

A Phase II Study of Trastuzumab-DM1 (T-DM1), a Novel HER2 Antibody–Drug Conjugate, in Patients with HER2+ Metastatic Breast Cancer who were Previously Treated with an Anthracycline, a Taxane, Capecitabine, Lapatinib, and Trastuzumab

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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).¹
 - T-DM1 combines the HER2-targeting properties of trastuzumab² with targeted delivery of a highly potent anti-microtubule derivative, DM1.^{3,5}
 - It is hypothesized that after binding to HER2, T-DM1 undergoes receptor-mediated internalization,⁶ resulting in intracellular release of DM1.
- A prior proof-of-concept Phase II study, 4258g,⁷ of single-agent T-DM1 (3.6mg/kg every 3 weeks) in 112 patients (108 efficacy-evaluable) with previously-treated HER2-positive MBC, demonstrated (25 June 2009 data cut):
 - A confirmed objective response rate (ORR) of 26.9% by independent review (IRF) and 38.9% by investigator assessment (INV), and median PFS of 4.6 months per IRF and INV assessment.
 - T-DM1 demonstrated similar anti-tumor activity, ORR of 24.2% (IRF) and 34.8% (INV), in patients previously treated with lapatinib and trastuzumab (n=66).
 - HER2-positivity (retrospectively, centrally confirmed) was strongly correlated with activity. For centrally confirmed HER2-positive patients (n=74), ORR was 33.8% by IRF and 47.3% by INV.
 - T-DM1 was well tolerated by patients at the dose and schedule tested with no dose-limiting cardiotoxicity and an acceptable toxicity profile in this patient population.
- In order to confirm and extend the findings of the 4258g study, we conducted a phase II study that enrolled a homogenous population of HER2-positive MBC patients who had all received prior chemotherapy, trastuzumab, and lapatinib.

METHODS

4374g Study Design

- Multi-institutional, open-label, single-arm U.S.-based Phase II trial (N=110)
- HER2-positive MBC patients:
 - Prior exposure to an anthracycline, a taxane, capecitabine, lapatinib and trastuzumab
 - Two HER2-directed regimens in the metastatic setting
 - Progressive disease on last regimen received
- T-DM1 at 3.6 mg/kg IV Q3W
- Primary endpoint: ORR assessed by IRF
- Secondary endpoints:
 - ORR by INV assessment
 - Progression-free survival (PFS)
 - Duration of response (DoR)
 - Clinical benefit rate (CBR)
 } By both INV & IRF assessment
- Key exploratory objectives: assess response rates by IRF and INV in HER2-centrally confirmed patients.
- Primary efficacy analysis data cut at 24 weeks post LPI
- Follow-up: 30 days post last dose unless SAE (90 days)

Key Eligibility Criteria

- HER2+ disease by FISH or 3+ IHC by local lab
- Measurable disease by CT scan per RECIST
- 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 2 months of 1st dose

Assessments and Data Collection

- Tumor assessments (per RECIST) were performed every six weeks.
- Echocardiograms or MUGA scans were performed every six weeks.
- Pharmacokinetics (PK) samples for total trastuzumab, T-DM1, and DM1 were collected on Day 1 of Cycles 1-4, 6, 8, 12, and 16 pre- and post-dose, and weekly in Cycles 1 and 4; Cycle 1 PK data are reported in this poster.

RESULTS

Study Status and Primary Analysis Data

- Study fully enrolled with N=110, LPI April 2nd, 2009
 - Data cutoff for primary analysis is September 17, 2009
 - A total of 110 patients received at least one dose of T-DM1.
 - HER2 status was retrospectively assessed for 91 patients at a central laboratory: 76 (83.5%) patients were confirmed HER2-positive.
 - 109/110 patients had received prior trastuzumab, capecitabine, anthracycline, taxane and lapatinib.
 - Seventy patients are off-study.
 - Median follow-up is 8.3 months (range 0.7–13.1).

Table 1. Baseline Characteristics	(N=110)
Median age, years (range)	52.5 (34–77)
Median time since metastatic diagnosis, months (range)	41.4 (1–149)
ECOG PS, n (%)	
0	54 (49.1)
1	53 (48.2)
2	3 (2.7)
ER+ and/or PR+, n (%)	55 (50.0)
ER- and PR-, n (%)	51 (46.4)
Number of distinct metastatic sites, n (%)	
<3	29 (26.4)
≥3	81 (73.6)
Site of metastasis (for ≥40% patients), n (%)	
Local-regional	70 (63.6)
Lung	69 (62.7)
Bone	57 (51.8)
Liver	49 (44.5)

Table 2. Prior Chemotherapy and Anti-HER2 Therapy	(N=110)
Median number of agents for metastatic disease (range)*	7.0 (1–15)
Median number of agents in all therapy setting (range)*	8.0 (1–19)
Number of patients with 5 prior agents, n (%)**	109 (99.1)
Prior trastuzumab	
Median duration of prior trastuzumab in metastatic setting, months (range)	19.4 (2–116)
Prior lapatinib	
Median duration of prior lapatinib in metastatic setting, months (range)	6.9 (0–23)
* Includes all agents intended for the treatment of breast cancer except hormonal therapy	
** One patient did not receive a taxane.	

Table 3. Study Discontinuation	(N=110)
	n (%)
Patients on study as of September 17 th 2009 data cut	40 (36.4)
Patients discontinued treatment	70 (63.6)
Progressive disease	58 (52.7)
Adverse event*	6 (5.5)
Subject's decision	2 (1.8)
Physician's decision	3 (2.7)
Other	1 (0.9)
* Reasons for discontinuation include: abnormal hepatic function (Grade 5), spinal cord compression (Grade 4), fatigue (Grade 3), cholelithiasis/pancreatitis (Grade 3), atelectasis (Grade 2), thrombocytopenia (Grade 2).	

Pharmacokinetics

- PK parameters for T-DM1 conjugate in this phase II study were similar to those reported at the MTD in the phase I study, and to PK parameters for the previously reported 112 patient proof-of-concept Phase II Study TDM4258g.
 - Mean T-DM1 C_{max} was 76.8 µg/ml (standard deviation [SD] of 24.7 µg/ml), terminal half-life was 4.0 days (SD of 1.0 days), and clearance was 8.3 mL/day/kg (SD of 3.1 mL/day/kg)
- Mean (SD) Plasma C_{max} for DM1 at Cycle 4 was 4.8 (2.2) ng/mL

Table 4. T-DM1 Exposure	(N=110)
# Doses Administered, median (range)	7.0 (1–19)
Exposure Duration (weeks), median (range)	19.3 (0–56)
Average T-DM1 Dose (mg/kg), median (range)	3.57 (2.5–3.9)
Dose Reductions	(n=17)
Number of Patients with Dose Reductions to 3.0 mg/kg*	11
Number of Patients with Dose Reductions to 2.4 mg/kg*	6
* Reasons for Dose Reduction Include: Grade 4 thrombocytopenia, Grade 3 elevation AST+ALT, Grade 3 AST elevation, Grade 2 thrombocytopenia, Grade 2 leukopenia, Grade 2 AST+ALT, Grade 2 AST, Grade 1 AST.	

Adverse Events (AEs)

- One hundred and ten patients (100%) experienced an AE (of any grade).
- Twenty-five (22.7%) patients experienced a serious AE.
- Forty-six patients (41.8%) experienced a Grade ≥3 AE.

Table 5. AEs that Occurred in ≥10% Patients (All Grades)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades
Patients with AEs (%)						
Fatigue	30.0	26.4	2.7	0	0	59.1
Nausea	26.4	10.0	0.9	0	0	37.3
Thrombocytopenia	10.9	12.7	3.6	1.8	0	29.1
AST Increased	10.9	10.9	2.7	0	0	24.5
Pyrexia	12.7	8.2	0.9	0	0	21.8
Constipation	17.3	2.7	0.9	0	0	20.9
Dry mouth	17.3	3.7	0	0	0	20.0
Headache	17.3	2.7	0	0	0	20.0
Back pain	13.6	1.8	2.7	0.9	0	19.1
Hypokalemia	16.4	0.9	0.9	0	0	18.2
Anemia	5.5	10.0	1.8	0	0	17.3
Decreased appetite	10.9	6.4	0	0	0	17.3
Cough	12.7	4.5	0	0	0	17.3
Epistaxis	13.6	2.7	0.9	0	0	17.3
Dyspnea	10.0	3.6	1.8	0	0	15.5
Vomiting	8.2	5.5	0	0	0	13.6
Peripheral neuropathy	9.1	4.5	0	0	0	13.6
Diarrhea	9.1	3.6	0	0	0	12.7
Arthralgia	8.2	2.7	1.8	0	0	12.7
Myalgia	11.8	0.9	0	0	0	12.7
Infusion reactions	7.3	4.5	0	0	0	11.8
ALT Increased	6.4	2.7	2.7	0	0	11.8
ALP Increased	8.2	2.7	0	0	0	10.9
Muscle spasms	8.2	2.7	0	0	0	10.9
Pain in extremity	8.2	0.9	1.8	0	0	10.9
Chills	10.0	0	0	0	0	10.0

Table 6. Serious AEs that Occurred in ≥2 Patients (All Grades)*

Patients with AEs (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades
Pyrexia, n (%)	0 (0)	3 (2.7)	0(0)	0 (0)	0 (0)	3 (2.7)
Cellulitis, n (%)	0 (0)	0 (0)	2 (1.8)	1 (0.9)	0 (0)	3 (2.7)
Pneumonia, n (%)	0 (0)	0 (0)	3 (2.7)	0 (0)	0 (0)	3 (2.7)
Nausea, n (%)	1 (0.9)	0 (0)	1 (0.9)	0 (0)	0 (0)	2 (1.8)
Axillary Pain, n (%)	1 (0.9)	0 (0)	1 (0.9)	0 (0)	0 (0)	2 (1.8)
Convulsion, n (%)	0 (0)	0 (0)	1 (0.9)	0 (0)	1 (0.9)	2 (1.8)

*One patient had a grade 5 hepatic dysfunction.

- Of the 107 patients with local left ventricular ejection fraction (LVEF) assessment, no patients had lowest post-baseline LVEF value of <45%, and no patients had maximum decrease from baseline of ≥25%. Two patients had a maximum decrease in LVEF from baseline of between ≥15% to <25%.

Deaths and Causes of Death

- 2 deaths on study within 30 days from last T-DM1 dose:
 - One patient with co-existing non-alcoholic fatty liver disease (NAFLD) along with multiple co-morbidities including contrast-induced renal dysfunction died with hepatic dysfunction.
 - Grade 5 hepatic dysfunction, cause of death listed as adverse event
- One patient died of progressive CNS disease
 - Grade 5 convulsion, cause of death listed as disease progression

Efficacy

Table 7. Antitumor Activity in Treated Patients

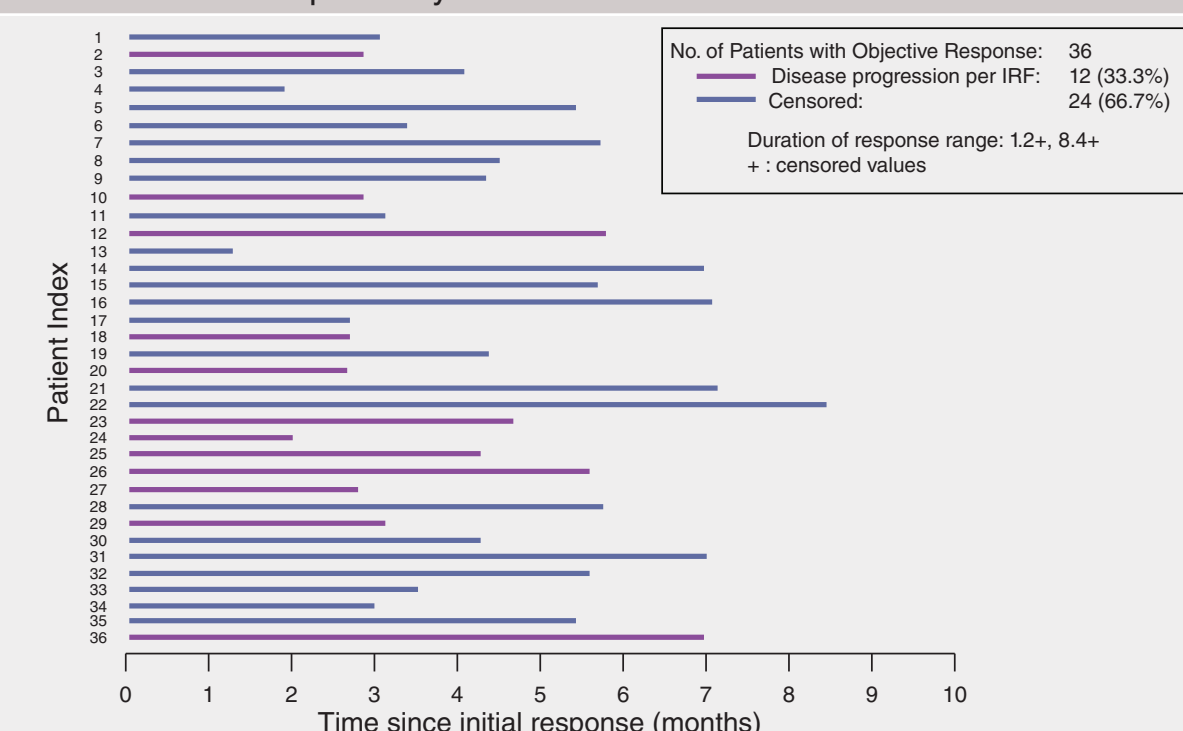
Tumor Response	IRF (N=110)	Investigator (N=110)
Objective Response Rate, % (95% CI)	32.7 (24.1–42.1)	30.0 (22.0–39.4)
CR	0	1.8
PR	32.7	28.2
SD*	46.4	52.7
PD	18.2	13.6
UE	1.8	0.9
Missing	0.9	2.7
Clinical Benefit Rate, % (95% CI)	44.5 (35.1–54.3)	40.0 (31.1–49.3)
IRF - Independent Review Facility, Objective Response - CR or PR determined by two consecutive tumor assessments at least 28 days apart. Clinical Benefit - objective response or SD maintained for at least 6 months. *Including unconfirmed PRs.		

Table 8. Antitumor Activity in Patients by Retrospectively Centrally Confirmed HER2 Status

	IRF	INV
Patients with HER2-positive	n=76	n=76
ORR, %	39.5	36.8
Clinical benefit rate, %	52.6	47.4
Patients with HER2 normal	n=15	n=15
ORR, %	20.0	13.3
Clinical benefit rate, %	26.7	20.0

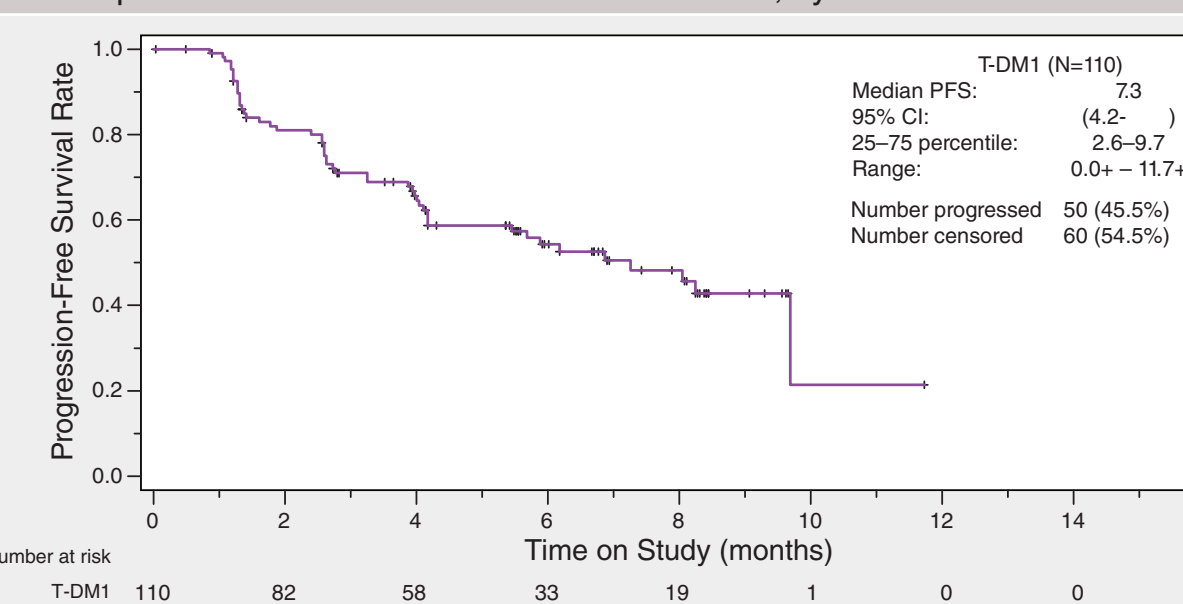
IRF - Independent Review Facility, Objective Response - CR or PR determined by two consecutive tumor assessments at least 28 days apart. Clinical Benefit - objective response or SD maintained for at least 6 months.

Figure 1. Duration of Response by IRF Assessment



Censored = patients without IRF-determined disease progression, as of last tumor assessment.

Figure 2. Kaplan-Meier Plots of PFS in Treated Patients, by IRF Assessment



Censored = patients without IRF-determined disease progression, as of last tumor assessment.

CONCLUSIONS

- Single agent T-DM1, a novel HER2-directed, antibody-drug conjugate demonstrated robust anti-tumor activity in this extensively pretreated population that had a median time from metastatic diagnosis of over 3 years and received over 2 years of prior HER2-directed therapy:
 - ORR: 32.7% IRF, 30.0% INV
 - CBR: 44.5% IRF, 40.0% INV
- Substantial clinical benefit was seen in this prespecified patient population that has not been previously studied:
 - Pre-defined treatment with an anthracycline, a taxane, capecitabine, trastuzumab, and lapatinib
 - Received two HER2-directed regimens in the metastatic setting
 - Progressive disease on last regimen received
- T-DM1 is well tolerated by patients at the dose and schedule tested with no dose-limiting cardiotoxicity or new safety signals.
- The toxicities observed are acceptable and manageable in this extensively pretreated patient population.

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