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ZW327

A Topoisomerase-1 inhibitor ADC Designed to Target Ly6E-Expressing Tumors

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Zymeworks

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Agenda

1. Molecule design	Antibody and linker-payload properties
2. Ly6E as a target	Target characteristics & expression profile
3. In vitro profile	Binding, internalization, and potency
4. In vivo profile	Anti-tumor activity, PK, and tolerability
5. TOPO1i platform clinical PoC	ZW191 clinical data demonstrating safety & early activity of ZD06519 payload
6. Conclusions	
7. Q&A	

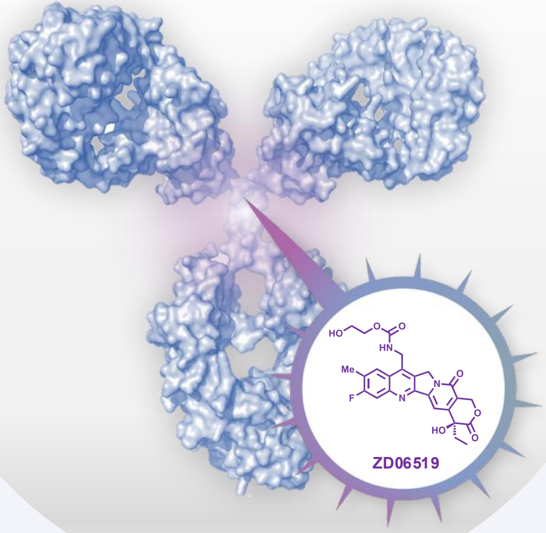
ZW327: A Ly6E-targeting Topoisomerase-1 Inhibitor ADC

ZW327

Antibody Selected for Optimal ADC Properties

- Novel Fc-silent IgG1 antibody
- Exceptional PK profile
- High levels of **internalization**
- Superior **payload delivery**
- Enhanced **tumor penetration**

Optimal ADC Antibody



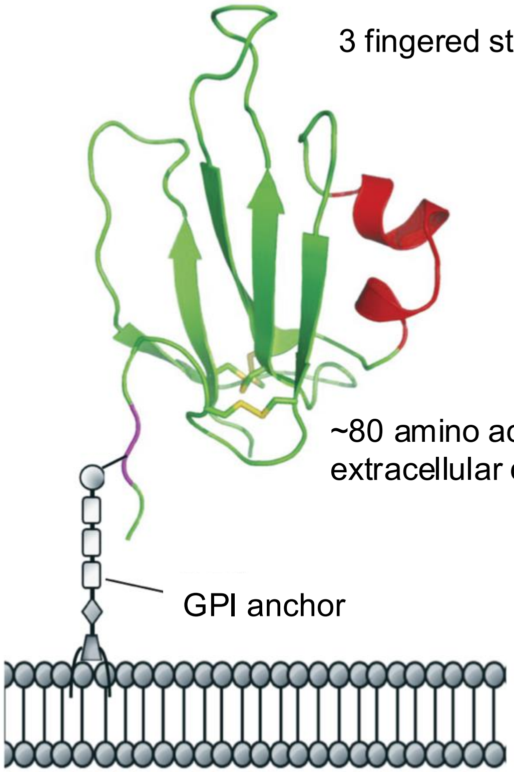
DAR 8

Linker-Payload Selected to Balance Efficacy and Tolerability

- Novel topoisomerase-1 inhibitor
- Peptide cleavable linker
- **Moderate potency** (1-10 nM)
- Strong **bystander activity**
- **Moderate Ab-linker stability**

Clinical PoC with linker-payload (ZW191)

Lymphocyte Antigen 6 Complex, Locus E (Ly6E)



Structural modeling of mouse Ly6G, a GPI-anchored surface protein demonstrating the three finger-fold structure common across the Ly6 family[4]

- Ly6E expressed in subset of lymphocyte cells and proposed to play a role in T-cell proliferation, differentiation, and activation[1]
- LY6E can interact with viruses, either promoting (HIV-1, West Nile virus, and Zika virus) or restricting (SARS-CoV, MERS-CoV, and SARS-CoV-2) entry[2]
- Ly6E expression reported in TNBC, NSCLC, PDAC, OVCA, HNSCC, GC, and CRC[3]

[1] J. Immunol. (1995) 155: 5574–5581
[2] Viruses (2019) 11 (11): 1020
[3] Clin Cancer Res (2020) 26 (21): 5588–5597
[4] J. Leukoc. Biol. (2013) 94 (4): 585–594

Ly6E Gene Expression Observed to be the Highest Amongst Several ADC Targets Across Key Indications of Interest

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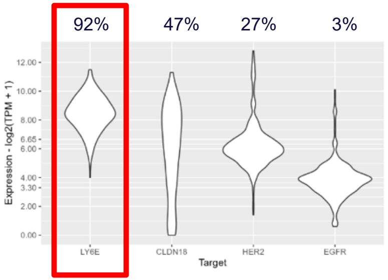
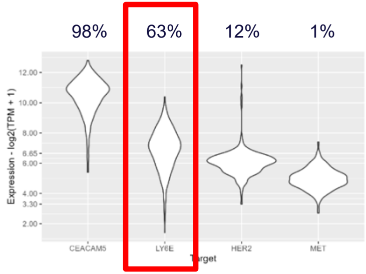
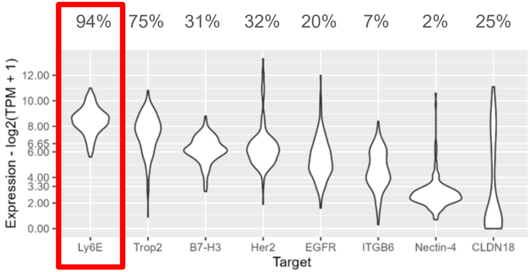
Gastric Cancer (n=413)



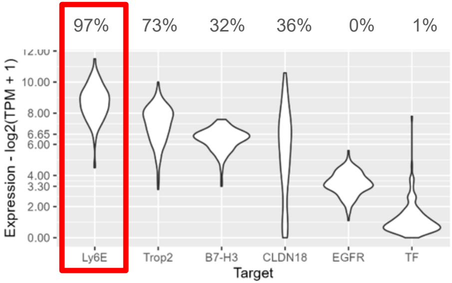
Colorectal Adenocarcinoma (n=379)



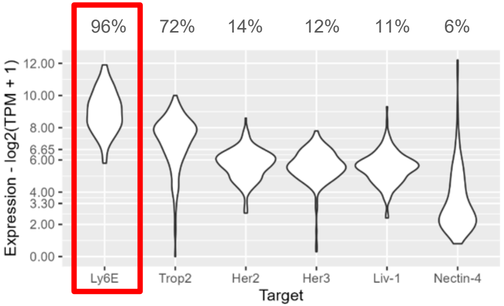
Esophageal Carcinoma (n=181)



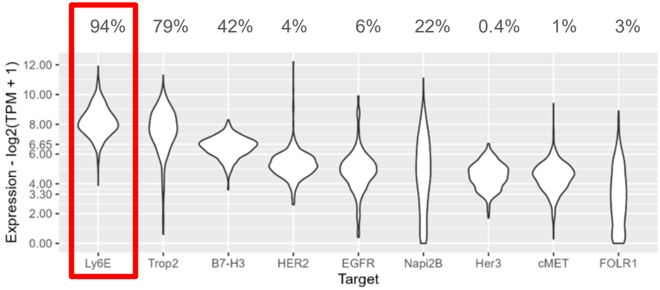
PDAC (n=147)



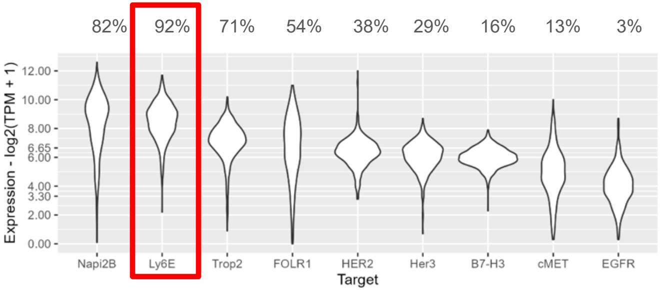
TNBC (n=191)



NSCLC - Squamous (n=477)



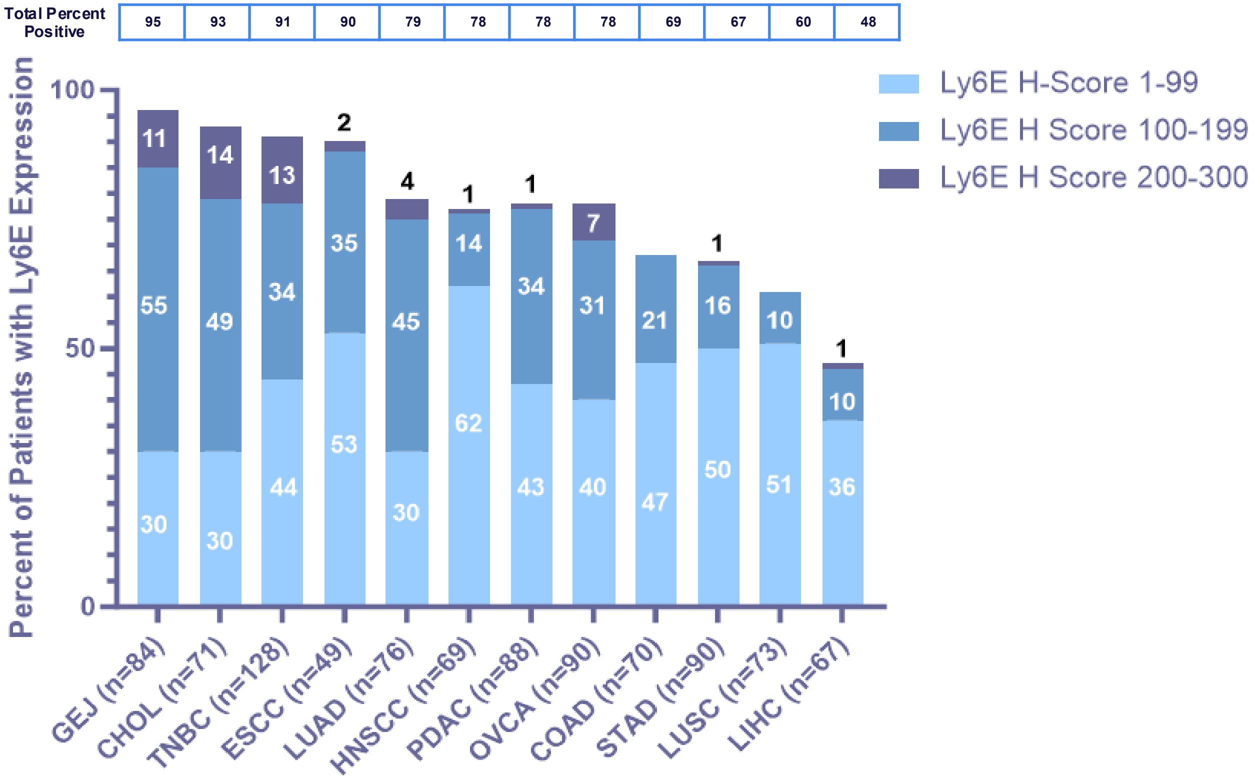
NSCLC - Adenocarcinoma (n=512)



- **Bulk RNAseq** data from the **TCGA PanCancer project** was analyzed for expression of ADC targets across nine indications (HNSCC and cholangioarcinoma data not shown)

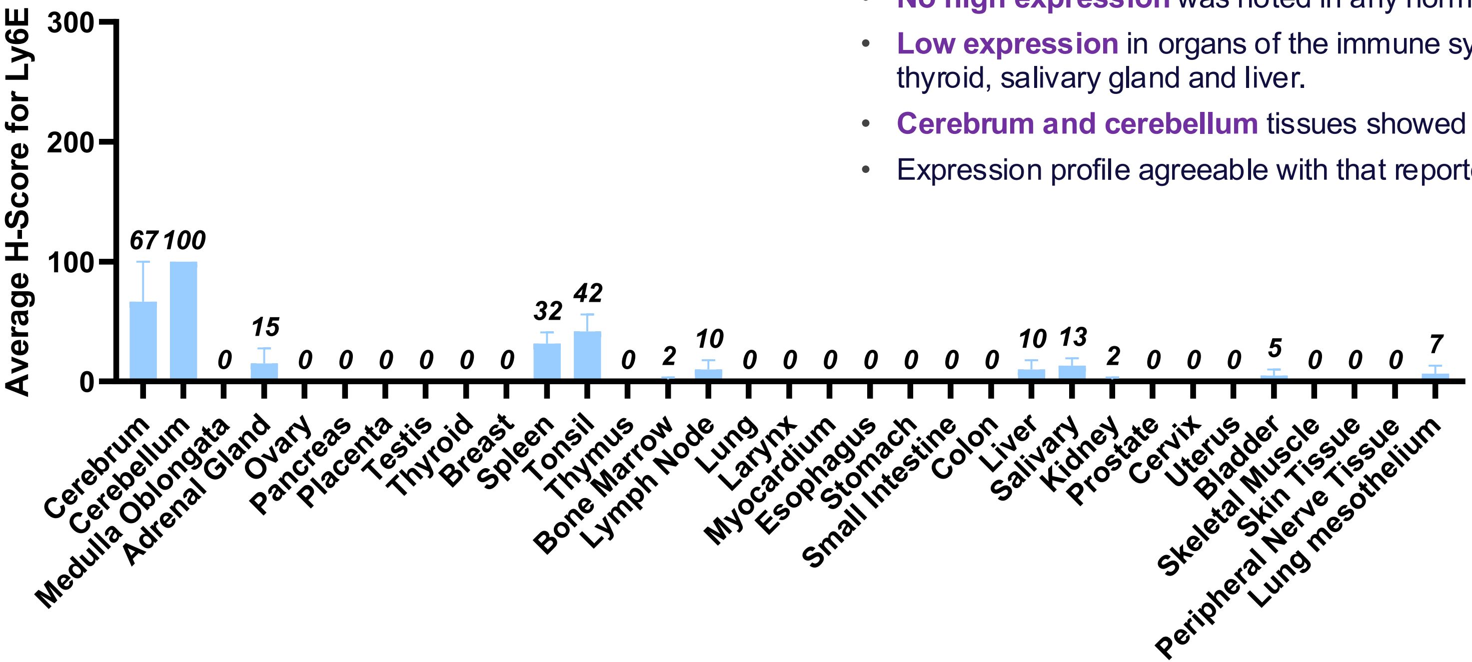
The median TPM (Transcript per Million) for each gene in each patient was plotted on a violin plot using ggplot2. The width of the shape/violins indicates the density of samples. Percentages indicate patients with expression >100 TPM. Analysis performed by Zymeworks Bioinformatics Team

Ly6E Expression in >75% Patients in GEJ, CHOL, TNBC, ESCC, LUAD, HNSCC, OVCA, PDAC by IHC



Urosev et al., Abstract #2874 Presented at AACR 2025

Minimal Ly6E Expression Noted in Normal Tissues

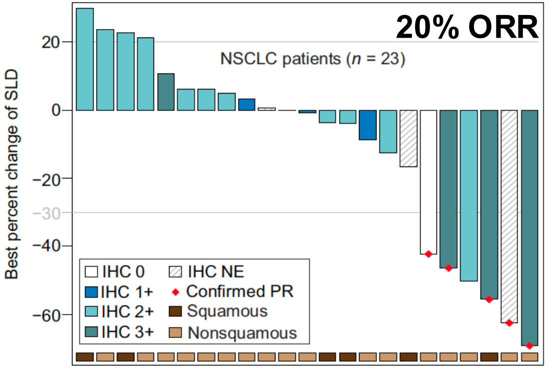


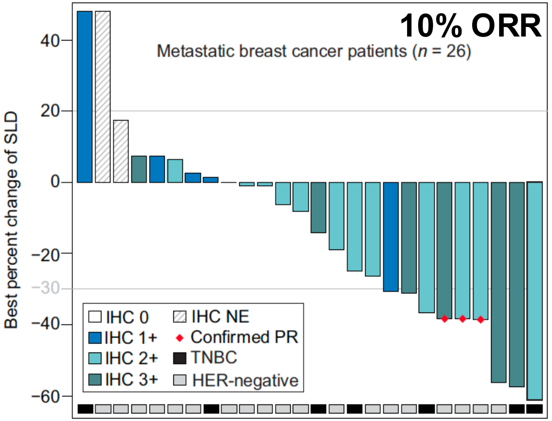
Ly6E Expression

- **No high expression** was noted in any normal tissues
- **Low expression** in organs of the immune system but also in adrenals, thyroid, salivary gland and liver.
- **Cerebrum and cerebellum** tissues showed moderate expression
- Expression profile agreeable with that reported in the literature.

Urosev et al., Abstract #2874 Presented at AACR 2025

DLYE5953A Provides Clinical PoC for a Ly6E ADC

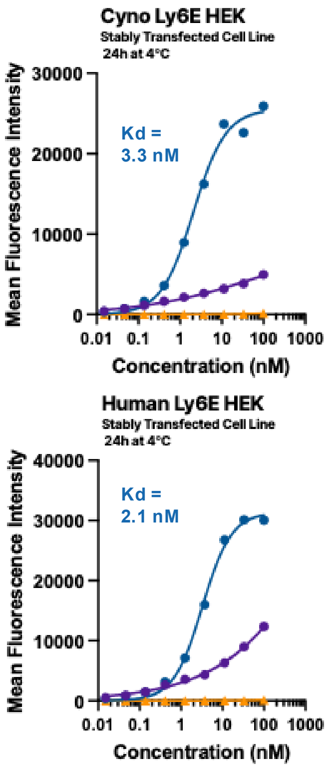


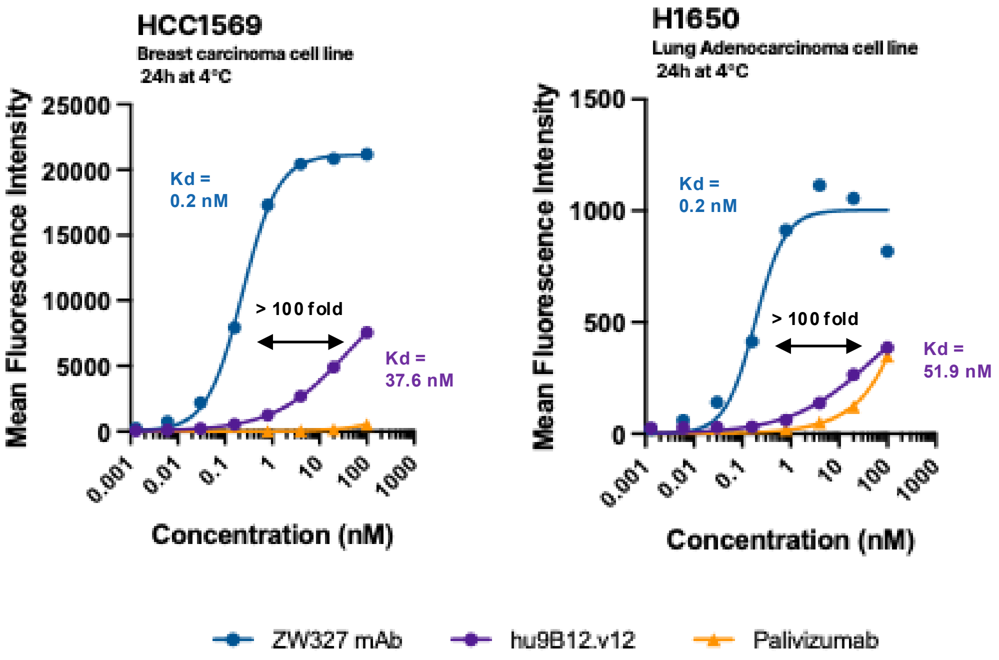


- DLYE5953A = hu9B12.v12-MCvcPABC-MMAE
- 12% ORR at expansion dose of 2.4 mg/kg q3w in NSCLC and metastatic breast cancer
- Common TRAEs alopecia, fatigue, nausea, peripheral neuropathy; Gr.3+ neutropenia 13%
- Linear PK at and above 0.8 mg/kg dose

Clin Cancer Res (2020) 26 (21): 5588–5597

ZW327 mAb is Cross-reactive to Cyno Ly6E and Efficiently Binds to Ly6E-expressing Cancer Cell Lines at Nanomolar Concentration

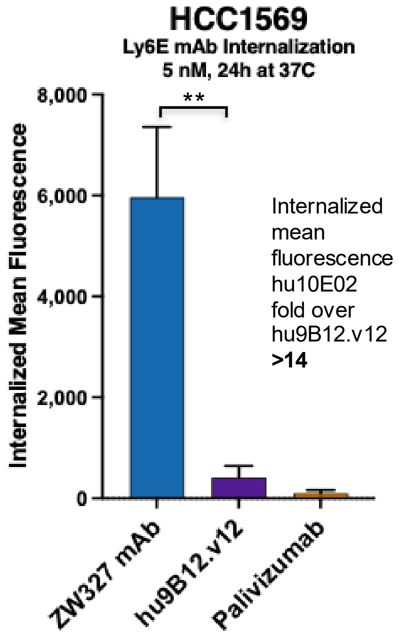




Urosev et al., Abstract #2874 Presented at AACR 2025

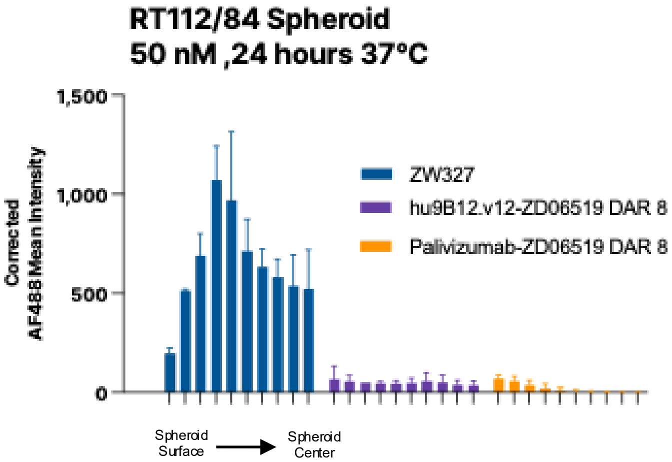
ZW327 Displays Advantageous Characteristics for Efficient Payload Delivery within Cancer Cells and Spheroids *in vitro*

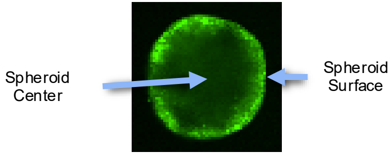
ZW327 mAb showed strong internalization



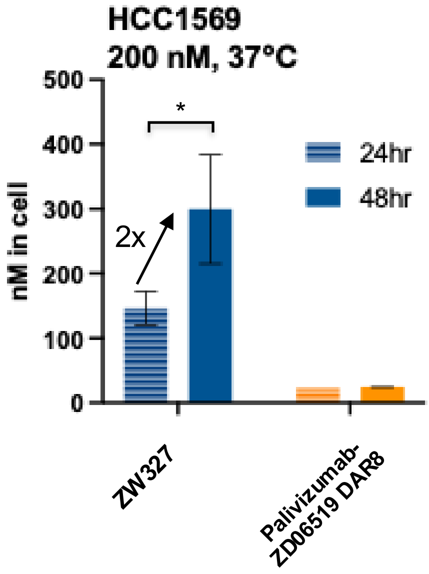
Unpaired T-test, ** p-value < 0.01

ZW327 demonstrated rapid cancer spheroid penetration





ZW327 induced efficient payload delivery in cancer cells

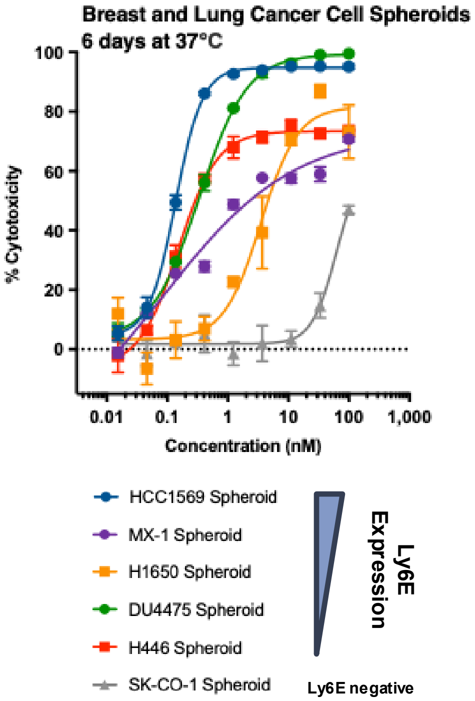


Two-way ANOVA,, *p-value < 0.05

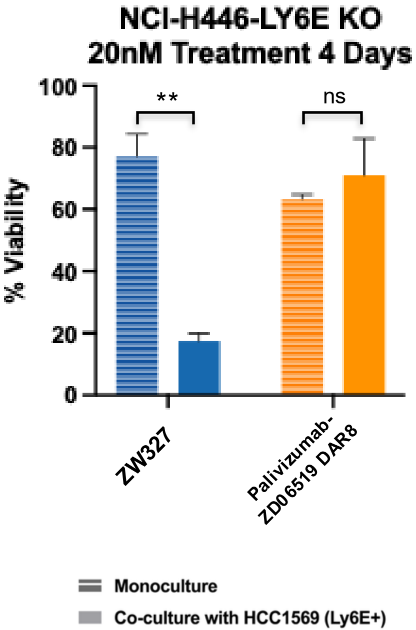
Urosev et al., Abstract #2874 Presented at AACR 2025

ZW327 Efficiently Induces Direct and Bystander-driven Cytotoxicity in Cancer Spheroids and is on Average 10x More Potent Compared to DLYE5953A *in vitro*

ZW327 induced cytotoxicity in breast and lung cancer spheroids

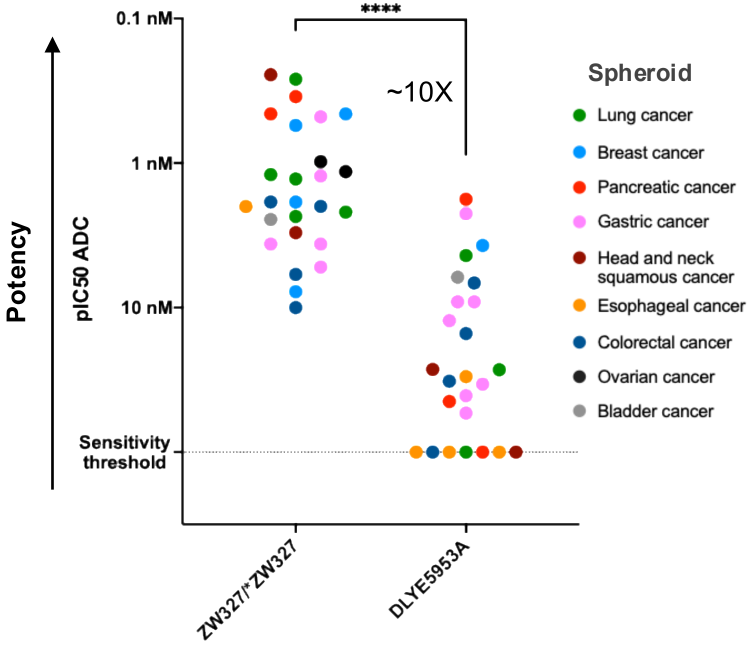


ZW327 induced robust bystander activity



Two-way ANOVA, ns: non-significant, **p-value < 0.01

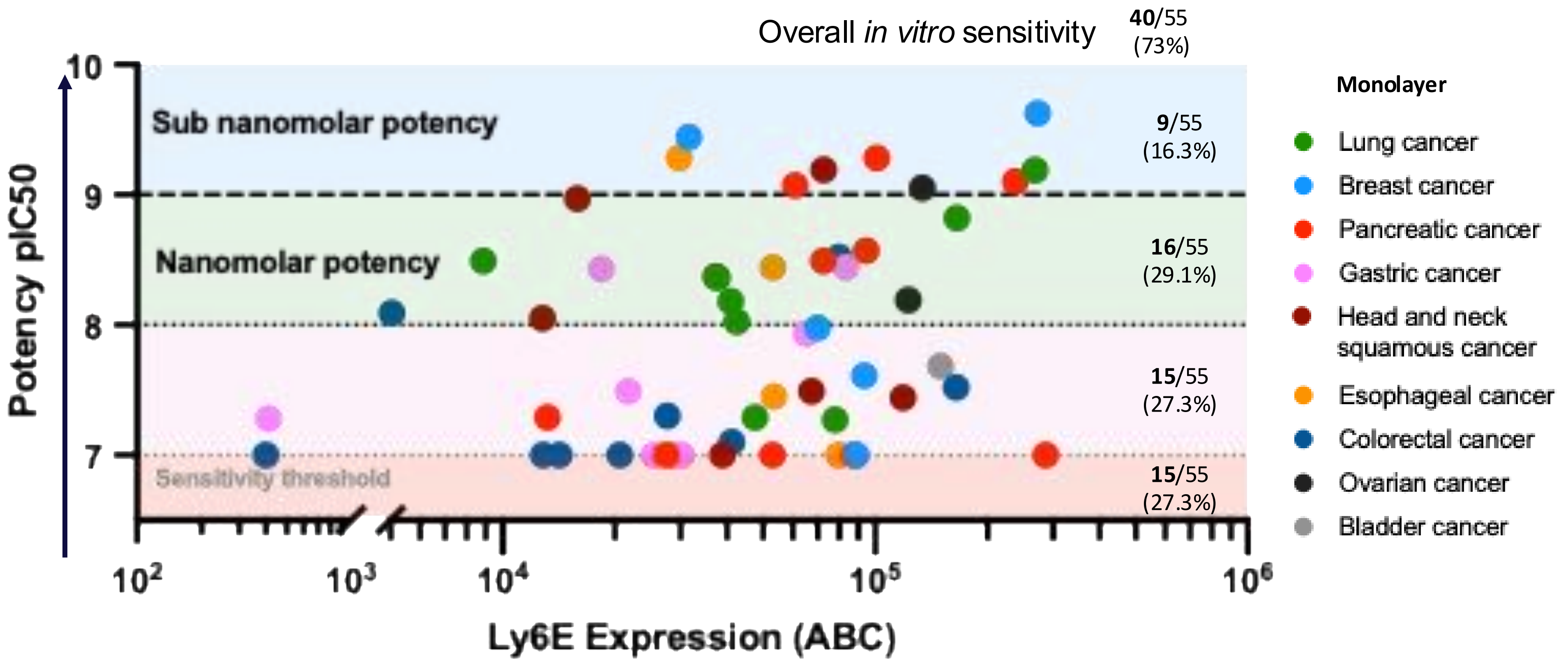
ZW327 demonstrated superior in vitro potency against the clinical benchmark DLYE5953A



ZW327*: ZW327 WT Fc, Unpaired T-test, ****p-value < 0.0001

Urosev et al., Abstract #2874 Presented at AACR 2025

ZW327 Displayed Robust Low Nanomolar Potency (pIC50≥8) in At Least 9 Solid Tumor Indications with Various Level of Expression



ZW327 Demonstrates Strong Activity at Single Dose 2-6mg/kg in Models Across Multiple Oncology Indications

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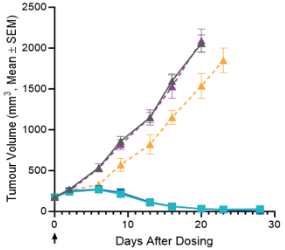
PDX models

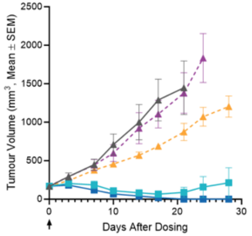
TNBC

BR1282 (H-Score 55)



NSCLC

LU2512 (H-Score 95)

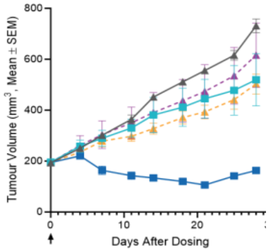


- Vehicle
- ZW327 2mg/kg
- ZW327 6mg/kg
- ZW327 mAb 6mg/kg
- Palivizumab LALADS - ZD06519 6mg/kg

Strong activity observed across 19 CDX models, including low expressing models precluding an expression-response relationship

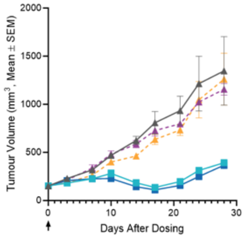
PDAC

BxPC3 (H-Score 120)



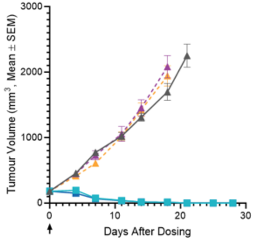
STAD

MKN45 (H-Score 75)



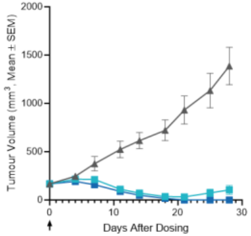
HNSCC

FaDu (H-Score 150)



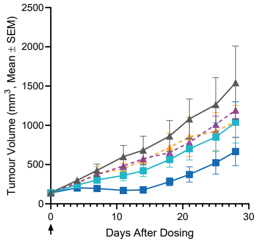
TNBC

MX1 (H-Score 145)



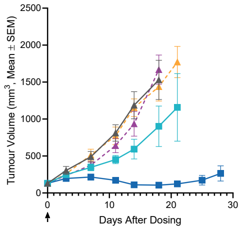
COAD

COLO205 (H-Score 15)



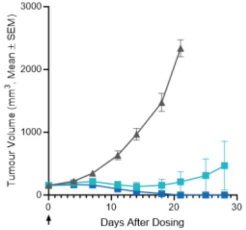
ESCC

KYSE-150 (H-Score 135)



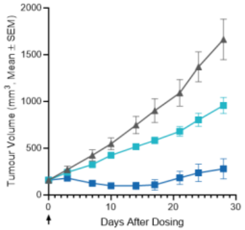
SCLC

NCI-H446 (H-Score 105)



NSCLC

NCI-H1650 (H-Score 190)



Summary of Activity

	CDX Models
TNBC	DU4475
	MX1
BC	HCC1569
SCLC	NCI-H446
NSCLC	NCI-H2228
	SW900
	NCI-H1650
PDAC	BxPC3
	Capan1
	HPAFII
HNSCC	Detroit562
	FaDu
CRC	HCT-116
	HT-29
	COLO205
STAD	MKN45
	NCI-N87
ESCC	KYSE-30
	KYSE-150

	PDX Models
TNBC	BR1282
	BR0438
NSCLC	LU0876
	LU2071
	LU2512
	LU6918

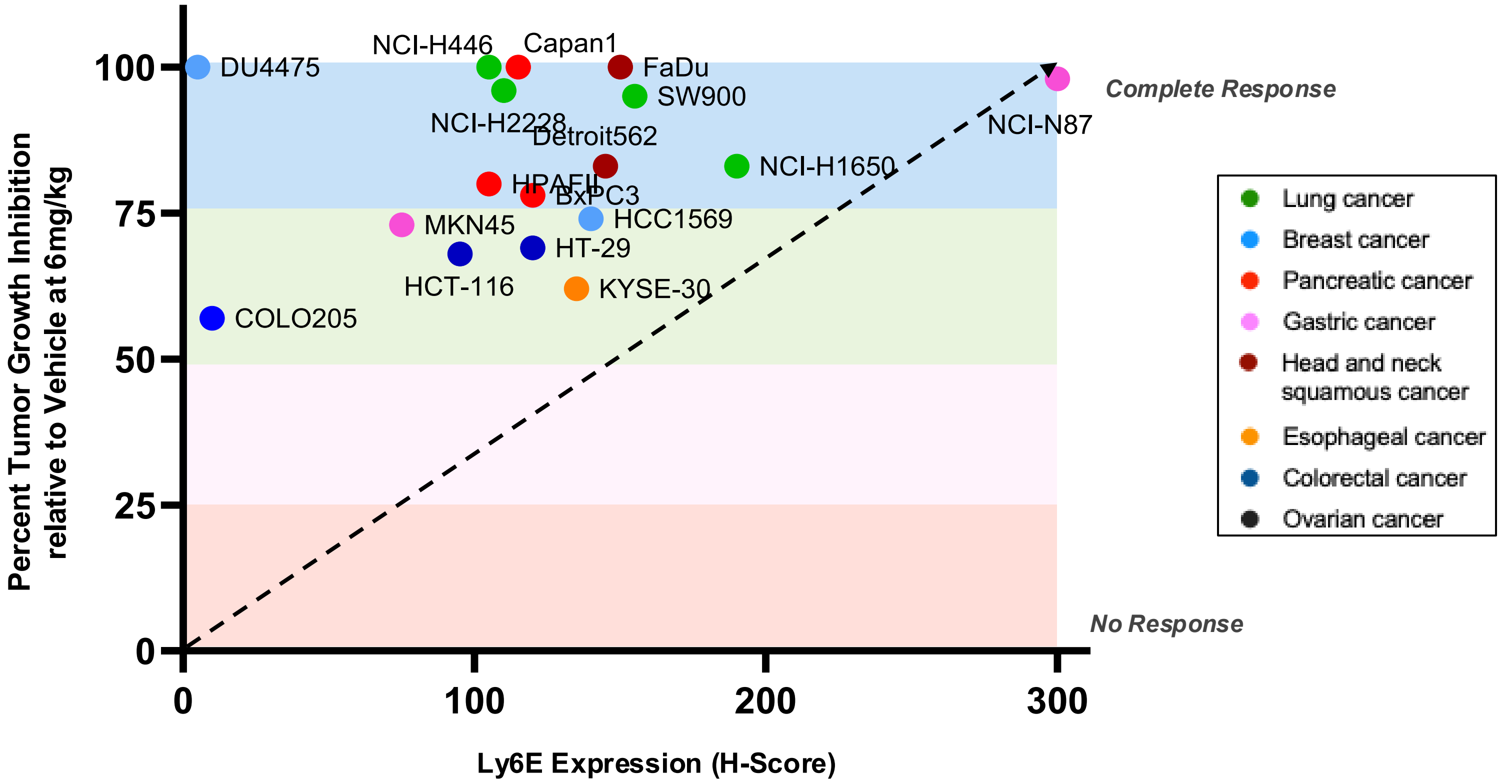
Tumor Growth Inhibition

Stasis

Regressions

Complete Regressions

Activity observed across all expression levels in multiple indications



ZW327 is Well-Tolerated in NHP at 60 mg/kg

Non-human primate (NHP) toxicology (non-GLP)

2-dose non-GLP NHP toxicology study ZW327, Q3Wx2

Dose levels:
30 mg/kg
60 mg/kg

Dose 1
Day 1

Dose 2
Day 22

3M per group

Terminal necropsy day 29

NHP MTD = > 60 mg/kg

Dose (mg/kg) q3w x 2	Clinical Pathology	Histopathology
30	↓ lymphocyte count	↑ thyroid weight; ↓ thymus weight; ↓ lymph. cellularity in thymus, spleen & lymph nodes
60	↓ lymphocyte count; ↓ phosphorus	

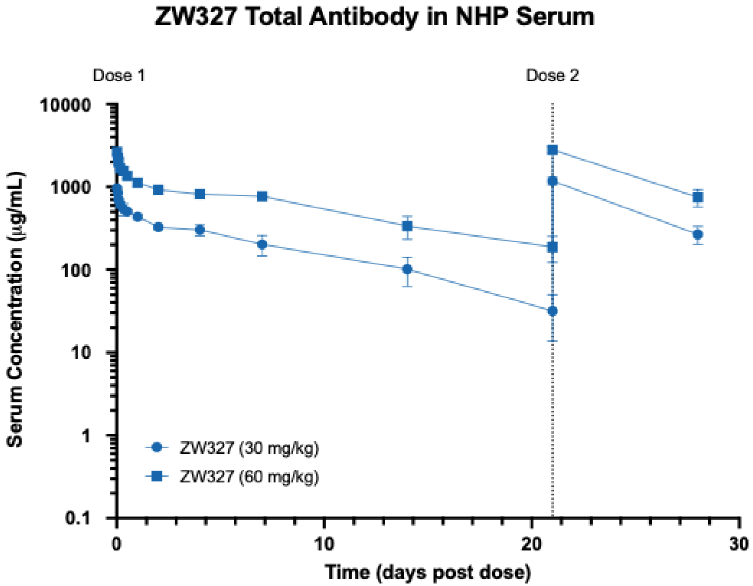
- Male cynomolgus monkeys (n=3/group) dosed via IV bolus injection Q3Wx2 with necropsy 1 week after 2nd dose
- **Endpoints evaluated:** clinical signs, body weight, food consumption, clinical pathology (serum chemistry, hematology & coagulation), immunophenotyping, organ weights, histopathology, and PK (total antibody, ac-payload & free payload)

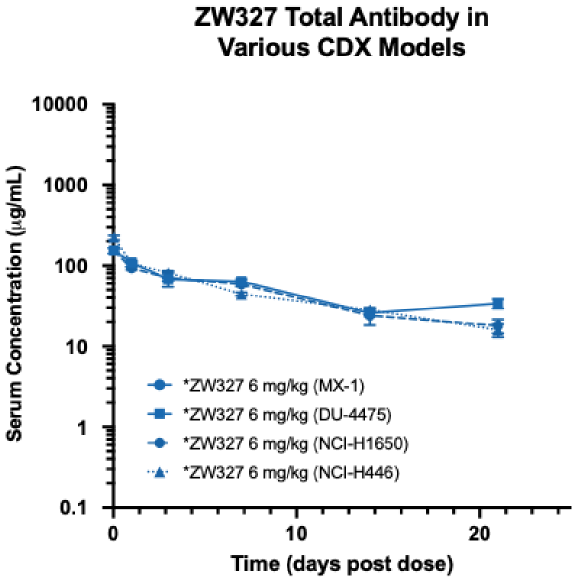
- MTD ≥ 60 mg/kg in a 2-dose non-GLP non-human primate (NHP) toxicology study
- Clinical observations were limited to post-dose minimal decrease in body weight and food consumption at both 30 and 60 mg/kg
- Hematology and histopathology findings at 30 and 60 mg/kg were considered mild, primarily reflective of decreased lymphocyte cellularity in lymphoid tissues
- **Dose and findings consistent with other ZD06519 DAR8 ADCs (ZW191)**

Urosev et al., Abstract #2874 Presented at AACR 2025

ZW327 Displays Favorable PK in Non-human Primates and Mice

Harmonized PK slide NHP on left and mouse on right





ZW327 half-life of **5.1-7.6 days** with MTD ≥ 60 mg/kg reflective of expectation to achieve efficacious dose level

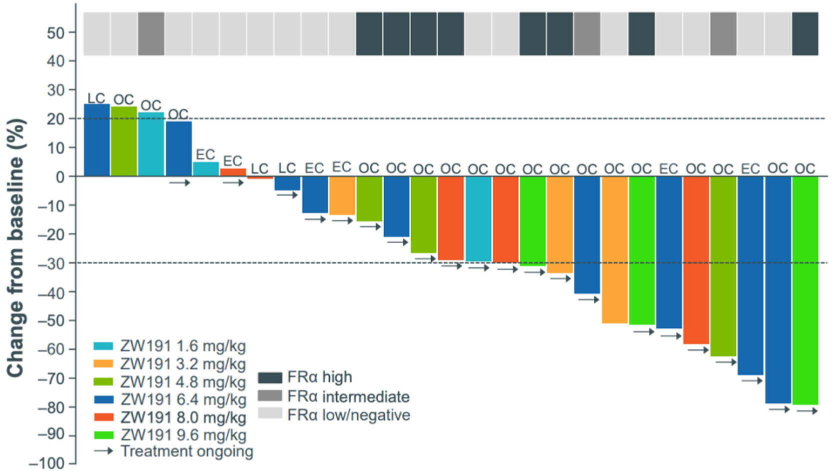
Favourable PK of ZW327 across CDX mice models (half-life of **8.5-11.4 days**)

Urosev et al., Abstract #2874 Presented at AACR 2025

TOPO1i Platform Validation: ZW191 Initial Phase 1 data

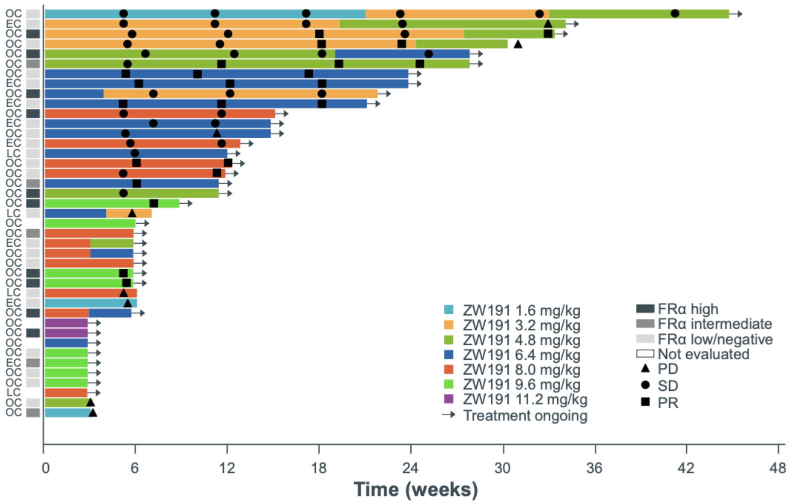
ORRs across doses 6.4-9.6 mg/kg were 53% (overall) and 64% (gynecological cancers)

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.

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.

LoRusso et al., Presented at 2025 Molecular Targets and Cancer Therapeutics

TOPO1i Platform Validation: ZW191 Initial Phase 1 data

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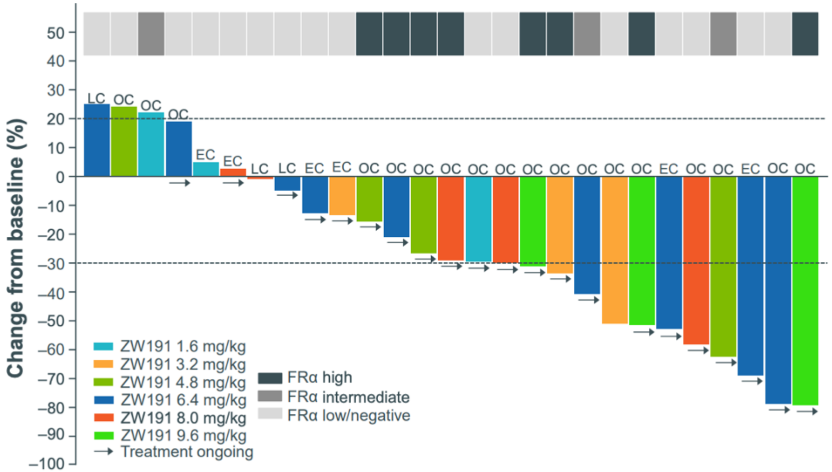

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EC, endometrial cancer; FRα, folate receptor alpha; LC, non-small cell lung cancer; OC, ovarian cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

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.

LoRusso et al., Presented at 2025 Molecular Targets and Cancer Therapeutics

Conclusions

- **ZW327 is a first-in-class Ly6E-directed, topoisomerase I inhibitor ADC**
  - TOPO1i platform has been clinically validated with ZW191
- **Ly6E is a promising ADC target broadly expressed across multiple tumor types.**
  - Expressed in >75% patients in GEJ, CHOL, TNBC, ESCC, LUAD, HNSCC, OVCA, PDAC
- **ZW327 demonstrates robust preclinical activity and is tolerated at 60 mg/kg in NHP**
  - Activity observed at all expression levels in 17 models across 9 indications

We are seeking a partner to accelerate development of ZW327

Thank you for your attention!

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Acknowledgments

- Jamie Rich, Sr. Director ADCTD Technology
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- Elizabeth Porter, Bioconjugation lead
- Linglan Fu, Biophysics lead
- Diego Alonzo, Analytics lead
- Kurt Stahl, Toxicology lead
- Donna Labayo, PM
- Germanna Righetto (Ab Eng)
- Michael Lee (Ab Discovery)
- Jesse Leblanc (CL Eng)
- Katina Mak (Bioconjugation)
- Matthew Bonderud and Amos Chua (In Vitro)
- Spencer Boisjoli, Edward Lau, Janice Tsui (Analytics)
- Alex Wu (In Vivo)
- Mark E. Petersen (Chemistry)

Q&A

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