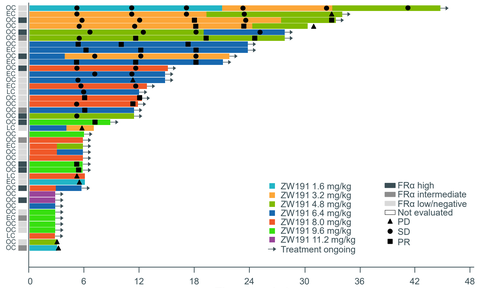
[a]PR includes confirmed and unconfirmed. The 5 participants with unconfirmed PR are awaiting confirmation.
Note: Percentages are out of gynecological cancer (OC and EC) participants.
cPR, confirmed partial response; EC, endometrial cancer; OC, ovarian cancer; PD, progressive disease; PR, partial response; SD, stable disease

Figure 3. Best percent change in target lesion size from baseline



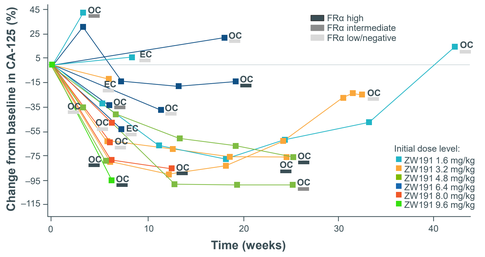
27 participants were response-evaluable by having at least 1 post-baseline scan. Response based on RECIST v1.1 (response and progression defined as –30% and +20% change from baseline, respectively).
EC, endometrial cancer; FRα, folate receptor alpha; LC, non-small cell lung cancer; OC, ovarian cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

Figure 4. Duration of treatment and overall response



Duration of treatment and overall response for 41 participants.
EC, endometrial cancer; FRα, folate receptor alpha; LC, non-small cell lung cancer; OC, ovarian cancer; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 5. Percent change from baseline in CA-125

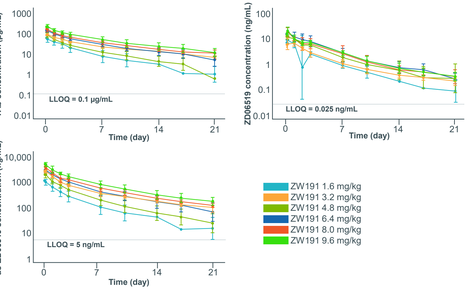


Percent change from baseline in CA-125 for 19 participants
CA-125, cancer antigen 125; EC, endometrial cancer; FRα, folate receptor alpha; OC, ovarian cancer.

Pharmacokinetics

- Pharmacokinetics of ZW191 were characterized by monitoring 3 analytes:
  - Total antibody (TAb), which measures fully conjugated, partially deconjugated, and fully deconjugated antibodies
  - Antibody-conjugated payload (ac-ZD06519), which quantifies the payload (ZD06519) conjugated to the antibody
  - Free payload (ZD06519)
- Preliminary PK analysis (n=31) showed that exposure generally increased in a dose-proportional manner for all 3 analytes of ZW191 (**Figure 6**)
- Following first IV infusion, concentrations declined with a mean terminal half-life of approximately 6.3 days and 5.7 days for TAb and ac-ZD06519, respectively
- As measured by mean C_{max}, free payload exposure was ~100- to 200-fold lower than ac-payload exposure; free payload C_{max} ranged from 7.8 to 31.0 ng/mL across dose levels (1.6-9.6 mg/kg), with a median time to maximum observed serum/plasma concentration (T_{max}) of 4 hours
- Minimal accumulation after repeated dosing (Q3W)

Figure 6. Systemic concentration of ZW191 after first dose administration



ac-ZD06519, antibody-conjugated payload; LLOQ, lower limit of quantification; TAb, total antibody; ZD06519, free payload.

CONCLUSIONS

- ZW191 has been safely administered during dose escalation up to 11.2 mg/kg, with most participants still on treatment
  - Low rates of dose reduction, dose delays, and Grade ≥3 TRAEs
  - No discontinuations or deaths due to AEs
- Preliminary efficacy is promising, starting at 3.2 mg/kg
  - ORRs across doses 6.4-9.6 mg/kg were 53% (overall) and 64% (gynecological cancers)
- ZW191 appears to have a broad therapeutic window, justifying further investigation in advanced solid tumors

References

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Disclosures

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