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 FR α positive cells, and FR α 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

FR α 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^m) for FR α -high expressing ovarian cancer¹.

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 FR α -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
FRa expression:	High (36%)	High, Mid, Low (~80%)
Efficacy:	32% ORR 6.9 mo DoR	 ↑ ORR ↑ DOR
Tolerability:	Ocular tox	Avoid ocular tox







best response from each of 3 mice per treatment group. Tumor regression is defined as <0% change from baseline.



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).







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



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







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 IGROVcells with 150 nM ADC for the indicated times.



ADC bearing the ZD06519 payload.







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

- MTD \geq 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 \uparrow ; ABRETIC \downarrow
80	No	Thymus, kidney, testis, and brain; AST \uparrow ; BUN \uparrow ; ABRETIC \downarrow ; ABLYMP \downarrow

ZW191 has a favorable pharmacokinetic profile



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 topoisomerase Linhibitor payload.
- A compelling preclinical activity profile supports potential activity of ZW191 in patients with FR α -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 FR α .
- 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

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