Session II.

The Role of Kadcyla in HER2+ Early Breast Cancer & Experience Sharing

Dr Roland Leung

Honorary Clinical Associate Professor in Medical Oncology
University Department of Medicine
Li Ka Shing Faculty of Medicine
The University of Hong Kong

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Disclosures

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What are the options for a newly diagnosed HER2 amplified HR –ve clinically T2 N1 breast cancer

- 1) Surgery followed by chemotherapy and 1 year of trastuzumab based therapy
- 2) Neoadjuvant chemotherapy and trastuzumab based therapy followed by surgery and continue trastuzumab based maintenance therapy
- 3) Neoadjuvant chemotherapy and trastuzumab based therapy followed by surgery and new Her2 targeted therapy with alternative MOA for those with residual cancer in their pathology specimen

The St. Gallen Expert Consensus, ESMO Guideline, and NCCN guidelines recommend neoadjuvant treatment to patients with ≥ T2 or ≥ N1 HER2-positive early breast cancer.

St. Gallen Expert Consensus[1]

Neoadjuvant therapy remains preferred for **stage II or III**, HER2-positive breast cancers. Preferred neoadjuvant regimens for HER2-positive tumors (**trastuzumab and pertuzumab**, paired with taxane chemotherapy and either anthracycline- or platinum-based chemotherapy)

ESMO Clinical Practice Guidelines[2]

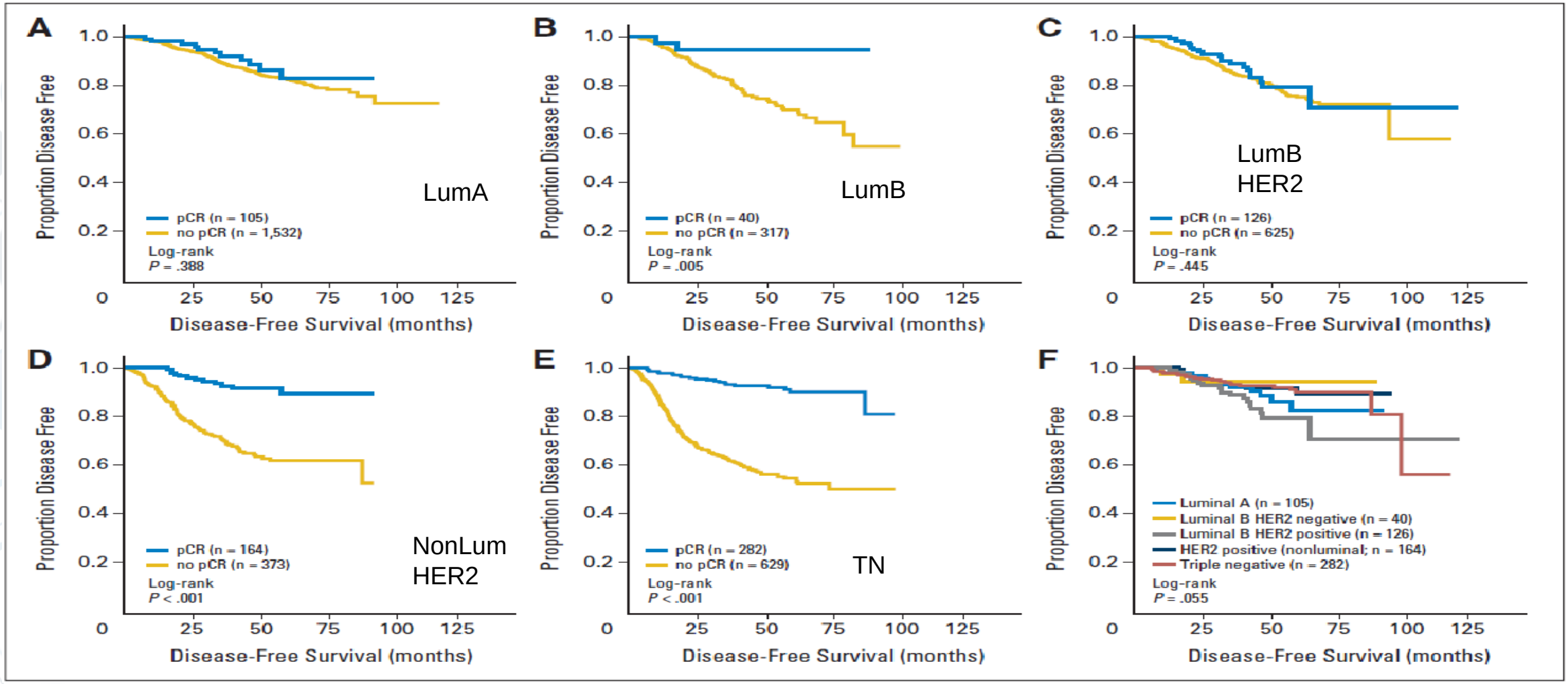
A neoadjuvant approach should be preferred in subtypes highly sensitive to ChT, such as **triple-negative** and **HER2-positive**, in **tumours >2 cm** and/or a **positive axilla**

NCCN Breast Cancer Guidelines[3]

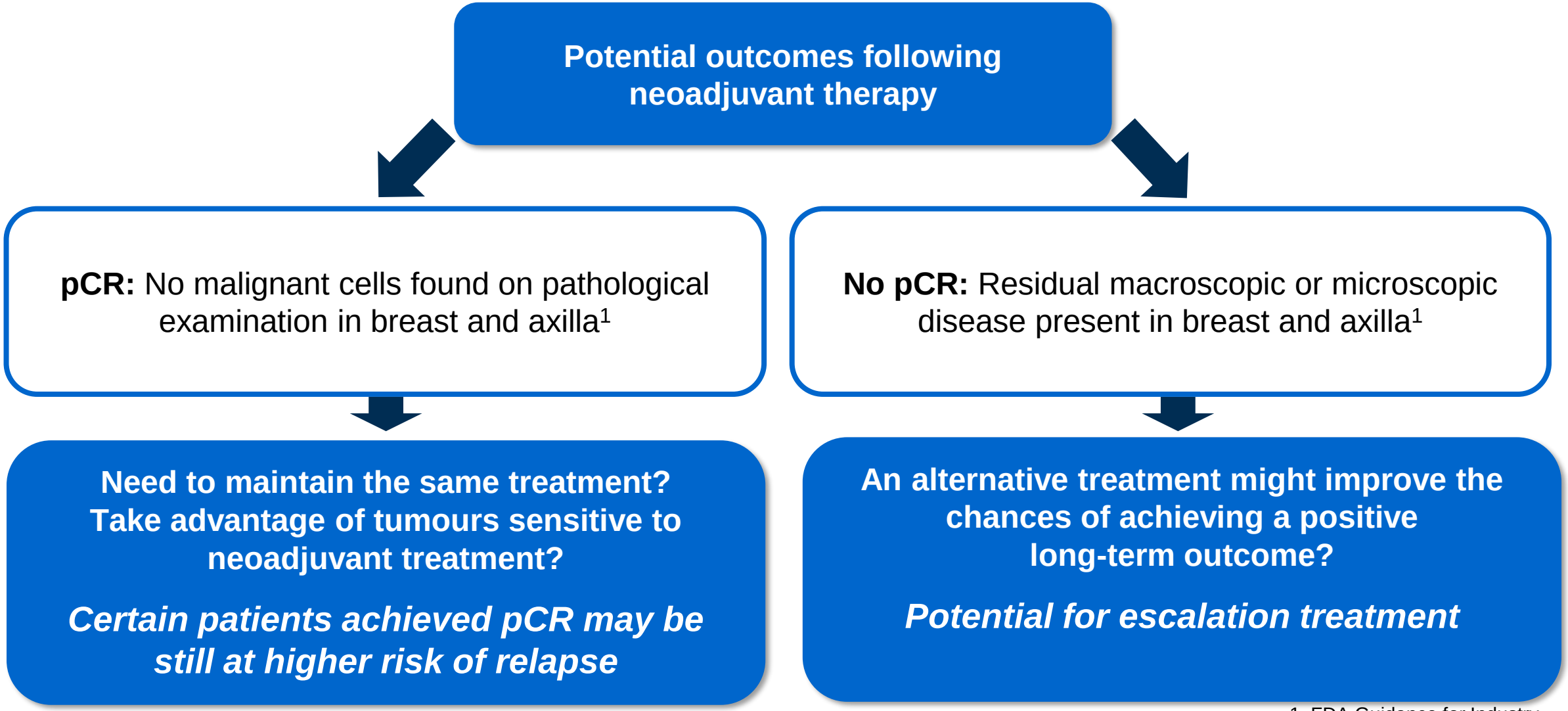
Patients with **HER2-positive** tumors should be treated with preoperative systemic therapy… A pertuzumab-containing regimen may be administered preoperatively to patients with **greater than or equal to T2** or **greater than or equal to N1**, HER2-positive early-stage breast cancer.

1. H J Burstein, et al. Ann Oncol. 2021 Oct;32(10):1216-1235
2. Early Breast Cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2019
3. NCCN Breast Cancer Guidelines. Version 4, 2023

PCR as a predictor of survival subtypes



The outcome of neoadjuvant therapy may still influence subsequent treatment decisions



pCR, pathologic complete response.

1. FDA Guidance for Industry. https://www.fda.gov/downloads/drugs/guidances/ucm305501.pdf.

KATHERINE was designed to optimise outcomes for patients with HER2-positive BC with residual invasive disease

Prior to KATHERINE there were **no data available to guide treatment decisions** for patients with residual disease following neoadjuvant chemotherapy plus anti-HER2 therapy, due to a lack of existing evidence for using residual invasive disease as a clinical decision point[1–3]

The **CREATE-X study in patients with HER2-negative BC** with residual disease **supported the approach of treatment optimisation** dependent on neoadjuvant response[4]

In the metastatic setting, **Kadcyla has shown activity** in patients who have **progressed after chemotherapy and HER2-directed therapy,** including those who relapsed within 6 months of eBC treatment[5,6]

KATHERINE was designed **to provide evidence for optimising therapy by changing to Kadcyla** in patients with HER2-positive eBC who have **residual invasive disease in the breast and/or axilla following neoadjuvant Herceptin-containing therapy**[7]

1. Curigliano G, *et al*. *Ann Oncol* 2017; **28:**1700–1712; 2. NCCN Breast Cancer Guidelines. Version 3, 2018.
3. Senkus E, *et al*. *Ann Oncol* 2015; **26**(Suppl 5):v8–v30; 4. Masuda N, *et al., N Engl J Med* 2017; **376*:*** 2147–2159;
5. Verma S, *et al. N Engl J Med* 2012; **367:**1783–1791; 6. Verma S, *et al.* ESMO 2012 (Abstract LBA12; oral presentation);
7. Geyer CE, *et al*. SABCS 2013 (Abstract P3-04-02; poster).

BC, breast cancer.

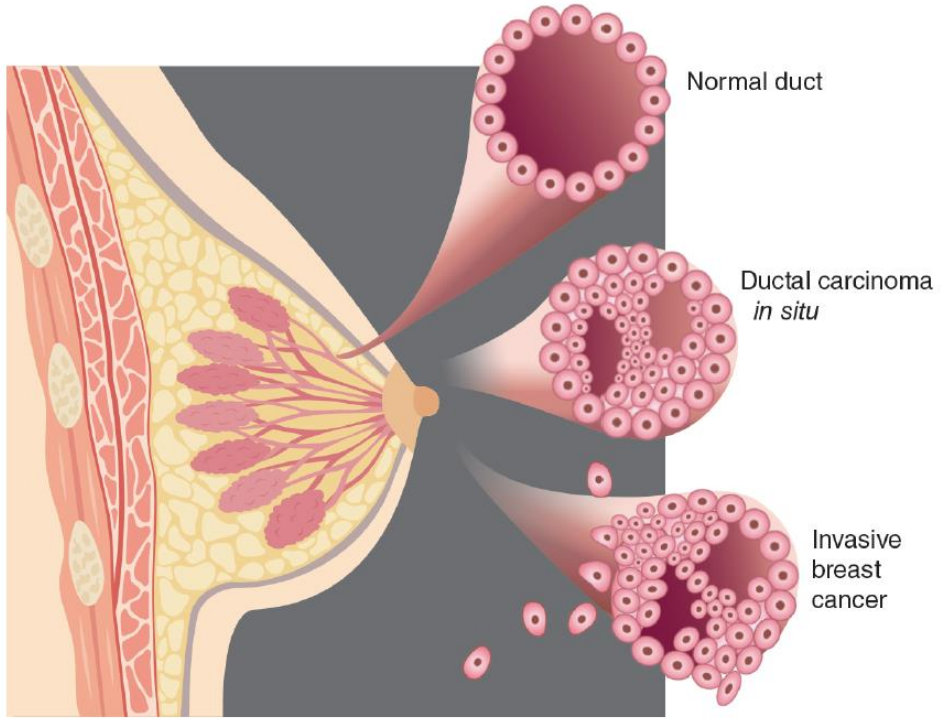
Defining residual disease

Residual disease in breast cancer

- Response to neoadjuvant treatment can be assessed by either:
  - **Clinical assessment** (pre-surgery) by palpation, ultrasound or MRI[1,2]
  - **Pathological assessment** (post-surgery) of the removed breast tissue and axillary lymph nodes[2]
- Residual disease present in the resected tissues may consist of invasive or *in situ* cancer cells[3]

Only patients with **residual invasive disease** were eligible for the KATHERINE study

In situ vs. invasive disease



1. Eisenhauer EA, *et al. Eur J Cancer* 2009; **45:**228–247; 2. Bossuyt V, *et al. Ann Oncol* 2015; **26:**1280–1291;
3. von Minckwitz G, *et al. J Clin Oncol* 2012; **30:**1796–1804.

Defining pathological complete response (pCR)

pCR in breast cancer

- pCR is the absence of cancerous cells in resected breast tissue or lymph node specimens[1]
- Patients who had a total pCR (tpCR) were not permitted in the KATHERINE trial[2]
  - Therefore, patients with residual *in situ* carcinomas only were not eligible for KATHERINE
- tpCR is the most widely accepted definition of pCR in clinical practice[3,4]

The definition of pCR can vary[1]

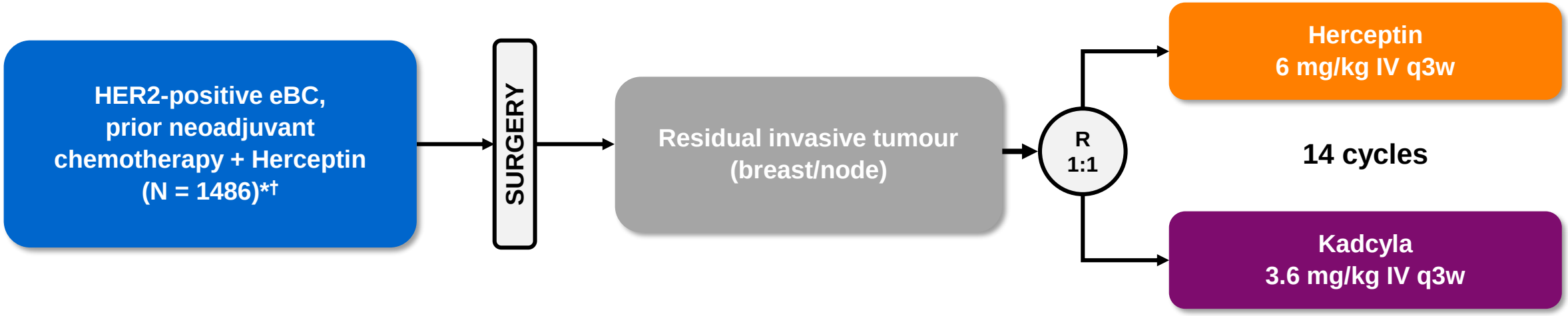
Commonly called	TMN code	Definition
Breast pCR (bpCR)	ypT0/is ypN0/+	Absence of invasive cancer in breast (irrespective of ductal carcinoma *in situ*). Invasive disease in lymph nodes is permitted
Total pCR (tpCR)	ypT0/is ypN0	Absence of invasive cancer in breast and axillary nodes (irrespective of ductal carcinoma *in situ*)
German Breast Group (GBG) pCR	ypT0 ypN0	Absence of invasive cancer and *in situ* cancer in breast and axillary nodes

pCR, pathological complete response.

1. von Minckwitz G, *et al. J Clin Oncol* 2012; **30:**1796–1804;
2. Roche. Data on file. Protocol BO27938 (KATHERINE) – version 7;
3. Cortazar P, *et al. Lancet* 2014; **384:**164–172;
4. Stebbing J, *et al. Expert Rev Anticancer Ther* 2018; **18:**531-541.

KATHERINE STUDY DESIGN

KATHERINE (BO27938/NSABP B-50-I/GBG 77)
Phase III randomised, open-label adjuvant study[1,2]



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: Herceptin vs. dual HER2 targeting
- Pathological nodal status evaluated after neoadjuvant therapy

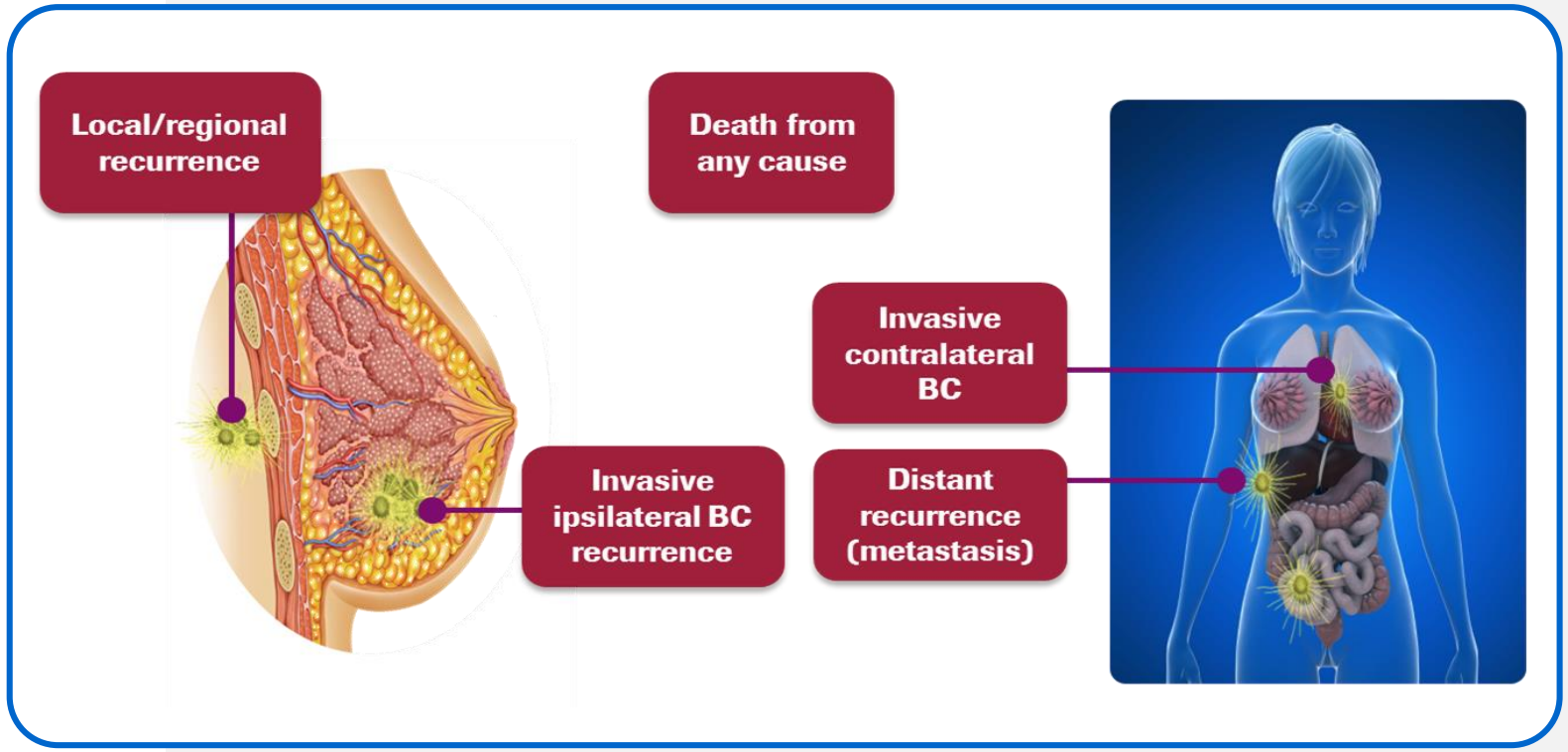
Primary endpoint: IDFS

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

* 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).
† Dual anti-HER2 therapy was also permitted in the neoadjuvant setting.
DFS, disease-free survival; DRFI, distant recurrence-free interval; eBC, early breast cancer; ER, oestrogen receptor; IDFS, invasive disease-free survival; IV, intravenous; OS, overall survival; PR, progesterone receptor; q3w, every 3 weeks.

1. Roche. Data on File. Protocol BO27938 (KATHERINE) – version 7;
2. von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628.

IDFS definition used for KATHERINE primary endpoint



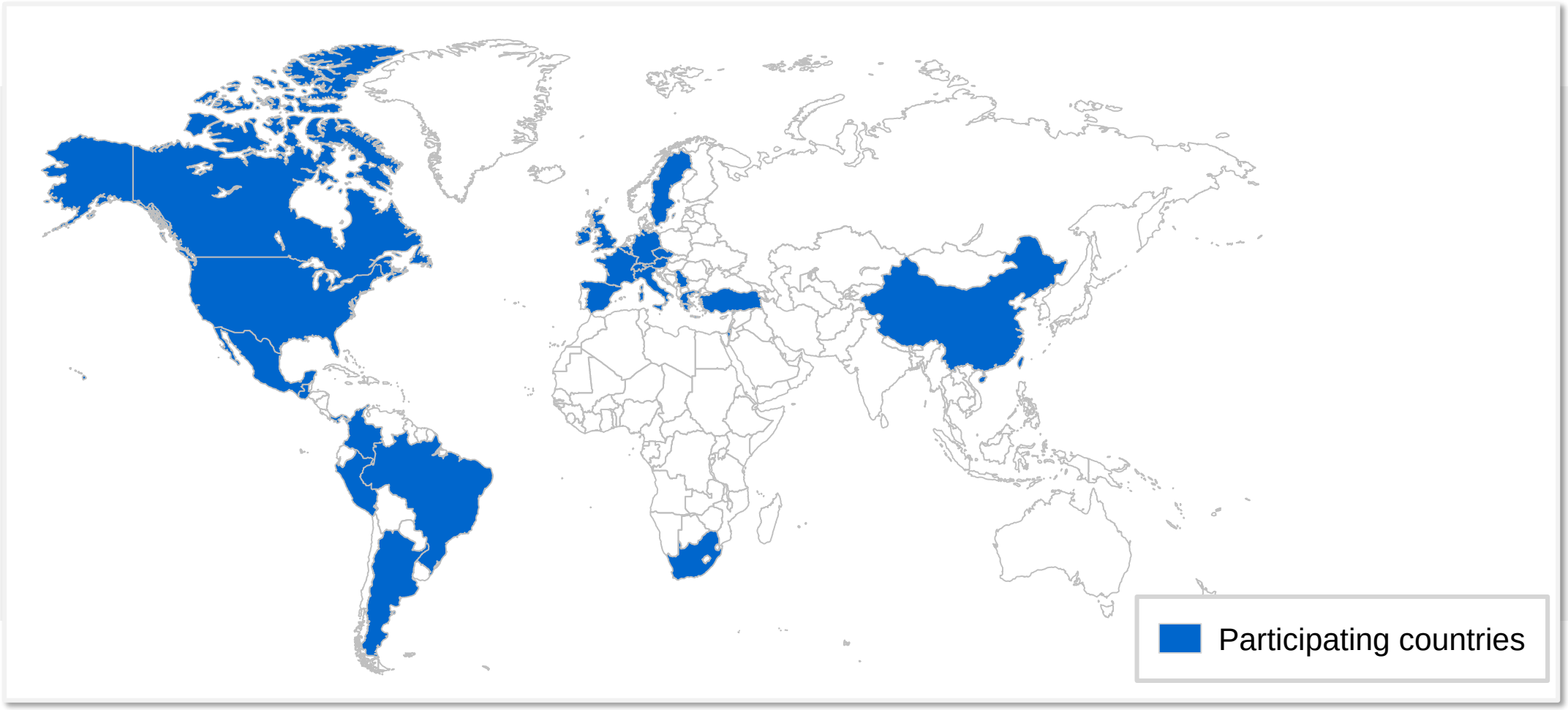
Differing from the STEEP definition of IDFS,[1] the KATHERINE definition excludes second primary non-BC tumours[2,3]

The events included in the IDFS and DFS endpoint definitions used in the KATHERINE study correlate with those used in the APHINITY study[4]

BC, breast cancer; DCIS, ductal carcinoma *in situ*; DFS, disease-free survival; IDFS, invasive disease-free survival; LCIS, lobular carcinoma *in situ*.

1. Hudis CA, *et al. J Clin Oncol* 2007; **25:**2127-2132; 2. Geyer CE, *et al.* SABCS 2013 (abstract P3-04-02); 3. von Minckwitz G, *et al. N Engl J Med* 2019; **380:**617–628; 4. von Minckwitz G, *et al. N Engl J Med* 2017; **377:**122–131.

Participating countries:
342 sites across 28 countries[1,2]



1. Geyer CE, *et al*. SABCS 2013 (Abstract P3-04-02; poster);
2. https://clinicaltrials.gov/study/NCT01772472 (accessed November 2023).

Study population

	Herceptin	Kadcyla
Randomised, ITT, n[1,2]	743	743
Treated, n[1,2]	720	740
Switched from Kadcyla to Herceptin, n[1]	N/A	71
Median duration of follow-up, months		
PA IDFS (incl. 1IA OS)[1]	40.9	41.4
FA IDFS (incl. 2IA OS)[2]	100.8	101.4
Alive and on study at FA IDFS, n (% of ITT)[2]	461 (62.0)	521 (70.1)
Discontinued from study at FA IDFS, n (%)[2]		
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 Herceptin arm and 77 (10.4%) in the Kadcyla arm; lost to follow-up, 28 (3.8%) in the Herceptin arm and 30 (4.0%) in the Kadcyla arm; other, 7 (0.9%) in the Herceptin arm and 5 (0.7%) in the Kadcyla arm; physician decision: 0 in the Herceptin arm and 5 (0.7%) in the Kadcyla arm.

1IA, first interim analysis; 2IA, second interim analysis; FA, final analysis; IDFS, invasive disease-free survival; ITT, intention to treat; OS, overall survival; PA, primary analysis.

1. von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628.
2. Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

Stratification factors[1,2]

No. patients, n (%)	Herceptin 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		
Herceptin alone	596 (80.2)	600 (80.8)
Herceptin plus additional HER2-directed agent(s)*	147 (19.8)	143 (19.2)
Pathological nodal status evaluated after neoadjuvant therapy†		
Node-positive	345 (46.4)	343 (46.2)
Node-negative/not done	398 (53.6)	400 (53.8)

* Other HER2-targeted agents were PERJETA, neratinib, dacomitinib, afatinib or lapatinib. † Nodal status updated for one patient since PA of IDFS.
ER, oestrogen receptor; IDFS, invasive disease-free survival; PA, primary analysis; PR, progesterone receptor.

1. von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628;
2. Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

Demographic and baseline characteristics (1/3)

No. patients, n (%)	Herceptin 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*	530 (71.3)	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		
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)

* One patient had race updated from 'White' to 'multiple' since PA of IDFS.
IDFS, invasive disease-free survival; PA, primary analysis.

Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

Demographic and baseline characteristics (2/3)

No. patients, n (%)	Herceptin 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	332 (44.7)	341 (45.9)
ypN1	212 (28.5)	220 (29.6)
ypN2	103 (13.9)	86 (11.6)
ypN3	30 (4.0)	37 (5.0)
ypNX	66 (8.9)	56 (7.9)

* Nodal status updated for seven patients since PA of IDFS.
IDFS, invasive disease-free survival; PA, primary analysis.

Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

Demographic and baseline characteristics (3/3)[1,2]

No. patients, n (%)	Herceptin 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		
Herceptin alone	596 (80.2)	600 (80.8)
PERJETA–Herceptin	139 (18.7)	133 (17.9)
Herceptin plus other HER2-directed agent(s)*	8 (1.1)	10 (1.3)

Baseline characteristics and prior therapy were balanced across both treatment arms

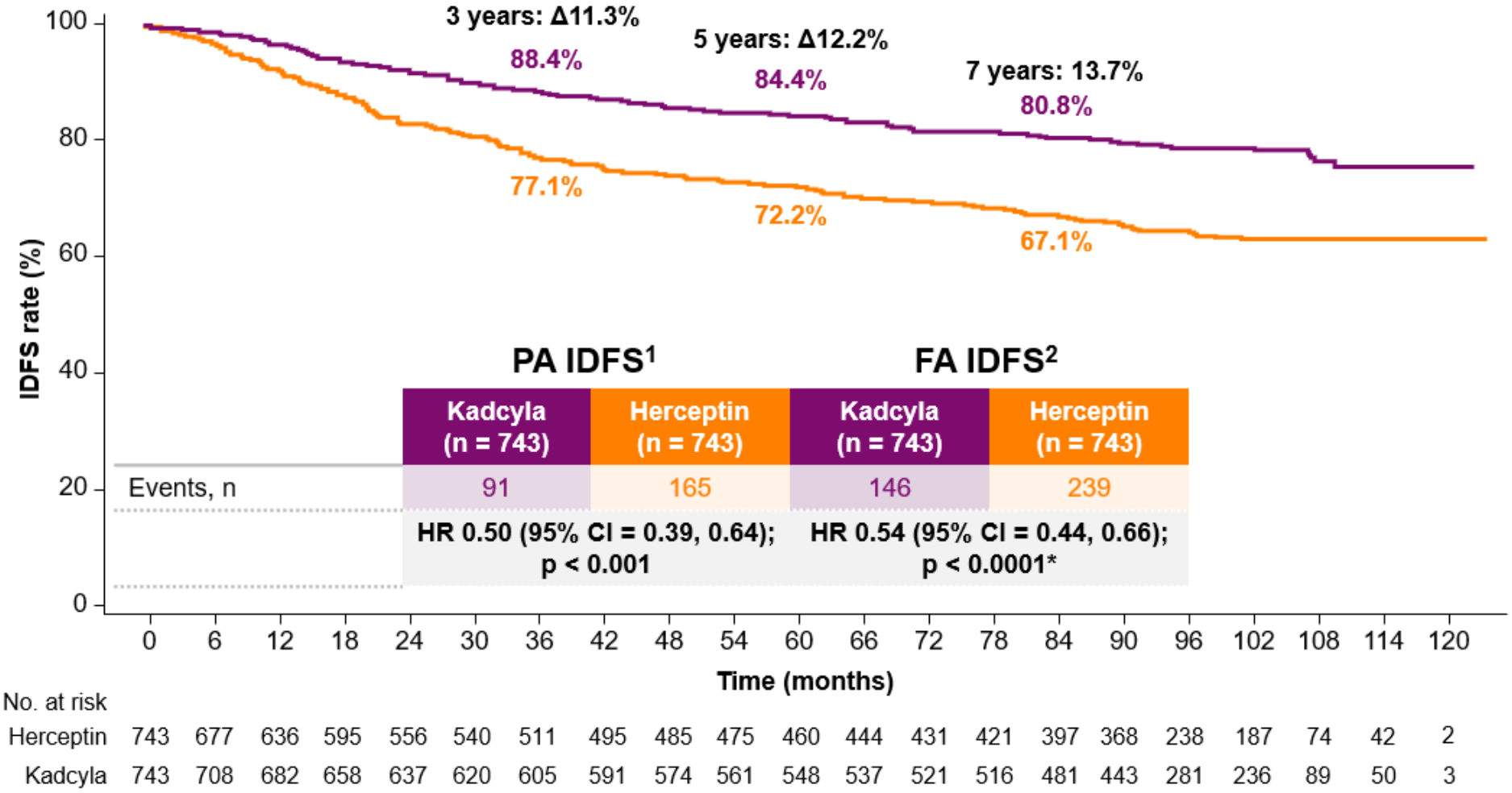
* Other HER2-targeted agents were neratinib, dacomitinib, afatinib, and lapatinib

Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

EFFICACY OUTCOMES

IDFS (PRIMARY ENDPOINT)

IDFS

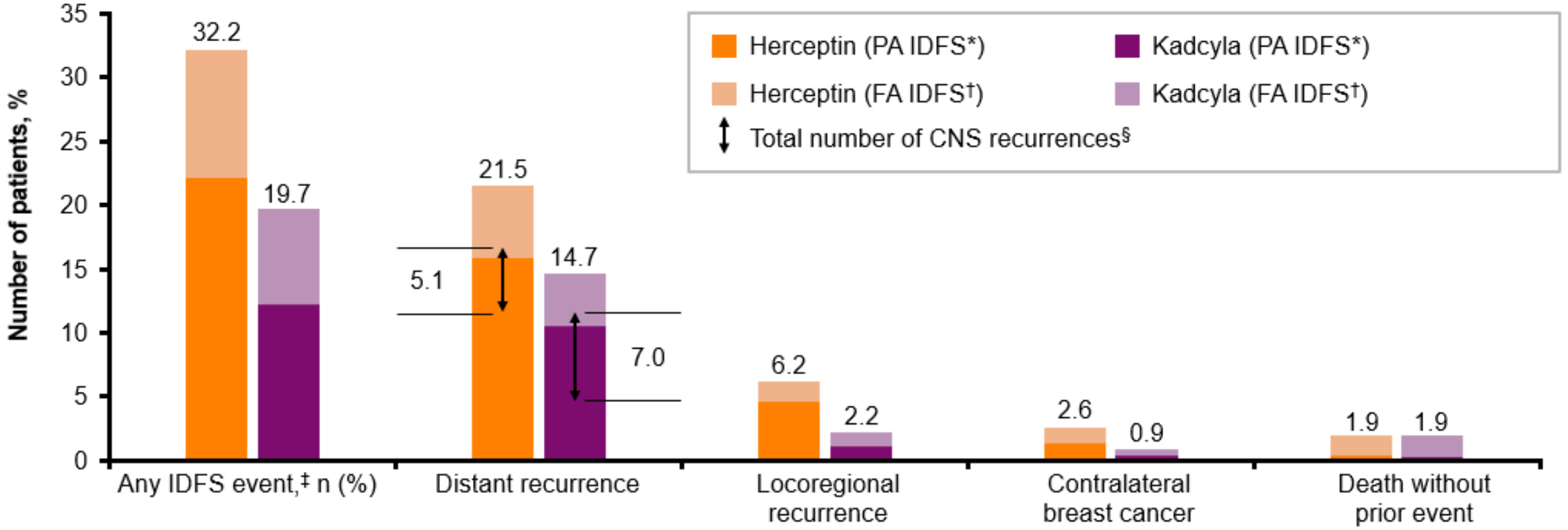


IDFS benefit of Kadcyla was sustained with longer median follow-up (101 mo), with a 46% reduction in risk of recurrence of invasive disease or death vs. Herceptin

* p-value for IDFS at the FA is exploratory given that statistical significance was established at the PA.
CI, confidence interval; FA, final analysis; HR, hazard ratio; IDFS, invasive disease-free survival; mo, months; PA, primary analysis.

1. von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628;
2. Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

First occurrence of an IDFS event[1,2]*



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

* PA of IDFS, including 1IA of OS (CCOD 2018). ‡ FA of IDFS, including 2IA of OS (CCOD 2023). ‡ 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 within other sites).
At PA IDFS: 4.3% with Herceptin vs. 5.9% with Kadcyla. At FA IDFS: 5.1% with Herceptin vs. 7.0 with Kadcyla.
1IA, first interim analysis; 2IA, second interim analysis; CCOD, clinical cut-off date; CNS, central nervous system; FA, final analysis; IDFS, invasive disease-free survival; OS, overall survival; PA, primary analysis.

1. von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628;
2. Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

Exploratory analysis (at PA of IDFS): CNS recurrence[1]

	Herceptin n = 743	Kadcyla n = 743
Patients with CNS recurrence, n (%)	40 (5.4)	45 (6.1)
As first IDFS event*	32 (4.3)	44 (5.9)
After first IDFS event†	8 (1.1)	1 (0.1)
Patients with CNS recurrence as only event, n (%)‡	21 (2.8)	36 (4.8)
Median time to CNS recurrence, months	11.9	17.5

Numerically higher incidence of CNS recurrence as the first IDFS event in the Kadcyla vs. Herceptin arm is likely due to competing risk,[2,3] as previously observed in adjuvant Herceptin trials[4]

The substantial reduction in the incidence of non-CNS recurrences as a first event observed with Kadcyla leads to an increased likelihood of a CNS recurrence as a first event and as the only recurrence

This is supported by:

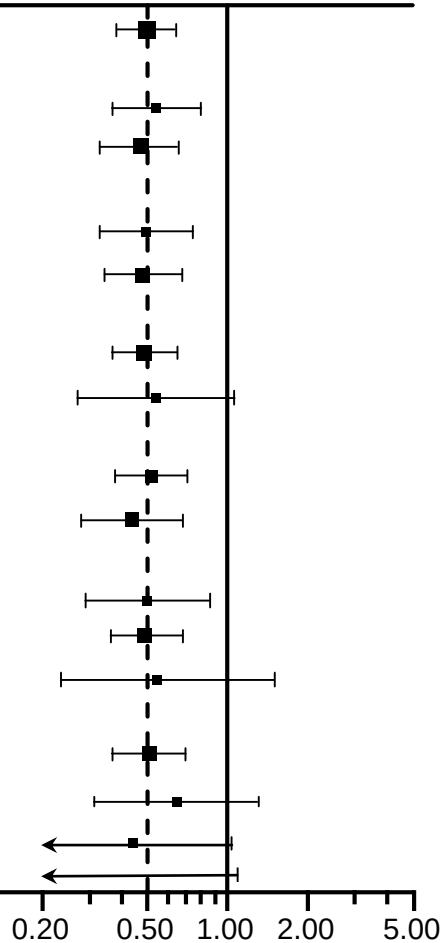
- Similar cumulative risk of CNS recurrence in both arms[1]
- Longer time (Δ 5.6 months) to CNS recurrence in the Kadcyla arm[1]
- Higher incidence of CNS recurrence as the only recurrence in the Kadcyla arm[1]

* CNS recurrence within 61 days of first IDFS event.
† CNS recurrence after 61 days of first IDFS event.
‡ CNS recurrence at any time.
CNS, central nervous system; IDFS, invasive disease-free survival.

1. Untch M, *et al*. ESMO 2019 (Abstract LBA19; oral presentation);
2. Wolkewitz M, *et al*. *BMJ* 2014; **349:**g5060;
3. Gooley TA, *et al*. *Stat Med* 1999; **18:**695–706;
4. Pestalozzi BC, *et al*. *Lancet Oncol* 2013;**14:**244–248.

Primary IDFS analysis: IDFS subgroup analysis (1)*

Group	Total N	Herceptin (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 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‡					
Herceptin alone	1196	75.9	87.7	0.49	(0.37–0.65)
Herceptin 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)



CCOD 25 July 2018.

* 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.

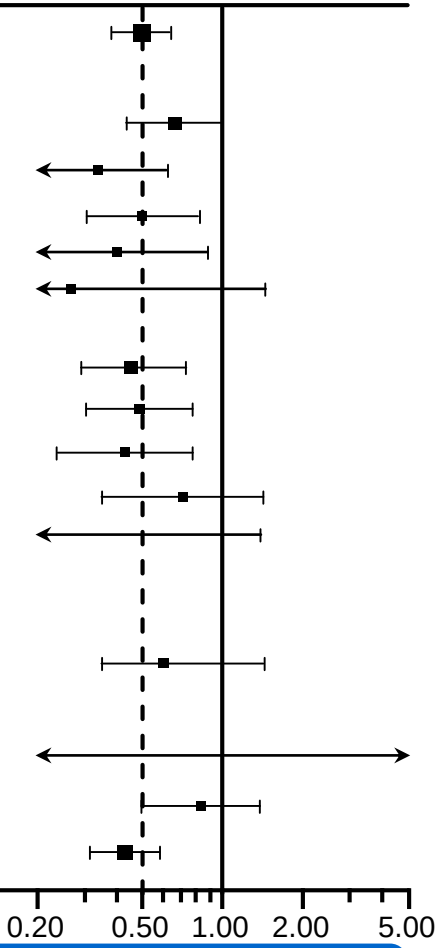
§ 149 were of multiple races or unknown race.

ER, oestrogen receptor; CI, confidence interval; IDFS, invasive disease-free survival; PR, progesterone receptor.

von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628.

Primary IDFS analysis: IDFS subgroup analysis (2)[1,2]

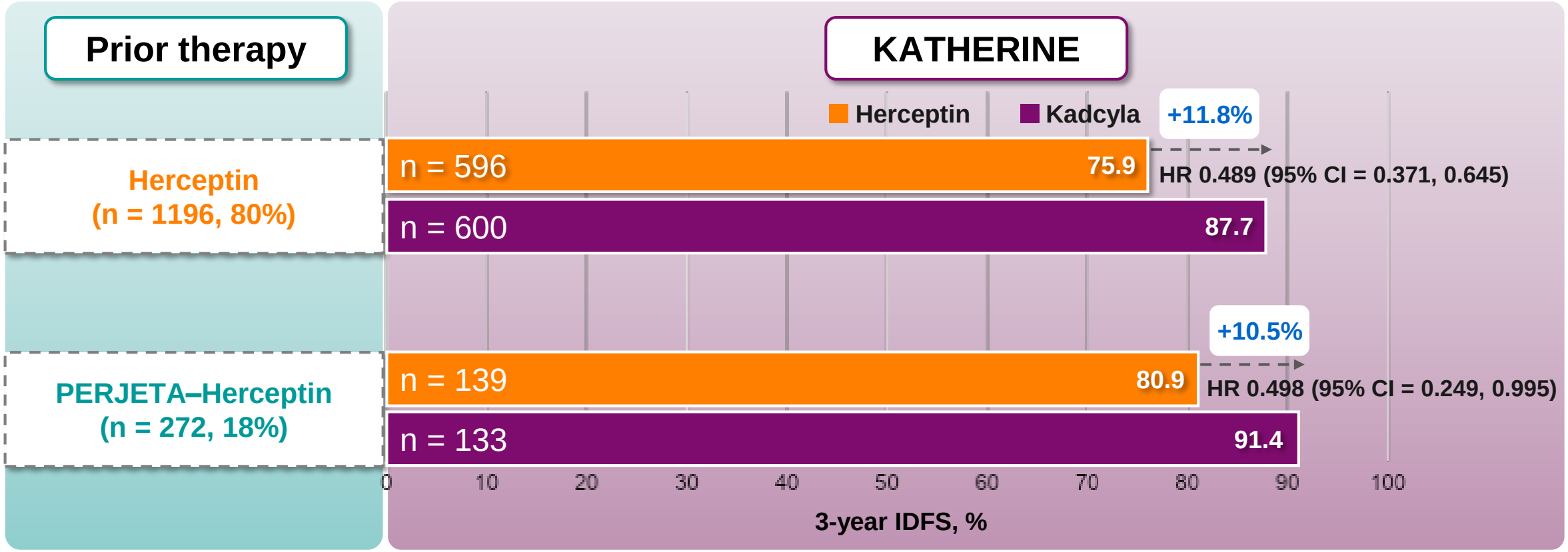
Group	Total N	Herceptin (n = 743) 3-Year IDFS	Kadcyla (n = 743) 3-Year IDFS	Hazard Ratio	95% CI
All[1]	1486	77.0	88.3	0.50	(0.39–0.64)
Primary tumour stage (at definitive surgery)[1]					
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	637	83.6	88.3	0.66	(0.44–1.00)
ypT1, ypT1c	359	75.9	91.9	0.34	(0.19–0.62)
ypT2	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 invasive 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)



- The magnitude of IDFS benefit in all subgroups was consistent with the ITT result[1,2]
- Data for subgroups at the final IDFS analysis were consistent with those reported at the PA of IDFS[3]

Footnotes, abbreviations and references in slide notes.

IDFS by neoadjuvant PERJETA (at PA)



This exploratory analysis shows that Kadcyla gave a consistent magnitude of IDFS benefit regardless of prior HER2-directed therapy*

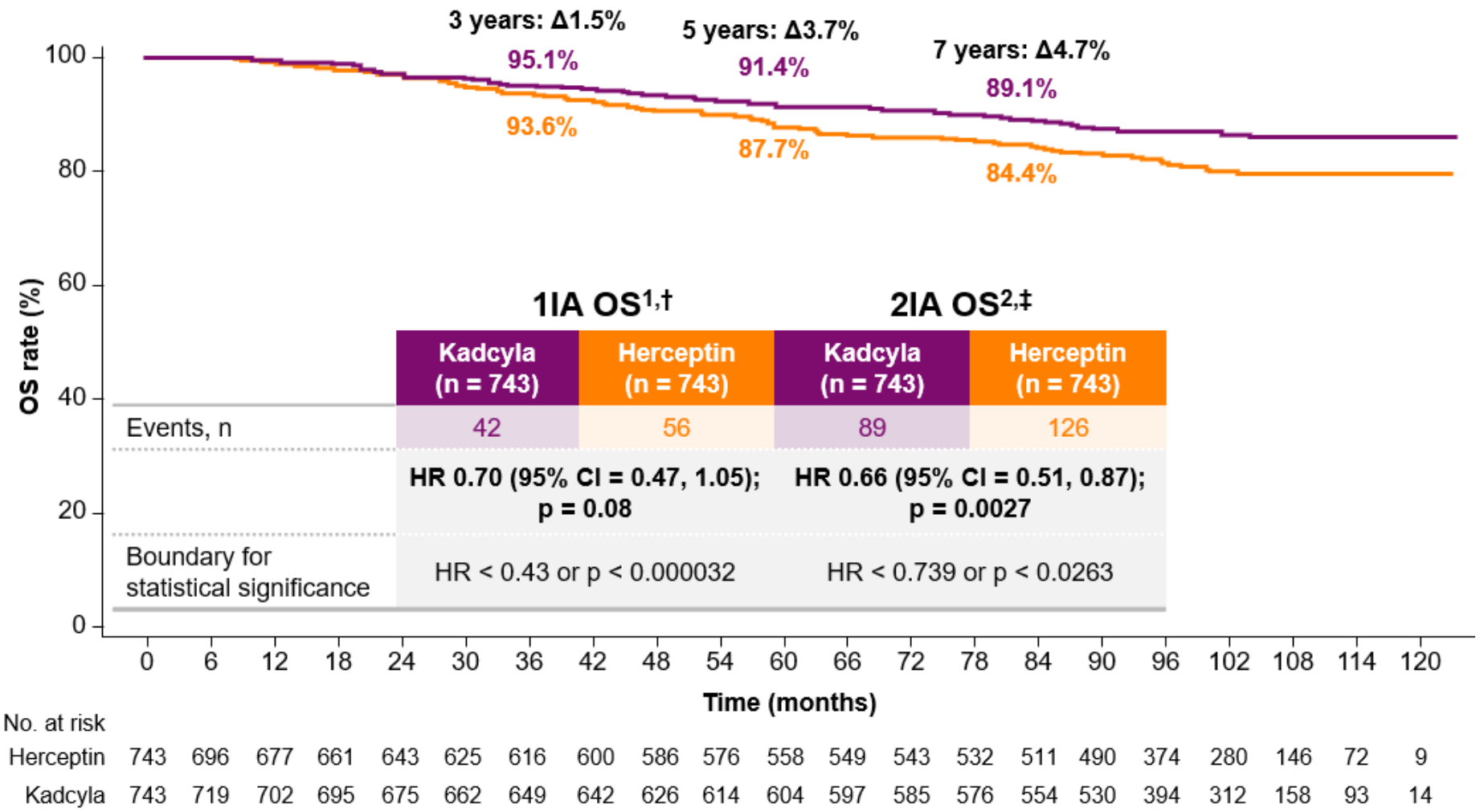
* Caution must be exercised as this exploratory analysis involves low patient numbers and the study is not powered to determine the statistical significance of these data.

CI, confidence interval; HR, hazard ratio; IDFS, invasive disease-free survival; PA, primary analysis.

von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628 suppl. appendix.

OS (SECONDARY ENDPOINT)

OS*



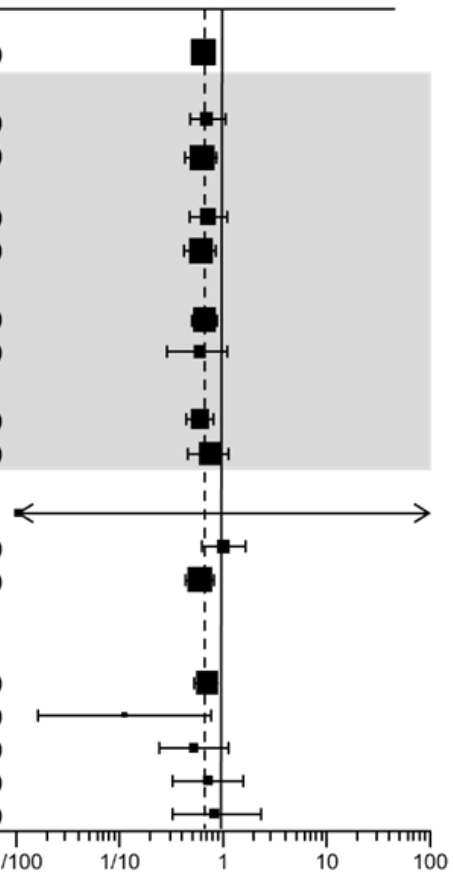
- **OS data were immature at 1IA but were supportive of the primary endpoint of IDFS**
- **At the 2IA of OS (mFU = 101 mo), Kadcyla significantly improved OS vs. Herceptin**
- **Kadcyla is the first targeted therapy to demonstrate a significant survival benefit post-surgery in patients with HER2-positive eBC with residual invasive disease after neoadjuvant therapy**

* The final OS analysis will be performed 12 years after FPI; † PA of IDFS, including 1IA of OS (CCOD 2018);
‡ FA of IDFS, including 2IA of OS (CCOD 2023).
1IA, first interim analysis; 2IA, second interim analysis; CI, confidence interval; eBC, early breast cancer; FPI, first patient in; HR, hazard ratio; IDFS, invasive disease-free survival; mFU, median follow-up; OS, overall survival.

1. von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628;
2. Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

2IA of OS:* Subgroup analysis (1)

Baseline risk factors	Total n	Herceptin (n = 743) Patients per group	Herceptin (n = 743) n events	Herceptin (n = 743) 7-year OS	Kadcyla (n = 743) Patients per group	Kadcyla (n = 743) n events	Kadcyla (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									
Herceptin alone	1196	596	105	84.1	600	77	88.6	0.68	(0.51, 0.91)
Herceptin plus additional HER2-directed agent(s)	290	147	21	85.7	143	12	91.0	0.57	(0.28, 1.16)
Pathological nodal status after preoperative therapy									
Node-positive	688	345	90	75.6	343	62	83.4	0.61	(0.44, 0.84)
Node-negative/not done	798	398	36	91.4	400	27	94.0	0.74	(0.45, 1.21)
Central HER2 status by IHC									
0/1+	25	13	4	75.0	12	0	100.0	<0.01	(0.00, NE)
2+	326	168	28	83.4	158	28	83.3	1.03	(0.61, 1.73)
3+	1132	559	94	84.8	573	61	90.4	0.59	(0.43, 0.82)
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)
American Indian or Alaska Native	86	50	14	68.9	36	8	78.8	0.75	(0.31, 1.78)
Other or multiple or unknown	150	80	9	89.3	70	7	92.3	0.87	(0.32, 2.32)



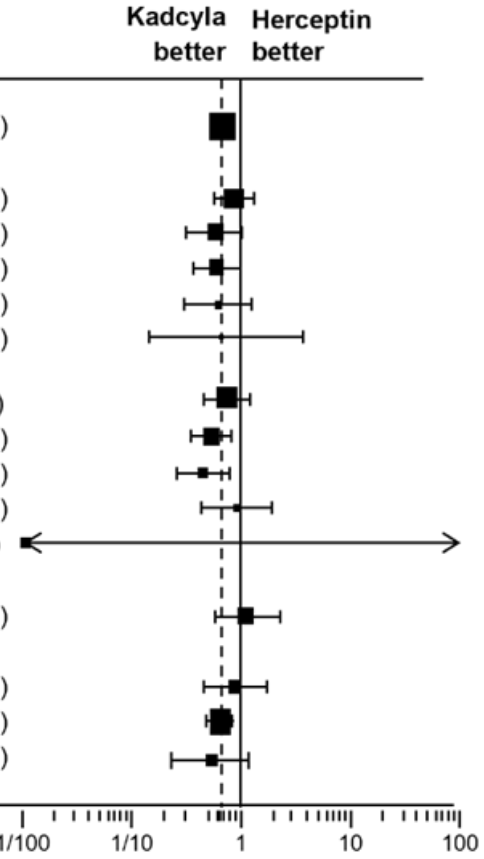
* FA of IDFS, including 2IA of OS (CCOD 2023).

2IA, second interim analysis; CCOD, clinical cut-off date; CI, confidence interval; ER, oestrogen receptor; FA, final analysis; IDFS, invasive disease-free survival; NE, not evaluable; OS, overall survival; PgR, progesterone receptor.

Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

2IA of OS:* Subgroup analysis (2)

Baseline risk factors	Total n	Herceptin (n = 743) Patients per group	Herceptin (n = 743) n events	Herceptin (n = 743) 7-year OS	Kadcyla (n = 743) Patients per group	Kadcyla (n = 743) n events	Kadcyla (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)									
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	637	306	41	89.4	331	38	89.5	0.86	(0.55, 1.34)
ypT1, ypT1c	359	184	27	84.6	175	15	91.1	0.55	(0.29, 1.03)
ypT2	359	185	38	79.9	174	23	89.8	0.57	(0.34, 0.95)
ypT3	108	57	17	74.1	51	10	78.2	0.59	(0.27, 1.29)
ypT4	23	11	3	63.5	12	3	80.0	0.72	(0.14, 3.58)
Regional lymph node stage (at definitive surgery)									
ypN0	673	332	32	90.7	341	27	92.8	0.82	(0.49,1.37)
ypN1	432	212	46	80.9	220	30	86.6	0.57	(0.36, 0.90)
ypN2	189	103	33	70.0	86	16	87.1	0.48	(0.26, 0.87)
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)

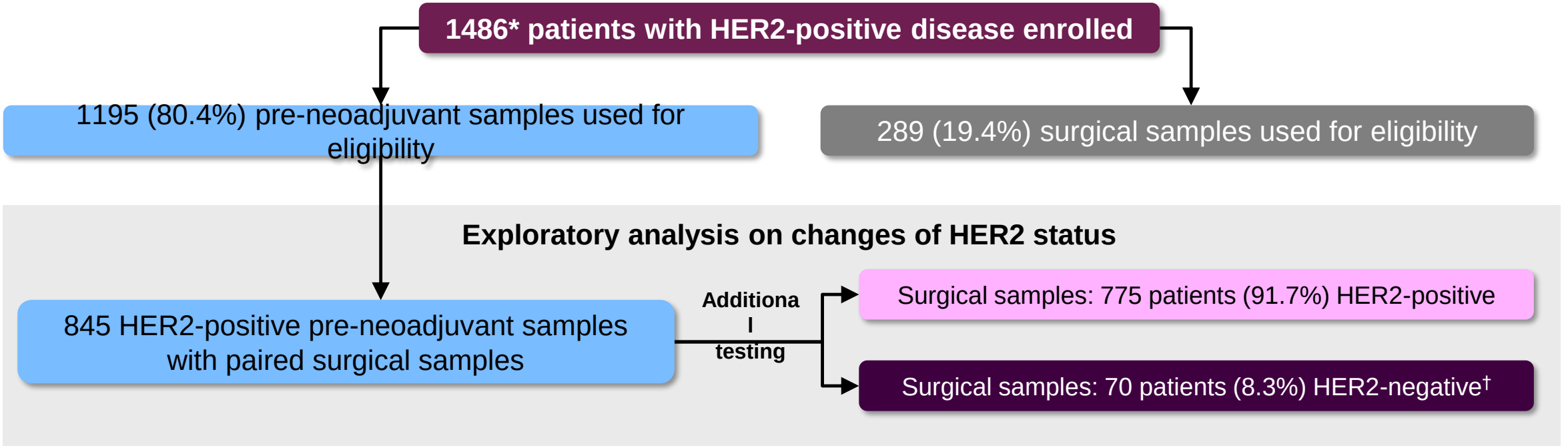


OS benefit with Kadcyla was seen across key subgroups, including clinical stage at presentation, hormone receptor status, pathological nodal status, and prior HER2-directed therapy

* FA of IDFS, including 2IA of OS (CCOD 2023).
Abbreviations in slide notes.

Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

KATHERINE exploratory analyses:
HER2-negative status at surgery did not impact on the efficacy of T-DM1



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

- **No IDFS events in patients randomised to the T-DM1 arm (n = 28)**
- **11 IDFS events in patients randomised to the trastuzumab arm (n = 42)**

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

* 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.
† Fifty-three HER2-negative and 17 HER2-unknown by IHC 0-1+/ISH unknown.
IDFS, invasive disease-free survival.

Loibl S, *et al*. ESMO Breast Cancer 2020 (Abstract 96O and oral presentation).

KATHERINE: Efficacy summary[1–2]

- The study met the primary objective of IDFS
  - Kadcyla reduced the risk of an IDFS event by 50% compared with Herceptin (HR 0.50; 95% CI = 0.39, 0.64; p < 0.001)
  - The IDFS benefit with Kadcyla vs. Herceptin was maintained with longer follow-up (mFU = 101 mo): HR 0.54; 95% CI = 0.44; 0.66; p < 0.0001
  - Estimated absolute IDFS benefit increased with longer follow-up (Δ = 11.3% at 3 years, 12.2% at 5 years, and 13.7% at 7 years)
- Kadcyla significantly improved OS after longer follow-up: HR 0.66; 95% CI 0.51, 0.87; p = 0.0027
  - The magnitude of OS benefit was consistent across all subgroups, including hormone receptor status, pathological nodal status and prior dual HER2 blockade

CI, confidence interval; HR, hazard ratio; IDFS, invasive disease-free survival; mFU, median follow-up; OS, overall survival.

1. von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–62;
2. Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation

SAFETY DATA

Study treatment exposure*

No. patients, n (%)	Herceptin n = 720	Kadcyla n = 740
Patients completing at least X cycles of planned study treatment:[1]		
7 cycles	664 (92.2)	637 (86.1)
14 cycles†	583 (81.0)	528 (71.4)
Patients completing 14 cycles of any study treatment‡[1]	583 (81.0)	593 (80.1)
Number of patients with a dose reduction§[1]		
No dose reduction	N/A**	634 (85.7)
Dose reduction by one level (3.0 mg/kg)	N/A	77 (10.4)
Dose reduction by two levels (2.4 mg/kg)	N/A	29 (3.9)
Number of cycles completed of any study treatment[2]		
Median (range)	14 (1–14)	14 (1–14)

>70% of patients completed 14 cycles of Kadcyla treatment

* The safety analysis included all patients who received at least one dose of study drug.
† As some patients switched to Herceptin treatment during the trial, a lower number of patients completed the full 14 cycles of Kadcyla treatment.
‡ Patients who discontinued Kadcyla because of an adverse event and switched to Herceptin are included (n = 71).
§ Most dose reductions occurred after Cycle 3.
** Herceptin dose reductions were not allowed.

1. von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628;
2. Roche. Data on file. Clinical Study Report BO27938 (KATHERINE).

Safety overview[1]

No. patients, n (%)	Herceptin 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)

- **AE increases with Kadcyla were in line with what was expected[1]**
- **Minimal changes were observed with longer follow-up[2]**

* The fatal AE was an intracranial hemorrhage 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 randomization. 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%).[3]
1IA, first interim analysis; 2IA, second interim analysis; AE, adverse event; IDFS, invasive disease-free survival; OS, overall survival; PA, primary analysis.

1. von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628;
2. Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation);
3. Verma S, *et al. N Engl J Med* 2012; **367:**1783–1791.

Summary of deaths

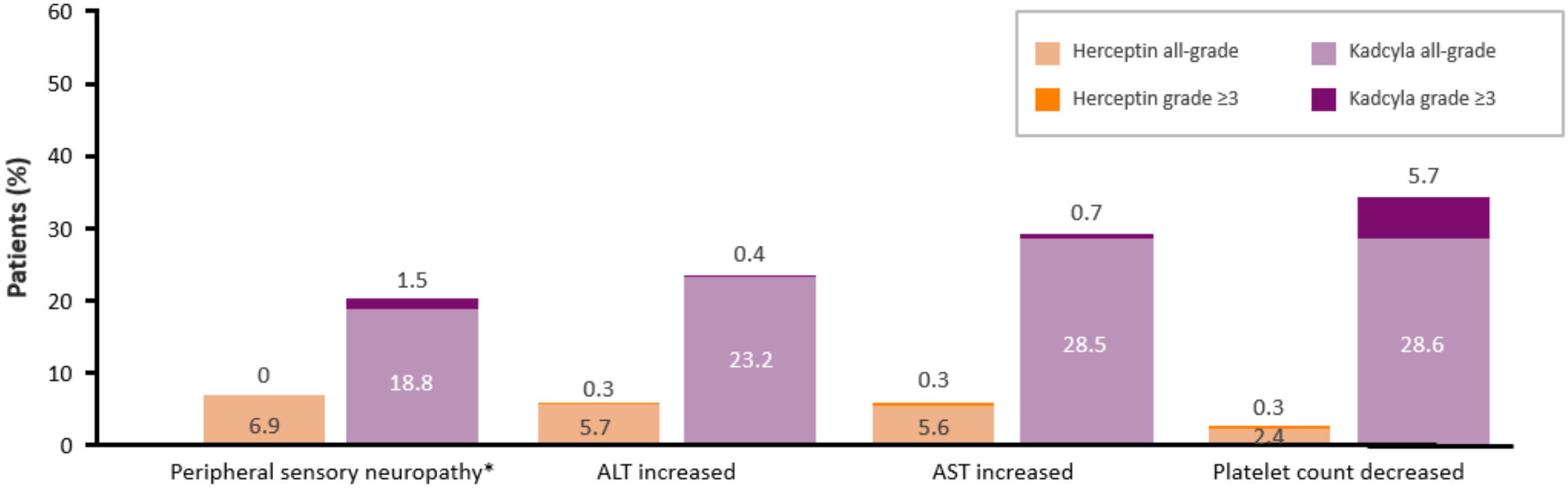
No. patients, n (%)	**PA IDFS** (incl.1IA OS)[1] Herceptin n = 720	**PA IDFS** (incl.1IA OS)[1] Kadcyla n = 740	**FA IDFS** (incl. 2IA OS)[2] Herceptin n = 720	**FA IDFS** (incl. 2IA OS)[2] Kadcyla n = 740
Total number of deaths	56 (7.8)	42 (5.7)	126 (17.5%)	89 (12.0%)
Cause of death:				
Breast cancer	52 (7.2)	39 (5.3)	108 (15.0%)	70 (9.5%)
AE	0	1 (0.1)*	0	1 (0.1%)*
Other	4 (0.5)	2 (0.3)	18 (2.5%)†	18 (2.4%)†

Breast cancer was the most frequent cause of death in both study arms, at PA IDFS and FA IDFS

* AEs leading to death due to intracranial haemorrhage.
† At the final IDFS analysis, other causes of death with Herceptin vs. Kadcyla were respiratory disorders (n = 5 vs. n = 1), cardiac disorders (n = 2 vs. n = 3), infections (n = 3 vs. n = 1), cerebrovascular disorders (n = 1 vs. n = 2), secondary malignancies (n = 6 vs. n = 4), unknown (n = 1 vs. n = 6) and surgical procedure (n = 0 vs. n = 1). These were non-reportable adverse events because they occurred >30 days after last study treatment and were not related to study treatment or study procedures.
1IA, first interim analysis; 2IA, second interim analysis; AE, adverse event; IDFS, invasive disease-free survival; OS, overall survival; PA, primary analysis.

1. Roche. Data on file. Clinical Study Report BO27938 (KATHERINE);
2. Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

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

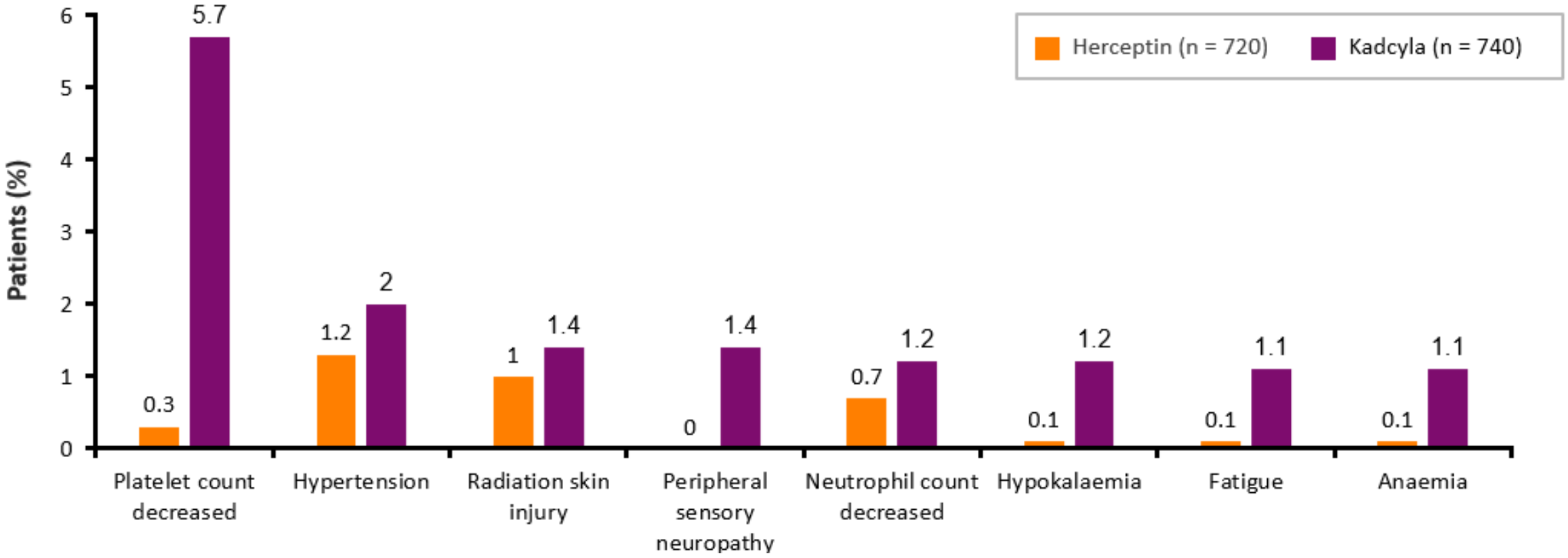


***75% of cases of peripheral sensory neuropathy were resolved and 9% were resolving at the time of DBL**

* PA of IDFS, including 1IA of OS (CCOD 2018).
AE, adverse event; DBL, database lock; IDFS, invasive disease-free survival; PA, primary analysis.

von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628.

PA IDFS:* Grade ≥3 AEs with ≥1% incidence in either arm

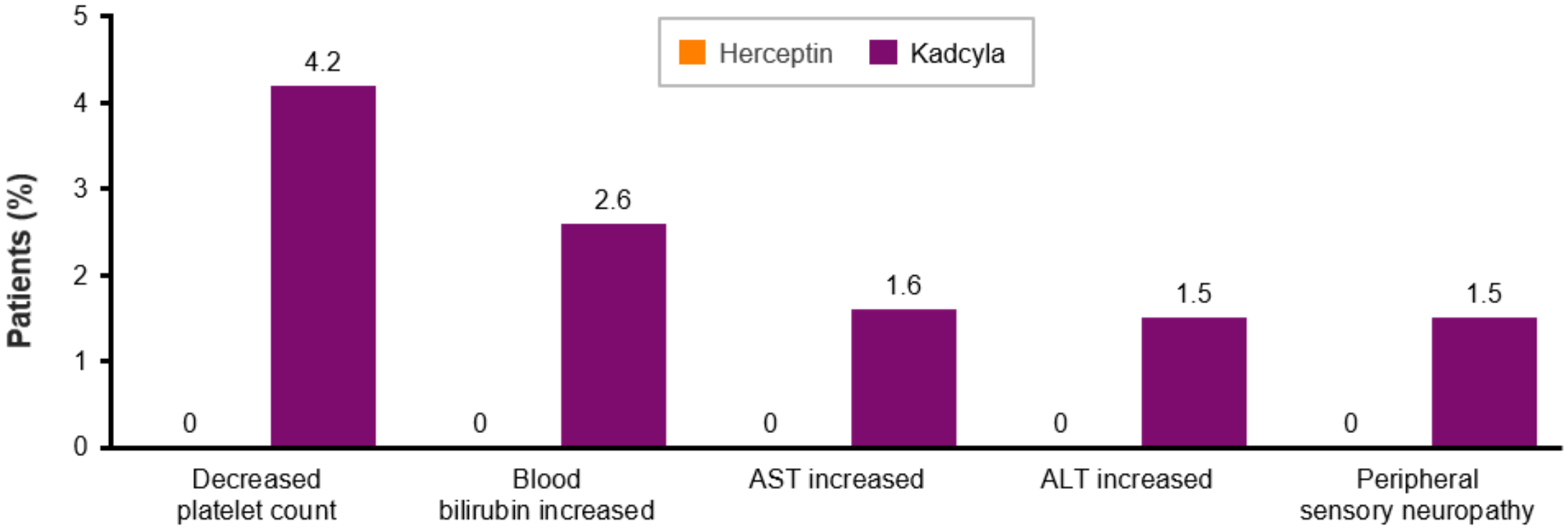


Despite a higher incidence of decreased platelet count (thrombocytopenia) in the Kadcyla arm, rates of grade ≥3 haemorrhage were similar between groups†

* PA of IDFS, including 1IA of OS (CCOD 2018).
† Grade ≥3 haemorrhage rates: 0.4% Kadcyla arm, 0.3% Herceptin arm. One fatal intracranial haemorrhage was reported in the Kadcyla arm.
AE, adverse event; IDFS, invasive disease-free survival; PA, primary analysis.

von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628.

PA IDFS:* Other AEs of interest[1,2]

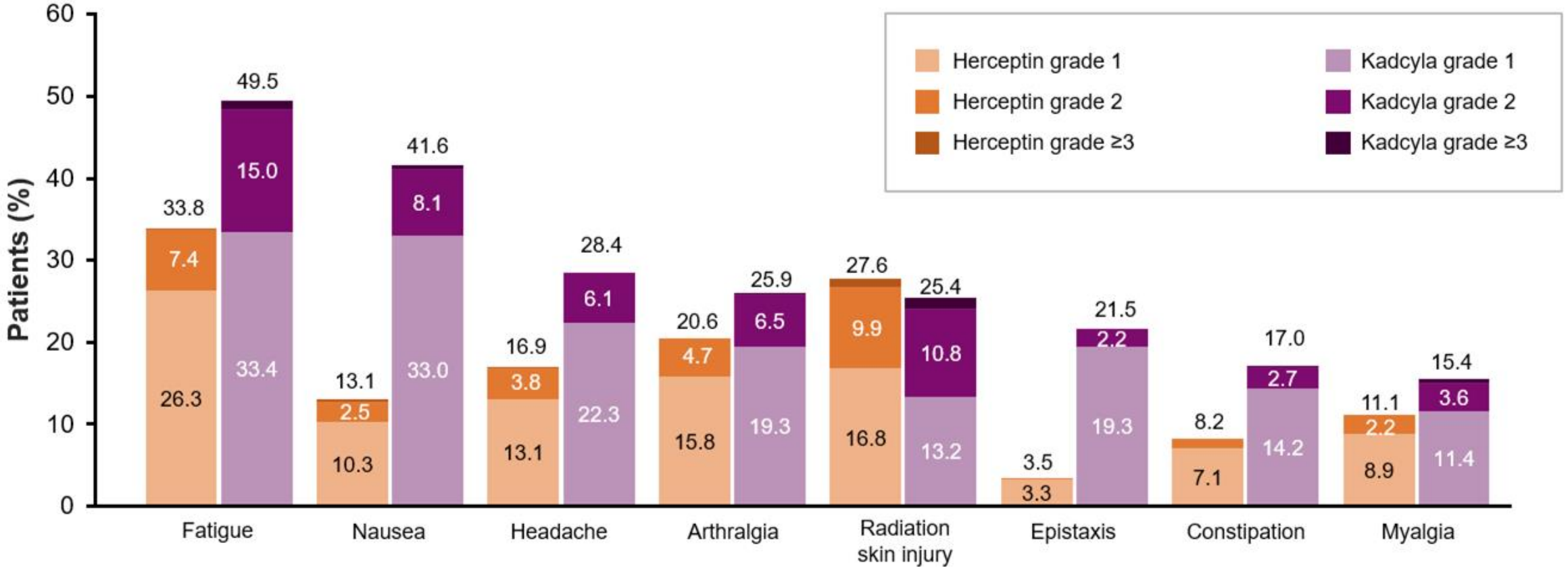


The AEs observed in the Kadcyla arm are consistent with the known safety profile[3,4]

* PA of IDFS, including 1IA of OS (CCOD 2018). † Discontinuation of study treatment assigned at randomisation.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IDFS, invasive disease-free survival; PA, primary analysis.

1. von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628;
2. Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation);
3. Verma S, *et al. N Engl J Med* 2012; **367:**1783–1791;
4. Krop IE, *et al. J Clin Oncol* 2015; **33:**1136–1142.

PA IDFS:* Other AEs with ≥15% incidence in either arm



- **Kadcyla safety profile was consistent with previous studies**
- **The Kadcyla-related AEs in KATHERINE were generally low grade and manageable**

* PA of IDFS, including 1IA of OS (CCOD 2018).
1IA, first interim analysis; AE, adverse event; CCOD, clinical cut-off date; FA, final analysis; IDFS, invasive disease-free survival; OS, overall survival; PA, primary analysis.

von Minckwitz G, *et al. N Engl J Med* 2019; **380:**617–628;

Treatment-related AEs during the post-treatment period*

Patients, n (%) with ≥1:	Herceptin (n = 720)	Kadcyla (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)
SAE	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)

Incidence of AEs was low after treatment had stopped in KATHERINE

CCOD 2023.
* Includes AEs with date of onset >30 days after last dose of study treatment. AE reporting period closed at PA of IDFS – reporting in the follow-up period was limited to deaths, SAEs or other AEs of concern assessed as related to prior treatment with study drug.
AE, adverse event; CCOD, clinical cut-off date; IDFS, invasive disease-free survival; PA, primary analysis; SAE, serious adverse event.

Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

KATHERINE: Safety summary

- The overall safety data in KATHERINE are consistent with the known safety profile of Kadcyla[1–5]
- Grade ≥3 AEs (25.7% vs. 15.4%) and SAEs (12.7% vs. 8.1%) were more frequent with Kadcyla[1]
  - Incidences of AEs in the Kadcyla arm were generally low grade and manageable[1]
  - No new safety concerns emerged with longer median follow-up (101 mo)[4,5]
- Rates of pulmonary toxicity with Kadcyla were very low (all grade: 2.7%; grade ≥3: 0.4%); no cases of ILD were reported with longer follow-up[5]
- There was a higher rate of discontinuations in the Kadcyla arm (133 patients, 18.0%) compared with the Herceptin arm (15, 2.1%)[1]
  - The most common AEs leading to Kadcyla discontinuations were laboratory abnormalities
  - Of the 133 patients who discontinued Kadcyla early, 71 continued on Herceptin, of whom 63 completed a total of 14 cycles of HER2-targeted treatment
- Despite a higher incidence of decreased platelet count (thrombocytopenia) in the Kadcyla arm, rates of grade ≥3 haemorrhage were similar between groups[1]*

* Grade ≥3 haemorrhage rates: 0.4% Kadcyla arm, 0.3% Herceptin arm. One fatal intracranial haemorrhage was reported in the Kadcyla arm.
AE, adverse event; mo, months; ILD, interstitial lung disease; SAE, serious adverse event.

1. von Minckwitz G, *et al*. *N Engl J Med* 2019; **380:**617–628;
2. Verma S, *et al. N Engl J Med* 2012; **367:**1783–1791;
3. Krop IE, *et al. J Clin Oncol* 2015; **33:**1136–1142;
4. Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation)

The KATHERINE regimen is recommended by international breast cancer guidelines

NCCN Breast Cancer Guidelines[1]

Category 1 listing*

If residual invasive disease:

Kadcyla alone for 14 cycles

} **Administered concurrently with radiation and endocrine therapy, if indicated**

If pCR (or if Kadcyla is discontinued in the event of toxicity):

Complete up to 1 year (18 cycles) of HER2-targeted therapy with PH / H

ESMO eBC Guidelines[2]

Category (I, A) listing†

If residual invasive disease:

Kadcyla recommended for up to 14 cycles

If pCR (cN+ or pN+ at initial diagnosis):

Complete 1 year of PH

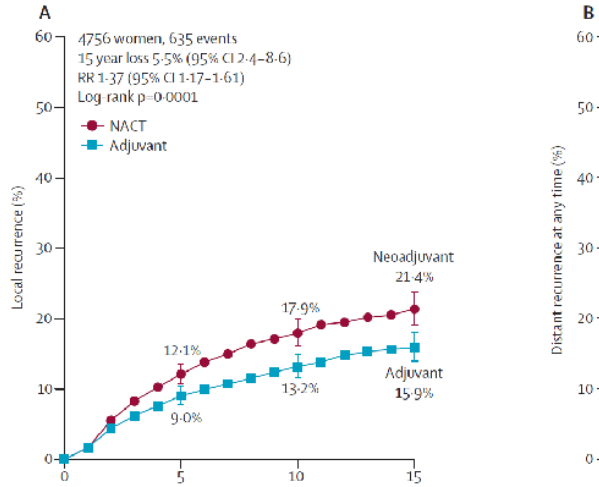
If pCR (cN0 at initial diagnosis):

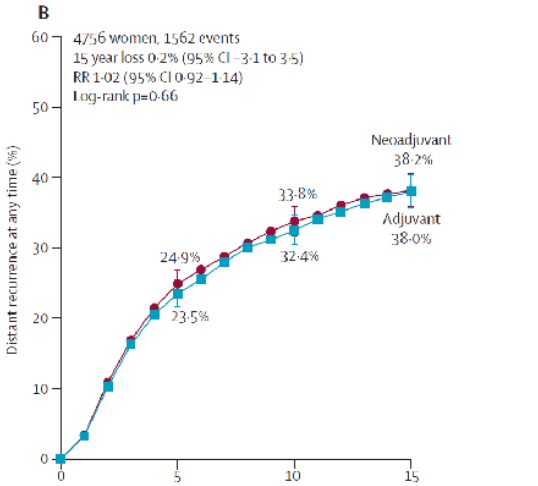
Complete 1 year of H

The presence of *any amount of residual invasive disease* should inform the decision to change treatment to Kadcyla in the adjuvant setting

* Category 1 listings are based on high-level evidence with uniform NCCN consensus that the intervention is appropriate.
† Level I: based on evidence from at least one large, randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity. Grade A: strong evidence for efficacy with a substantial clinical benefit, strongly recommended.
eBC, early breast cancer; ER, oestrogen receptor; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; pCR, pathological complete response; P, pertuzumab; H, trastuzumab

1. NCCN Breast Cancer Guidelines – Version 4. 2024;
2. Loibl, S. et al.Annals of Oncology, Volume 35, Issue 2, 159-182.



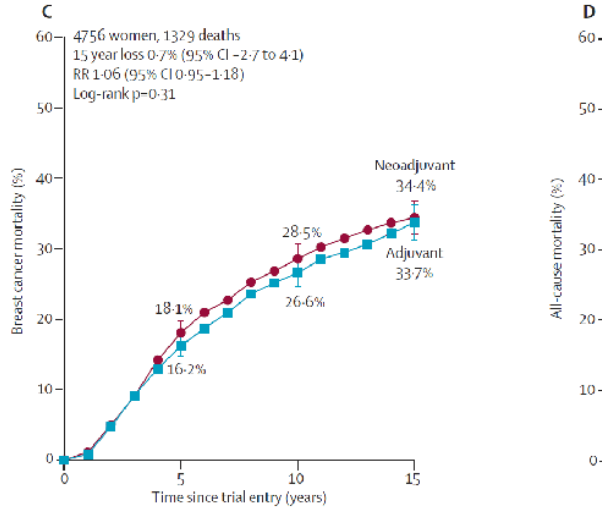


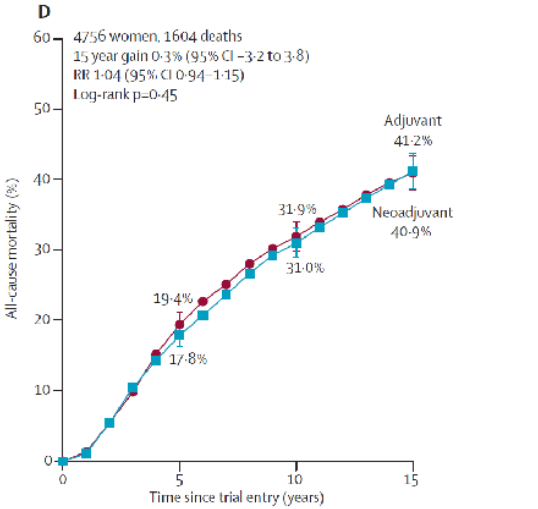
Local recurrence crude rates (events per woman-years) and log-rank analyses

	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Neoadjuvant	2·58 (245/9493)	1·43 (79/5528)	0·93 (26/2784)	2·16 (16/740)
Adjuvant	1·95 (185/9477)	0·96 (54/5618)	0·69 (19/2769)	1·42 (11/772)
Rate ratio	1·35 (1·11–1·64)	1·53 (1·08–2·17)	1·29 (0·70–2·38)	1·11 (0·48–2·57)
(95% CI) from (O−E)/V	30·4/102·0	13·6/31·8	2·7/10·3	0·6/5·4

Distant recurrence at any time crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
5·69 (568/9983)	2·58 (162/6291)	1·49 (50/3351)	1·44 (14/974)
5·44 (535/9840)	2·54 (157/6187)	1·84 (60/3270)	1·74 (16/919)
1·07 (0·94–1·21)	0·99 (0·79–1·24)	0·80 (0·55–1·18)	0·75 (0·35–1·61)
16·5/251·5	−0·6/75·5	−5·7/25·8	−1·9/6·7





Breast cancer mortality crude rates (events per woman-years) and log-rank analyses

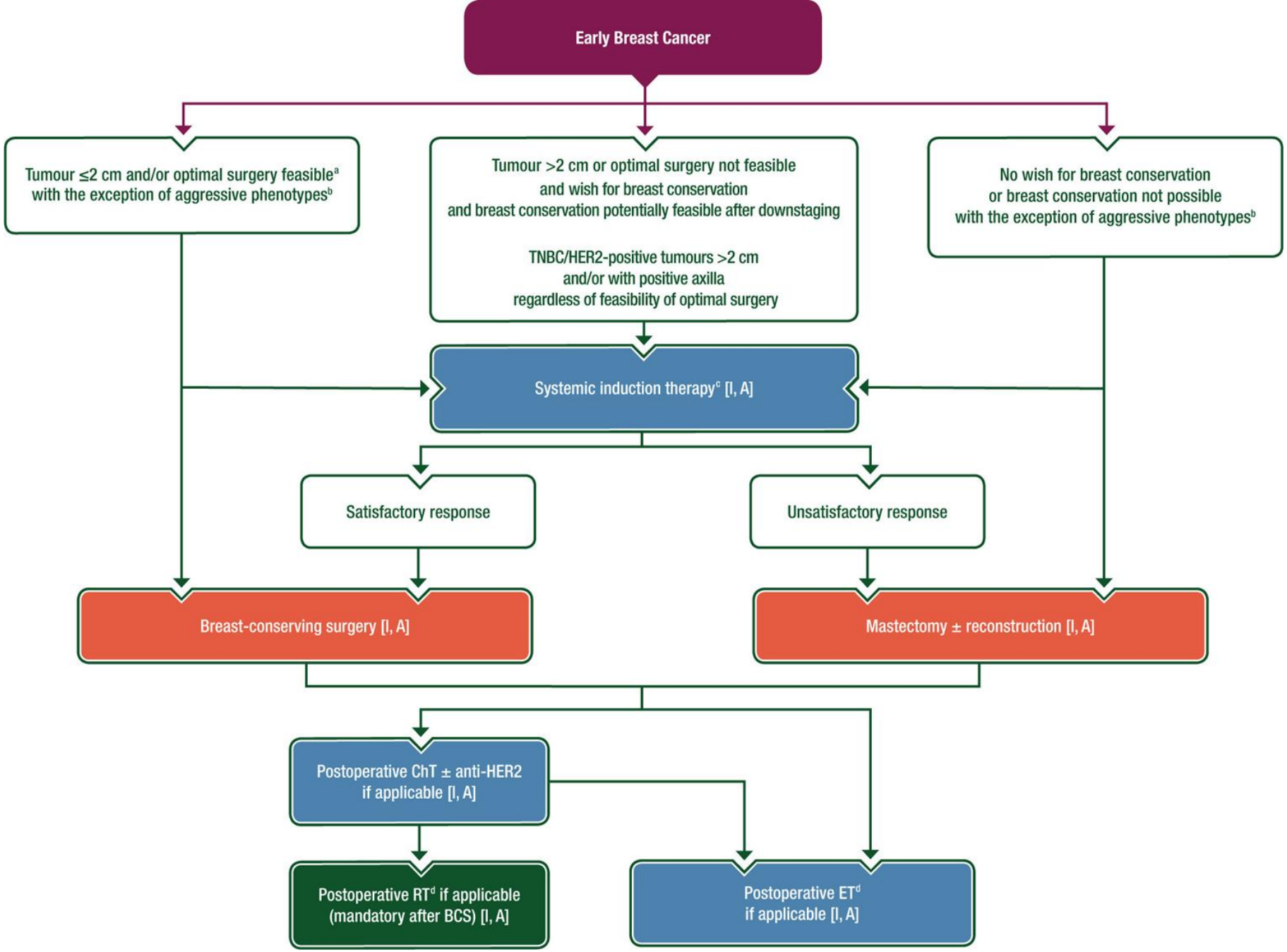
	Years 0–4	Years 5–9	Years 10–14	Years ≥15
Neoadjuvant	3·90 (412/10567)	2·82 (191/6785)	1·93 (69/3570)	1·24 (13/1050)
Adjuvant	3·49 (364/10432)	2·81 (190/6771)	2·19 (78/3559)	1·18 (12/1014)
Rate ratio	1·12 (0·97–1·30)	1·03 (0·84–1·27)	0·88 (0·63–1·21)	0·90 (0·41–1·97)
(95% CI) from (O−E)/V	20·5/179·6	2·8/91·6	−4·8/36·6	−0·7/6·2

Any death crude rates (events per woman-years) and log-rank analyses

Years 0–4	Years 5–9	Years 10–14	Years ≥15
4·22 (446/10567)	3·51 (238/6785)	2·91 (104/3570)	3·52 (37/1050)
3·86 (403/10432)	3·56 (241/6771)	3·20 (114/3559)	2·07 (21/1014)
1·09 (0·95–1·25)	0·98 (0·81–1·17)	0·90 (0·68–1·18)	1·69 (0·95–2·99)
16·7/196·6	−2·7/112·2	−5·6/51·3	6·1/11·7

EBCTG Lancet Oncology 2018 27 19-39

IMPACT ON CLINICAL PRACTICE



Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up† Cardoso, F. et al. Annals of Oncology, Volume 30, Issue 8, 1194 - 12

The transition of our HK experience

Table 1 Basic patient demographics and treatment outcome

	Overall	Chemo	Chemo-H	Chemo-DH	P value
No of patients	221*	41	138	43	
No of cases	226	42	141	43	
Ethnicity	206 (93.2%)	36 (87.8%)	128 (92.8%)	43 (100.0%)	0.110
► Chinese	14 (6.3%)	5 (12.2%)	9 (6.5%)	0 (0.0%)	
► Southeast Asian	1 (0.5%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	
► Other					
Median onset age (years)	50	48.5	50	49	0.198
Premenopausal	133 (59.6%)	24 (57.1%)	78 (56.5%)	31 (72.1%)	0.181
Staging	2 (0.9%)	0 (0.0%)	2 (1.4%)	0 (0.0%)	0.858†
► IA	40 (17.7%)	6 (14.3%)	25 (17.7%)	9 (20.9%)	
► IIA	56 (24.8%)	12 (28.6%)	33 (23.4%)	11 (25.6%)	
► IIB	67 (29.6%)	12 (28.6%)	48 (34.0%)	7 (16.3%)	
► IIIA	17 (7.5%)	5 (11.9%)	10 (7.1%)	2 (4.7%)	
► IIIB	44 (19.5%)	7 (16.7%)	23 (16.3%)	14 (32.6%)	
► IIIC					
ER/PR positive	119 (52.7%)	15 (35.7%)	78 (55.3%)	26 (60.5%)	0.045
Anthracycline-containing regimens	58 (26.0%)	40 (95.2%)	16 (11.6%)	2 (4.7%)	<0.0001
Taxane-containing regimens	204 (91.5%)	25 (59.5%)	137 (99.3%)	42 (97.7%)	<0.0001
Median time to surgery (months)	4.7	5.4	4.7	4.6	0.001
Clinical significant anti-HER2-related cardiomyopathy	4	NA	2 (1.4%)	2 (4.7%)	
Breast conservative therapy	74 (32.7%)	13 (31.0%)	39 (28.3%)	21 (48.8%)	0.046
pCR	64 (28.3%)	2 (4.8%)	36 (25.5%)	26 (60.5%)	<0.0001
Additional adjuvant chemotherapy	59 (26.5%)	20 (47.6%)	32 (23.4%)	7 (16.3%)	0.003
► pCR	5	0	5	0	
► Residual disease	54	20	27	7	

Chiu et al Postgraduate Medical Journal, Volume 95, Issue 1121, March 2019,

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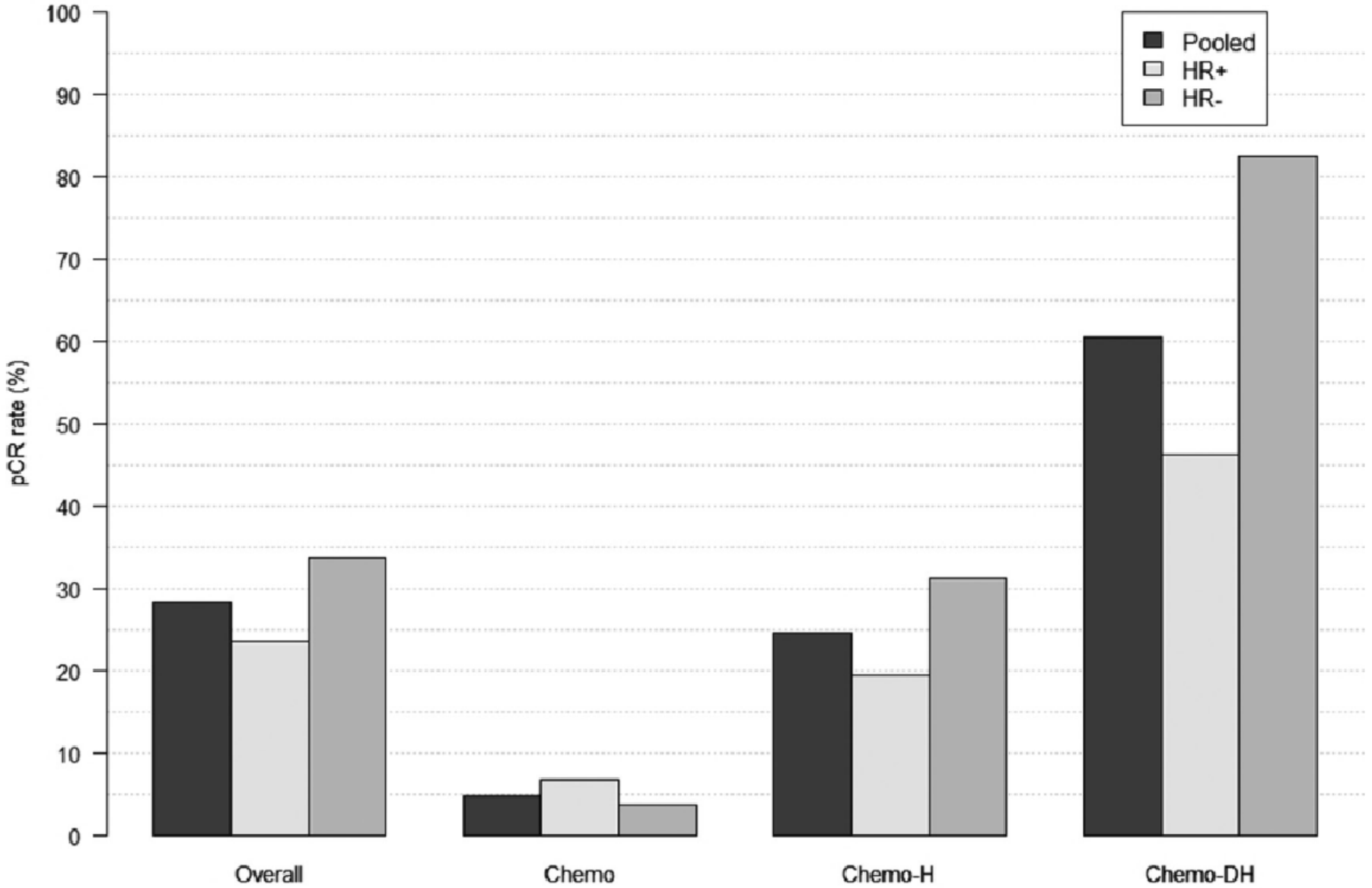

Chiu et al Postgraduate Medical Journal, Volume 95, Issue 1121, March 2019,

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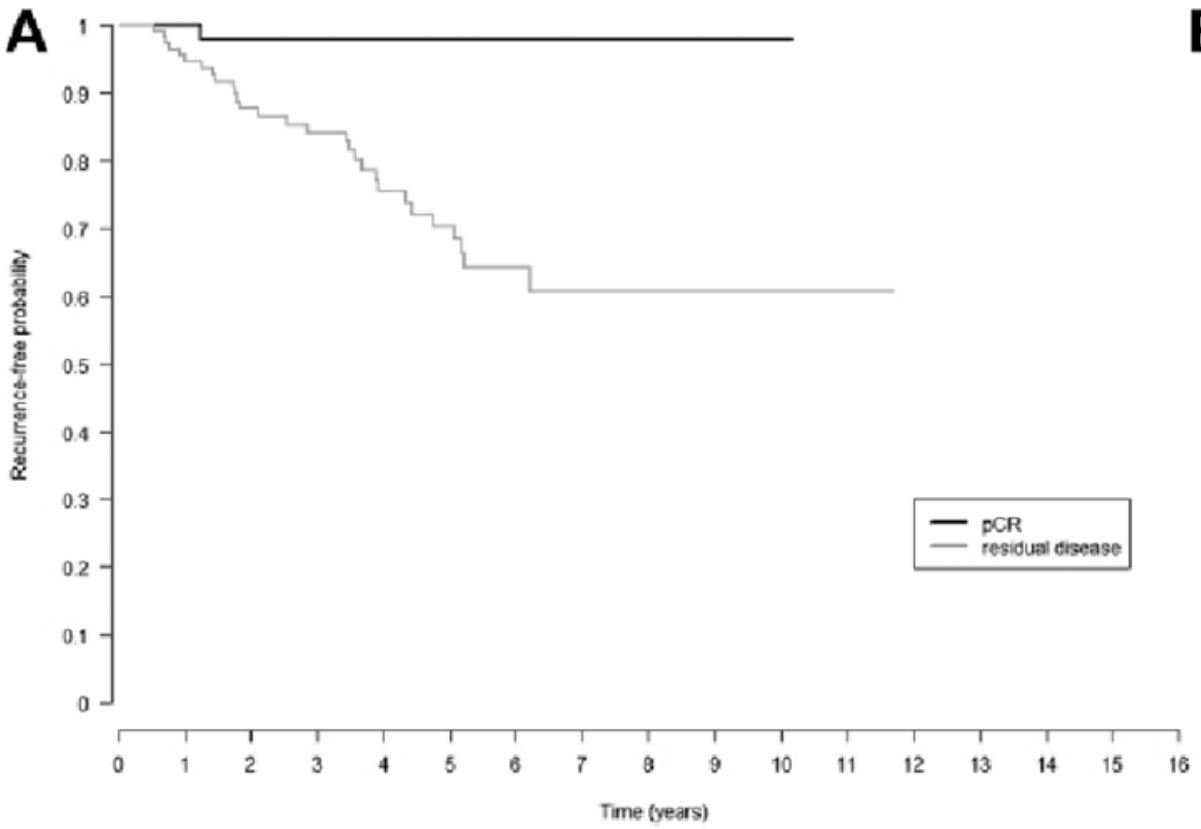
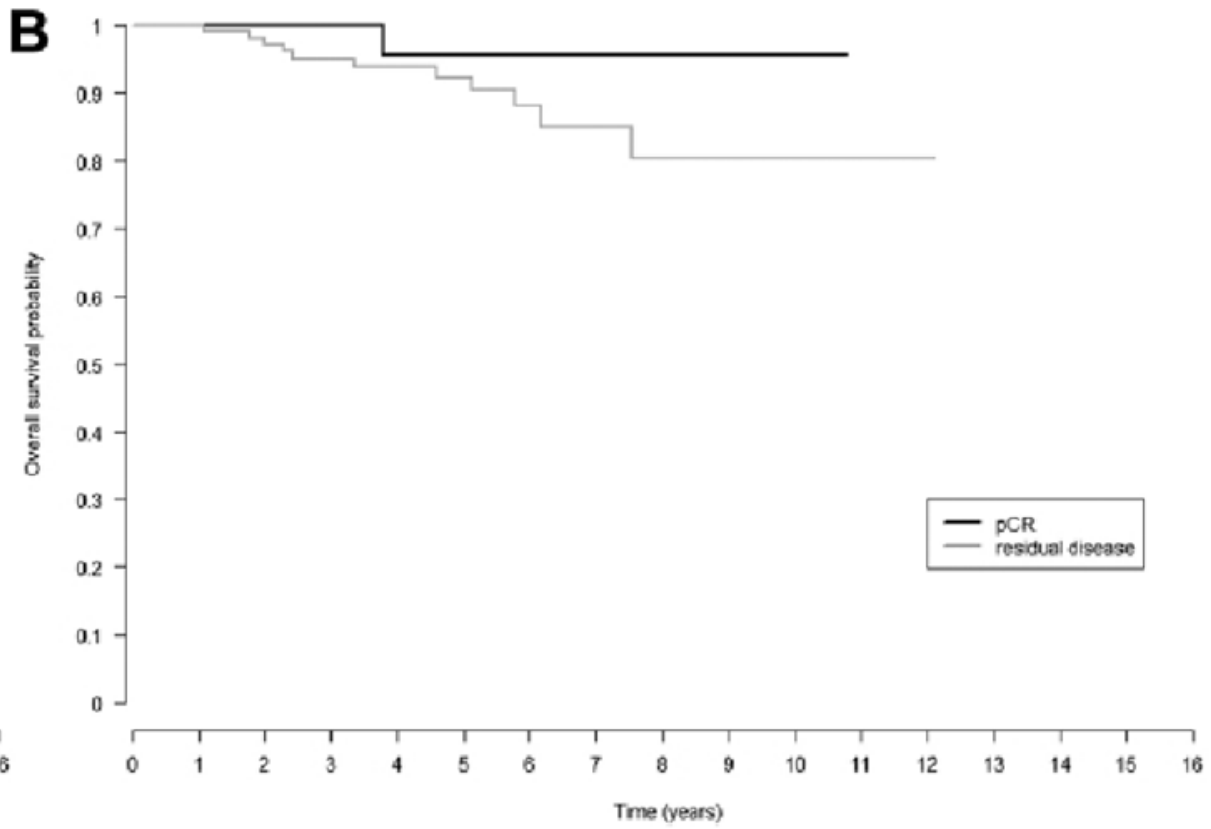
Trastuzumab alone



Trastuzumab and Pertuzumab



Chiu et al Postgraduate Medical Journal, Volume 95, Issue 1121, March 2019,

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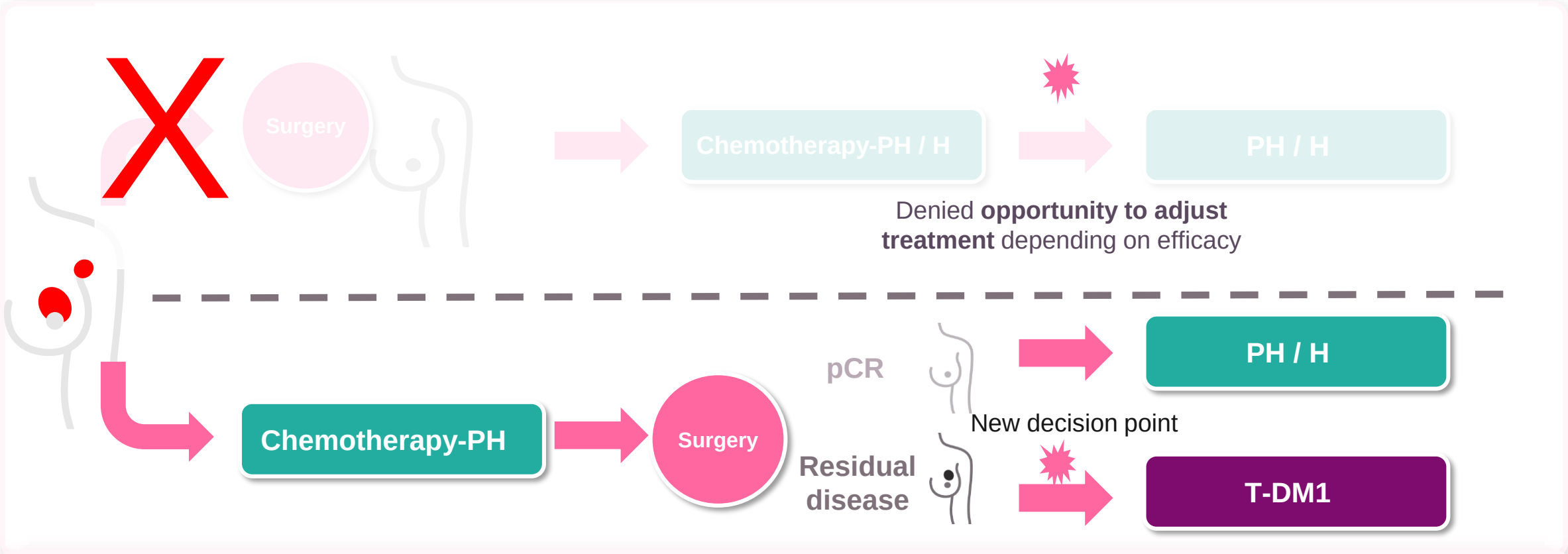
Neoadjuvant treatment for intermediate/ high-risk HER2-positive and triple-negative breast cancers: no longer an 'option' but an ethical obligation

Mariana Brandão,[1] Fabien Reyal,[2,3] Anne-Sophie Hamy,[3] Martine Piccart-Gebhart[1]

"…Patients with intermediate to high-risk ***TNBC or HER2-positive disease (≥T2 and/or lymph-node positive tumours) must receive neoadjuvant treatment****, as this strategy not only increases the chance of less aggressive surgery, but identifies patients who will* ***benefit from 'salvage' adjuvant therapy with an impact on long-term outcomes.****"*

Brandão M, Reyal F, Hamy A, et al. ESMO Open 2019;4:e000515. doi: 10.1136/esmoopen-2019-000515

KATHERINE data are transformative: Upfront surgery in high-risk HER2-positive BC is no longer an acceptable option



All patients should be given the opportunity to optimise treatment after surgery according to their response to neoadjuvant therapy

Follow-up medications after IDFS events

	Herceptin (n = 743)	Kadcyla (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)
PERJETA	73 (43.2)	30 (31.9)
Trastuzumab	114 (67.5)	52 (55.3)
Kadcyla	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)

Most patients received further treatment with a HER2-directed therapy following an IDFS event (usually Herceptin ± PERJETA)

* Percentages based on number of patients who received ≥1 follow-up medication. Data on follow-up medications were available for 70.7% (169/239) of patients in the trastuzumab arm who had an IDFS event and 64.4% (94/146) of patients in the Kadcyla arm who had an IDFS event.

IDFS, invasive disease-free survival.

Loibl S, *et al.* SABCS 2023 (Abstract GS03-12; oral presentation).

Take Home Message

- Patients with intermediate to **high-risk TNBC or HER2-positive disease (≥T2 and/or lymph-node positive tumours**) must receive **neoadjuvant treatment**[1]
  - as this strategy not only increases the chance of less aggressive surgery, but identifies patients who will benefit from ‘salvage’ adjuvant therapy with an **impact on long-term outcomes**.”
- KATHERINE data are transformative: **Upfront surgery in high-risk HER2-positive BC is no longer an acceptable option**[2-6]
- All patients should be given the opportunity to **optimise treatment after surgery** according to their response to neoadjuvant therapy[2-6]
- **T-DM1** is currently the main anti-HER2 therapy **endorsed by international treatment guidelines for treatment of patients who did not achieve pCR (non-pCR)** post neoadjuvant treatment[2-6]

1. Brandão M, Reyal F, Hamy A, et al. ESMO Open 2019;4:e000515. doi: 10.1136/esmoopen-2019-000515. 2. NCCN Breast Cancer Guidelines. Version 4, 2024 https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf; 3. AGO Breast Cancer Guidelines. 2023; 4. Cardoso F, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology. 2019;30(8):1194-1220. doi: https://doi.org/10.1093/annonc/mdz173; 5. Burstein HJ, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. Ann Oncol.2021;32(10):1216-1235. doi:10.1016/j.annonc.2021.06.023 6. K.H Park et al. ESMO Open. Volume 9, Issue 5, May 2024 https://doi.org/10.1016/j.esmoop.2024.102974