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

M. Beeram¹, E. Hamilton², D. Hanna³, J. Ajani⁴, M. Blum Murphy⁴, J. Bendell², A. El-Khoueiry³, D. Hausman⁵, H.J. Lenz³, A. Patnaik¹, M. Press³, G. Rowse⁵, J. Thimmarayappa⁵, F. Meric-Bernstam⁴

¹The START Center For Cancer Care, San Antonio, TX
²Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN
³University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA
⁴The University of Texas MD Anderson Cancer Center, Houston, TX
⁵Zymeworks Inc., Vancouver, BC
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 tumors\(^1\)
- 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 1\(^{st}\) 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

\(^1\)Yan 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**

![Graph showing tumor cell binding with concentration (nM)]

**HER2 Receptor Clustering**

- **Single ZW25 Antibody**
- **ZW25-HER2 Cluster**

**Enhanced Internalization**

- **Transmission Electron Microscopy**
- **Internalization 37°C, 24h**

**HER2 IHC**

- **MCF7 (0/1+)**
- **JIMT-1 (2+)**
- **SKOV3 (2/3+)**
- **BT474 (3+)**

**JIMT-1 (HER2 2+)**

**Table:**

<table>
<thead>
<tr>
<th>HER2 IHC</th>
<th>MCF7 (0/1+)</th>
<th>JIMT-1 (2+)</th>
<th>SKOV3 (2/3+)</th>
<th>BT474 (3+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MFI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ZW25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 2

1 Expansion Cohorts

1 Enrollment 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**

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

---

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

2 3 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.
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 ≥ 10% during treatment
Incidence of Most Common Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th>Grade</th>
<th>GEA (n=10)</th>
<th>CRC (n=5)</th>
<th>Other (n=9)</th>
<th>Total (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>9 (90)</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>8 (80)</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (40)</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (10)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (30)</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Dermatitis Acneiform</td>
<td>3 (30)</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (40)</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

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

• Consistent with previously reported results\(^1\), 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

\(^1\)ASCO 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*

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

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)

*Data snapshot from unlocked database 16 October 2018 and subject to change.*
Change in Target Lesions Across Cancer Types

Decrease in target lesions in majority of patients with measurable disease\(^1\)

1 Patients 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

Data snapshot from unlocked database 16 October 2018 and subject to change.
Time on Treatment
Durable disease control disease in heavily pretreated patients

H: trastuzumab; P: pertuzumab; K: T-DM1; L: lapatinib; I: investigational HER2 agent; cPR: confirmed partial response.

Data snapshot from unlocked database 16 October 2018 and subject to change.
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
Acknowledgements

We sincerely thank all patients and their families

Thanks to all investigators and clinical trial personnel

MD Anderson Cancer Center, Houston  Hoag Family Cancer Institute, Los Angeles
Sarah Cannon Research Institute, Nashville  USC Norris Cancer Center, Los Angeles
START, San Antonio  Rush University Medical Center, Chicago
University of Colorado Cancer Center, Denver  Northwest Medical Specialties, Tacoma
UAB Comprehensive Cancer Center, Birmingham  Jewish General Hospital, Montreal
Ottawa Hospital Cancer Centre, Ottawa  Princess Margaret Cancer Center, Toronto

Thanks also to Ms. Ivonne Villalobos at USC Medical Center Pathology Lab for support of HER2 testing