

A Phase Ib/II Trial of Trastuzumab-DM1 (T-DM1) with Pertuzumab for Patients with HER2-Positive, Locally Advanced or Metastatic Breast Cancer: Interim Efficacy and Safety Results

Dieras V,¹ Harbeck N,² Albain K,³ Burris HA III,⁴ Awada A,⁵ Crivellari D,⁶ Andre F,⁷ Choi YJ,⁸ Huang J,⁸ Miller KD⁹

¹Institut Curie, Paris, France; ²Interdisciplinary Breast Center, University of Cologne, Germany; ³Loyola University, Maywood, IL; ⁴Sarah Cannon Research Institute, Nashville, TN; ⁵Institut Jules Bordet, Brussels, Belgium; ⁶Centro di Riferimento Oncologico, Aviano, Italy;

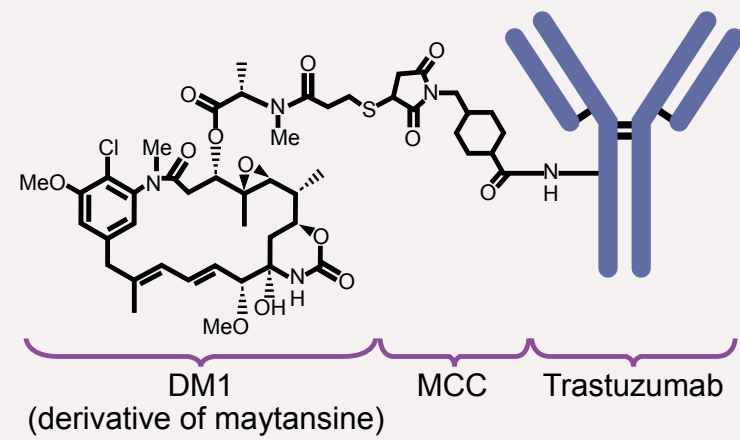
⁷Institut Gustave Roussy, Villejuif, France; ⁸Genentech, Inc., South San Francisco, CA; ⁹Indiana University Melvin and Bren Simon Cancer Center

BACKGROUND

T-DM1

T-DM1 is a HER2-targeted antibody drug-conjugate (ADC) composed of the cytotoxic agent DM1 (a maytansinoid anti-microtubule agent) conjugated to the monoclonal antibody trastuzumab via the highly-stable thioether linker (N-maleimidomethyl) cyclohexane-1-carboxylate (MCC) (Figure 1).^{1,2}

Figure 1. Schematic of Trastuzumab-DM1 (T-DM1)



Includes the (N-maleimidomethyl) cyclohexane-1-carboxylate (MCC) linker. An average of 3.5 DM1 molecules are conjugated to the Fc region of trastuzumab.

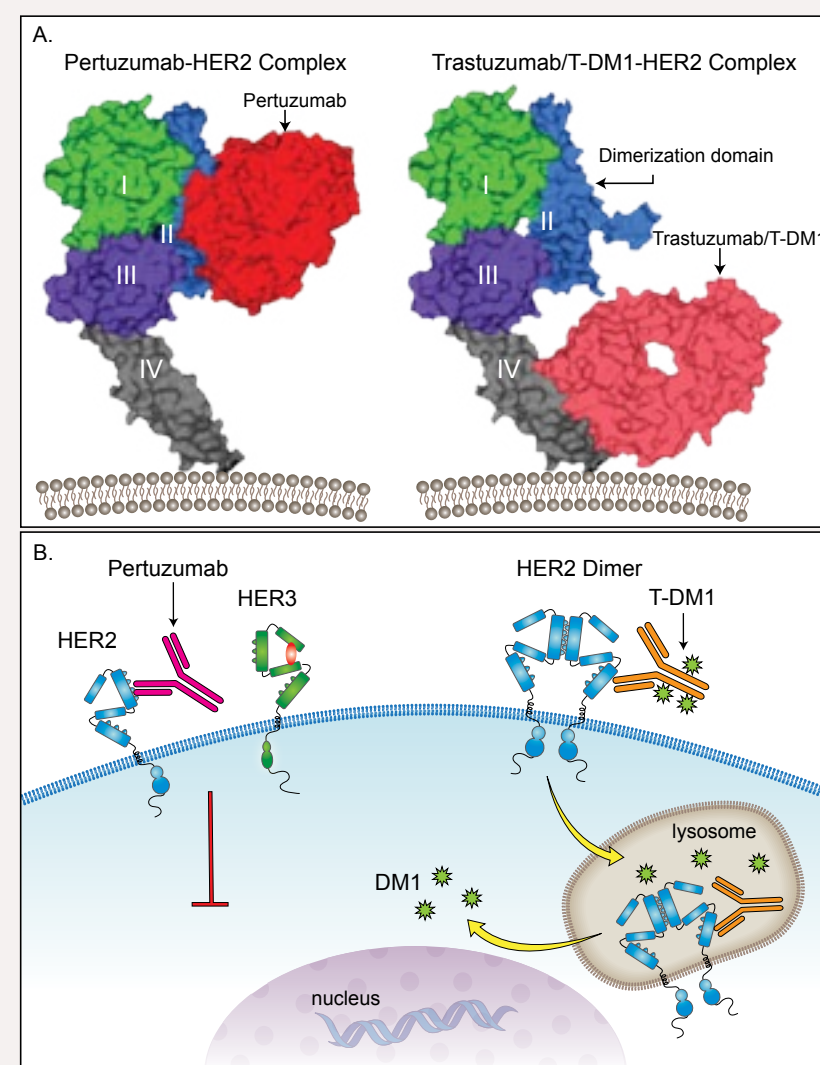
T-DM1 has shown encouraging single-agent efficacy coupled with a good safety profile in patients with heavily pre-treated HER2-positive metastatic breast cancer (MBC) in two Phase II single-arm studies,^{3,4} and in patients with previously untreated HER2-positive MBC in an ongoing randomized Phase II study comparing T-DM1 to trastuzumab + docetaxel.⁵

Pertuzumab

Pertuzumab, a recombinant, humanized monoclonal antibody directed against HER2, binds a domain of HER2 that is distinct from the epitope recognized by trastuzumab (Figure 2A). Pertuzumab inhibits ligand-activated heterodimerization with other HER receptors, most notably HER3 (Figure 2B).^{6,7}

A recent single-arm, two-stage, phase II combination study of pertuzumab and trastuzumab in patients with HER2-positive MBC who progressed on prior trastuzumab-based therapy (BO17929) showed an ORR of 24.2% and median PFS of 5.5 months with a good safety profile.⁸

Figure 2. Comparison of T-DM1 and Pertuzumab. A) Binding to HER2 and B) Mechanisms of Action



The combination of pertuzumab with trastuzumab or T-DM1 provides complementary modes of action (Figure 2) that may be more efficacious for treatment of HER2-overexpressing diseases.⁹

Combination of pertuzumab with T-DM1 has shown synergistic anti-tumor activity in HER2-positive xenograft models.¹⁰

METHODS

Study TDM4373g

This global, single-arm, Phase Ib/II study is investigating the safety and efficacy of the combination of T-DM1 with pertuzumab in patients with HER2-positive recurrent locally advanced or MBC.

Study enrolled patients who had received prior systemic anti-cancer treatment for recurrent locally advanced or metastatic disease (relapsed) and patients with newly diagnosed or previously untreated MBC (first-line)

Primary Objectives

- To characterize the safety and tolerability of the combination of T-DM1 and pertuzumab
- To evaluate the pharmacokinetics of T-DM1
- To make a preliminary assessment of the efficacy of T-DM1 and pertuzumab, as measured by objective response rate (ORR) based on investigator assessment.

Secondary Objective

- To estimate PFS and duration of response for patients who receive T-DM1 and pertuzumab administered on this schedule.
 - PFS and duration of response data were not mature as of the Sept. 1, 2010 data cut.

Key Inclusion Criteria

- Histologically-documented recurrent locally advanced or metastatic HER2-positive BC (HER2-positivity documented as FISH+ or CISH+ or IHC 3+ by local laboratory assessment)
- Measurable disease
- No prior T-DM1 or pertuzumab therapy
- Cardiac ejection fraction >55% by either echocardiogram (ECHO) or multiple gated acquisition (MUGA) scan

Key Exclusion Criteria

- Prior cumulative anthracycline dose >500 mg/m² doxorubicin
- History of clinically significant cardiac dysfunction

Statistical Analysis

- Efficacy evaluable and safety evaluable patients were defined as those who received any study treatment.
 - Patients who had disease progression or died prior to the first scheduled tumor assessment were considered efficacy evaluable and treated as non-responders for calculation of ORR.
- Investigator-assessed objective response is defined as a complete or partial response using modified RECIST v 1.0 determined on two consecutive occasions ≥4 weeks apart.

RESULTS

- Data cutoff: Sept. 1, 2010 (study enrollment period: May 2009–March 2010).
- The Phase 1b dose escalation study established the dose schedule of T-DM1 every three weeks at 3.6 mg/kg in combination with pertuzumab, 840 mg loading dose at first cycle followed by 420 mg maintenance dose every three weeks thereafter.¹¹
- Sixty-seven patients (46 relapsed, 21 first-line) enrolled in the study and are considered safety evaluable and efficacy evaluable. Three relapsed patients (in the Phase 1b study) received TDM-1 at 3.0 mg/kg and the rest of the patients received T-DM1 at 3.6 mg/kg.

Table 1. Demographics and Baseline Characteristics

| | Relapsed (n=46) | First-line (n=21) | Total (n=67) |
|----------------------------------|-----------------|-------------------|--------------|
| Median age, years (range) | 55.5 (29–74) | 52.0 (28–73) | 53.0 (28–74) |
| Race, n (%) ^a | | | |
| White | 42 (91.3) | 18 (85.7) | 60 (89.6) |
| African-American | 3 (6.5) | 1 (4.8) | 4 (6.0) |
| Asian | 1 (2.2) | 1 (4.8) | 2 (3.0) |
| Sex, male, n (%) | 1 (2.2) | 0 | 1 (1.5) |
| ECOG PS, n (%) | | | |
| 0 | 27 (58.7) | 14 (66.7) | 41 (61.2) |
| 1 | 19 (41.3) | 6 (28.6) | 25 (37.3) |
| 2 | 0 | 1 (4.8) | 1 (1.5) |
| Prior hormonal therapy, n (%) | 22 (47.8) | 6 (28.6) | 27 (40.3) |
| ER/PR status, n (%) ^b | | | |
| ER+ and/or PR+ | 20 (43.5) | 10 (47.4) | 30 (44.8) |
| ER- and PR- | 24 (52.2) | 11 (52.4) | 35 (52.2) |

ER=estrogen receptor; PR=progesterone receptor

^aData not available for one first-line patient; ^bData not available for 2 relapsed patients.

Table 2. Prior Systemic Therapies

| | Relapsed (n=46) | First-line (n=21) | Total (n=67) |
|--|-----------------|-------------------|--------------|
| Systemic therapies, n (%) | 46 (100) | 21 (100) | 67 (100) |
| Any Chemotherapy | 46 (100) | 19 (90.5) | 65 (97.0) |
| Taxane | 35 (76.1) | 15 (71.4) | 50 (74.6) |
| Anthracycline | 40 (87.0) | 13 (61.9) | 53 (79.1) |
| Capecitabine | 37 (80.4) | 3 (14.3) | 40 (59.7) |
| Trastuzumab | 46 (100) | 18 (85.7) | 64 (95.5) |
| Lapatinib | 34 (73.9) | 2 (9.5) | 36 (53.7) |
| Other Biologic ^a | 10 (21.7) | 0 | 10 (14.9) |
| Other targeted therapy ^b | 8 (17.4) | 0 | 8 (11.9) |
| Experimental | 5 (10.9) | 1 (4.8) | 6 (9.0) |
| Cancer vaccine (theratope) | 1 (2.2) | 0 | 1 (1.5) |
| Other ^c | 6 (13.0) | 0 | 6 (9.0) |
| Number of prior systemic agents in all settings, ^d median (range) | 8.0 (2–16) | 4.0 (1–6) | 7.0 (1–16) |
| Number of prior systemic agents in metastatic setting, ^d median (range) | 6.0 (2–14) | 0 | 6.0 (2–14) |
| Median time since metastatic diagnosis to enrollment, mos (range) | 34.7 (5–150) | 0.6 (0–12) | 21.8 (0–150) |

^aBevacizumab and rituximab; ^bEverolimus and erlotinib; ^cPrednisone and zoledronic acid; ^dExcluding hormone.

On-Study Treatment

- Patients received a median of 8.0 cycles (range, 1–19) of study treatment in the relapsed group and 8.0 cycles (range 1–16) in the first-line group.

Efficacy

Table 3. Objective Responses among First-Line and Relapsed Patients

| | Relapsed (n=46) | First-line (n=21) |
|--|-----------------------|-----------------------|
| Confirmed ORR, n (%) (95% CI) | 16 (34.8) (22.2–50.0) | 12 (57.1) (34.0–78.2) |
| Clinical benefit rate, [*] n (%) (95% CI) | 21 (45.7) (30.9–60.2) | 13 (61.9) (39.8–80.3) |
| Best responses, n (%) | | |
| Complete response, | 1 (2.2) | 2 (9.5) |
| Partial response, | 15 (32.6) | 10 (47.6) |
| Stable disease, | 22 (47.8) | 5 (23.8) |
| Progressive disease | 7 (15.2) | 4 (19.0) |
| Missing | 1 (2.2) | 0 |

^{*}Objective response or maintenance of stable disease for at least 6 months from start of study treatment; ORR=objective response rate

Safety

- The Phase Ib portion of the study showed that it was safe to combine full doses of T-DM1 and pertuzumab.¹¹
- Grade ≥3 AEs
 - Among the 46 relapsed patients, the most frequent Grade ≥3 AEs were fatigue (n=7), thrombocytopenia (n=4) and cellulitis (n=4).
 - Among the 21 first-line patients, the most frequent Grade ≥3 AEs were thrombocytopenia (n=4) and increased alanine aminotransferase (ALT) (n=4) and aspartate aminotransferase (AST) (n=2).
- Twenty patients (29.9%) experienced serious AEs, including pleural effusion (3 relapsed), dyspnea (2 relapsed, 1 first-line), abdominal pain (2 first-line), vomiting (1 relapsed, 1 first-line), cellulitis (2 relapsed) and pneumonia (2 relapsed).

- One grade 5 event was reported: pneumonia in a relapsed patient who died prior to the first tumor assessment. The patient was also noted to have clinical progression of disease.
- No relapsed patients and one first line patient experienced a left ventricular ejection fraction (LVEF) decline of ≥25% from baseline value. One relapsed patient discontinued from the study due to Grade 3 LVEF dysfunction.

Table 4. Adverse Events of any Grade with >20% Incidence^{*}

| AE, n (%) | All grades (n=67) |
|--------------------------------------|-------------------|
| Fatigue | 41 (61.2) |
| Nausea | 30 (44.8) |
| Diarrhea | 24 (35.8) |
| Cough | 23 (34.3) |
| Decreased appetite | 23 (34.3) |
| Chills | 21 (31.3) |
| Thrombocytopenia | 21 (31.3) |
| Pyrexia | 19 (28.4) |
| Constipation | 18 (26.9) |
| Dysgeusia | 18 (26.9) |
| Headache | 18 (26.9) |
| Dyspnea | 17 (25.4) |
| Epistaxis | 17 (25.4) |
| Vomiting | 17 (25.4) |
| Peripheral sensory neuropathy | 16 (23.9) |
| Rash | 16 (23.9) |
| Aspartate aminotransferase increased | 15 (22.4) |
| Mucosal inflammation | 15 (22.4) |
| Alanine aminotransferase increased | 14 (20.9) |

^{*}Data reflect the number of patients, not the number of events; some patients experienced ≥ one grade of AE

Table 5. All Grade ≥3 AEs Occurring in more than One Patient^{*}

| AE, n (%) | Total** (n=67) |
|--------------------------------------|----------------|
| Fatigue | 8 (11.9) |
| Thrombocytopenia | 8 (11.9) |
| Alanine aminotransferase increased | 6 (9.0) |
| Aspartate aminotransferase increased | 5 (7.5) |
| Cellulitis | 4 (6.0) |
| Dyspnea | 4 (6.0) |
| Anemia | 3 (4.5) |
| Pleural effusion | 3 (4.5) |
| Infection | 2 (3.0) |
| Nausea | 2 (3.0) |
| Neutropenia | 2 (3.0) |
| Pneumonia | 2 (3.0) |
| Vomiting | 2 (3.0) |

^{*}Data reflect the number of patients, not the number of events; some patients experienced an AE at more than one grade. ^{**}includes one grade 5 pneumonia event and four grade 4 events (3 thrombocytopenia and one pain).

Table 6. Dose Reductions

| Dose reductions, n | Relapsed (n=46) | First-line (n=21) |
|--|-----------------|-------------------|
| to 3.0 mg/kg | 6 | 4 |
| to 2.4 mg/kg | 2 | 1 |
| Most common AEs leading to dose reduction [*] (n) | | |
| Increased ALT levels | 1 | 4 |
| Increased AST levels ^{**} | 2 | 1 |
| Thrombocytopenia | 2 | 1 |

^{*}AEs that led to dose reduction in 3 or more patients

^{**}includes one relapsed and one first-line patient with both increased ALT and AST levels.

Study treatment discontinuations

- Six relapsed patients discontinued both T-DM1 and pertuzumab due to AEs (hemoptysis; pleural effusion; left ventricular systolic dysfunction; and fatigue, dyspnea; and fatigue, pyrexia and chills in one patient).
 - Four of these six patients had concomitant progressive disease.
- Two relapsed patients discontinued pertuzumab but not T-DM1, both due to fatigue.
- No first-line patients discontinued study treatment due to AEs.

Table 7. Study Treatment Termination (as of Sept. 1, 2010)

| Termination before Sept. 1, 2010 due to: n (%) | Relapsed (n=46) | First-line (n=21) |
|--|-----------------|-------------------|
| Adverse event | 3 (6.5) | 0 |
| Death | 1 (2.2) | 0 |
| Disease progression | 29 (63.0) | 9 (42.9) |
| Physician decision | 1 (2.2) | 1 (4.8) |
| Subject/legal guardian decision | 2 (4.3) | 1 (4.8) |

CONCLUSIONS

- Dose Evaluation
 - T-DM1 and pertuzumab were well tolerated at full single-agent doses as used in other clinical studies
- Safety
 - The combination of T-DM1 and pertuzumab has an acceptable safety and tolerability profile.
 - Most AEs were Grade ≤2 and led to relatively few dose reductions or discontinuations.
 - Peripheral neuropathy was mild.
 - Cardiotoxicity was mild, with only one discontinuation for LVEF dysfunction.
- Efficacy
 - Efficacy of this combination in relapsed (confirmed ORR of 34.8%) and first-line (confirmed ORR of 57.1%) MBC patients by investigator assessment is encouraging.
 - Robust activity was seen in first-line MBC patients who received prior trastuzumab and taxane therapy in the early breast cancer setting.
- The combination of T-DM1 and pertuzumab is being studied in the ongoing phase III MARIANNE trial (BO22589/TDM4788g), comparing T-DM1 or T-DM1 + pertuzumab to trastuzumab + a taxane for first-line treatment of HER2-positive MBC.

REFERENCES

- Remillard S, et al. Science 189:1002–1005, 1975.
- Lewis-Phillips GD, et al. Cancer Res 6:9280–9290, 2008.
- Burris HA, et al. J Clin Oncol. in press, 2010
- Krop I, et al. San Antonio Breast Cancer Symposium San Antonio Breast Cancer Symposium December 2009, Abstract 5091.
- Perez et al., abstract #BA3, European Society for Medical Oncology Annual Meeting, 2010
- Adams CW, et al. Cancer Immunol Immunother 55:717–727, 2006.
- Cho HS, et al. Nature 421:756–760, 2003.
- Baselga J, et al. J Clin Oncol. 28:1138–1144, 2010.
- Agus DB, et al. Cancer Cell 2:127–137, 2002.
- Fields CT, et al. Proc Amer Assoc Cancer Res 51:1360 (abstract 5607), 2010.
- Miller et al. J Clin Oncol 28:15s, (suppl; abstr 1012) 2010

ACKNOWLEDGEMENTS

We would like to thank the patients and investigators who participated in this trial. At Genentech, we also thank Yu-Way Chu and Ted Shin for clinical support and Liang Fang for biostatistics support in preparation of this poster.

Genentech, Inc. provided support for the preparation of this poster.

33rd Annual San Antonio Breast Cancer Symposium (SABCS), San Antonio, TX, Dec. 8–12, 2010