

Early Stage HER2+ Breast Cancer

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Pre-Presentation Case

51 yo post-menopausal female with right-sided cT2 N2 M0 IDC G3 ER/PR+ HER2+. She underwent neoadjuvant therapy with TCHP x6.

Scenario 1

Patient underwent right side MRM and surgical pathology showed complete pathological response. Radiation therapy and Endocrine therapy aside, what adjuvant systemic therapy would you offer:

1. HP 1y
2. HP 1y -> Neratinib 1y
3. T-DM1 1y
4. T-DM1 1y -> Neratinib 1y

Scenario 2

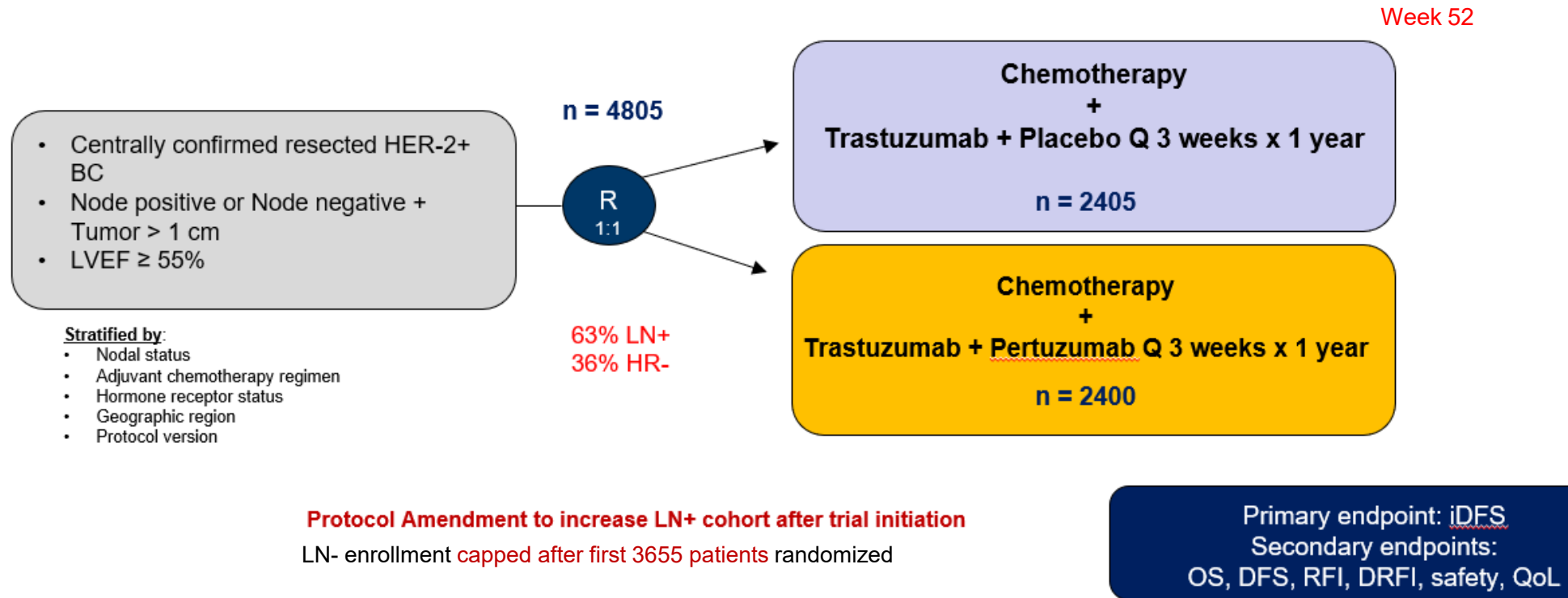
Patient underwent right side MRM and surgical pathology showed 2.2 cm residual disease with 30% cellularity and 4+/16 LN. Radiation therapy aside, what adjuvant systemic therapy would you offer:

1. HP 1y
2. HP 1y -> Neratinib 1y
3. T-DM1 1y
4. T-DM1 1y -> Neratinib 1y

Early Stage HER2+ Breast Cancer

Role of pertuzumab in the adjuvant setting?

APHINITY: Phase III Trial of Adjuvant Pertuzumab added to Trastuzumab in Resected HER2+ BC



Chemotherapy regimens: Anthracycline- and/or Taxane-based regimens (FEC→T, AC/EC→T, TC (docetaxel/carboplatin))
Trastuzumab 8 mg/kg IV loading dose, followed by 6 mg/kg IV Q 3 weeks
Pertuzumab 840 mg IV loading dose, followed by 420 mg IV Q 3 weeks

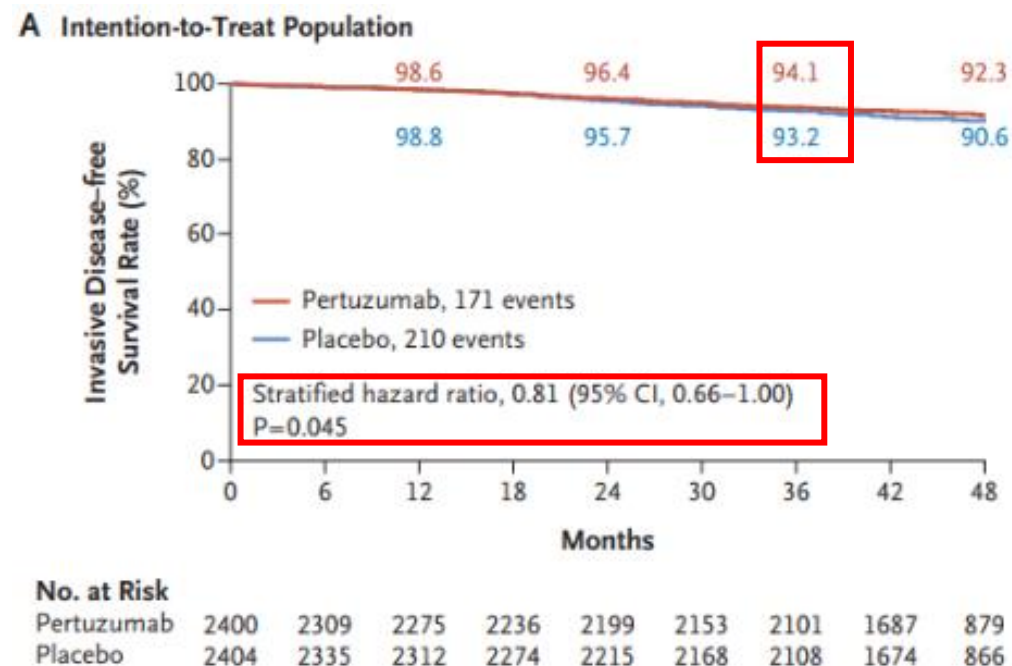
iDFS: Disease free survival events included invasive local, regional or distant recurrence, contralateral invasive breast cancer or death from any cause.
RFI: Relapse free interval; DRFI: Distant relapse free interval
QoL: Quality of life

APHINITY: Does adding Pertuzumab to adjuvant Trastuzumab improve outcomes?

Median follow-up: 45.4 months

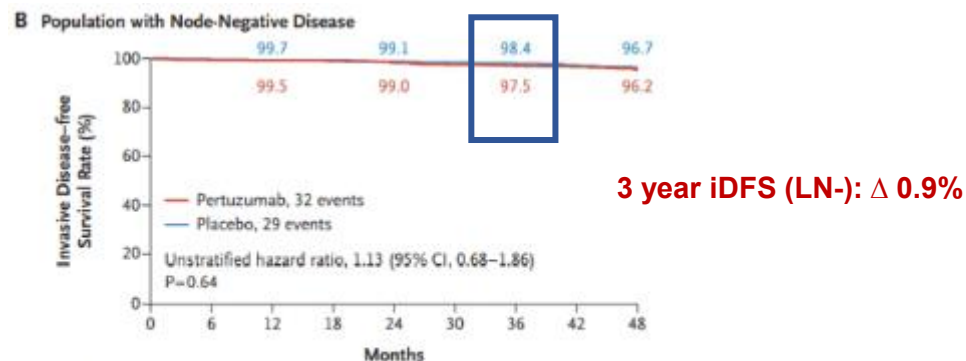
3 year iDFS (ITT): Δ 0.9%

Event	Pertuzumab Group (N=2400)	Placebo Group (N=2404)
	<i>no. of patients (%)</i>	
Any invasive-disease event	171 (7.1)	210 (8.7)
Category of first invasive-disease event		
Distant recurrence	112 (4.7)	139 (5.8)
CNS metastases	45 (1.9)	44 (1.8)
Locoregional recurrence	26 (1.1)	34 (1.4)
Contralateral breast cancer	5 (0.2)	11 (0.5)
Death without previous event	28 (1.2)	26 (1.1)

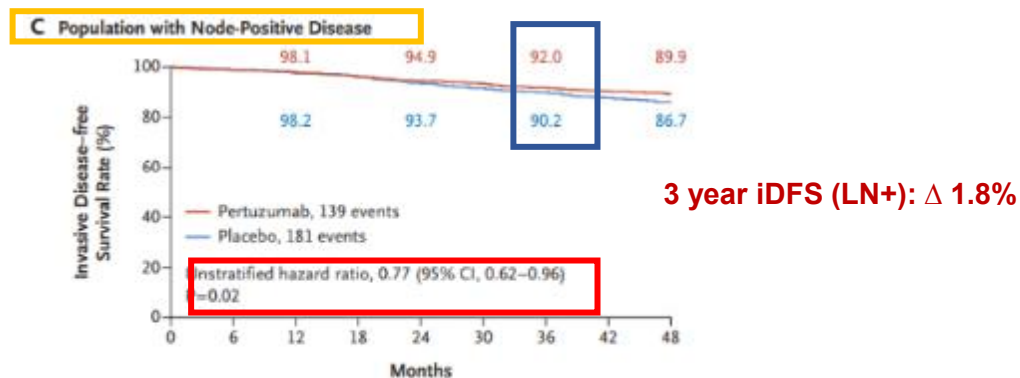


APHINITY: Does adding Pertuzumab to adjuvant Trastuzumab improve outcomes?

Median follow-up: 45.4 months



No. at Risk	0	6	12	18	24	30	36	42	48
Pertuzumab	897	865	856	849	841	826	818	775	456
Placebo	902	882	873	866	856	849	844	792	461



No. at Risk	0	6	12	18	24	30	36	42	48
Pertuzumab	1503	1444	1419	1387	1358	1327	1283	912	423
Placebo	1502	1453	1439	1408	1359	1319	1264	882	405

Subgroup	Pertuzumab (%)	Placebo (%)	Δ	HR
No. of positive nodes				
1-3	94.9	93.8	1.1	0.73 (0.52-1.04)
≥ 4	87.5	84.7	2.8	0.79 (0.59-1.05)
Hormone receptor status				
HR+	94.8	94.4	0.4	0.86 (0.66-1.13)
HR-	92.8	91.2	1.6	0.76 (0.56-1.04)

Safety:

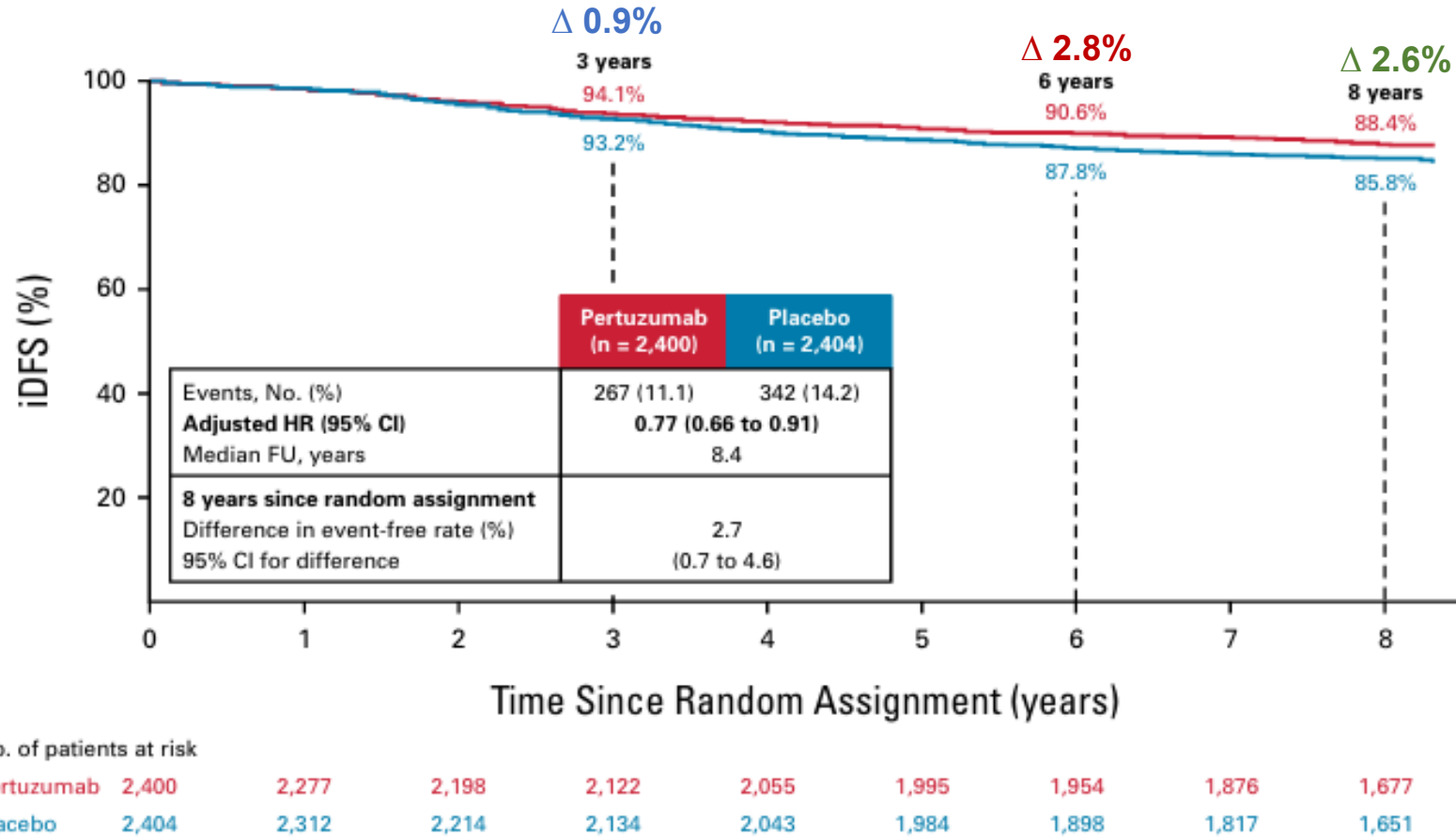
Infrequent cardiac related events

Grade ≥ 3 diarrhea more common with Pertuzumab (9.8% vs 3.7%)

APHINITY: iDFS in ITT population at 8 year follow up

Median follow-up:
8.4 years

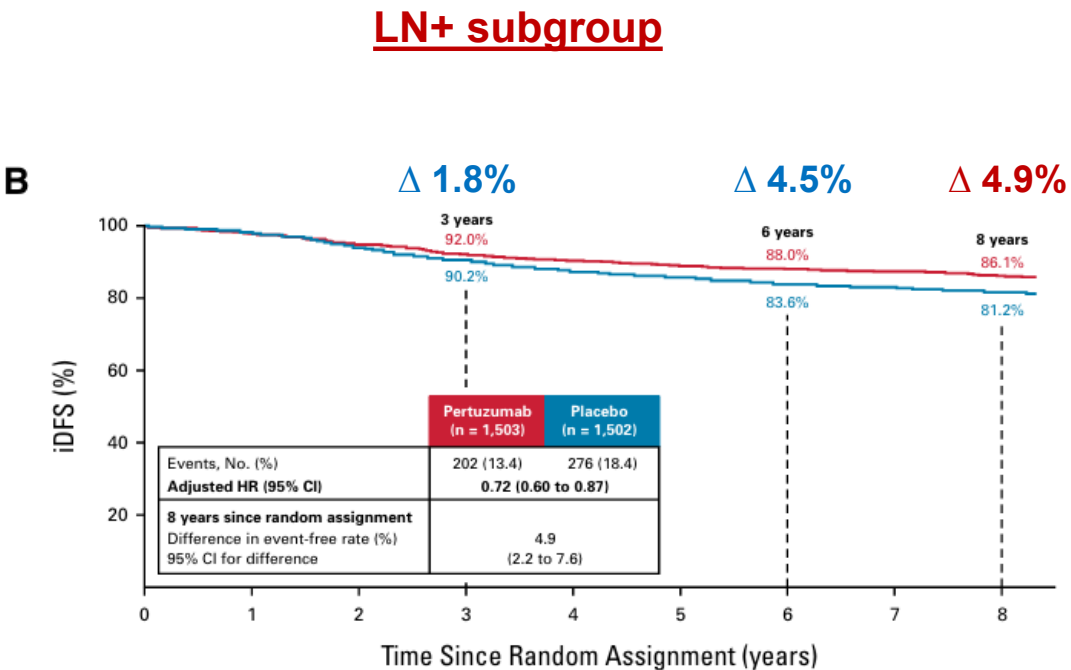
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APHINITY: iDFS at 8 year follow up by nodal status

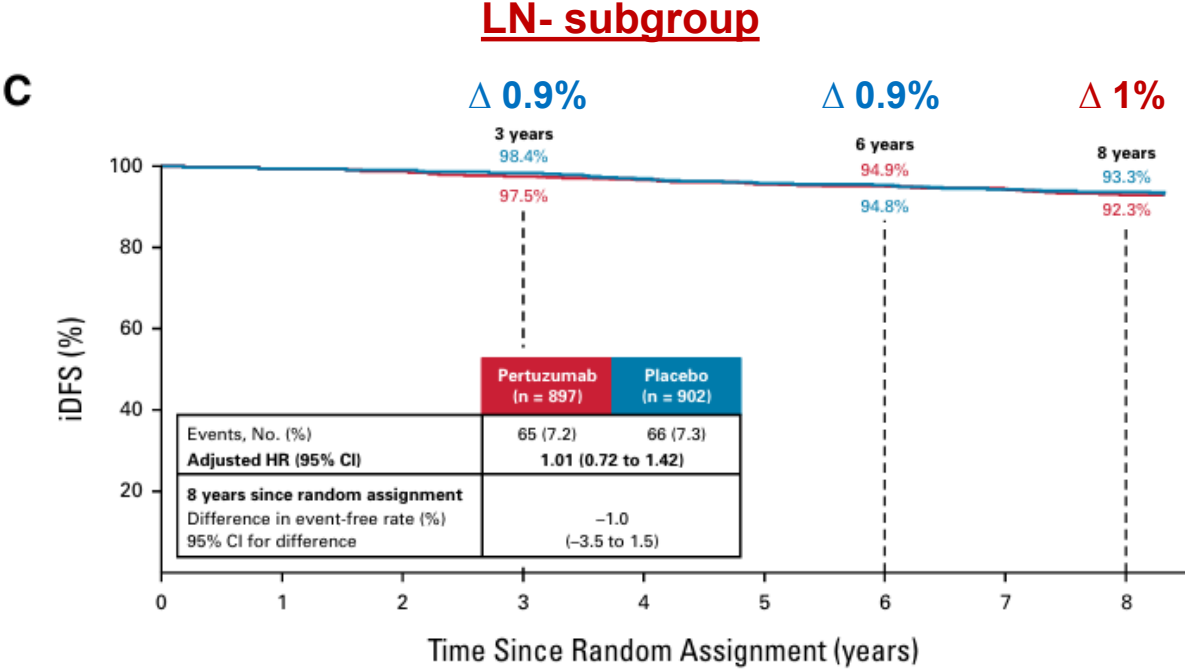
Median follow-up:
8.4 years

Benefit limited to LN+ subgroup of patients



No. of patients at risk

Pertuzumab	1,503	1,420	1,357	1,301	1,257	1,218	1,190	1,142	1,003
Placebo	1,502	1,439	1,358	1,288	1,226	1,190	1,126	1,076	953



No. of patients at risk

Pertuzumab	897	857	841	821	798	777	764	734	674
Placebo	902	873	856	846	817	794	772	741	698

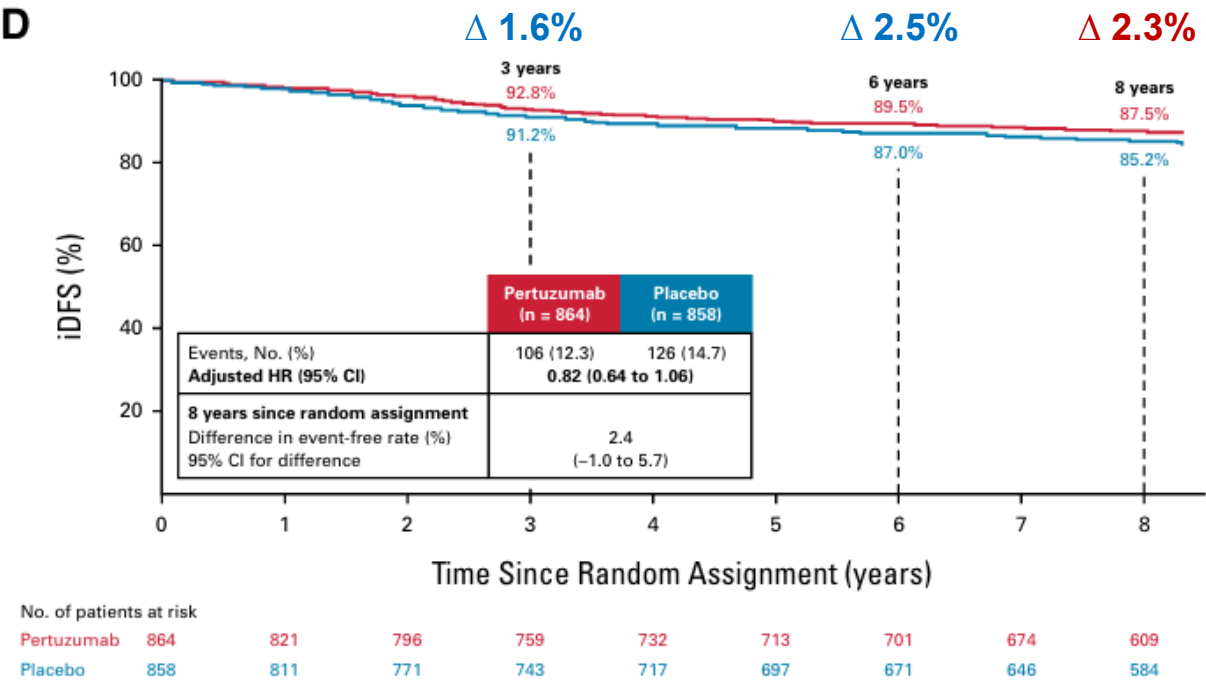
LN: Lymph node

APHINITY: iDFS at 8 year follow up by hormone receptor status

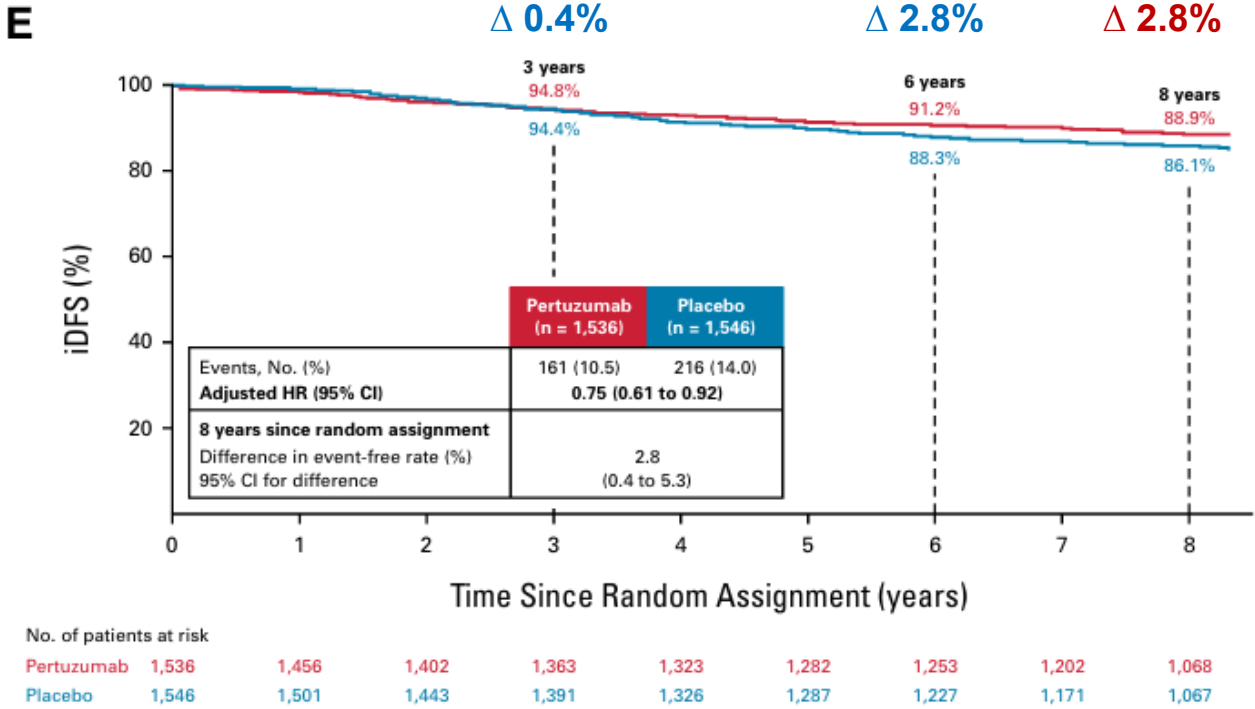
Median follow-up:
8.4 years

Benefit seen in both HR- and HR+ subgroups

HR- subgroup



HR+ subgroup



HR: Hormone receptor

APHINITY: iDFS at 8 year follow up by hormone receptor status

TABLE 2. Site of First Invasive-Disease Event

Event	ITT Population		Node-Positive Cohort		Node-Negative Cohort	
	Pertuzumab (n = 2,400), No. (%)	Placebo (n = 2,404), No. (%)	Pertuzumab (n = 1,503), No. (%)	Placebo (n = 1,502), No. (%)	Pertuzumab (n = 897), No. (%)	Placebo (n = 902), No. (%)
Any invasive-disease event	267 (11.1)	342 (14.2)	202 (13.4)	276 (18.4)	65 (7.2)	66 (7.3)
Category of first invasive-disease event						
Distant recurrence	149 (6.2)	204 (8.5)	131 (8.7)	184 (12.3)	18 (2.0)	20 (2.2)
CNS metastases	51 (2.1)	53 (2.2)	43 (2.9)	48 (3.2)	8 (0.9)	5 (0.6)
Locoregional recurrence	32 (1.3)	57 (2.4)	23 (1.5)	39 (2.6)	9 (1.0)	18 (2.0)
Contralateral breast cancer	28 (1.2)	22 (0.9)	13 (0.9)	16 (1.1)	15 (1.7)	6 (0.7)
Death without previous event	58 (2.4)	59 (2.5)	35 (2.3)	37 (2.5)	23 (2.6)	22 (2.4)

When to consider adjuvant pertuzumab?

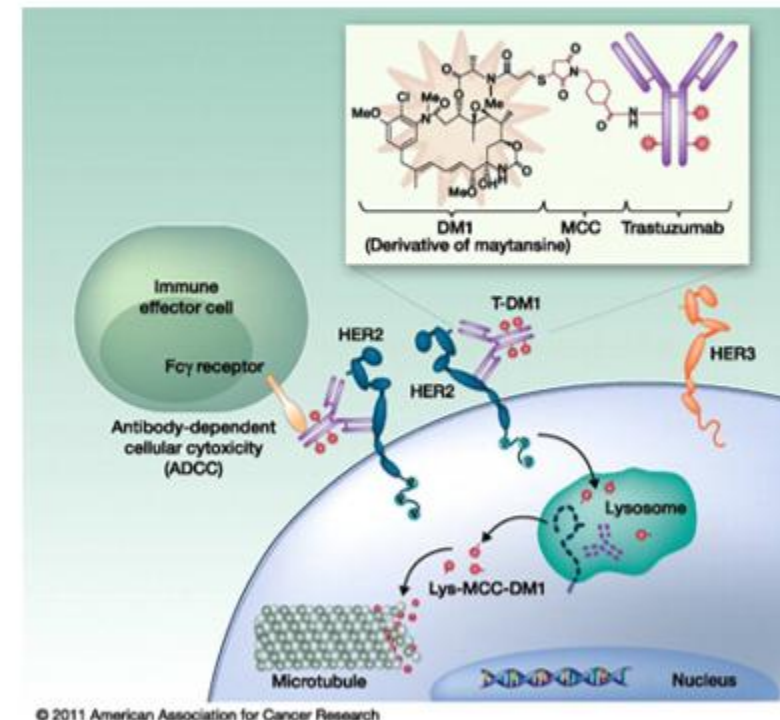
- Adjuvant pertuzumab:
 - When received in Neoadjuvant setting: Standard of care is to continue adjuvantly
 - No data as to role of continuing pertuzumab post neoadjuvant in pCR versus non-pCR
 - Adjuvant: **LN+** tumors only
 - With longer follow up, similar benefit between HR+ vs HR-

Early Stage HER2+ Breast Cancer

Role of Trastuzumab emtansine (T-DM1)?

T-DM1 (ado-trastuzumab emtansine)

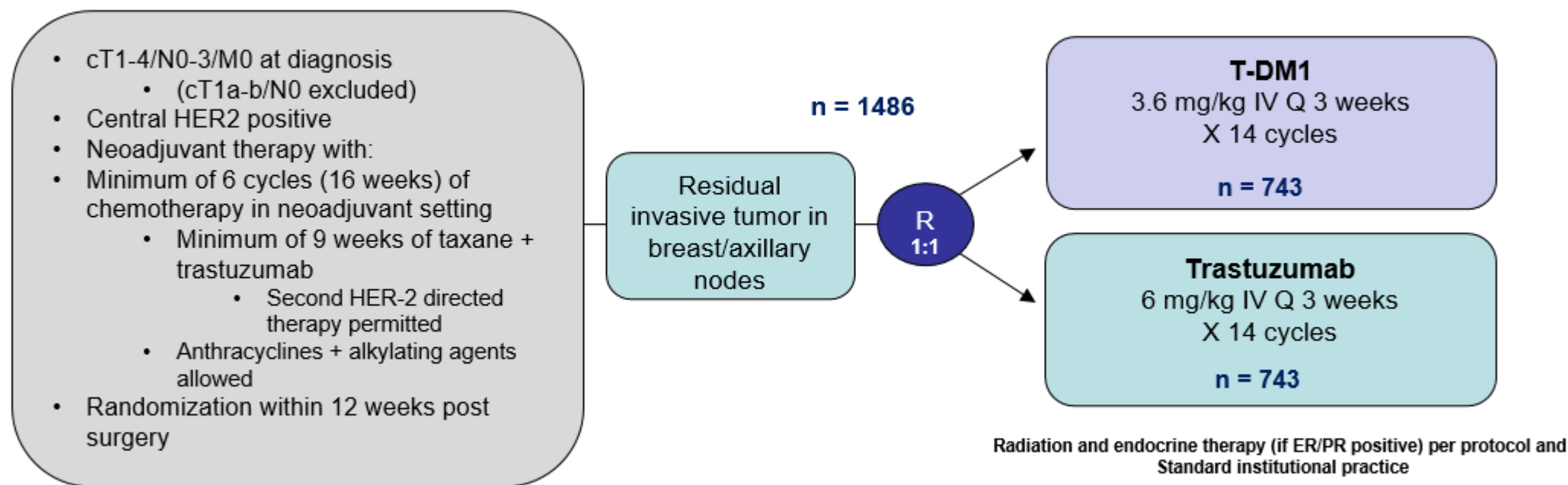
- Novel Antibody-drug conjugate
 - Trastuzumab linked to emtansine (DM1), a maytansine derivative and microtubule inhibitor
- T-DM1 binds to HER-2 with similar affinity as trastuzumab



Lo Russo et al, Clinical Can Res, 2011

Approved in 2013 for treatment of HER2+ metastatic breast cancer

KATHERINE: T-DM1 in residual disease



Stratification factors:

- Inoperable (cT4 or cN2-3) vs operable (cT1-3/N0-1)
- HR status
- Neoadjuvant Trastuzumab vs Trastuzumab + other HER-2 directed agent
- ypN status

Patients who discontinued T-DM1 for toxicity allowed to switch to trastuzumab to complete 14 cycles

Primary endpoint: iDFS
Secondary endpoints include: DRFS, OS, safety

KATHERINE: Patient Characteristics

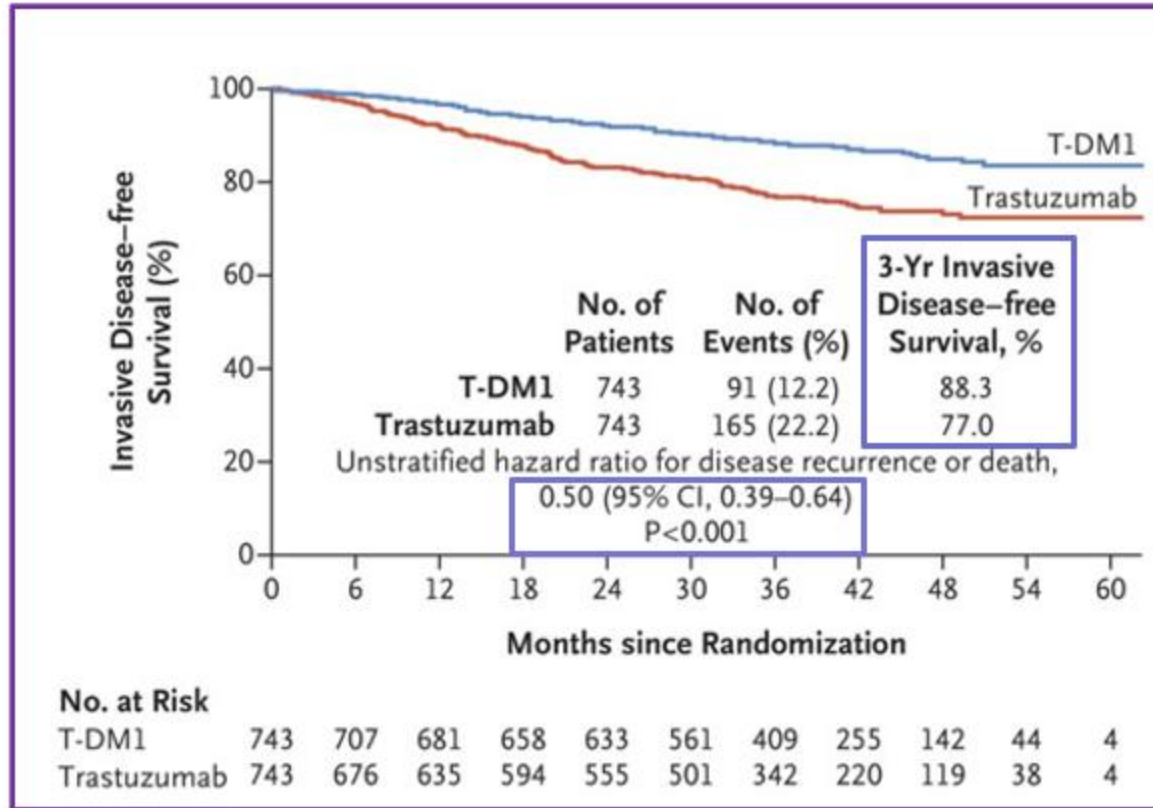
Characteristic	Trastuzumab (n = 743)	T-DM1 (n = 743)
Age, median (range), years	49 (23-80)	49 (24-79)
Race or ethnic group, no. (%)		
<i>White</i>	531 (71.5)	551 (74.2)
<i>Asian</i>	64 (8.6)	65 (8.7)
<i>Black</i>	19 (2.6)	21 (2.8)
<i>American Indian or Alaska Native</i>	50 (6.7)	36 (4.8)
<i>Multiple or unknown</i>	79 (10.6)	70 (9.4)
Clinical stage at presentation, no. (%)		
<i>Inoperable</i>	190 (25.6)	185 (24.9)
<i>Operable</i>	553 (74.4)	558 (75.1)
HR status, no. (%)		
<i>ER/PR negative or unknown</i>	203 (27.3)	209 (28.1)
<i>ER/PR positive or both</i>	540 (72.7)	534 (71.9)
Previous use of anthracycline, no. (%)	564 (75.9)	579 (77.9)
Neoadjuvant HER-2 directed therapy, no. (%)		
<i>Trastuzumab alone</i>	596 (80.2)	600 (80.8)
<i>Trastuzumab + pertuzumab</i>	139 (18.7)	133 (17.9)
<i>Trastuzumab + other HER-2 targeted agent</i>	8 (1.1)	10 (1.3)

Inoperable (cT4 or cN2-3)

Operable (cT1-3/N0-1)

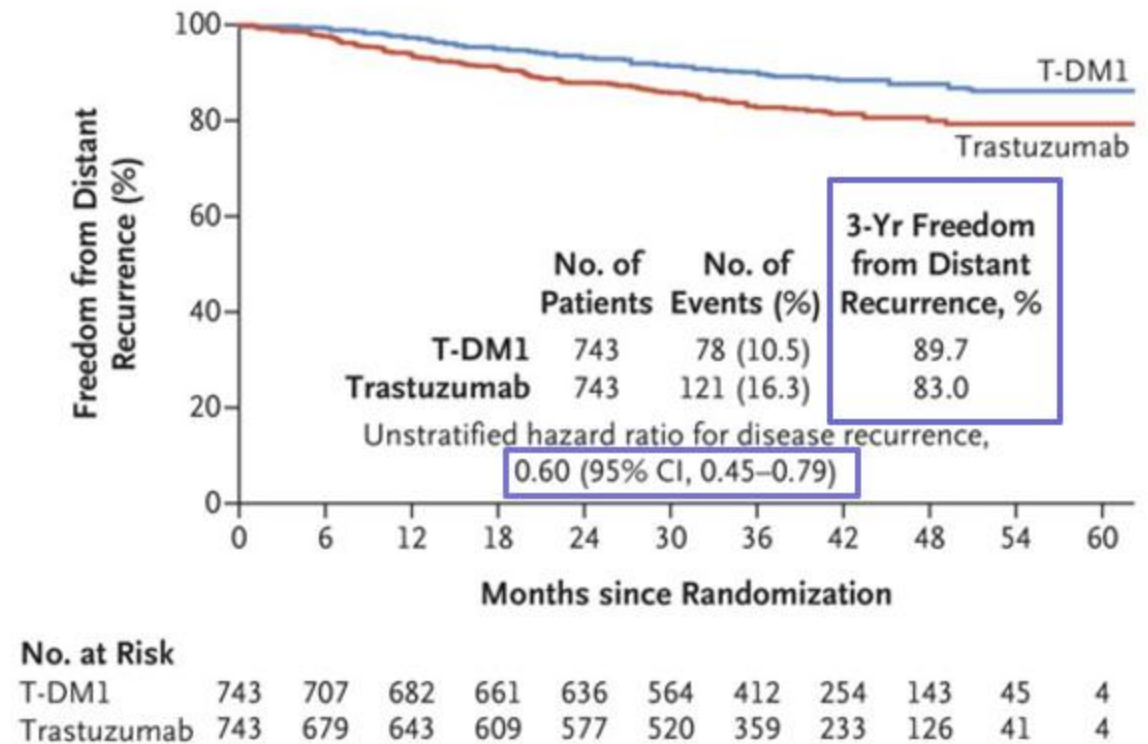
KATHERINE: Efficacy Outcomes

Risk of recurrence or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone



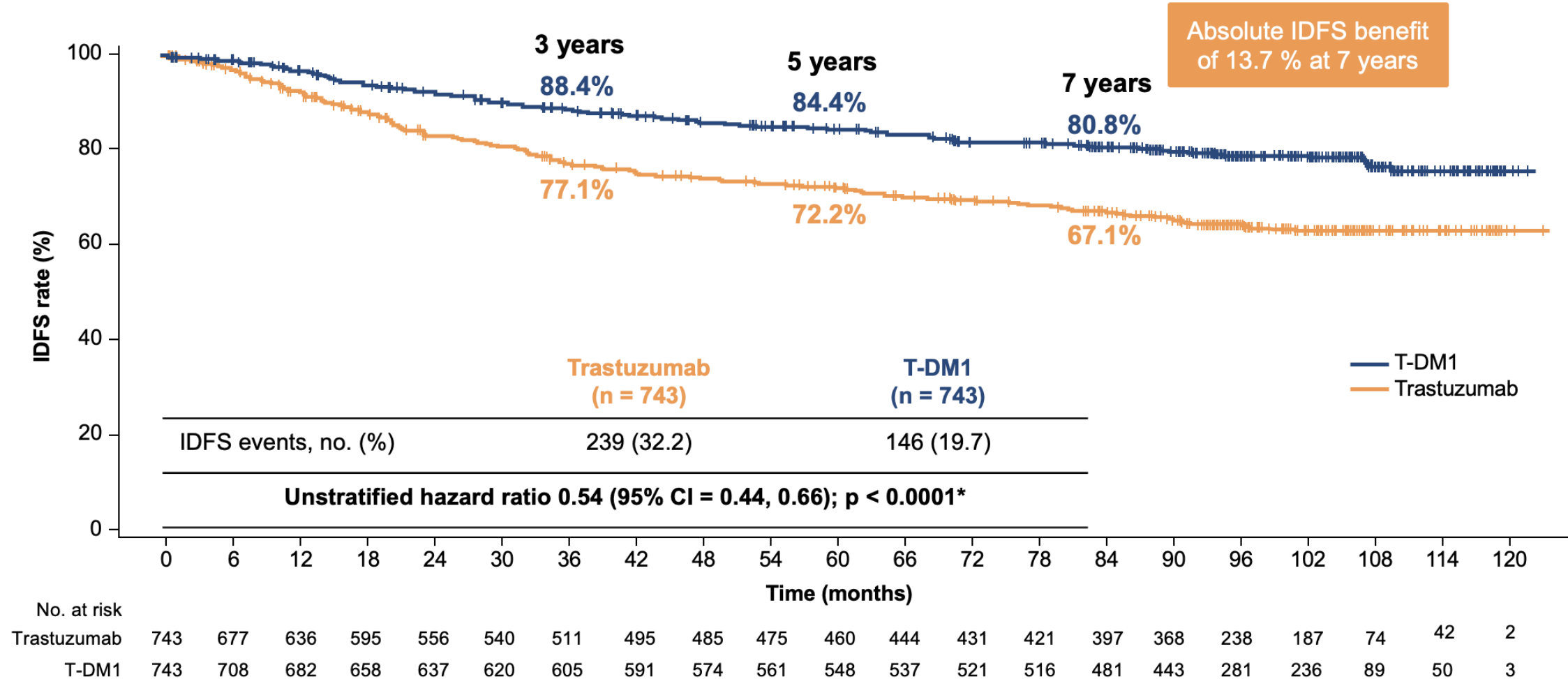
Invasive disease events 12.2% T-DM1 (n=91) vs 22.2% Trastuzumab (n=165)

Interim analysis, median follow up 41.4 mths T-DM1, 40.9 mths trastuzumab



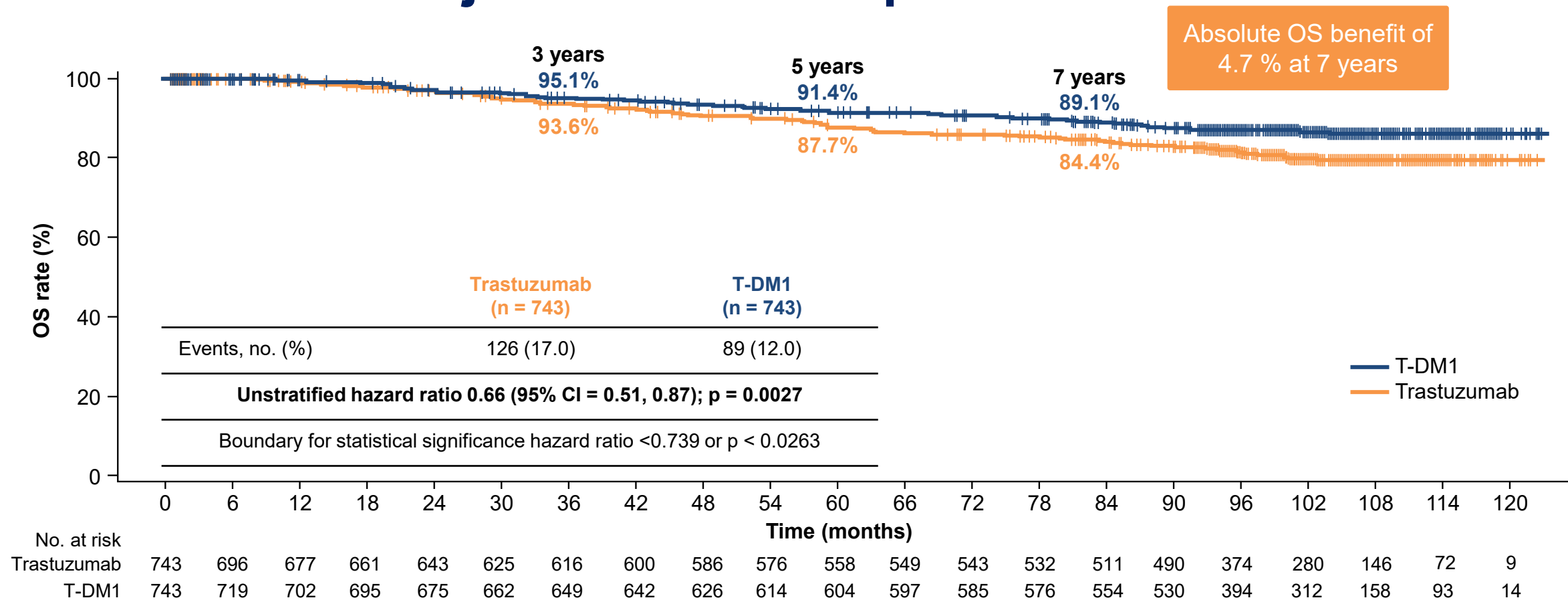
Distant recurrence as first event 10.5% T-DM1 (n=78) vs 15.9% Trastuzumab (n=118)

KATHERINE: Final iDFS Analysis – Median f/u 8.4 years



* 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.

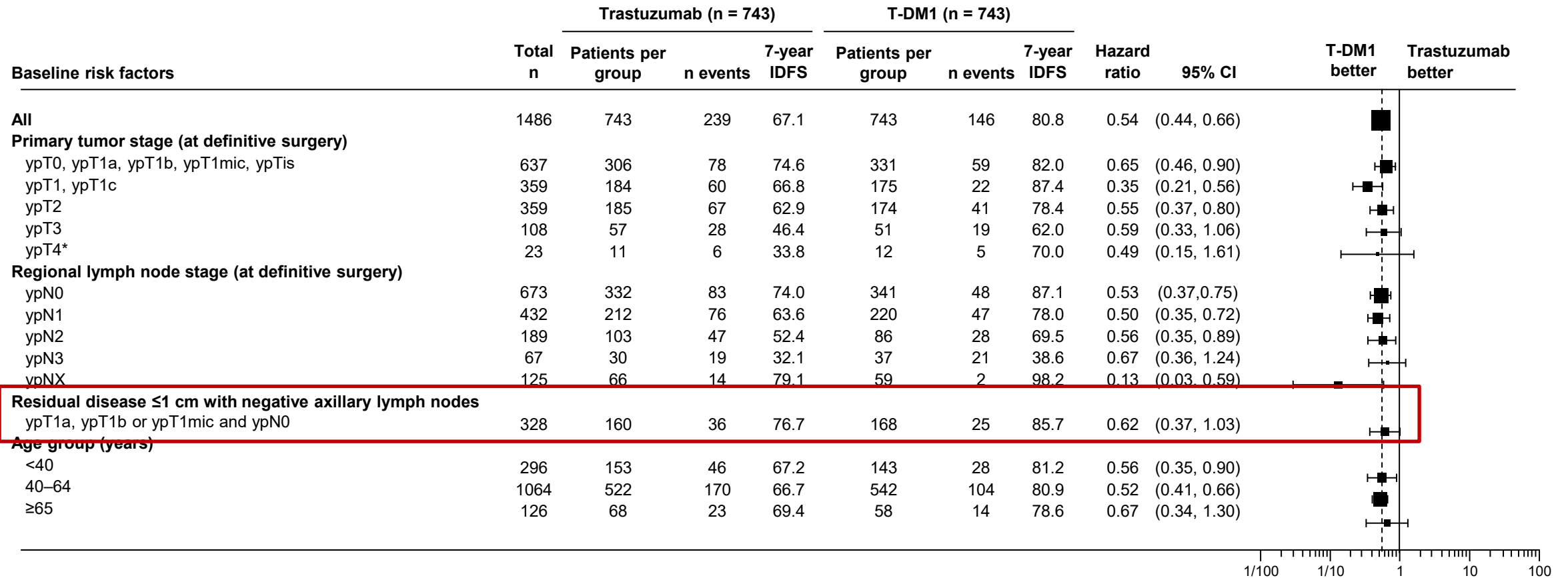
KATHERINE: Adjuvant T-DM1 Improves Overall Survival



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

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

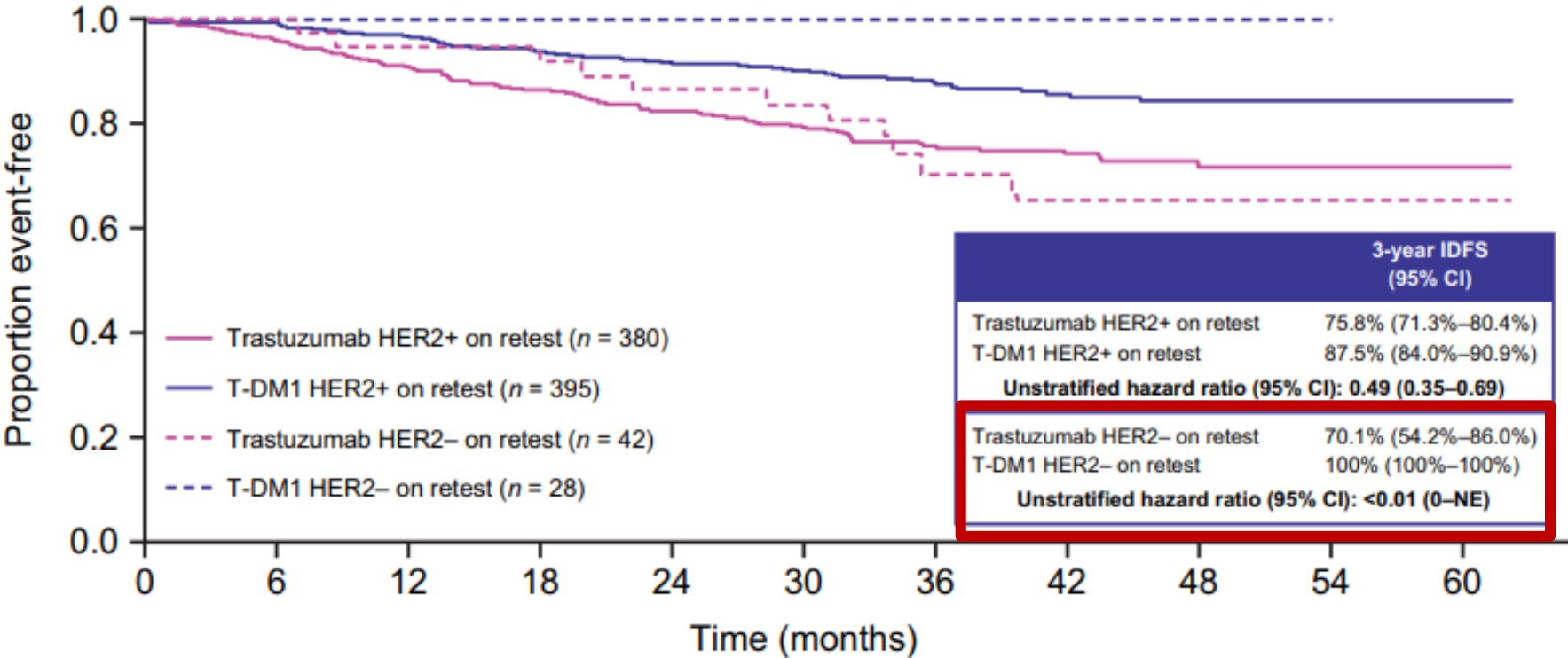
What if There is a Small Amount of Residual Disease in the Breast?



* Includes all ypT4 and one patient with ypTX.

CI, confidence interval; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

What if Disease is HER2-Negative at Time of Surgery?



Number at risk:

Trastuzumab HER2+ on retest	380	344	325	306	288	262	184	113	64	22	2
T-DM1 HER2+ on retest	395	377	365	352	340	309	224	138	79	30	3
Trastuzumab HER2- on retest	42	38	35	34	31	29	17	9	5	2	1
T-DM1 HER2- on retest	28	25	24	24	23	21	14	5	2	1	0

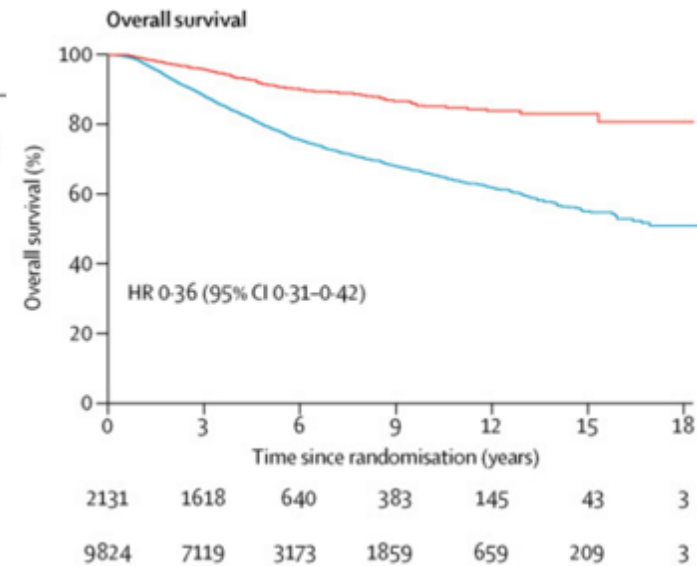
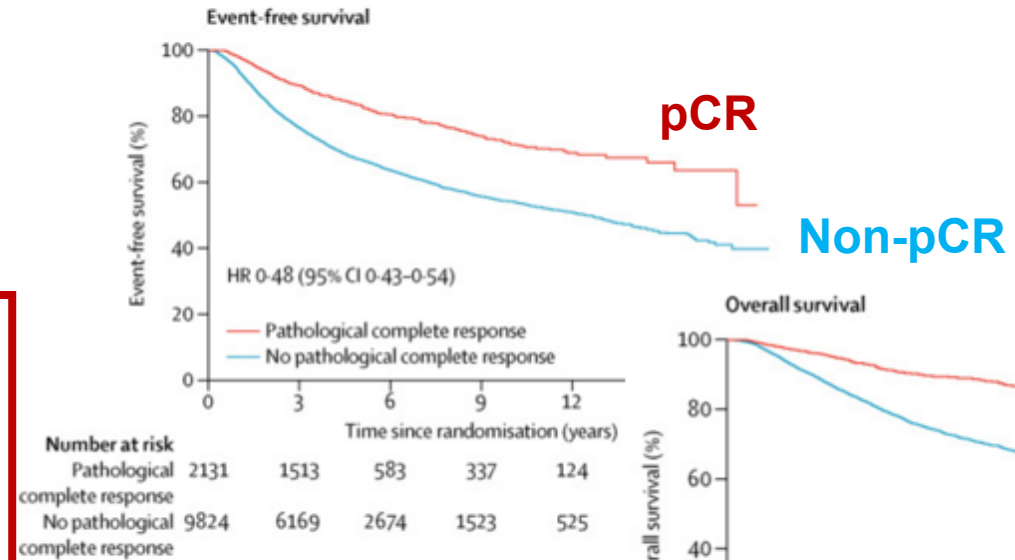
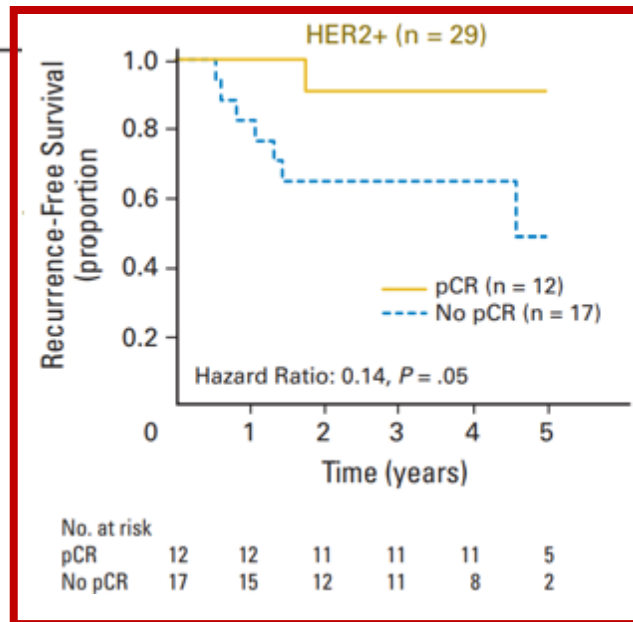
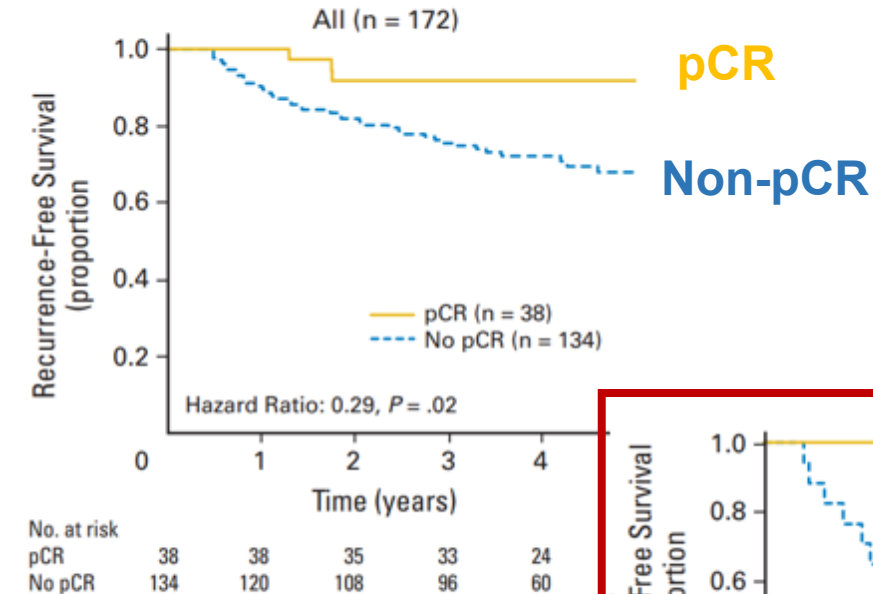
CAN WE IMPROVE UPON KATHERINE?

- 7-year iDFS for N+ patients: 72%
- No improvement in rates of CNS recurrence (will be discussed later)
- May want to consider further treatment escalation

How can we Improve The Outcomes for Early Stage HER2+ Breast Cancer

1. Is pCR the “great equalizer”?

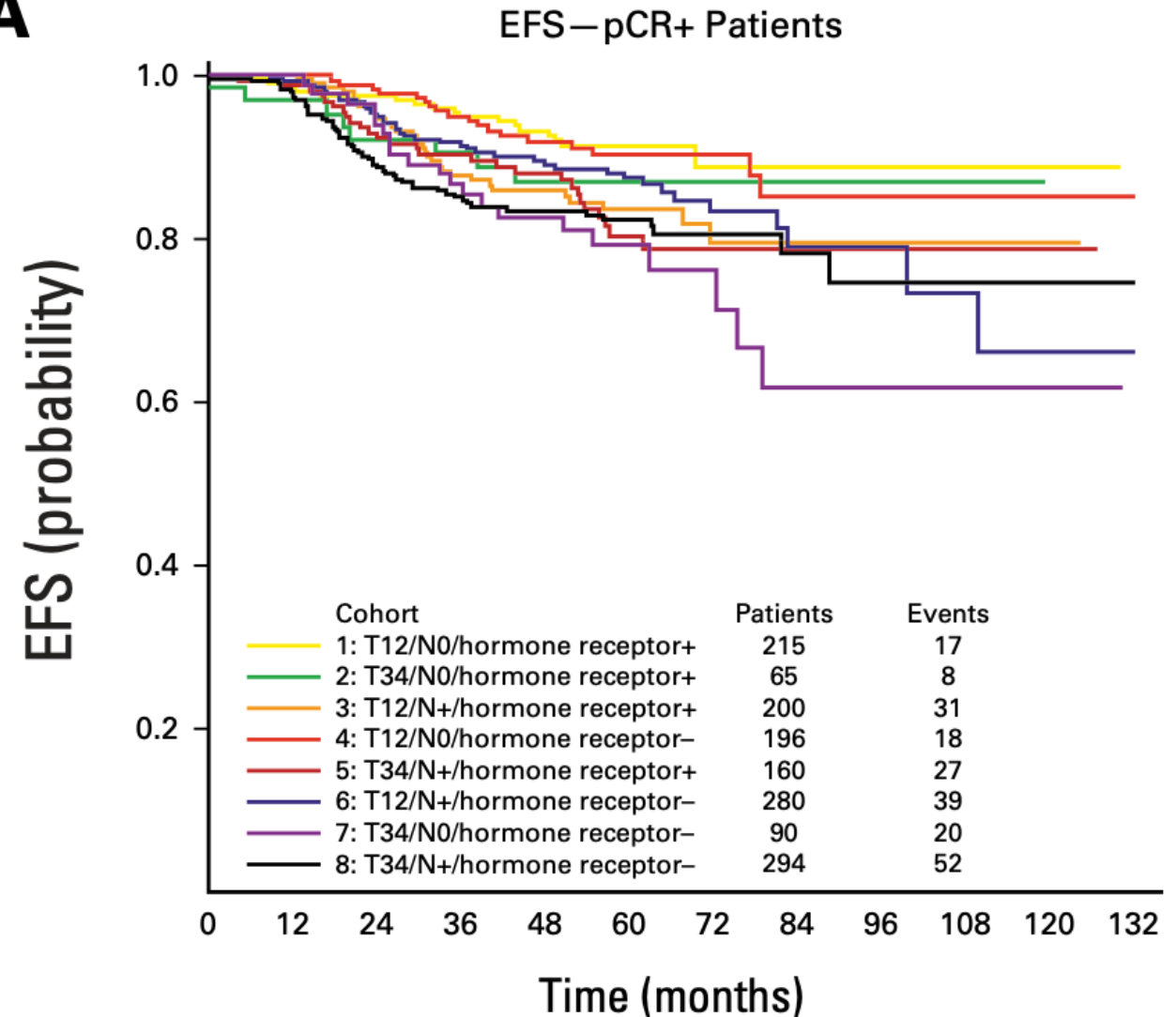
pCR is an important predictor of long term outcomes in aggressive tumor subtypes



Not all pCR are the same!

- pCR improves iDFS and EFS but does **NOT** overcome the prognostic impact of baseline tumor size and nodal status
- N+ and pCR = up to **20%** recurrence in 5 years
- N+ and non-pCR = up to **50%** recurrence in 5 years

A



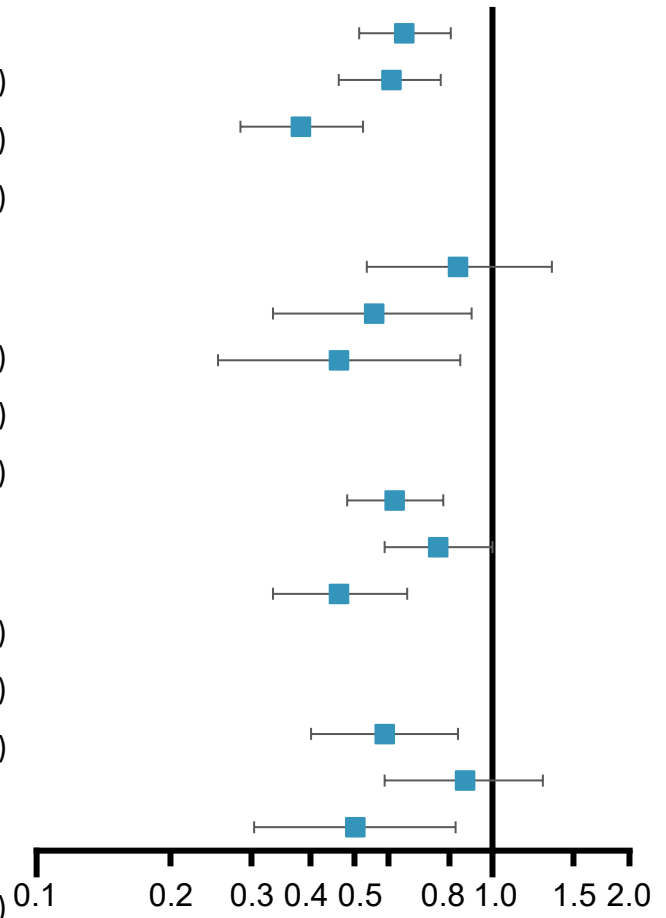
Achieving pCR improves iDFS but cannot overcome the prognostic impact of baseline tumour size and nodal status, still facing ~20% risk of recurrence

pCR and prognosis: iDFS

- HER2+ early breast cancer
- Neoadjuvant chemotherapy plus anti-HER2 therapy

Patients with pCR and high tumour burden have a high rate of metastatic disease

			N	5-y rate	Hazard ratio ^a	95% CI	Hazard ratio (95% CI)
HR+	pCR-	T1-2/N- (reference)	377	84.5%			
		T3-4/N- vs T1-2/N-	143	73.2%	0.64	(0.51–0.81)	
		T1-2/N+ vs T1-2/N-	488	72.1%	0.60	(0.46–0.77)	
		T3-4/N+ vs T1-2/N-	431	60.9%	0.38	(0.28–0.52)	
HR+	pCR+	T1-2/N- (reference)	212	91.4%			
		T3-4/N- vs T1-2/N-	65	87.0%	0.84	(0.53–1.35)	
		T1-2/N+ vs T1-2/N-	200	83.6%	0.55	(0.33–0.90)	
		T3-4/N+ vs T1-2/N-	160	80.4%	0.46	(0.25–0.85)	
HR-	pCR-	T1-2/N- (reference)	140	66.6%			
		T3-4/N- vs T1-2/N-	78	59.1%	0.61	(0.48–0.78)	
		T1-2/N+ vs T1-2/N-	251	64.9%	0.76	(0.58–1.00)	
		T3-4/N+ vs T1-2/N-	345	45.4%	0.46	(0.33–0.65)	
HR-	pCR+	T1-2/N- (reference)	196	90.3%			
		T3-4/N- vs T1-2/N-	90	79.3%	0.58	(0.40–0.84)	
		T1-2/N+ vs T1-2/N-	280	87.5%	0.87	(0.58–1.29)	
		T3-4/N+ vs T1-2/N-	294	82.4%	0.50	(0.30–0.83)	



How can we Improve The Outcomes for Early Stage HER2+ Breast Cancer

1. What do we know about CNS recurrence risk factors?
2. How can we reduce the risk of CNS recurrence?

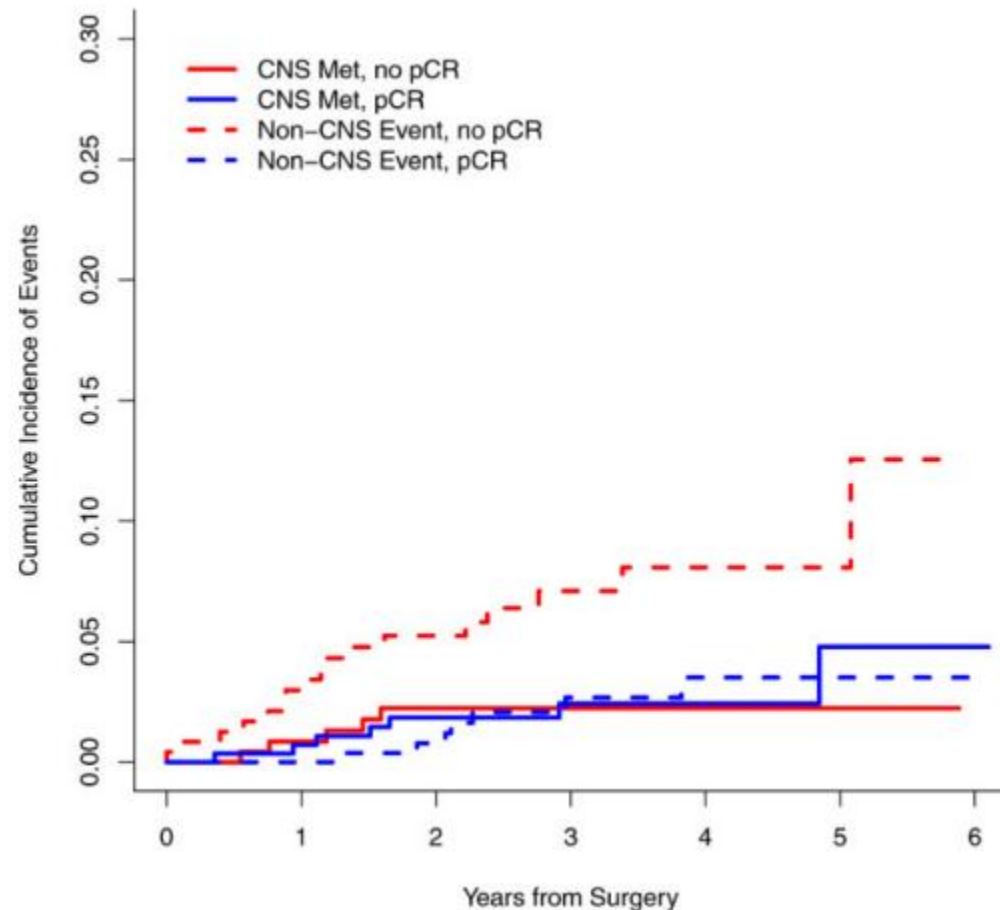
The CNS remains a common site of distant recurrence in HER2+ breast cancer!

- Up to 50% of **HER2+** patients with metastatic breast cancer will develop brain metastases (BM)
 - Risk factors:
 - **HER2 amplification or overexpression**
 - Younger age at diagnosis (age<50)
 - Hormone receptor negative status
 - High histologic grade
 - High Ki-67
 - Higher tumor stage (>2 cm)
 - Nodal involvement
 - Short time to distant relapse

The CNS remains a common site of distant recurrence in HER2+ breast cancer

- BM are associated with significant morbidity and mortality, negatively impacting quality of life
- No guidelines currently support CNS imaging as part of routine surveillance strategy in asymptomatic patients
- Historically, breast cancer patients with BM have been excluded from enrollment in trials

MSKCC: Incidence of brain metastases post neoadjuvant chemotherapy + dual anti HER2 therapy



pCR (n=286)

BM events: 2.4%

Median time to development of BM:

19 months
(range: 4-58 months)

Non-pCR (n=240)

BM events 2.0%

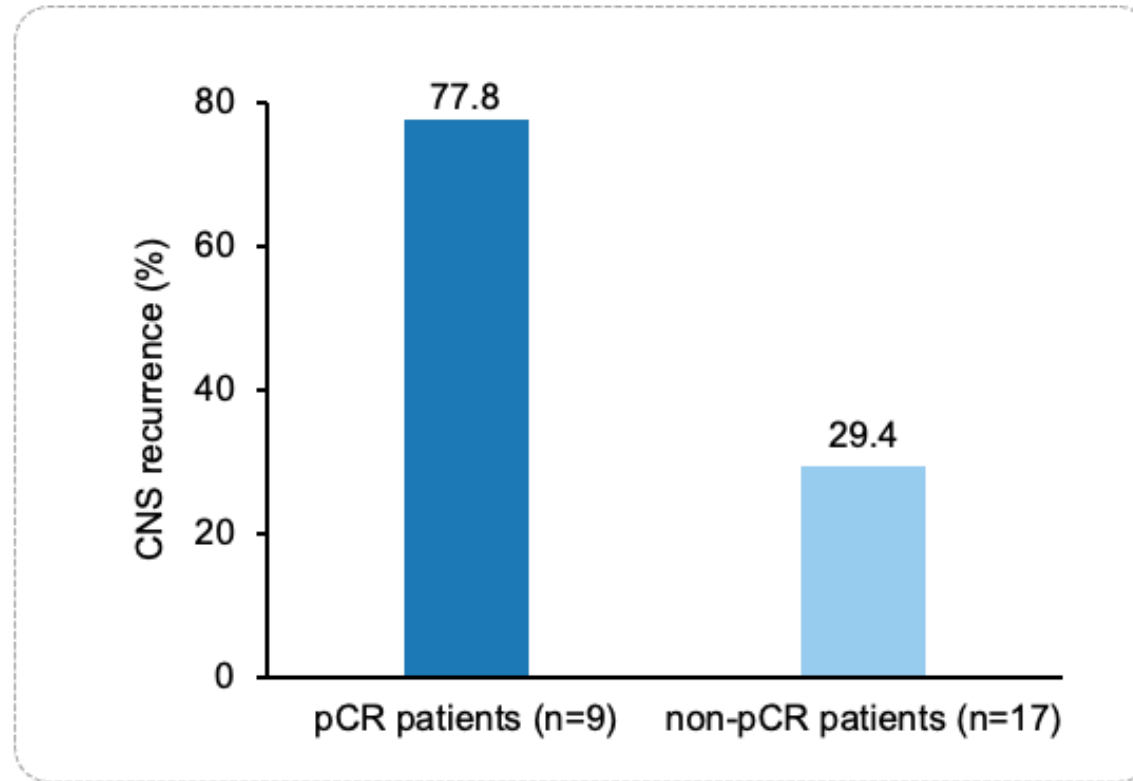
Median time to development of BM:

6.5 months
(range: 6.5-17 months)

Incidence of Brain Metastases in Early-Stage HER2+ Breast Cancer is Not Associated with pCR

The Rate of CNS Recurrence in Patients that experience Distant Recurrence based on pCR status

The Rate of CNS Recurrence in Distant Recurrence



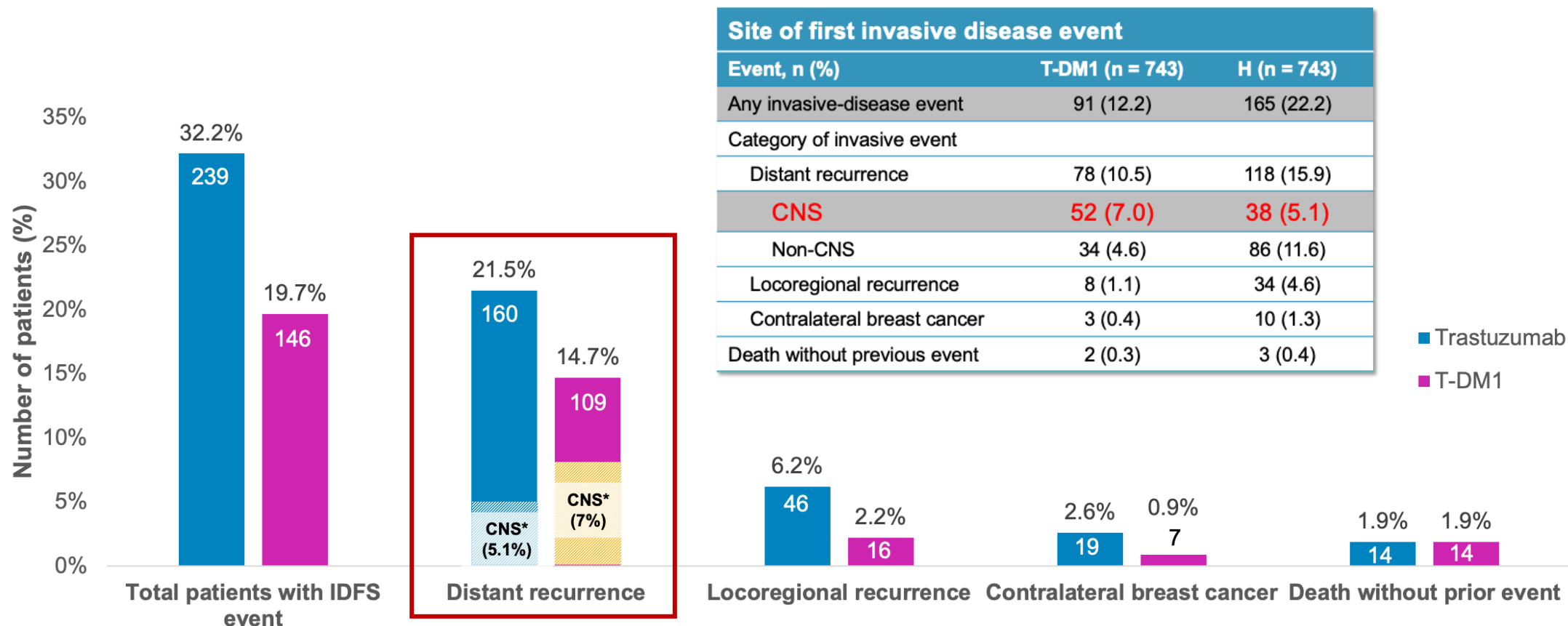
A deeper dive into CNS recurrence rates in the key pivotal early HER2+ breast cancer adjuvant trials

- *APHINITY: Adjuvant Pertuzumab (2017)*
- *KATHERINE: Adjuvant T-DM1 (2019)*
- *ExteNET: Adjuvant Neratinib (2017)*

APHINITY: Although pertuzumab reduced distant recurrence, there was no effect on CNS recurrence rates

	Pertuzumab (n, %) (n=2400)	Placebo (n, %) (n=2404)	Δ
Total iDFS events	221 (9.2%)	287 (11.9%)	2.7% absolute benefit
Type of iDFS event			
Distant Recurrence	141 (5.9%)	184 (7.7%)	1.8% absolute benefit
CNS Recurrence	49 (2.0%)	49 (2.0%)	No difference
Locoregional Recurrence	28 (1.2%)	49 (2.0%)	0.8% absolute benefit
Death without prior event	39 (1.6%)	39 (1.6%)	No difference

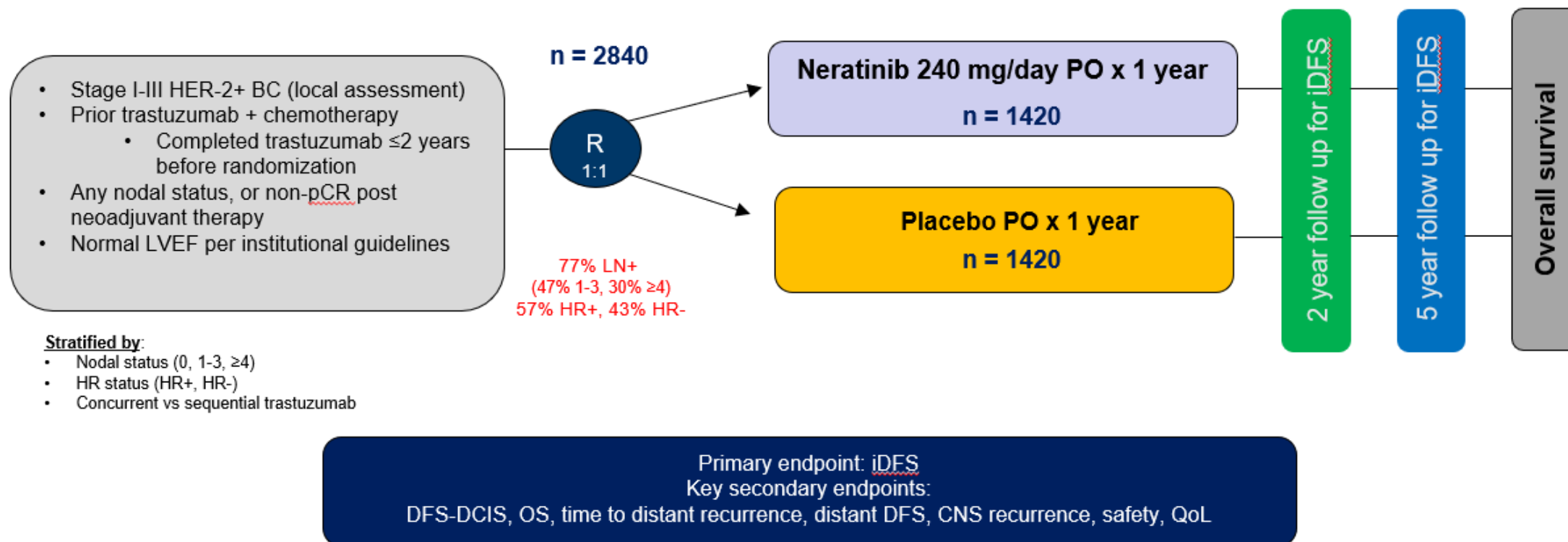
KATHERINE: CNS recurrences



Early Stage HER2+ Breast Cancer

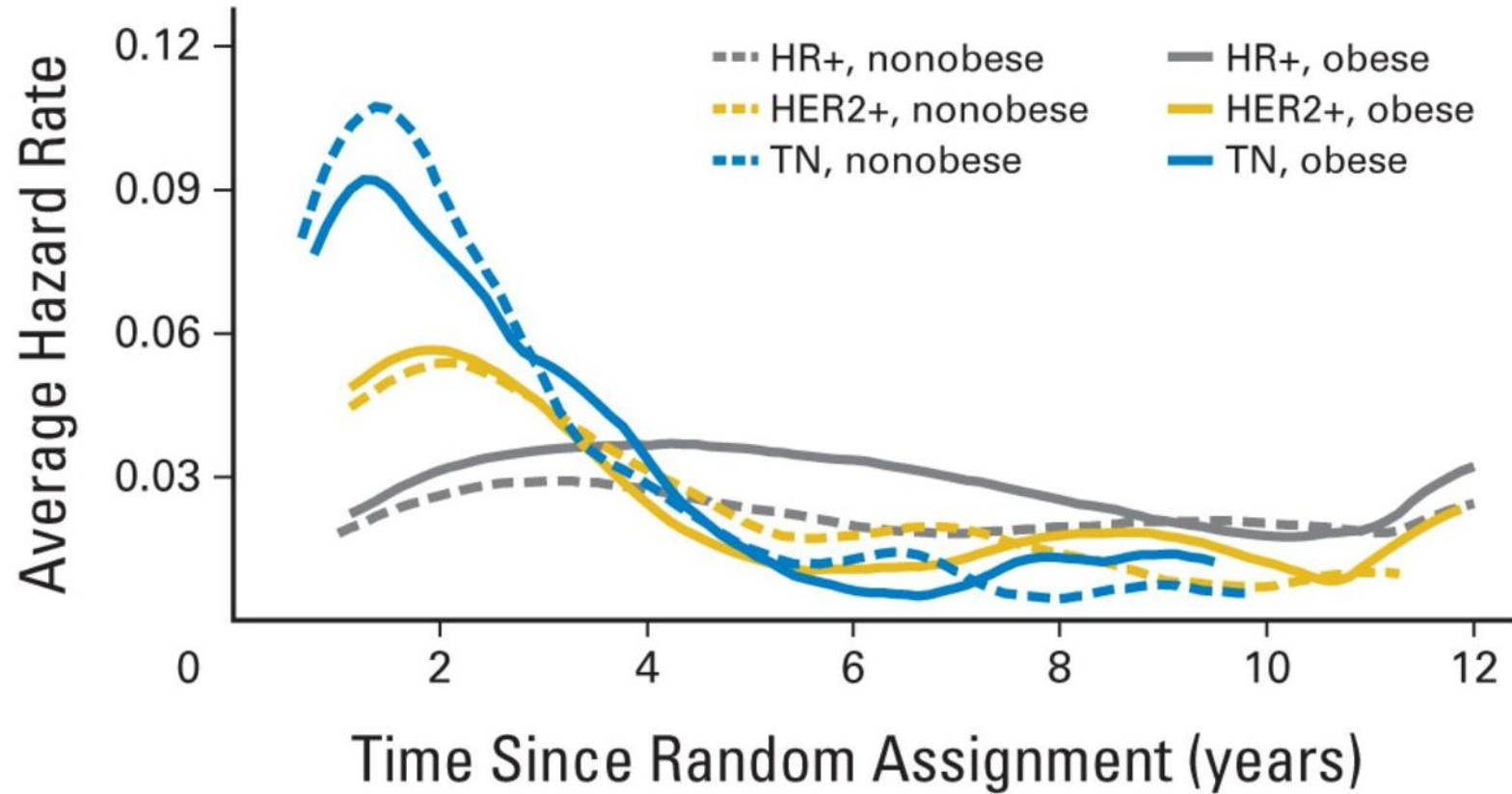
What about HER2-directed TKIs in the
adjuvant setting?

ExteNET: Neratinib after trastuzumab in HER2+ EBC



Protocol Amendment (Feb 2010) to include Stage II-III patients who had completed trastuzumab up to 1 year prior

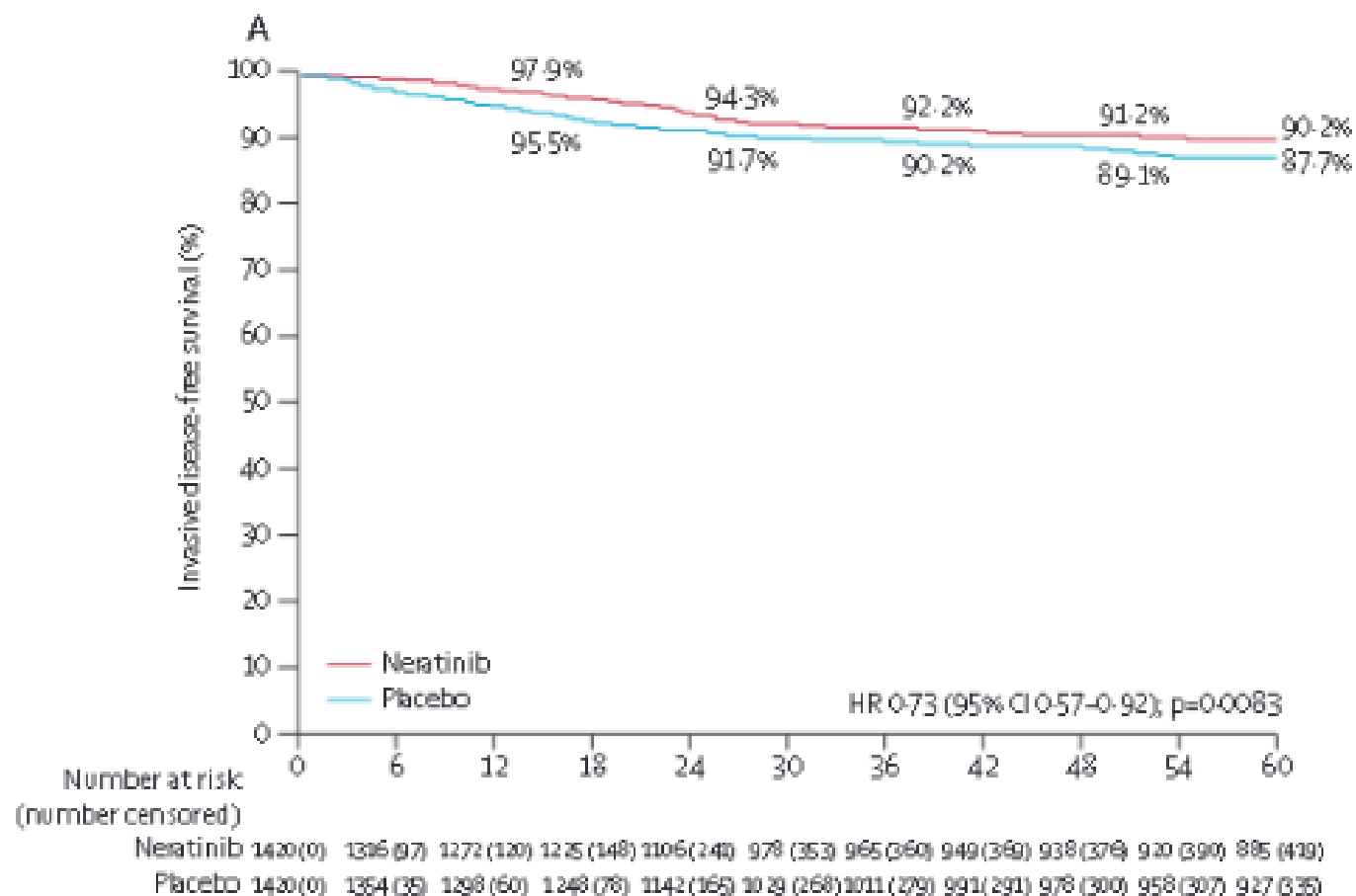
Recurrence in ER-ve Breast Cancer



Sparano et al. JCO, 2015

ExteNET: Neratinib after trastuzumab in HER2+ EBC at 5 years

5 year follow up



5 year iDFS
90.2% neratinib vs
87.7% placebo

Δ 2.5%

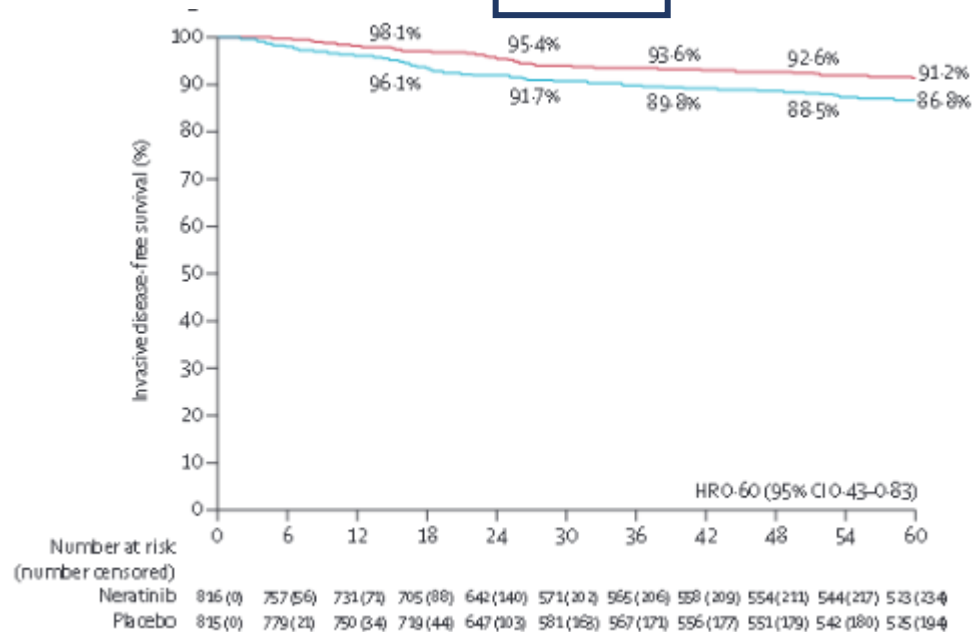
ExteNET: Neratinib after trastuzumab in HER2+ EBC by hormone receptor status (exploratory analysis)

5 year follow up

HR+ subgroup:

91.2% neratinib vs 86.8% placebo

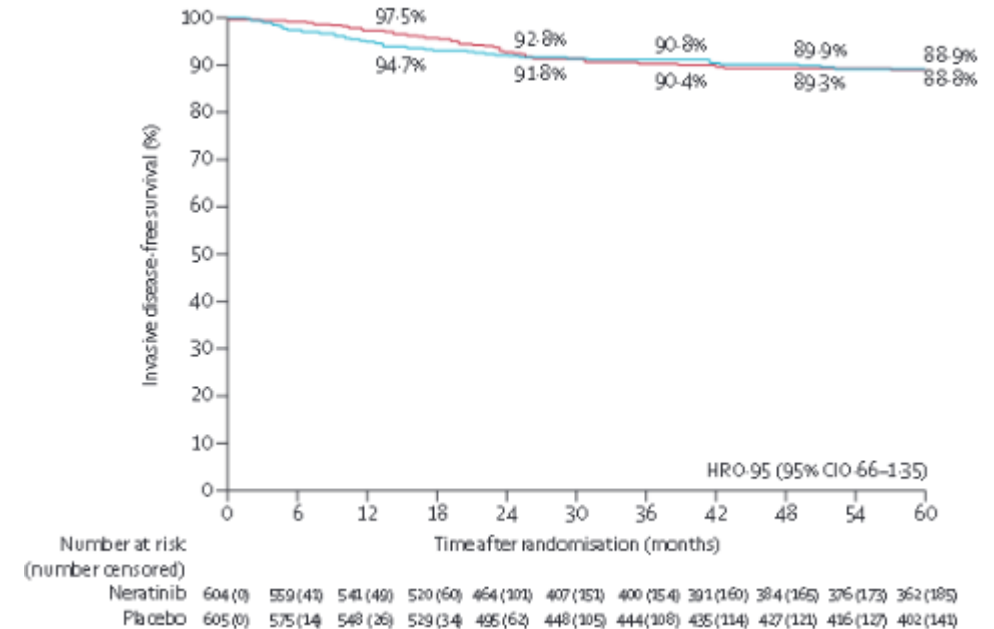
Δ 4.4%



HR- subgroup:

88.8% neratinib vs 88.9% placebo

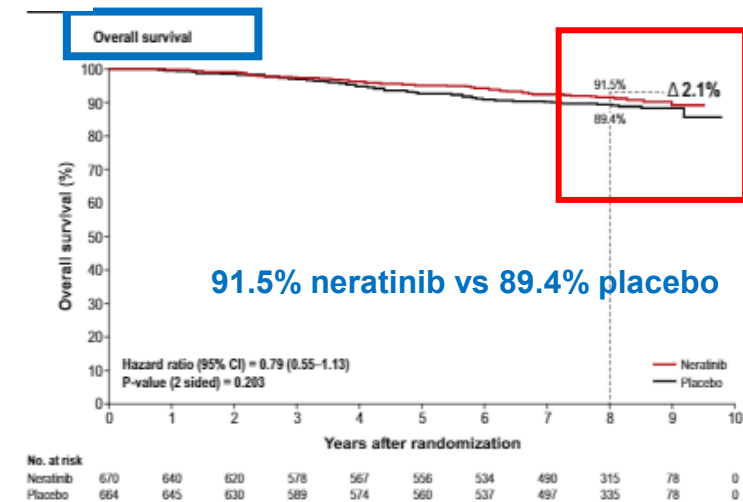
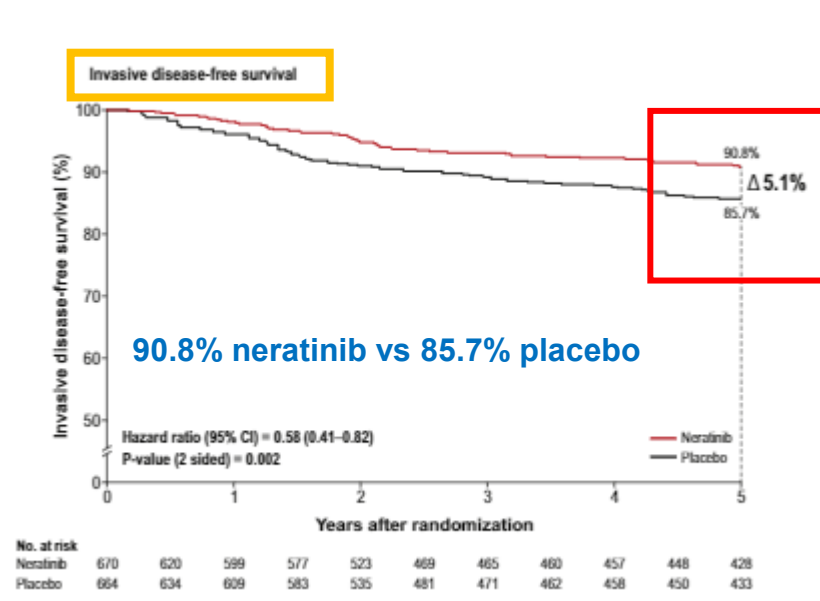
Δ -0.1%



The benefit of neratinib was predominately demonstrated in those with **HR+ disease**

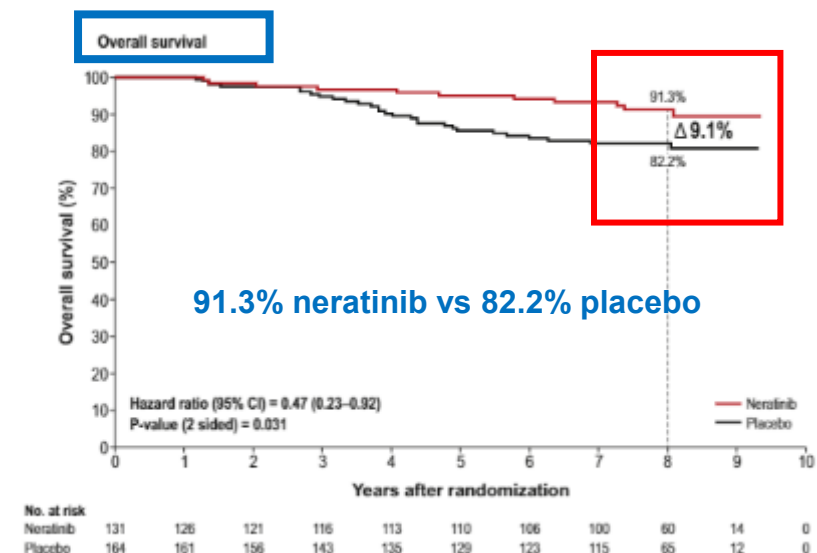
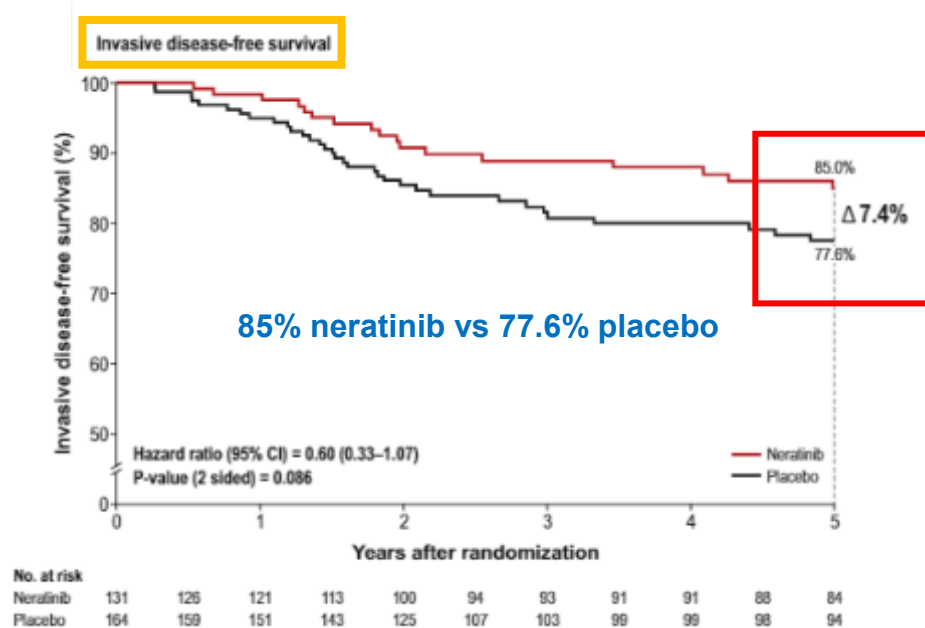
ExteNET: Adjuvant neratinib in HR+/HER2+ EBC, ≤1 year post trastuzumab

- **Descriptive analysis** performed in HR+ subgroup who initiated neratinib within 1 year of trastuzumab (HR+/ ≤ 1 year)
 - **HR+, ≤ 1 year** includes **n=1334** (neratinib n=670, placebo n=664)
 - **Absolute 5-year iDFS benefit: 5.1%**, HR 0.58, 95% CI 0.41-0.82; [1.3% HR+/ >1 year, HR 0.74]
 - **Absolute 8-year OS benefit: 2.1%**, HR 0.79, 95% CI 0.55-1.13



ExteNET: Adjuvant neratinib in HR+/HER2+ EBC, ≤1 year post trastuzumab – non-pCR group

- **Descriptive analysis** performed in HR+ subgroup who initiated neratinib within 1 year of trastuzumab (HR+/ ≤ 1 year)
 - **Non-pCR** to neoadjuvant therapy included **n=295** (83% of 354 total pts received neo therapy)
 - Absolute 5-year iDFS benefit: **7.4%**, HR 0.60, 95% CI 0.33-1.07; [1.3% HR+/ >1 year, HR 0.74]
 - Absolute 8-year OS benefit: **9.1%**, HR 0.47, 95% CI 0.23-0.92



ExteNET: Adjuvant neratinib in HR+/HER2+ EBC, ≤1 year post trastuzumab

- **Descriptive analysis** performed in HR+ subgroup who initiated neratinib within 1 year of trastuzumab (HR+/ ≤1 year)
 - Patients who received neratinib had fewer CNS relapses, including those with residual disease following neoadjuvant therapy

Population or Subgroup	CNS Events (No. Patients)		Cumulative Incidence of CNS Recurrences at 5 Years, % (95% CI)	
	Neratinib	Placebo	Neratinib	Placebo
HR ⁺ /≤1-year population	4 (670)	12 (664)	0.7 (0.2–1.7)	2.1 (1.1–3.5)
Nodal status				
Positive	4 (540)	10 (539)	0.8 (0.3–2.0)	2.2 (1.1–3.8)
Negative	0 (130)	2 (125)	0 (NE)	1.9 (0.4–6.0)
Prior trastuzumab regimen				
Concurrent	2 (411)	8 (415)	0.6 (0.1–1.9)	2.3 (1.1–4.3)
Sequential	2 (259)	4 (249)	0.9 (0.2–3.0)	1.8 (0.6–4.3)
Adjuvant or neoadjuvant therapy				
Adjuvant	3 (508)	6 (472)	0.7 (0.2–2.0)	1.5 (0.6–3.0)
Neoadjuvant	1 (162)	6 (192)	0.7 (0.1–3.3)	3.7 (1.5–7.4)
pCR status ^a				
No	1 (131)	5 (164)	0.8 (0.1–4.0)	3.6 (1.3–7.8)
Yes	0 (17)	1 (21)	0 (NE)	5.0 (0.3–21.2)

Abbreviations: CI = confidence interval; CNS = central nervous system; HR⁺ = hormone receptor-positive; NE = not estimable; pCR = pathologic complete response.

^aAmong the 354 patients who had received neoadjuvant therapy, 295 patients had no pCR, 38 patients achieved a pCR, and 21 patients had no outcome reported.

pCR status



CNS Recurrence as the First Site of Metastasis in Studies of Adjuvant Therapy in HER2+ EBC

Trial and Population*	Analysis Timepoint	N	Neoadjuvant Population	CNS Recurrence, %	
				Control	Treatment
Adjuvant trast Meta-analysis ¹	-	9020	N/A	1.9	2.5
ALTTO ²	3 yr	4190	~8	2	2
ExteNET ^{3,4}	ITT	2840	25%	1.8	1.3
	HR+/ $\leq$ 1yr post trast.	1334	27%	2.1	0.7
APHINITY ⁵	8 yr	4805	0	3.2	2.9
No pCR Post Neoadjuvant Tx					
KATHERINE ^{6,7} high-risk	7 yr	1486	N/A	5.1	7.0
ExteNET ³ HR +/ $\leq$ 1yr post trast	5 yr	295	N/A	3.6	0.8

For informational purposes only. Cross-study comparisons should not be made.

HR+/ $\leq$ 1yr, hormone receptor positive with start of neratinib $\leq$ 1 year following trastuzumab adjuvant therapy; CNS = central nervous system; EBC = early breast cancer; HER2 = human epidermal growth factor 2;

HR+ = hormone receptor positive; ITT = intention-to-treat; trast = trastuzumab; pCR = pathologic complete response

*Using all patients in the trials as a denominator

1. Olson EM, et al. *Ann Oncol.* 2013;1526-1533 2. Piccart-Gebhart M, et al. *J Clin Oncol.* 2016;34(10):1034-1042 [supplemental appendix]. 3. Chan A, et al. *Clin Breast Cancer.* 2021;21(1):80-91.e7. 4. Holmes FA, et al. SABCS 2020 poster presentation. Abstract PD3-03. 5. von Minckwitz G, et al. *N Engl J Med.* 2017;377(2):122-131. 6. Mamounas EP, et al. *J Ann Oncol.* 2021; <https://doi.org/10.1016/j.annonc.2021.04.011>. 7. : Loibl S, et al. 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. SABCS 2023. GS03-12. <https://medically.gene.com/global/en/unrestricted/oncology/SABCS-2023/sabcs-2023-presentation-loibl-phase-iii-study-of-adjuva.html>

Patterns in use and tolerance of adjuvant neratinib in patients with hormone receptor (HR)-positive, HER2-positive early-stage breast cancer

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BACKGROUND

- Current NCCN guidelines recommend extended adjuvant neratinib following trastuzumab-based therapy for patients with high-risk HR+ HER2+ disease, based on the data from the ExteNET study
- Limitations to use of neratinib include significant gastrointestinal side effects which often result in treatment disruption or discontinuation

OBJECTIVE

- To identify high-risk clinical features and characteristics of patients who were offered adjuvant neratinib therapy and factors that impacted treatment completion versus discontinuation.

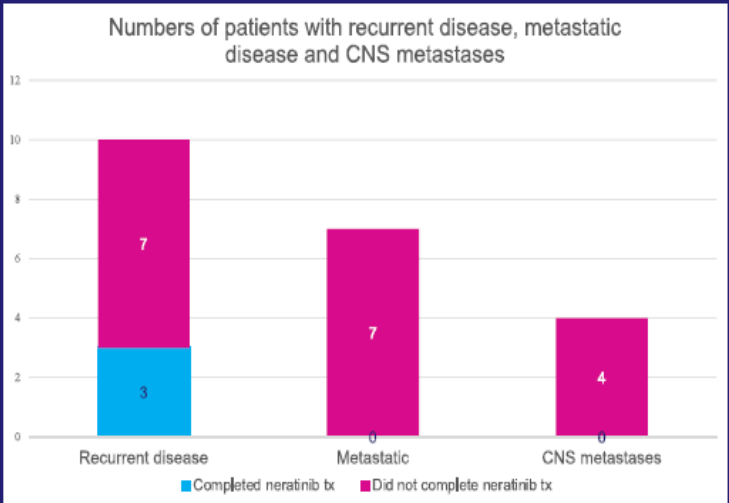
METHODS

- Study Cohort:** Patients with early-stage HR+ HER2+ breast cancer who were prescribed neratinib from 2017-2023 at Mount Sinai.
- Retrospective review was performed using electronic medical records (EMR)
- Information on patient characteristics, clinical features and high-risk features were extracted from the EMR.
- High-risk was defined as any of the following: at least 4 lymph nodes positive for disease, 1-3 lymph nodes positive for disease and a grade 3 (poorly differentiated) tumor, tumor > 5 cm, or Ki67 > 20%.
- Length of time on treatment, treatment holds, dose reductions and up-titrations were documented
- Statistical Analysis:**
 - Analysis was performed using two-sided T-tests and chi-square tests.

Patients are more likely to complete 1 year of adjuvant neratinib with dose up-titration.

Dose reductions and interruptions do not affect neratinib adherence.

Seven patients in our study developed metastatic disease, all of whom *did not* complete adjuvant neratinib treatment.

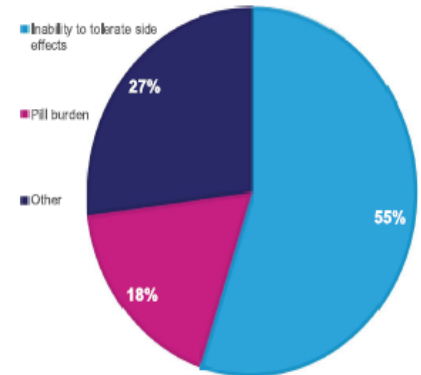


	Clinical Features of Patients Prescribed Neratinib			p-value
	Completed neratinib course	Did not complete neratinib course	All patients	
n (%)	34	28	62	
Tumor grade 3 (poorly differentiated)	22 (64.7%)	16 (57.1%)	38 (61.3%)	0.893
Mean Ki67 %	30.27	21.86	26.07	0.299
Pathologic T stage				0.392
T1	20 (58.8%)	14 (50.0%)	34 (54.8%)	
T2	9 (26.5%)	3 (12.5%)	12 (19.4%)	
T3-4	2 (5.9%)	4 (14.3%)	6 (9.7%)	
Pathologic N stage				0.702
N0	16 (47.1%)	12 (50.0%)	28 (45.2%)	
N1	14 (41.2%)	8 (28.6%)	22 (35.5%)	
N2	3 (8.8%)	3 (12.5%)	6 (9.7%)	
N3	0 (0.0%)	1 (4.2%)	1 (1.6%)	
High-risk at diagnosis	20 (58.8%)	17 (60.7%)	37 (59.7%)	1.000
Median neratinib starting dose	140 mg	240 mg		0.016

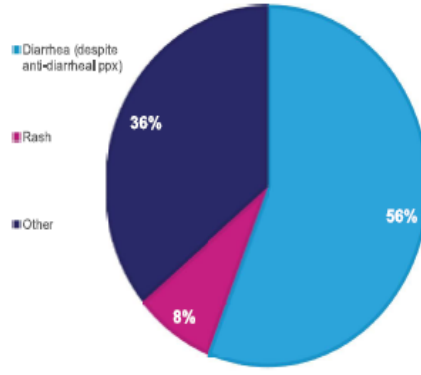
RESULTS

- Patients who received an up-titration of neratinib were more likely to complete the full course of neratinib when compared to those who did not (76% vs. 40.5%, $p = 0.013$).
- Neither group experienced a statistically significant greater likelihood of treatment holds or dose reductions

REASONS FOR NERATINIB DISCONTINUATION



SIDE EFFECTS OF NERATINIB TREATMENT

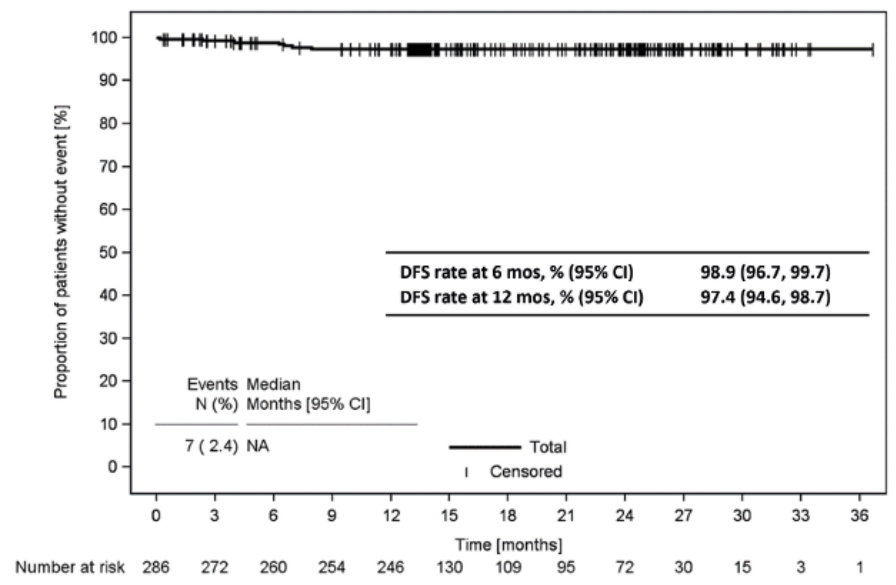
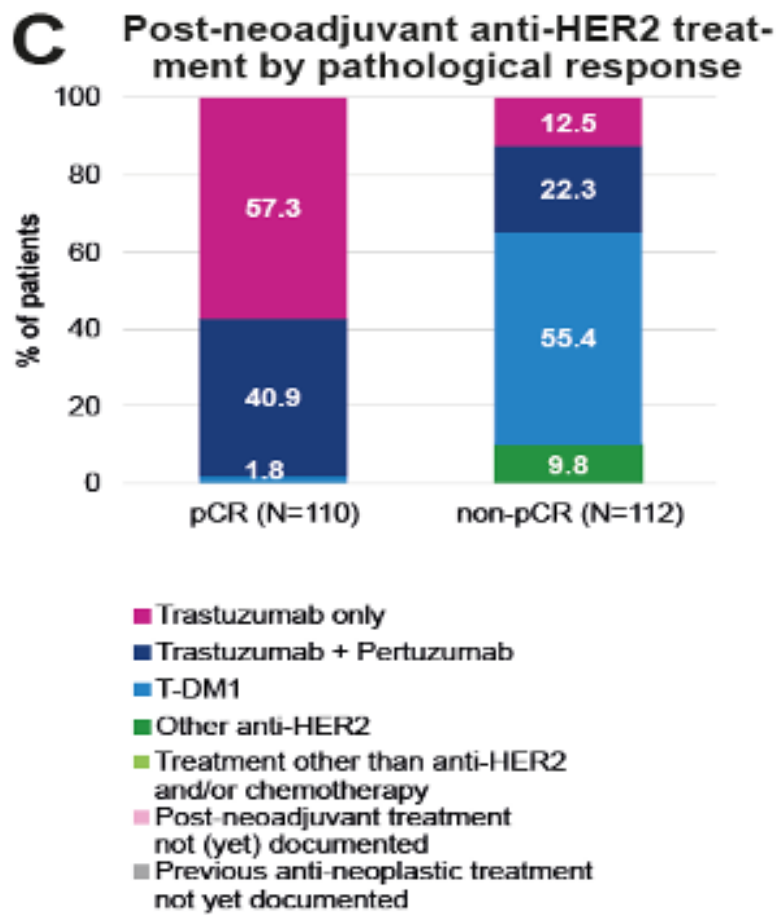


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Does Neratinib work after T-DM1? – ELENOR Trial

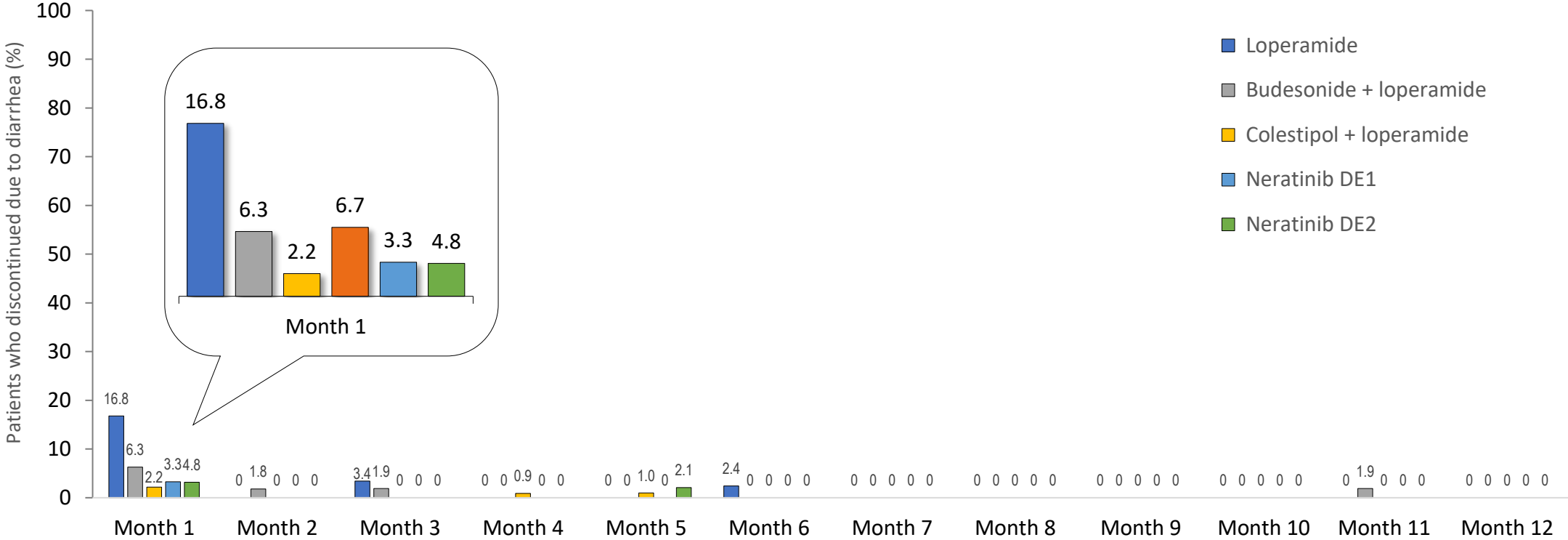


Location(s) of first relapse per patient, n (%) MAS, N=286	
• Distant recurrence	2 (0.7)
• Contralateral invasive breast cancer	1 (0.3)
• Ipsilateral invasive breast cancer	1 (0.3)
• Local and regional recurrence	1 (0.3)
• Missing	1 (0.3)

Take home message:

- Recurrences are low!
- No CNS relapse!

CONTROL: Treatment Discontinuations Due to Diarrhea in All Cohorts

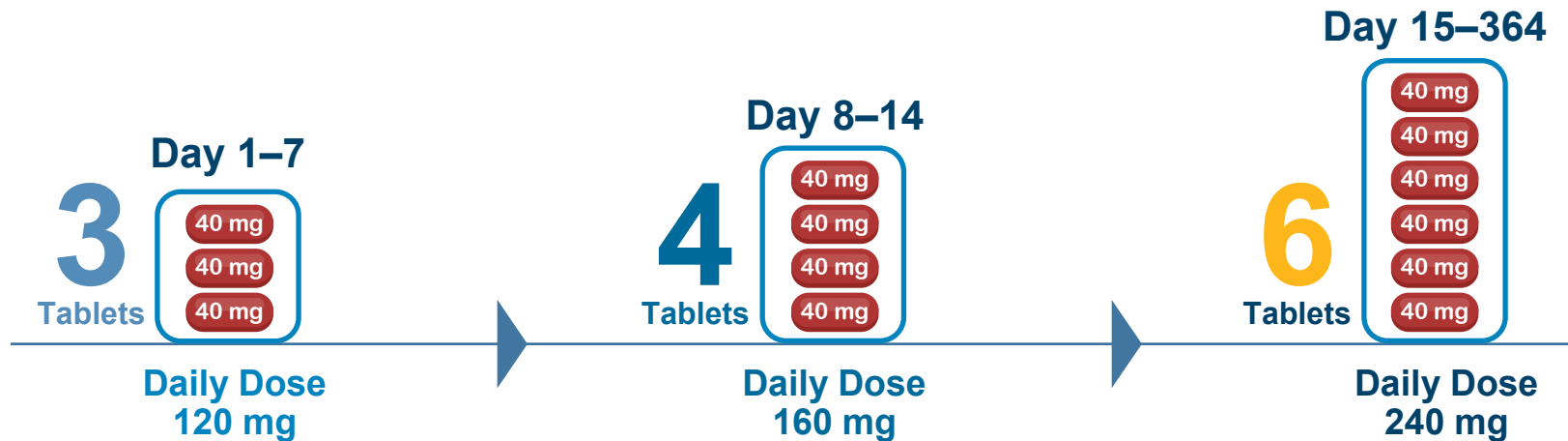


No. of patients who discontinued due to diarrhea / Total No. of patients treated at the beginning of the month

Loperamide	23/137	0/93	3/89	0/84	0/83	2/83	0/81	0/80	0/78	0/77	0/76	0/75
Budesonide + loperamide	4/64	1/57	1/54	0/53	0/53	0/53	0/53	0/53	0/53	0/53	1/53	0/51
Colestipol + loperamide	3/136	0/115	0/112	1/107	1/105	0/104	0/103	0/103	0/102	0/102	0/99	0/99
Colestipol + loperamide prn	7/104	0/86	0/85	0/84	0/82	0/81	0/80	0/79	0/79	0/77	0/77	1/75
DE1	2/60	0/55	0/53	0/53	0/52	0/51	0/50	0/50	0/50	0/49	0/47	0/46
DE2	3/62	0/56	0/49	0/49	1/49	0/47	0/47	0/47	0/46	0/46	0/46	0/46

CONTROL: Treatment Discontinuations Due to Diarrhea in All Cohorts

- Neratinib administered as a dose escalation during Cycle 1 (28 days); loperamide was given as needed (≤ 16 mg/day)^{1,2}



- There appears to be some adaptation to the effects of neratinib, as higher-grade diarrhea occurred early and did not typically recur¹
- Subjects may have an opportunity to acclimate to neratinib, which may increase tolerability and optimize management of toxic effects¹
- Dose escalation has been included in the latest neratinib prescribing information as an option for diarrhea management²

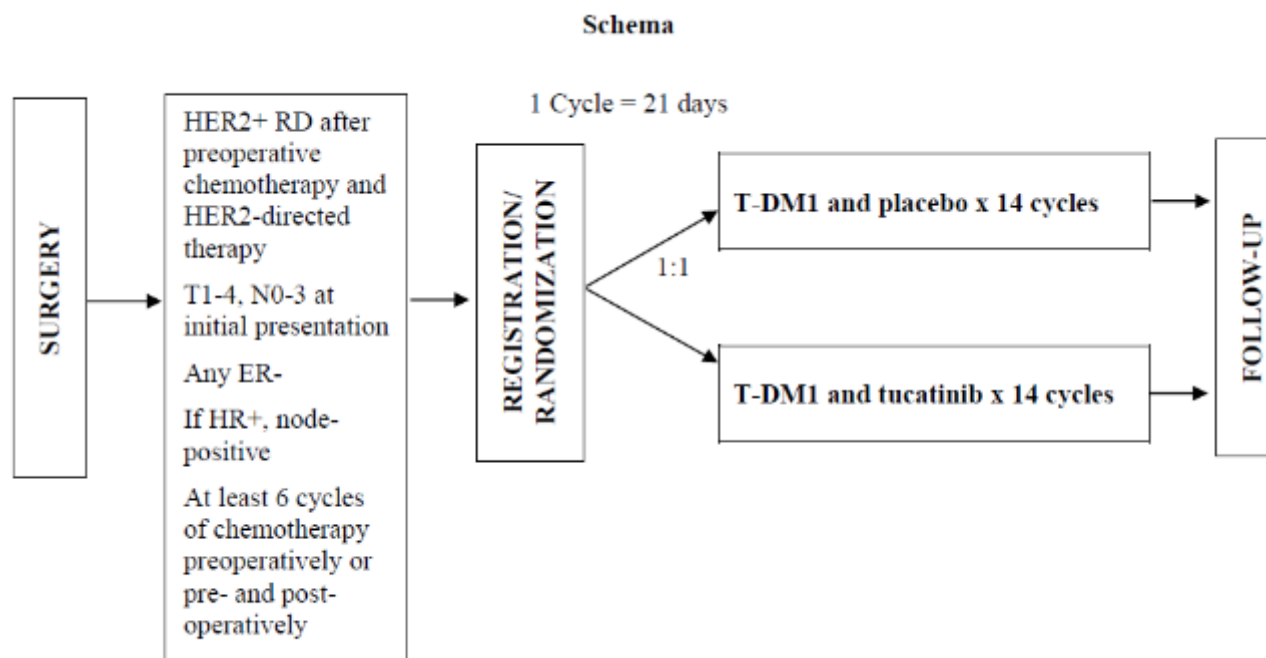
When to consider adjuvant neratinib?

- Adjuvant neratinib:
 - To reduce overall recurrence: Likely HR+*, non-pCR post neoadjuvant therapy
 - To reduce CNS recurrence: All patients with HER2+ should be offered Neratinib
 - Aim start ≤ 1 year post trastuzumab completion
 - Role post T-DM1 and pertuzumab unclear based on trial population
 - Extra care with diarrhea management
 - **CONTROL** trial demonstrates excellent diarrhea control with dose escalation strategies

Ongoing clinical trials in the early-stage HER2+ setting
will provide key insight on:

*Therapy escalation
&
CNS relapse risk reduction strategies*

CompassHER2 RD Trial (A011801): Adjuvant T-DM1 +/- tucatinib for residual disease



Note: HR stands for “hormone-receptor.”

Primary objective

To determine if the iDFS with T-DM1 and tucatinib is superior to the iDFS in the control arm (T-DM1 + placebo) when administered to high risk patients with HER2-positive breast cancer and residual disease after neoadjuvant HER2-directed therapy.

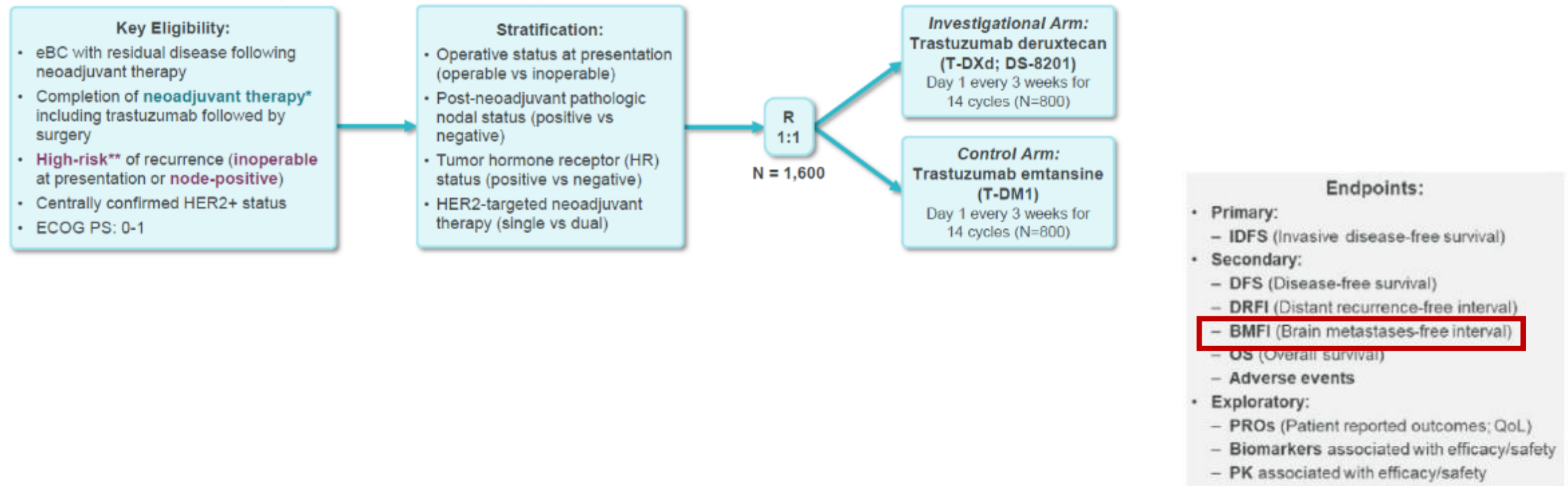
Secondary objectives

To evaluate whether treatment with tucatinib plus T-DM1 compared to treatment with T-DM1 alone (T-DM1 plus placebo) improves the following:

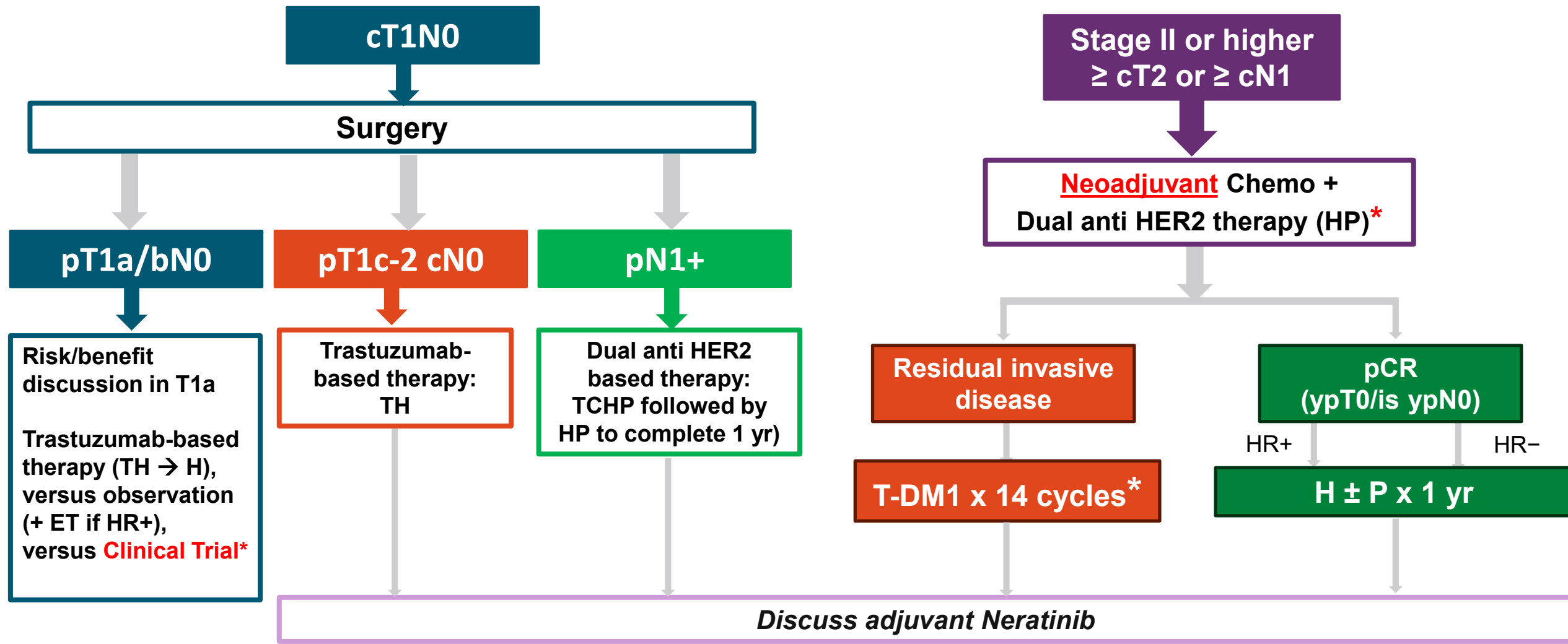
- overall survival (OS)
- breast cancer free survival (BCFS)
- distant recurrence-free survival (DRFS)
- disease-free survival (DFS)
- brain metastases-free survival (BMFS).

DESTINY-Breast05:

Trastuzumab Deruxtecan versus T-DM1
in high-risk HER2+ BC patients with residual disease



Proposed Treatment Approach for Patients with Stage I-III HER2+ BC



***Clinical Trial**



Post-Presentation Case

51 yo post-menopausal female with right-sided cT2 N2 M0 IDC G3 ER/PR+ HER2+. She underwent neoadjuvant therapy with TCHP x6.

Scenario 1

Patient underwent right side MRM and surgical pathology showed complete pathological response. Radiation therapy and Endocrine therapy aside, what adjuvant systemic therapy would you offer:

1. HP 1y
2. HP 1y -> Neratinib 1y
3. T-DM1 1y
4. T-DM1 1y -> Neratinib 1y

Scenario 2

Patient underwent right side MRM and surgical pathology showed 2.2 cm residual disease with 30% cellularity and 4+/16 LN. Radiation therapy aside, what adjuvant systemic therapy would you offer:

1. HP 1y
2. HP 1y -> Neratinib 1y
3. T-DM1 1y
4. T-DM1 1y -> Neratinib 1y

Thank you!