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TBCRC 033: A Randomized Phase 2 Trial of Adjuvant Trastuzumab Emtansine (T-DM1) vs. Paclitaxel with Trastuzumab for Stage 1 HER2+ Breast Cancer (ATEMPT)

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tbcrc

TBCRC 033: A Randomized Phase 2 Trial of Adjuvant Trastuzumab Emtansine (T-DM1) vs. Paclitaxel with Trastuzumab for Stage 1 HER2+ Breast Cancer (ATEMPT)

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Background

- Many patients with Stage I HER2+ breast cancers have a sufficiently high risk of recurrence to justify the administration of adjuvant therapy[1,2]
- Paclitaxel and trastuzumab (TH) is associated with 7 year DFS 93% in patients with node-negative HER2+ disease with tumors ≤ 3cm[3,4]
- Trastuzumab emtansine (T-DM1) is active in metastatic HER2+ breast cancer and in patients with residual disease after preoperative HER2-directed therapy[5,6,7]
  - Associated with less toxicity compared to chemotherapy with trastuzumab[8,9]
- ATEMPT investigated whether T-DM1 is associated with a clinically acceptable event rate in patients with Stage I HER2+ breast cancer and if T-DM1 is associated with less clinically relevant toxicity compared to TH

[1]Gonzalez-Angulo AM et al. JCO 2009; [2]Vaz-Luis I et al. JCO 2014; [3]Tolaney SM et al. NEJM 2015; [4]Tolaney SM et al. JCO 2019; [5]Verma S et al. NEJM 2012; [6]Perez EA. JCO 2017; [7]von Minckwitz G et al. NEJM 2019 ; [8]Hurvitz SA et al. JCO 2013 ; [9]Hurvitz SA et al. Lancet Onc 2018

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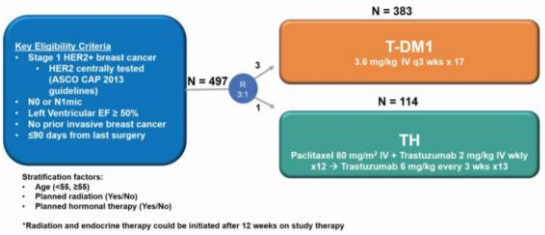
Study Design: ATEMPT Trial



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Study Endpoints

- Co-primary Endpoints:
  - Evaluate 3 year disease-free survival (DFS) in the T-DM1 arm
  - Compare the incidence of clinically relevant toxicities (CRT) between the 2 arms
    - grade ≥3 non-hematologic toxicity
    - grade ≥2 neurotoxicity
    - grade ≥4 hematologic toxicity
    - febrile neutropenia
    - any toxicity requiring dose delay or discontinuation of protocol therapy

*The study is not powered to evaluate the efficacy of TH or to compare the efficacy of T-DM1 to TH

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Statistical Considerations

- For evaluation of DFS, the T-DM1 arm (n=375) was designed to have 95% power to distinguish between 3-year failure rates of 9% vs. 5%
- With 375 and 125 pts randomized to T-DM1 and TH, respectively, there was 81% power to detect a 40% difference in clinically relevant toxicities (CRT)
- Planned interim analyses were designed to stop early for futility and T-DM1 would be deemed worthy of further study with <39 failures after 1600 patient years of follow-up (PYFU)
- Study activated 5/17/2013; closed to accrual 12/13/2016 (34 sites in United States)
- Results are based on all data available as of 8/26/2019; median follow-up 3.1 years, PYFU:1650 years

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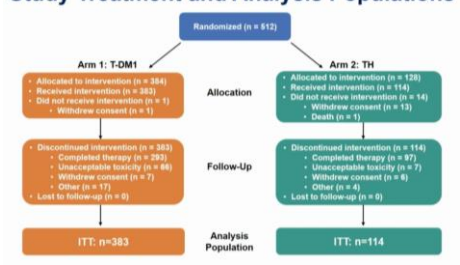
Study Treatment and Analysis Populations



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Study Population

	T-DM1 (n = 383)	TH (n = 114)	All Patients (n = 497)	
Median Age (Range)	56 (32-85)	55 (23-82)	56 (23-85)	
Tumor Size				
<0.5 cm	42 (11%)	14 (12%)	56 (11%)	43%
≥0.5-1.0 cm	121 (32%)	38 (33%)	159 (32%)	
≥1.0-1.5 cm	118 (31%)	29 (25%)	147 (30%)	57%
≥1.5-2.0 cm	102 (27%)	33 (29%)	135 (27%)	
Histologic Grade				
Well Differentiated	11 (3%)	4 (4%)	15 (3%)	
Moderately Differentiated	148 (39%)	46 (40%)	194 (39%)	
Poorly Differentiated	219 (57%)	62 (54%)	281 (57%)	
Unknown	5 (1%)	2 (2%)	7 (2%)	
HR status				
Positive	289 (75%)	84 (74%)	373 (75%)	
Negative	94 (25%)	30 (26%)	124 (25%)	
HER2 Status (Central)				
1+	5 (1%)	1 (1%)	6 (1%)	
2+	92 (24%)	25 (22%)	117 (24%)	
3+	277 (72%)	87 (76%)	364 (73%)	
Not done*	9 (2%)	1 (1%)	10 (2%)	

*FISH performed centrally without IHC

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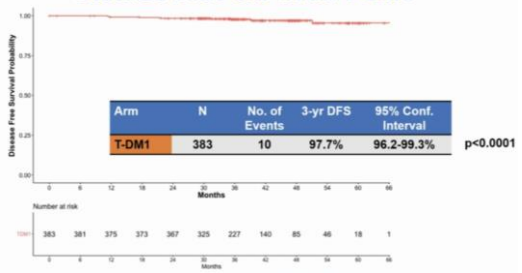
Disease-Free Survival: T-DM1



Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
T-DM1	383	10	97.7%	96.2-99.3%

p<0.0001

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Disease-Free Survival Events: T-DM1

DFS Event: T-DM1	N (of 383)	Time to event (months)
Any recurrence or death	10	
Local/Regional Recurrence*		
Ipsilateral axilla (HER2+)	1	35
Ipsilateral breast (HER2-)	1	11
New Contralateral Primary Breast Cancer		
HER2+	0	
HER2-	3	12, 18, 21
Distant Recurrence	2	22, 51
Death		
Non-breast cancer related*	3	12, 32, 39

*Deaths due to: Diabetic coma, Stroke, Creutzfeldt Jakob disease

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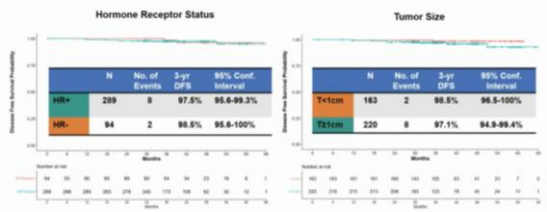
Disease-Free Survival: T-DM1



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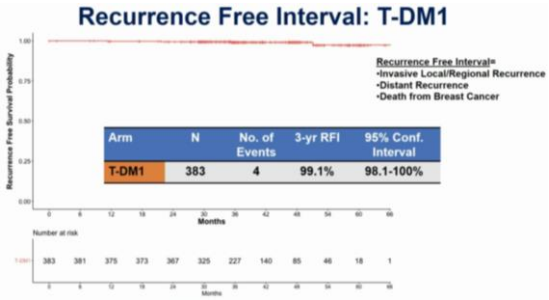
Recurrence Free Interval: T-DM1



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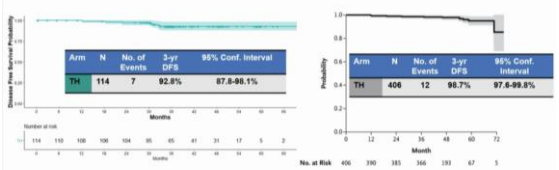
Disease-Free Survival: TH

TH (ATEMPT Trial): n=114

Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
TH	114	7	92.8%	87.8-98.1%

TH (APT Trial): n=406

Arm	N	No. of Events	3-yr DFS	95% Conf. Interval
TH	406	12	98.7%	97.6-99.8%



Tolaney S et al, NEJM 2015

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Disease-Free Survival Events: TH

DFS Event: TH	N (of 114)	Time to event (months)
Any recurrence or death	7	
Local/Regional Recurrence*		
Ipsilateral axilla (HER2+)	2	18, 33
Ipsilateral breast (HER2+)	2	31, 32
New Contralateral Primary Breast Cancer		
HER2+	0	
HER2-	1	23
Distant Recurrence	2	12, 30
Death	0	

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Clinically Relevant Toxicity

Clinically Relevant Toxicity	T-DM1 (n = 383) N (%)	TH (n = 114) N (%)
Grade ≥3 non-hematologic toxicity	37 (10%)	13 (11%)
Grade ≥ 2 neurotoxicity	42 (11%)	26 (23%)
Grade ≥4 hematologic toxicity	4 (1%)	0 (0%)
Febrile neutropenia	0 (0%)	2 (2%)
Any toxicity requiring dose delay	106 (28%)	30 (26%)
Any toxicity requiring early discontinuation	67 (17%)	7 (6%)
Total	176 (46%)	53 (46%)

p=0.91

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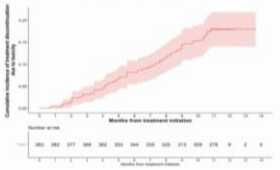
T-DM1 discontinuations

	n (%)
Discontinuations for any reason	90 (23.5%)
Discontinuations for toxicity[1]	67 (17.0%)
Discontinuations for toxicity that were protocol mandated	33 (9%)

[1]Most common toxicities leading to discontinuation include: liver enzyme elevation, bilirubin elevation, neuropathy, and thrombocytopenia

- 66% of patients who discontinued T-DM1 early for toxicity received further therapy with trastuzumab

Timing of Discontinuation



- Probability of discontinuing within 6 months: 8.2%
- Probability of discontinuing between months 6-12: 10.7%

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Treatment Related Adverse Events: Grade ≥2 by Arm

	T-DM1 (n = 383)	TH (n = 114)
Fatigue	84 (22%)	26 (23%)
Neuropathy	44 (11%)	27 (24%)
Neutropenia	13 (3%)	15 (13%)
Thrombocytopenia	43 (11%)	1 (1%)
Nausea	39 (10%)	8 (7%)
Hypertension	35 (9%)	7 (6%)
ALT increase	33 (9%)	5 (4%)
Headache	24 (6%)	4 (4%)
Bilirubin increase	21 (5%)	1 (1%)
Infusion related reaction	19 (5%)	12 (11%)
Arthralgia	18 (5%)	2 (2%)
Anemia	18 (5%)	2 (2%)

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Cardiac Toxicity

	Arm 1: T-DM1 (n = 383)	Arm 2: TH (n = 114)
Symptomatic Congestive Heart Failure	3 (0.8%)	1 (0.9%)
Asymptomatic declines in LVEF (≥15%)	5 (1.3%)	7 (6.1%)

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Conclusions (1)

- This represents the first report of patients receiving T-DM1 monotherapy for adjuvant treatment of Stage I HER2+ breast cancer
- T-DM1 was associated with very few recurrences in the study population
  - 3 year DFS 97.7% (95% CI: 96.2-99.3), RFI 99.1% (95% CI: 98.1-100)
  - Longer follow-up needed in a population with predominantly hormone-receptor positive disease
- T-DM1 was not associated with significantly fewer clinically relevant toxicities than TH
  - Safety and rates of discontinuation are similar to KATHERINE, with no new toxicities identified
  - T-DM1 was associated with more early discontinuation of therapy, though only 9% of patients discontinued T-DM1 early for toxicity that was protocol mandated

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Conclusions (2)

- No difference seen in the overall incidence of clinically relevant toxicities (CRT) between the two arms, but there were differences in toxicity profiles between T-DM1 and TH
- Not all toxicities are captured in the CRT endpoint, including alopecia, and patient reported outcomes (PROs) should be considered when assessing tolerability
  - PROs were collected serially during this trial and favored T-DM1
  - Partridge A et al, Abstract # 1159, Friday (12/13/19) Spotlight Session 7-9am
  - Ruddy K et al, Abstract #454, Thursday (12/12/19) Poster Session 7-9am

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Conclusions (3)

- Given the low event rate seen in this trial, T-DM1 may be an alternative to TH for select patients with stage I HER2+ disease who are concerned about specific TH related side effects and understand the potential T-DM1 toxicities
- Further evaluation of shorter duration therapy with T-DM1 followed by trastuzumab should be considered

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