Enhancing the therapeutic potential of topoisomerase 1 inhibitor ADCs: from concept to clinic

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Chief Scientific Officer, Zymeworks

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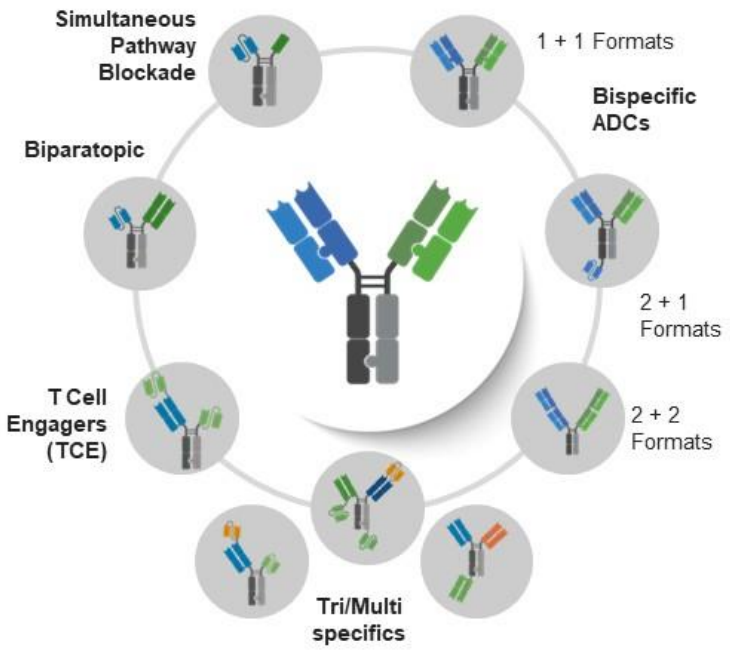
Zymeworks R&D: pushing the boundaries of antibody-based therapeutics through multispecifics and antibody drug conjugates

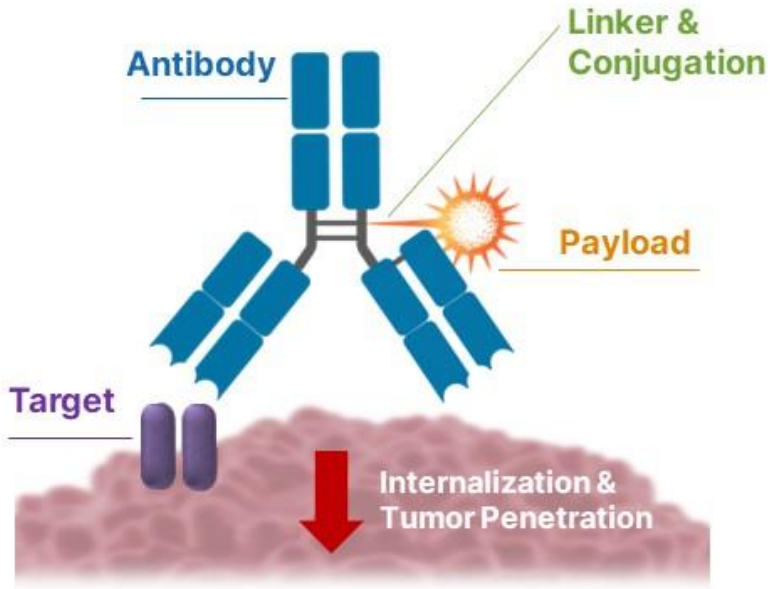
MULTISPECIFIC ANTIBODIES

Unlocking new biology and therapeutic possibilities through optimal design and format



ANTIBODY-DRUG CONJUGATES

Utilizing antibodies to more effectively deliver small molecules through optimal linker-payload design and antibody format



Pipeline of multifunctional therapeutics

Program	Technology	Target	Indication	Discovery	Preclinical	Phase 1	Phase 2	Phase 3
Solid Tumor Oncology: Antibody-Drug Conjugates (ADC)								
ZW191 Topo1i ADC | DAR 8 | Fc WT	ZD06519 Payload	FRα	Gynecological Thoracic			NCT06555744		
ZW251 Topo1i ADC | DAR 4 | Fc WT	ZD06519 Payload	GPC3	Digestive System (HCC)			NCT07164313		
ZW220 Topo1i ADC | DAR 4 | Fc Mut	ZD06519 Payload	NaPi2b	Gynecological Thoracic					
ZW327 Topo1i ADC | DAR 8 | Fc Mut	ZD06519 Payload	Ly6E	Multiple indications					
Solid Tumor Oncology: Multispecific Antibody Therapeutics (MSAT)								
Zanidatamab Bispecific	Azymetric™	HER2	Multiple indications			Development partners: Jazz Pharmaceuticals and BeOne		
ZW209 Trispecific TCE | Tri-TCE Costim	Azymetric™, Novel anti-CD3 Conditional CD28	DLL3 x CD3 x CD28	Thoracic				Anticipated IND in 2026	
ZW239 Trispecific TCE | Tri-TCE Costim	Azymetric™, Novel anti-CD3 Conditional CD28	CLDN18.2 x CD3 x CD28	Digestive System					
Autoimmune & Inflammatory Diseases								
ZW1528 Dual Cytokine Blocker	Azymetric™ Hetero-Fab | YTE	IL4Rα x IL-33				Anticipated regulatory submission in 2026		
ZW1572 Dual Cytokine Blocker	Azymetric™ Hetero-Fab | YTE	IL4Rα x IL-31						

Enhancing the therapeutic potential of topoisomerase inhibitor ADCs: from concept to clinic

- **Learnings from 40+ years of ADC clinical development to guide ZD06519 Topo1i linker-payload**
- **Antibody binder/format screening to optimize payload delivery and address target/tumor specific biology**
- **Proof of concept clinical dose escalation studies with ZW191, a potential best-in-class Folate Receptor alpha targeting ADC**
- Expanding application to additional linker-payloads and antibody formats

Cancer Cell

Commentary

The therapeutic window of antibody drug conjugates: A dogma in need of revision

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https://doi.org/10.1016/j.ccell.2022.09.016

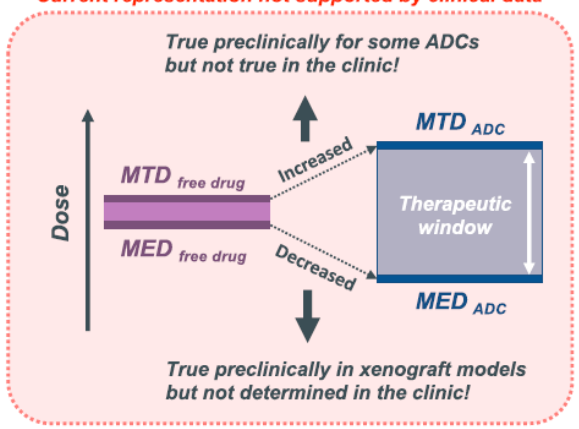
CANCER DISCOVERY

REVIEW

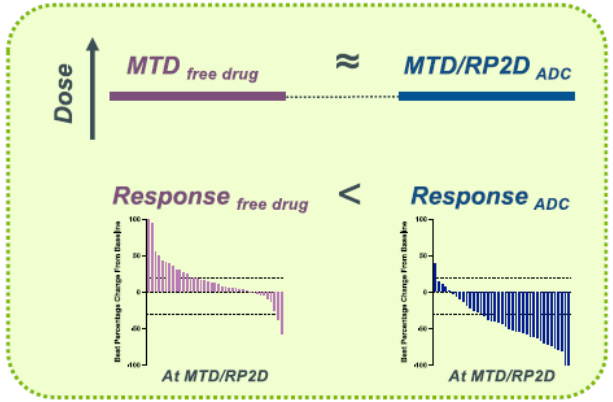
The Journey of Antibody–Drug Conjugates: Lessons Learned from 40 Years of Development

Raffaele Colombo[1], Paolo Tarantino[2,3,4], Jamie R. Rich[1], Patricia M. LoRusso[5], and Elisabeth G.E. de Vries[6]

Current representation not supported by clinical data



Revised representation based on emerging clinical data



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Beyond the Guided Missile Paradigm: Embracing the Complexity of Antibody-Drug Conjugates

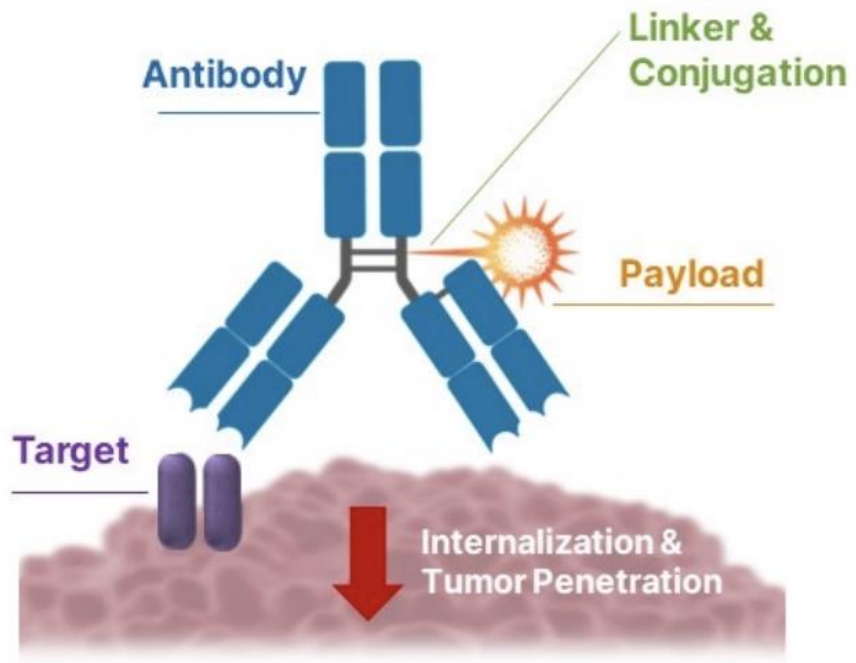
Matthew Vogel, MBA[1,2]; Raffaele Colombo, PhD[3]; and Paolo Tarantino, MD, PhD[1,4,5]

DOI https://doi.org/10.1200/JCO-25-01235

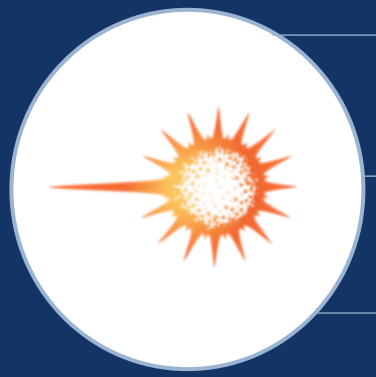
Applying 40+ years of ADC research to next generation design

ANTIBODY-DRUG CONJUGATES

Utilizing antibodies to more effectively deliver small molecules through optimal linker-payload design and antibody format

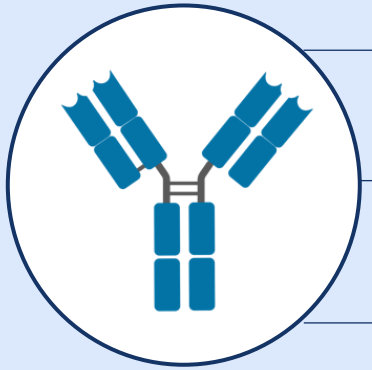


Payload



- Payload mechanisms tailored to **priority indications**
- Emphasis on **drug-like properties** of payloads
- **Bystander activity** is a key payload feature

Antibody

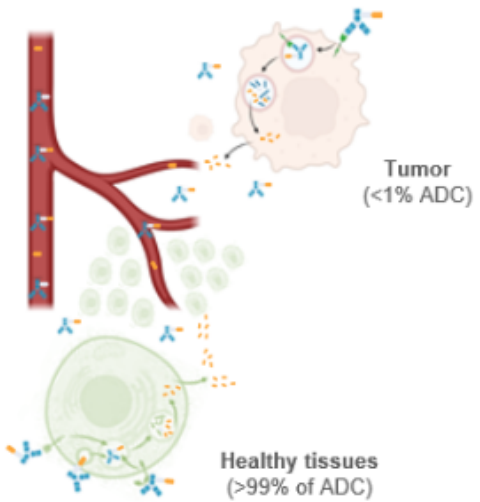


- Antibodies selected for **optimal ADC properties**
- Innovating across **multiple antibody formats**
- Application to **novel targets**

Key understandings driving our ADC design hypothesis

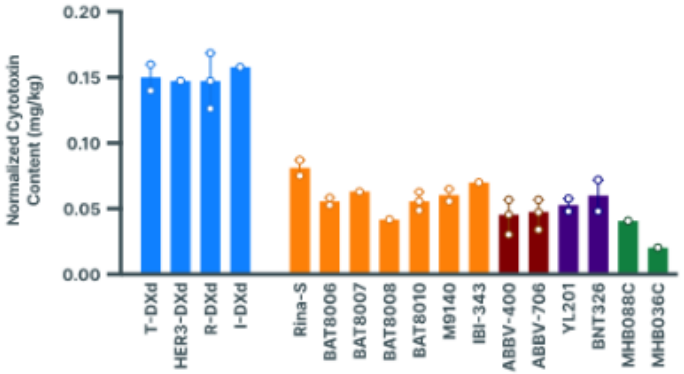
1

Most ADC catabolism occurs in normal tissue



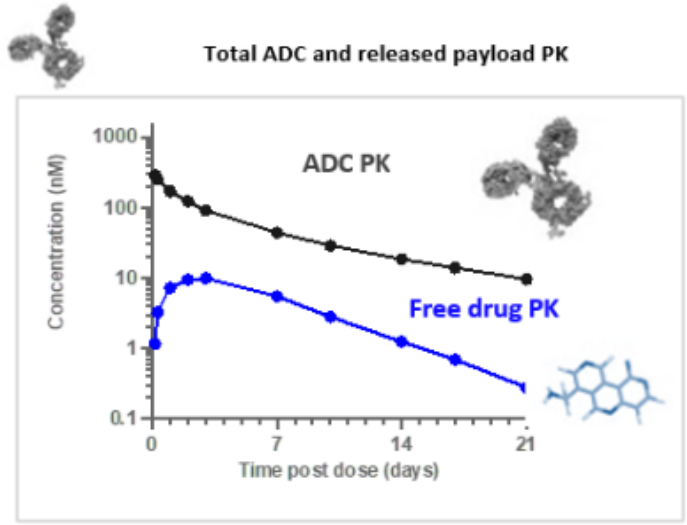
2

More potent payloads limit protein dose[2]



3

Bystander activity is a key payload feature



Payload Criteria:

1. Moderate potency to enable higher protein dose
2. Bystander activity
3. Evidence of activity in disease indication of interest

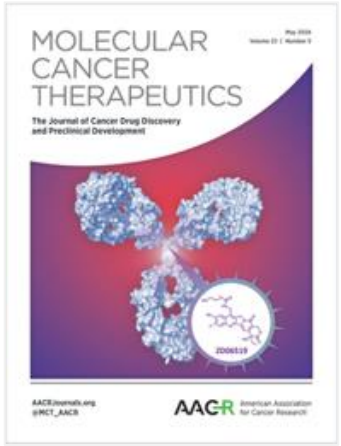
Ongoing Approaches:

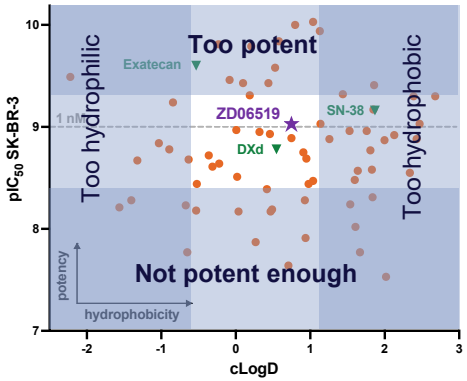
1. **Enhance therapeutic potential of Topo1i ADCs**
2. Expand application to targeted therapies and novel cytotoxics
3. Dual payload and bispecific ADCs

1. R. Colombo and J.R. Rich, Cancer Cell 2022, 40(11):1255-1263; 2. R. Colombo et al, Cancer Discov 2024, 14(11):2089–2108.

Selection of optimal payload

Zymeworks topoisomerase ADC platform embeds our philosophy





Payload synthesis & screening

~100 payloads prepared and tested in vitro

ADC in vitro potency

In vitro potency: target-dependency and bystander activity

Conjugation of select payloads

Payloads conjugated as DAR4 and DAR8, multiple mAbs

In vivo efficacy & PK

Robust efficacy in multiple CDX and PDX models

ADC characterization

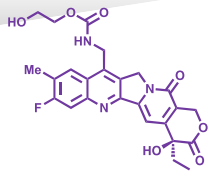
ADC properties: monodispersity, plasma stability, hydrophilicity

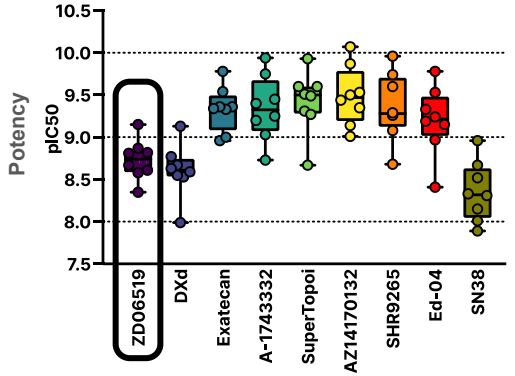
NHP toxicology & TK

MTD in NHPs:
DAR8: ≥30 mg/kg
DAR4: ≥120 mg/kg

Lead selection and application

ZD06519



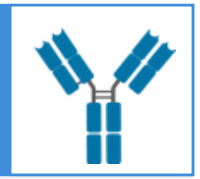


- Optimized potency to enable higher ADC dose
- Bystander active
- **ZW191 (FRa)** in dose optimization (PROC)
- **ZW251 (GPC3)** in dose escalation (HCC)

M.E. Petersen, M.G. Brant et al, Mol Cancer Ther 2024, 23(5):606-618.
CDX: cell line-derived xenograft, MTD: maximum tolerated dose, NHP: non-human primates, PDX: Patient-derived xenograft, TK: Toxicokinetic

Selection of optimal antibody
Flexible antibody discovery and optionality of Azymetric platform

Monospecific



Binds to single epitope on a single target

- Suitable for targets with some normal tissue expression
- May be only format available for targets with restricted epitope space
- Internalization dependent on target biology and specific epitope

Biparatopic

Binds to two distinct epitopes on a single target

- Suitable for targets with limited normal expression
- Targets with large epitope space may be most suitable
- Internalization can be enhanced via increased surface decoration and antigen clustering

Bispecific

Binds to two distinct targets

- Suitable for targets with biologic association or targets with high 'tumor coverage'
- Valency can be tuned to suit tumor and normal expression of each target
- Internalization may be enhanced due to target co-engagement

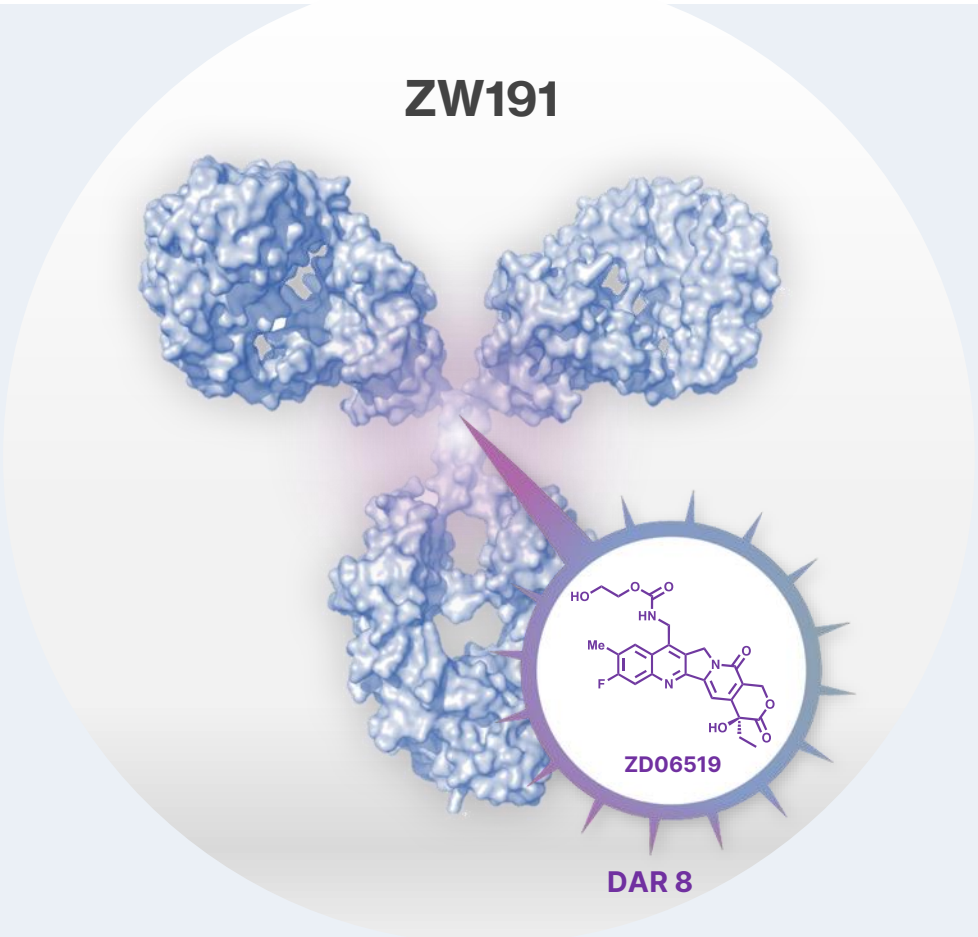
Target expression and biology may dictate the use of one format over another

ZW191: FRα-targeting ADC differentiated by design

Antibody Selected for Optimal ADC Properties

- Novel IgG1 antibody[1]
- Distinct epitope[1]
- High levels of **internalization**[2]
- Superior **payload delivery**[2]
- Enhanced **tumor penetration**[2]

Enables **targeting of low FRα tumors with enhanced anti-tumor activity**



Linker-Payload Selected to Balance Efficacy and Tolerability

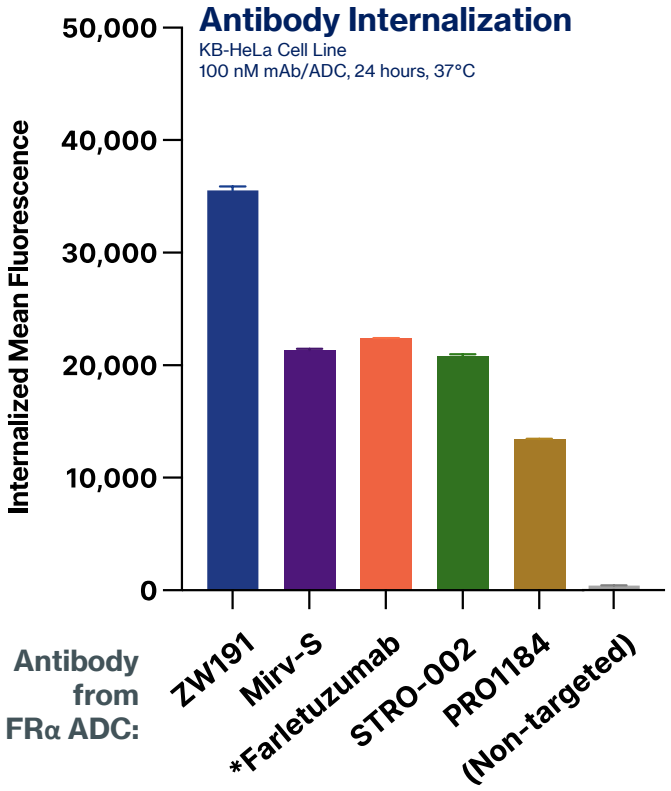
- Novel topoisomerase-1 inhibitor[3]
- Peptide cleavable linker[3]
- **Moderate potency** (1-10 nM)[3]
- Strong **bystander activity**[1,2,3]
- **Validated Ab-linker stability**[2,4]

Supports **tolerability, high protein dosing, and targeting of low/heterogeneous FRα tumors**

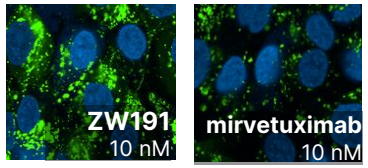
1 Lawn S. et al. Abstract # 2641 presented at American Association for Cancer Research annual meeting 2023.
2 Lawn S. et al. Abstract # 1862 presented at American Association for Cancer Research annual meeting 2024
3 Petersen M.E., Brant M.G. et al, Mol Cancer Ther 2024, 23(5):606-618.
4 Colombo R. Mol Cancer Ther (2023) 22 (12_Supplement): IA003.

ZW191 antibody selected for optimal ADC properties

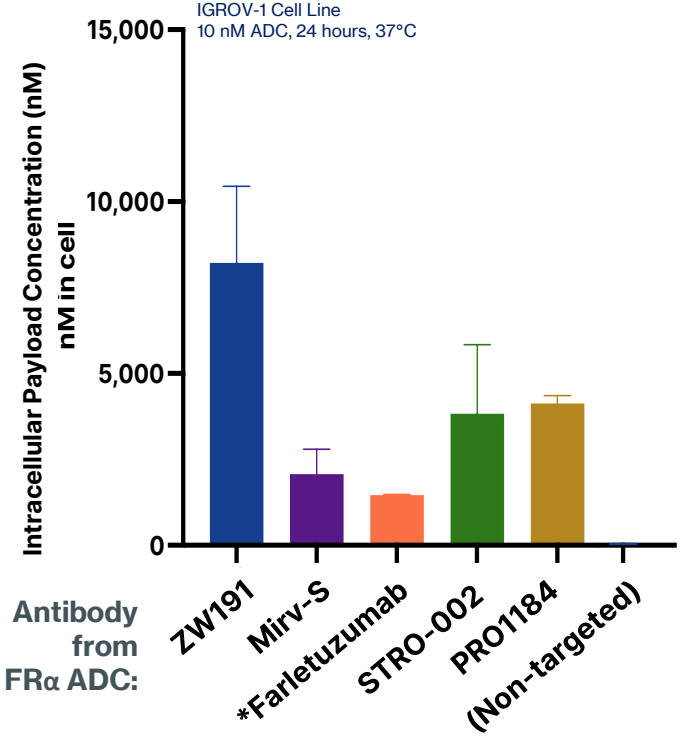
ZW191 mAb Selected for *Superior Internalization*



* Farletuzumab mAb used in LY4170156 and MORab-202 ADCs

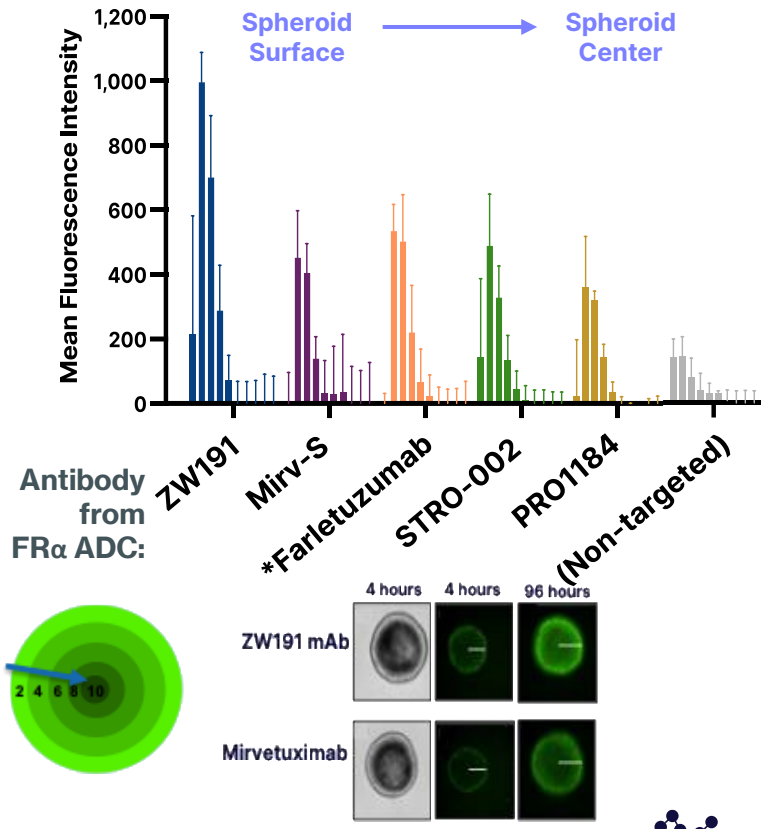


ZW191 mAb Selected for *Superior Payload Delivery*



(Payload delivery study utilizes ZymeLink Auristatin (ZLA) payload)

ZW191 mAb Selected for *Superior Penetration*

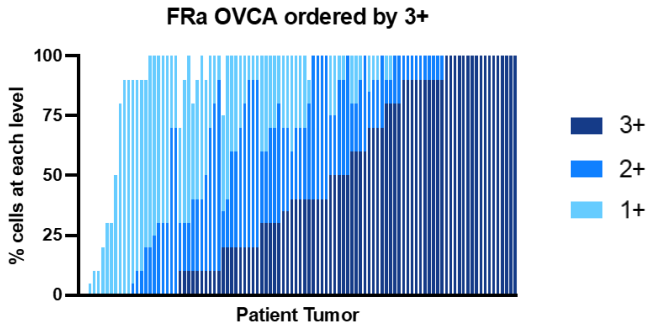


Lawn S. et al. ZW191 – a FRα-targeting antibody-drug conjugate with strong preclinical activity across multiple FRα-expressing indications. Abstract # 1862 presented at American Association for Cancer Research annual meeting 2024.

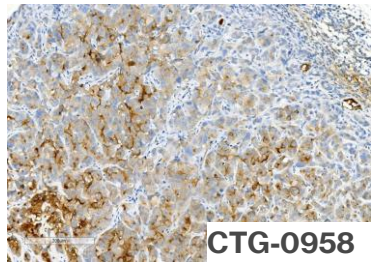
ZW191 exhibits bystander activity

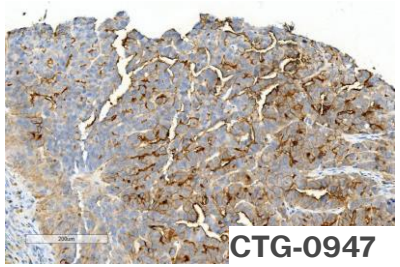
Active in heterogenous FRa expressing PDX models

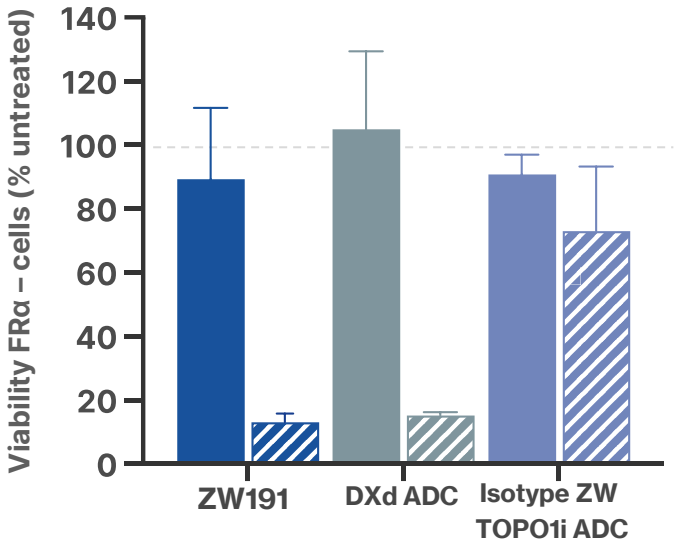
FRa expression can be low & heterogenous

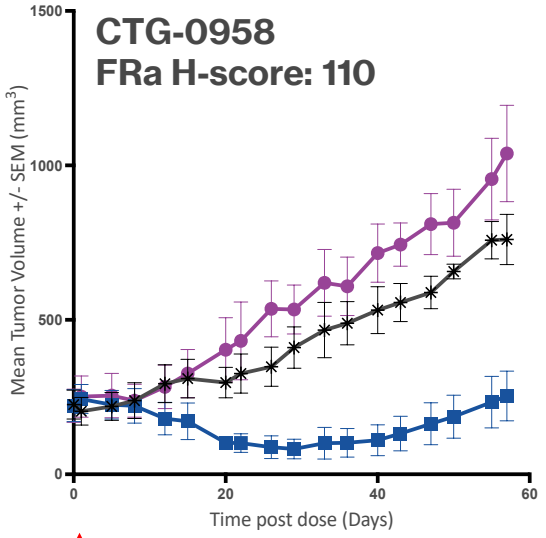


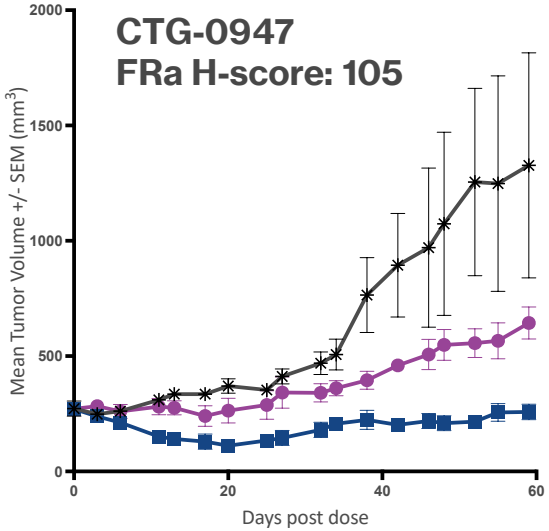
FRa expression can be low & heterogenous











Vehicle
ZW191
Mirvetuximab Soravtansine

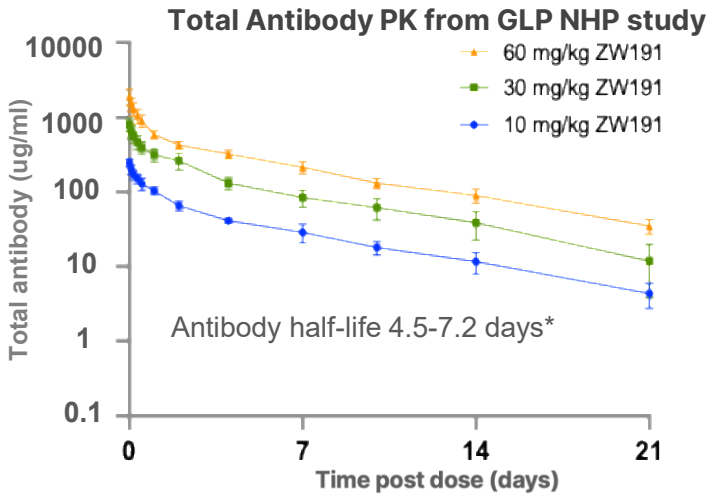
ZW191 is well tolerated in non-human primates

ZW191 shows a compelling tolerability profile of 60 mg/kg in NHP

Dose mg/kg (Q3W x3)	n	Clinical observations	Histopathology	Clinical Chemistry	Hematology & coagulation	Adverse effects	HNSTD
10	4F, 4M	None	None	↑ AST, ALT (n=1)	No effects	None	**60 mg/kg**
30	6F, 6M	Emesis/vomitus	↓ Thymic lymphocytes; ↓ PACS (n=2)	↑ AST, ALT			
60	6F, 6M	Liquid/discolored feces; Emesis/vomitus; ↓ activity level (n=1)	↓ Thymic lymphocytes; ↓ PACS (n=1)	↑ AST, ALT ↑ CK			

- No mortality or body weight effects
- No ophthalmic effects
- All effects were non-adverse and reversible
- **HNSTD in NHP of 60 mg/kg**

ZW191 has a favorable pharmacokinetic (PK) profile



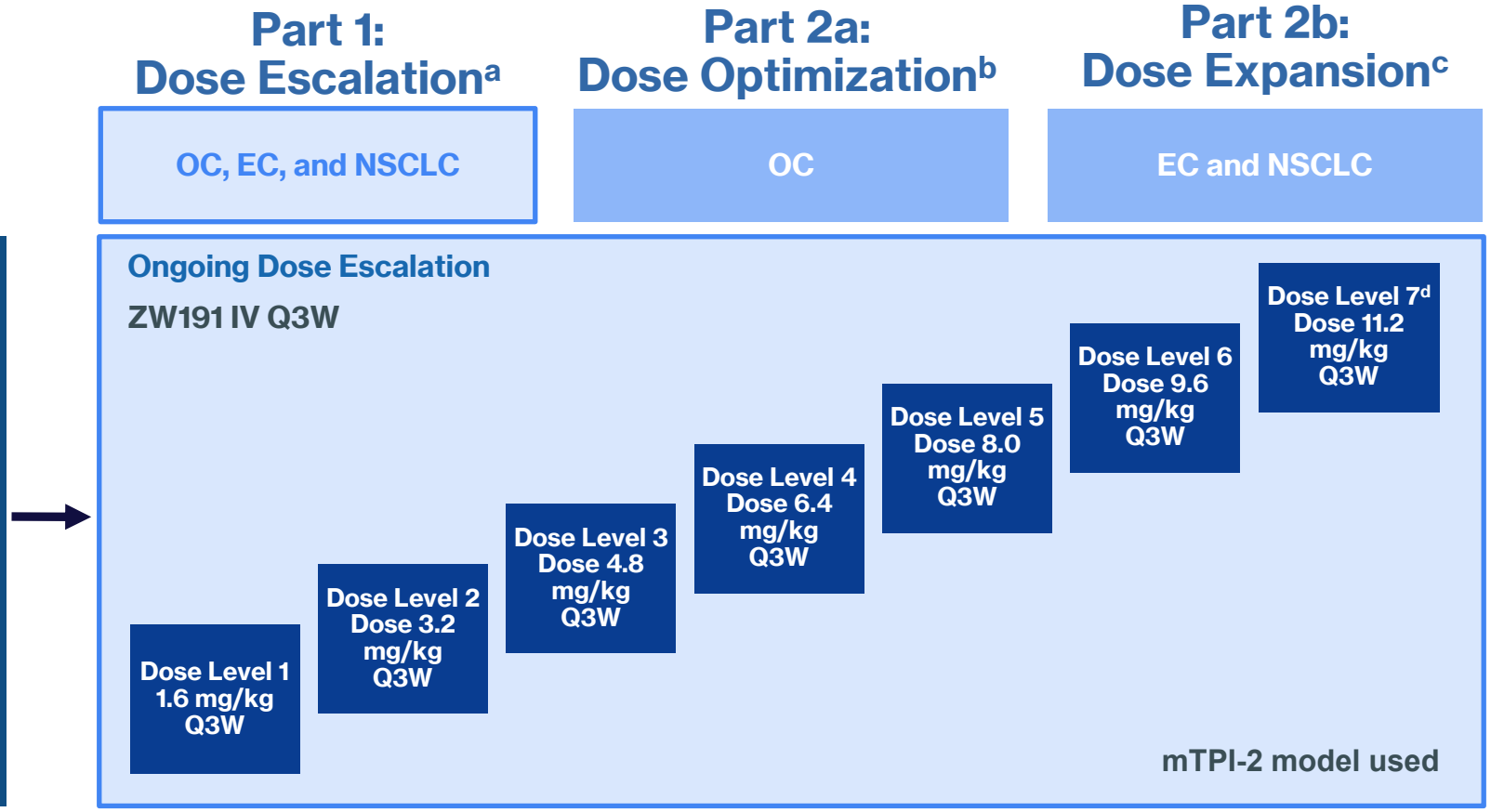
- **ZW191 displays favorable PK** and is **well tolerated in NHP at exposure levels** above those projected to be efficacious
- A **best-in-class HNSTD** provides flexibility to **explore a wider dose range in the first-in-human Phase 1 trial**

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; GMP: good manufacturing practices; HNSTD: highest non-severely toxic dose; MTD: maximum tolerated dose; NHP: non-human primates; PACS: pancreatic acinar cell secretion.
* across dose levels and dose cycles

ZWI-ZW191-101 study design

KEY ELIGIBILITY CRITERIA

- Aged ≥18 years with confirmed diagnosis of recurrent cancers:
  - Platinum-resistant OC (epithelial)
  - EC (serous or endometrioid)
  - NSCLC (adenocarcinoma)
- Exhausted available systemic treatment options[b]
- FRα expression evaluated retrospectively
- ECOG PS score of 0 or 1



High doses of ZW191 were achievable as predicted from selection of moderate payload potency and high HNSTD from GLP NHP study

aCT/MRI testing every 6 weeks (first 4 assessments) or every 9 weeks timed from Cycle 1 Day 1 and a 21-day DLT evaluation period. 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. bNo limits on the number of prior treatments received. cTo be initiated with recommended doses for optimization based on safety monitoring data from Part 1. dParticipants at dose level 7 are ongoing and have not completed the DLT window as of 10 September 2025 data cutoff.
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

ZW191 demonstrates a favorable clinical safety profile

TRAE, n (%) Data cutoff: September 10, 2025	ZW191 1.6 mg/kg (n=3)	ZW191 3.2 mg/kg (n=3)	ZW191 4.8 mg/kg (n=4)	ZW191 6.4 mg/kg (n=10)	ZW191 8.0 mg/kg (n=11)	ZW191 9.6 mg/kg (n=8)	ZW191 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 event[a]	**0**	**0**	**0**	**1 (20)**	**0**	**0**	**0**	**1 (4)**

No serious TRAEs, discontinuations due to AEs, or deaths reported

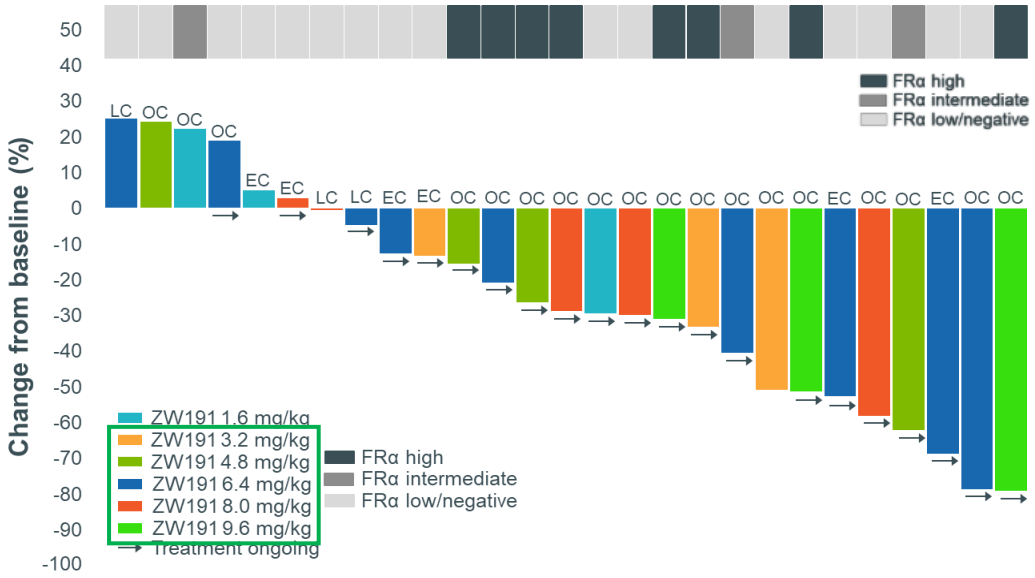
Presented at 2025 AACR-NCI-EORTC Conference on Molecular Targets and Cancer Therapeutics

a. Percentages calculated based on the number of participants in the DLT evaluable set (n=25; n=5 at dose level 6.4 mg/kg). Treatment is ongoing and not all participants have completed the DLT window.
LoRusso P. et al. Abstract # LB-A011 Presented at AACR-NCI-EORTC 2025.
DLT: dose-limiting toxicity; TRAE: treatment-related adverse event; AE: adverse event.

ZWI-ZW191-101 | preliminary clinical results
Efficacy across broad dose range

Best percent change in target lesion size from baseline (n=27)

Data cutoff: September 10, 2025



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).

Preliminary efficacy for response-evaluable participants with gynecological cancer

Data cutoff: September 10, 2025

Best response	ZW191 1.6 mg/kg (n=3)	ZW191 3.2 mg/kg (n=3)	ZW191 4.8 mg/kg (n=4)	ZW191 6.4 mg/kg (n=7)	ZW191 8.0 mg/kg (n=4)	ZW191 9.6 mg/kg (n=3)	ZW191 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 all awaiting confirmation.
Note: Percentages are out of gynecological cancer (OC and EC) participants.

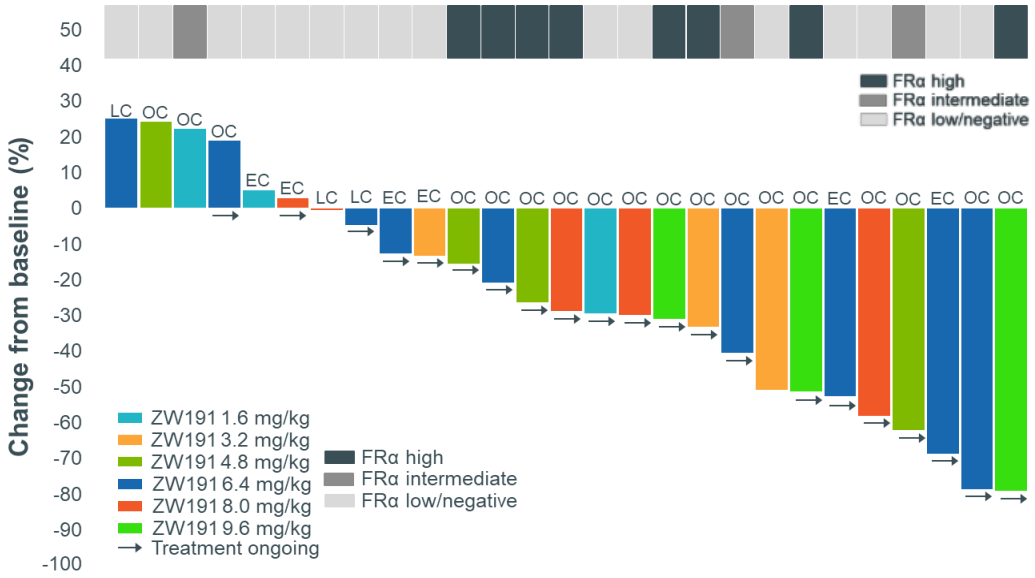
Broad therapeutic window from 3.2mg/kg to 9.6 mg/kg

LoRusso P. et al. Abstract # LB-A011 Presented at AACR-NCI-EORTC 2025.
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; cPR: confirmed partial response; EC, endometrial cancer; OC, ovarian cancer; PD: progressive disease; PR: partial response; SD: stable disease

ZWI-ZW191-101 | preliminary clinical results
Efficacy across broad dose range

Best percent change in target lesion size from baseline (n=27)

Data cutoff: September 10, 2025



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).

Preliminary efficacy for response-evaluable participants with gynecological cancer

Data cutoff: September 10, 2025

Best response	ZW191 1.6 mg/kg (n=3)	ZW191 3.2 mg/kg (n=3)	ZW191 4.8 mg/kg (n=4)	ZW191 6.4 mg/kg (n=7)	ZW191 8.0 mg/kg (n=4)	ZW191 9.6 mg/kg (n=3)	ZW191 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 all awaiting confirmation.
Note: Percentages are out of gynecological cancer (OC and EC) participants.

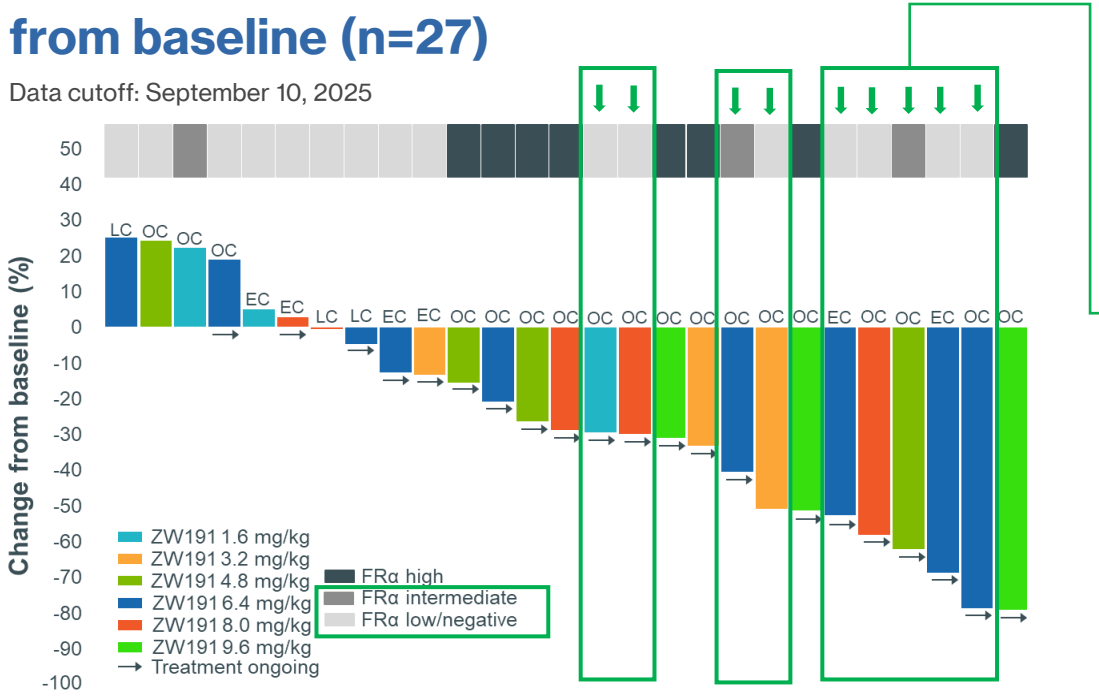
Higher doses enabled by moderate potency payload
64% ORR at doses of 6.4 – 9.6 mg/kg

LoRusso P. et al. Abstract # LB-A011 Presented at AACR-NCI-EORTC 2025.
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;
cPR: confirmed partial response; EC, endometrial cancer; OC, ovarian cancer; PD: progressive disease; PR: partial response; SD: stable disease

ZWI-ZW191-101 | preliminary clinical results
Efficacy observed independent of FRa level

Best percent change in target lesion size from baseline (n=27)

Data cutoff: September 10, 2025



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).

Preliminary efficacy for response-evaluable participants with gynecological cancer

- Anti-tumor activity is observed across all FRα expression levels across a range of doses
  - Activity observed in intermediate FRα expressing tumors (H-score: 75-199)
  - Activity observed in low/negative FRα expressing tumors (H-score: 0-74)
- Opportunity to treat broader range of FRα-expressing cancers

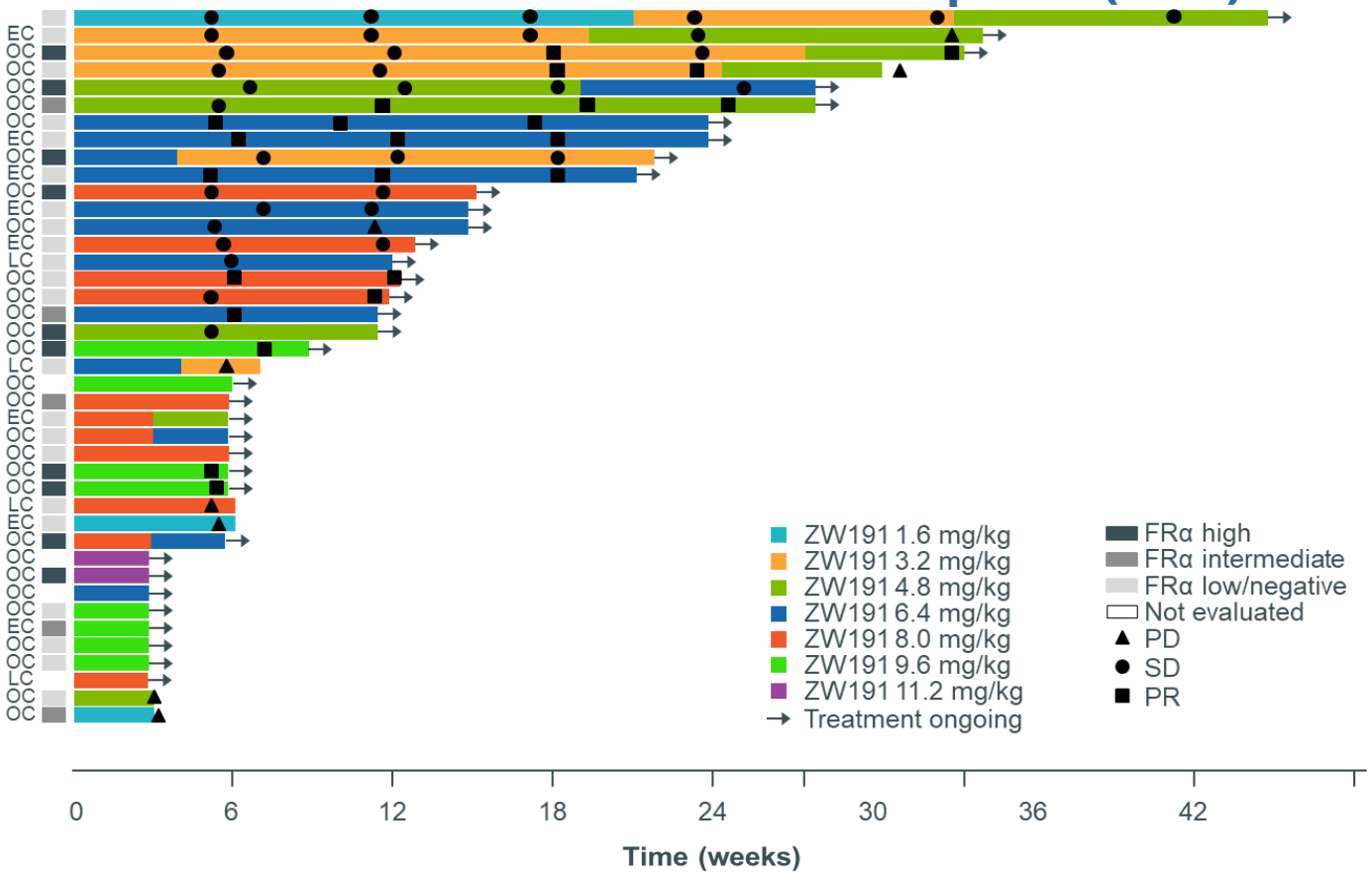
FRα expression was measured by immunohistochemistry on archival or newly collected formalin-fixed, paraffin-embedded biopsies with the VENTANA® FOLR1 (FOLR1-2.1) assay

High internalizing antibody and payload bystander activity
Activity observed in FRα intermediate and FRα low/negative tumors

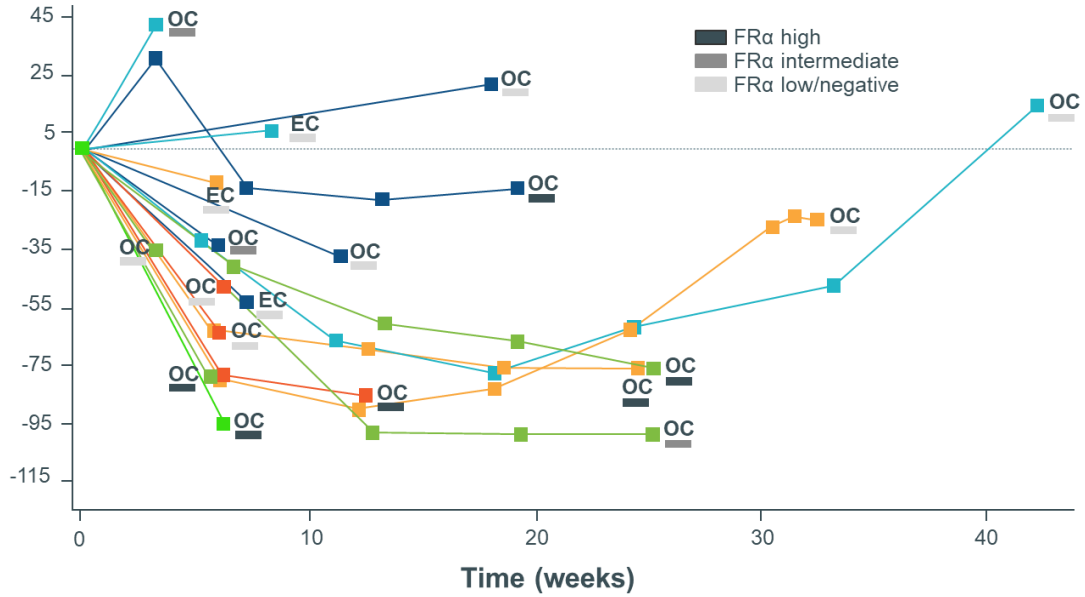
LoRusso P. et al. Abstract # LB-A011 Presented at AACR-NCI-EORTC 2025.
EC: endometrial cancer; FRα: folate receptor alpha; LC: non-small cell lung cancer; OC: ovarian cancer; RECIST v1.1: Response Evaluation Criteria in Solid Tumors, version 1.1; cPR: confirmed partial response; EC, endometrial cancer; OC, ovarian cancer; PD: progressive disease; PR: partial response; SD: stable disease

ZWI-ZW191-101 | preliminary clinical results

Duration of treatment and overall response (n=41)



Percent change from baseline in CA-125 (n=19)



Administered up to 11.6 mg/kg in Dose Escalation
Low Rates of Dose Modification with Majority of Patients Still On Treatment

CA-125: cancer antigen 125; 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

Data cutoff: September 10, 2025

ZW191 | Next steps

Data-driven development

Building confidence in our ADC platform through safety, pharmacokinetics, and efficacy with emerging clinical data

Optimization & differentiation

11.2 mg/kg dose defined as MTD since this data-cut

Randomized dose optimization began in 4Q-2025 in platinum resistant ovarian cancer at 9.6 and 6.4 mg/kg doses (~30 pts/cohort)

Early data supports best-in-class potential

Strategic growth potential

Emerging data will inform registration and combination strategies, including earlier-line opportunities

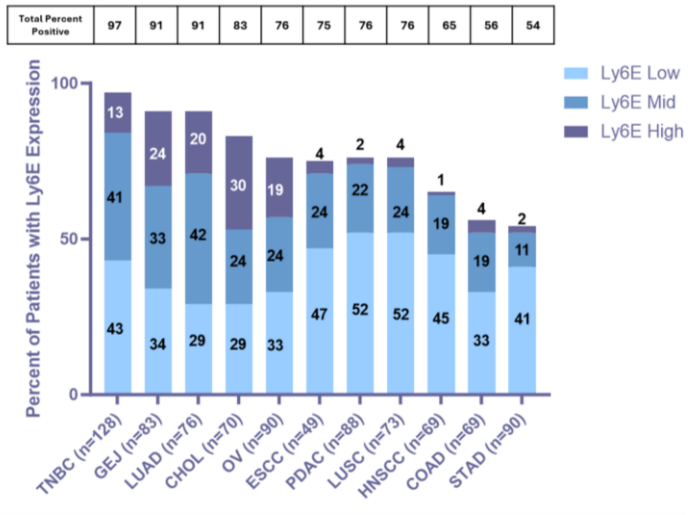
In parallel, partnership discussions are underway to further refine and accelerate development

Fit for purpose Topo1i ADC pipeline
Tailored to cancer and target biology

	Phase 1		Preclinical		
					
Target	**ZW191** FRα	**ZW251** GPC3	**ZW220** NaPi2b	**ZW327** Ly6E	**ZW318** PTK7
DAR	8	4	4	8	8
Antibody	Monospecific	Monospecific	Monospecific	Monospecific	Biparatopic
Fc	Wild-type	Wild-type	Fc-silenced	Fc-silenced	Wild-type
Potential Indications	OVCA, EC, NSCLC	HCC	OVCA, EC, NSCLC	NSCLC, TNBC, OVCA, PDAC, HNSCC, ESCC. GI tumors	NSCLC, OVCA, TNBC, CRC, HNSCC, ESCC

ZW327: A potential first-in-class ADC against Ly6E

Ly6E is overexpressed in many solid tumors



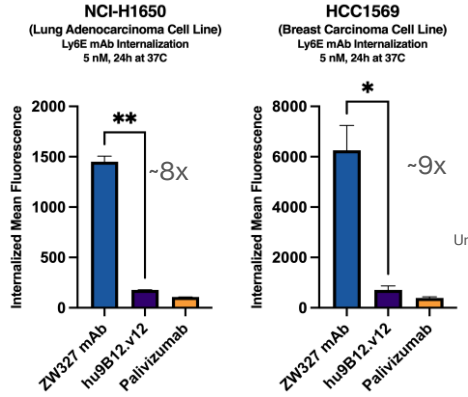
Ly6E is overexpressed in indications of high unmet medical need, including NSCLC (LUAD+LUSC), TNBC, HNSCC, and GI cancers: ESCC, PDAC, GEJ, CHOL, COAD, and STAD tissues with minimal presence in normal tissues.

ZW327 A Novel Ly6E-targeting ADC

- Novel TOPO1i inhibitor payload, ZD06519
- Drug-to-antibody ratio ~8
- ZW327's ZD06519 payload and novel antibody enable strong cytotoxicity across a range of solid tumor indications
- ZW327 is well-tolerated in NHP at 60 mg/kg

Activity is consistently superior to benchmark ADC

Enhanced payload internalization relative to benchmark



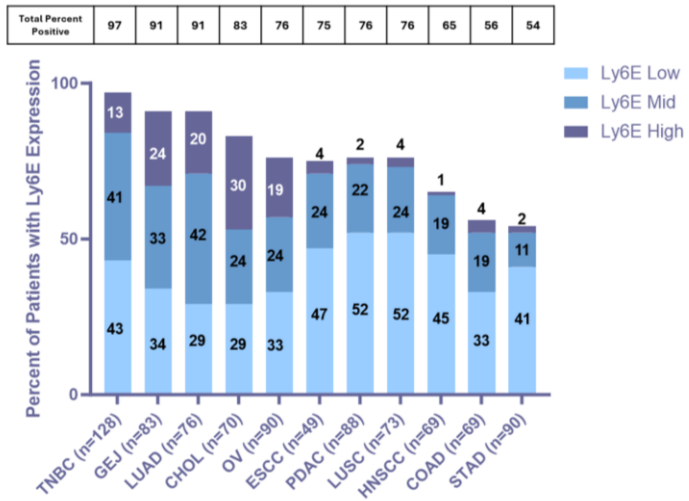
Unpaired t-test: *p<0.05, **p<0.01

Clinical Benchmark: DLYE5953A Anti-Ly6E antibody (hu9B12) covalently linked to MMAE (DAR 4)

Urosev D et al., Abstract #2874 presented at AACR 2025;
TNBC: Triple-Negative Breast Cancer; GEJ: Gastroesophageal Junction; LUAD: Lung Adenocarcinoma; CDX: cell-line derived xenografts; CHOL: Cholangiocarcinoma; OV: Ovarian; ESCC: Esophageal Squamous Cell Carcinoma; PDAC: Pancreatic Ductal Adenocarcinoma; PDX: patient derived xenografts; LUSC: Lung Squamous Cell Carcinoma; HNSCC: Head and Neck Squamous Cell Carcinoma; COAD: Colon Adenocarcinoma; STAD: Stomach Adenocarcinoma; NSCLC: Non-Small Cell Lung Cancer; TOPOi1: Topoisomerase 1; NHP: Non-Human Primate.

ZW327: A potential first-in-class ADC against Ly6E

Ly6E is overexpressed in many solid tumors



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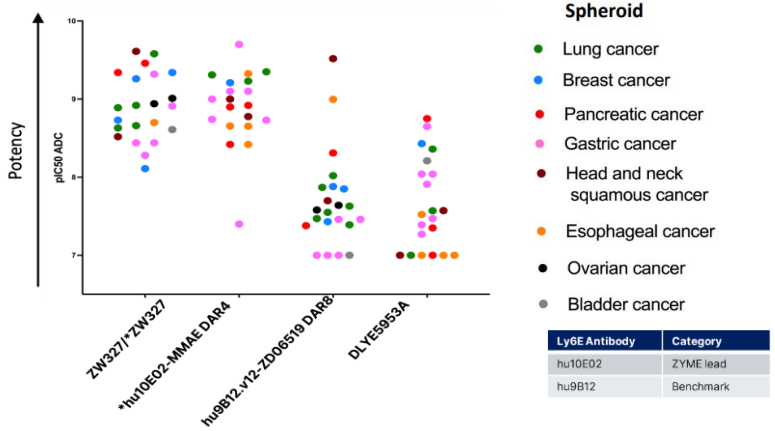
- Drug-to-antibody ratio ~8
- ZW327's ZD06519 payload and novel antibody enable strong cytotoxicity across a range of solid tumor indications
- **ZW327 is well-tolerated in NHP at 60 mg/kg**

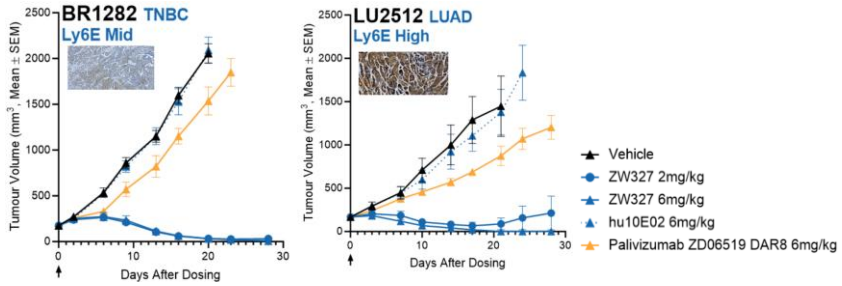
Activity is consistently superior to benchmark ADC

In vitro ZW327 cytotoxic activity against range of Ly6E spheroid (3D) cancer models



Ly6E Antibody	Category
hu10E02	ZYME lead
hu9B12	Benchmark

Enhanced In vivo efficacy in PDX models of NSCLC and TNBC



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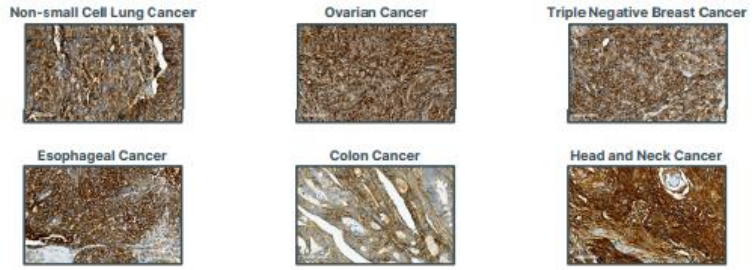
ZW318: Biparatopic PTK7 TOPO1i ADC

Overexpression of PTK7 has also been observed in several cancers

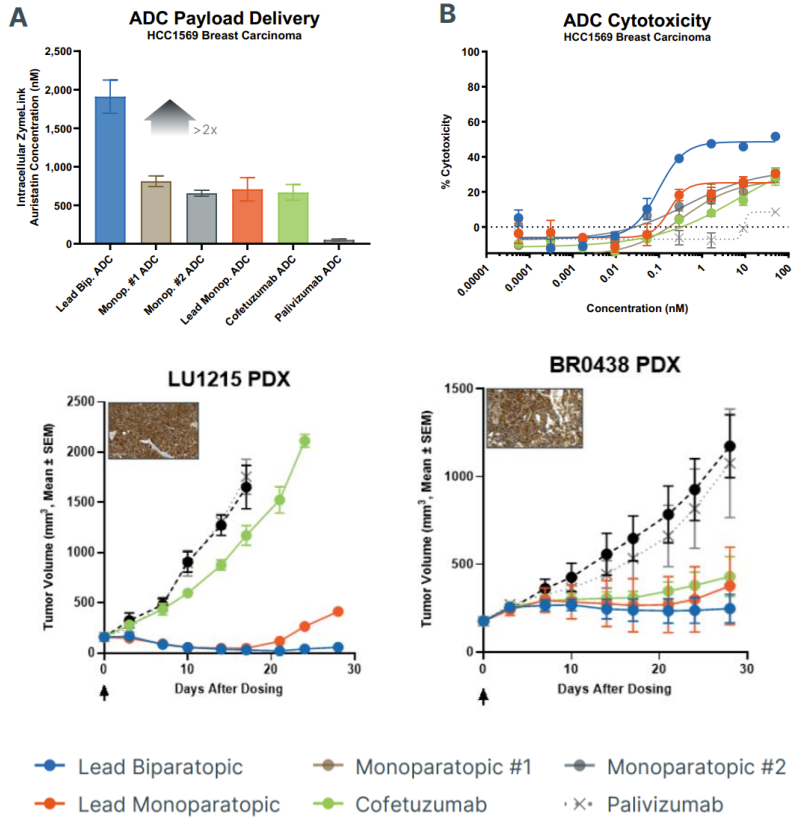


- PTK7 over expression across multiple tumor types including breast, digestive tract, and lung cancers, makes it an attractive target for ADCs.
- The protein's large extracellular region allows for antibodies to distinct PTK7 epitopes, enabling biparatopic antibodies and ADCs development.

A novel PTK7-targeting biparatopic ADC

- Novel TOPOi1 inhibitor payload, ZD06519
- Drug-to-antibody ratio ~8
- Biparatopic targeting of PTK7 results in superior antibody properties, relative to conventional monoparatopic antibodies
- **Biparatopic PTK7 TOPO1i ADC is well tolerated in NHP (60 mg/kg) and has good PK**

Activity is consistently superior to benchmark ADC

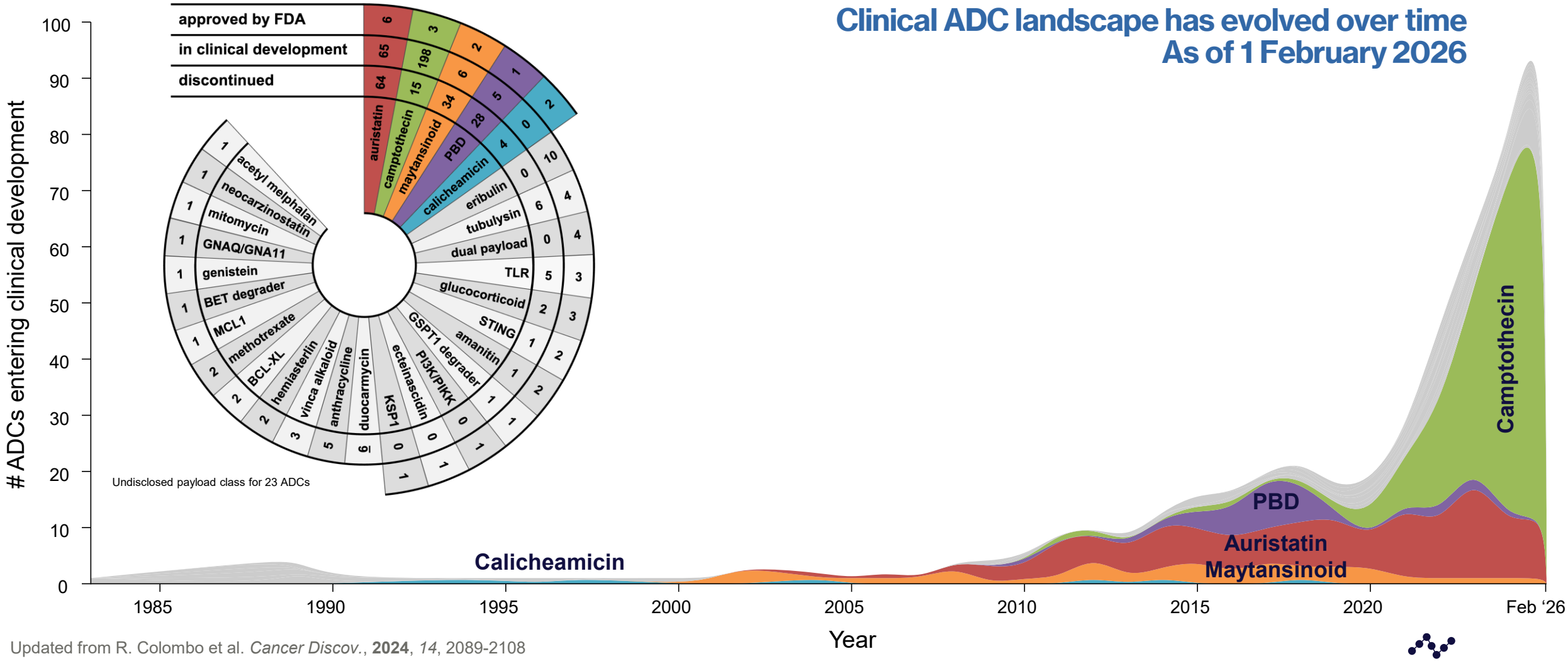


Fung V et al., Abstract #1565 presented at AACR 2025;
PDX: Patient-Derived Xenograft.

Enhancing the Therapeutic Potential of Topoisomerase Inhibitor ADCs: From Concept to Clinic

- Learnings from 40+ years of ADC clinical development to guide ZD06519 Topo1i linker-payload
- Antibody binder/format screening to optimize payload delivery and address target/tumor specific biology
- Proof of concept clinical dose escalation studies with ZW191, a potential best-in-class Folate Receptor alpha targeting ADC
- **Expanding application to additional linker-payloads and antibody formats**

Novel payload development is a priority

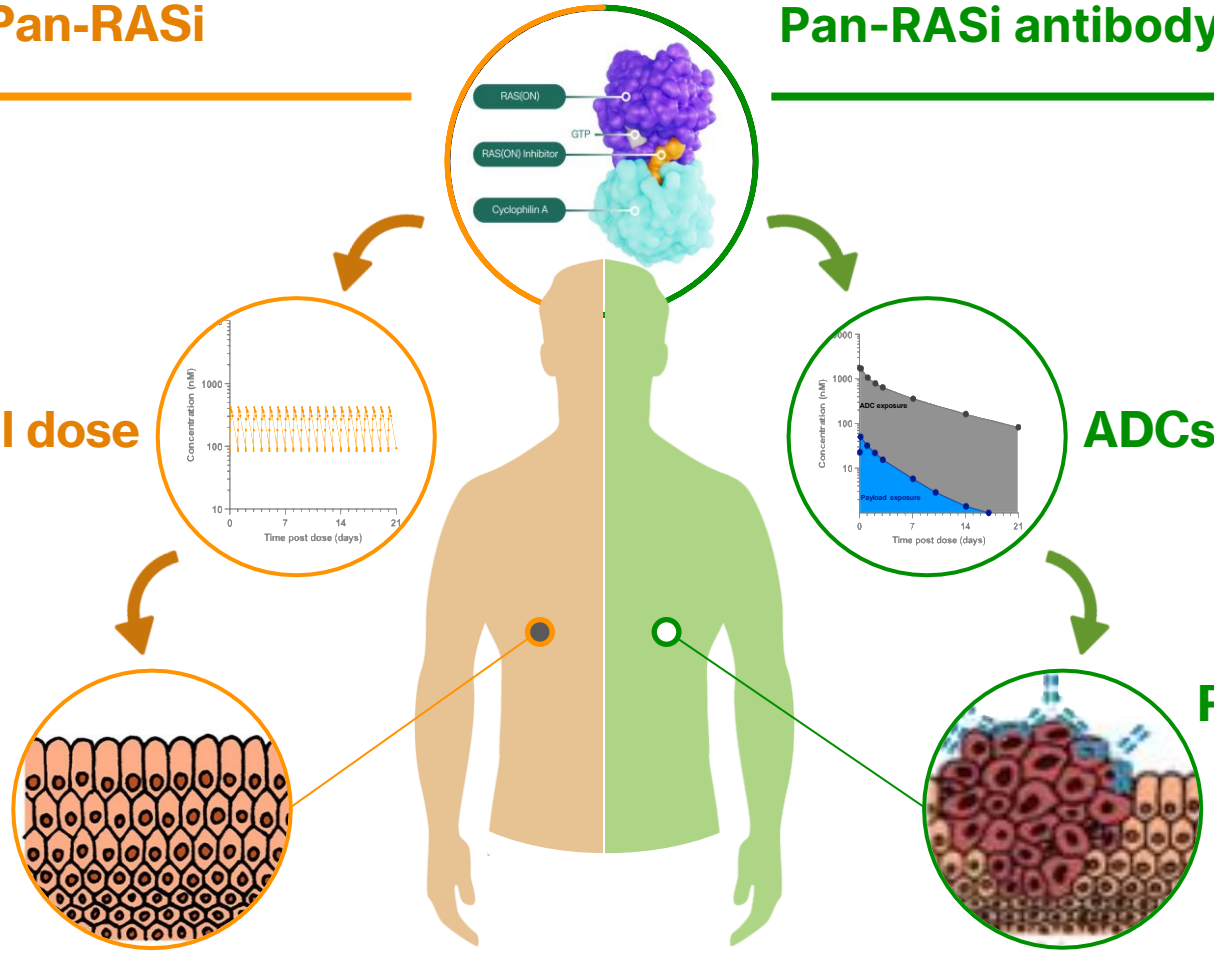


Updated from R. Colombo et al. *Cancer Discov.*, **2024**, *14*, 2089-2108

ADCs offer potential to improve treatment of RAS-driven cancers

Small molecule Pan-RASi

Pan-RASi antibody conjugate



High daily oral dose

ADCs: Improved tumor exposure

Side effects
(skin, stomatitis, GI tox)

Rasi ADCs opportunities:

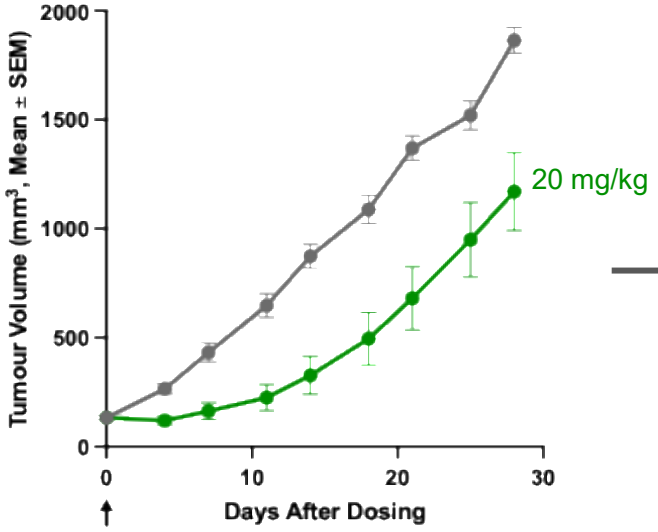
↑ Improved efficacy
↓ Reduced side effects
↑ Improved combination

Optimized RAS inhibitor ADCs highly active in RAS^{MUT} xenograft models

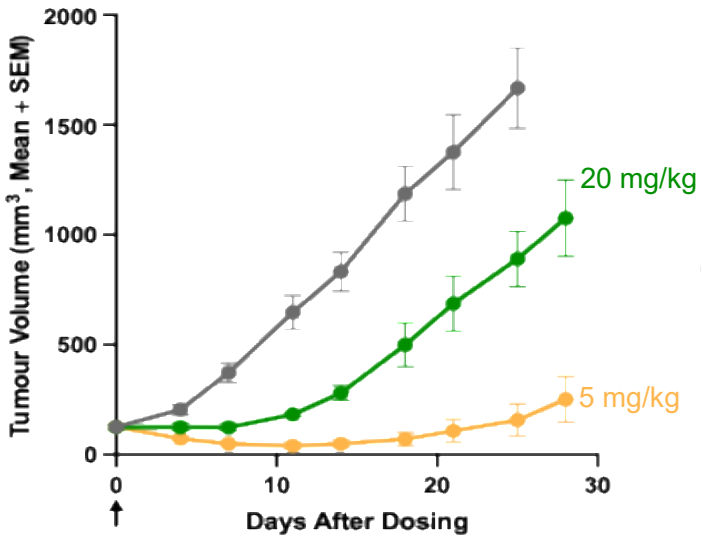
Pan-RASi ADCs:

- Potential application in NSCLC, PDAC, and CRC
- Optimal overlap between TAA expression and RAS-driven tumors

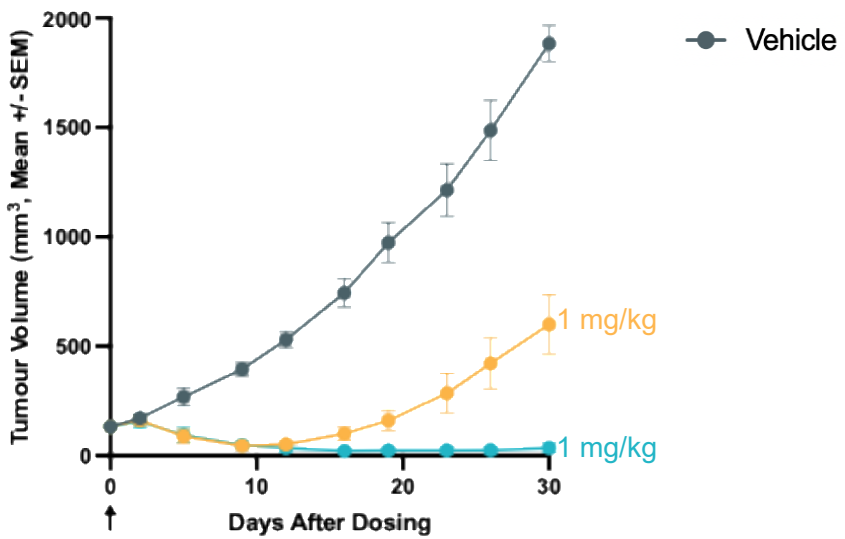
Lung Adenocarcinoma Model (KRAS G12C)



Proof of concept for Pan-RAS inhibitor ADC with clinically validated Pan-RASi



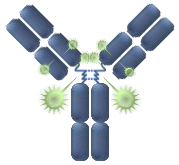
Iterative optimization yields Prototype ADC



Lead drug linker selected

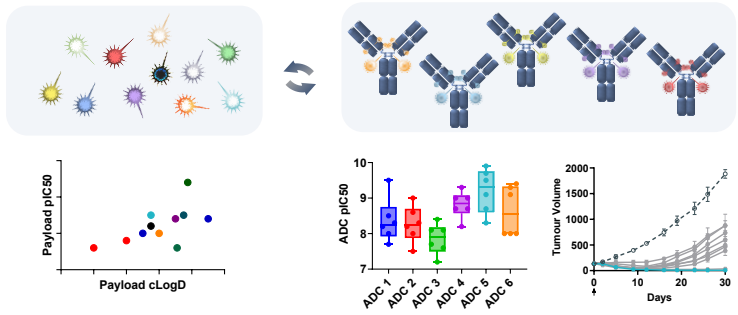
Platform development → Three pipeline programs

Proof of concept for RASi ADC



Incorporates clinically validated Pan-RASi

Platform development



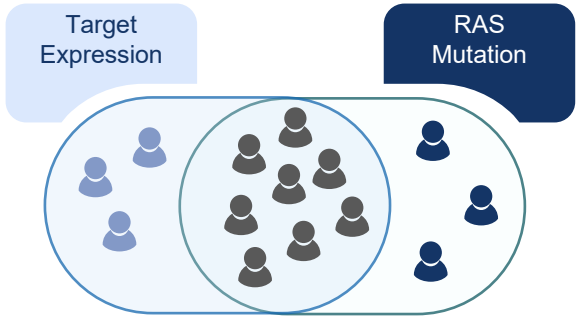
RASi ADC Features

- Novel, potent, bystander-capable pan-RASi
- Novel linkers optimized for favorable PK
- Anti-tumor activity in >20 CDX models
- Decreased RAS suppression in normal tissue
- Murine MTD >200 mg/kg, NHP proof of concept

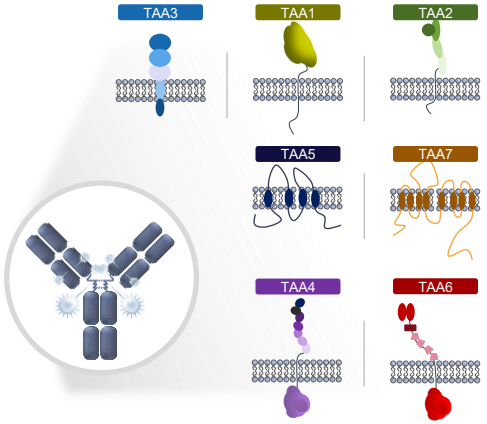
Platform Development

Program Development

Target expression and RAS mutational status



Target-mechanism compatibility



Final candidate selection

ZW418 PTK7 RASi ADC | DAR 8 | Biparatopic	RAS^{MUT} NSCLC
Program #2 TAA RASi ADC	RAS^{MUT} NSCLC, CRC, PDAC
Program #3 TAA RASi ADC	RAS^{MUT} PDAC

Acknowledgements - A global team effort

ADC Therapeutics Group (Vancouver)

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

Patricia LoRusso,[1] Daniel S.W. Tan,[2] Jung-Yun Lee,[3] Noboru Yamamoto,[4] David Sommerhalder,[5] David O'Malley,[6] Kosei Hasegawa,[7] David Shao Peng Tan,[8] Sabeen Mekan,[9] Akira Kojima,[9] Joseph Hirman,[9] Pranshul Chauhan,[9] Sarah Church,[9] Marylou Vallejo,[9] Kathleen N. Moore[10]

[1]Yale Cancer Center, New Haven, CT, US; [2]National Cancer Centre, Singapore, Republic of Singapore; [3]Yonsei Cancer Center and Severance Hospital, Seoul, Republic of Korea; [4]National Cancer Center Hospital, Tokyo, Japan; [5]NEXT Oncology, San Antonio, TX, US; [6]The Ohio State University and the James Comprehensive Cancer Center, Columbus, OH, US; [7]Saitama Medical University International Medical Center, Hidaka, Saitama, Japan; [8]National University Cancer Institute, Singapore, Republic of Singapore; [9]Zymeworks BC Inc., Vancouver, BC, Canada; [10]Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK, US

Presented at 2025 AACR-NCI-EORTC Conference on Molecular Targets and Cancer Therapeutics

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