

The safety, efficacy and biomarker results of the HER2-targeted bispecific antibody ZW25 in HER2-expressing solid tumors

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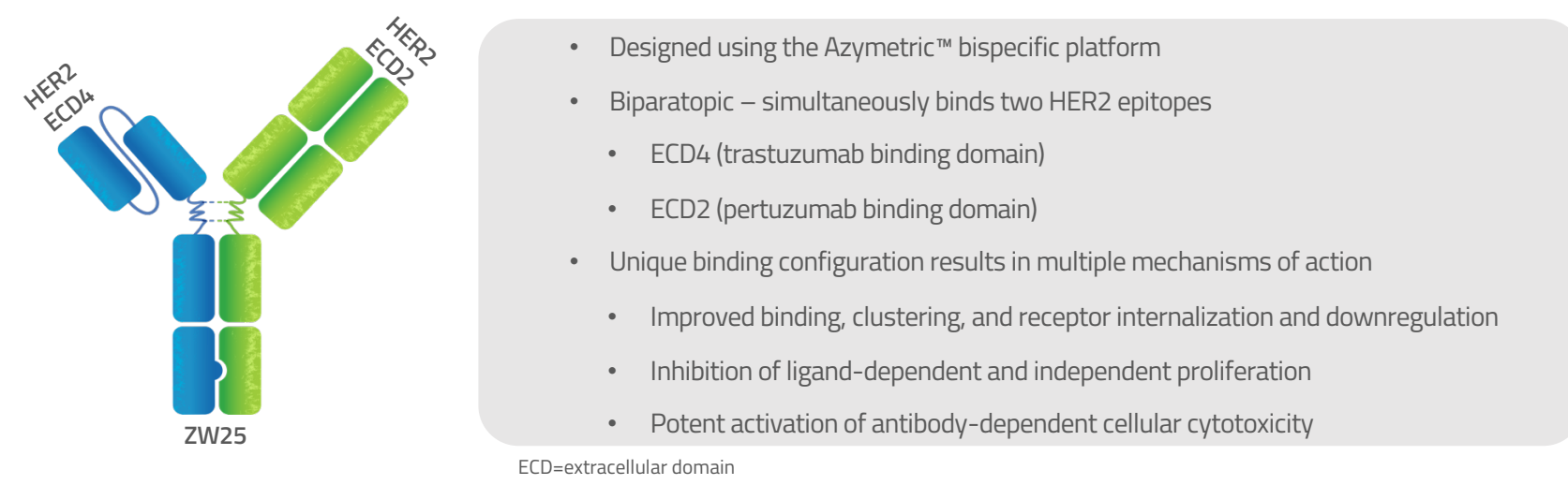
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Background

- Human epidermal growth factor receptor 2 (HER2) is a validated therapeutic target for HER2+ (IHC 3+ or IHC 2+/fluorescence in situ hybridization [FISH]+) breast and gastroesophageal (GEA) cancers
- HER2 overexpression and gene amplification also present in colorectal, biliary tract, gynecologic, and other cancers
- Despite 5 approved therapies for HER2+ breast cancer*, only trastuzumab is approved for HER2+ GEA and there are no approved HER2-targeted agents for other cancers
- ZW25 is a novel HER2-targeted, bispecific antibody designed to address unmet need across a wide range of HER2-expressing cancers

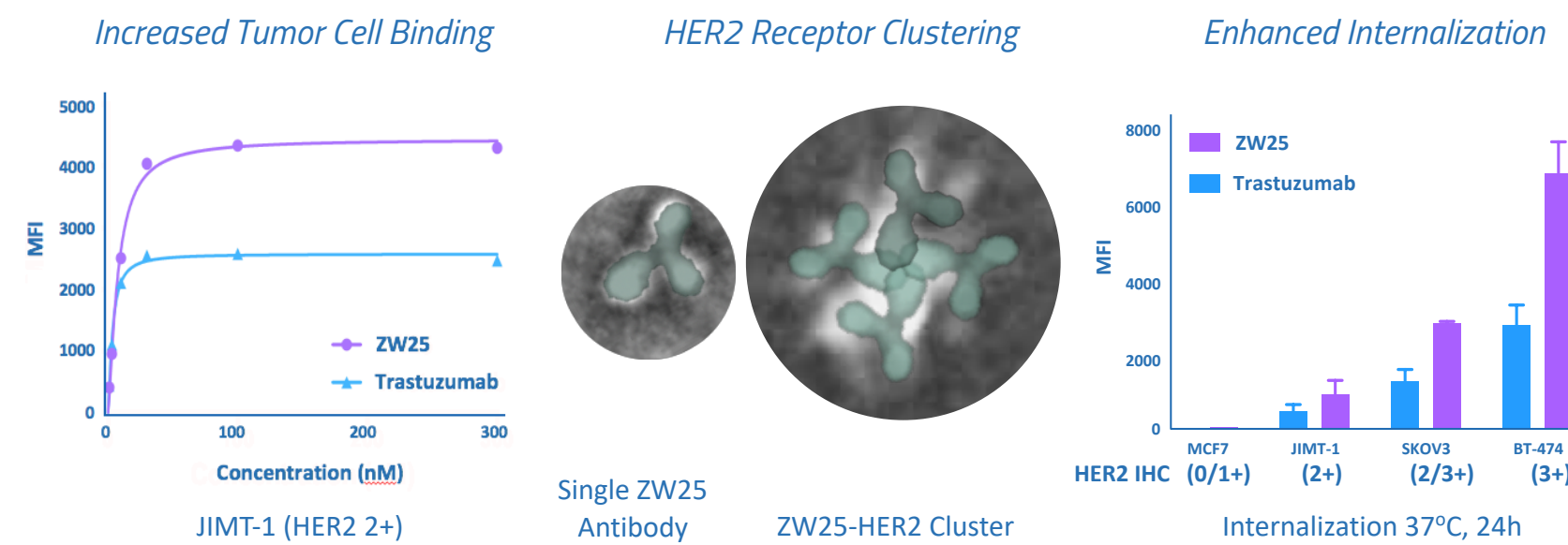
*Approved HER2 agents for breast cancer include trastuzumab, pertuzumab, lapatinib, T-DM1, and neratinib

ZW25: Bispecific HER2-Targeted Antibody



ZW25: Unique Binding Configuration Drives Novel Mechanisms of Action

Enhanced tumor cell binding and internalization relative to trastuzumab



Phase 1 Study of ZW25 in Advanced HER2-Expressing Cancers (NCT02892123)

Key Eligibility Criteria

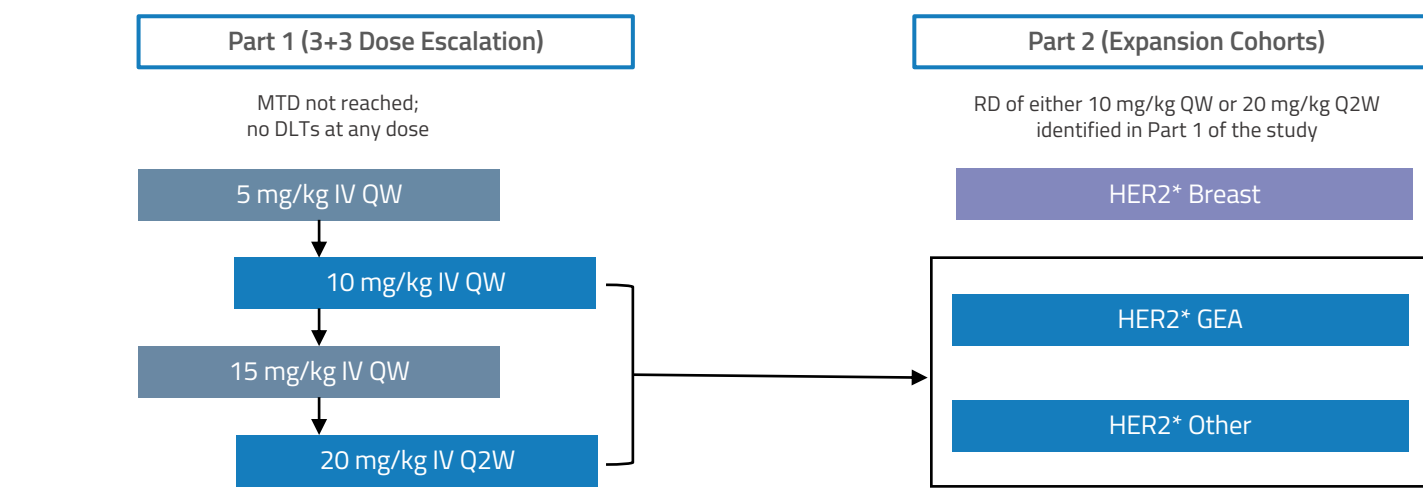
- Advanced HER2-expressing cancer with progression after standard of care therapies
 - GEA patients should have progressed after prior treatment with trastuzumab
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Tissue requirements for HER2 assessment:
 - Part 1: Local assessment of fresh or archived tissue for enrollment followed by retrospective central review
 - Part 2:
 - Fresh tissue sample for central assessment; archival tissue specimen allowed if collected ≤ 6 months prior to enrollment and no intervening HER2-targeted treatment
 - Measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1*

*Eisenhauer EA, et al. Eur J Cancer. 2009;45(2):228-47.

Objectives

- Primary Objectives**
- Determine maximum tolerated dose (MTD) or recommended dose (RD) of ZW25
 - Characterize safety and tolerability
- Secondary Objectives**
- Evaluate potential anti-tumor effects
 - Evaluate potential serum and tumor biomarkers

Study Design



DLT=dose-limiting toxicity; MTD=maximum-tolerated dose; QW=weekly; Q2W=every 2 weeks; RD=recommended dose

*HER2 high (IHC3+ or IHC2+/FISH+) or intermediate (IHC2+/FISH+) for breast cancer and GEA; HER2 high for other tumors

Assessments

- Tumor response assessments per RECIST 1.1 (every 8 weeks)
- Blood samples for circulating tumor DNA (ctDNA) (pre-dose Cycle 1 Day 1) and other markers

Safety and efficacy results for patients with solid tumors other than breast cancer who received 10 mg/kg QW or 20 mg/kg Q2W ZW25 in either Part 1 or Part 2 of the study presented here

Patient Characteristics

Median of 4 prior systemic regimens, including HER2-targeted therapies

	BTC (N=9)	CRC (N=13)	GEA (N=23)	Other* (N=13)	Total (N=58)
Male (n, [%])	4 (44)	7 (54)	19 (83)	7 (38)	35 (60)
Median age (range)	61 (45–74)	61 (36–71)	62 (26–81)	58 (27–75)	61.0 (26–81)
Baseline ECOG 0 (n, [%])	0	4 (31)	2 (9)	2 (15)	8 (14)
1 (n, [%])	9 (100)	9 (69)	21 (91)	11 (85)	50 (86)
Median prior systemic regimens (range)	4.5 (1–8)	6 (3–10)	3.5 (1–10)	4 (1–7)	4 (1–10)
HER2 status per central assessment† (IHC 3+ or IHC 2+/FISH+) (n, [%])	8 (89)	13 (100)	20 (87)	13 (100)	54 (93)
Prior HER2 therapy (n, [%])	2 (22)	3 (23)	20 (87)	7 (54)	32 (55)
Prior HER2 agents received (n, [%])					
Trastuzumab	2 (22)	3 (23)	20 (87)†	7 (54)	32 (55)
Pertuzumab	0 (0)	2 (15)	0 (0)	4 (31)	6 (10)
T-DM1	0 (0)	1 (8)	1 (4)	3 (23)	5 (9)
Lapatinib	0 (0)	1 (8)	0 (0)	1 (8)	2 (3)
Neratinib	0 (0)	0 (0)	1 (4)	0 (0)	1 (2)

BTC=biliary tract cancer; CRC=colorectal cancer; ECOG=Eastern Cooperative Oncology Group; FISH=fluorescence in situ hybridization; GEA=gastroesophageal adenocarcinoma; IHC=immunohistochemistry

*Adnexal cancer of skin (n=1), cervical (n=1), duodenum (n=1), endometrial (n=3), fallopian tube (n=1), lacrimal gland (n=1), ovarian (n=1), pancreatic (n=2), salivary gland (n=2).

†Four patients (GEA, n=3; BTC, n=1) had no central IHC nor central FISH assessment. Of these four patients, one GEA patient was IHC 3+ (local), another GEA patient was FISH+ (local), and the BTC patient was IHC3+/FISH+ (local). HER2 status is not currently available for one GEA patient.

‡1 additional patient confirmed to have received prior trastuzumab, but data not entered into database.

Treatment-Related Adverse Events*

ZW25 well tolerated as outpatient therapy

	BTC (N=9)	CRC (N=13)	GEA (N=23)	Other (N=13)	Total (N=58)
Grade	Any ≥3	Any ≥3	Any ≥3	Any ≥3	Any ≥3
Any AE (n, %)	5 (56)	0	9 (61)	0	10 (77)
Diarrhea	3 (33)	0	5 (38)	0	8 (62)
Infusion related reaction	2 (22)	0	3 (23)	0	3 (23)
Nausea	0	0	3 (23)	0	2 (15)
Dermatitis acneiform	0	0	2 (15)	0	2 (15)
Fatigue	1 (11)	0	1 (8)	0	1 (8)

AE=adverse events

*Occurring in ≥ 10% of patients within a cancer type who received 10 mg/kg QW or 20 mg/kg Q2W ZW25

- All treatment-related adverse events (AEs) Grade 1 or 2
- One treatment-related serious AE (SAE) of Grade 2 fatigue in BTC patient
- No ZW25-related >10% changes in left ventricular ejection fraction (LVEF)

Response in RECIST 1.1 Evaluable Patients*

	BTC (N=6)	CRC (N=11)	GEA (N=19)	Other† (N=10)	Total (N=46)
Partial response (PR)	4 (66.7)	4 (36.4)	6 (31.6)	2 (20)	16 (34.8)
Stable disease (SD)	1 (16.7)	5 (45.5)	5 (26.3)	6 (60)	17 (36.9)
Progressive disease (PD)	1 (16.7)	2 (18.2)	8 (42.1)	2 (20)	13 (28.2)
Disease control‡	5 (83.3)	9 (81.8)	11 (57.9)	8 (80)	33 (71.7)

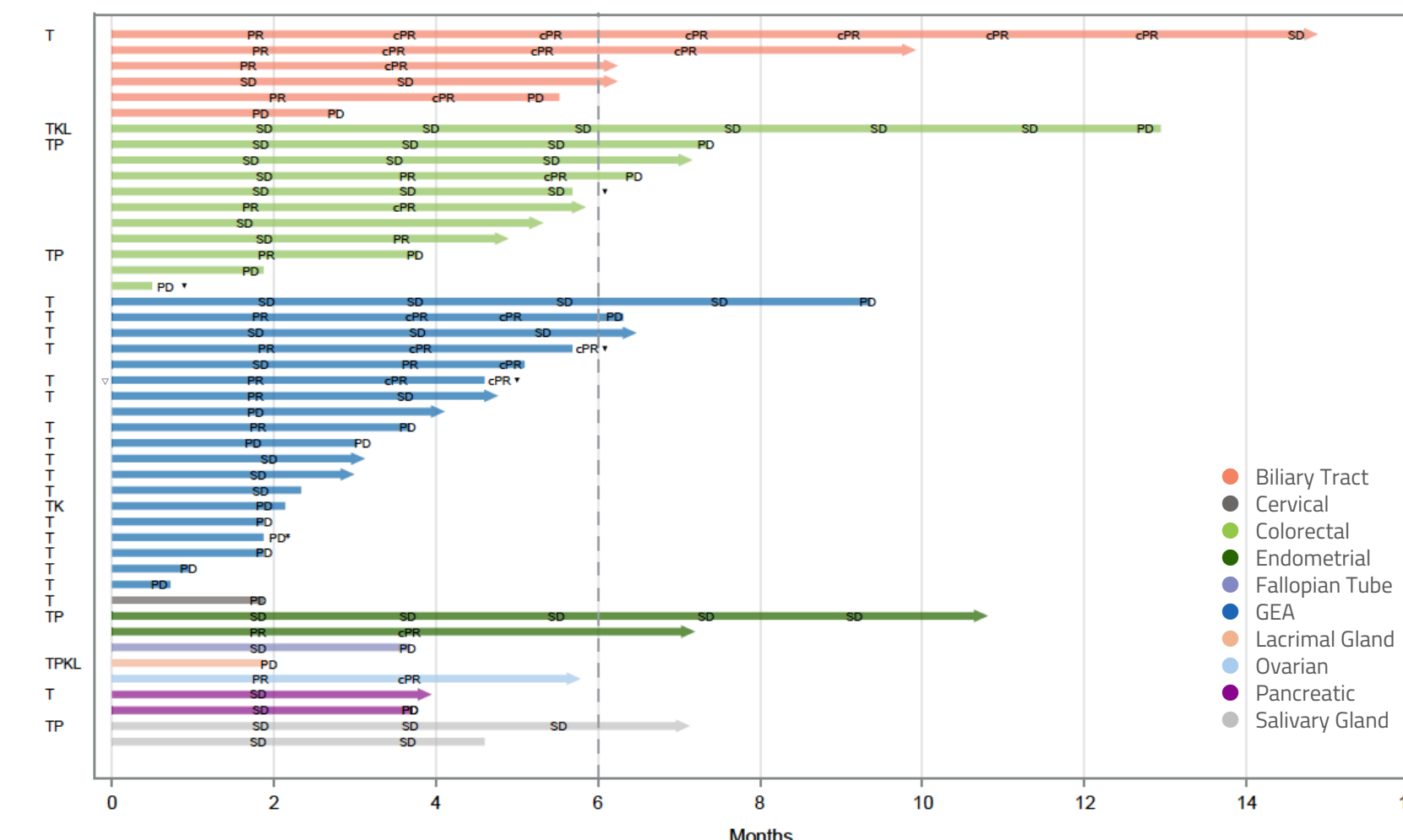
*Response evaluable includes all patients with measurable disease who had at least one evaluable, post-baseline disease assessment (per RECIST 1.1) or discontinued study treatment prior to reassessment due to death from any cause or clinical progression (response imputed as PD for the analysis). Twelve patients considered non-evaluable: too early (n=9), no measurable disease (n=3).

†Cervical (n=1), endometrial (n=2), fallopian tube (n=1), lacrimal gland (n=1), ovarian (n=1), pancreatic (n=2), salivary gland (n=2).

‡Percent of patients with complete response (CR), partial response (PR), or stable disease (SD) per RECIST version 1.1.

Time on Treatment for Response-Evaluable Patients

Overall median progression-free survival (PFS) 5.2 months (95% CI 3.6, 6.2)



cPR=confirmed partial response; K+T-DL1=Lapatinib; P=pertuzumab; PD=progressive disease; PR=partial response; SD=stable disease; T=trastuzumab

*Clinical progression

†This patient was FISH+ and IHC 2+. All others were FISH+ or IHC3+.

*Patient died and did not have any post-baseline tumor assessments.

Exploratory Analysis of Pre-treatment ctDNA

Dx Modality	FISH (Gold Standard)		Tumor	N with both FISH and ctDNA
	+	-		
ctDNA	+	4	BTC	5
	-	1	CRC	5
			Other	3
			Total	29

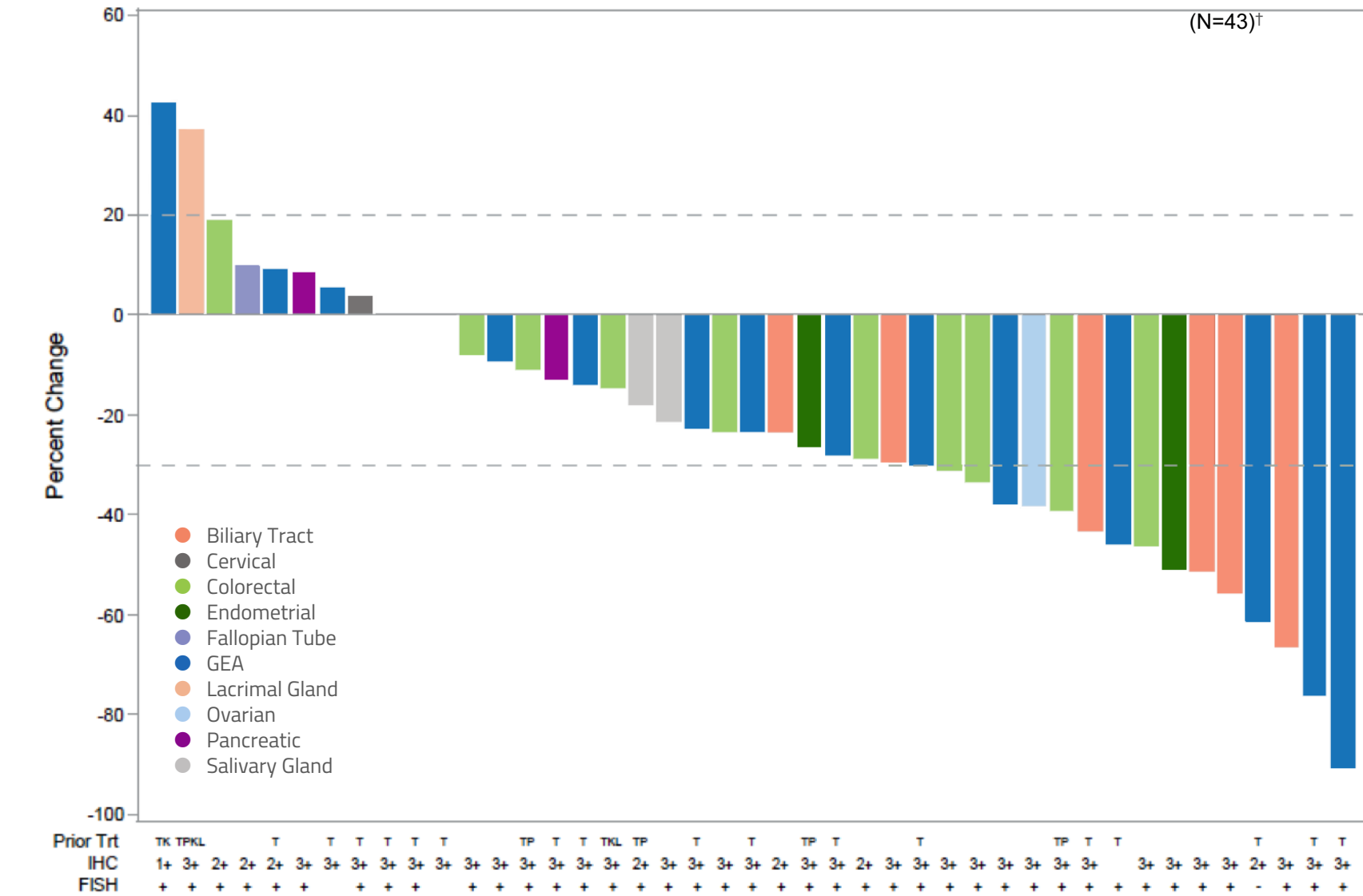
Statistics	Value	95% CI
Sensitivity	100%	85% – 100%
Specificity	20%	0.5% – 71.6%
Positive Predictive Value	85.7%	79.5% – 90.3%
Negative Predictive Value	100%	100% – 100%
Concordance	86.2%	68.3% – 96.1%

BTC=biliary tract cancer; CI=confidence interval; CRC=colorectal cancer; ctDNA=circulating tumor DNA; Dx=diagnostic; FISH=fluorescence in situ hybridization; GEA=gastroesophageal adenocarcinoma

- HER2 ctDNA copy numbers (cutoff 2.2) and mutational allele fractions (MAF) assessed by Guardant 360 73 gene panel (CNV, SNV and Indel)
- High concordance for ctDNA and FISH in pre-selected HER2+ patient population
- Current data do not demonstrate an association of MAF with duration on treatment or objective response (p = 0.28, p = 0.17 respectively).

Change in Target Lesions Across Cancer Types

Majority of response-evaluable patients had a decrease in target lesions



† 13 of the 46 response-evaluable patients had no post-baseline disease assessment of their target lesions

Conclusions

- ZW25 is well tolerated with promising single-agent anti-tumor activity in heavily pre-treated patients
 - All treatment-related AEs Grade 1 or 2
 - Durable disease control and confirmed responses
 - Objective response rate of 67% in BTC, >30% in CRC and GEA
 - These data demonstrate the potential of ZW25 to provide a cytotoxin-free treatment for patients with high unmet medical need
- Next Steps**
- Initiation of single agent Phase 2 study in HER2+ BTC
 - Continue expansion of single agent data set for CRC, Gynecological, and other cancers
 - Enrolling patients into Phase 2 study of ZW25 in combination with standard of care chemotherapy in first-line HER2+ GEA (NCT03929666)

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