ZW191, a novel FRα-targeting antibody-drug conjugate bearing a topoisomerase I inhibitor payload

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Introduction

ZW191

ZW191 is an antibody-drug conjugate (ADC) targeting human Folate Receptor Alpha (FRα). ZW191 is comprised of a novel fully humanized IgG1 antibody covalently conjugated to a novel topoisomerase I inhibitor ZD06519, a camptothecin (CPT) derivative, via endogenous interchain cysteines with a drug to antibody ratio (DAR) of 8. The linker in ZW191 consists of a maleimidocaproyl (MC) anchor and a GGFG-aminomethyl (AM) protease cleavable sequence.

Mechanism of Action

Upon target binding and receptor-mediated internalization of ZW191, intracellular release of bystander-active ZD06519 induces cell death of FRα positive cells, and FRα negative cells through bystander-mediated killing.

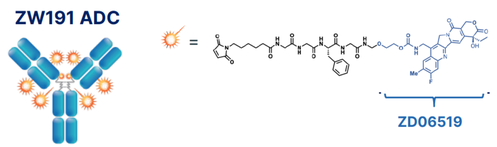


Figure 1. ZW191 comprises a novel FRα targeting IgG1 mAb conjugated to a novel camptothecin derivative at a DAR of 8 using a protease cleavable linker

FRα is a clinically validated target

- FRα is overexpressed in a wide range of indications with high unmet clinical need.
- FRα is a clinically validated target, as demonstrated by the recent approval of mirvetuximab soravtansine (Elahere™) for FRα-high expressing ovarian cancer[1].

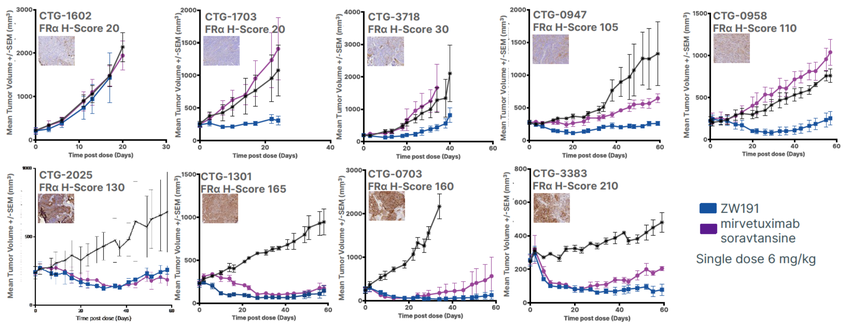
Significant opportunities for a differentiated FRα-targeting ADC

- Mirvetuximab soravtansine is an option for a limited subset of ovarian cancer patients and there is room to improve on both response rate and duration of response.
- Preclinical data highlight the potential of ZW191 to expand into FRα-mid and low ovarian cancer settings.
- Potential additional FRα expressing indications for ZW191 include NSCLC and TNBC, which are compatible with the ADC modality and topoisomerase I inhibition.

	mirvetuximab soravtansine[1]	Potential for ZW191
Indication:	Ovarian	Ovarian, Endometrial, NSCLC, TNBC…
FRα expression:	High (36%)	High, Mid, Low (~80%)
Efficacy:	32% ORR 6.9 mo DoR	↑ ORR ↑ DOR
Tolerability:	Ocular tox	Avoid ocular tox

ZW191 demonstrates superior efficacy in PDX models across a range of FRα expression levels

A Superior activity in lower FRα expressing ovarian cancer models



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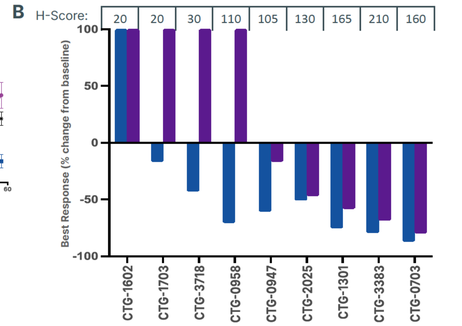


FRα Expression (H-Score)	Incidence of Tumor Regression: ZW191	Incidence of Tumor Regression: mirvetuximab soravtansine
>150	100% (3/3)	100% (3/3)
<150	83% (5/6)	33% (2/6)

Figure 2. *In vivo* efficacy of ZW191 and mirvetuximab soravtansine was assessed in patient derived xenograft (PDX) models of ovarian cancer in Nude mice, n=3 per group. H-scores determined by pathologist from research level IHC assay (A) Tumor volume plots (B) Waterfall plots of mean best response from each of 3 mice per treatment group. Tumor regression is defined as <0% change from baseline.

ZW191's novel mAb drives superior internalization, payload delivery, and tissue penetration

Targets a distinct epitope

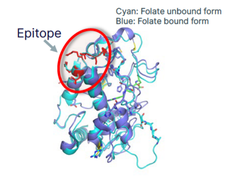
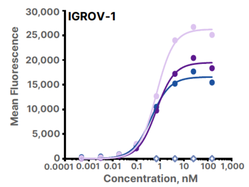
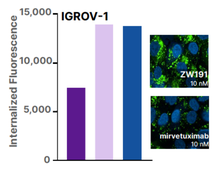


Figure 3. The FRα epitope of ZW191 was identified by hydrogen deuterium exchange mass-spec in a region unaffected by folate binding (folate shown in green). Competition binding assays indicate ZW191 binds a distinct epitope from mirvetuximab (not shown).

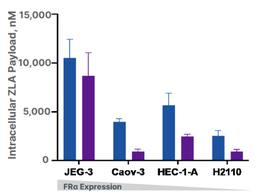
A Subnanomolar binding



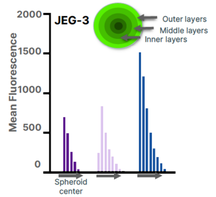
B Optimal internalization



C Superior payload delivery



D Superior penetration



ZW191 mAb Mirvetuximab IMGN151 Biparatopic

Figure 4. Functional properties of ZW191 were assessed and compared to mirvetuximab and the IMGN151 biparatopic (A) Cell binding to IGROV-1 cells by flow cytometry (B) Internalization of AF488 labelled antibodies to IGROV-1 cells after 24 hrs at 10 nM (C) Mass-spec quantification of internalized payload following treatment of cells with 10 nM of ADCs comprising ZW191 mAb or mirvetuximab conjugated to ZymeLink Auristatin (ZLA) (D) Penetration of AF488 labelled antibodies as quantified by high content imaging of spheroid layers at 96 hrs post-treatment at 25 nM.

- ZW191 mAb is cross-reactive to monkey FRα and not cross-reactive to mouse FRα, as demonstrated by flow cytometry binding (data not shown).
- ZW191 mAb is highly specific to FRα, as demonstrated by a binding screen of over 6000 membrane bound targets (data not shown).

ZW191's novel payload enables strong ADC bystander activity and cytotoxicity

ZD06519 payload profile

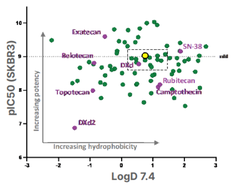


Figure 5. Potency/hydrophobicity profile of ZW191's ZD06519 payload (yellow) - a moderate potency camptothecin derivative with favorable biophysical properties. Platform development ZW topoisomerase I inhibitors (green) and benchmark payloads/ chemotherapeutic compounds (purple) shown for context.

ZD06519 delivery

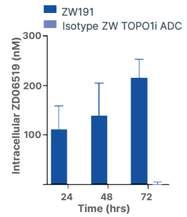


Figure 6. Intracellular levels of free ZD06519 were determined by mass-spec following treatment of IGROV-1 cells with 150 nM ADC for the indicated times.

Strong bystander activity

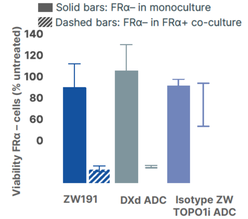
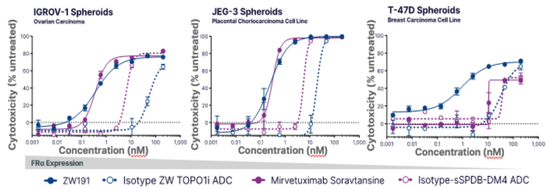


Figure 7. Bystander activity of ZW191 as shown by the decreased viability of FRα negative cells (EBC1) when co-cultured with FRα positive cells (IGROV-1). DXd ADC comprises the same mAb as ZW191 conjugated to MC-GGFG-DXd DAR8. Isotype ZW TOPO1i ADC is a non-targeting ADC bearing the ZD06519 payload.

Target-specific activity across a range of FRα expression levels



- **Superior activity to mirvetuximab soravtansine in lower FRα expressing model**

Figure 8. Cytotoxicity of ZW191 and mirvetuximab soravtansine against 3D spheroid cancer cell lines expressing a range of FRα levels. Degree of target specificity is indicated by the differential sensitivity to targeted and non-targeting isotype ADCs.

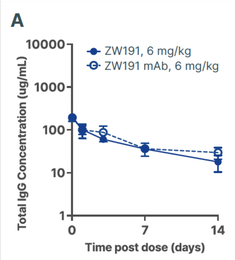
ZW191 is well-tolerated in non-human primate (NHP) at 30 mg/kg

- MTD ≥ 30 mg/kg in a 2-dose non-GLP NHP toxicology study.
- Histopathology findings at 30 mg/kg were considered as background/low severity and not adverse.
- Clinical chemistry and hematology findings at 30 mg/kg were considered mild and/or non-dose responsive.
- At 30 mg/kg, clinical observations were limited to fecal abnormalities, with no effect on body weight.

Dose mg/kg q3w x2	Tolerated?	Histopathology; Clinical Chemistry; Hematology
30	Yes	Thymus, stomach; AST ↑; ABRETIC↓
80	No	Thymus, kidney, testis, and brain; AST ↑; BUN ↑; ABRETIC↓; ABLYMP↓

ZW191 has a favorable pharmacokinetic profile

A



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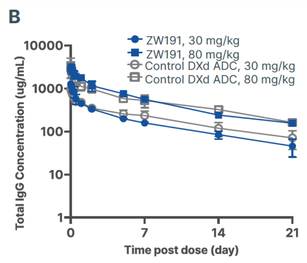

Figure 9. (A) Total antibody PK from a xenograft study in nude mice indicates ZW191 maintains a favorable PK profile similar to its parent mAb (B) Total antibody PK from NHP shows ZW191 to have a favorable PK profile comparable to that of a control DXd ADC comprising the same mAb as ZW191 conjugated to MC-GGFG-DXd DAR8.

Conclusions

- ZW191 is a FRα-targeting ADC differentiated by its novel antibody and novel topoisomerase I inhibitor payload.
- A compelling preclinical activity profile supports potential activity of ZW191 in patients with FRα-high/mid/low ovarian cancers.
- Strong responses in FRα-low expressing PDX models set a precedent for potential activity in other indications with lower levels of FRα.
- ZW191 displays favorable PK and is well tolerated in NHP at exposure levels above those projected to be efficacious.
- GMP process development is underway to support a 2024 IND.

References

1. Young-A Heo, Mirvetuximab Soravtansine: First Approval. 2023 Feb;83(3):265-273