Design and Functional Characterization of Zanidatamab Zovodotin (ZW49), a HER2-targeting Biparatopic Antibody Drug Conjugate in Clinical Development

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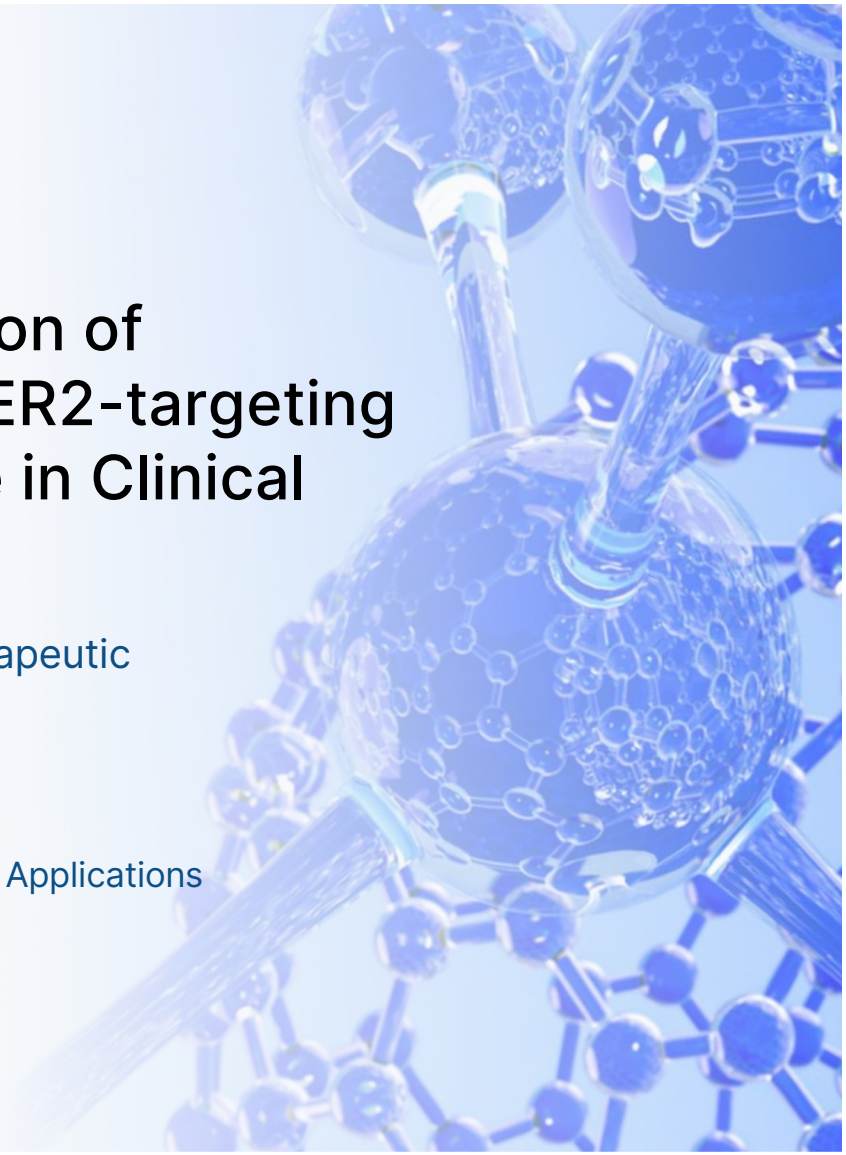
European Bispecific & Multispecific Antibody Congress | Therapeutic Applications



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A Growing Product Candidate Pipeline of Potential Best-in-Class Therapeutics

Zanidatamab	Preclinical	Phase 1	Phase 2	Pivotal	Collaboration Partner
1st-Line Gastroesophageal Adenocarcinomas HERIZON-GEA-01 Chemotherapy Combination					BeiGene Jazz Pharmaceuticals
2nd-Line Biliary Tract Cancers HERIZON-BTC-01 Monotherapy					BeiGene Jazz Pharmaceuticals
1st-Line Gastrointestinal Cancers Gastroesophageal Adenocarcinoma, Biliary Tract Cancer, and Colorectal Cancer Chemotherapy Combination					BeiGene Jazz Pharmaceuticals
Zanidatamab Monotherapy & Chemotherapy Combination					BeiGene Jazz Pharmaceuticals

A Growing Product Candidate Pipeline of Potential Best-in-Class Therapeutics

Early Development and Early R&D	Preclinical	Phase 1	Phase 2	Pivotal	Partner
Zanidatamab Zovodotin HER2-Expressing Cancers Indications: NSCLC, GEA, CRC, OVCA, BC					BeiGene
ZW191 Folate Receptor-α Targeted Topoisomerase 1 Inhibitor Antibody Drug Conjugate Indications: OVCA, Gynecological, NSCLC					
ZW171 2+1 MSLN x CD3 Bispecific Antibody Indications: Pancreatic, OVCA, CRC					
ZW251 Glypican-3 Targeted Topoisomerase 1 Inhibitor Antibody Drug Conjugate Indications: Hepatocellular carcinoma					
ZW220 NaPi2b Targeted Topoisomerase 1 Inhibitor Antibody Drug Conjugate Indication: OVCA, NSCLC, other solid tumors					

BC: breast cancer; CRC: Colorectal cancer; GEA: gastroesophageal adenocarcinoma; NSCLC: non-small cell lung cancer; OVCA: ovarian cancer

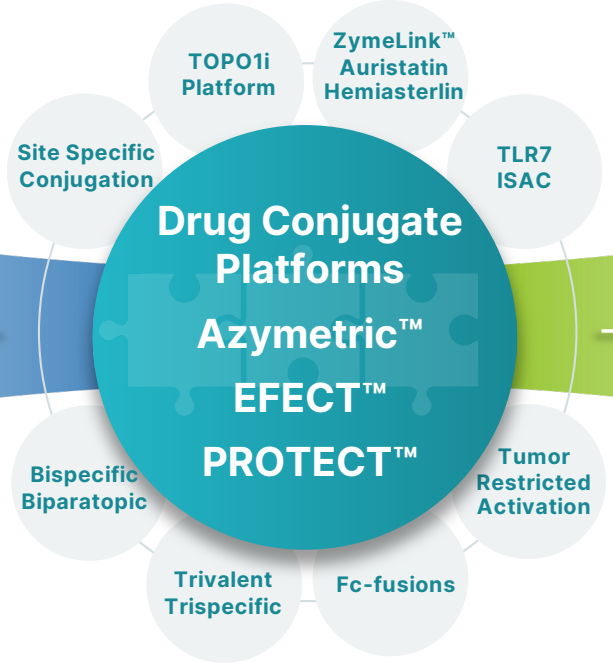
Clinically Proven: Zymeworks Technology Platforms Yield Therapeutics

Zanidatamab (ZW25)

Biparatopic anti-HER2

Unique biology lends additional benefit achieved by mAb combinations

Pivotal clinical studies



Zanidatamab Zovodotin (ZW49)

Biparatopic anti-HER2 with proprietary auristatin payload

Efficient internalization and payload delivery

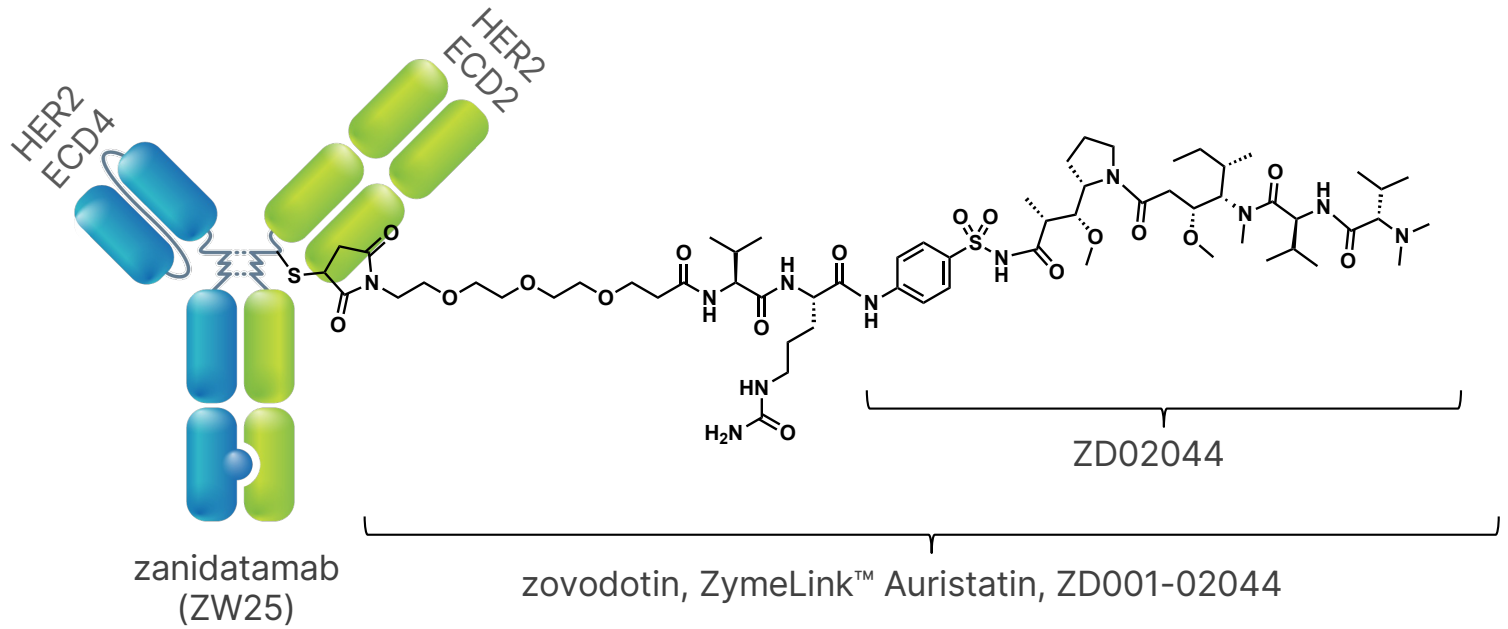
Clinical POC study

Presentation Overview

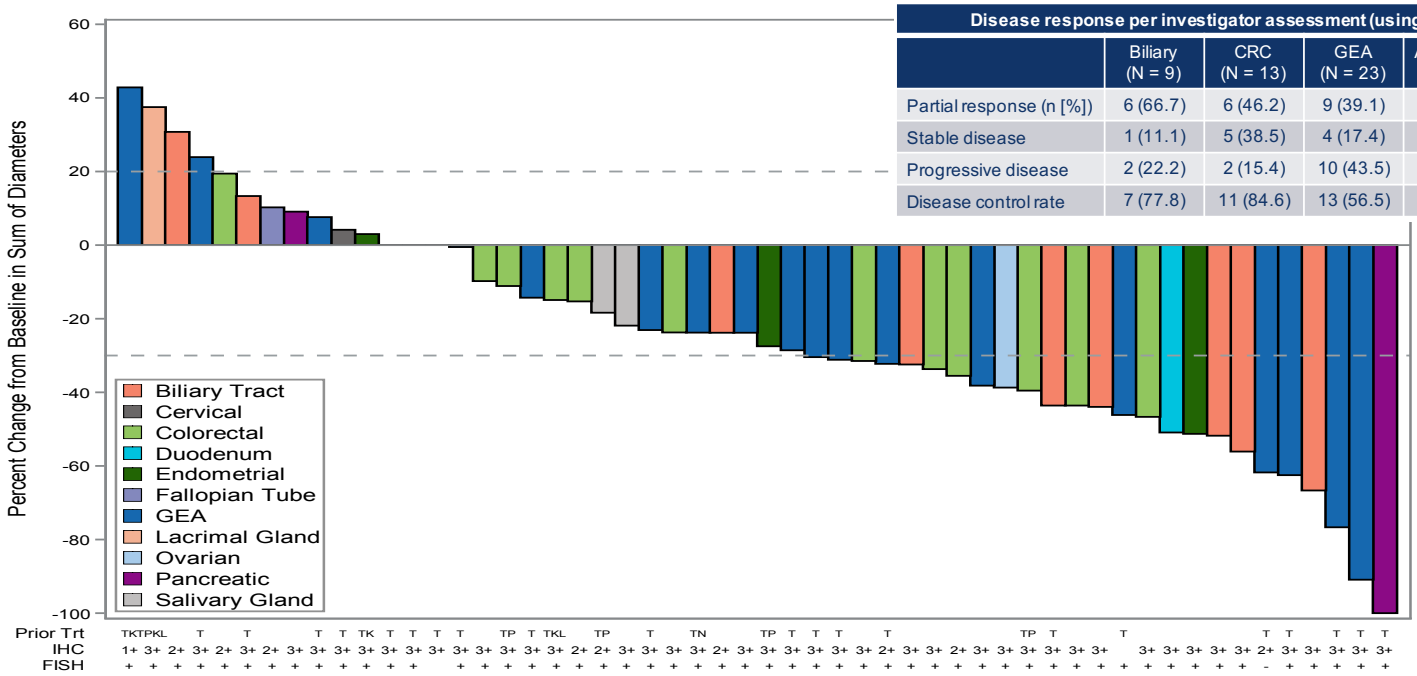
- Zanidatamab characterization and features supporting ADC application
- Zanidatamab zovodotin ADC Design
- Profiling zanidatamab zovodotin's internalization and payload delivery
- Zanidatamab zovodotin's anti-tumor activity
- Immunogenic cell death potential of zanidatamab zovodotin
- Clinical validation of zanidatamab zovodotin

Zanidatamab Zovodotin Combines the Biparatopic Targeting of Zanidatamab with a Novel Auristatin Payload (ZD02044)

Zanidatamab zovodotin consists of the humanized IgG1 anti-HER2 biparatopic mAb, zanidatamab, and two molecules of the potent microtubule disrupting payload ZD02044 conjugated using thiol-maleimide chemistry and a protease cleavable linker



Zanidatamab Monotherapy Shows Anti-Tumor Activity in Patients with Advanced HER2-Expressing Cancers



Disease response per investigator assessment (using RECIST 1.1)					
	Biliary (N = 9)	CRC (N = 13)	GEA (N = 23)	All others (N = 12)	Total (N = 57)
Partial response (n [%])	6 (66.7)	6 (46.2)	9 (39.1)	4 (33.3)	25 (43.9)
Stable disease	1 (11.1)	5 (38.5)	4 (17.4)	5 (41.7)	15 (26.3)
Progressive disease	2 (22.2)	2 (15.4)	10 (43.5)	3 (25.0)	17 (29.8)
Disease control rate	7 (77.8)	11 (84.6)	13 (56.5)	9 (75.0)	40 (70.2)

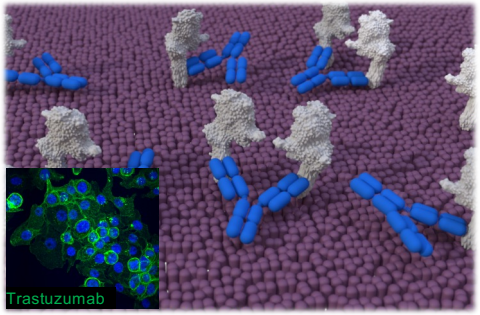
Zanidatamab has promising anti-tumor activity as monotherapy in patients with advanced HER2-expressing cancers that have progressed after standard of care therapies (median of 3 prior lines of therapy). Results from ZW25-101 (NCT02892123), a first-in-human Phase 1 study that evaluates zanidatamab in HER2-expressing cancers. Data cutoff: Sept 18, 2019.[1]

[1] D.-Y. Oh et al. ESMO Asia 2019, Nov. 22-24, Singapore

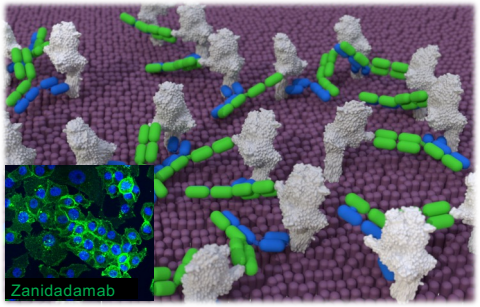
Zanidatamab Binds Tumor Cells with Higher Density and Mediates Enhanced Internalization Compared to Monospecific mAbs

- Zanidatamab binds tumor cells with 1.3 to 1.6-fold higher Bmax compared to tras or pert
- Zanidatamab mediates ~2-fold higher internalization compared to tras or pert

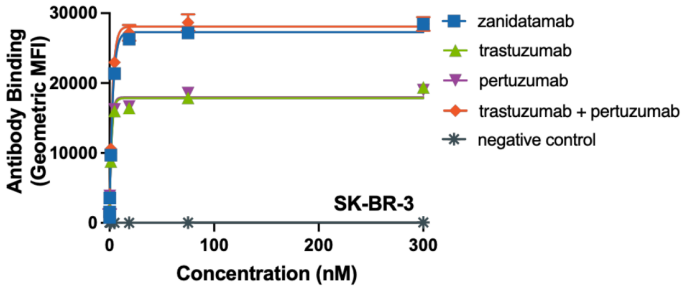
Monoclonal Binding



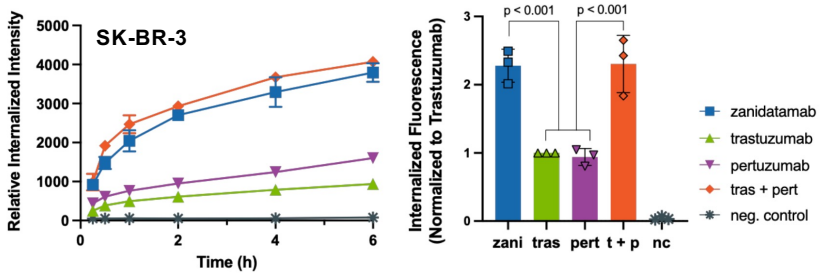
Biparatopic Binding



Tumor Cell Binding



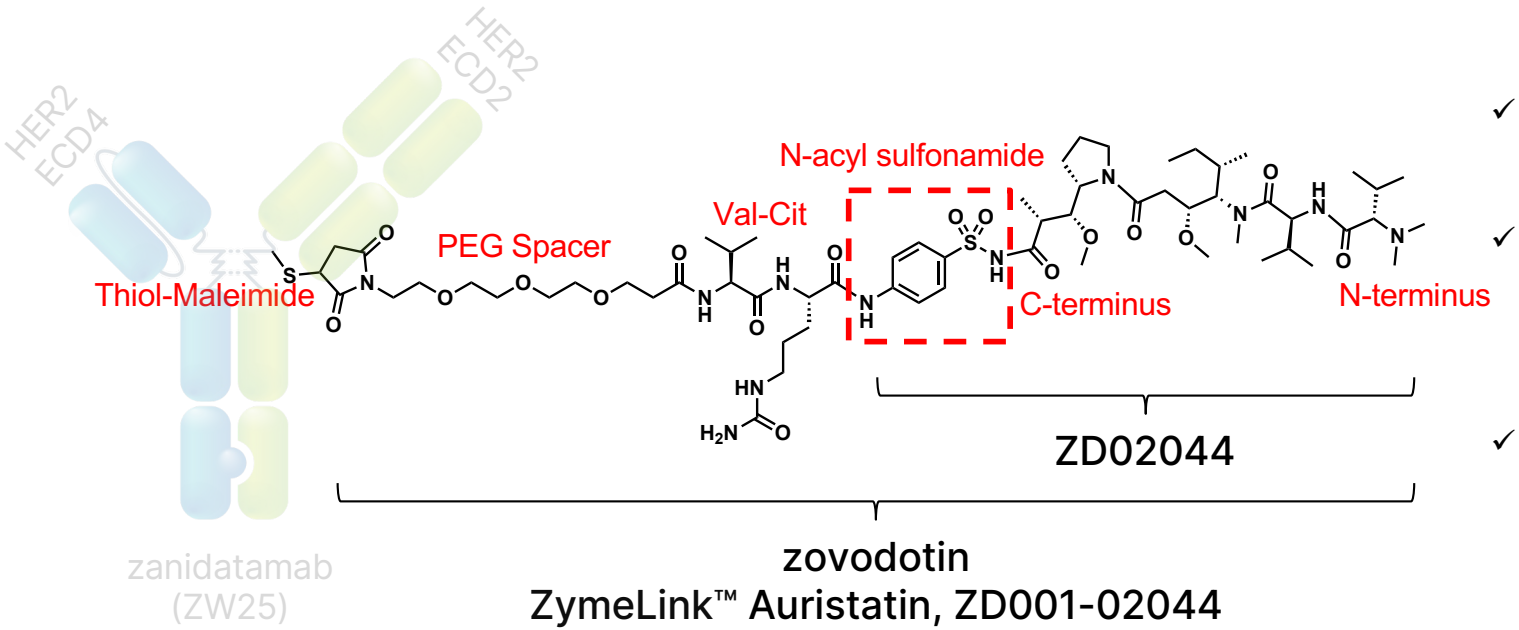
Tumor Cell Internalization



Key features that make zanidatamab an ideal ADC antibody

- ✓ Biparatopic - targets two distinct HER2 epitopes
- ✓ Optimized format to enhance activity
- ✓ Increased tumor cell binding
- ✓ Extended chain formation and HER2 receptor clustering
- ✓ Enhanced HER2 internalization

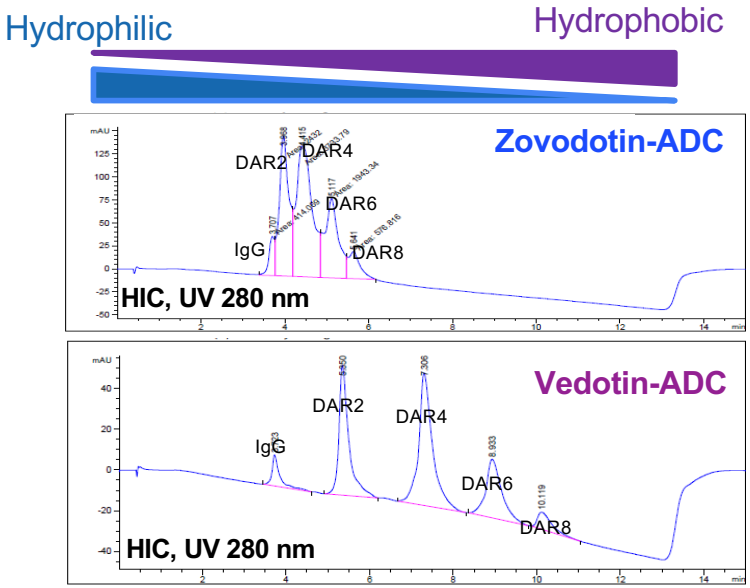
Zanidatamab Zovodotin has a Novel Auristatin Drug-Linker that Contributes Minimal hydrophobicity and is Stable in Circulation

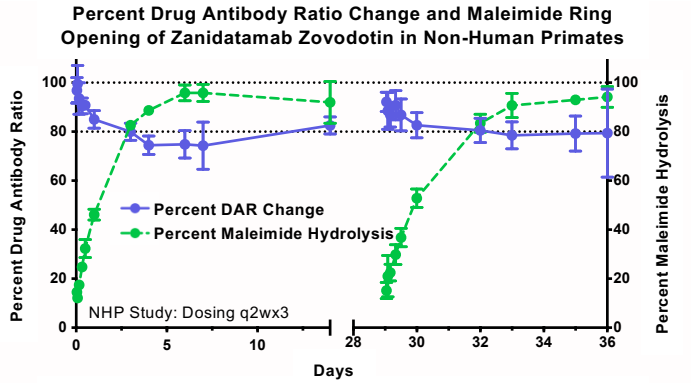


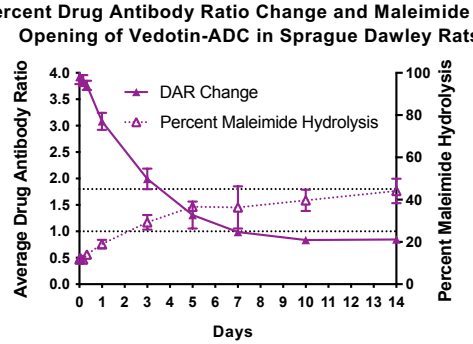
- ✓ Novel C-terminally linked auristatin drug-linker technology
- ✓ Functionalization of auristatin core with NAcS allows for direct cleavage of linker without hydrophobic PABC spacer
- ✓ PEG spacer increases hydrophilicity

Zanidatamab Zovodotin has a Novel Auristatin Drug-Linker that Contributes Minimal Hydrophobicity and is Stable in Circulation

- The N-acyl sulfonamide moiety reduces hydrophobicity compared to the commonly used PABC moiety
- Linkage through the C-terminus improves polarity through N-terminal ionizable amine
- PEG spacer of zovodotin facilitates maleimide ring opening and reduces deconjugation and payload loss







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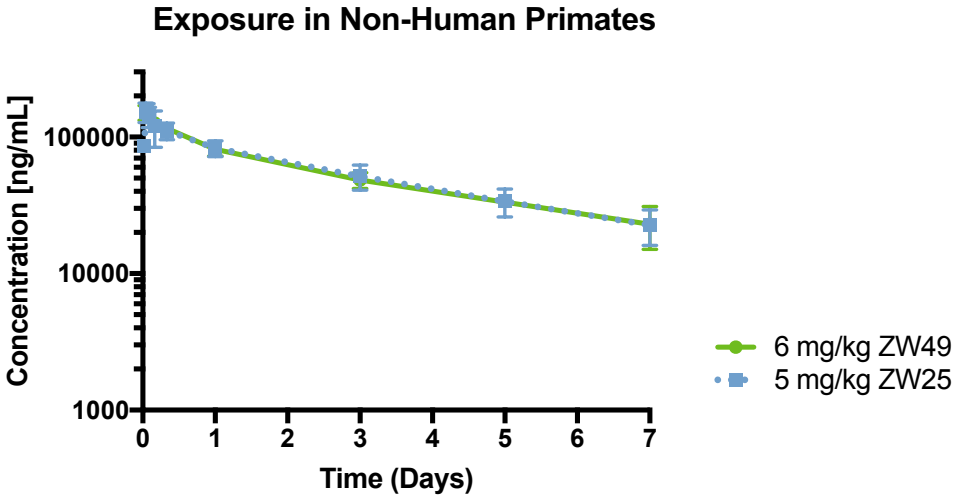
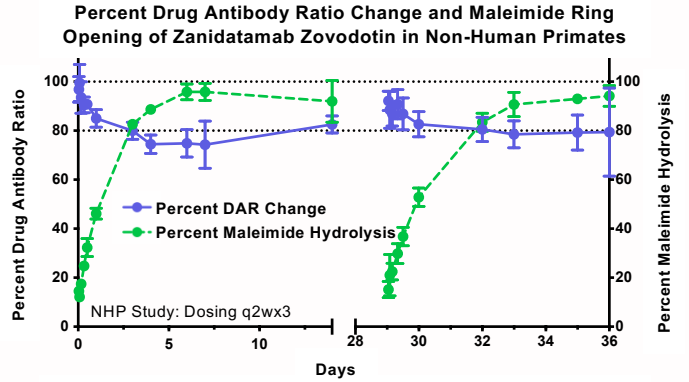
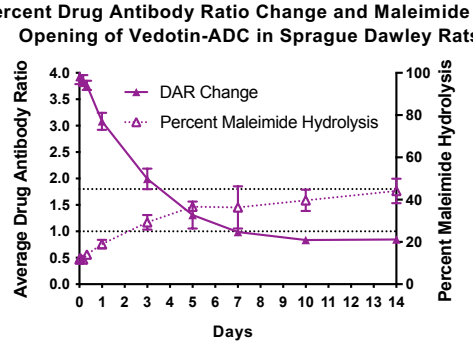
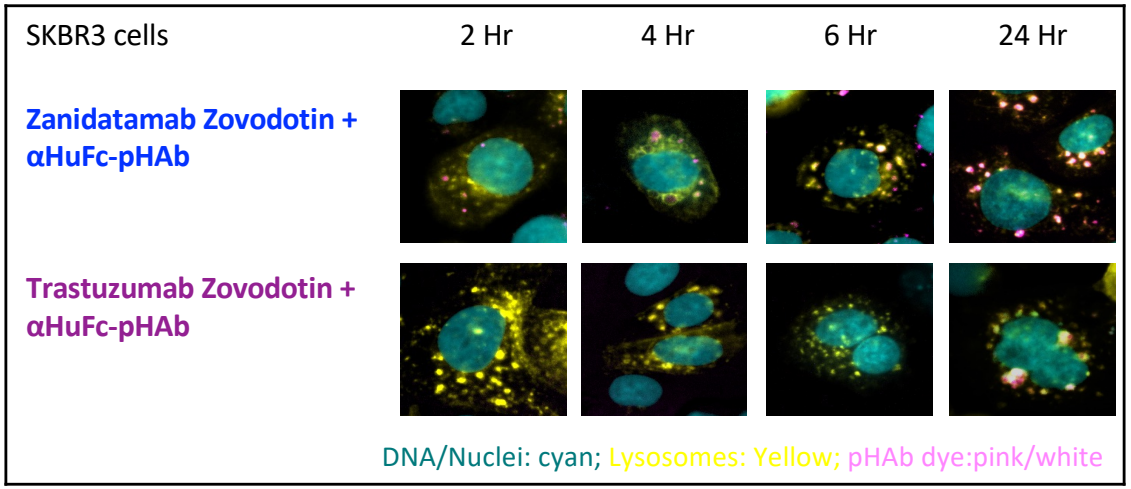






Zanidatamab Zovodotin is Rapidly Internalized and Trafficks to Lysosomes

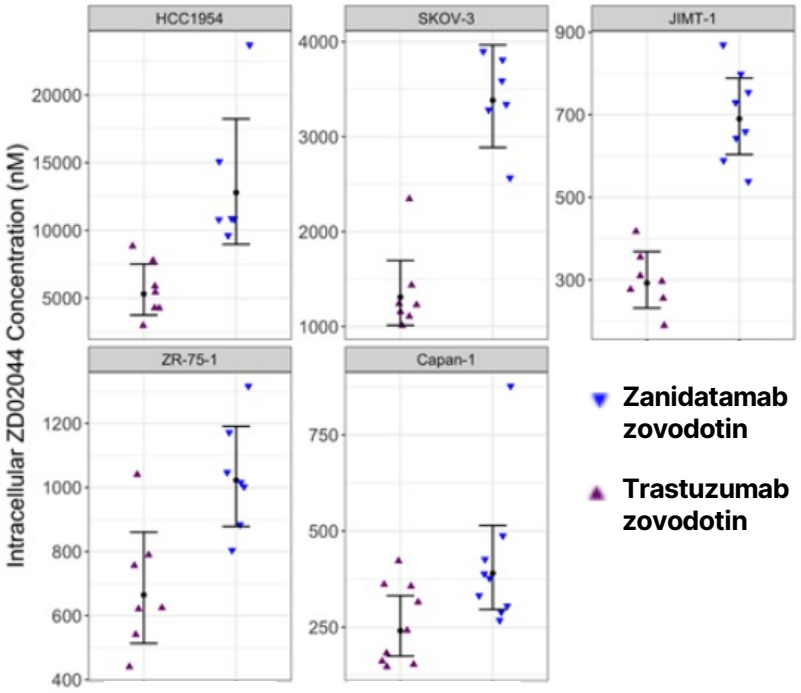
- Increased tumor cell binding of zanidatamab zovodotin leads to enhanced internalization
- Trafficking to the lysosomal compartment is observed after 2 hours



To determine internalization, pHAb, a highly fluorescent dye at acidic pH, was coupled to amines of a αHuFc. αHuFc-pHAb and ADCs were incubated with HER2 expressing cell lines and fluorescence measured using a high content CellInsight™.

Zanidatamab Zovodotin Efficiently Delivers ZD02044 to HER2+ Tumor Cells

Enhanced binding and internalization profile of zanidatamab zovodotin leads to a 1.54 to 2.58-fold increase in intracellular payload concentration compared to a trastuzumab ADC



Cell Type	Cell Line	HER2 Receptors/cell	Fold Difference zanidatamab zovodotin/trastuzumab ZD001-02044	P-value
Breast carcinoma	HCC1954	4,930,000	2.41	0.003
Ovarian adenocarcinoma	SKOV-3	1,310,000	2.58	<0.0001
Breast carcinoma	JIMT-1	336,000	2.36	<0.0001
Breast carcinoma	ZR-75-1	352,000	1.54	0.0116
Pancreatic adenocarcinoma	Capan-1	167,000	1.62	0.0184

5 nM treatment for 24 hours
After 24 hours at 37°C/5% CO2, cells were collected, counted, frozen, lysed, centrifuged and resulting supernatant was injected into LC-MS/MS

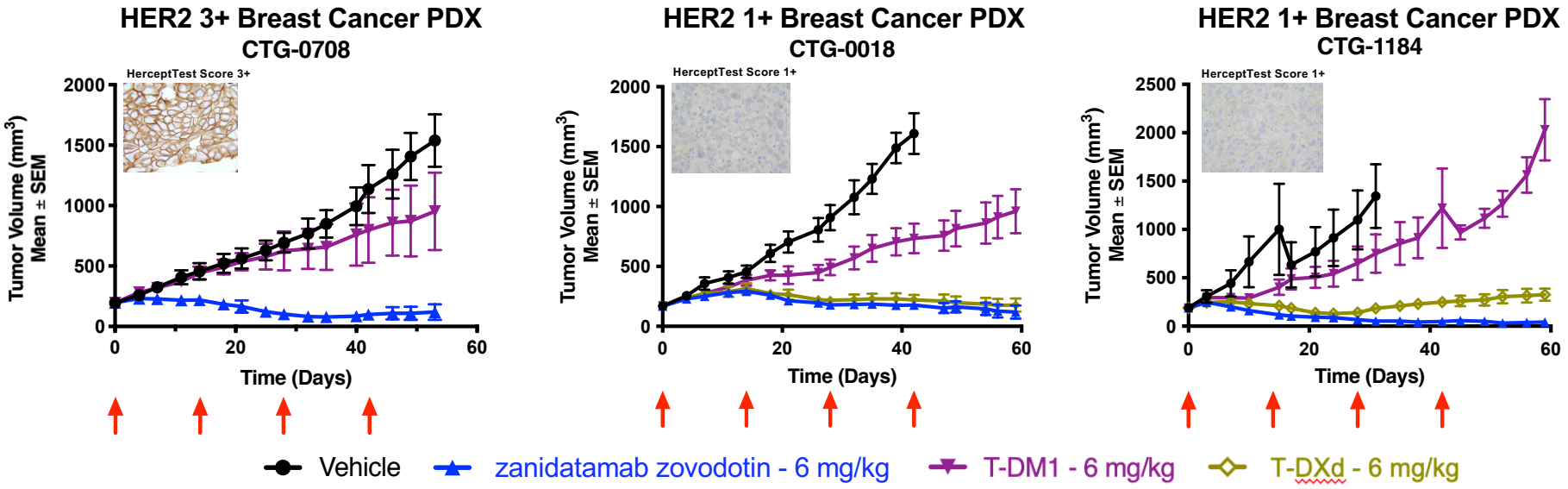
Zanidatamab Zovodotin has Potent Cytotoxic Activity Against HER2-Expressing Breast Cancer Cells in Vitro

Zanidatamab zovodotin potently kills breast cancer cells with EC50 values in the sub-nanomolar range

Cell Type	Cell Line	HER2 Receptors/cell	EC50 (nM)		
			ZW49	ZW25	ZD02044
Breast cancer	HCC1954	6,000,000	0.04	No activity	4.7
	SK-BR-3	3,660,000	0.04	0.31	10
	JIMT-1	526,000	0.50	No activity	44
	ZR-75-1	378,00	0.58	No activity	20
	MDA-MB-175	287,000	0.62	1.96	14
	T-47D	206,000	No activity	No activity	62
	MDA-MB-468	0	No activity	No activity	27

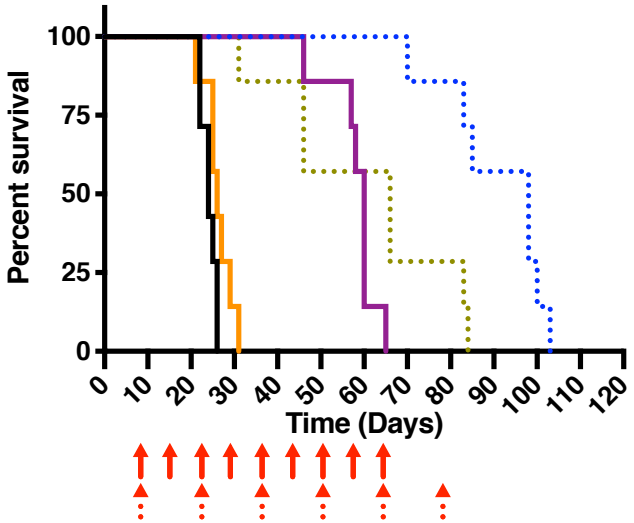
Zanidatamab Zovodotin Demonstrates Anti-Tumor Activity in HER2-High and HER2-Low Patient Derived Xenograft Models of Breast Cancer

Zanidatamab zovodotin demonstrates superior anti-tumor activity compared to T-DM1 and similar anti-tumor activity to T-DXd in PDX models of breast cancer



- N=6/cohort
- IV dosing on Day 0, 14, 28, and 42

Zanidatamab Zovodotin Improved Survival in a HER2-High Breast Cancer Brain Metastasis Model in Comparison to T-Exatecan Derivative and T-DM1



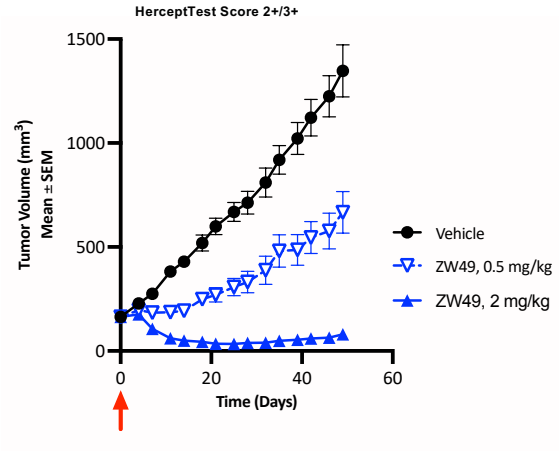
- Vehicle
- Control Conjugate, 6 mg/kg qw
- T-DM1, 6 mg/kg qw
- T-DXd, 6 mg/kg q2w
- zanidatamab zovodotin, 6 mg/kg q2w

- BT-474 HER2 positive ductal breast carcinoma
- Animals intracranially implanted on Day 0
- N=7/cohort
- IV dosing commencing on Day 8
  - once weekly (qw) for T-DM1, Control conjugate, and Vehicle
  - once every two weeks for 6 doses (q2wx6) for Zanidatamab zovodotin and T-DXd

Test Article	Dose (mg/kg)	Schedule	Median Survival (days)	p-value compared to T-DM1	p-value compared to T-DXd
Zanidatamab zovodotin	6	q2wx6	98	0.00323	0.0224
T-DXd	6	q2wx6	66	0.396	N/A
T-DM1	6	qw	60	N/A	0.396

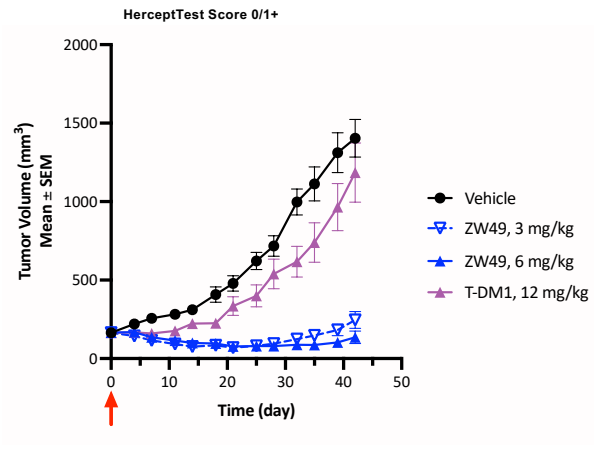
Zanidatamab Zovodotin is Active in Solid Tumor Models Representing Gastric Cancer, Pancreatic Cancer, and Ovarian Cancer

HER2 3+ Gastric Cancer CDX NCI-N87



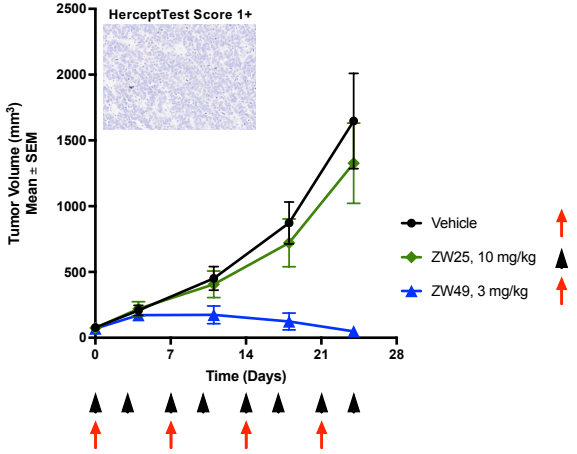
- N=10/cohort
- IV dosing on Day 0

HER2 0/1+ Pancreatic Cancer CDX Capan-1



- N=8/cohort
- IV dosing on Day 0

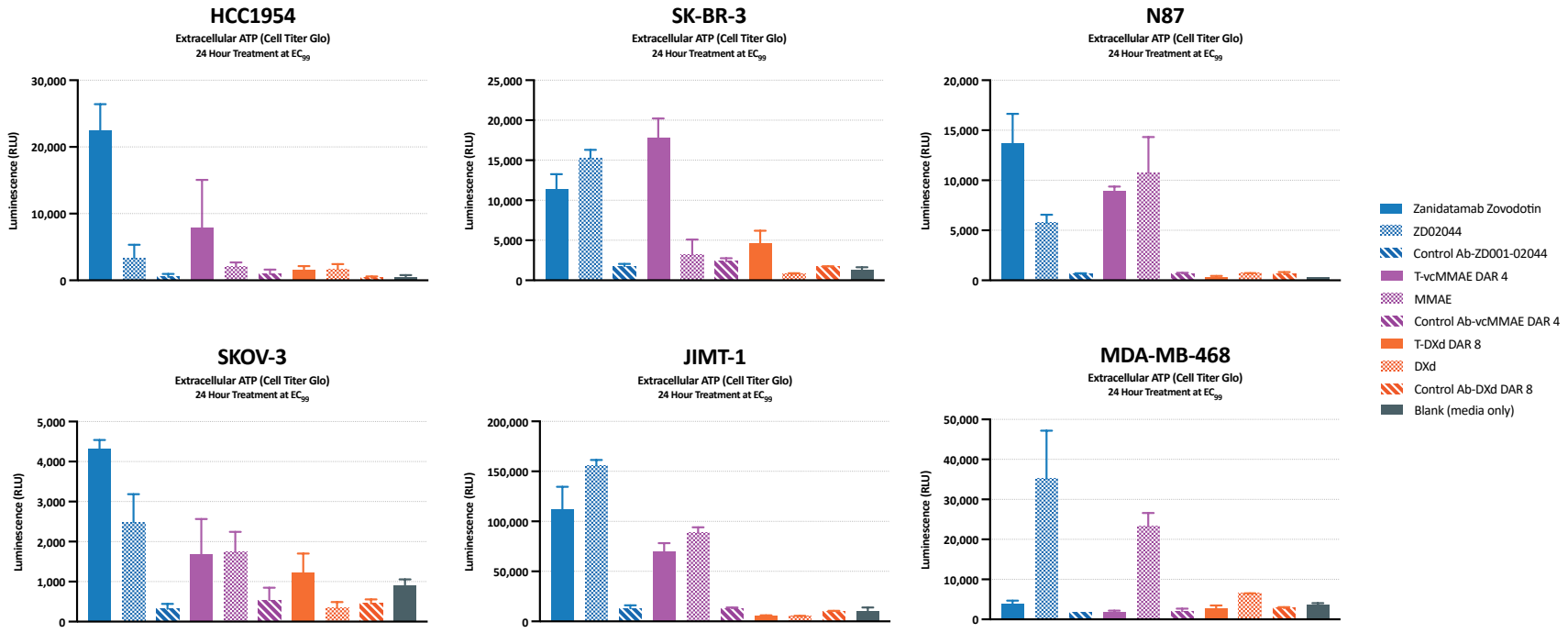
HER2 1+ Ovarian Cancer PDX LTL-654



- N=6/cohort
- IV dosing on Day 0, 7, 14, and 21

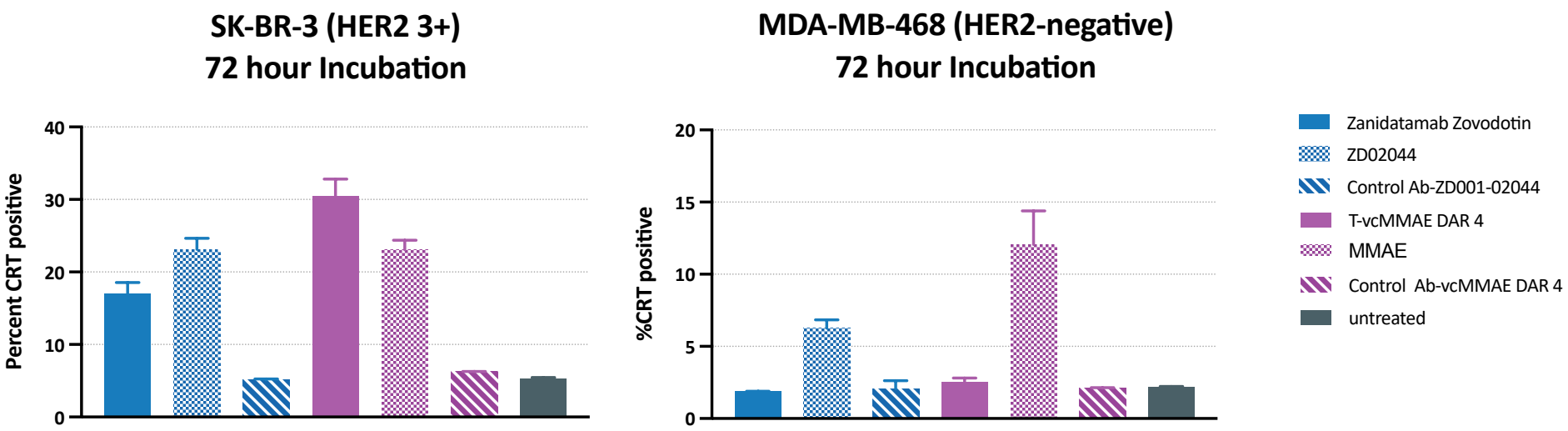
Zanidatamab Zovodotin Induces In Vitro Hallmarks of Immunogenic Cell Death (ICD): Extracellular ATP (eATP)

Zanidatamab zovodotin induces extracellular ATP secretion in a HER2 dependent manner



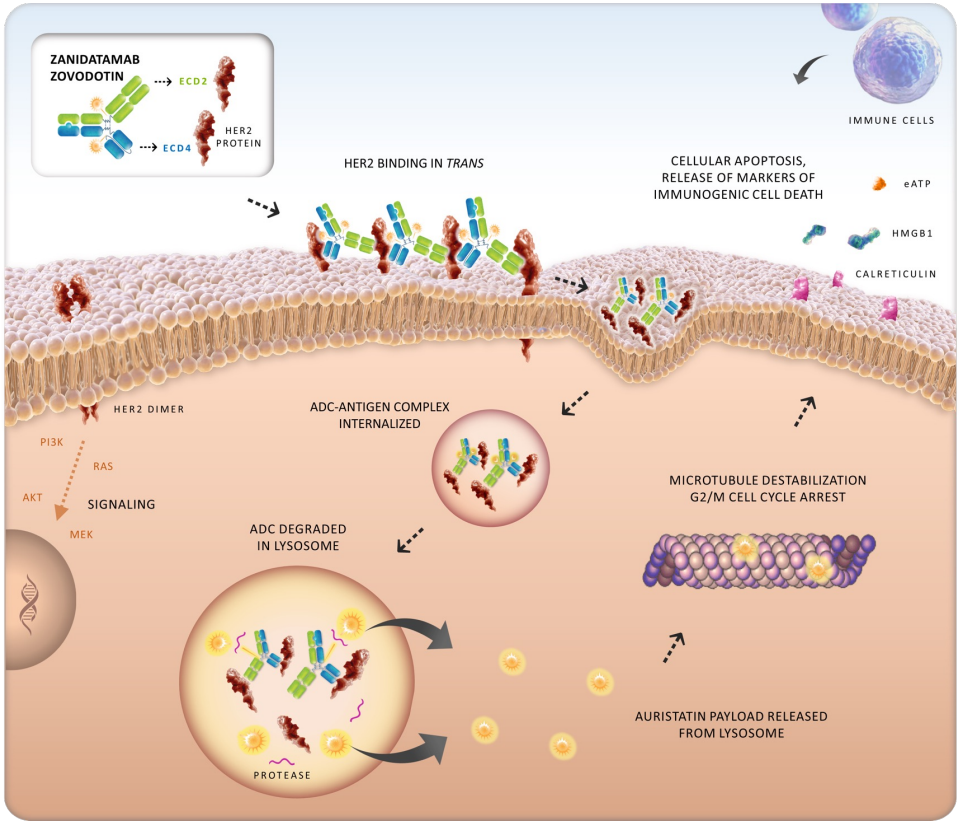
Zanidatamab Zovodotin Induces In Vitro Hallmarks of Immunogenic Cell Death (ICD): Cell Surface Calreticulin

Zanidatamab zovodotin induces cell surface calreticulin in a HER2 dependent manner



Zanidatamab Zovodotin: A Biparatopic ADC for HER2-Targeted Therapy

- IgG1-like biparatopic antibody backbone directed against ECD4 & ECD2 of HER2
- Antibody sequence identical to zanidatamab
- Proprietary auristatin payload covalently linked to the antibody via a protease-cleavable linker
- Average drug-to-antibody ratio (DAR) of 2
- Biparatopic antibody induced internalization followed by auristatin-mediated cytotoxicity and immunogenic cell death

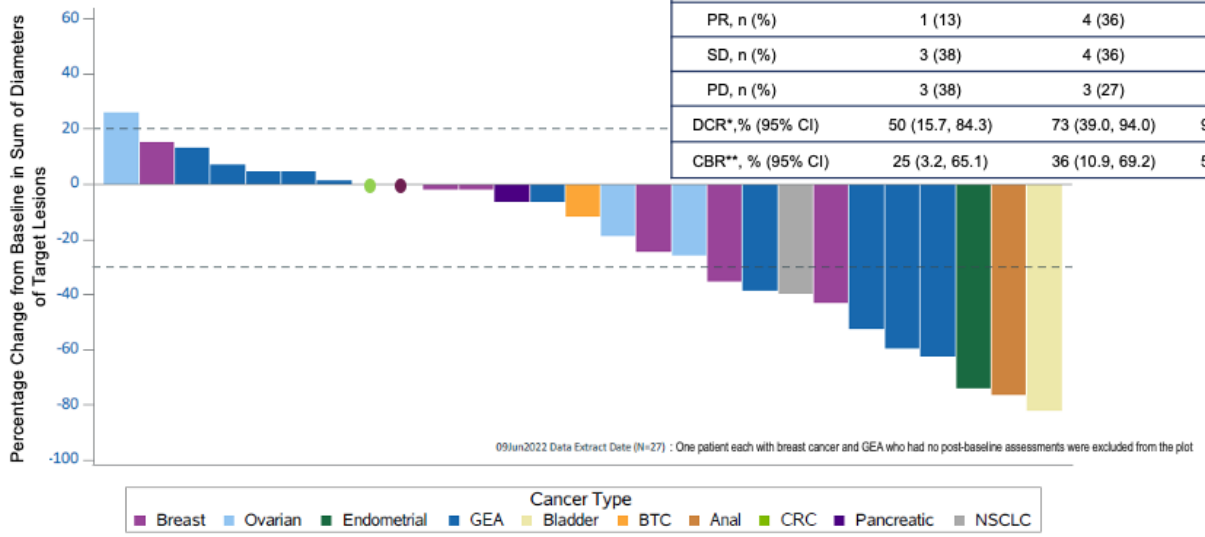


ADC, antibody-drug conjugate; AKT, serine-threonine protein kinase family; eATP, extracellular adenosine 5'-triphosphate; ECD, extracellular domain; HER, human epidermal growth factor receptor; HMGB1, high mobility group box 1; G2/M, second gap phase/mitotic phase; MEK, mitogen-activated protein kinase kinase; PI3K, phosphatidylinositol 3-kinase; RAS, rat sarcoma pathway

Zanidatamab Zovodotin Monotherapy Shows Anti-Tumor Activity in Patients with Advanced HER2-Expressing Cancers

Change in Sum of Target Lesions: Patients with HER2+ Cancers treated with ZW49 at 2.5 mg/kg Q3W (DE + DX)

	Breast (n=8)	GEA (n=11)	All Other (n=10)	Total (N=29)#
cORR, % (95% CI)	13 (0.3, 52.7)	36 (10.9, 69.2)	40 (12.2, 73.8)	31 (15.3, 50.8)
PR, n (%)	1 (13)	4 (36)	4 (40)	9 (31)
SD, n (%)	3 (38)	4 (36)	5 (50)	12 (41)
PD, n (%)	3 (38)	3 (27)	1 (10)	7 (24)
DCR*,% (95% CI)	50 (15.7, 84.3)	73 (39.0, 94.0)	90 (55.5, 99.7)	72 (52.8, 87.3)
CBR**, % (95% CI)	25 (3.2, 65.1)	36 (10.9, 69.2)	50 (18.7, 81.3)	38 (20.7, 57.7)



#One patient of the 30 treated at 2.5 mg/kg Q3W was HER2 negative per central review and not included. *DCR = CR, PR, or SD. **CBR = SD ≥ 24 weeks or best overall response of CR or PR.
BTC = biliary tract cancer; CBR = clinical benefit rate; cORR = confirmed objective response rate; CRC = colorectal cancer; DCR = disease control rate; DE = dose escalation; DX = dose expansion; GEA = gastroesophageal adenocarcinoma; NSCLC = non-small cell lung cancer; PD = progressive disease; PR = partial response; Q3W = once every 3 weeks; SD = stable disease

PARIS 2022 ESMO congress

Dr. Komal Jhaveri

Zanidatamab Zovodotin: Differentiated HER2-Targeted ADC

Zanidatamab zovodotin

has shown single-agent activity in multiple tumor types with a differentiated tolerability profile amongst other HER2-targeted ADCs and has multiple pathways for development

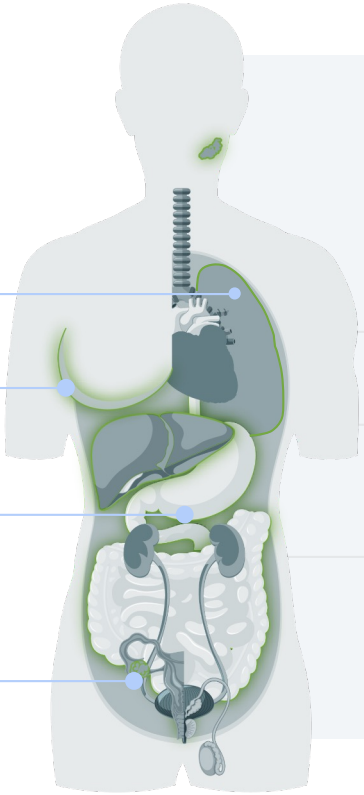
Non-Small Cell Lung Cancer (NSCLC)
HER2-amplified NSCLC

Metastatic Breast Cancer (mBC)
HER2-positive mBC after progression with T-DXd; HER2-low mBC

Gastroesophageal Adenocarcinoma (GEA)
Previously treated HER2-positive GEA

Colorectal Cancer (CRC)
HER2-amplified CRC

Pan Tumor Indications
Ovarian and endometrial



DIFFERENTIATED STRATEGY

Differentiated tolerability profile with no interstitial lung disease, no significant neuropathy, and no significant neutropenia noted to date

Single-agent activity across multiple HER2-expressing tumor types

Potential combinability with standards of care across indications, with no known overlapping toxicities

Incrementally staged investment in clinical development to **preserve and maintain** cash runway

Phase 1 data (NCT03821233) as reported at ESMO | Sep 2022

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zymeworks
Thank You