Dr. Geyer has served on breast cancer advisory boards for Roche/Genentech (uncompensated); has received travel support from Roche/Genentech and AstraZeneca, medical writing support from AbbVie and Roche/Genentech; and honoraria from Celgene. These relationships do not impact his ability to present an unbiased presentation.

Phase III Study of Trastuzumab Emtansine (T-DM1) vs Trastuzumab as Adjuvant Therapy in Patients with HER2-Positive Early Breast Cancer with Residual Invasive Disease after Neoadjuvant Chemotherapy and HER2-Targeted Therapy Including Trastuzumab: Primary Results from KATHERINE (NSABP B-50-I, GBG 77 and Roche BO27938)

Charles E. Geyer, Jr., Chiun-Sheng Huang, Max S. Mano, Sibylle Loibl, Eleftherios P. Mamounas, Michael Untch, Norman Wolmark, Priya Rastogi, Andreas Schneeweiss, Andrés Redondo, Hans H. Fischer, William Jacot, Alison K. Conlin, Claudia Arce-Salinas, Irene L. Wapnir, Christian Jackisch, Michael P. DiGiovanna, Peter A. Fasching, John P. Crown, Pia Wülfing, Zhimin Shao, Elena Rota Caremoli, Haiyan Wu, Lisa H. Lam, David Tesarowski, Melanie Smitt, Hannah Douthwaite, Stina M. Singel, and Gunter von Minckwitz, on behalf of the KATHERINE investigators

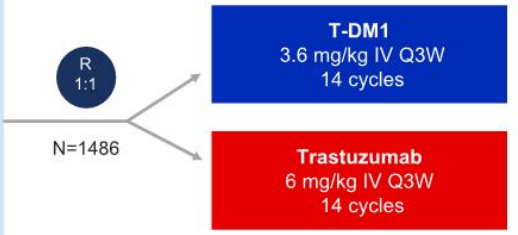
Rationale for KATHERINE Study Design

- HER2-positive early breast cancer patients with residual invasive disease following neoadjuvant chemotherapy combined with HER2-targeted therapy have an increased risk of recurrence and death[1-5]
- T-DM1 is active in HER2-positive metastatic breast cancer following prior exposure to taxanes and HER2-targeted therapy[6-9]
- A phase 2 study demonstrated that administration of T-DM1 following an anthracycline-containing regimen was feasible in patients with EBC[10]
- KATHERINE investigated whether substituting adjuvant T-DM1 for trastuzumab would improve outcomes for patients with residual invasive cancer following neoadjuvant therapy

[1]Untch et al. *J Clin Oncol* 2011;29:3351; [2]Cortazar et al. *Lancet* 2014;384:164; [3]de Azambuja et al. *Lancet Oncol* 2014;15:1137; [4]Gianni et al. *Lancet Oncol* 2014;15:640; [5]Schneeweiss et al. *Eur J Cancer* 2018;89:27; [6]Verma et al. *N Engl J Med* 2012;367:1783; [7]Krop et al. *Lancet Oncol* 2014;15:689; [8]Dieras et al. *Lancet Oncol* 2017;18:743; [9]Krop et al. *Lancet Oncol* 2017;18:743; [10]Krop et al. *J Clin Oncol* 2015;33:1136.

KATHERINE Study Design

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Statistical Considerations

Primary Endpoint: IDFS

IDFS analyses

Final IDFS

- Adjuvant trastuzumab assumed to provide 3-year IDFS of 70% and improvement with T-DM1 to 76.5% (HR=0.75) would be clinically meaningful
- To provide 80% power with 2-sided alpha 5%, 384 events required

Single Pre-specified Interim Analysis of IDFS

- When 67% of events (~257) occurred
- Early reporting boundary:
  - HR < 0.732 or
  - *P* < 0.0124

First Interim OS analysis

- Performed at time of interim IDFS analysis IF boundary is crossed
- The overall type I error controlled at 0.05 using the Lan−DeMets alpha spending function with O'Brien−Fleming boundary

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Study Population

	Trastuzumab (n=743)	T-DM1 (n=743)
Randomized ITT (efficacy analyses)	743	743
Treated (safety analyses)	720	740
Median duration of follow up (months)	40.9	41.4

First patient in: 03 April, 2013
Last patient in: 31 December, 2015
Clinical data cutoff: 25 July, 2018
IDMC review of interim analysis: 28 September, 2018

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Baseline Characteristics of ITT Population (1)

	Trastuzumab (n=743)	T-DM1 (n=743)
Median age (range), years	49 (23–80)	49 (24–79)
<40 years, n (%)	153 (20.6)	143 (19.2)
40–64 years, n (%)	522 (70.3)	542 (72.9)
≥65 years, n (%)	68 (9.2)	58 (7.8)
Race, n (%)		
White	531 (71.5)	551 (74.2)
Asian	64 (8.6)	65 (8.7)
American Indian^ or Alaska Native	50 (6.7)	36 (4.8)
Black or African American	19 (2.6)	21 (2.8)
Multiple/Unknown/Other	79 (10.6)	70 (9.4)
Region, n (%)		
North America	164 (22.1)	170 (22.9)
Western Europe	403 (54.2)	403 (54.2)
Rest of world	176 (23.7)	170 (22.9)
Prior anthracycline, n (%)	564 (75.9)	579 (77.9)

^Includes North, Central, and South American Indians.

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Characteristics of ITT Population (2): Stratification Factors

	Trastuzumab (n=743)	T-DM1 (n=743)
Clinical stage at presentation, n (%)		
Operable (stages cT1-3N0–1M0)	553 (74.4)	558 (75.1)
Inoperable (stage cT4NxM0 or cTxN2–3M0)	190 (25.6)	185 (24.9)
Hormone receptor status, n (%)		
ER and/or PgR positive	540 (72.7)	534 (71.9)
ER negative and PgR negative/unknown	203 (27.3)	209 (28.1)
Preoperative HER2-targeted therapy, n (%)		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab plus additional HER2-targeted agent(s)^ - Trastuzumab plus pertuzumab*	147 (19.8) 139 (18.7)	143 (19.2) 133 (17.9)
Pathologic nodal status after preoperative therapy, n (%)		
Node positive	346 (46.6)	343 (46.2)
Node negative/not done	397 (53.4)	400 (53.8)

^Non-pertuzumab HER2-targeted agents included: neratinib, dacomitinib, afatinib, lapatinib.
*Not a stratification factor, included for informational purposes.

Baseline Characteristics of ITT Population (3)

	Trastuzumab (n=743)	T-DM1 (n=743)
Primary tumor stage (at definitive surgery)^, n (%)		
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	306 (41.2)	331 (44.5)
ypT1/ypT1c	184 (24.8)	175 (23.6)
ypT2	185 (24.9)	174 (23.4)
ypT3, ypT4	67 (9.0)	63 (8.5)
Regional lymph node stage (at definitive surgery), n (%)		
ypN0	335 (45.1)	344 (46.3)
ypN1	213 (28.7)	220 (29.6)
ypN2, ypN3	133 (17.9)	123 (16.6)
ypNX	62 (8.3)	56 (7.5)
Residual invasive disease 1 cm or less AND negative axillary nodes (ypT1a, ypT1b or ypT1mic and ypN0)	161 (21.7)	170 (22.9)

^One patient in the trastuzumab arm was reported as ypTX; Five patients had ypT1 disease without further subspecification.

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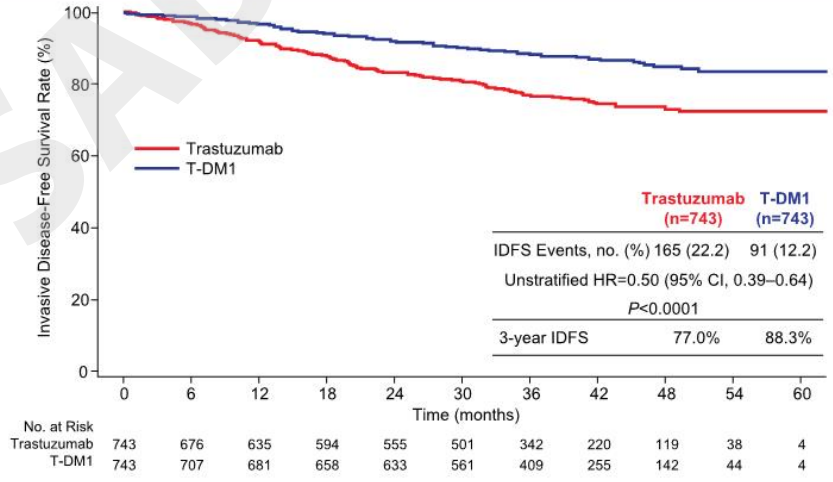
Invasive Disease-Free Survival



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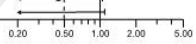
IDFS Subgroup Analysis (1)

Group	Total N	Trastuzumab (n=743) 3-Year IDFS	T-DM1 (n=743) 3-Year IDFS	Hazard Ratio	95% CI
All	1486	77.0	88.3	0.50	(0.39–0.64)
Clinical stage at presentation					
Operable	1111	82.8	92.3	0.47	(0.33–0.66)
Inoperable	375	60.2	76.0	0.54	(0.37–0.80)
Hormone receptor status					
Negative (ER negative and PgR negative/unknown)	412	66.6	82.1	0.50	(0.33–0.74)
Positive (ER and/or PgR positive)	1074	80.7	90.7	0.48	(0.35–0.67)
Preoperative HER2-directed therapy					
Trastuzumab alone	1196	75.9	87.7	0.49	(0.37–0.65)
Trastuzumab plus additional HER2-directed agent(s)	290	81.8	90.9	0.54	(0.27–1.06)
Pathological nodal status after preoperative therapy					
Node positive	689	67.7	83.0	0.52	(0.38–0.71)
Node negative/not done	797	84.6	92.8	0.44	(0.28–0.68)
Age group (years)					
<40	296	74.9	86.5	0.50	(0.29–0.86)
40–64	1064	77.1	88.8	0.49	(0.36–0.67)
≥65	126	81.1	87.4	0.55	(0.22–1.34)
Race^					
White	1082	79.1	88.8	0.51	(0.37–0.69)
Asian	129	71.9	82.5	0.65	(0.32–1.32)
American Indian or Alaska Native	86	60.3	81.8	0.44	(0.18–1.03)
Black or African American	40	66.0	94.7	0.13	(0.02–1.10)



^149 were of multiple races or unknown race.

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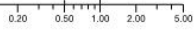
IDFS Subgroup Analysis (2)

Group	Total N	Trastuzumab (n=743) 3-Year IDFS	T-DM1 (n=743) 3-Year IDFS	Hazard Ratio	95% CI
All	1486	77.0	88.3	0.50	(0.39–0.64)
Primary tumor stage (at definitive surgery)					
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	637	83.6	88.3	0.66	(0.44–1.00)
ypT1, ypT1c	359	75.9	91.9	0.34	(0.19–0.62)
ypT2	359	74.3	88.3	0.50	(0.31–0.82)
ypT3	108	61.1	79.8	0.40	(0.18–0.88)
ypT4^	23	30.0	70.0	0.29	(0.07–1.17)
Regional lymph node stage (at definitive surgery)					
ypN0	679	83.9	91.9	0.46	(0.30–0.73)
ypN1	433	75.8	88.9	0.49	(0.31–0.78)
ypN2	189	58.2	81.1	0.43	(0.24–0.77)
ypN3	67	40.6	52.0	0.71	(0.35–1.42)
ypNX	118	88.7	98.1	0.17	(0.02–1.38)
Residual disease ≤1 cm with negative axillary lymph nodes					
ypT1a, ypT1b or ypT1mic and ypN0	331	85.3	90.0	0.60	(0.33–1.12)
Central HER2 status by IHC*					
0/1+	25	83.9	100.0	<0.01	(0.00–NE)
2+	326	80.9	84.7	0.83	(0.50–1.38)
3+	1132	75.7	89.0	0.43	(0.32–0.58)



^Includes all ypT4 and 1 patient with ypTX; *Three patients had "unknown" HER2 IHC status.

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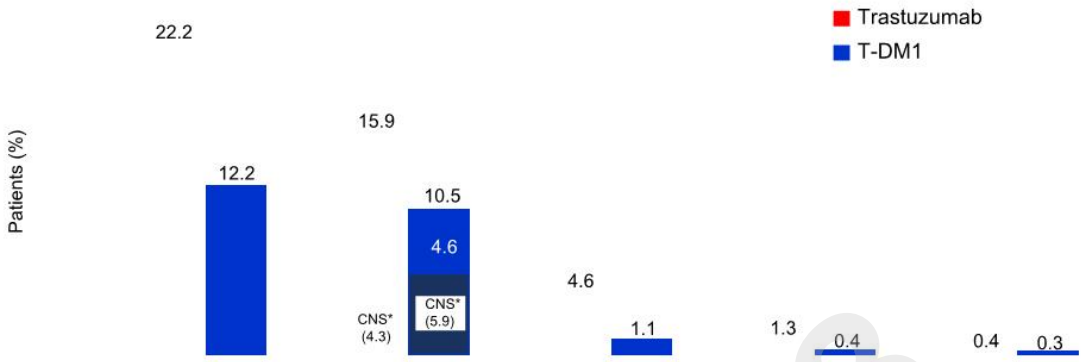
First IDFS Events



*Patients who experience additional IDFS event(s) within 61 days of their first IDFS event are reported in the category according to the following hierarchy: [1] Distant recurrence; [2] Locoregional recurrence; [3] Contralateral breast cancer; [4] Death without prior event.
***CNS metastases as component of distant recurrence (isolated or with other sites).** Trastuzumab T-DM1

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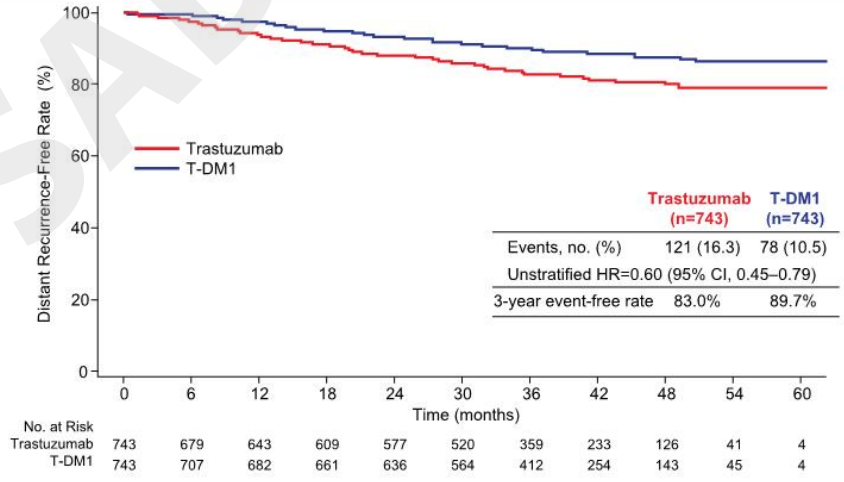
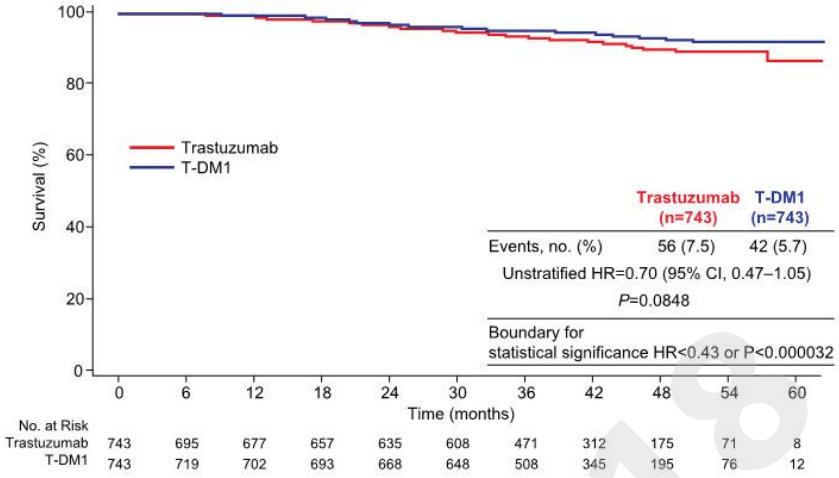
Distant Recurrence



	Trastuzumab (n=743)	T-DM1 (n=743)
Events, no. (%)	121 (16.3)	78 (10.5)
Unstratified HR=0.60 (95% CI, 0.45–0.79)		
3-year event-free rate	83.0%	89.7%

No. at Risk											
Trastuzumab	743	679	643	609	577	520	359	233	126	41	4
T-DM1	743	707	682	661	636	564	412	254	143	45	4

Overall Survival



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Exposure to Study Treatment

	Trastuzumab (n=720)	T-DM1 (n=740)
Cycles of trastuzumab/T-DM1 completed, n (%)		
7 cycles	664 (92.2)	637 (86.1)
14 cycles	583 (81.0)	528 (71.4)
Patients with a dose reduction, n (%)		
No dose reduction	N/A	634 (85.7)
One dose level reduction (3.0 mg/kg)	N/A	77 (10.4)
Two dose level reductions (2.4 mg/kg)	N/A	29 (3.9)

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Safety Overview

	Trastuzumab n=720	T-DM1 n=740
Number of patients with at least one , n (%)		
Grade ≥3 AEs	111 (15.4)	190 (25.7)
Serious AEs	58 (8.1)	94 (12.7)
AE leading to treatment discontinuation	15 (2.1)	133 (18.0)
AE with fatal outcome^	0	1 (0.1)

^Fatal AE was intracranial hemorrhage diagnosed after a fall with platelet count of 55,000.

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AEs Leading to Treatment Discontinuation (≥1% Incidence Either Arm)

	Trastuzumab n=720	T-DM1 n=740
Patients discontinuing due to adverse events	15 (2.1%)	133 (18.0%)
Platelet count decreased	0	31 (4.2%)
Blood bilirubin increased	0	19 (2.6%)
Aspartate aminotransferase (AST) increased	0	12 (1.6%)
Alanine aminotransferase (ALT) increased	0	11 (1.5%)
Peripheral sensory neuropathy	0	11 (1.5%)
Ejection fraction decreased	10 (1.4%)	9 (1.2%)

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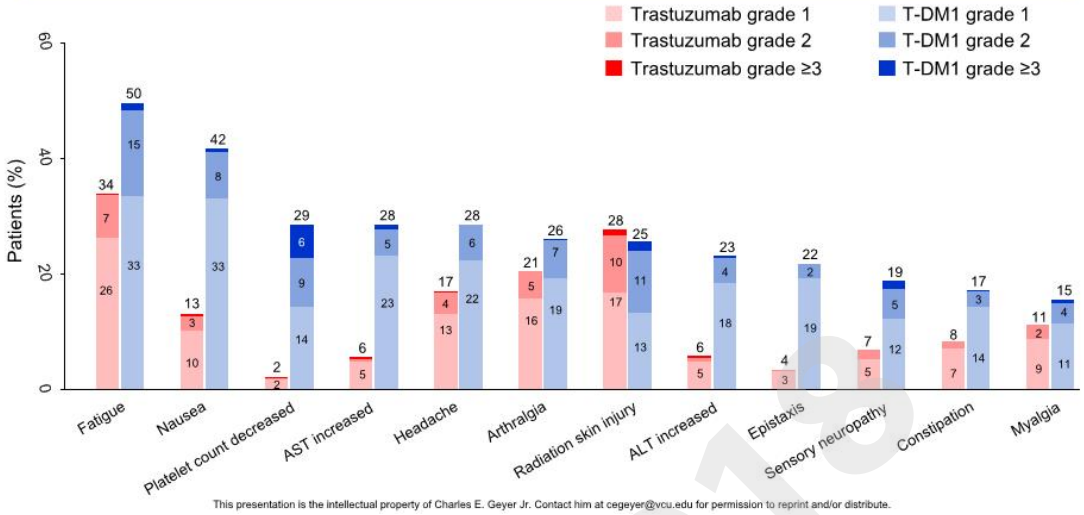
All Grade AEs ≥15% Incidence in Either Arm



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KATHERINE Summary and Conclusions

- Adjuvant T-DM1 demonstrated both a statistically significant and clinically meaningful improvement in IDFS compared with trastuzumab
  - Unstratified HR=0.50; 95% CI 0.39–0.64; *P*<0.0001
  - 3-year IDFS rate improved from 77.0% to 88.3% (difference=11.3%)
- Benefit of T-DM1 was consistent across all key subgroups including HR status, extent of residual invasive disease, and single or dual HER2-targeted neoadjuvant therapy
- The safety data were consistent with the known manageable toxicities of T-DM1, with expected increases in AEs associated with T-DM1 compared to trastuzumab
- Additional follow-up will be necessary to evaluate the effect of T-DM1 on OS
- The KATHERINE data will likely form the foundation of a new standard of care in this population and increase the use of neoadjuvant therapy in HER2-positive EBC

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Thank You

To all of the patients who participated in KATHERINE along with their families, with special acknowledgment to those on the control arm

To the KATHERINE investigators and their research staffs at the 273 sites in 28 countries

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ORIGINAL ARTICLE

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

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