

A Phase I Study of Trastuzumab-DM1, a First-in-Class HER2 Antibody-Drug Conjugate (ADC), Given Every 3 Weeks to Patients with HER2+ Metastatic Breast Cancer

1028

Muralidhar Beeram, MD;¹ Howard A. Burris, MD;² Shanu Modi, MD;³ Merrill Birkner, PhD;⁴ Sandhya Girish, PhD;⁴ Jay Tibbitts, DVM, PhD;⁴ Scott N. Holden, MD;⁴ Stuart G. Lutzker, MD, PhD;⁴ Ian E. Krop, MD, PhD⁵
¹Medical Oncology, Sarah Cannon Research Institute, Nashville, TN; ²Medical Oncology, Institute for Drug Development, San Antonio, TX; ³Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY; ⁴BioOncology, Genentech, South San

BACKGROUND/RATIONALE

Trastuzumab-DM1 (T-DM1) is a first-in-class HER2 antibody drug-conjugate (ADC) in development for HER2-positive breast cancer. T-DM1 is designed to combine trastuzumab's HER2-blocking activity with targeted delivery of a highly potent antimicrotubule agent to HER2-expressing cells. Focusing the delivery of such chemotherapeutic agents to tumor cells via high-specificity monoclonal antibodies (MoAbs) that bind unique and/or over-expressed cell-surface tumor antigens is intended to improve the therapeutic window for such agents, allowing their potential to be applied to the clinic.

The MoAb in T-DM1 is trastuzumab and the chemotherapeutic agent is an anti-microtubule maytansine derivative, DM1 (Figure 1). Maytansines bind to tubulin competitively with vinca alkaloids but 20 to 100 times more potently than vincristine.¹⁻³ The parent molecule of DM1, maytansine, has induced responses in patients with breast and lung cancer, with principal toxicities of nausea, vomiting, diarrhea, and sensory neuropathy.⁴⁻⁶ The non-reducible MOC linker molecule has been engineered to minimize systemic exposure to free DM1 and improve exposure to T-DM1, potentially enhancing the therapeutic window of DM1. T-DM1 is the first ADC with an MOC linker to be evaluated in the clinic.

T-DM1 binds to HER2 with affinity similar to that of trastuzumab,^{7,8} and such binding is required for its antitumor activity. The level of surface HER2 expression reflects a dynamic equilibrium of HER2 movement between the cell membrane and the cytoplasm, and that equilibrium is not altered when HER2 is bound by trastuzumab.⁹ It is hypothesized that after binding to HER2, T-DM1 undergoes receptor-mediated internalization, resulting in intracellular release of DM1. T-DM1 has activity in trastuzumab-sensitive and -insensitive HER2-positive preclinical models. In cynomolgus monkeys, T-DM1's principal toxicities were reversible elevations in hepatic transaminases, reversible decreases in platelet count, and dose-related neuropathy; no cardiac toxicity was observed.⁷

Figure 1. Anatomy of Trastuzumab-DM1.



*Average number of DM1 molecules/MoAb = 3.5.

STUDY OBJECTIVES

Primary Objectives

- To assess the safety, tolerability, and pharmacokinetics of T-DM1 given every 3 weeks continuously to patients with HER2-positive breast cancer who have progressed on prior trastuzumab-based therapy.

- To determine the maximum tolerated dose (MTD) of T-DM1 on an every-3-week schedule.

Secondary Objectives

- To assess antitumor activity in this population.
- To assess the formation of antibodies to T-DM1.

STUDY DESIGN

Table 1. Key Eligibility Requirements.

Inclusion	Exclusion
HER2-positive disease by FISH or 3+ IHC	History of significant cardiac disease requiring medication
Progression within 60 days of receiving a trastuzumab-containing chemotherapy regimen (minimum 6-week trastuzumab exposure)	Left ventricular ejection fraction (LVEF) <50% (or lower limit of normal) by ECHO or MUGA
Previous treatment with chemotherapy for metastatic breast cancer (MBC)	History of trastuzumab hypersensitivity or toxicity requiring permanent discontinuation
Measurable or evaluable disease	Grade ≥2 peripheral neuropathy

Treatment Administration

- T-DM1 was administered once per cycle as a 30- to 90-minute intravenous infusion.
- Cycles were 21 days in length (28 days if needed for recovery from toxicity).

Data Collection

- Weekly:** Interim history and physical; CBCs, chemistries, PT/APTT; liver function tests
- Every cycle:** Cardiac troponin I, anti-therapeutic antibody levels, peak and trough pharmacokinetic (PK) samples (T-DM1, total trastuzumab, free DM1)
 - Cycle 1 only: PK samples on Days 2, 3, 4/5, 8, 11, 15, 18/19; LVEF
 - Every 2 cycles: Tumor assessments; LVEF

Dose-Limiting Toxicity

Grade ≥3 non-hematologic, non-hepatic major organ toxicity, excluding:

Grade 3 diarrhea, nausea, or vomiting that responds to therapy

Grade 3 nausea and vomiting in the absence of premedication that responds to therapy

Grade ≥2 cardiac toxicity, including:

Any cardiac troponin I elevation (i.e., a level of ≥0.2 ng/mL)

Any new segmental wall motion abnormality as determined by non-invasive cardiac imaging

Grade ≥4 thrombocytopenia

Grade ≥4 neuropathy lasting ≥4 days, or accompanied by fever

Grade ≥4 anemia

Grade ≥2 serum bilirubin, hepatic transaminase, or alkaline phosphatase

>10x ULN for transaminases/alkaline phosphatase if Grade 2 at baseline due to tumor

RESULTS

Table 2. Patient Baseline Demographics and Disease Characteristics.

Total patients	n=24
Median age, years (range)	50.5 (35-70)
Median number of prior metastatic chemotherapy agents (range)	4.0 (1-8)
Median duration of prior trastuzumab therapy, weeks (range)	91.6 (17-284)

- The first cohort (0.3 mg/kg) enrolled 3 patients; subsequent dose levels were doubled until a related Grade ≥2 AE was observed in Cycle 1 (Table 3).

Table 3. Study Enrollment by Dose Levels.

Cohort	Dose Level (mg/kg)	Number of Patients	Total Number of Doses (Range per Patient)
1	0.3	3	12 (2-6)
2	0.6	1	2
3	1.2	1	4
4	2.4	1	26*
5	4.8	3	14 (1-12)
6	3.6	15	146* (1-19*)
	TOTAL	24	206*

* signifies that patients are still on study as of data cut-off date, February 29, 2008.

Safety

- A total of 318 adverse events (AEs) have been reported (worst grade per patient). Sixty-two (20%) of these were Grade ≥2; 12 (4%) were Grade ≥3. All Grade ≥3 AEs, Grade 2 AEs possibly related to study drug, and AEs occurring at Grade 2 severity in >1 patient are summarized in Table 4.
- Dose-limiting toxicity (consisting of rapidly reversible asymptomatic Grade 4 thrombocytopenia) was observed in 2 of 3 patients at 4.8 mg/kg. No other Grade 4 AEs and no cardiac-specific toxicity have been observed.
- The most common AEs reported on this schedule were Grade 1 and 2 thrombocytopenia, fatigue, nausea, transaminase elevation, anemia, headache, and constipation (Table 4). No Grade ≥2 nausea, vomiting, alopecia, or neuropathy has been observed.
- Platelet nadirs were observed on approximately Day 8; recovery was rapid with recovery by approximately Day 15. No clinically significant bleeding events were observed. Thrombocytopenia at the MTD has been generally Grade ≤2, noncumulative, and reversible.
- One serious AE (SAE) (pulmonary hypertension) was considered possibly related to study drug. All other reported SAEs were not considered study drug-related and consist of cellulitis, cerebral hemorrhage, convulsions, dysarthria, dyspnea, humerus fracture, and pleural effusion.

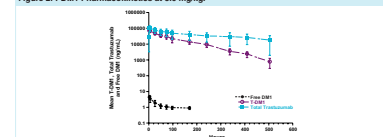
Table 4. Adverse Events, Grade ≥2*, Displayed by Grade (1-4), Dose, and Relation to Study Drug.

	Dose (mg/kg)					Total (n=24)
	0.3 (n=3)	0.6 (n=1)	1.2 (n=1)	2.4 (n=1)	4.8 (n=3)	
Blood and Lymphatic System						
Anemia	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	4/2/1/
Thrombocytopenia	-/-/-	-/-/-	-/-/-	-/-/-	1/1/2	5/2/1/
Leukopenia	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
Neutropenia	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
Metabolic						
Transaminase [†]	-/-/-	-/-/-	-/-/-	1/1/-	2/1/-	8/2/1/
Alkaline phosphatase [†]	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
Lactate dehydrogenase [†]	-/-/-	-/-/-	-/-/-	-/-/-	1/1/-	1/1/1/
INR [†]	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
Constitutional						
Fatigue	1/1/-	-/-/-	-/-/-	1/1/-	3/4/1/1/-	4/5/1/2/1/
Infection reaction	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
Nervous System						
Convulsion	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
Headache	-/-/-	-/-/-	-/-/-	1/1/-	-/-/-	3/3/1/-
Infections						
Cellulitis	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
Oral candidiasis	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-
URI	-/-/-	-/-/-	-/-/-	1/1/-	1/1/-	5/2/1/-
Urinary tract infection	-/-/-	-/-/-	-/-/-	1/1/-	2/3/-	3/3/-
Viral infection	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/2/-
Gastrointestinal						
Constipation	1/1/-	-/-/-	-/-/-	1/1/-	1/1/-	4/1/2/-
Musculoskeletal and Connective Tissue						
Arthralgia	-/-/-	-/-/-	-/-/-	1/1/-	-/-/-	2/1/3/-
Back pain	-/-/-	-/-/-	-/-/-	1/1/-	-/-/-	2/2/1/
Fracture	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	1/2/1/
Muscular weakness	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/1/-
Musculoskeletal chest pain	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/3/1/
Respiratory, Thoracic, and Mediastinal Disorders						
Dyspnea	1/1/-	-/-/-	-/-/-	-/-/-	-/-/-	2/1/1/
Pleural effusion	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/1/-
Pulmonary hypertension	-/-/-	-/-/-	-/-/-	-/-/-	-/-/-	-/1/1/

Pharmacokinetics

- Mean (SD) total trastuzumab, T-DM1, and free DM1 from Cycle 1 are presented in Figure 2.
- Consistent with preclinical studies, the clearance of T-DM1 is faster than the clearance of total trastuzumab.
- The average terminal half-life observed at lower dose levels was shorter than at higher doses (data not shown), and was 3.5 days for T-DM1 administered every three weeks at 3.6 mg/kg.
- Exposure to free DM1 relative to conjugated T-DM1 was very low with maximum free DM1 levels of <10 ng/mL.

Figure 2. T-DM1 Pharmacokinetics at 3.6 mg/kg.



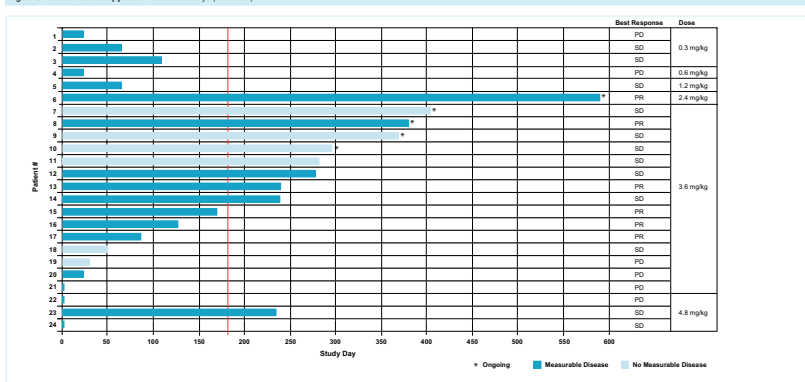
Antitumor Activity

- Fifteen patients were treated at the MTD (3.6 mg/kg).
- Median PFS at the MTD was 9.8 months (range 0.2 to 13.0+); the clinical benefit rate (CRA/PFS ≥ 6 months) in this group was 52%.
- Nine patients had measurable disease at baseline, and 5 of those had objective responses (4 confirmed) for a confirmed response rate of 44%.
- In addition to trastuzumab, all patients with objective responses had previously been treated with paclitaxel, docetaxel, and/or vinorelbine.
- Study treatment was ongoing for 4 patients (longest over 12 months) as of February 29, 2008.

Table 5. Patient Baseline Demographics and Disease Characteristics for Patients with Objective Responses at the MTD.

Total	n=6
Median age, years (range)	47 (41-63)
Median number of prior metastatic chemotherapy agents (range)	3.0 (1-5)
Median duration of prior trastuzumab therapy, weeks (range)	95.2 (36-143)

Figure 3. Duration of therapy. Red line is at 180 days (6 months).



CONCLUSIONS

- T-DM1 administered every 3 weeks has demonstrated significant activity in a trastuzumab-pretreated population of patients with HER2-positive metastatic breast cancer at doses associated with an acceptable safety profile.
- The MTD of T-DM1 administered to patients intravenously every 3 weeks is 3.6 mg/kg.
- Dose-limiting toxicity was observed at 4.8 mg/kg (rapidly reversible, asymptomatic Grade 4 thrombocytopenia).
- No other Grade 4 AEs and no cardiac-specific toxicity have been observed.
- The most common AEs reported on this schedule were Grade 1 or 2 thrombocytopenia, fatigue, nausea, transaminase elevation, anemia, headache, and constipation.
- Median PFS in patients treated at the MTD (n=15) was 9.8 months; the clinical benefit rate in this group was 52%. The confirmed response rate in patients at the MTD with measurable disease treated (n=5) was 44%.
- Treatment is ongoing for 6 of the 24 patients enrolled.

- A Phase II study of T-DM1 3.6 mg/kg every 3 weeks in patients with HER2-positive metastatic breast cancer who have progressed on HER2-directed therapy has been initiated; preliminary results are expected later this year.

REFERENCES

- Laennec JH, Wharley DN. Synthesis of microtubule protein in HeLa cells approaching division. *Cytosins*. 1975;15:167-173.
- Issell BF, Cronin ST. Maytansine. *Cancer Treatment Reviews*. 1978;5:169-207.
- Reinhard S, et al. Antitumor activity of the potent tubulin inhibitor maytansine. *Science*. 1975;189:1003-1005. 2006;49:4335-4408.
- Wadlow WC, et al. Semisynthetic maytansine analogues for the targeted treatment of cancer. *J Med Chem*. 2006;49:4335-4408.
- Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute. Maytansine, NCI 153858-IND 11857. Annual report to the Food and Drug Administration, February 1994.
- Cassidy JM, et al. Recent developments in the maytansinoid antitumor agents. *Chem Pharm Bull*. 2004;52:126.
- Data on file, Genentech, Inc., South San Francisco, CA.
- Trastuzumab (Herceptin) Investigator Brochure, July 2007.
- Austin CD, et al. Endoypoxys and sorting of ESRB and the site of action of cancer therapeutics trastuzumab and getanermin. *Mol Biol Cell*. 2004;15:5268-5282.

This study was supported by Genentech, Inc., South San Francisco, CA, USA. Writing assistance for this poster was provided by Genentech, Inc. American Society of Clinical Oncology Annual Meeting, Chicago, IL, May 29-June 3, 2008.