Trastuzumab-DM1 (T-DM1) Antibody-Drug Conjugate
Bridging Targeted Therapy and Conventional Chemotherapy

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Cancer Targeting – the Magic Bullet?

Transform Cancer Treatment by Optimizing the Therapeutic Window

- Develop new drug to bridge the specificity of targeted therapy and the potent cyto-reduction effect of conventional therapy with the goal of increasing efficacy and minimizing toxicity
- Antibody drug conjugate (ADC) – the magic bullet?
The Concept of Antibody-Drug Conjugate (ADC)

- ADC is a monoclonal antibody conjugated with a highly potent cytotoxic drug.
- ADCs preferentially deliver highly potent cytotoxic agents to tumor cells via tumor-specific and/or overexpressed cell surface antigens with the goal of:
  - Increasing cytotoxic drug delivery to tumor.
  - Reducing normal tissue drug exposure.

**Increased drug delivery**

**Reduced normal tissue drug exposure**

**Improved therapeutic window**

Cell surface-expressed antigen (e.g. HER2)

Targeted delivery

HER2-positive tumor cell
Critical Considerations for Developing a Successful ADC

- Adequate PK profile
  - Low immunogenicity
- Cytotoxic agent - highly potent; proven MOA
- Linker - suitable stability to deliver ADC to target
- Monoclonal antibody – high affinity and selectivity; therapeutic activity
- Tumor-associated antigen expression high in tumor and low in normal tissue
- Target-dependent cytotoxic activity
- Promotes internalisation of antigen
T-DM1 Structure and Complexity

- Potent cytotoxic agent
- Uncleaveable
- Systemically stable
- Highly specific for tumor targeting

**MW:**
- DM1: 738
- MCC: 238
- Trastuzumab: ~150,000

**Ratio:**
- DM1: 3.5
- MCC: 3.5
- Trastuzumab: 1

**Definitions:**
- DM1 = emtansine = Derivative of Maytansine, a microtubule destabilizing agent
- MCC = maleimidomethyl]cyclohexane-1-carboxylate, a nonreducible thioether linkage
- Trastuzumab = Herceptin
Trastuzumab Biologic Activity

- Blocks downstream HER2 signaling to inhibit proliferation of cells
- Flags HER2 positive tumor cells for destruction via antibody-dependent cell-mediated cytotoxicity (ADCC)

Targeted Intracellular Delivery of DM1

- By exploiting the overexpression of HER2 receptors on tumor cells, and the use of a highly stable MCC linker, T–DM1 preferentially delivers emtansine to these cells, thereby limiting systemic toxicity associated with the cytotoxic agent
T-DM1 Mechanism of Action (MoA)

T-DM1 binds to the HER2 protein on cell

Receptor-T-DM1 complex is internalized into HER2 positive cell

Antimicrotubule agent is released inside HER2+ cell

Trastuzumab-like activity by binding to HER2

Targeted intracellular delivery of DM1

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T-DM1 Pre-Clinical Proof of Concept


- T-DM1 retains all of the MOA of trastuzumab, with additional efficacy/cytotoxicity provided by DM1 (Junttila TT et al, Breast Cancer Res Treat, 2010)

- Intact T-DM1 is more active than the components (trastuzumab plus DM1) (Parsons K, et al. AACR, 14-18 April 2007; Abstract 649)
  - Linker stability associated with higher activity and lower toxicity (Lewis Phillips GD et al, Cancer Res. 2008 Nov 15;68(22):9280-90)

- Pre-clinical data suggests potential to combine T-DM1 with other targeted therapies and/or conventional chemotherapies
  - Anti-HER2 MAb Pertuzumab (Fields CT. et al. AACR, 17-21 April 2010; Abstract 5607)
  - PI3K inhibitor (Sampath D, Lewis Phillips GD et al. SABCS, 8-12 Dec 2010)
  - Docetaxel (Lewis Phillips GD et al. AACR, 12-16 April 2008; Abstract 2133)

* T-DM1 has the potential to provide proof of ADC concept and transform HER2 targeted cancer therapy
Clinical Development Overview: Selected studies

Ph I and Ph II studies in Relapse / Refractory Patients:
- Ph I (TDM3569g) confirmed 3.6 mg/kg q3w = Recommended Ph II dose
- Ph II studies confirmed T-DM1 3.6 mg/kg as safe and active in heavily pretreated (trastuzumab, lapatinib, chemotherapy) patients

Pivotal Studies:
- **EMILIA**: An Open-Label Phase III Study of T-DM1 vs. Capecitabine + Lapatinib in Patients With HER2-Positive Locally Advanced or MBC
- **MARIANNE**: A Phase III Study of T-DM1 or T-DM1 + Pertuzumab Versus Trastuzumab [Herceptin] + a Taxane in Patients With MBC

Exploratory Studies:
- Front Line randomized Ph II (TDM4450g) T-DM1 vs trastuzumab + docetaxel
- Phase Ib or Ib/II Combination studies:
  - T-DM1 + docetaxel
  - T-DM1 + paclitaxel
  - T-DM1 + PI3K inhibitor (GDC0941)
  - T-DM1 + Pertuzumab (N=67 fully enrolled)
**Safety**: Similar for Q3 weekly and weekly schedules

- Most common AEs were G1-2 thrombocytopenia, transaminase elevations, fatigue, anemia, and nausea
- Dose limiting toxicity was transient, reversible G3-4 thrombocytopenia

**MTD**: Determined for each of the schedules tested

- q3w schedule: 3.6 mg/kg
- weekly schedule 2.4 mg/kg

**Efficacy**: Similar between q3w and weekly schedules

- 15 patients were treated at MTD (3.6 mg/kg)
- Median PFS was 10.4 months
- Clinical benefit rate (CR+PR+SD at 6 months) = 73%
- 9 patients had measurable disease; confirmed response rate in these patients was 44%

Phase II: T-DM1 Single Agent in Relapsed/Refractory HER2+ MBC

2 Phase II studies in heavily pretreated relapsed / refractory HER2+ MBC patients
  • TDM4258g: median of 5 prior agents for the treatment of MBC
  • TDM4374g: median of 7 prior agents for the treatment of MBC

<table>
<thead>
<tr>
<th></th>
<th>TDM4258g (n=112)</th>
<th>TDM4374g (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>55 (33–82)</td>
<td>53 (34–77)</td>
</tr>
<tr>
<td>Median time since metastatic diagnosis, mo (range)</td>
<td>33 (2–258)</td>
<td>41 (1–149)</td>
</tr>
<tr>
<td>ER+ and/or PR+, n (%)</td>
<td>53 (47)</td>
<td>55 (50)</td>
</tr>
<tr>
<td>ER- and PR-, n (%)</td>
<td>56 (50)</td>
<td>51 (46)</td>
</tr>
<tr>
<td>Median # agents for metastatic disease (range)</td>
<td>5 (1 – 17)</td>
<td>7 (3 – 17)</td>
</tr>
<tr>
<td>Median # agents in all therapy settings (range)</td>
<td>8 (2 – 19)</td>
<td>9 (5 – 19)</td>
</tr>
<tr>
<td># pts w/ prior trastuzumab, n(%)</td>
<td>112 (100)</td>
<td>110 (100)</td>
</tr>
<tr>
<td># pts w/ prior lapatinib, n (%)</td>
<td>67 (60)</td>
<td>110 (100)</td>
</tr>
</tbody>
</table>

TDM4258g: Burris, et al., manuscript accepted JCO. 2011
TDM4374g: Krop I, et al. ASCO 2009; ESMO 2010
### Phase II Studies:
T-DM1 Single Agent Clinical Proof of Concept - Efficacy

<table>
<thead>
<tr>
<th></th>
<th>TDM4258g (N=112) n (%)</th>
<th>TDM4374g (N=110) n (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>INV</td>
<td>IRF</td>
</tr>
<tr>
<td>Objective Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>42 (38)</td>
<td>29 (26)</td>
</tr>
<tr>
<td></td>
<td>(28.6, 46.6)</td>
<td>(18.4, 34.4)</td>
</tr>
<tr>
<td>Clinical Benefit Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>50 (46.3)</td>
<td>46 (39.3)</td>
</tr>
<tr>
<td></td>
<td>(36.7, 56.2)</td>
<td>(30.3, 48.3)</td>
</tr>
</tbody>
</table>

INV = Investigator Assessment
IRF = Independent Review Facility Assessment
Clinical Benefit: a patient is considered as having clinical benefit if the patient had objective response, or at least 6 months of stable disease from start of study treatment

- **Single agent T-DM1 at 3.6 mg/kg q3w demonstrates robust and durable anti-tumor activity in patients with HER2+ MBC that had previously received standard HER2-directed agents**
- **Studies in front line setting and in combination with other agents are warranted**

TDM4258g: Burris, et al., manuscript accepted JCO. 2011
TDM4374g: Krop I, et al. ASCO 2009; ESMO 2010
Randomized, phase II, international, open-label study
First line, HER2 positive, recurrent locally advanced or MBC;
  Measurable disease required
Stratification factors:
  World region, prior adjuvant trastuzumab therapy, disease-free interval
Key Primary endpoint: PFS by INV
Key Secondary endpoints: ORR, CBR, OS

**TMD4450g Objective Response by Investigator**
Randomized Patients

<table>
<thead>
<tr>
<th>Interim Response Data with approximately 6 months median follow up</th>
<th>T-DM1 (n=67)</th>
<th>Trastuzumab + Docetaxel (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with an Objective Response</strong>*</td>
<td>32 (47.8%)</td>
<td>29 (41.4%)</td>
</tr>
<tr>
<td>95% CI for Objective Response Rate</td>
<td>(35.4%, 60.3%)</td>
<td>(30.2%, 53.8%)</td>
</tr>
<tr>
<td><strong>Patients with Clinical Benefit</strong></td>
<td>37 (55.2%)</td>
<td>40 (57.1%)</td>
</tr>
<tr>
<td>95% CI for Clinical Benefit Rate</td>
<td>(43.1%, 67.2%)</td>
<td>(44.8%, 68.9%)</td>
</tr>
<tr>
<td><strong>Objective Responses, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>3 (4.5%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>29 (43.3%)</td>
<td>28 (40.0%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>22 (32.8%)</td>
<td>29 (41.4%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>8 (11.9%)</td>
<td>4 (5.7%)</td>
</tr>
<tr>
<td>Unable to Evaluate***</td>
<td>4 (6.0%)</td>
<td>4 (5.7%)</td>
</tr>
</tbody>
</table>

* Objective response = complete or partial response based on RECIST determined on two consecutive tumor assessments at least 4 weeks apart.
** Clinical benefit = objective response or maintained stable disease for at least 6 months from start of study treatment.
*** Per principal investigator assessment


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<table>
<thead>
<tr>
<th></th>
<th>T-DM1 (n=67)</th>
<th>Trastuzumab+ Docetaxel (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any AE, n (%)</strong></td>
<td>63 (94.0)</td>
<td>68 (100.0)</td>
</tr>
<tr>
<td><strong>Grade ≥3 AE</strong></td>
<td>25 (37.3)</td>
<td>51 (75.0)</td>
</tr>
<tr>
<td><strong>Serious AE</strong></td>
<td>13 (19.4)</td>
<td>15 (22.1)</td>
</tr>
<tr>
<td><strong>AEs Leading to Discontinuation of T-DM1</strong>*</td>
<td>6 (9.0)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>AEs Leading to Discontinuation of trastuzumab</strong></td>
<td>N/A</td>
<td>4 (5.9)</td>
</tr>
<tr>
<td><strong>AEs Leading to Discontinuation of docetaxel</strong></td>
<td>N/A</td>
<td>12 (17.6)</td>
</tr>
<tr>
<td><strong>Three most common AEs in T-DM1 arm:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (47.8)</td>
<td>27 (39.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31 (46.3)</td>
<td>29 (46.2)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>24 (35.8)</td>
<td>14 (20.6)</td>
</tr>
<tr>
<td><strong>Three most common AEs in trastuzumab + docetaxel arm:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>1 (1.5)</td>
<td>45 (66.2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5 (7.5)</td>
<td>39 (57.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (10.4)</td>
<td>31 (45.6)</td>
</tr>
</tbody>
</table>

*Reasons for discontinuation in T-DM1 arm: Grade 5 tumor flare, Grade 3 increased alanine and aspartate aminotransferase, thrombocytopenia, supraventricular extrastoles, sepsis, and skin neoplasm, and Grade 2 hepatotoxicity.*
**Occurring with ≥10% Difference in Incidence between Arms, n (%)**

<table>
<thead>
<tr>
<th>NCI CTCAE Grade</th>
<th>T-DM1 (n=67)</th>
<th>Trastuzumab + Docetaxel (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neutropenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Total -</td>
<td>(0.0)</td>
<td>36 (52.9)</td>
</tr>
<tr>
<td>3</td>
<td>(0.0)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>4</td>
<td>(0.0)</td>
<td>30 (44.1)</td>
</tr>
<tr>
<td><strong>Leukopenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Total -</td>
<td>(0.0)</td>
<td>17 (25.0)</td>
</tr>
<tr>
<td>3</td>
<td>(0.0)</td>
<td>12 (17.6)</td>
</tr>
<tr>
<td>4</td>
<td>(0.0)</td>
<td>5 (7.4)</td>
</tr>
<tr>
<td><strong>Febrile neutropenia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Total -</td>
<td>(0.0)</td>
<td>7 (10.3)</td>
</tr>
<tr>
<td>3</td>
<td>(0.0)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>4</td>
<td>(0.0)</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

Most common Gr ≥3 AEs in T-DM1 arm (vs. trastuzumab + docetaxel arm):
- aspartate aminotransferase (AST) increased (7.5% vs. 0%),
- thrombocytopenia (6.0% vs. 1.5%),
- alanine aminotransferase (ALT) increased (4.5% vs. 0%),
- fatigue (4.5% vs. 4.4%),
- pneumonia (4.5% vs. 1.5%)

Efficacy: Encouraging ORR results: 47.8% for T-DM1 vs. 41.4% for trastuzumab + docetaxel by investigator assessment, although CI’s overlap

Safety: T-DM1 appears to have a favorable overall safety profile compared with trastuzumab + docetaxel in 1\textsuperscript{st} Line MBC.

- Incidence of Grade $\geq$3 AEs in the T-DM1 arm is half that in the trastuzumab + docetaxel arm: 37% vs. 75%
- T-DM1 was not associated with an increased risk of cardiotoxicity compared with trastuzumab + docetaxel

The encouraging results support the concept of a chemotherapy-sparing strategy in the first line HER2-positive MBC setting

Phase III Trial Design: EMILIA, TDM4370g

An Open-Label Study of Trastuzumab-MCC-DM1 (T-DM1) vs. Capecitabine + Lapatinib in Patients With HER2-Positive Locally Advanced or MBC

Key inclusion criteria

- Prior treatment to include a taxane and trastuzumab in adjuvant, locally advanced or metastatic setting
- Documented progression of disease during or after treatment for advanced/metastatic disease, or within 6 months of completing adjuvant therapy
- Silent as to line of therapy but assume majority of patients will be 2nd (or 2nd/3rd line)

Primary end points: PFS and OS
Secondary end points: QOL: FACT-B

Treatment continues until disease progression or unmanageable toxicity
No provision for cross-over

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1st Line mBC Phase III MARIANNE Study: BO22589/TDM4788g

Patients with HER2 positive progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer

**Primary endpoints:** PFS as assessed by IRF; Safety
PFS Analysis: Superiority design with a Non-inferiority analysis between each of the experimental arms and the control arm

**Secondary endpoints:** OS; PFS by investigator; PRO analyses; Biomarkers

**Interim futility analysis:** Option to drop experimental arm

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**Patients stratified by:**
- World region
- Neo/Adjuvant therapy (Y/N)
  - Trastuzumab and/or lapatinib based therapy (Y/N)
- Visceral disease (Y/N)

**FPI July 2010**

- **Arm A**
  - Trastuzumab + taxane (until PD)
  - n=364

- **Arm B**
  - T-DM1 + pertuzumab (until PD)
  - n=364

- **Arm C**
  - T-DM1 + pertuzumab placebo (until PD)
  - n=364

**n=1092**

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Rationale for Phase III T-DM1 + pertuzumab Trial Design

Single agent T-DM1 appears to have robust single agent activity

Pertuzumab appears to add to the efficacy of trastuzumab (Phase II data)

Pertuzumab is expected to add to the efficacy of T-DM1

Opportunity for T-DM1/Pertuzumab as replacement for traditional chemotherapy and trastuzumab

- Promising opportunity for improved efficacy
- Improved tolerability expected
Overall Summary and Conclusions: T-DM1 Clinical Development

T-DM1 has demonstrated clinically meaningful efficacy with a favourable toxicity profile as a single agent in heavily pre-treated HER2+ MBC.

Preliminary clinical data has suggested potential conventional chemotherapy-sparing effect of T-DM1 as a front line therapy for MBC.

T-DM1 is being evaluated in two registrational Phase III studies in previously treated and 1st line HER2 + MBC patients as single agent and/or in combination with other targeted therapies.

The emerging data of T-DM1 may serve as a proof of concept to move the platform of ADC technology to the forefront of cancer care.