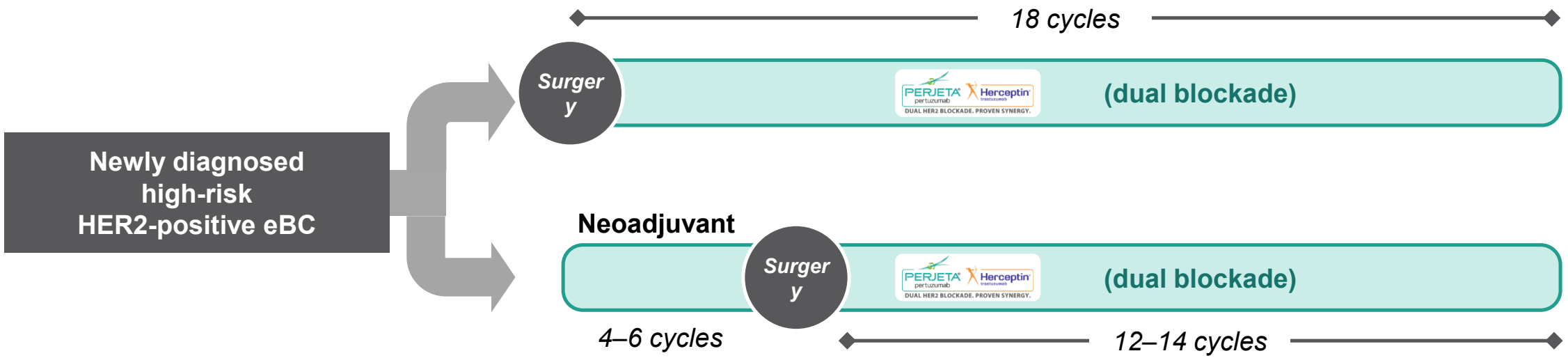
Prior to KATHERINE, 18 cycles of PH was SoC for patients with HER2-positive eBC at high risk of recurrence or death* irrespective of neoadjuvant response[1–5]



Patients received the same SoC treatment in the adjuvant setting, regardless of response to neoadjuvant therapy, due to a lack of evidence to support changing therapy[1–5]

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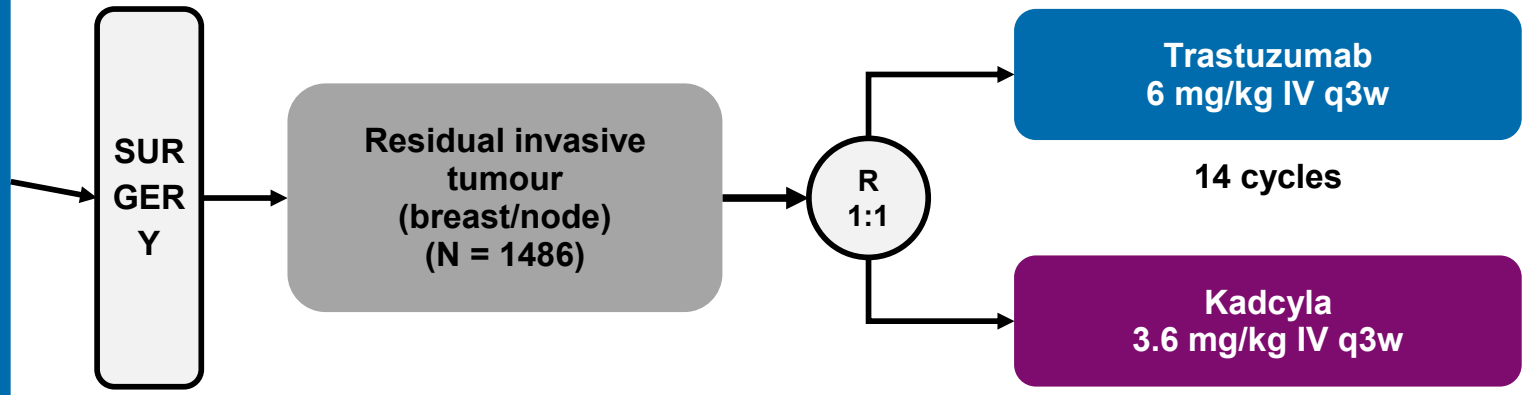
* Patients at high risk of recurrence or death defined as having node-positive or hormone receptor-negative disease;
eBC, early breast cancer; pCR, pathological complete response; PH, PERJETA–Trastuzumab; SoC, standard of care.
1. PERJETA US PI 2017; 2. PERJETA SmPC 2018; 3. Curigliano G, *et al. Ann Oncol* 2017; 4. NCCN Breast Cancer Guidelines Version 3 – 2018; 5. AGO guidelines 2018.

KATHERINE study design[1,2]

- **cT1–4/N0–3/M0 at presentation (cT1a–b/N0 excluded)**
- **HER2-positive eBC***
- **Neoadjuvant therapy†**
  - Minimum 6 cycles chemo
    - Minimum 9 weeks taxane
    - Anthracyclines and alkylating agents allowed
    - All chemo prior to surgery
  - Minimum 9 weeks trastuzumab
    - Second HER2-targeted agent allowed
- **Residual invasive tumour in the breast or axillary nodes**



Stratification factors:

- Clinical stage at presentation: inoperable vs. operable
- Hormone receptor status: ER- or PR-positive vs. ER- and PR-negative
- Neoadjuvant HER2-directed therapy: Trastuzumab vs. dual HER2 targeting
- Pathological nodal status evaluated after neoadjuvant therapy

Primary endpoint: IDFS

Key secondary endpoints: IDFS (second primary non-breast cancers included), DFS, OS, DRFI, Safety

* Centrally confirmed.
† Neoadjuvant systemic treatment was given for at least 6 cycles, with a total duration of at least 16 weeks, including at least 9 weeks of anti-HER2 therapy and at least 9 weeks of taxane-based chemotherapy (or, if receiving dose-dense chemotherapy regimens, at least 8 weeks of taxane-based therapy and at least 8 weeks of anti-HER2 therapy).
DFS, disease-free survival; DRFI, distant recurrence-free interval;
ER, oestrogen receptor; IDFS, invasive disease-free survival; OS, overall survival; PR, progesterone receptor.
1. Roche. Data on File. Protocol BO27938 (KATHERINE) – version 6; 2. von Minckwitz G, *et al. N Engl J Med* 2019.

Stratification factors were balanced between treatment arms[1]

No. patients, n (%)	Trastuzumab n = 743	Kadcyla n = 743
Clinical stage at presentation		
Inoperable (Stage T4 Nx M0 or Tx N2–3 M0)	190 (25.6)	185 (24.9)
Operable (Stages T1–3 N0–1 M0)	553 (74.4)	558 (75.1)
Hormone receptor status		
ER- and/or PR-positive	540 (72.7)	534 (71.9)
ER-negative and PR-negative/unknown	203 (27.3)	209 (28.1)
Neoadjuvant HER2-directed therapy		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab plus additional HER2-targeted agent(s)*	147 (19.8)	143 (19.2)
Pathological nodal status evaluated after neoadjuvant therapy		
Node-positive	346 (46.6)	343 (46.2)
Node-negative/not done	397 (53.4)	400 (53.8)

Lower pCR rates for patients with hormone receptor-positive disease[2] meant that the KATHERINE population was enriched in this subgroup

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* Other HER2-targeted agents were PERJETA, neratinib, dacomitinib, afatinib and lapatinib.

1. von Minckwitz G, *et al*. *N Engl J Med* 2019; 2. Harbeck N. *Ther Adv Med Oncol* 2018.

Baseline demographics were balanced between treatment arms

No. patients, n (%)	Trastuzumab n = 743	Kadcyla n = 743
Age		
Median, years (range)	49 (23–80)	49 (24–79)
<40	153 (20.6)	143 (19.2)
40–64	522 (70.3)	542 (72.9)
≥65	68 (9.2)	58 (7.8)
Race		
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/other	79 (10.6)	70 (9.4)
Region		
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)

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von Minckwitz G, *et al. N Engl J Med* 2019.

Extent of residual invasive disease (including pathological nodal status) at time of surgery was balanced between treatment arms

No. patients, n (%)	Trastuzumab n = 743	Kadcyla n = 743
Primary tumour stage (at definitive surgery)		
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	57 (7.7)	51 (6.9)
ypT4/ypT4a–c	9 (1.2)	7 (0.9)
ypT4d	1 (0.1)	5 (0.7)
ypTX	1 (0.1)	0
Regional lymph node stage (at definitive surgery)		
ypN0	335 (45.1)	344 (46.3)
ypN1	213 (28.7)	220 (29.6)
ypN2	103 (13.9)	86 (11.6)
ypN3	30 (4.0)	37 (5.0)
ypNX	62 (8.3)	56 (7.5)

>40% of patients had only a small amount of residual invasive disease present after neoadjuvant therapy

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von Minckwitz G, *et al*. *N Engl J Med* 2019.

Prior therapy was balanced between treatment arms

No. patients, n (%)	Trastuzumab n = 743	Kadcyla n = 743
Prior anthracycline		
Received prior anthracycline	564 (75.9)	579 (77.9)
Did not receive prior anthracycline	179 (24.1)	164 (22.1)
Neoadjuvant therapy		
Trastuzumab alone	596 (80.2)	600 (80.8)
PERJETA–Trastuzumab	139 (18.7)	133 (17.9)
Trastuzumab plus other HER2-directed agent(s)*	8 (1.1)	10 (1.3)

Approximately 18% of patients had received prior PERJETA–Trastuzumab neoadjuvant therapy

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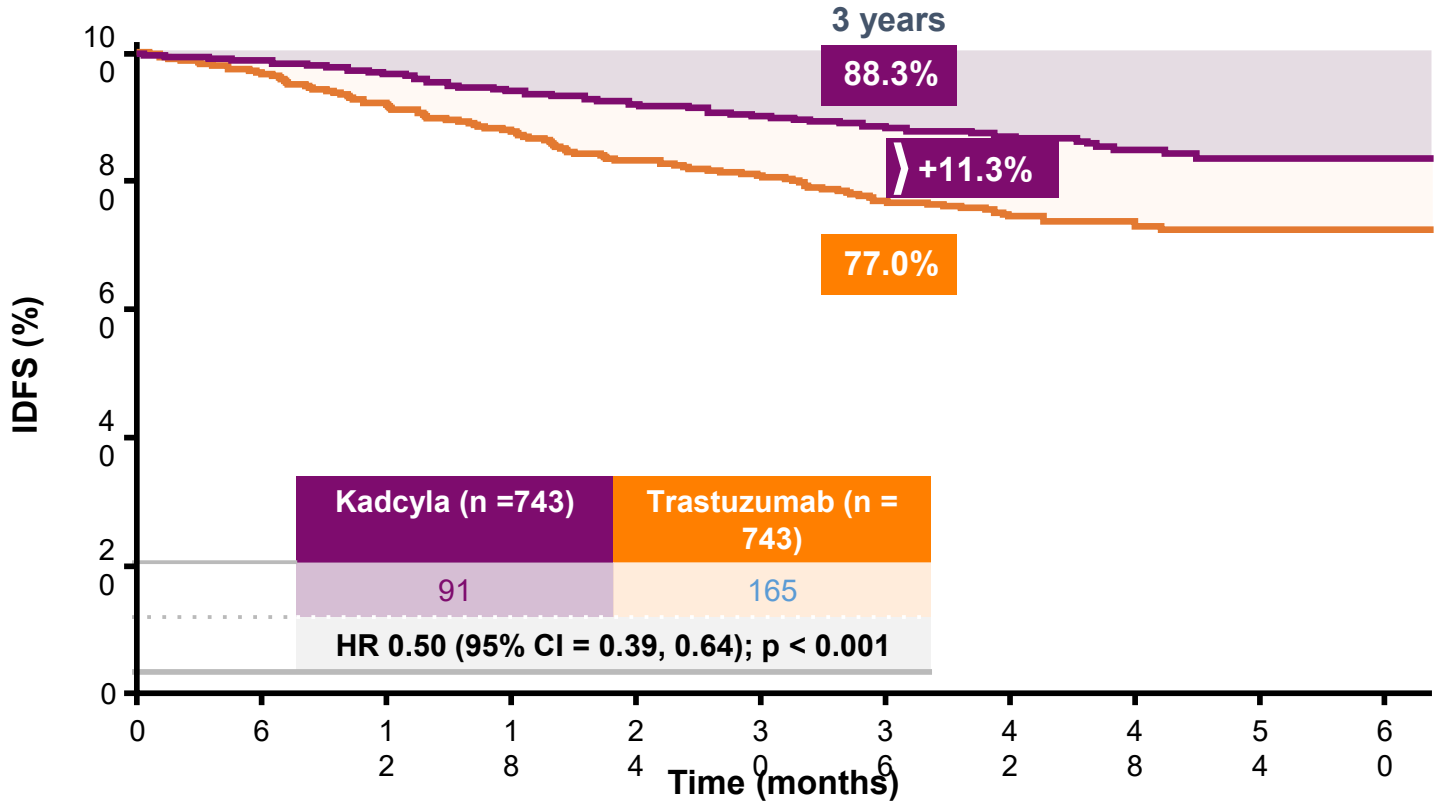
* Other HER2-targeted agents were neratinib, dacomitinib, afatinib, and lapatinib.

von Minckwitz G, *et al*. *N Engl J Med* 2019.

KATHERINE met its primary endpoint: Kadcyla reduced the risk of an IDFS event by 50% compared with Trastuzumab at a median follow-up of 41 months



50% REDUCTION in the risk of recurrence or death

Kadcyla increased the 3-year IDFS rate from 77.0% to 88.3%

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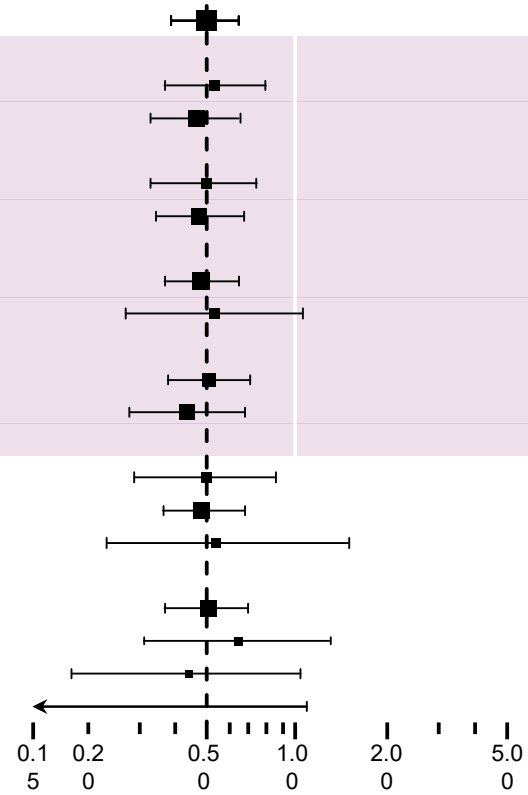
von Minckwitz G, *et al*. *N Engl J Med* 2019.

Magnitude of IDFS benefit in all subgroups was consistent with the ITT population, including across all stratification factors*

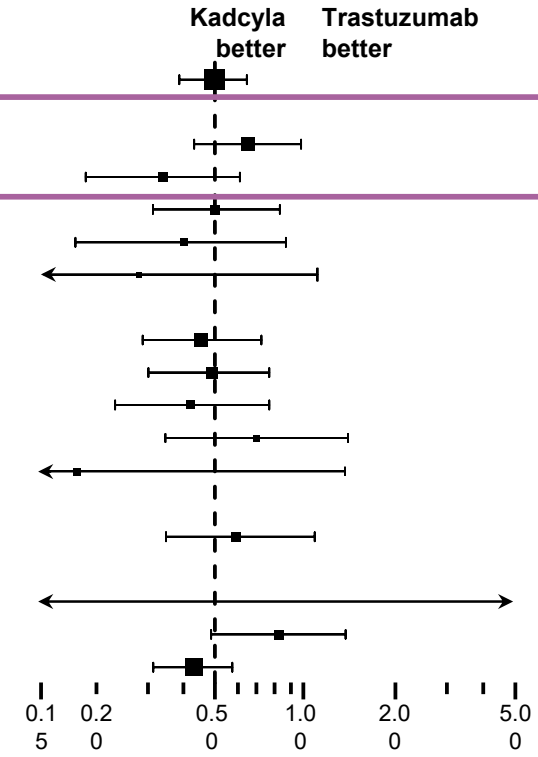
Group	Total N	Trastuzumab (n = 743) 3-year IDFS	Kadcyla (n = 743) 3-year IDFS	Hazard ratio	95% CI
All	1486	77.0	88.3	0.50	(0.39, 0.64)
Clinical stage at presentation†					
Inoperable	375	60.2	76.0	0.54	(0.37, 0.80)
Operable	1111	82.8	92.3	0.47	(0.33, 0.66)
Hormone receptor status					
Negative (ER-negative and PR-negative/unknown)	412	66.6	82.1	0.50	(0.33, 0.74)
Positive (ER- and/or PR-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)



* Stratification factors are shaded in grey.
† Inoperable tumours, stage T4NxM0 or TxN2–3M0; operable tumours, stages T1–3N0–1M0.
‡ 272 patients (93.8%) received PERJETA as the additional neoadjuvant HER2-directed agent. The remaining 18 patients received either neratinib, dacomitinib, afatinib or lapatinib.
§ 149 were of multiple races or unknown race.
ER, oestrogen receptor; CI, confidence interval; IDFS, invasive disease-free survival; PR, progesterone receptor.
von Minckwitz G, *et al. N Engl J Med* 2019.

Magnitude of IDFS benefit in all subgroups was consistent with the ITT population, even for patients with very small amounts of residual disease

Group	Total N	Trastuzumab (n = 743) 3-year IDFS	Kadcyla (n = 743) 3-year IDFS	Hazard ratio	95% CI
All[1]	1486	77.0	88.3	0.50	(0.39, 0.64)
Primary tumour stage (at definitive surgery)[1]					
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)[1]					
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[2]					
ypT1a, ypT1b or ypT1mic and ypN0	331	85.3	90.0	0.60	(0.33, 1.12)
Central HER2 status by IHC[†2]					
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)



Benefit of Kadcyla consistent, irrespective of tumour size and nodal status at surgery; including in patients with residual disease ≤1 cm and node-negative disease

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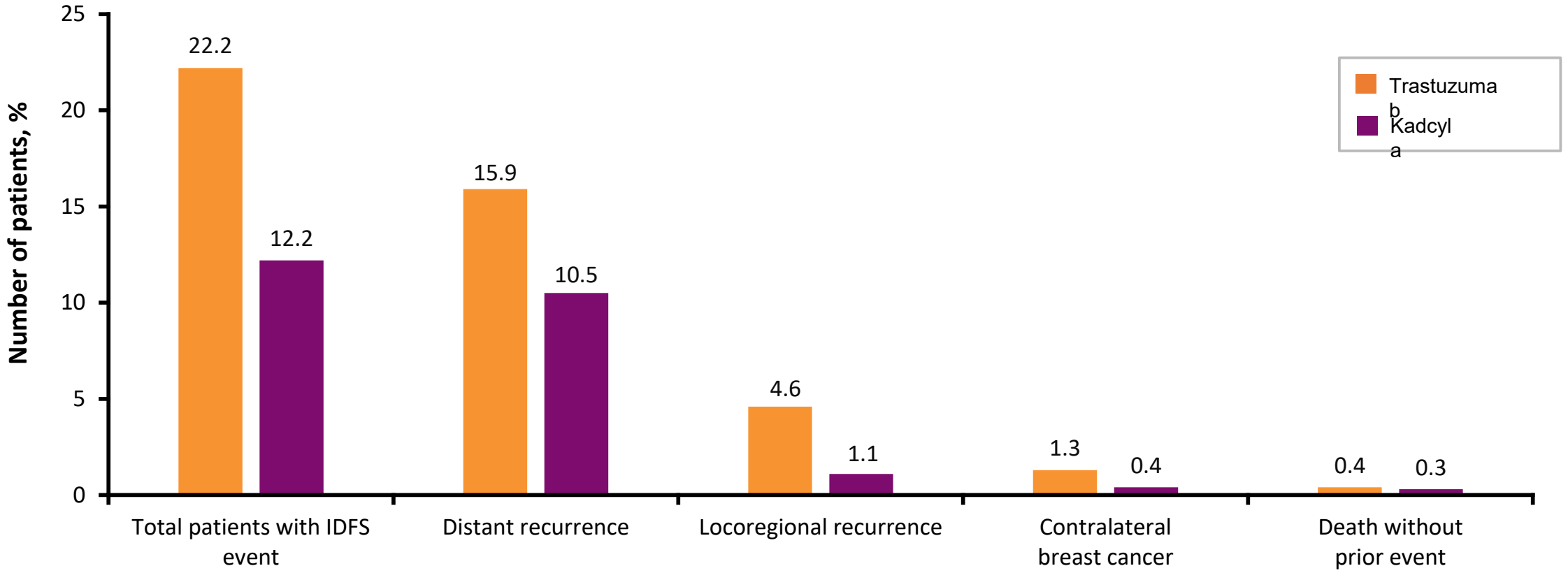
* Includes all ypT4 and 1 patient with ypTX.
† Three patients had "unknown" HER2 IHC status.
1. von Minckwitz G, *et al. N Engl J Med* 2019;
2. Geyer CE, *et al.* SABCS 2018 (abstract GS1-10).

The majority of recurrences were distant, with a reduced incidence in the Kadcyla arm

- **First occurrence of an IDFS event***



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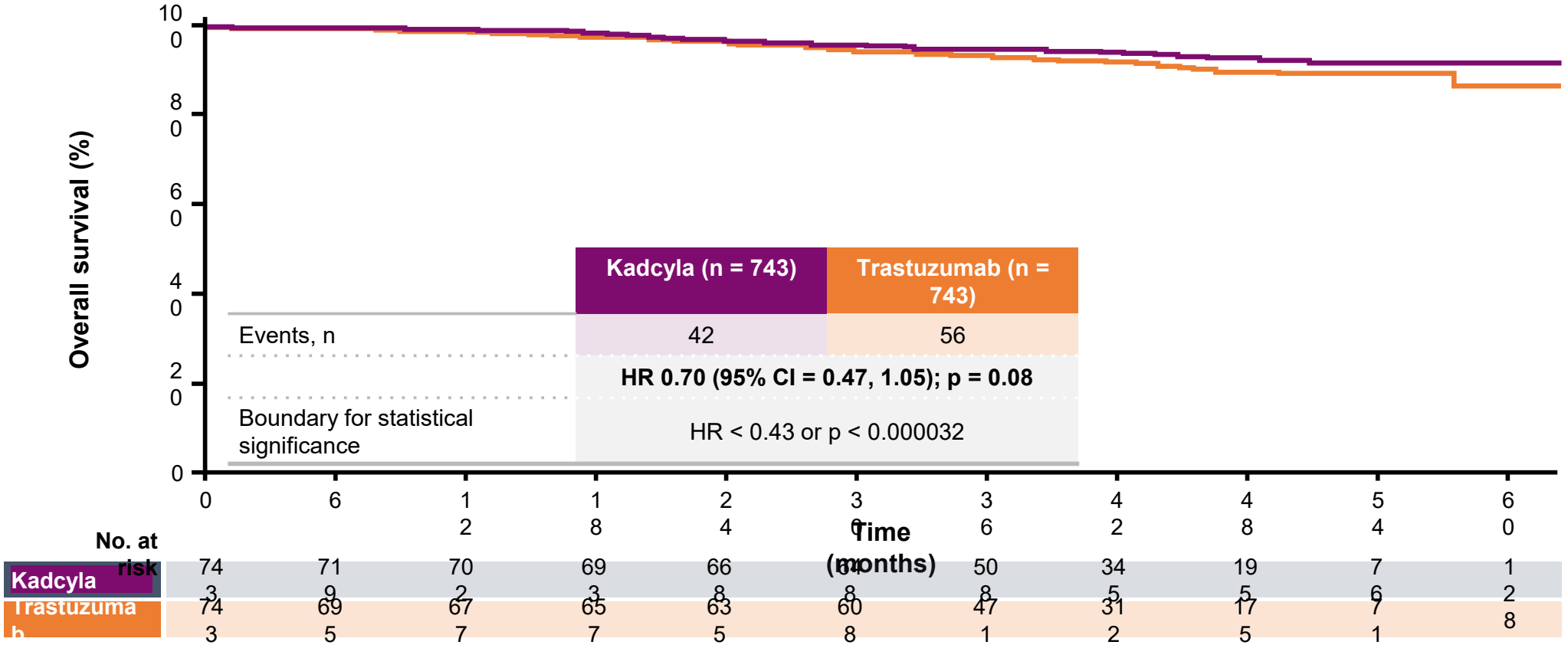
* Patients who experience additional IDFS event(s) within 61 days of their first IDFS event are reported in the category according to the following hierarchy:
1. Distant recurrence; 2. Locoregional recurrence; 3. Contralateral breast cancer; 4. Death without prior event.
CNS, central nervous system; IDFS, invasive disease-free survival.
von Minckwitz G, *et al*. *N Engl J Med* 2019.

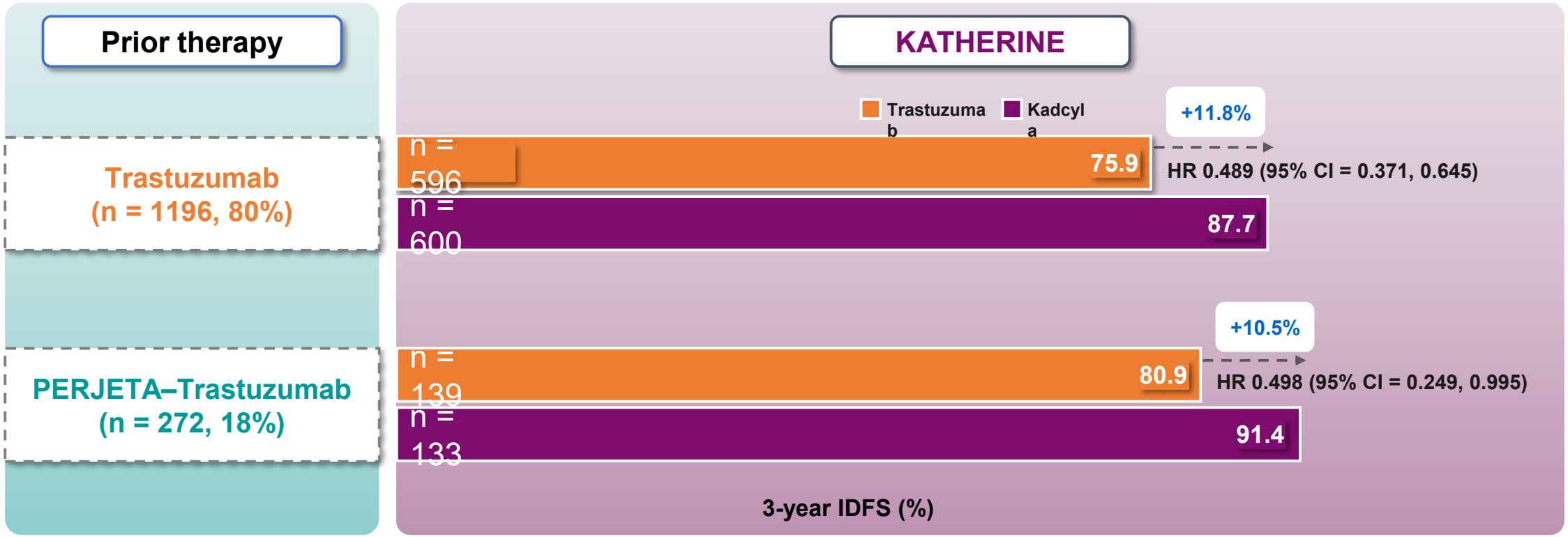
Secondary endpoints: OS data are immature but are supportive of the primary endpoint

- **OS at first interim analysis***



* Up to three formal interim OS analyses and one final OS analysis are planned. Data here represent the first interim OS analysis; the final OS analysis will be performed after 10 years of follow-up.
CI, confidence interval; HR, hazard ratio; OS, overall survival.
von Minckwitz G, *et al. N Engl J Med* 2019.

Kadcyla yielded a consistent magnitude of IDFS benefit, regardless of prior HER2-directed therapy*



Numerically better outcome was observed in patients pre-treated with PERJETA–Trastuzumab vs. Trastuzumab alone*

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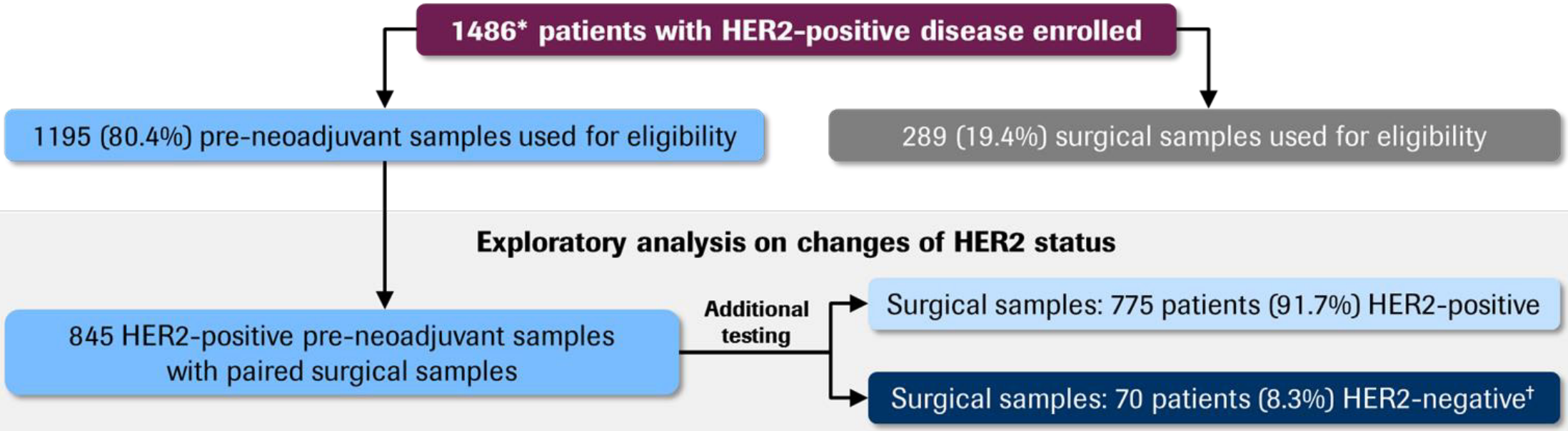
* Caution must be exercised as this exploratory analysis involves low patient numbers and the study is not powered to determine the statistical significance of these data.

von Minckwitz G, *et al*. *N Engl J Med* 2019.

HER2-negative status after neoadjuvant therapy did not impact the efficacy of T-DM1



In the 70 patients with HER2-negative disease after re-testing of surgical samples:

- There were no IDFS events in patients randomised to the Kadcyla arm (n = 28)
- There were 11 IDFS events in patients randomised to the Trastuzumab arm (n = 42)

These data should be interpreted with caution due to the small sample size

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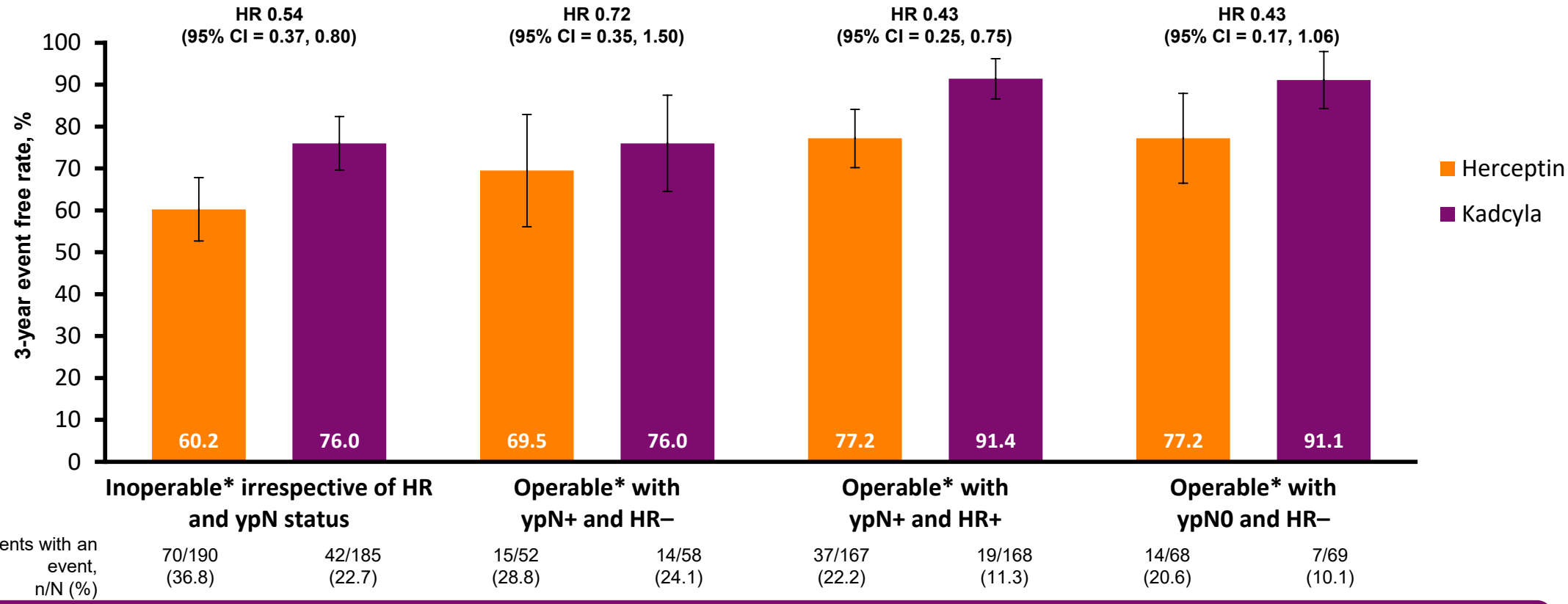
* Two patients (both in the Trastuzumab arm) were not included in this analysis: One did not have centrally confirmed HER2-positive disease and one was inadvertently randomised twice.
† 53 HER2-negative and 17 HER2-unknown by IHC 0-1+/ISH unknown
IDFS, invasive disease-free survival.
Loibl S, *et al.* ESMO Breast 2020 (Abstract 96O and oral presentation).

Exploratory analysis: Improved 3-year IDFS rates were seen with Kadcyla in all subgroups with a poor prognosis[1]



Unmet need remains in patients with inoperable tumours and in those with operable tumours with ypN+ and HR-negative disease; 3-year IDFS rates remained relatively low (<80%), despite receiving Kadcyla treatment

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* Inoperable (Stage T4 Nx M0 or Tx N2–3, M0); Operable (Stage T1–3 N0-1 M0).[2]
CI, confidence interval; HR, hazard ratio; HR–/+, hormone receptor-negative/-positive; IDFS, invasive disease-free survival.

1. Mano MS, *et al*. SABCS 2019 (Abstract P3-14-01; poster presentation);
2. von Minckwitz G, *et al*. *N Engl J Med* 2019.

AE rates with Kadcyla were as expected based on previous trials[1]

No. patients, n (%)	Trastuzumab n = 720	Kadcyla n = 740
Any AE	672 (93.3)	731 (98.8)
Grade ≥3 AEs	111 (15.4)	190 (25.7)
Serious AE	58 (8.1)	94 (12.7)
AE with fatal outcome*	0	1 (0.1)
Discontinued randomised treatment due to AE†	15 (2.1)	133 (18.0)

Higher rate of discontinuations in the Kadcyla arm vs. the Trastuzumab arm

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* The fatal AE was an intracranial haemorrhage that occurred after a fall at home in a patient with a platelet count of 55 x 10^9/L;
† Withdrawal from randomised study treatment refers to assigned treatment at time of randomisation. The most common reasons for Kadcyla discontinuation were laboratory abnormalities. The thresholds for initiating a dose reduction or discontinuation due to liver lab abnormalities in KATHERINE were lower than those specified for EMILIA due to FDA feedback (EMILIA discontinuation rate 5.9%).[2]
AE, adverse event.
1. von Minckwitz G, *et al. N Engl J Med* 2019; 2. Verma S, *et al. N Engl J Med* 2012.

Most common AEs leading to Kadcyla discontinuation were laboratory abnormalities, consistent with the known safety profile1–3

Event leading to discontinuation[1]* (≥1% incidence in either arm) Patients, n (%)	Trastuzumab n = 720	Kadcyla 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)
AST increased	0	12 (1.6)
ALT increased	0	11 (1.5)
Peripheral sensory neuropathy	0	11 (1.5)
Ejection fraction decreased	10 (1.4)	9 (1.2)

Observed laboratory abnormalities were generally low-grade, asymptomatic and reversible

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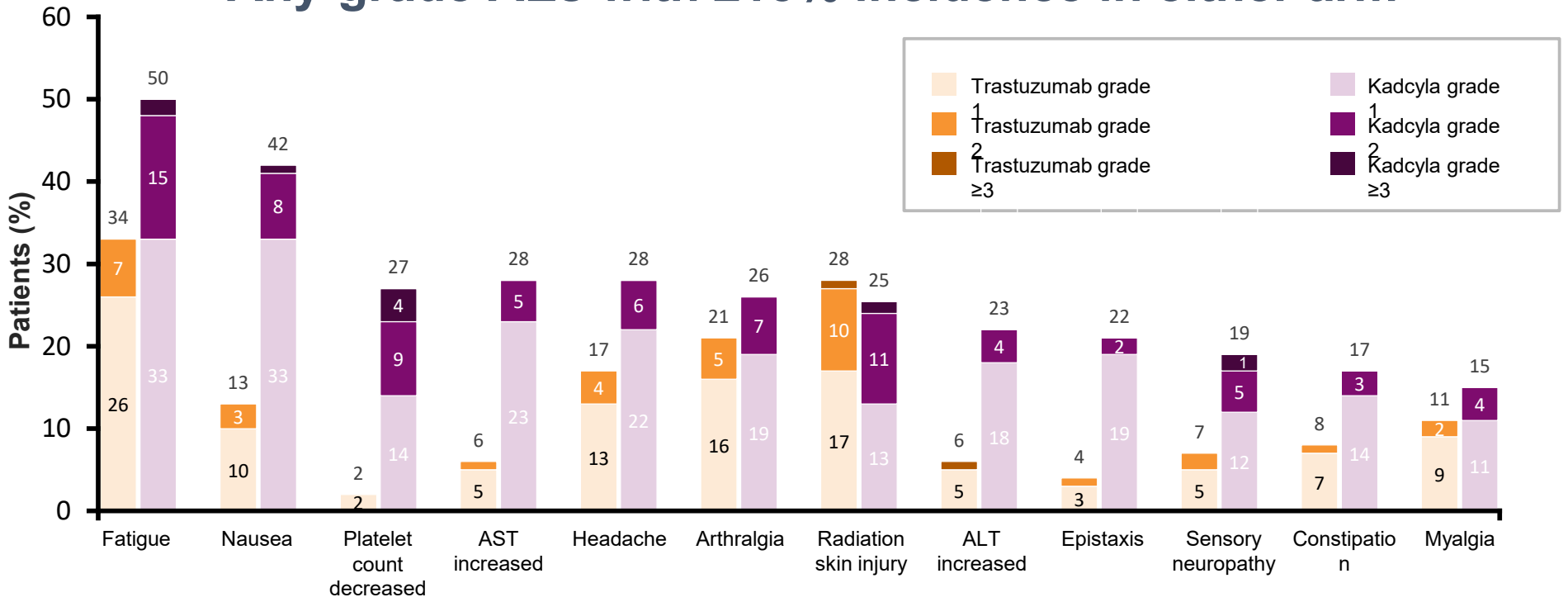
* Discontinuation of study treatment assigned at randomisation.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
1. von Minckwitz G, *et al. N Engl J Med* 2019; 2. Verma S, *et al. N Engl J Med* 2012; 3. Krop IE, *et al. J Clin Oncol* 2015.

Safety data were consistent with the known safety profile of Kadcyla

- Any-grade AEs with ≥15% incidence in either arm



Kadcyla-related AEs were generally low grade, manageable and easily monitored

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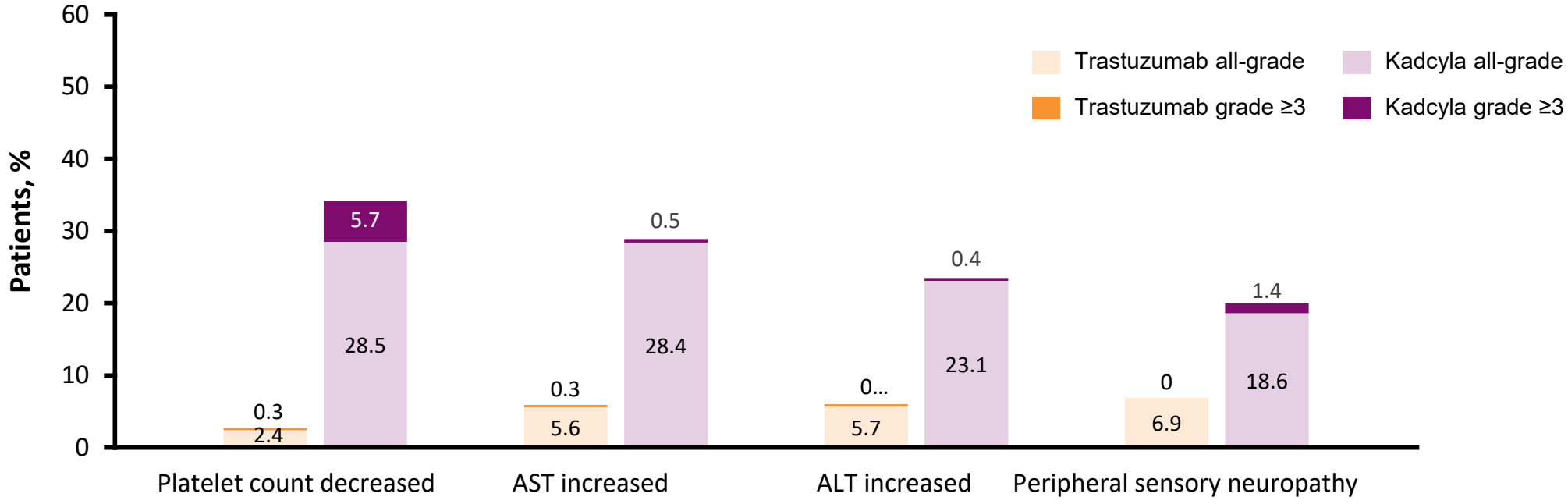
von Minckwitz G, *et al. N Engl J Med* 2019.

AEs with an increased incidence in the Kadcyla arm vs. the Trastuzumab arm were generally low grade and manageable

- Selected any-grade AEs (≥5% difference between arms and ≥10% incidence in either arm)



75% of cases of peripheral sensory neuropathy were resolved and 9% were resolving at the time of database lock

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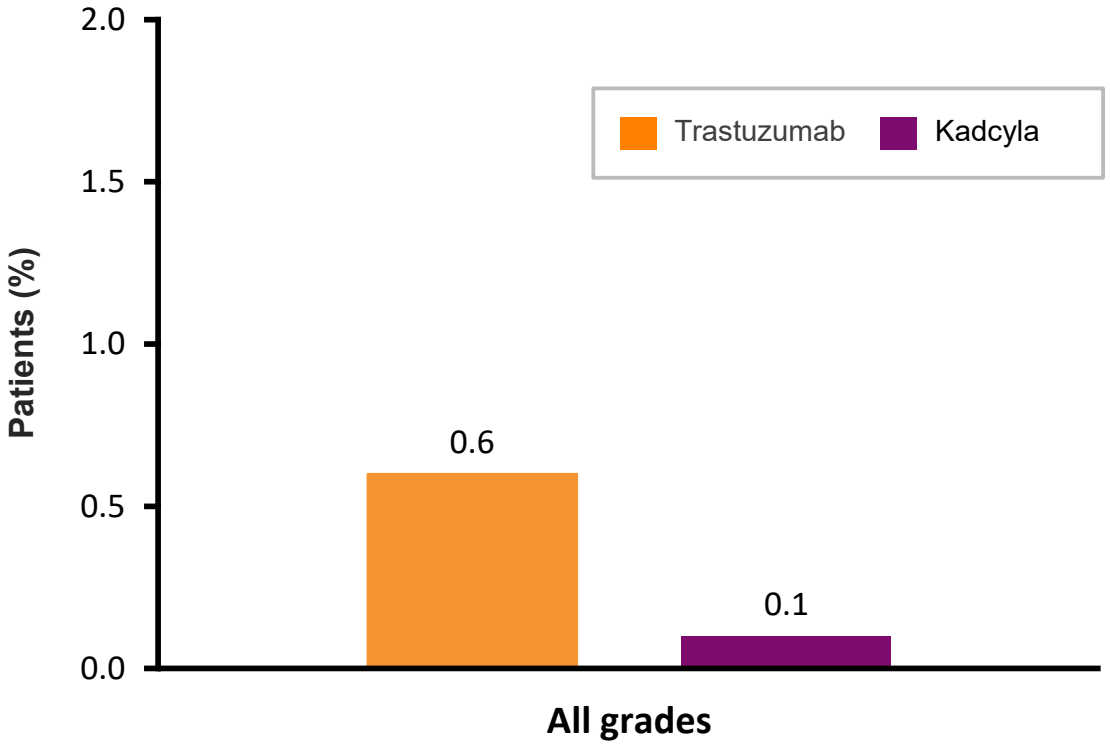
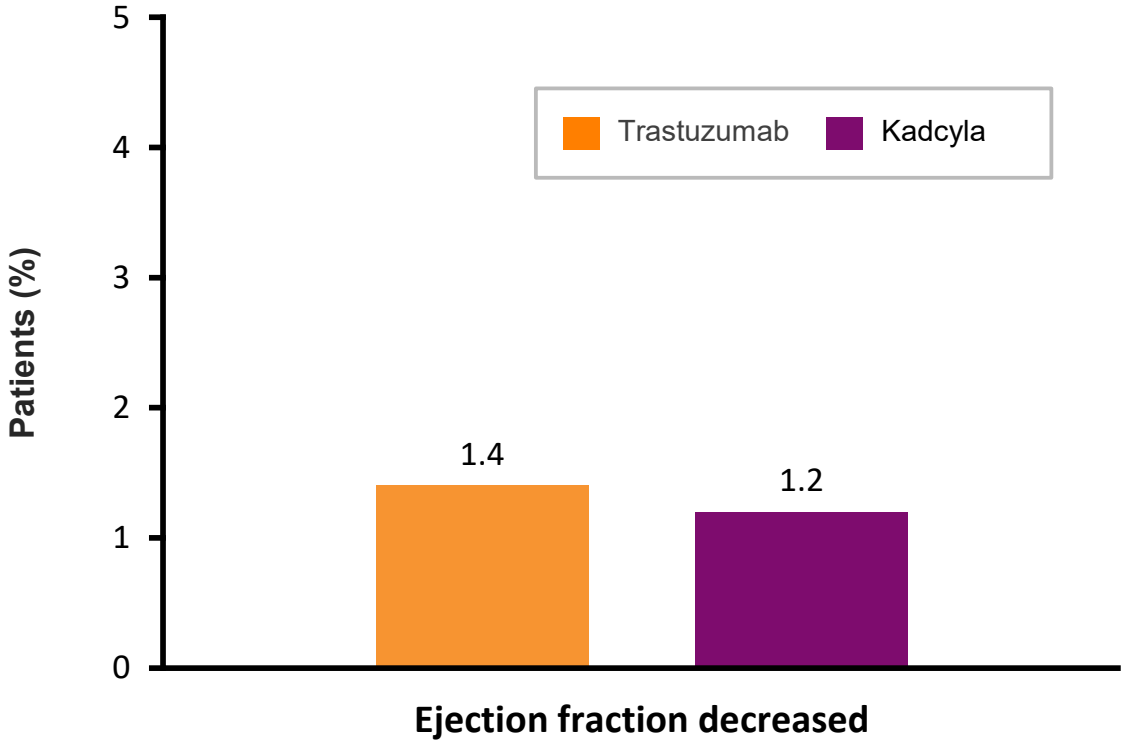
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
von Minckwitz G, *et al. N Engl J Med* 2019.

Incidence of cardiac events was low in both arms

Adjudicated cardiac events*



Cardiac event* leading to discontinuation



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von Minckwitz G, *et al*. *N Engl J Med* 2019.

* Cardiac events and potential cases of hepatic dysfunction were adjudicated by an independent clinical events committee. Cardiac events were defined as death from cardiac cause or New York Heart Association class III or IV heart failure with a decrease in left ventricular ejection fraction of 10 percentage points or more from baseline to a value of <50%..

Kadcyla is approved for the adjuvant treatment of patients with residual invasive disease after HER2-targeted neoadjuvant therapy

EMA label indication[1]

Kadcyla, as a single agent, is indicated for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have residual invasive disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy

FDA label indication[2]

Kadcyla is indicated for the adjuvant treatment of patients with HER2-positive early breast cancer with residual invasive disease after neoadjuvant taxane and Trastuzumab-based treatment

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1. Kadcyla SmPC; 2. Kadcyla Prescribing Information.

Guidelines recommending Kadcyla in eBC

NCCN Breast Cancer Guidelines (v4 – 2022)[1]

Category 1 listing*
If residual invasive disease: Kadcyla alone for 14 cycles

AGO Guidelines (2022)[2]

If residual invasive disease: Patients with HER2+ disease who did not achieve a pCR received 14 cycles of T-DM1 (LoE1b/B/AGO+)

ESMO Guidelines for eBC (2019)[3]

Grade A recommendation‡
If residual invasive disease: Kadcyla recommended

St. Gallen Guidelines (2021)[4]

If residual invasive disease:
Kadcyla recommended for women with residual invasive cancer following neoadjuvant systemic treatment with Trastuzumab- or with Trastuzumab–PERJETA-based regimens

* Category 1 listings are based on high-level evidence with uniform NCCN consensus that the intervention is appropriate;
† Based on evidence of individual randomised controlled trials;
‡ Grade A recommendation based on strong evidence for efficacy with a substantial clinical benefit; strongly recommended.
1. NCCN Breast Cancer Guidelines. Version 4 2022; 2, AGO Breast Cancer Guidelines 2022; 3. Cardoso F, *et al*. *Ann Oncol* 2019;
4. H. J. Burstein et al, July 2021, https://doi.org/10.1016/j.annonc.2021.06.023

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Key messages

KATHERINE marks a new standard of care for patients with HER2-positive eBC

- eBC treatment has a curative intent; patients should receive the most efficacious treatment as early as possible to help prevent distant recurrence and provide the best chance of cure
- Despite the proven benefits of HER2-targeted neoadjuvant therapy, some patients with HER2-positive eBC are still at risk of recurrence, particularly those with residual invasive disease
- KATHERINE met its primary endpoint: Kadcyla reduced the risk of breast cancer recurrence or death by 50% in patients with any amount of residual invasive disease after HER2-targeted neoadjuvant therapy compared with Trastuzumab
- Overall safety data in KATHERINE were consistent with the known safety profile of Kadcyla
- KATHERINE introduced a new decision point in HER2-positive eBC: adjuvant treatment should be optimised based on response to neoadjuvant therapy
- Kadcyla is established in international guidelines as the recommended adjuvant therapy for patients with any amount of residual invasive disease after HER2-targeted neoadjuvant therapy

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Kindly use the QR code/ click on the link for the latest Prescribing Information (PI). For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory.

http://bit.ly/Roche_Perjeta_PI

http://bit.ly/Roche_Kadcyla_PI

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