PARIS 2022 ESMO congress

Preliminary Results From a Phase 1 Study Using the Bispecific, Human Epidermal Growth Factor 2 (HER2)-targeting Antibody-drug Conjugate (ADC) Zanidatamab Zovodotin (ZW49) in Solid Cancers

Komal Jhaveri,[1] Hyo S. Han,[2] Efrat Dotan,[3] Do-Youn Oh,[4] Cristiano Ferrario,[5] Anthony Tolcher,[6] Keun-Wook Lee,[7] Chih-Yi (Andy) Liao,[8] Yoon-Koo Kang,[9] Yeul Hong Kim,[10] Erika Hamilton,[11] Alexander Spira,[12] Niki Patel,[13] Christos S Karapetis,[14] Sun Young Rha,[15] Lisa Boyken,[16] Joseph Woolery,[16] Philippe L Bedard[17]

Komal Jhaveri, MD, FACP

[1]Memorial Sloan Kettering Cancer Center, New York, NY, US; [2]Moffitt Cancer Center, Tampa, FL, US; [3]Fox Chase Cancer Center, Philadelphia, PA, US; [4]Seoul National University Hospital, Seoul, South Korea; [5]Jewish General Hospital, Montreal, QC, Canada; [6]NEXT Oncology, San Antonio, TX, US; [7]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; [8]University of Chicago Medicine, Chicago, IL, US; [9]Asan Medical Center, Seoul, South Korea; [10]Korea University Anam Hospital, Seoul, South Korea; [11]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, US;[12]Virginia Cancer Specialists, PC, Fairfax, VA, US; [13]City of Hope, Duarte, CA, US; [14]Flinders Medical Centre and Flinders University, Adelaide, Australia;[15]Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; [16]Zymeworks Inc., Vancouver, BC, Canada; [17]Princess Margaret Cancer Centre, Toronto, ON, Canada

Declaration of Interests

Komal Jhaveri, MD, FACP

Consultant/Advisory Board:

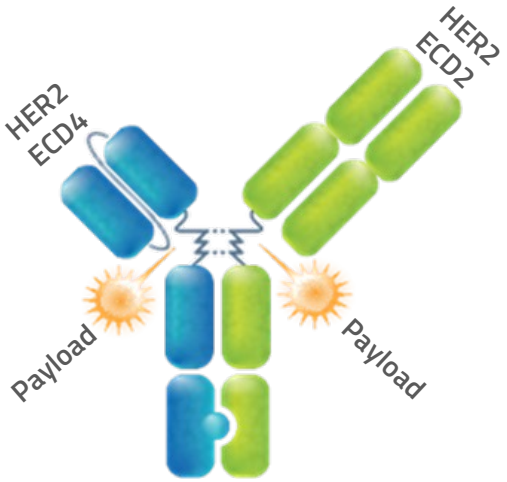
Novartis, Pfizer, BMS, Jounce Therapeutics, Taiho Oncology, Genentech/Roche, AbbVie, Eisai, Astra Zeneca, Blueprint Medicine, Daiichi Sankyo, Seattle Genetics, Lilly/Loxo Oncology, Sun Pharma Advanced Research Company Ltd

Research Funding:

Novartis, Genentech, Astra Zeneca, ADC Therapeutics, Novita Pharmaceuticals, Debio Pharmaceuticals, Pfizer, Lilly Pharmaceuticals, Zymeworks, Gilead, PUMA Biotechnology, Merck Pharmaceuticals

Zanidatamab Zovodotin (ZW49): Anti-HER2 Bispecific ADC

- Immunoglobulin 1-like antibody backbone directed against extracellular domain 4 (ECD4) & ECD2 of HER2
  - Antibody sequence is identical to zanidatamab (ZW25)
- Proprietary auristatin payload covalently linked via a protease cleavable valine-citruline linker
  - Average drug to antibody ratio (DAR) = 2
- Antibody-induced internalization with increased toxin-mediated cytotoxicity and immunogenic cell death

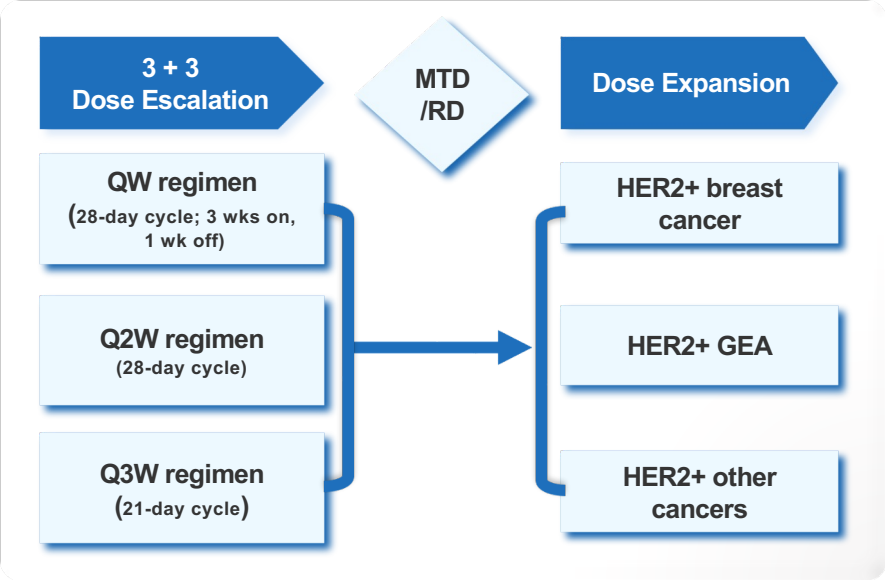


ZW49

This ongoing, first-in-human, dose escalation (DE) and dose expansion (DX) study (NCT03821233) is evaluating safety and efficacy of ZW49 in patients with HER2-expressing solid cancers

Methods

Study Design



For DE, HER2+ was defined as IHC3+, IHC2+/FISH+ or amplification (+) per FISH or NGS per local testing.
For DX, HER2+ was defined as IHC3+ or IHC2+/FISH+ per central testing.
DE = dose escalation; DX = dose expansion; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor 2; FISH = fluorescence *in situ* hybridization; GEA = gastroesophageal adenocarcinoma; IHC = immunohistochemistry; MTD = maximum tolerated dose; NGS = next-generation sequencing; QW = once every week; Q2W = once every 2 weeks; Q3W = once every 3 weeks; wk = week; RD = recommended dose

Primary Objectives

- To determine the maximum tolerated dose (MTD)/recommended dose (RD) of ZW49
- To characterize the safety and tolerability of ZW49

Secondary Objectives

To evaluate the anti-tumor activity of ZW49 in HER2-expressing cancers

Key Eligibility Criteria

- Refractory HER2-expressing or amplified cancers
  - Patients with HER2+ breast cancer must have received trastuzumab, pertuzumab, and T-DM1
  - Patients with HER2+ GEA must have received trastuzumab
- ECOG performance status 0 or 1

Baseline Disease Characteristics & Disposition

	DE (n=52)	DX (n=25)	Total (N = 77)
Median age (range), years	58.5 (24 – 83)	59 (32 – 75)	59 (24 – 83)
Female, n (%)	32 (62)	13 (52)	45 (58)
Race, n (%)			
White	33 (63)	11 (44)	44 (57)
Asian	11 (21)	12 (48)	23 (30)
Other*	8 (15)	2 (8)	10 (13)
ECOG PS 1, n (%)	36 (69)	15 (60)	51 (66)
Primary diagnosis, n (%)			
GEA	13 (25)	8 (32)	21 (27)
Breast Cancer	10 (19)	7 (28)	17 (22)
All other	29 (56)	10 (40)	39 (51)
HER2 Status, n (%)**			
IHC3+	26 (50)	19 (76)	45 (58)
IHC2+/FISH+	6 (12)	6 (24)	12 (16)
Patients with prior HER2-targeted therapies, n (%)	37 (71)	16 (64)	53 (69)
Median prior systemic regimens in metastatic setting, n (range)	3 (1 – 16)	3 (1 – 13)	3 (1 – 16)

*Other included: Black or African American and Not Reported/Unknown/Multiple.

Data cutoff: 09 Jun 2022

**HER2 status for the remaining 20 patients included: ERBB2 Gene Amp. = 17 (22%) and FISH amp. = 3 (4%)

DE = dose escalation; DX = dose expansion; ECOG PS = Eastern Cooperative Oncology Group performance status; FISH = fluorescence *in situ* hybridization; GEA = gastroesophageal adenocarcinoma; IHC = immunohistochemistry

- As of 09 Jun 2022, a total of 77 patients were treated across DE (all patients) and DX (2.5 mg/kg Q3W) parts of the study
  - 9 (12%) continue ZW49 treatment

Treatment-related Adverse Events

Preferred Term	Dose Escalation (DE)										Dose Expansion (DX)	DE+DX	DE+DX
	1 mg/kg QW* (n=4)	1.25 mg/kg QW (n=4)	1.5 mg/kg QW (n=6)	1.75 mg/kg QW** (n=7)	1 mg/kg Q2W* (n=6)	2 mg/kg Q2W* (n=8)	2 mg/kg Q3W (n=6)	2.5 mg/kg Q3W (n=5)	3 mg/kg Q3W (n=6)	Total (n=52)	2.5 mg/kg Q3W (n=25)	2.5 mg/kg Q3W (n=30)	Total (N=77)
TRAE of any Grade in ≥ 20% patients, n (%)													
Any AE	4 (100)	4 (100)	6 (100)	6 (86)	5 (83)	7 (88)	5 (83)	5 (100)	6 (100)	48 (92)	22 (88)	27 (90)	70 (91)
Keratitis	2 (50)	2 (50)	3 (50)	3 (43)	0	4 (50)	2 (33)	3 (60)	4 (67)	23 (44)	10 (40)	13 (43)	33 (43)
Alopecia	2 (50)	1 (25)	4 (67)	0	1 (17)	4 (50)	1 (17)	0	1 (17)	14 (27)	5 (20)	5 (17)	19 (25)
Diarrhoea	3 (75)	0	2 (33)	1 (14)	0	2 (25)	1 (17)	2 (40)	1 (17)	12 (23)	7 (28)	9 (30)	19 (25)
≥ Grade 3 TRAE in ≥ 1 patient, n (%)													
Any AE	0	1 (25)	0	1 (14)	0	2 (25)	0	0	0	4 (8)	5 (20)	5 (17)	9 (12)
Keratitis	0	0	0	1 (14)	0	1 (12)	0	0	0	2 (4)	1 (4)	1 (3)	3 (4)
TR SAEs of any Grade in ≥ 1 patient, n (%)													
Any SAE	0	0	0	0	0	0	1 (17)	0	0	1 (2)	2 (8)	2 (7)	3 (4)
IRR	0	0	0	0	0	0	1 (17)	0	0	1 (2)	1 (4)	1 (3)	2 (3)
ECG QT Prolonged	0	0	0	0	0	0	0	0	0	0	1 (4)	1 (3)	1 (1)

* Includes patients enrolled prior to mandatory ocular prophylaxis.
**One additional patient was enrolled in this cohort to account for a non-DLT evaluable patient.
AE = adverse event; DLT = dose-limiting toxicity; ECG = electrocardiogram; IRR = infusion-related reaction; QT = QT interval; QW = once every week; Q2W = once every 2 weeks; Q3W = once every 3 weeks; TRAE = treatment-related adverse event; SAE = serious adverse event

Data cutoff: 09 Jun 2022

Safety Summary (All Patients)

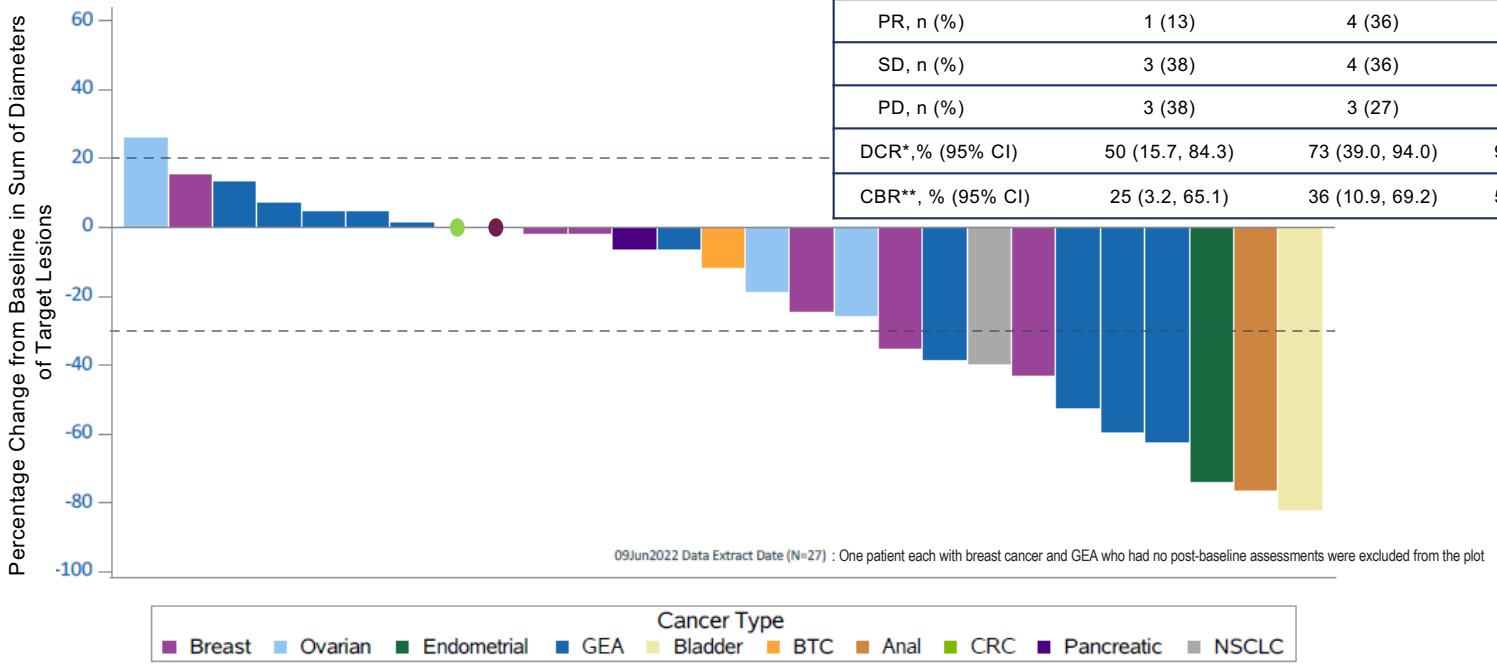
- The MTD has not been reached
- Two dose-limiting toxicities (Grade 2 keratitis > 14 days) were observed in 1 patient each at the 1.75 mg/kg QW (DE) and 2.5 mg/kg Q3W (DX) cohorts
- No interstitial lung disease (ILD) or pneumonitis were reported
- There were no treatment-related deaths
- Treatment-related keratitis was reported in 33 (43%) patients. All keratitis events decreased to Grade 1 or resolved.
    - Mandatory ocular prophylaxis:
        - Prednisolone, tetrahydrozoline (0.05%) or naphazoline (0.012%) or equivalent, and cooling masks
- Dose reduction was required in 16 (21%) patients due to treatment-related AEs* (10 [19%] patients in DE and 6 [24%] patients in DX). These patients continued receiving ZW49 at a reduced dose level.

*12 patients had keratitis (including 2 patients who also reported dry eye) and 1 patient each had an event of infusion-related reaction, punctuate keratitis, prolonged ECG QT, and neutrophil decreased. Data cutoff: 09 Jun 2022

AE = adverse event; DE= dose escalation; DX = dose expansion; ECG = electrocardiogram; MTD = maximum tolerated dose; Q3W = once every 3 weeks; QT = QT interval

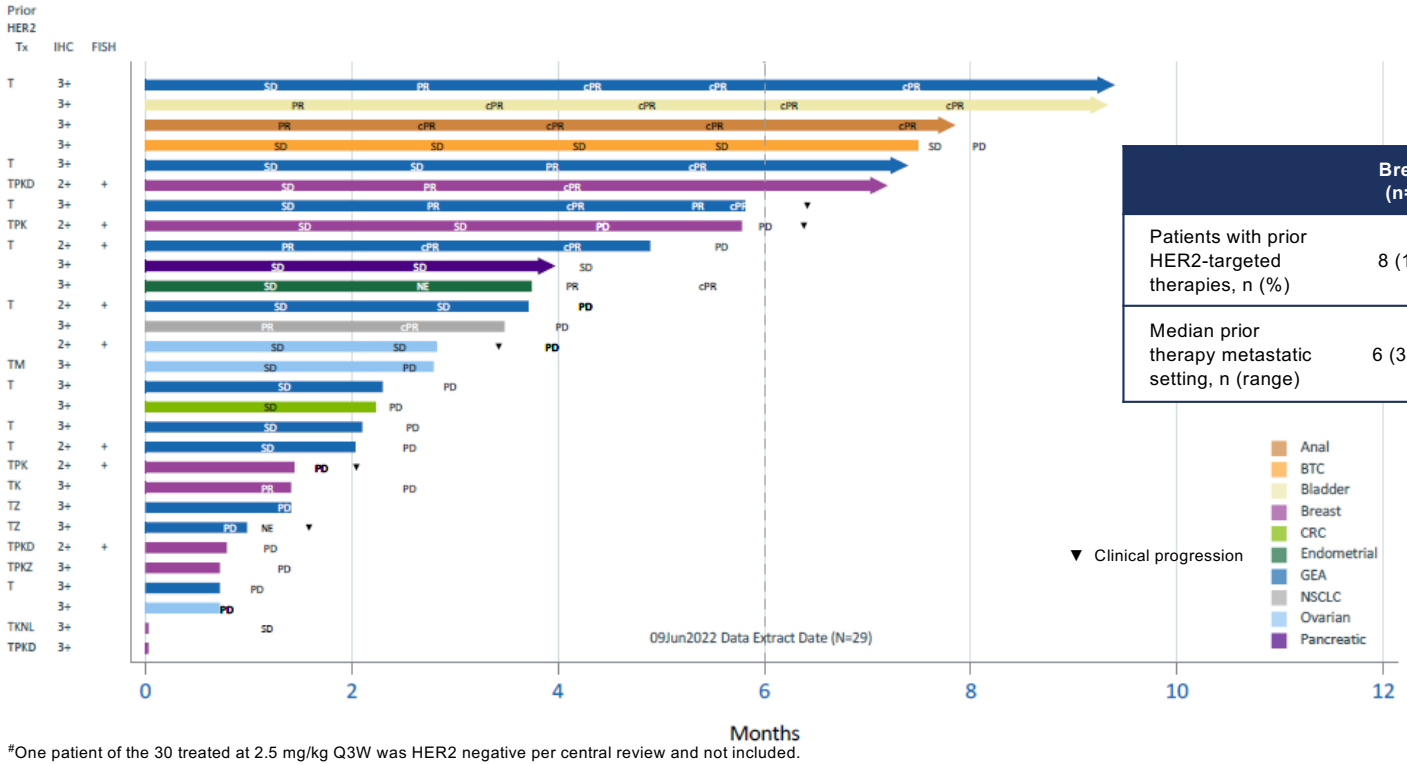
Change in Sum of Target Lesions: Patients with HER2+ Cancers treated with ZW49 at 2.5 mg/kg Q3W (DE + DX)

	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

Treatment Duration: 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)#
Patients with prior HER2-targeted therapies, n (%)	8 (100)	11 (100)	1 (10)	20 (69)
Median prior therapy metastatic setting, n (range)	6 (3, 13)	4 (1, 8)	2 (1, 6)	3 (1, 13)

#One patient of the 30 treated at 2.5 mg/kg Q3W was HER2 negative per central review and not included.

BTC = biliary tract cancer; cPR = confirmed partial response; CRC = colorectal cancer; D = T-DXd; DE = dose escalation; DX = dose expansion; FISH = fluorescence *in situ* hybridization; GEA = gastroesophageal adenocarcinoma; IHC = immunohistochemistry; K = T-DM1; L = lapatinib; M = margetuximab; N = neratinib; NE = not evaluable; NSCLC = non-small cell lung cancer; P = pertuzumab; PD = progressive disease; PR = partial response; Q3W = once every 3 weeks; SD = stable disease; T = trastuzumab; Tx = therapy; U = tucatinib; Z = zanidatamab

PARIS 2022 ESMO congress

Conclusions

- ZW49 has a manageable safety profile (with the majority of AEs Grade 1 or 2 in severity) and demonstrates encouraging single-agent antitumor activity in heavily pretreated patients with HER2+ solid cancers
- Recommended dose(s)
  - QW is still being evaluated
  - 2.5 mg/kg Q3W

Acknowledgements: We sincerely thank all patients and their families. We thank all the investigators, clinical trial researchers, personnel, and staff who contributed to the trial.

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org