

# A Phase II Study of Trastuzumab-DM1 (T-DM1), a HER2 Antibody-Drug Conjugate, in Patients with HER2-Positive Metastatic Breast Cancer

C.L. Vogel,<sup>1</sup> H.A. Burris,<sup>2</sup> S. Limentani,<sup>3</sup> R. Borson,<sup>4</sup> J. O'Shaughnessy,<sup>5</sup> S. Vukelja,<sup>6</sup> S. Agresta,<sup>7</sup> B. Klencke,<sup>7</sup> B. Tong,<sup>7</sup> H.S. Rugo<sup>8</sup>

<sup>1</sup>Lynn Cancer Institute, Boca Raton, FL; <sup>2</sup>Sarah Cannon Research Institute, Nashville, TN; <sup>3</sup>University of North Carolina, Blumenthal Cancer Center, Charlotte, NC; <sup>4</sup>St. Louis Cancer & Breast Institute, St. Louis, MO; Baylor-Sammons Cancer Center, Texas Oncology, Dallas, TX; <sup>5</sup>Texas Oncology, Dallas, TX; <sup>6</sup>Tyler Cancer Center, Texas Oncology PA, US Oncology, Tyler, TX; <sup>7</sup>Genentech, Inc., South San Francisco, CA; <sup>8</sup>UCSF Comprehensive Cancer Center, San Francisco, CA

## INTRODUCTION

- Trastuzumab-DM1 (T-DM1) is a novel anti-HER2 antibody drug-conjugate in development for the treatment of HER2-positive metastatic breast cancer (MBC).<sup>1</sup>
- T-DM1 combines the HER2-targeting properties of trastuzumab (Herceptin®)<sup>2</sup> with targeted delivery of a highly potent anti-microtubule derivative, DM1.<sup>3-5</sup>
  - T-DM1 binds to HER2 with an affinity similar to that of trastuzumab.<sup>6</sup>
  - It is hypothesized that after binding to HER2, T-DM1 undergoes receptor-mediated internalization,<sup>7</sup> resulting in intracellular release of DM1.

## OBJECTIVES

### Primary Objectives

- To assess the objective response rate (ORR; by independent radiologic review) for T-DM1 in patients with HER2-positive MBC who have progressed while receiving HER2-directed therapy
- To characterize the safety and tolerability of this T-DM1 regimen in this patient population

### Secondary Objectives

- To assess ORRs based on investigator measurements
- To assess PFS based on independent radiologic review or investigator assessments
- To characterize the pharmacokinetics (PK) of this T-DM1 regimen

## METHODS

### Study Description

- A multi-institutional, open-label, single-arm Phase II US study in patients with locally confirmed HER2-positive MBC who progressed while receiving HER2-directed therapy
  - T-DM1 (3.6 mg/kg) was given by IV infusion over 30–90 minutes every 3 weeks (q3w)

### Key Eligibility Criteria

- HER2-positive disease by FISH or 3+ IHC by local lab
- Measurable disease by CT scan per RECIST
- Progression on HER2-directed therapy or within 60 days after receiving trastuzumab (≥6 weeks exposure to HER2-directed therapy)
- Prior treatment with one or more chemotherapy agents for MBC
- No history of significant cardiac disease; left ventricular ejection fraction (LVEF) ≥50%
- No history of Grade ≥3 hypersensitivity to trastuzumab or toxicity requiring discontinuation
- No Grade ≥3 peripheral neuropathy
- No untreated or symptomatic brain metastases or any treatment for brain metastases within 3 months of treatment start

### Assessments and Data Collection

- Tumor assessments (per RECIST) were performed every 2 cycles.
- Echocardiograms or MUGA scans were performed after Cycles 1 and 2 and every other cycle thereafter.
- Serum cardiac troponin I levels were assessed on Day 8 of every other cycle.
- PK samples for total trastuzumab, T-DM1, and DM1 were collected on Day 1 of each cycle pre- and post-dose, and weekly in Cycles 1 and 4; Cycle 1 PK data are reported in this presentation.

## RESULTS

### Study Status

- 112 patients were enrolled at 32 sites in the United States.
  - Enrollment was from August 2007 to July 2008.
- As of the January 31, 2009 data cutoff
  - Median follow-up was 9.5 months.
  - Twenty-six (23.2%) patients were still receiving study treatment.
  - Eighty-six (76.8%) patients had discontinued from this study.

### Baseline Demographics and Disease Characteristics

Demographics	(n=112)
Median age, yr (range)	54.5 (33–82)
Race, n (%)	
White	101 (90.2)
Black	9 (8.0)
Asian or Pacific Islander	2 (1.8)
ECOG PS, n (%)	
0	60 (53.6)
1	43 (38.4)
2	8 (7.1)
3	1 (0.9)
ER+ or PR+, n (%)	56 (50)
ER- and PR-, n (%)	56 (50)
Median time since metastatic diagnosis, mo (range)	32.7 (1–258)
Number of distinct metastatic sites, n (%)	
<3	28 (25)
≥3	84 (75)
Metastatic sites (in ≥50% of patients), n (%)	
Lung	63 (56.3)
Liver	63 (56.3)
Bone	59 (52.7)

ECOG PS= Eastern Cooperative Oncology Group performance status, ER=estrogen receptor, PR=progesterone receptor

### Prior Chemotherapy and Anti-HER2 Therapy History

Prior Therapy	(n=112)
Median number of chemotherapeutic agents for metastatic disease (range)	3 (1–12)
Prior anthracycline, n (%)	78 (69.6)
Prior taxane, n (%)	94 (83.9)
Median duration of prior trastuzumab therapy, months (range)	17.8 (1–152)
Prior lapatinib therapy, n (%)	67 (59.8)
Median duration of lapatinib therapy, mo (range)	6.0 (1–24)

### Pharmacokinetics

- PK parameters for T-DM1 conjugate in this Phase II study were similar to those reported for the maximum tolerated dose in the Phase I study.

Parameter	
Mean peak plasma DM1 levels, ng/mL	5.4± 2.0
Individual peak plasma DM1 levels, ng/mL (range)	2–13
Mean PK parameters	
Maximum serum T-DM1 concentration (C <sub>max</sub> ), µg/mL	80.5±21.6
Terminal half-life (t <sub>1/2</sub> ), days	3.5±0.7
Volume of distribution, steady state (V <sub>SS</sub> ), mL/kg	30.2±20.2
Clearance (CL), mL/day/kg	9.0±7.3

### Antitumor Activity

	IRF (n=112)	Investigator (n=112)
<b>Best Objective Response, n (%)</b>		
CR	0	3 (2.7)
PR	28 (25.0)	40 (35.7)
SD	54 (48.2)	43 (38.4)
PD	21 (18.8)	22 (19.6)
Unknown	9 (8.0)	4 (3.6)
<b>Overall Response Rate (ORR), n (%)</b>	28 (25.0)	43 (38.4)
95% CI	17.5–33.6	29.8–47.5
<b>Clinical Benefit*</b>	39 (34.8)	50 (44.6)
95% CI	26.1–43.9	35.5–54.3

CI=confidence interval, CR=complete response, IRF=independent review facility, PD=progressive disease, PR=partial response, SD=stable disease  
\* Includes patients who achieved an objective CR, PR, or SD of ≥6 months.

Figure 1. Kaplan–Meier Estimated PFS

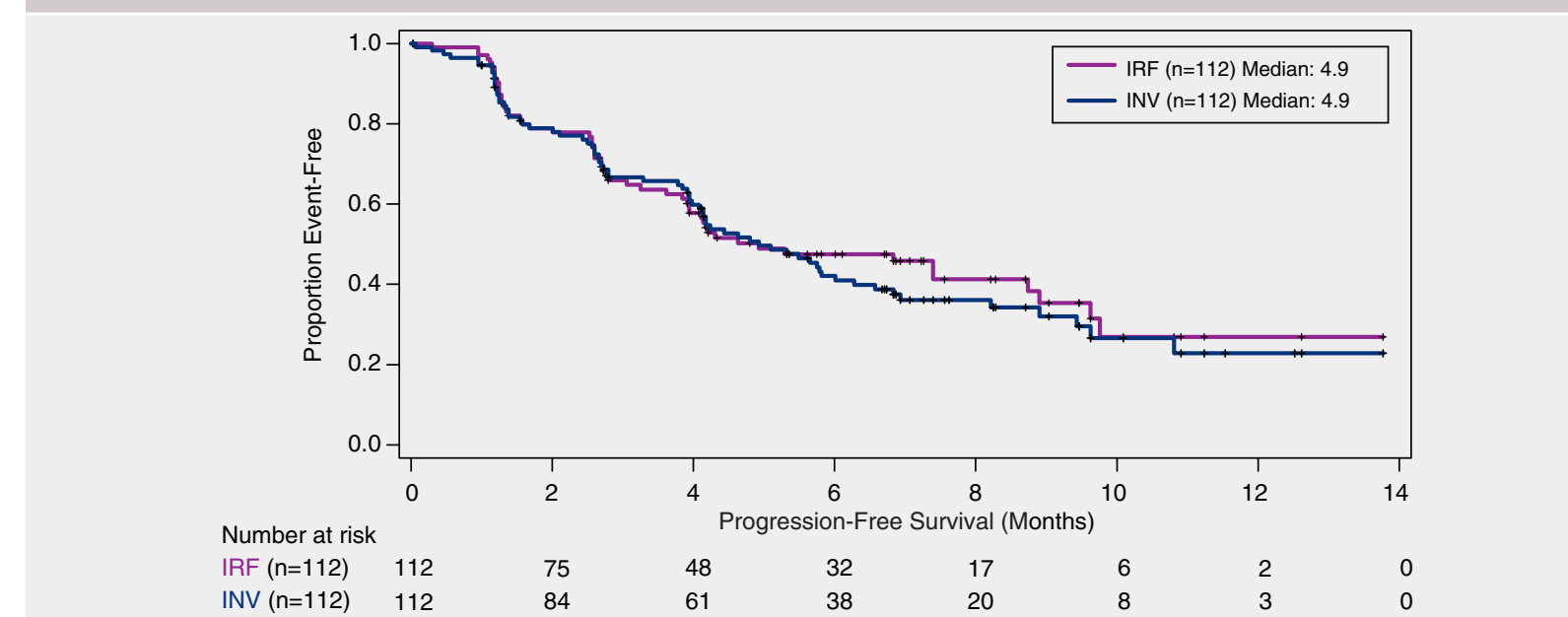
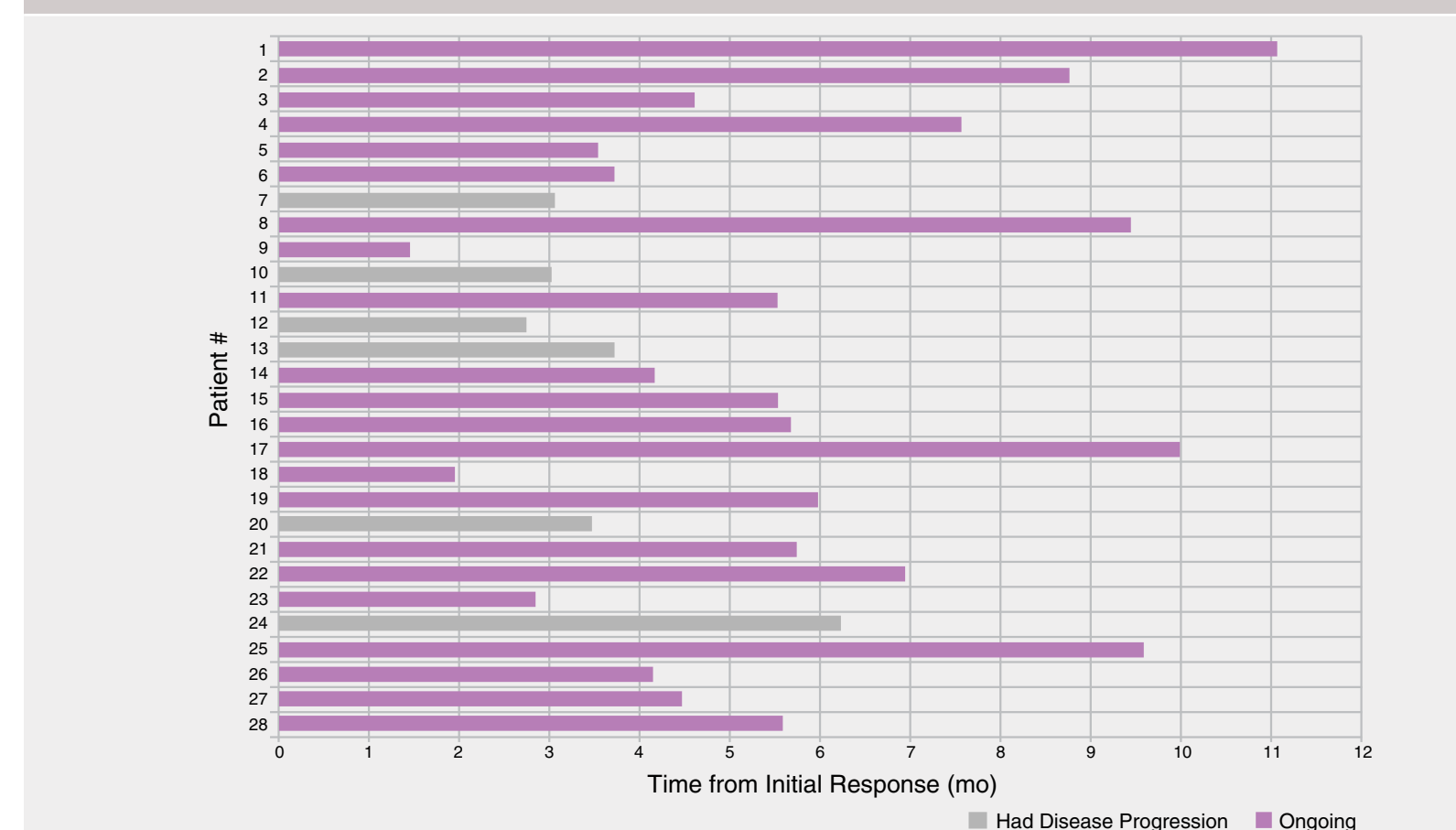


Figure 2. Duration of Response, Responders Only (per IRF). Responders only are shown. Patient 5 was HER2 normal by central lab assessment; central lab HER2 data unavailable for Patients 14, 18 and 27; all other responders had centrally confirmed HER2-positive disease.



Assessment	IRF (n=67)	INV (n=67)
Patients with OR, n (%)	16 (23.9)	24 (35.8)
95% CI for OR	14.3–35.4	25.2–48.2
Patients with clinical benefit*, n (%)	24 (35.8)	30 (44.8)
95% CI for clinical benefit	25.2–48.2	32.8–56.9

CI=confidence interval, INV=investigator, IRF=independent review facility, OR=objective response  
\* Includes patients who achieved an objective CR, PR, or SD of ≥6 months.

Assessment	IRF (n=75)	INV (n=75)
Patients with OR, n (%)	24 (32.0)	36 (48.0)
95% CI for OR	22.1–43.0	36.3–59.9
Patients with clinical benefit†, n (%)	33 (44.0)	41 (54.7)
95% CI for clinical benefit	33.2–55.5	43.0–66.2

CI=confidence interval, INV=investigator, IRF=independent review facility, OR=objective response  
\* Patients had received one or more doses of T-DM1 and had one or more post-baseline tumor assessment, or died on therapy.  
† Includes patients who achieved an objective CR, PR, or SD of ≥6 months.

### T-DM1 Exposure

T-DM1 Exposure	(n = 112)
Median number of doses administered (range)	7.0 (1–17)
Patients still receiving treatment, n (%)	26 (23.2)
Number of Patients with dose reduction*, n (%)	7 (6.2)

\*Dose reduced to 3.0 mg/kg; no further dose reductions were made  
-3 for Grade 3 or 4 thrombocytopenia  
-1 for Grade 3 peripheral neuropathy  
-1 for Grade 2 neutropenia, Grade 3 back pain, and Grade 2 epistaxis  
-2 for unspecified reasons

### Adverse Events (AEs)

- The most common AEs of any grade were fatigue and nausea.
- Most AEs were Grade 1 or 2; Grade ≥3 AEs were infrequent.
- The most common Grade 3 and 4 AEs were hypokalemia, thrombocytopenia, and fatigue.
- No Grade 5 treatment-related AEs were observed.
  - One non-therapy (underlying disease)-related Grade 5 respiratory failure occurred.

Any Adverse Events	Grade 1 or 2	Grade 3	Grade 4	All Grades
Fatigue	72 (64.3)	5 (4.5)	0	73 (62.2)
Nausea	55 (49.1)	1 (0.9)	0	56 (50.0)
Headache	43 (38.4)	0	0	43 (38.4)
Pyrexia	39 (34.8)	1 (0.9)	0	39 (34.8)
Epistaxis	36 (32.1)	2 (1.8)	0	38 (33.9)
Constipation	33 (29.5)	0	0	33 (29.5)
Eye disorders†	31 (27.7)	0	1 (0.9)	32 (28.6)
Cough	30 (26.8)	0	0	30 (26.8)
Diarrrhea	29 (25.9)	0	0	29 (25.9)
Hypokalemia	22 (19.6)	9 (8.0)	0	27 (24.1)
Dyspnea	23 (20.5)	2 (1.8)	1 (0.9)	24 (21.4)
Pain in extremity	24 (21.4)	0	0	24 (21.4)

\* Occurred in at least 20% of patients based on all grades; in some cases an AE was reported at more than one grade for a single patient and thus they may not be additive across the row.  
† Most common eye disorders: dry eye, increased lacrimation, blurred or impaired vision, and conjunctivitis.

Preferred Term	Grade 3	Grade 4
-Any Adverse Events-	42 (37.5)	14 (12.5)
Hypokalemia	9 (8.0)	0
Fatigue	5 (4.5)	0
Thrombocytopenia	5 (4.5)	3 (2.7)
Epistaxis	2 (1.8)	0
Dyspnea	2 (1.8)	1 (0.9)
Anemia	2 (1.8)	0
Chest pain	2 (1.8)	0
Musculoskeletal chest pain	2 (1.8)	0
Neutropenia	2 (1.8)	0
Dysphagia	2 (1.8)	0
Pleural effusion	2 (1.8)	0
Cellulitis	2 (1.8)	0
Convulsion	2 (1.8)	0
Ascites	2 (1.8)	0
Confusional state	0	2 (1.8)

\*One patient had Grade 4 elevation of hepatic transaminases identified as T-DM1-related.

### Patient Discontinuation

- Of the 112 patients, 83 (74.1%) discontinued study treatment (Table 10).

Reason	n (%)
Disease progression (1 death occurred after PD)	70 (62.5)
Death (due to PD)	1 (0.9)
Patient or physician's decision	8 (5.4)
AEs possibly related to T-DM1*	4 (3.6)
AEs unrelated to T-DM1†	1 (0.9)

\*Increased hepatic enzymes (Grade 4), dehydration (Grade 3), thrombocytopenia (Grade 2).  
† Secondary malignancy (Grade 4).

### Cardiac Function

- No Grade ≥3 left ventricular systolic dysfunction events (symptomatic congestive heart failure and/or LVEF of <40%) have been observed.
- Two declines below 45% in LVEF were reported; neither required discontinuation of study drug.
- No elevations in serum troponins were observed.

## CONCLUSIONS/FUTURE DIRECTIONS

- T-DM1 at 3.6 mg/kg IV q3w has robust single-agent activity in patients with previously treated HER2-positive MBC as measured by ORR, duration of response, and PFS.
  - T-DM1 demonstrated similar anti-tumor activity in patients previously treated with lapatinib (in addition to trastuzumab).
- In this study, HER2-positivity (centrally confirmed) was strongly correlated with objective response.
- T-DM1 is well tolerated by patients at the dose and schedule tested with no dose-limiting cardiotoxicity.
- T-DM1 is currently being studied in patients with HER2-positive MBC in Phase I through III trials.

## REFERENCES

- Beeram M, Burris HA, Modi S, et al. 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. J Clin Oncol 26:2009 (May 20 suppl; abstr 1029).
- Trastuzumab (Herceptin®) Investigator Brochure. Genentech, Inc., South San Francisco, CA, July 2007.
- Remillard S, Rebhun LI, Howie GA, et al. 1975. Antimitotic activity of the potent tumor inhibitor maytansine. Science 189(4207):1002–1005.
- Cassidy JM, Chan KK, Floss HG. 2004. Recent developments in the maytansinoid antitumor agents. Chem Pharm Bull 52(1):1–26.
- Widdison WC, Wilhelm SD, Cavanagh EE, et al. 2006. Semisynthetic maytansine analogues for the targeted treatment of cancer. J Med Chem 13:49(14):4392–4408.
- Data-on-file. Genentech, Inc., South San Francisco, CA, July 2007.
- August CD, De Mazziere AM, Piscacane PI, et al. 2004. Endocytosis and sorting of ErbB2 and the site of action of cancer therapeutics trastuzumab and geldanamycin. Mol Biol Cell 15(12):5268–5282.