HER2 T cell dependent bispecific antibody (HER2-TDB) for treatment of HER2 positive breast cancer

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Antitumor efficacy of HER2-TDB

Teemu Juntila
Genentech Inc.
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T cell dependent bispecific antibody (TDB) platform

- Produced using modular “knobs into holes” technology
- Effector functions removed (E. coli production / N297A)
- Minimal immunogenic potential
- PK is similar to conventional IgG1

Ridgeway...Carter. 1996 Proc. Engineering
Production of the TDBs

• Production in E. coli or CHO (with effector mutation)
• Standard purification methods
• Industrial scale (ontuzumab)
• High quality drug substance (No aggregation or αCD3-αCD3 homo dimers)

Rationale for developing HER2-TDB for HER2+ breast CA

• HER2 is a clinically validated target
• HER2+ cancer is not cured
• Novel MOA - may be effective in chemoresistant tumors

T-DM1 median PFS 9.6 mo (EMILIA)  T-DM1 median OS 31 mo (EMILIA)
4D5-TDB is more potent than 2C4 and 7C2-TDBs

<table>
<thead>
<tr>
<th>HER2-TDB</th>
<th>KD (nM)</th>
</tr>
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<tbody>
<tr>
<td>4D5</td>
<td>0.4</td>
</tr>
<tr>
<td>2C4</td>
<td>2.0</td>
</tr>
<tr>
<td>7C2</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*Small ECD size and proximity of epitope to membrane correlate with activity*

4D5 = Trastuzumab, 2C4 = Pertuzumab

T. Juntila, X. Chen, M. Dennis

TDB mechanism of action

No ADCC activity

Target dependent killing

Induces T cell proliferation

CD3+ cell fold change

Teemu Junttila, Ji Li
Pharmacokinetic profile of HER2-TDB

- Single 10 mg/kg IV dose in non-binding species (Rat)
- Slow clearance and expected long in vivo half-life

### HER2-TDB vs. Trastuzumab

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HER2-TDB</th>
<th>Trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (mL/day/kg)</td>
<td>10 ± 2</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>AUC (day*ug/mL)</td>
<td>1328 ± 247</td>
<td>1553 ± 176</td>
</tr>
<tr>
<td>C_max (ug/mL)</td>
<td>377 ± 31</td>
<td>314 ± 41</td>
</tr>
<tr>
<td>V_t (mL/kg)</td>
<td>33 ± 3</td>
<td>40 ± 5</td>
</tr>
<tr>
<td>HL_beta (Day)</td>
<td>7 ± 1</td>
<td>10 ± 1</td>
</tr>
</tbody>
</table>

Extremely potent & broad range activity

- EC_{50} 1-10 pM in 24h viability assay
- Only 10-500 HER2 occupied at EC_{50} (= 0.01-1%)

Teemu Juntila
**HER2-TDB kills T-DM1 resistant cells**

**Resistance mechanisms of T-DM1**

- Increased expression of drug efflux pumps
- Reduced HER2 expression
- Parallel growth factor signaling
- Up-regulated pro-survival signals
  
  ↑Bcl-2  ↑PTEN  ↑DUSP6  ↑CARPP32

Gail Phillips lab

**HER2-TDB sensitivity**

Viability (% CTRL)

![Graph showing HER2-TDB sensitivity](image)

EC_{50} 1.6 pM

EC_{50} 1.7 pM

Ginny Li, Gail Phillips, Ji Li

**Tumor regression in treatment of MMTV huHER2 GEMM**

**Vehicle**

**HER2-TDB**

![Graph showing tumor regression](image)

> 1000 mm³ tumors regress

- **Model:** MMTV-huHER2 GEMM (not allograft tumors)
- **TDB:** m4D5-2C11 (mlgG2)
- **Dose:** 0.5 mg/kg weekly (x5) IV

Clark, Wang, Dela Cruz, Totpal, Juntila T, Juntila M
Robust PD response

- CD45+, CD8+ and IFNγ+CD8+ cells increase in tumor (detectable at 4h)

**Response to treatment**

Vehicle  HER2-TDB

**Effect of HER2-TDB on TILs**

- CD45+ p<0.01
- CD8+ 0.0002

TIL data: 6D post 0.5 mg/kg HER2-TDB dose

Ji Li, Robyn Clark, Bu-Er Wang

Transient anti-tumor activity in treatment of syngeneic tumors

**Tumor Model:** CT26-HER2
HER2-TDB: 4D5:omCD3(2C11)
Dose: 0.5 mg/kg weekly (x5) IV

Vehicle  HER2-TDB

**Tumor vol (mm³)**

Day

M. Hristopoulos, K. Tolpal, T. Jurttila
Does PD-1/PD-L1 signaling inhibit TDB activity?

- Cellular analysis of CT26-HER2 tumors

Ji Li

MMTV-huHER2 tumors are PD-L1 negative
PD-L1 expression by tumor cell may affect TDB activity

- PD-L1-expression in target cells inhibits TDB activity
- Potential diagnostic for TDB activity
- Mechanistic rationale for combining HER2-TDB with anti-PD-L1

Ji Li

HER2-TDB anti-PDL1 combination is effective in treatment of CT26-HER2 tumors

- Combination of TDB and anti-PD-L1: Enhanced inhibition of tumor growth, increased response rates, durable responses

Tumor Model: CT26-HER2
- α-PDL1: 25A1 (DANA, tw13)
- HER2-TDB: 4D5-SP34 (mAb22a DANG, qwa3)

Rebny Clark, Maria-Hristopoulos, Klara Tolpet, Teemu Junttila
Target expression based therapeutic index for HER2-TDB

- HER2 amplified cells are significantly more sensitive vs. cells expressing low/normal levels of HER2
  → Therapeutic index
- Next: Evaluate safety of the HER2-TDB using appropriate preclinical models.

Teemu Junttila, Ji Li

Key messages

TDBs induce polyclonal T cell response to tumor cells

Full-length IgG1 bispecific format has favourable drug-like properties

HER2-TDB has impressive anti-tumor activity
  - pM activity in broad range of HER2+ cells
  - MOA effective for cells insensitive to HER2 targeted therapies and chemo
  - Induces regression of large MMTV-huHER2 tumors

PD-1/PD-L1 signaling restricts activity of bispecific T cell recruiting ABs
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