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Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis

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IDFS, invasive disease-free survival; OS, overall survival.

Disclosure information

Sibylle Loibl

I have the following relevant financial relationships to disclose:

Grants and other support from Roche during the conduct of the study; grants and other support from AstraZeneca, AbbVie, Amgen, DSI, Gilead, Celgene/BMS, Novartis, and Pfizer; grants from Molecular Health; other support from Seagen, Sanofi, Relay, Olema, EirGenix, Merck KGaA, Lilly, GSK, Pierre Fabre, and Eisai outside the submitted work; a patent for VM Scope with royalties paid; a patent for EP14153692.0 pending; a patent for EP21152186.9 pending; and a patent for EP15702464.7 pending

Please refer to the abstract for all author conflicts of interest. All authors have received research support in the form of third-party writing assistance for this presentation from F. Hoffmann-La Roche Ltd

The KATHERINE study is sponsored by F. Hoffmann-La Roche Ltd

KATHERINE study design

- Prior neoadjuvant therapy consisting of:
  - Minimum 6 cycles of chemotherapy
  - Minimum 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

R
1:1

N = 1486

T-DM1
3.6 mg/kg IV Q3W
14 cycles

Trastuzumab
6 mg/kg IV Q3W
14 cycles

- Radiation and endocrine therapy per protocol and local guidelines
- Switch to trastuzumab permitted if T-DM1 discontinued due to AEs

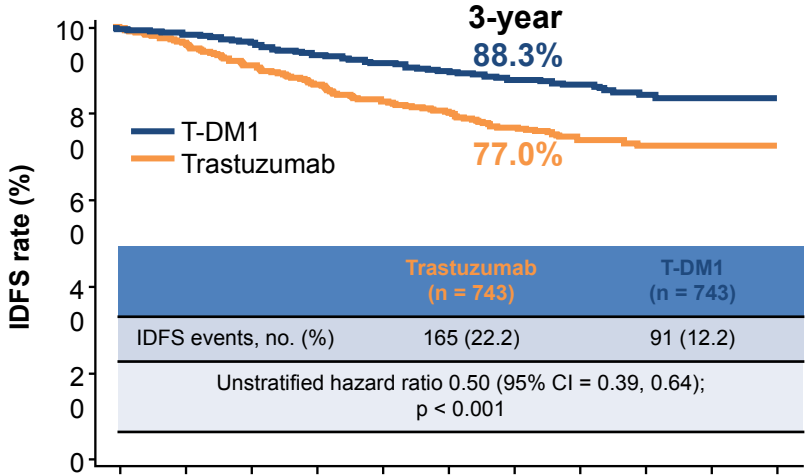
- **Primary endpoint:** IDFS
- **Secondary endpoints:** IDFS with second primary non-breast cancers included, DFS, OS, DRFI, safety, and QoL
- **Stratification factors:** Clinical stage at presentation (inoperable vs operable), HR status, preoperative HER2-directed therapy, pathologic nodal status after preoperative therapy

AE, adverse event; DFS, disease-free survival; DRFI, distant recurrence-free interval; HR, hormone receptor; IDFS, invasive disease-free survival; IV, intravenous; OS, overall survival; Q3W, every 3 weeks; QoL, quality of life; R, randomized; T-DM1, ado-trastuzumab emtansine.

Adapted from *N Engl J Med*, von Minckwitz *et al*., Trastuzumab emtansine for residual invasive HER2-positive breast cancer, Vol. 380, Pages 617–628.

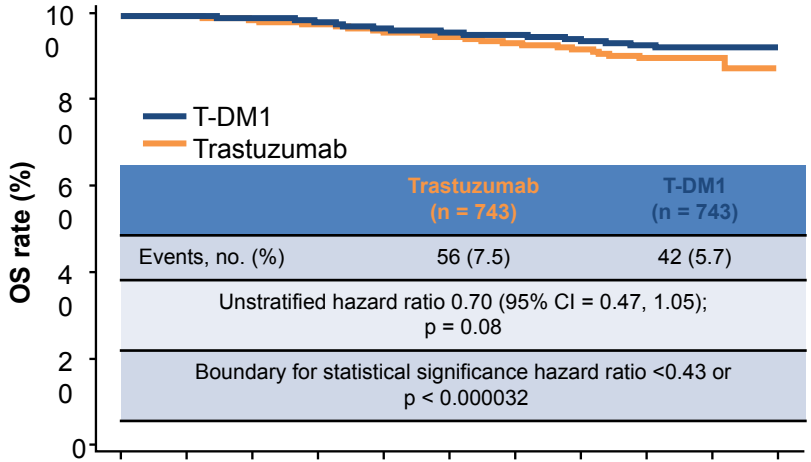
KATHERINE primary analysis (2018)

IDFS



	Trastuzumab (n = 743)	T-DM1 (n = 743)
IDFS events, no. (%)	165 (22.2)	91 (12.2)
Unstratified hazard ratio 0.50 (95% CI = 0.39, 0.64); p < 0.001		

OS



	Trastuzumab (n = 743)	T-DM1 (n = 743)
Events, no. (%)	56 (7.5)	42 (5.7)
Unstratified hazard ratio 0.70 (95% CI = 0.47, 1.05); p = 0.08		
Boundary for statistical significance hazard ratio <0.43 or p < 0.000032		

CCOD: July 25, 2018; median follow-up: 41.4 months (T-DM1) and 40.9 months (trastuzumab).
CCOD, clinical cutoff date; CI, confidence interval; IDFS, invasive disease-free survival; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

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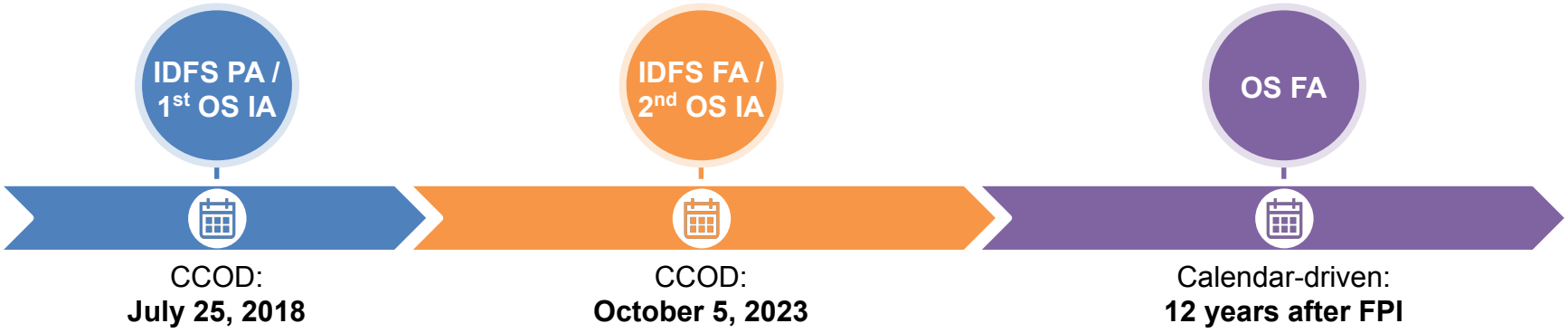
Analysis milestones



- FA of IDFS: Event-driven, after approximately 384 events have been recorded
  - There were 385 patients with an event (129 more than at the PA)
- 2nd OS IA: Pre-planned, occurred at the same time as the final IDFS analysis
  - Median follow-up time was 101 months, 60 months longer than at the PA
  - There were 215 OS events (117 more than at the PA)
- During the follow-up period, i.e. >30 days after the last dose of study drug, only deaths, serious AEs, or other AEs of concern that are believed to be related to prior treatment with study drug or study procedures were reported

AE, adverse event; CCOD, clinical cutoff date; FA, final analysis; FPI, first patient in; IA, interim analysis; IDFS, invasive disease-free survival; OS, overall survival; PA, primary analysis; T-DM1, ado-trastuzumab emtansine.

Patient disposition

	Trastuzumab	T-DM1
Randomized, ITT, n	743	743
Treated, n	720	740
Alive and on study, n (% of ITT)	461 (62.0)	521 (70.1)
Discontinued from study, n (%)		
With IDFS event reported	159 (21.4)	105 (14.1)
Prior to IDFS event*	123 (16.6)	117 (15.7)

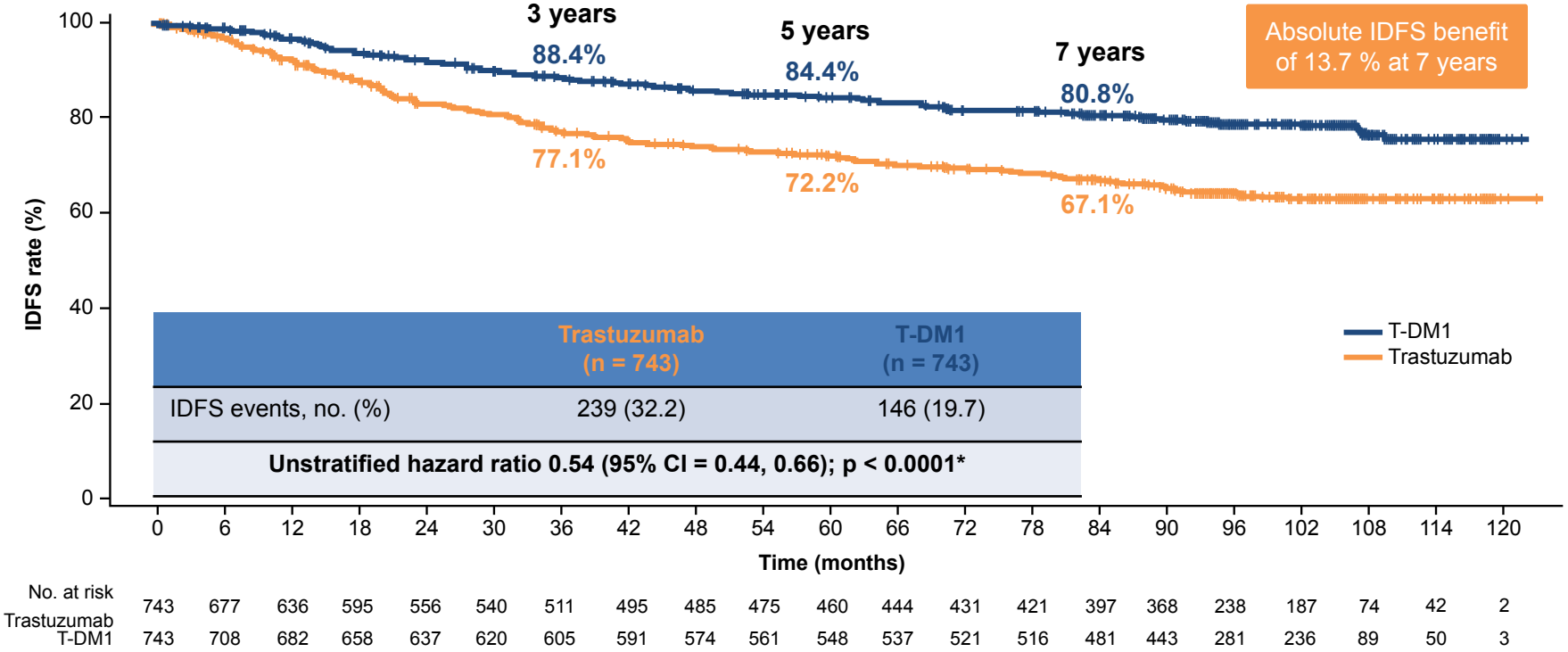
* Reasons include: Withdrawal by subject, 88 (11.8%) in the trastuzumab arm and 77 (10.4%) in the T-DM1 arm; lost to follow-up, 28 (3.8%) in the trastuzumab arm and 30 (4.0%) in the T-DM1 arm; other, 7 (0.9%) in the trastuzumab arm and 5 (0.7%) in the T-DM1 arm; physician decision, 0 in the trastuzumab arm and 5 (0.7%) in the T-DM1 arm.
IDFS, invasive disease-free survival; ITT, intention-to-treat; T-DM1, ado-trastuzumab emtansine.

Baseline characteristics of the ITT population

	Trastuzumab (n = 743)	T-DM1 (n = 743)
Clinical stage at presentation, n (%)		
Stages cT1–3N0–1M0 (operable)	553 (74.4)	558 (75.1)
Stage cT4NxM0 or cTxN2–3M0 (inoperable)	190 (25.6)	185 (24.9)
HR 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-directed therapy, n (%)		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab plus additional HER2-directed 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	345 (46.4)	343 (46.2)
Node-negative/not done	398 (53.6)	400 (53.8)
Prior anthracycline, n (%)	564 (75.9)	579 (77.9)

Data have been updated since the primary analysis.
* Non-pertuzumab HER2-directed agents included neratinib, afatinib, and lapatinib.
ER, estrogen receptor; HR, hormone receptor; ITT, intention-to-treat; PgR, progesterone receptor; T-DM1, ado-trastuzumab emtansine.

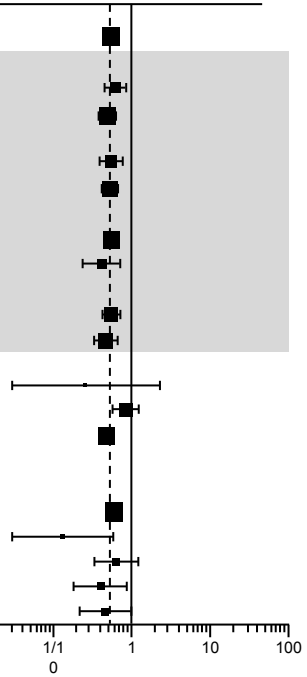
KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)



* p-value for IDFS is now exploratory given the statistical significance was established at the primary analysis.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Final IDFS analysis: Subgroups (1/2)

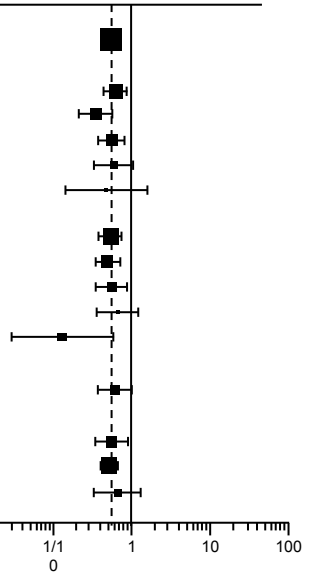
Baseline risk factors	Total n	Trastuzumab (n = 743) Patients per group	Trastuzumab (n = 743) n events	Trastuzumab (n = 743) 7-year IDFS	T-DM1 (n = 743) Patients per group	T-DM1 (n = 743) n events	T-DM1 (n = 743) 7-year IDFS	Hazard ratio	95% CI
All	1486	743	239	67.1	743	146	80.8	0.54	(0.44, 0.66)
Clinical stage at presentation									
Inoperable	375	190	87	51.3	185	62	66.7	0.63	(0.45, 0.87)
Operable	1111	553	152	72.3	558	84	85.4	0.48	(0.37, 0.63)
Hormone receptor status									
Negative (ER-negative and PgR-negative/-unknown)	412	203	75	59.4	209	53	75.0	0.55	(0.39, 0.78)
Positive (ER- and/or PgR-positive)	1074	540	164	69.8	534	93	83.1	0.52	(0.40, 0.67)
Preoperative HER2-directed therapy									
Trastuzumab alone	1196	596	198	66.4	600	128	79.5	0.56	(0.45, 0.70)
Trastuzumab plus additional HER2-directed agent(s)	290	147	41	69.8	143	18	87.2	0.42	(0.24, 0.72)
Pathologic nodal status after preoperative therapy									
Node-positive	688	345	142	57.7	343	96	71.6	0.56	(0.43, 0.72)
Node-negative/not done	798	398	97	74.8	400	50	88.8	0.47	(0.34, 0.66)
Central HER2 status by IHC									
0/1+	25	13	4	67.1	12	1	100.0	0.25	(0.03, 2.22)
2+	326	168	52	68.8	158	44	72.4	0.84	(0.56, 1.25)
3+	1132	559	183	66.5	573	101	82.8	0.47	(0.37, 0.60)
Unknown	3	3	0	100.0				NE	(NE, NE)
Race									
White	1081	530	158	69.3	551	110	80.7	0.59	(0.46, 0.75)
Black or African American	40	19	11	51.3	21	2	88.9	0.13	(0.03, 0.59)
Asian	129	64	22	62.9	65	16	75.3	0.65	(0.34, 1.23)
American Indian or Alaska Native	86	50	25	50.2	36	8	75.8	0.40	(0.18, 0.88)
Other or multiple or unknown	150	80	23	71.0	70	10	86.8	0.45	(0.22, 0.95)



CI, confidence interval; ER, estrogen receptor; IDFS, invasive disease-free survival;
IHC, immunohistochemistry; NE, not evaluable; PgR, progesterone receptor; T-DM1, ado-trastuzumab emtansine.

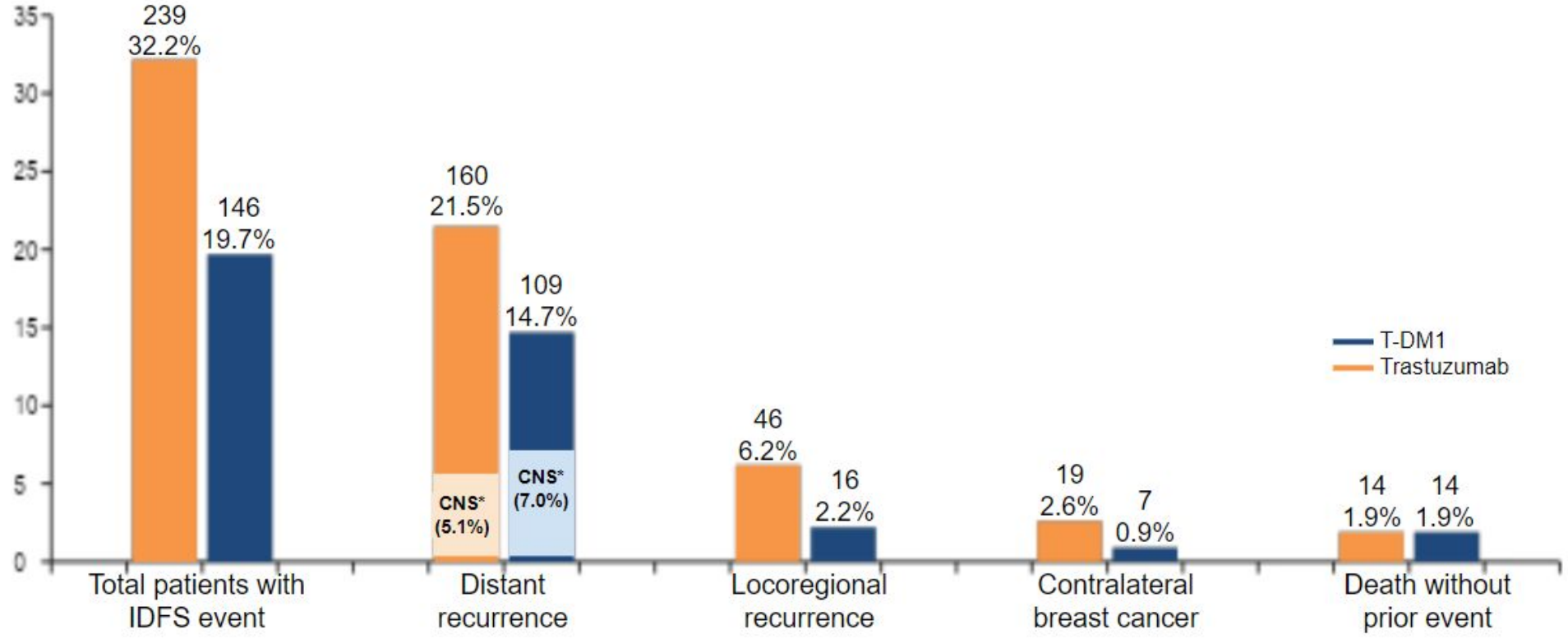
Final IDFS analysis: Subgroups (2/2)

Baseline risk factors	Total n	Trastuzumab (n = 743) Patients per group	Trastuzumab (n = 743) n events	Trastuzumab (n = 743) 7-year IDFS	T-DM1 (n = 743) Patients per group	T-DM1 (n = 743) n events	T-DM1 (n = 743) 7-year IDFS	Hazard ratio	95% CI
All	1486	743	239	67.1	743	146	80.8	0.54	(0.44, 0.66)
Primary tumor stage (at definitive surgery)									
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	637	306	78	74.6	331	59	82.0	0.65	(0.46, 0.90)
ypT1, ypT1c	359	184	60	66.8	175	22	87.4	0.35	(0.21, 0.56)
ypT2	359	185	67	62.9	174	41	78.4	0.55	(0.37, 0.80)
ypT3	108	57	28	46.4	51	19	62.0	0.59	(0.33, 1.06)
ypT4*	23	11	6	33.8	12	5	70.0	0.49	(0.15, 1.61)
Regional lymph node stage (at definitive surgery)									
ypN0	673	332	83	74.0	341	48	87.1	0.53	(0.37,0.75)
ypN1	432	212	76	63.6	220	47	78.0	0.50	(0.35, 0.72)
ypN2	189	103	47	52.4	86	28	69.5	0.56	(0.35, 0.89)
ypN3	67	30	19	32.1	37	21	38.6	0.67	(0.36, 1.24)
ypNX	125	66	14	79.1	59	2	98.2	0.13	(0.03, 0.59)
Residual disease ≤1 cm with negative axillary lymph nodes									
ypT1a, ypT1b or ypT1mic and ypN0	328	160	36	76.7	168	25	85.7	0.62	(0.37, 1.03)
Age group (years)									
<40	296	153	46	67.2	143	28	81.2	0.56	(0.35, 0.90)
40–64	1064	522	170	66.7	542	104	80.9	0.52	(0.41, 0.66)
≥65	126	68	23	69.4	58	14	78.6	0.67	(0.34, 1.30)



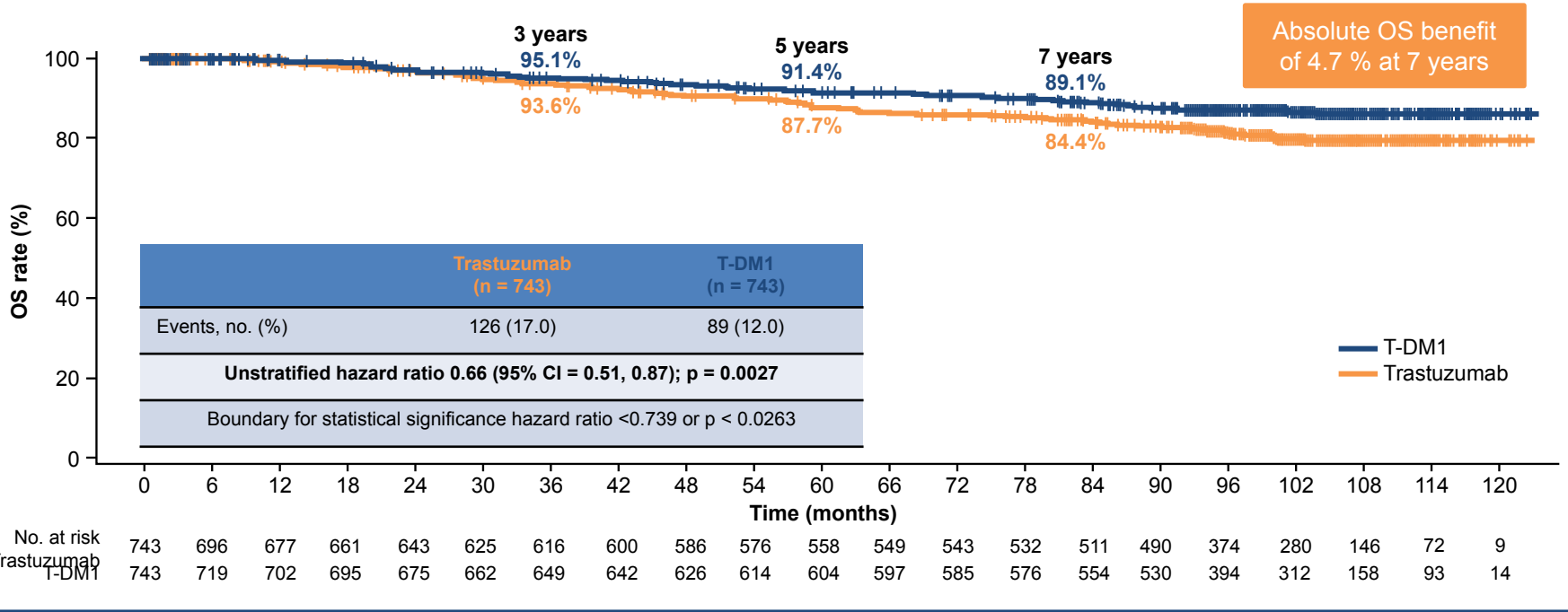
* Includes all ypT4 and one patient with ypTX.
CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

Site of first occurrence of an IDFS event



CNS metastases as component of distant recurrence (isolated or with other sites).
CNS recurrence after first IDFS event: 19 patients (2.6%) in the trastuzumab arm and four patients (0.5%) in the T-DM1 arm.
CNS, central nervous system; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)



Significant reduction in risk of death by 34% with T-DM1

CI, confidence interval; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

Summary of deaths

	Trastuzumab (n = 720)	T-DM1 (n = 740)
Total number of deaths, n (%)	126 (17.5)	89 (12.0)
Cause of death		
Breast cancer	108 (15.0)	70 (9.5)
Adverse event	0	1 (0.1)*
Other†	18 (2.5)	18 (2.4)

* Fatal adverse event was intracranial hemorrhage diagnosed after a fall with platelet count of 55,000.
† Other causes of death: Respiratory disorders, cardiac disorders, infections, cerebrovascular disorders, secondary malignancies, surgical procedures, and unknown.
T-DM1, ado-trastuzumab emtansine.

2nd OS interim analysis: Subgroups (1/2)

Baseline risk factors	Total n	Trastuzumab (n = 743) Patients per group	Trastuzumab (n = 743) n events	Trastuzumab (n = 743) 7-year OS	T-DM1 (n = 743) Patients per group	T-DM1 (n = 743) n events	T-DM1 (n = 743) 7-year OS	Hazard ratio	95% CI
All	1486	743	126	84.4	743	89	89.1	0.66	(0.51, 0.87)
Clinical stage at presentation									
Inoperable	375	190	57	69.0	185	44	77.5	0.71	(0.48, 1.05)
Operable	1111	553	69	89.4	558	45	92.7	0.62	(0.42, 0.90)
Hormone receptor status									
Negative (ER-negative and PgR-negative/-unknown)	412	203	44	79.9	209	38	83.4	0.73	(0.48, 1.13)
Positive (ER- and/or PgR-positive)	1074	540	82	85.9	534	51	91.3	0.60	(0.42, 0.85)
Preoperative HER2-directed therapy									
Trastuzumab alone	1196	596	105	84.1	600	77	88.6	0.68	(0.51, 0.91)
Trastuzumab plus additional HER2-directed agent(s)	290	147	21	85.7	143	12	91.0	0.57	(0.28, 1.16)
Pathologic nodal status after preoperative therapy									
Node-positive	688	345	90	75.6	343	62	83.4	0.61	(0.44, 0.84)
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Central HER2 status by IHC									
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2+	326	168	28	83.4	158	28	83.3	1.03	(0.61, 1.73)
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Unknown	3	3	0	100.0				NE	(NE, NE)
Race									
White	1081	530	80	86.3	551	64	89.0	0.72	(0.52, 1.01)
Black or African American	40	19	8	73.3	21	1	94.1	0.10	(0.01, 0.80)
Asian	129	64	15	78.0	65	9	90.0	0.53	(0.23, 1.21)
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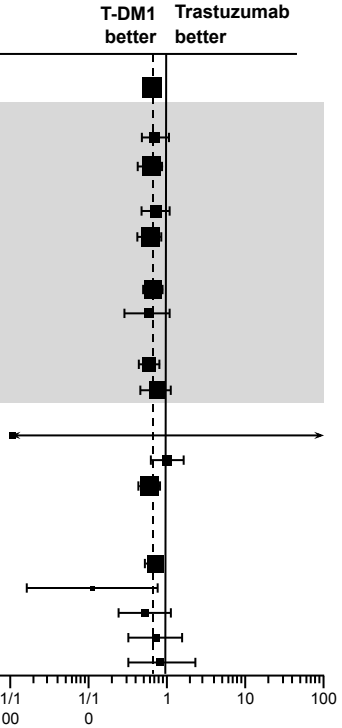
Other or multiple or unknown	150	80	9	89.3	70	7	92.3	0.87	(0.32, 2.32)



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2nd OS interim analysis: Subgroups (2/2)

Baseline risk factors	Total n	Trastuzumab (n = 743) Patients per group	Trastuzumab (n = 743) n events	Trastuzumab (n = 743) 7-year OS	T-DM1 (n = 743) Patients per group	T-DM1 (n = 743) n events	T-DM1 (n = 743) 7-year OS	Hazard ratio	95% CI
All	1486	743	126	84.4	743	89	89.1	0.66	(0.51, 0.87)
Primary tumor stage (at definitive surgery)									
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Regional lymph node stage (at definitive surgery)									
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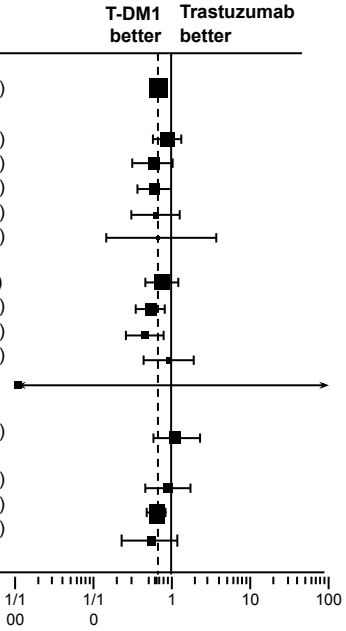
ypN3	67	30	11	53.8	37	16	54.2	0.93	(0.43, 2.00)
ypNX	125	66	4	94.8	59	0	100.0	<0.01	(0.00, NE)
Residual disease ≤1 cm with negative axillary lymph nodes									
ypT1a, ypT1b or ypT1mic and ypN0	328	160	13	93.1	168	16	92.3	1.18	(0.57, 2.45)
Age group (years)									
<40	296	153	16	89.2	143	15	88.4	0.93	(0.46, 1.88)
40–64	1064	522	92	83.9	542	66	89.3	0.65	(0.47, 0.89)
≥65	126	68	18	77.6	58	8	88.8	0.50	(0.22, 1.14)



* Includes all ypT4 and one patient with ypTX. CI, confidence interval; NE, not evaluable; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

Follow-up medications after IDFS events (ITT)

	Trastuzumab (n = 743)	T-DM1 (n = 743)
Total number of patients with an IDFS event, n	239	146
Total number of patients with documentation of ≥1 treatment following an IDFS event, n (%)	169 (70.7)	94 (64.4)
Class, n (%)*		
HER2-directed therapies	132 (78.1)	61 (64.9)
Pertuzumab	73 (43.2)	30 (31.9)
Trastuzumab	114 (67.5)	52 (55.3)
T-DM1	53 (31.4)	12 (12.8)
T-DXd	3 (1.8)	6 (6.4)
Tyrosine kinase inhibitors (lapatinib, neratinib, pyrotinib, pazopanib)	31 (18.3)	26 (27.7)
Platinum compounds	17 (10.1)	10 (10.6)
Taxanes	102 (60.4)	40 (42.6)
Capecitabine	51 (30.2)	44 (46.8)

* Percentages based on number of patients who received ≥1 follow-up medication.
IDFS, invasive disease-free survival; ITT, intention-to-treat; T-DM1, ado-trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Related AEs during the post-treatment period*

Patients, n (%) with ≥1:	Trastuzumab (n = 720)	T-DM1 (n = 740)
AE (any grade, >1 patient in either arm)	12 (1.7)	24 (3.2)
Investigations	5 (0.7)	9 (1.2)
Cardiac disorders	5 (0.7)	5 (0.7)
Nervous system disorders	0	4 (0.5)
Hepatobiliary disorders	0	2 (0.3)
Metabolism and nutrition disorders	0	2 (0.3)
Skin and subcutaneous tissue disorders	0	2 (0.3)
Serious AE	4 (0.6)	2 (0.3)
Cardiac disorders	3 (0.4)	0
Hepatobiliary disorders	0	2 (0.3)
Vascular disorders	1 (0.1)	0
Grade ≥3 AE	3 (0.4)	3 (0.4)
Cardiac disorders	3 (0.4)	1 (0.1)
Hepatobiliary disorders	0	2 (0.3)

* Related to study treatment or to study procedures.
Includes AEs with date of onset >30 days after last dose of study treatment. During the follow-up period, only deaths, serious AEs, or other AEs of concern that are believed to be related to prior treatment with study drug or study procedures were reported.
AE, adverse event; T-DM1, ado-trastuzumab emtansine.

KATHERINE summary and conclusions

- After 8.4 years (101 months) median follow-up, T-DM1 significantly improved OS in patients with HER2-positive early breast cancer with residual invasive disease after neoadjuvant therapy
  - Hazard ratio 0.66 (95% CI 0.51, 0.87), p = 0.0027
  - 7-year OS rates: 89.1% (T-DM1) vs 84.4% (trastuzumab), a difference of 4.7%
- IDFS benefit of T-DM1 was sustained in the ITT population with longer follow-up with a hazard ratio of 0.54 (95% CI 0.44, 0.66) as well as in key subgroups
  - 7-year IDFS rates: 80.8% (T-DM1) vs 67.1% (trastuzumab), a difference of 13.7%
- No new safety issues emerged with longer follow-up
  - Cardiac toxicity was rare in both arms
- T-DM1 is the first therapy to show improved survival post-surgery in patients with HER2-positive early breast cancer with residual invasive disease after neoadjuvant therapy
- Follow-up is ongoing for the final OS analysis

CI, confidence interval; HR, hormone receptor; IDFS, invasive disease-free survival; ITT, intention-to-treat; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

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