ZW191 – a differentiated FRα-targeted topoisomerase I antibody-drug conjugate active in combination with standard of care drugs

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Introduction

ZW191 is a clinical-stage (NCT06555744) antibody-drug conjugate (ADC) differentiated by the superior ADC properties of its novel Folate Receptor Alpha (FRα) targeted antibody and by its novel moderate potency, bystander active topoisomerase I inhibitor payload (TOPO1i), ZD06519.

Together, these features drive improved efficacy over mirvetuximab soravtansine in multiple nonclinical tumor models, demonstrating activity in models with all levels of FRα expression, and impart best in class tolerability in non-human primate (NHP) compared to FRα-TOPO1i ADCs with higher potency payloads.

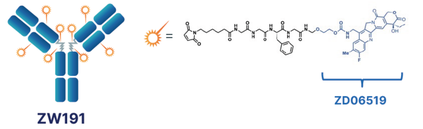
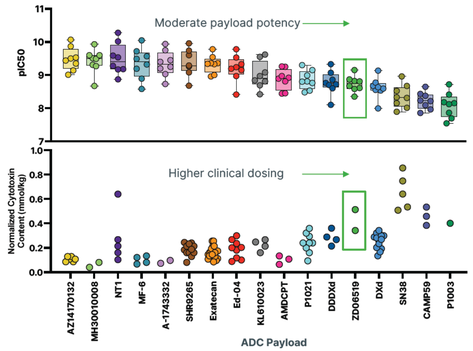


Figure 1. ZW191 comprises a novel FRα targeting IgG1 mAb conjugated to a novel camptothecin derivative at a drug-to-antibody ratio (DAR) of 8 using a protease cleavable linker.

Here, we demonstrate ZW191's nonclinical activity in combination with standard of care therapeutics across multiple modes of action, which together with its favorable tolerability profile potentially enable such combinations in the clinic.

ZW191's moderate potency TOPO1i payload supports higher dosing in the clinic



- **ZW191 is in clinical development** to assess its safety, tolerability, pharmacokinetics, and preliminary anti-tumor activity in patients with advanced solid tumors including ovarian cancer (NCT06555744)
- **Payload potency** can impact the clinically achievable dose levels of TOPO1i ADCs, as indicated by a clinical landscape analysis
- **Dose optimization** of ZW191, with its moderate potency TOPO1i payload, is currently ongoing at 6.4 and 9.6 mg/kg in ovarian cancer patients[3]
- **ZW191's tolerability profile**, supported by current clinical data, appears more favorable than ADCs with higher potency TOPO1i payloads, potentially enabling its combination with standard of care chemotherapeutics

Figure 3. Top panel: Potency of the ZW191 payload ZD06519 and other ADC TOPO1i payloads as represented by pIC50 cytotoxicity values (−log[IC50 (M)]) in a panel of cancer cell lines in 2D (each circle symbol represents a single cell line): SK-BR-3, N87, MDA-MB-468, OVK18, THP-1, H441, OCI-AML5, SK-CO-1 in 2D monolayer by CellTiter-Glo viability assay after 4 days of drug treatment. **Lower panel:** Clinical ADC payload doses identified from publicly disclosed early clinical phase expansion/optimization, RP2D, Ph3 doses, and approved drug doses. Most featured ADCs are dosed Q3W. Each symbol represents a different ADC. Within each payload grouping ADCs may feature a range of tumor antigen targets and a range of drug-linkers and conjugation methods. Formula for normal zed cytotox n conte t = dose (in mg/kg)/150 * DAR. Clinical doses reported in mg/m2 were converted to mg/kg by dividing by 37.

ADC payload potency	Key tox profile	Chemotherapy combination potential
Moderate potency – ZW191 with ZD06519 payload	**Lower** incidence and severity of thrombocytopenia, neutropenia	Potentially **favorable** combination with standard of care (SOC) including platins, taxanes
High potency e.g. TOPO1i ADCs with exatecan payload	**Higher** incidence and severity of thrombocytopenia, neutropenia	Potentially **limited** combination with SOC including platins, taxanes

ZW191 is a potential best-in-class differentiated FRα-targeting ADC

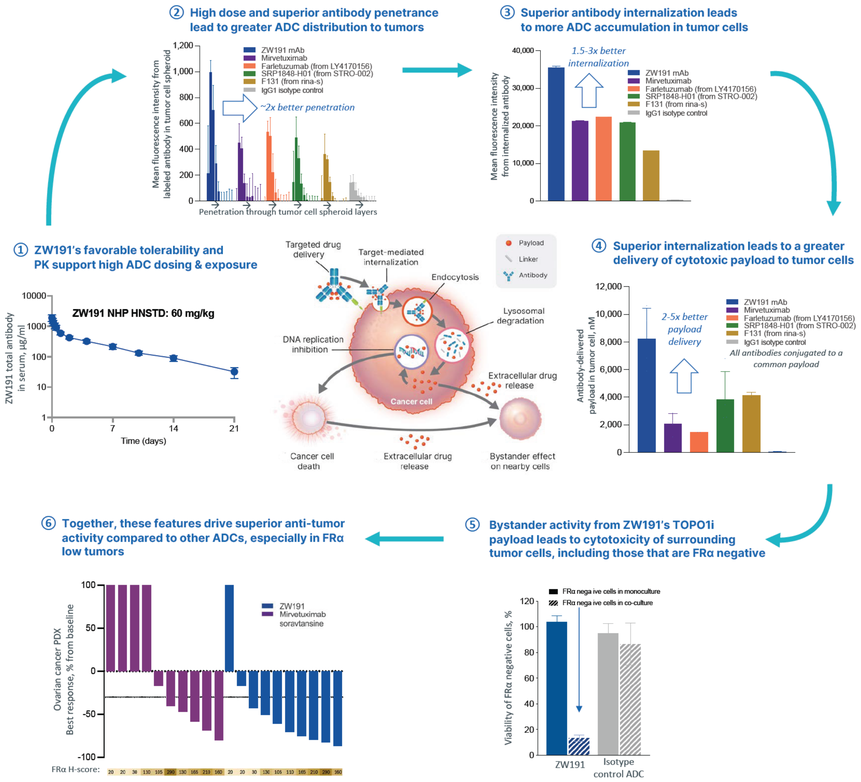


Figure 2. The mechanism of action of ZW191 as supported by its nonclinical data package[1]. **(1)** ZW191 demonstrates a best-in-class nonclinical tolerability profile of 60 mg/kg HNSTD in a GLP NHP study, with favorable PK. **(2)** The tumor cell spheroid penetration of the ZW191 antibody was compared to antibodies from other FRα-targeted ADCs after treating for 24 h at 50 nM. **(3)** The tumor cell internalization of the ZW191 antibody was compared to antibodies from other FRα-targeted ADCs at 100 nM after 24 h. **(4)** The ability to deliver a common ADC payload to FRα expressing tumor cells was compared between the ZW191 antibody and antibodies from other FRα-targeted ADCs at 10 nM after 24 h. **(5)** The bystander activity of ZW191 was determined in a tumor cell co-culture system in which the viability of FRα negative cells was measured in response to ZW191 in the presence and absence of FRα positive cells. **(6)** The *in vivo* antitumor activity of ZW191 was compared to that of mirvetuximab soravtansine in a panel of ovarian cancer PDX models in immunocompromised mice. ADCs were dosed once at 6 mg/kg and the best response relative to starting tumor volume was calculated. For each PDX model, the expression of FRα was assessed by IHC and quantified by a pathologist as indicated by H-Score.

ZW191 is efficacious in combination with platinum-based drugs, taxanes, bevacizumab

- **ZW191 combines with carboplatin, paclitaxel and bevacizumab in the OV-90 xenograft model of ovarian cancer**
- **ZW191 dosed at a non-maximally efficacious dose to allow for assessment of drug combination effect**
- **ZW191 did not exacerbate any body weight loss from carboplatin or paclitaxel**

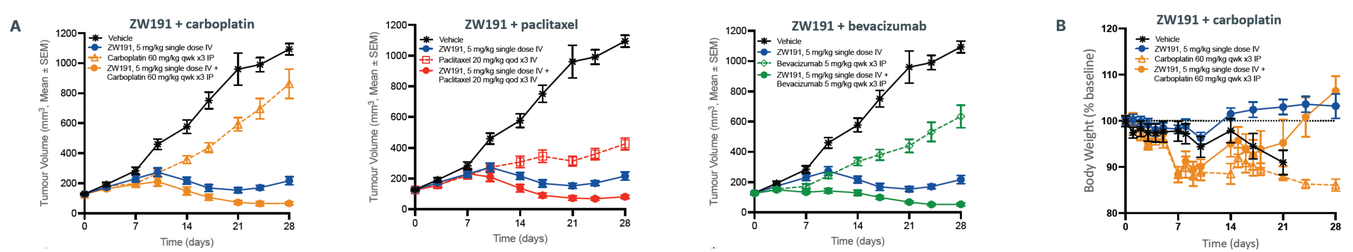


Figure 4. A *In vivo* antitumor activity of ZW191 in drug combinations in the OV-90 xenograft model of ovarian cancer. Data was generated from a single study and are separated by each drug combination for clarity of presentation. Mean tumor volume (TV) ± SEM are shown representing at least 75 % of the mice randomized to treatment for each group, n=8 (SCID mice). Four mice from the 'vehicle + carboplatin' group, and two mice from the 'ZW191 + carboplatin' group missed one dose each of carboplatin due to carboplatin-related body weight loss. **B** Body weight of mice following dosing of ZW191 and carboplatin alone or in combination.

ZW191 in combination with platins and PARPi results in greater cytotoxicity and enhances DNA damage in tumor cells

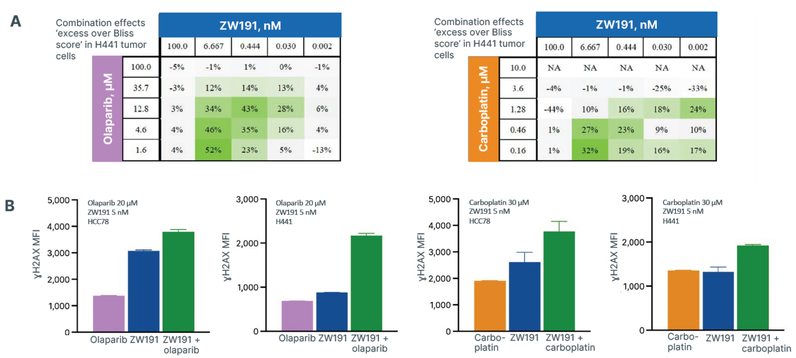


Figure 6. *In vitro* cytotoxicity of ZW191 alone and in drug combinations. **A** Cell growth inhibition assessment was performed in a panel of 3D spheroid cancer cell lines in a 5x5 dose response matrix for ZW191 with PARPi or platinum drugs, with data from the H441 cell line shown. Percent cell growth inhibition compared to vehicle control was calculated for each test article or combination and the Bliss independence model[2] was used to assess the drug combination effects in combination matrices, with this model assuming combined drugs act independently. Shown are the 'excess over Bliss' scores for each point across the concentration matrix, with positive values indicating greater cytotoxicity than expected from the additive activity of each drug effect alone. **B** Phosphorylation of histone H2AX (γH2AX) for detection of DNA damage by flow cytometry following treatment with the indicated concentrations of ZW191 alone and in combination with carboplatin or olaparib to tumor cell spheroids, with the degree of DNA damage corresponding to the geometric mean fluorescence intensity in the AF488 channel area of live cells.

Conclusions

- **Differentiated**: ZW191 is a FRα-targeting ADC differentiated by its superior internalizing novel antibody and moderate potency novel topoisomerase I inhibitor payload.
- **Clinical translation**: ZW191's favorable tolerability profile, attributed to its moderate potency TOPO1i payload and its moderate stability linker, potentially achieves higher ADC dosing, better tolerability and improved combination potential with standard of care chemotherapeutics.
- **Combinations**: Nonclinical *in vitro* and *in vivo* studies support the efficacious combination of ZW191 with standard of care therapies across multiple modes of action.

References

1. Lawn et al, AACR Annual Meeting poster 2024, Abstract 1862, *Cancer Research* **2024**
2. Liu et al, *Stat. Biopharm*, **2018**
3. LoRusso et al, AACR-NCI-EORTC Conference on Molecular Targets and Cancer Therapeutics poster **2025**

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