

Single Agent Activity of ZW25, a HER2-Targeted Bispecific Antibody, in HER2-Expressing Gastroesophageal and Other Cancers

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‘MOLECULAR TARGETS AND CANCER THERAPEUTICS’

30TH EORTC-NCI-AACR SYMPOSIUM

DUBLIN, IRELAND

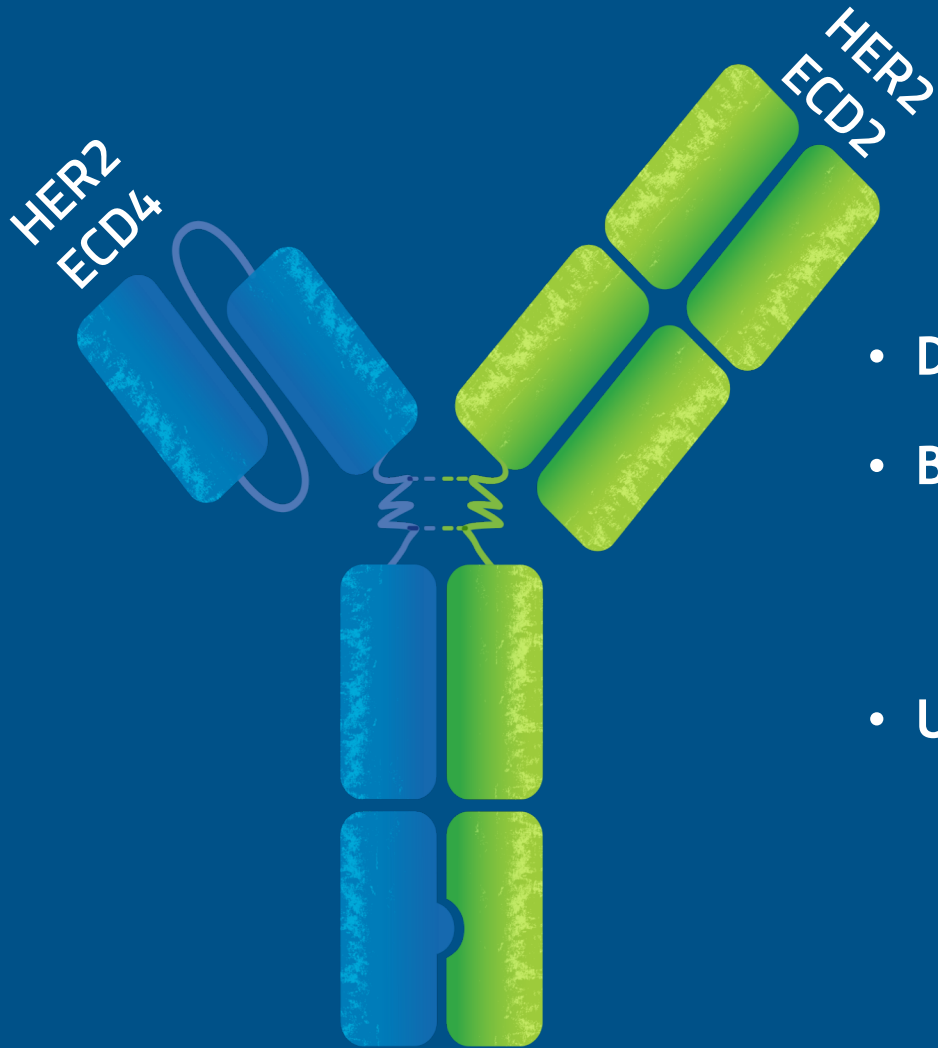
Presented by Dr. Murali Beeram

Unmet Need in HER2-Expressing Cancers

- HER2 is overexpressed across a diverse range of cancers, including breast, gastroesophageal (GEA), colorectal, biliary, salivary gland, and other tumors¹
- The magnitude of benefit obtained with HER2-targeted therapy in breast cancer has not translated to other cancers
- In GEA, the only approved HER2 agent is trastuzumab for 1st line metastatic disease, with no approved agents for later lines of treatment
- No approved HER2-targeted agents for other cancers
- Challenges: overcome resistance mechanisms and minimize toxicity

¹Yan *et al* Cancer Metastasis Rev (2015)

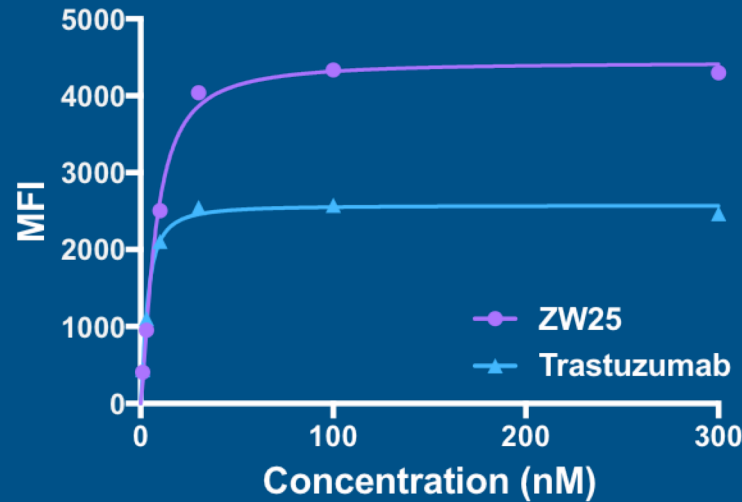
ZW25: Azymetric™ Bispecific HER2-Targeted Antibody



- Designed using the Azymetric™ bispecific platform
- Biparatopic - simultaneously binds two HER2 epitopes
 - ECD4 (trastuzumab binding domain)
 - ECD2 (pertuzumab binding domain)
- Unique binding geometry drives novel mechanisms of action

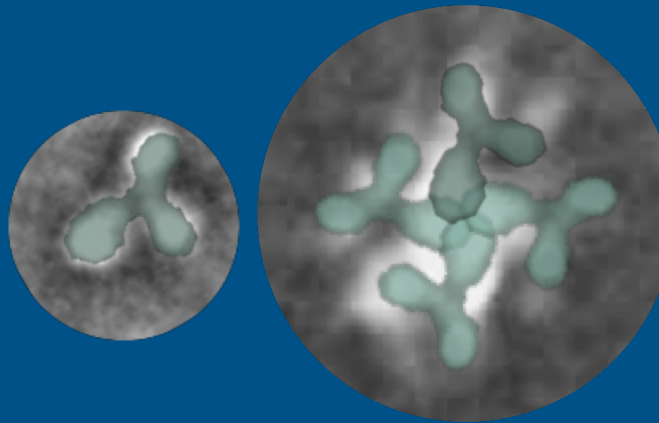
Unique Binding Geometry Drives Additional Mechanisms of Action

Increased Tumor Cell Binding



JIMT-1 (HER2 2+)

HER2 Receptor Clustering

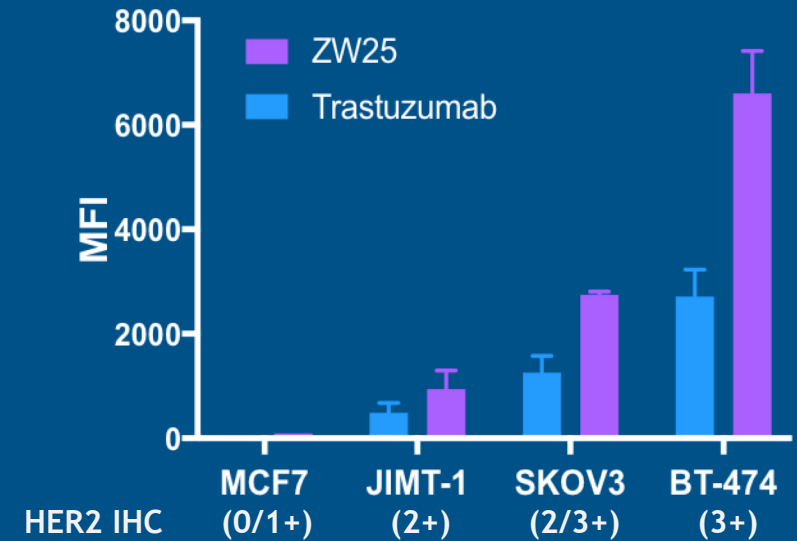


Single ZW25
Antibody

ZW25-HER2
Cluster

Transmission Electron Microscopy

Enhanced Internalization



Internalization 37°C, 24h

Phase 1 Study Design

Recommended dose and schedule: 20 mg/kg every two weeks

Eligibility

- Advanced HER2-expressing cancer with progression after standard of care therapies
- ECOG performance status 0 or 1
- No known untreated brain metastases
- Tumor biopsy for assessment (local and central) of HER2 status

Assessments

- Safety including LVEF and PK
- Tumor response per RECIST 1.1 (q 8 weeks)

Part 1 3+3 Dose Escalation

MTD not reached
No DLTs at any dose

5 mg/kg IV QW



10 mg/kg IV QW



15 mg/kg IV QW



20 mg/kg IV Q2W



Part 2¹ Expansion Cohorts

HER2-Breast

HER2-GEA

HER2-Basket

¹Enrollment ongoing. Data presented is snapshot from unlocked database 16 October 2018 of all GEA and basket patients treated at RD and subject to change.

Patient Characteristics

Heavily pretreated with median 3 prior systemic regimens; 71% of pts with prior trastuzumab

	GEA n=10	CRC n=5	Other ¹ n=9	Total n=24
Male:Female (n)	8:2	2:3	3:6	13:11
Median age (range)	68 (35-75)	63 (53-71)	63 (27-71)	63 (27-75)
Baseline ECOG (n; 0:1)	1:9	3:2	1:8	5:19
Median prior systemic regimens (range)	4 (4-7)	3 (0-10)	3 (0-10)	3 (0-10)
HER2 status per central assessment ² (n; HER2 High Yes:No)	6:2	5:0	8:0	19:2
Prior HER2 therapy Yes:No (n)	10:0	3:2	4:5	17:7
Prior HER2 agents received (n)				
Trastuzumab	10	3	4	17 (71%)
Pertuzumab	0	1	2	3 (13%)
T-DM1	1	1	1	3 (13%)
Lapatinib	0	1	0	1 (4%)

¹Gall bladder (3); cholangiocarcinoma (1); cervical (1); fallopian tube (1); endometrial (1), adnexal ca. of skin (1); salivary gland (1).

²3 patients without biopsy for central review. Central review based on most recent new or archived biopsy available. All GEA patients historically considered to be HER2 High (IHC 3+ and/or FISH+) based on local evaluation.

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Safety Overview

- Majority of all adverse events (AEs) Grade 1 or 2
- Most common AEs diarrhoea, infusion reaction, and nausea, all Grade 1 or 2
- No treatment-related serious AEs
- No Grade 4 or 5 AEs
- No LVEF decreases $\geq 10\%$ during treatment

Incidence of Most Common Treatment Emergent Adverse Events

	GEA (n=10)				CRC (n=5)				Other (n=9)				Total (n=24)			
Grade	Any	1	2	3	Any	1	2	3	Any	1	2	3	Any	1	2	3
Adverse Event	n (%)				n (%)				n (%)				n (%)			
Diarrhoea	9 (90)	6	3	0	3 (60)	0	3	0	6 (67)	4	2	0	18 (75)	10	8	0
Infusion reaction	8 (80)	0	8	0	2 (40)	0	2	0	4 (44)	0	4	0	14 (58)	0	14	0
Nausea	4 (40)	3	1	0	2 (40)	1	1	0	0	0	0	0	6 (25)	4	2	0
Cough	1 (10)	1	0	0	2 (40)	0	2	0	2 (22)	2	0	0	5 (21)	3	2	0
Anorexia	3 (30)	1	0	2	1 (20)	1	0	0	1 (11)	1	0	0	5 (21)	3	0	2
Dermatitis Acneiform	3 (30)	3	0	0	2 (40)	2	0	0	0	0	0	0	5 (21)	5	0	0
Fatigue	4 (40)	1	2	1	1 (20)	0	1	0	0	0	0	0	5 (21)	1	3	1

Treatment emergent adverse events reported in $\geq 20\%$ of patients regardless of relationship to study drug.
Data snapshot from unlocked database 16 October 2018 and subject to change.

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PK Overview

- Consistent with previously reported results¹, PK dose proportional and non-linear, with steady state reached by end of Cycle 2
 - $T_{1/2}$ 10 mg/kg QW ~123 hrs; 20 mg/kg Q2W ~150 hrs
- Overall exposure similar for 10 mg/kg QW and 20 mg/kg Q2W
- Trough values maintained above minimum predicted efficacious level

¹ASCO 2018 Abstract 2500 Meric-Bernstam *et al.*

Response in RECIST 1.1 Evaluable Patients

Median PFS 6.21 months (95% CI 1.94-9.33)¹

	GEA (n=10)	CRC (n=5)	Other (n=9)	Total (n=24)
Response evaluable (n) ²	8	4	5	17
Partial response (PR)	4 (50%)	1 (25%)	2 (40%)	7 (41%) ³
Stable disease (SD)	2 (25%)	3 (75%)	2 (40%)	7 (41%)
Progressive disease (PD)	2 (25%)	0	1 (20%)	3 (18%)
Disease control (PR + SD)	6 (75%)	4 (100%)	4 (80%)	14 (82%)

¹Median PFS based on safety evaluable population (n=24). Patients without re-staging scan, documented radiologic progression or death were censored in calculation of PFS

²Response evaluable defined as measurable disease and at least one re-staging scan. Not evaluable for response: no measurable disease (n=2; GEA, Other); PD due to brain met during C1 (n=1; GEA); too early (n=4; CRC 1, Other 3).

³Confirmed PR (6)

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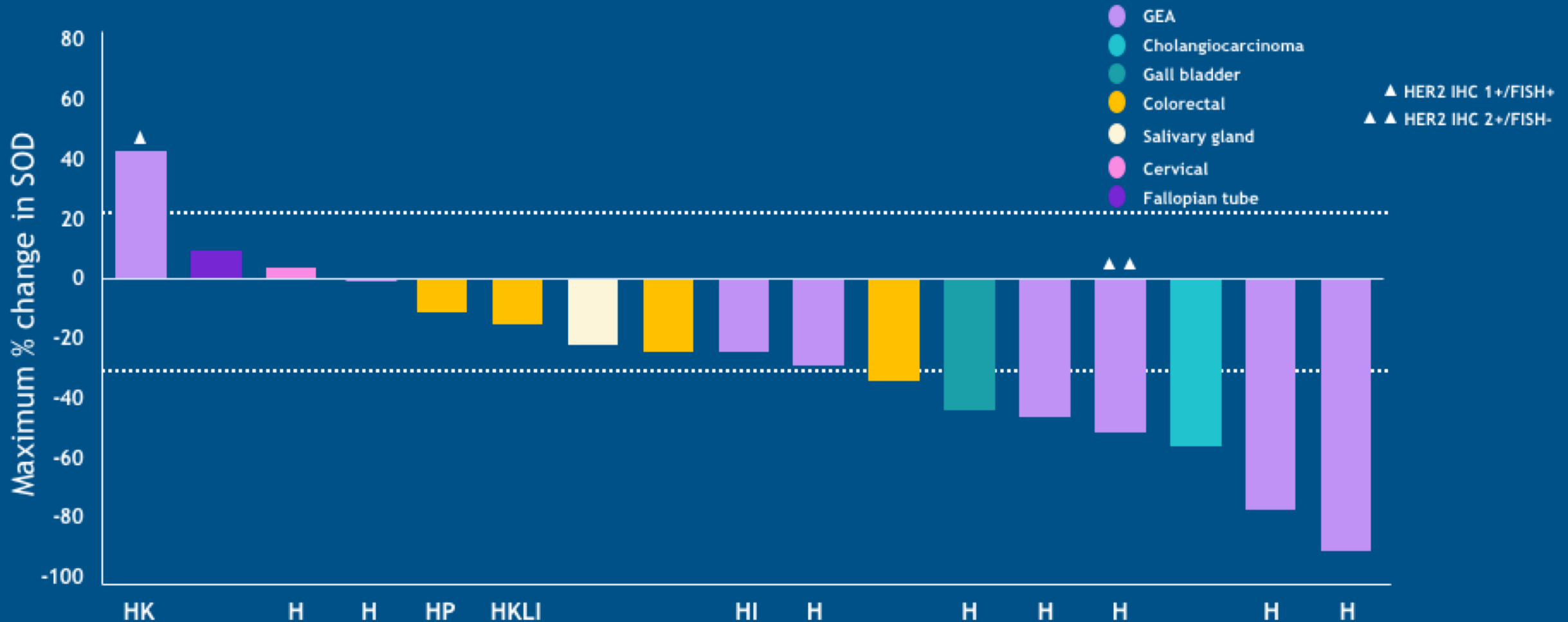
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Change in Target Lesions Across Cancer Types

Decrease in target lesions in majority of patients with measurable disease¹



¹Patients with measurable disease and at least one repeat scan. Maximum change regardless of best response. No measurable disease (n=2); no restaging scan due to brain met at Day 14 (n=1); too early (n=4).
H: trastuzumab; P: pertuzumab; K: T-DM1; L: lapatinib; I: investigational HER2 agent

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Durable disease control disease in heavily pretreated patients

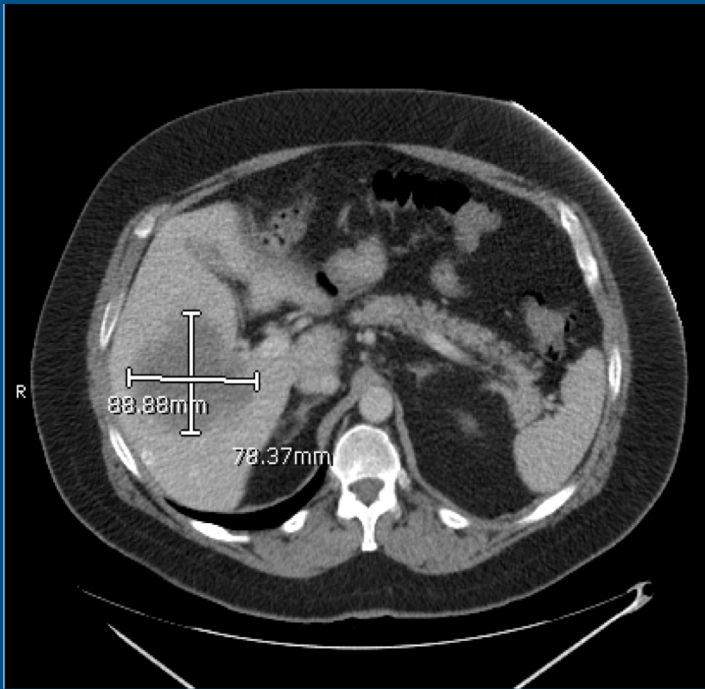


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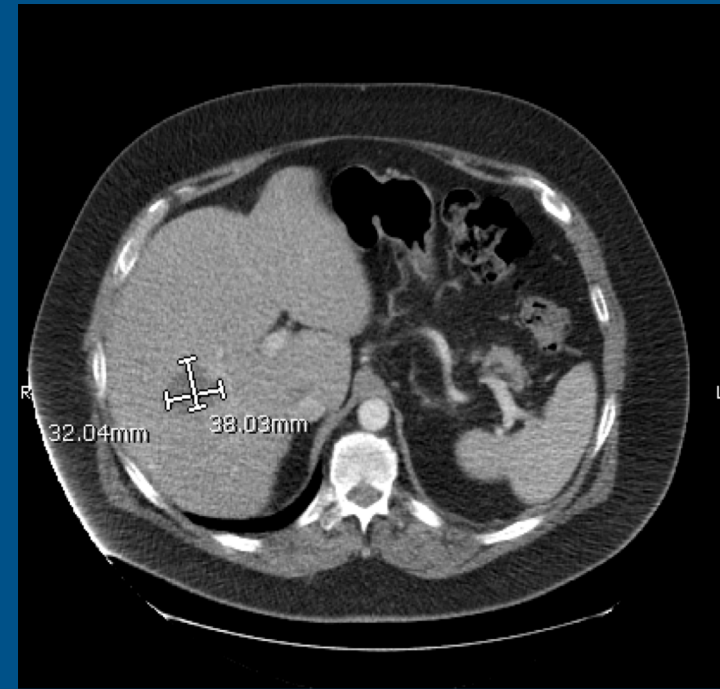
Colorectal Cancer: Anti-Tumor Activity

- 53 year old male with HER2 High metastatic colorectal cancer
- Progression after prior FOLFOX, FOLFIRI, trastuzumab and pertuzumab
- Response at time of first restaging scan with decrease in liver metastasis

Baseline scan



End Cycle 2



Scan obtained after 16 October 2018 data cutoff. Patient not included in waterfall or ORR, and censored in PFS analysis

Summary of ZW25 Single Agent Experience

- Well tolerated in heavily pretreated patients with majority of AEs Grade 1 or 2 and no treatment-related SAEs
- Durable single agent cytotoxin-free anti-tumor activity across a range of HER2-expressing cancers, including GEA, CRC, and biliary cancers
 - ORR 41%, disease control rate 82%, median PFS >6 months
- Data support further development as single agent and in combination with other agents

ZW25 Ongoing Activities and Opportunities

- Exploring opportunities to develop ZW25 as single agent therapy in HER2 gene amplified tumor agnostic setting
- Evaluating combination with chemotherapy and other agents to enable use in earlier lines of therapy for breast, GEA and other cancers

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