SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

OPTIMIZING THE MANAGEMENT OF LOCALIZED HER2-POSITIVE BREAST CANCER

Sara M. Tolaney

Dana-Farber Cancer Institute

CAN ANTHRACYCLINES BE SUBSTITUTED BY TAXANES?

IS ANTHRACYCLINE-BASED CHEMOTHERAPY NECESSARY?

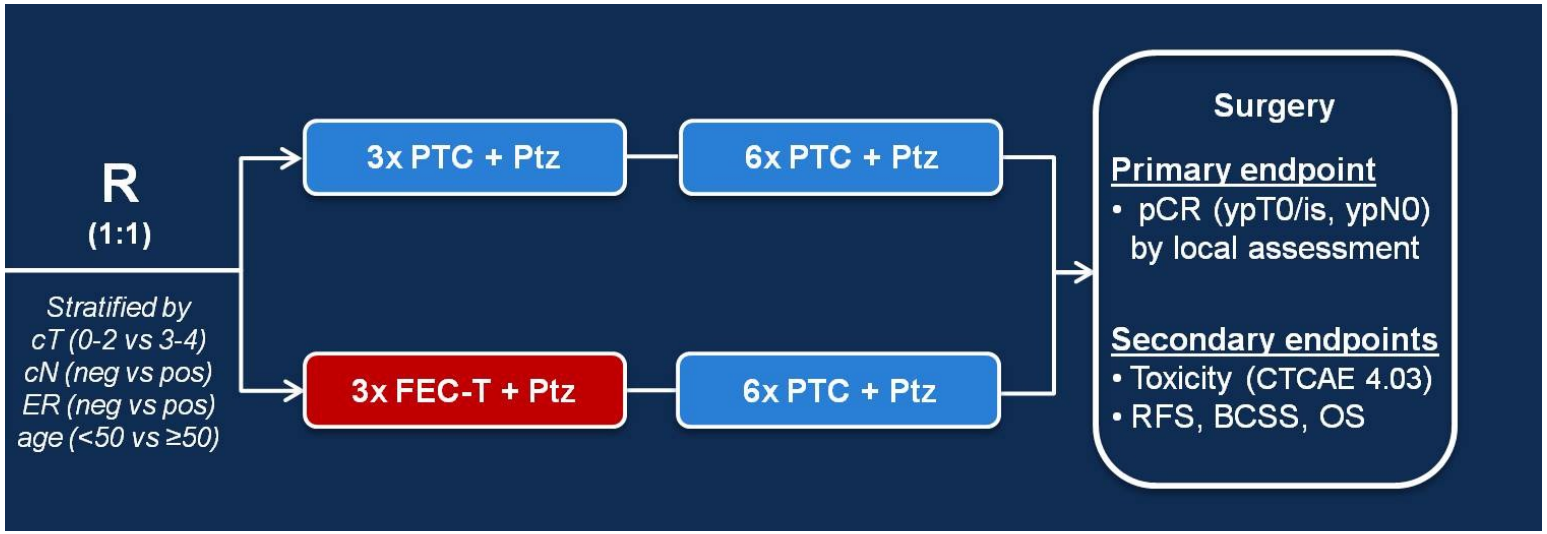
BCIRG006: 10.3 YRS FOLLOW-UP

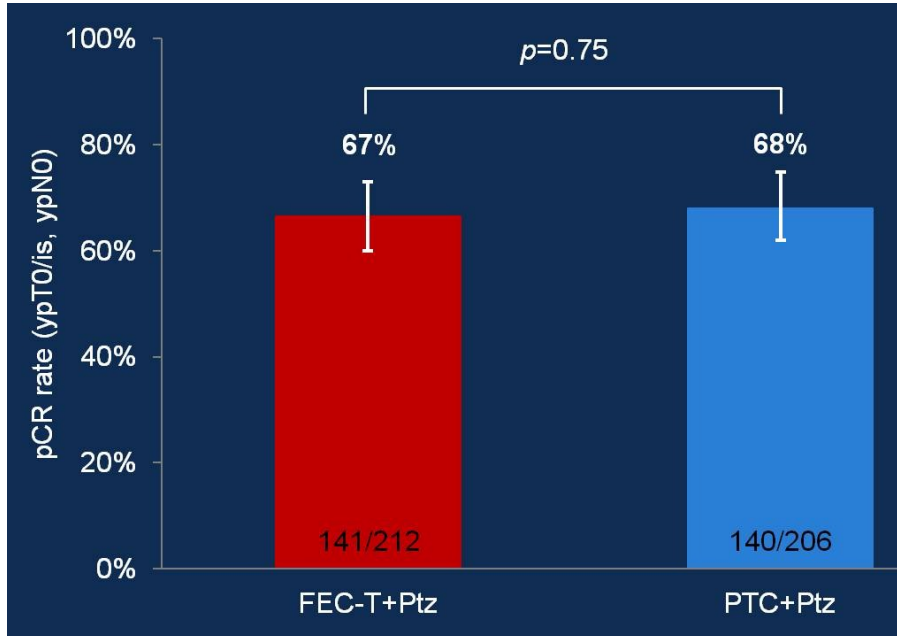
Outcome	AC → T (n = 1073)	AC → TH (n = 1074)	TCH (n = 1075)
DFS, % (n/N) HR (95% CI)	67.9 (328/1073) 1	74.6 (269/1074) 0.72 (0.61-0.85); *P* < .0001	73.0 (279/1075) 0.77 (0.65-0.90); *P* = .0011
OS, % (n/N) HR (95% CI)	78.7 (203/1073) 1	85.9 (141/1074) 0.63 (0.51-0.79); *P* < .0001	83.3 (167/1075) 0.76 (0.62-0.93); *P* = .0075
DFS in LN+ pts, % (n/N) HR (95% CI)	62.2 (265/764) 1	69.6 (217/764) 0.72 (0.61-0.87); *P* < .001	68.4 (224/766) 0.75 (0.63-0.90); *P* = .0018

TCH ASSOCIATED WITH LESS CARDIAC TOXICITY AND NUMERICALLY FEWER CASES OF SECONDARY LEUKEMIA

Slamon D et al. SABCS 2015. Abstract S5-05.

SUBSTITUTING ANTHRACYCLINE WITH TAXANE: TRAIN-2

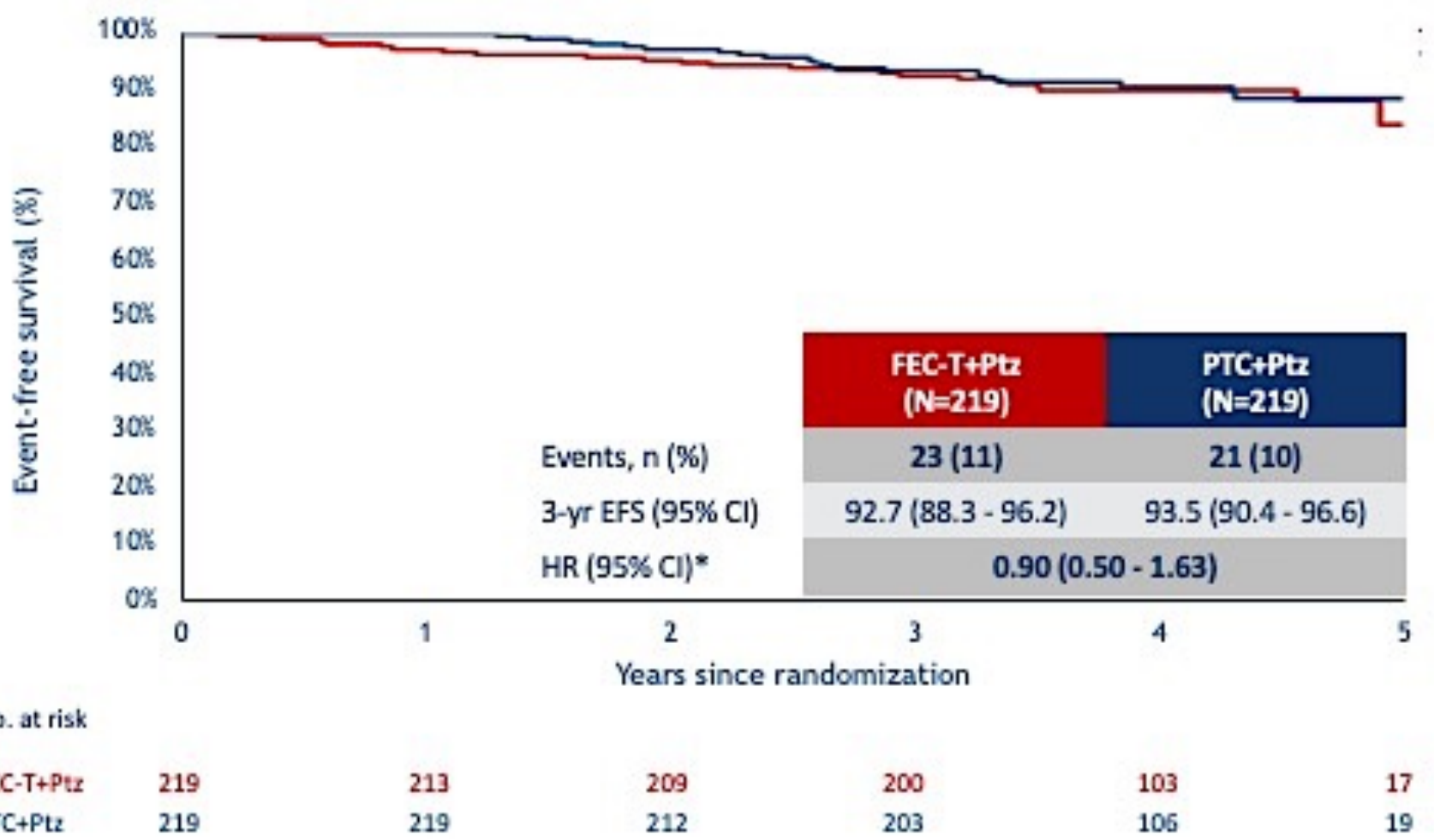




- 64% node positive, 42% HR negative
- pCR was consistent across all subgroups
- More pts completed 1 year trastuzumab in PTC/Ptz arm (97% vs 89%)
- Significantly more grade 3/4 febrile neutropenia (10% vs 1%) in anthracycline arm

Van Ramshorst MS, et al. ASCO 2017. Abstract 507.
Van Ramshorst MS, et al. *Lancet Oncol*. 2018;19(12):1630-1640.

TRAIN-2: EFS



- Significantly less cardiac toxicity PTCPtz
- 2 leukemia in FEC-arm

Van der Voort A et al. ASCO 2020. Abstract 501.

ANTHRACYCLINE CAN BE SUBSTITUTED WITH TAXANE-BASED HER2 DIRECTED THERAPY

- BCIRG006 and TRAIN-2 demonstrate similar long term outcomes with taxane-based therapy as with anthracycline-based therapy, even in high risk node-positive patients
- Less cardiac toxicity and numerically less leukemia
- Standard approach is TCH(P) for stage 2/3 HER2+ disease
- Hard to justify use of anthracyclines in era of HER2-directed therapies

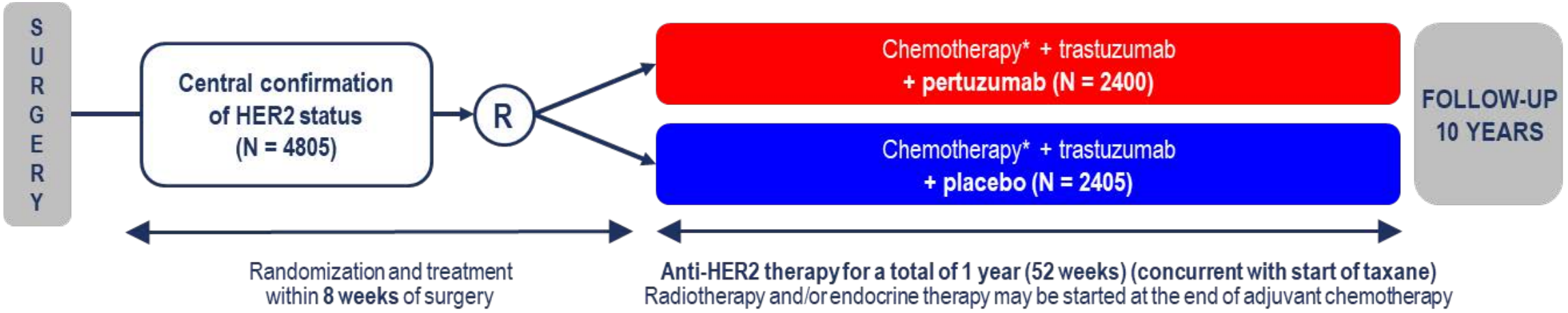
CAN WE ADD THERAPY TO IMPROVE OUTCOMES?

NEOADJUVANT PERTUZUMAB/TRASTUZUMAB (3 REGIMENS FDA APPROVED 9/2013)

	NEOSPHERE[1]	TRYPHAENA[2]	TRYPHAENA[2]
Treatment	Pertuzumab, Trastuzumab, Docetaxel THP x 4 FEC x 3 post-op)	Docetaxel/Carbo/ Trastuzumab/ Pertuzumab TCHP x 6	 FEC x 3 → THP x 3
N	107	77	75
ypT0/is ypN0 (%)	39.3	63.6	54.6

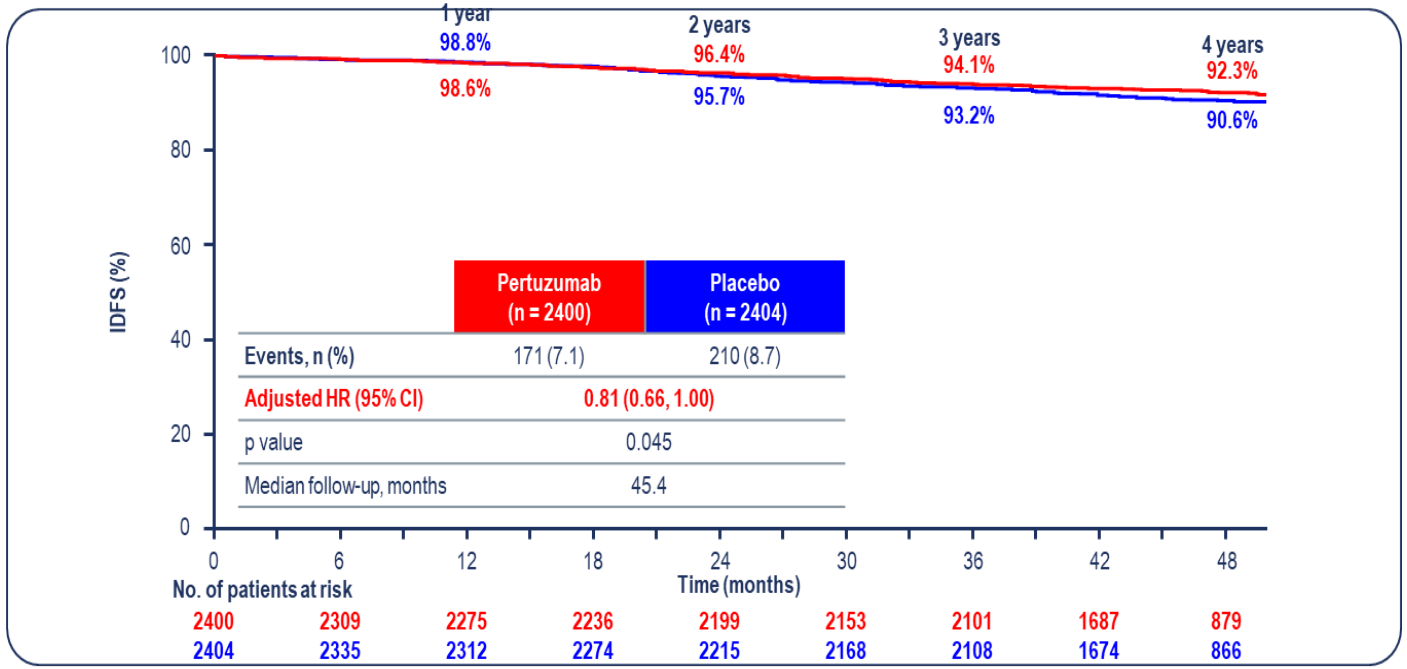
1. Gianni L, et al. *Lancet Oncol*. 2012;13(1):25-32.
2. Schneeweiss A, et al. *Ann Oncol*. 2013;24(9):2278-84.

Can we increase the efficacy of adjuvant trastuzumab? APHINITY Trial



- **Primary endpoint:** IDFS (APHINITY definition differs from STEEP definition)
- **Secondary endpoints:** IDFS with 2nd primary non-breast primary cancers included, DFS, OS, RFI, DRFI, safety, and HRQoL

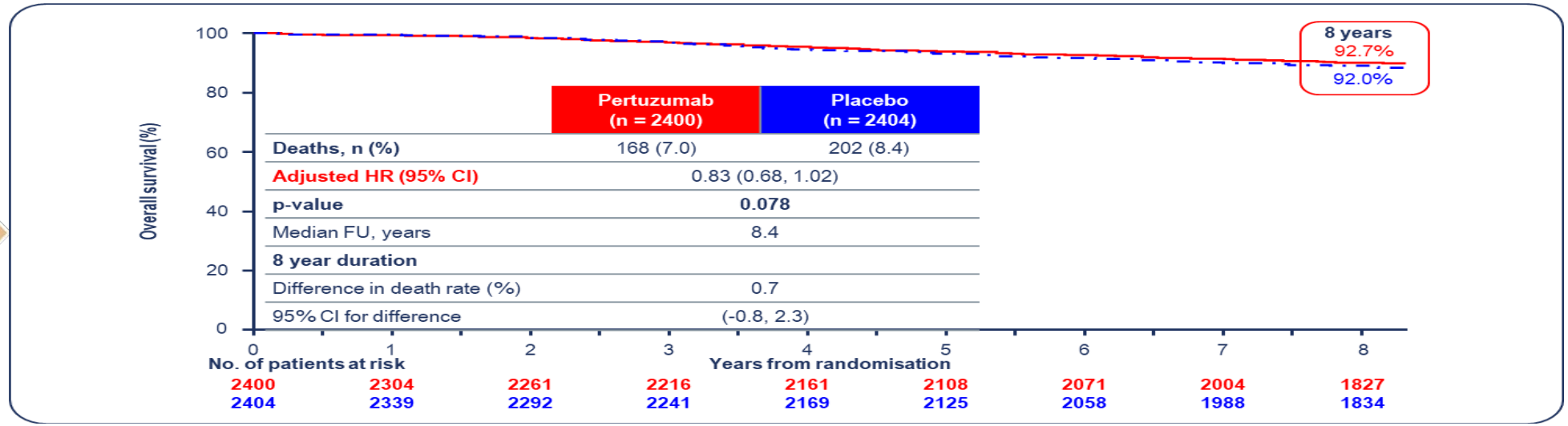
Node involvement	
Node negative	38%
1-3 nodes	37%
≥4 nodes	25%



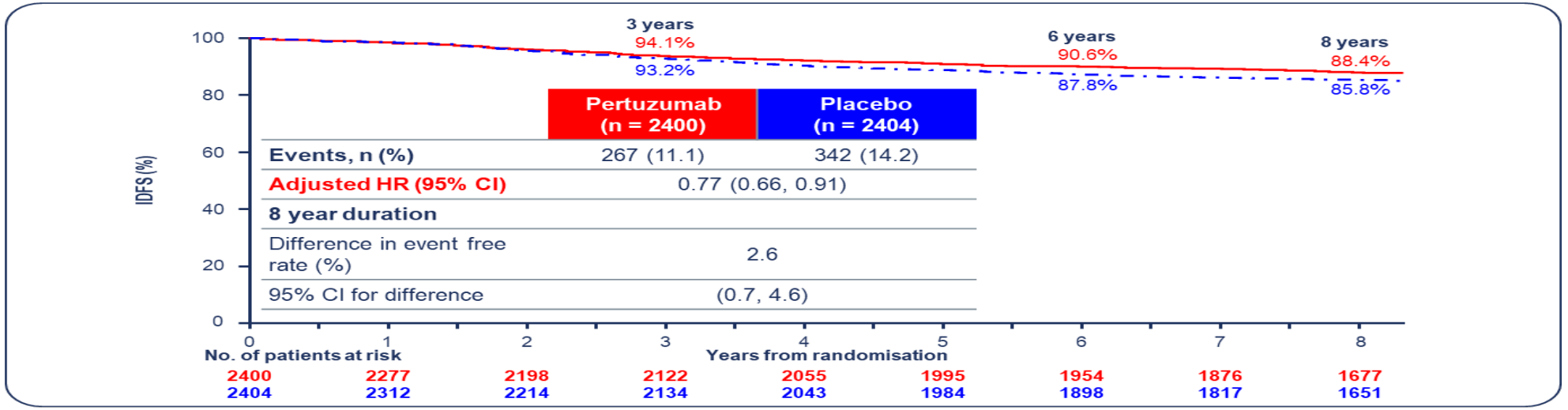
Adapted from von Minckwitz G, et al. *N Engl J Med*. 2017;377(2):122-131.
Slide courtesy of Javier Cortes

Updated results of APHINITY at 8.4 years median follow up

3rd interim OS analysis CCOD: Jan 10 2022



Updated Descriptive IDFS Analysis by Treatment Regimen



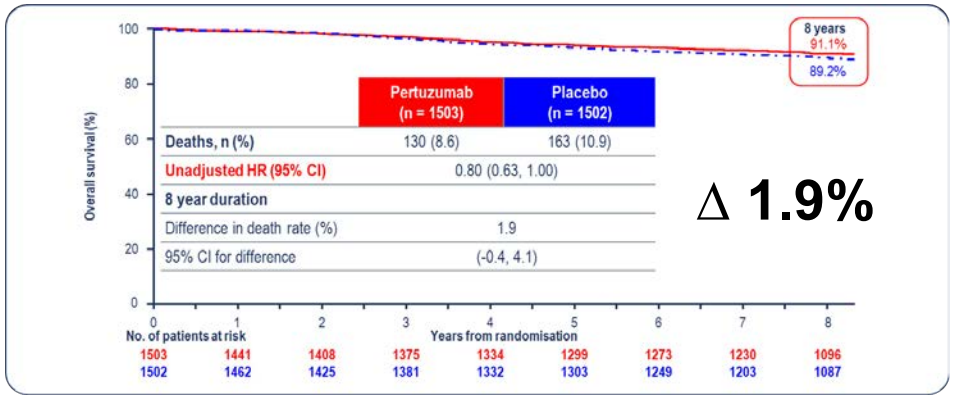
Loibl S, et al. ESMO Virtual Plenary 2022.

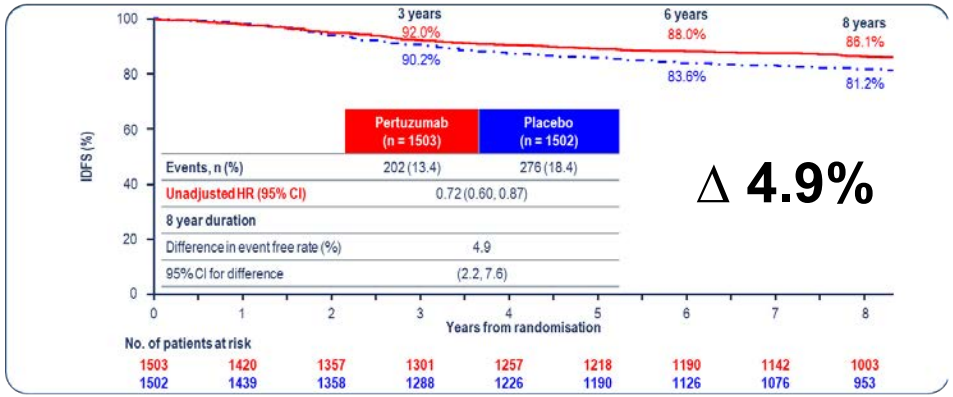
Updated results of APHINITY at 8.4 years median follow up

3rd interim OS analysis CCOD: Jan 10 2022

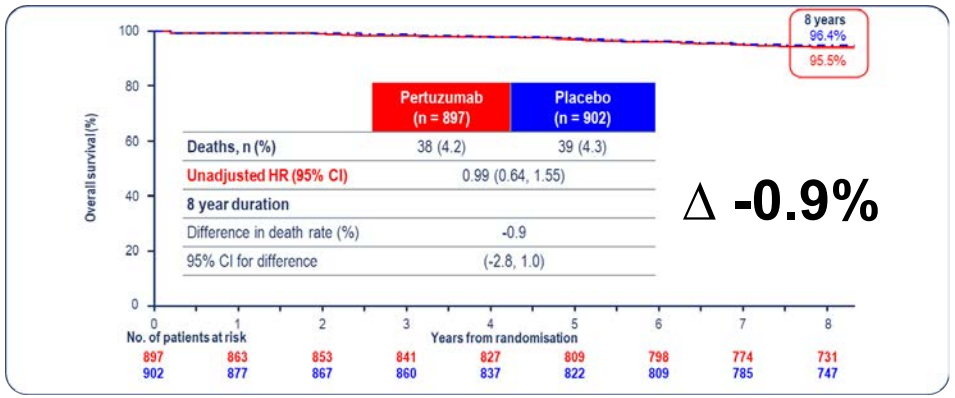
Updated Descriptive IDFS Analysis by Treatment Regimen

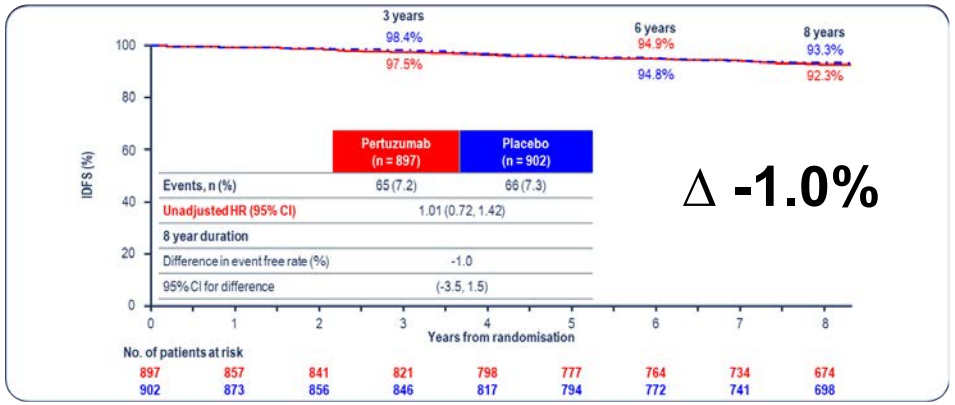
Node positive





Node negative





Loibl S, et al. ESMO Virtual Plenary 2022.

Updated results of APHINITY at 8.4 years compared with at 4 and 6 years median follow up

	4 yr IDFS (TP vs T)	4 yr IDFS Δ	6 yr IDFS (TP vs T)	6 yr IDFS Δ	8 yr IDFS (TP vs T)	8 yr IDFS Δ
ITT	92.3 vs 90.6%	1.7%	90.6 vs 87.8%	2.8%	88.4 vs 84.8%	2.6%
N0	96.7 vs 96.2%	0.5%	95.0 vs 94.9%	0.1%	92.3 vs 93.3	-1%
N+	**89.9 vs 86.7%**	**3.2%**	**87.9 vs 83.4%**	**4.5%**	**86.1 vs 81.2%**	**4.9%**
ER/PR+	93.0 vs 91.6%	1.4%	91.2 vs 88.2%	3%	88.9 vs 86.1%	2.8%
ER/PR-	91.0 vs 88.7%	2.3%	89.5 vs 87.0%	2.5%	87.5 vs 85.2%	2.3%

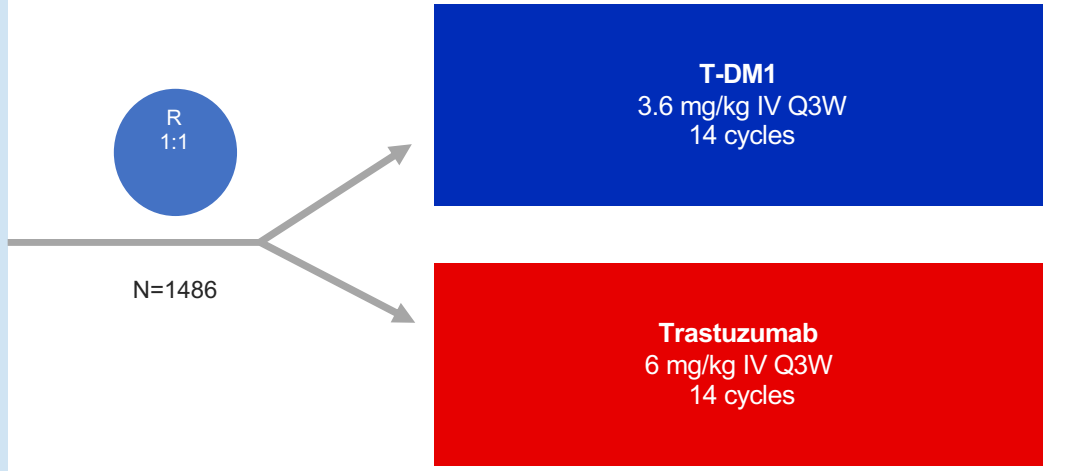
Von Minckwitz G, et al. *N Engl J Med*. 2017;377(2):122-131; Piccart M, et al. *J Clin Oncol*. 2021;39(13):1448-1457; Loibl S, et al. ESMO Virtual Plenary 2022.

WHEN DO WE THEN GIVE PERTUZUMAB?

- Most patients with HER2+ tumors >2cm or clinically node positive disease receive preoperative therapy
- The addition of pertuzumab improves pCR, but will not improve DFS in *all* patients (ie. not node negative patients)
- Administration of preoperative pertuzumab to all patients may result in some overtreatment, but challenging to discern which patients need pertuzumab upfront
- Adjuvant HP is reasonable for pts achieving pCR given APHINITY administered one year of HP therapy, given uncertainty of upfront nodal status in pts receiving preop therapy

KATHERINE: STUDY DESIGN

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery

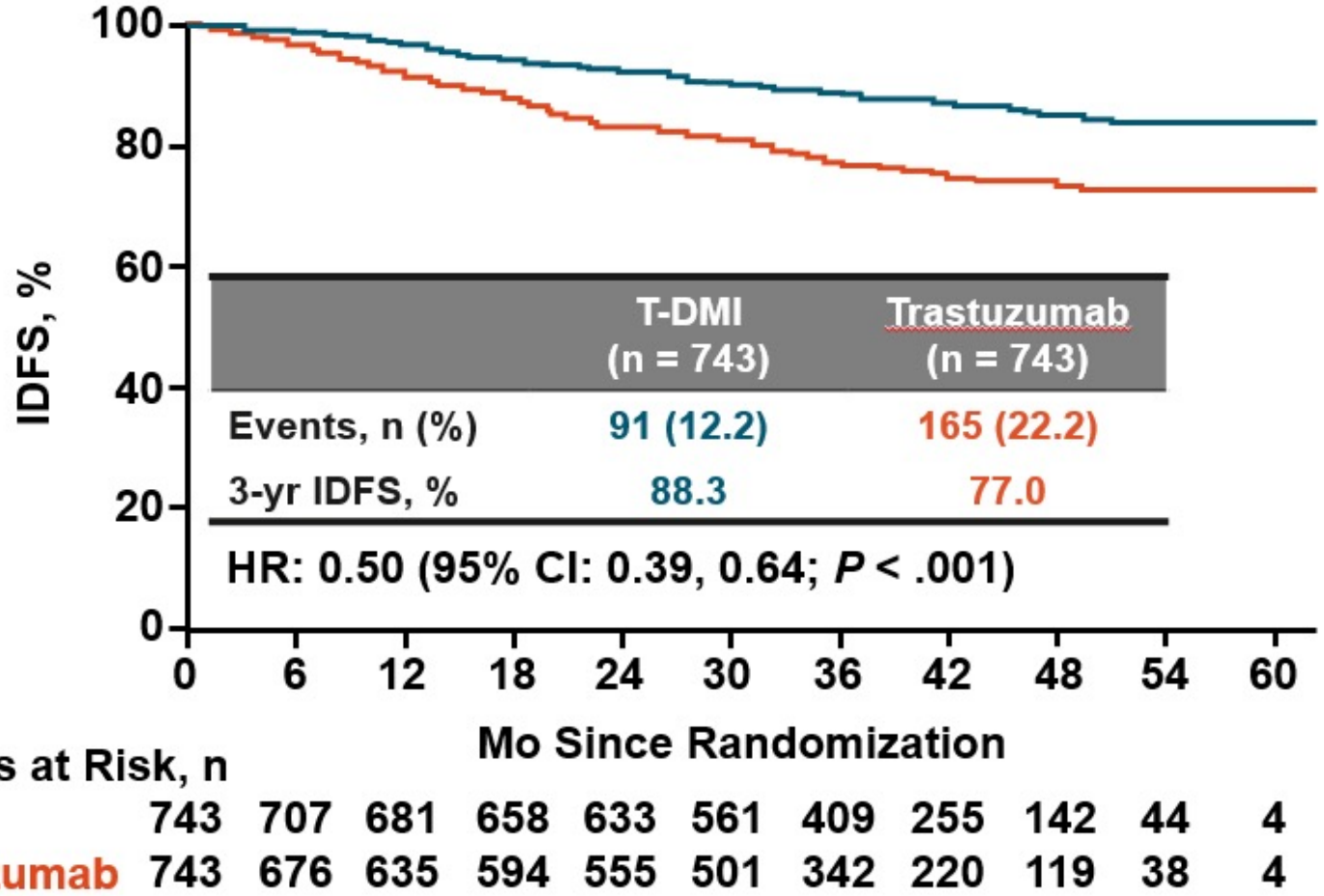


Radiation and endocrine therapy per protocol and local guidelines

Stratification factors:
- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

Geyer C, et al. SABCS 2018. Abstract GS1-10.
von Minckwitz G, et al. *N Engl J Med.* 2019;380(7) 617-628.

RESPONSE TO NEOADJUVANT TREATMENT CLEARLY IDENTIFIES HIGH RISK PATIENTS FOR TREATMENT WITH T-DM1 (KATHERINE)

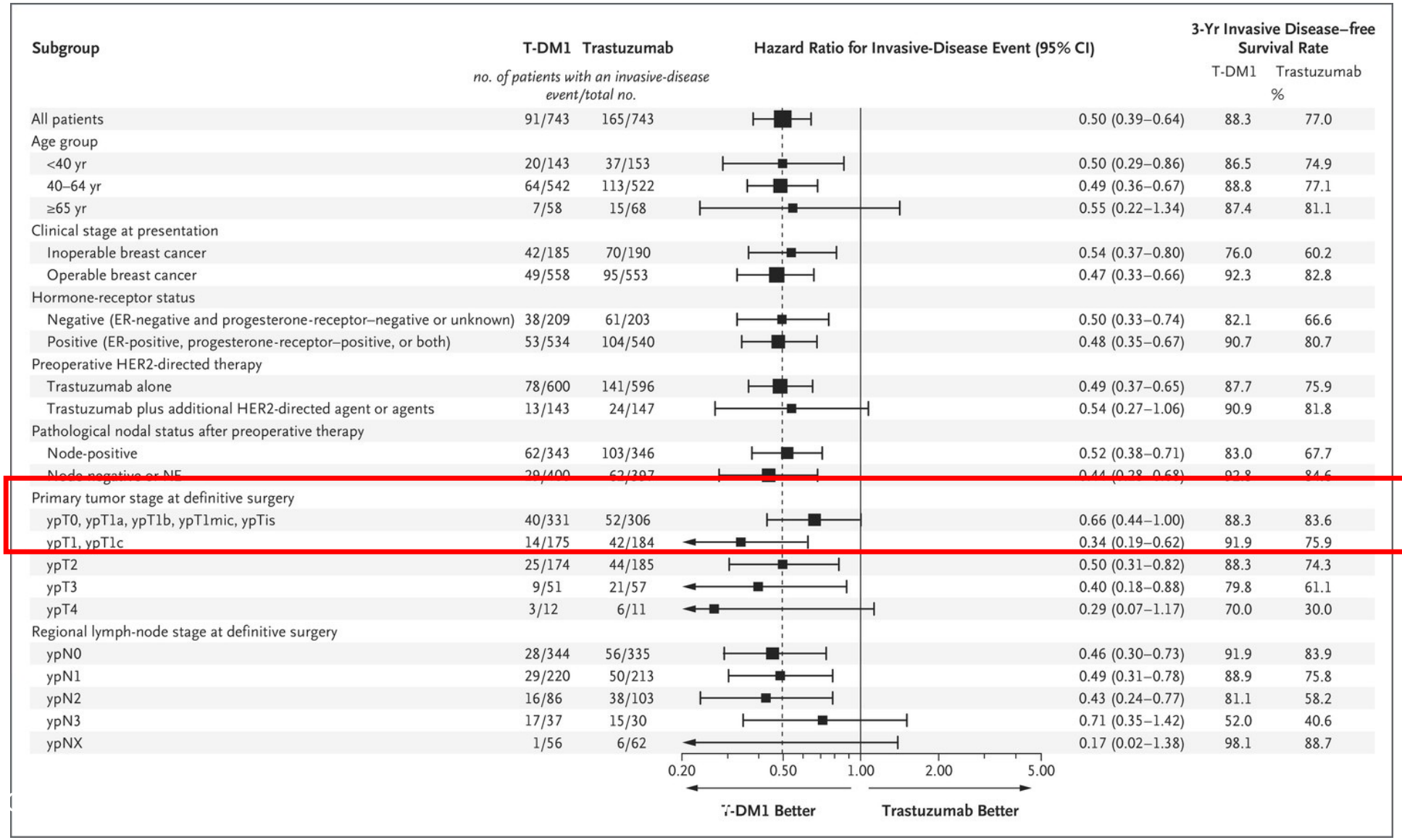


First IDFS Event, %	T-DM1	T
Any	12.2	22.2
Distant recurrence	10.5*	15.9†
Locoregional recurrence	1.1	4.6
Contralateral breast cancer	0.4	1.3
Death without prior event	0.3	0.4

CNS events: *5.9% vs †4.3%.

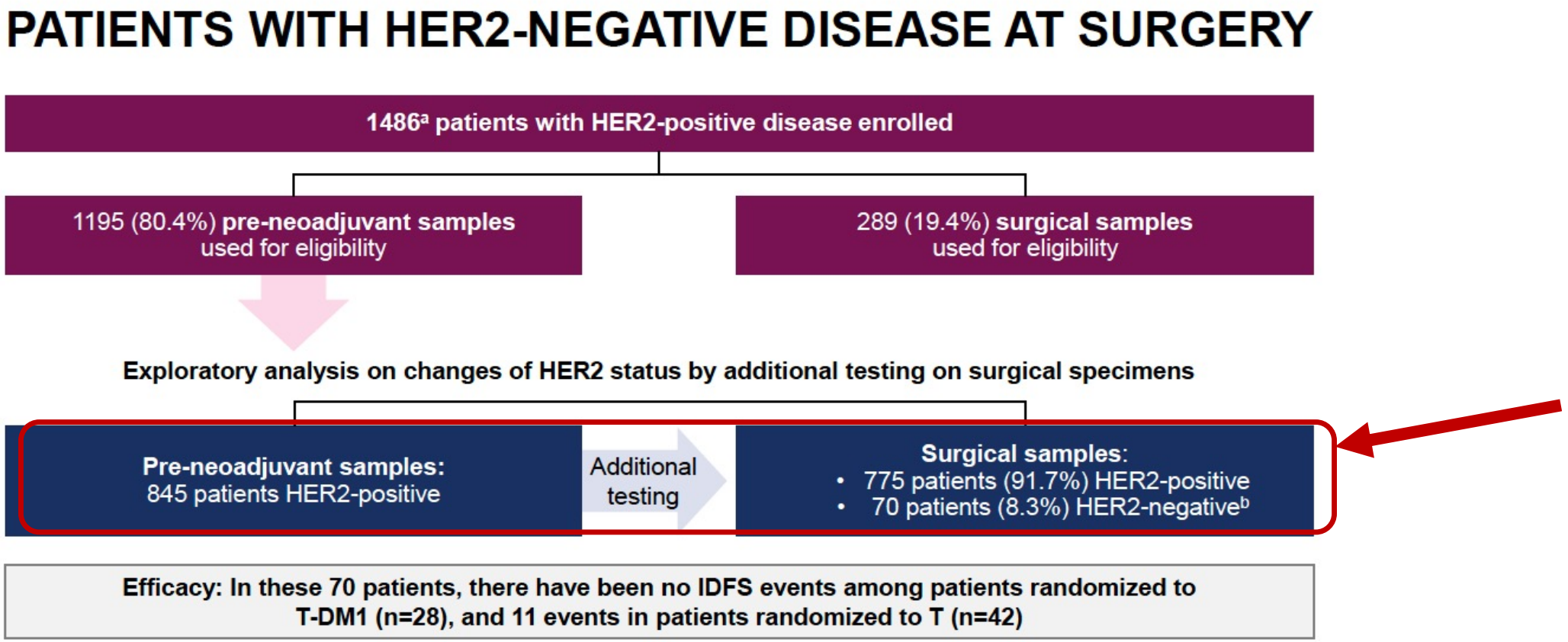
Geyer C, et al. SABCS 2018. Abstract GS1-10.
von Minckwitz G, et al. *N Engl J Med.* 2019;380(7) 617-628.

KATHERINE:
All benefit even those with small amounts of residual tumor



Subgroup	T-DM1 (no. of patients with an invasive-disease event/total no.)	Trastuzumab (no. of patients with an invasive-disease event/total no.)	Hazard Ratio for Invasive-Disease Event (95% CI)	3-Yr Invasive Disease–free Survival Rate, T-DM1 (%)	3-Yr Invasive Disease–free Survival Rate, Trastuzumab (%)
All patients	91/743	165/743	0.50 (0.39–0.64)	88.3	77.0
Age group					
<40 yr	20/143	37/153	0.50 (0.29–0.86)	86.5	74.9
40–64 yr	64/542	113/522	0.49 (0.36–0.67)	88.8	77.1
≥65 yr	7/58	15/68	0.55 (0.22–1.34)	87.4	81.1
Clinical stage at presentation					
Inoperable breast cancer	42/185	70/190	0.54 (0.37–0.80)	76.0	60.2
Operable breast cancer	49/558	95/553	0.47 (0.33–0.66)	92.3	82.8
Hormone-receptor status					
Negative (ER-negative and progesterone-receptor–negative or unknown)	38/209	61/203	0.50 (0.33–0.74)	82.1	66.6
Positive (ER-positive, progesterone-receptor–positive, or both)	53/534	104/540	0.48 (0.35–0.67)	90.7	80.7
Preoperative HER2-directed therapy					
Trastuzumab alone	78/600	141/596	0.49 (0.37–0.65)	87.7	75.9
Trastuzumab plus additional HER2-directed agent or agents	13/143	24/147	0.54 (0.27–1.06)	90.9	81.8
Pathological nodal status after preoperative therapy					
Node-positive	62/343	103/346	0.52 (0.38–0.71)	83.0	67.7
Node-negative or NE	29/400	62/397	0.44 (0.28–0.68)	92.8	84.6
Primary tumor stage at definitive surgery					
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	40/331	52/306	0.66 (0.44–1.00)	88.3	83.6
ypT1, ypT1c	14/175	42/184	0.34 (0.19–0.62)	91.9	75.9
ypT2	25/174	44/185	0.50 (0.31–0.82)	88.3	74.3
ypT3	9/51	21/57	0.40 (0.18–0.88)	79.8	61.1
ypT4	3/12	6/11	0.29 (0.07–1.17)	70.0	30.0
Regional lymph-node stage at definitive surgery					
ypN0	28/344	56/335	0.46 (0.30–0.73)	91.9	83.9
ypN1	29/220	50/213	0.49 (0.31–0.78)	88.9	75.8
ypN2	16/86	38/103	0.43 (0.24–0.77)	81.1	58.2
ypN3	17/37	15/30	0.71 (0.35–1.42)	52.0	40.6
ypNX	1/56	6/62	0.17 (0.02–1.38)	98.1	88.7

KATHERINE:
What about those with HER2- residual disease?



TREAT PATIENTS WITH HER2+ PRIMARY TUMORS WITH ADJUVANT T-DM1

EVEN IF RESIDUAL DISEASE IS HER2-NEGATIVE

Loibl S, et al. ESMO Breast 2020.

COMPASSHER2 TRIALS

Eligibility:
Stage II or IIIA HER2+ BC (T2-3, N0-2)

- cN0 eligible if ≥ 2.0 cm
- cN1-2 eligible ≥ 1.5cm
- ER+ and ER- eligible

REGISTRATION

Preoperative Phase: all patients

THP x 4 Cycles
Paclitaxel qwk x12
OR
Docetaxel q3 wk x4
with
Trastuzumab (H)
& Pertuzumab (P) q3 wk x4

* nab-pacl allowed

SURGERY

pCR (ypT0/Tis ypN0) *40%*

No pCR *60%*

Arm A: pCR (no invasive disease)

EA1181
CompassHER2-pCR

- Complete 1 yr HP
- Radiation and endocrine Rx (if appropriate)

ECOG-ACRIN cancer research group
Reshaping the future of patient care

A011801
CompassHER2-RD

Alliance for Clinical Trials in Oncology

Grp 1: pre-op THP-> AC, Cb/HP x 4
Grp 2: pre-op TCHP, *AC-THP* -> no further chemo

Eligibility
HER2+ RD
ER- & ER+
(ER+ must be N+)
(~30% of A011801 expected to come from EA1181)

Registration

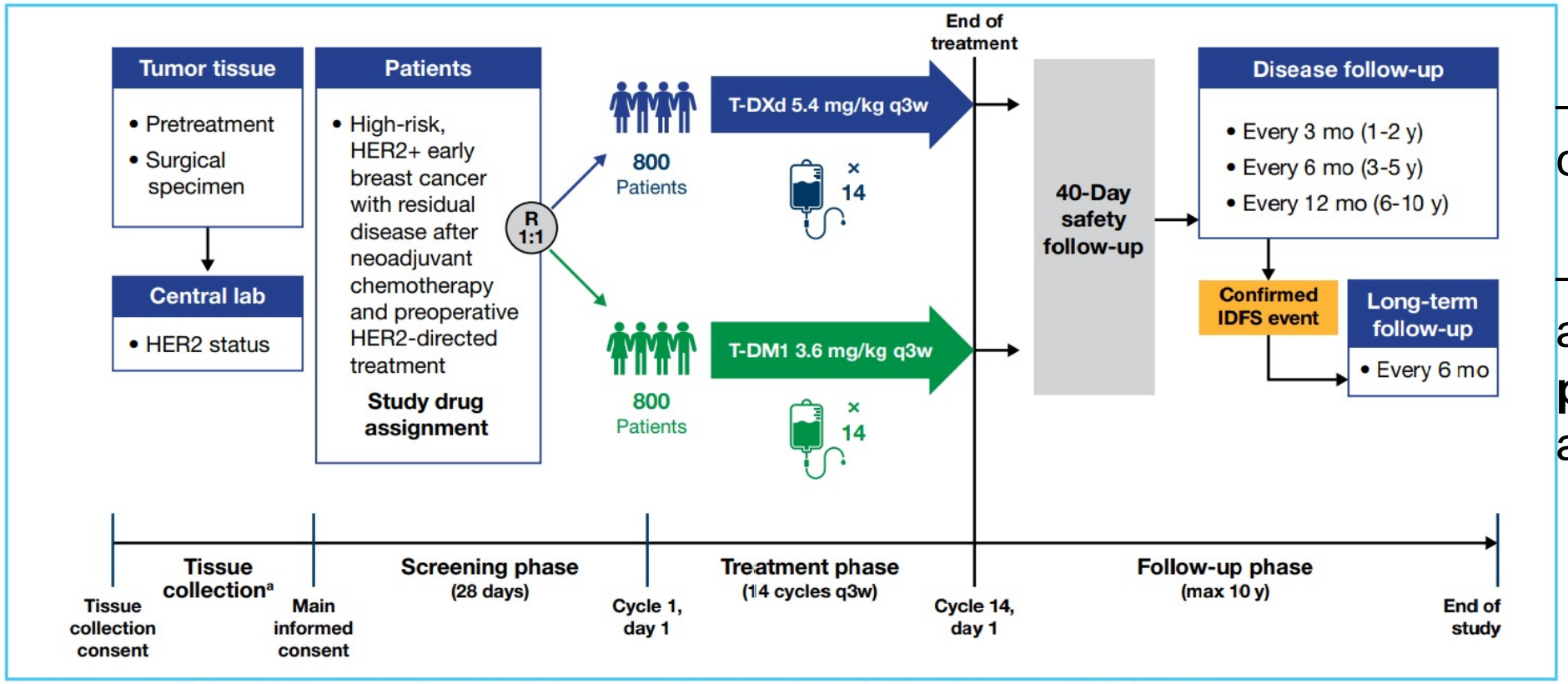
R

T-DM1 x 14 doses

T-DM1/tucatinib x 14 doses

DESTINY-Breast05 phase 3 trial

DESTINY-Breast05: A Multicenter, Open-Label, Randomized Phase 3 Trial Comparing the Efficacy and Safety of T-DXd vs T-DM1 in High-Risk Patients With HER2-Positive, Residual, Invasive Breast Cancer After Neoadjuvant Therapy (N≈1600)



HER2, human epidermal growth factor receptor 2; IDFS, invasive disease–free survival; lab, laboratory; max, maximum; q3w, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a] Patients may move into the main screening phase before HER2 status results are available from the central laboratory.

– **Inoperable** breast cancer at presentation

– Operable breast cancer at presentation with **node–positive (ypN1-3) disease** after neoadjuvant therapy

Geyer et al. SABCS 2020. Abstract OT-03-01.

Escalation based on clinical risk: DESTINY-Breast11 Trial

Population

HER2+ EBC

HR+ or HR-

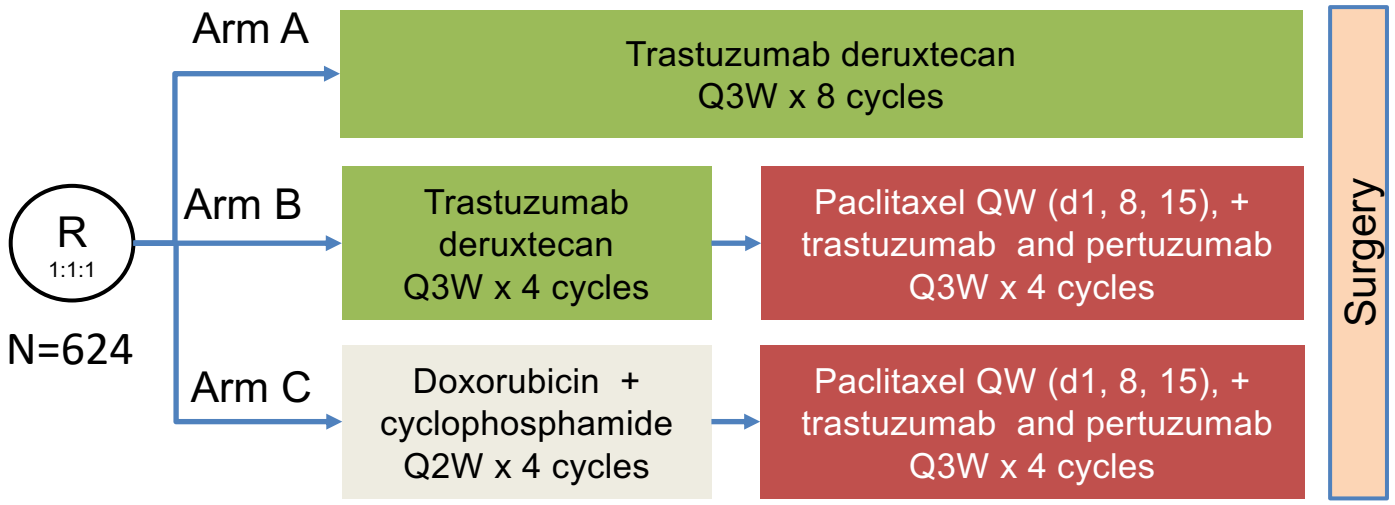
High-risk defined as one of the following:

- $T_xN_{1-3}M_0$
- $T_{3-4}N_xM_0$
- Inflammatory BC

Stratification factors:

- HR Status
  - HR+ vs HR-
- HER2 IHC
  - IHC3+ vs Other

Study Design



Endpoints

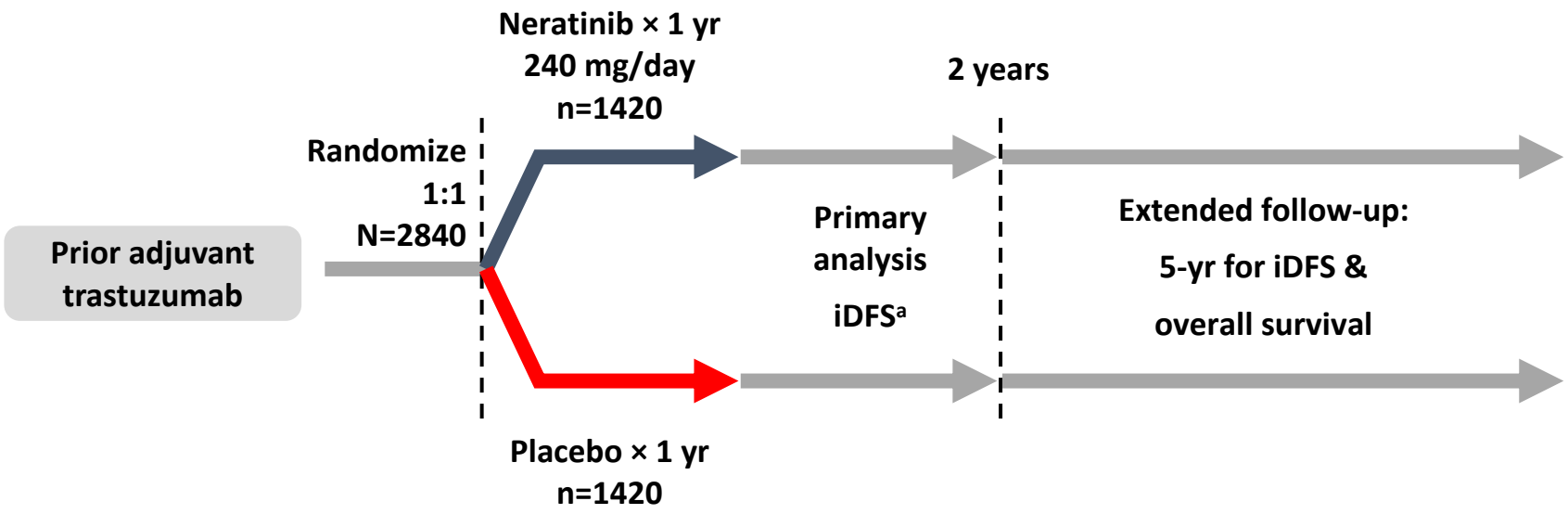
Primary Endpoint:

- pCR (ypT0/Tis ypN0)

Secondary Endpoints:

- pCR (ypT0 ypN0)
- EFS
- IDFS
- OS
- HRQoL
- Safety
- PK and immunogenicity

ADDING NERATINIB: EXTENET STUDY



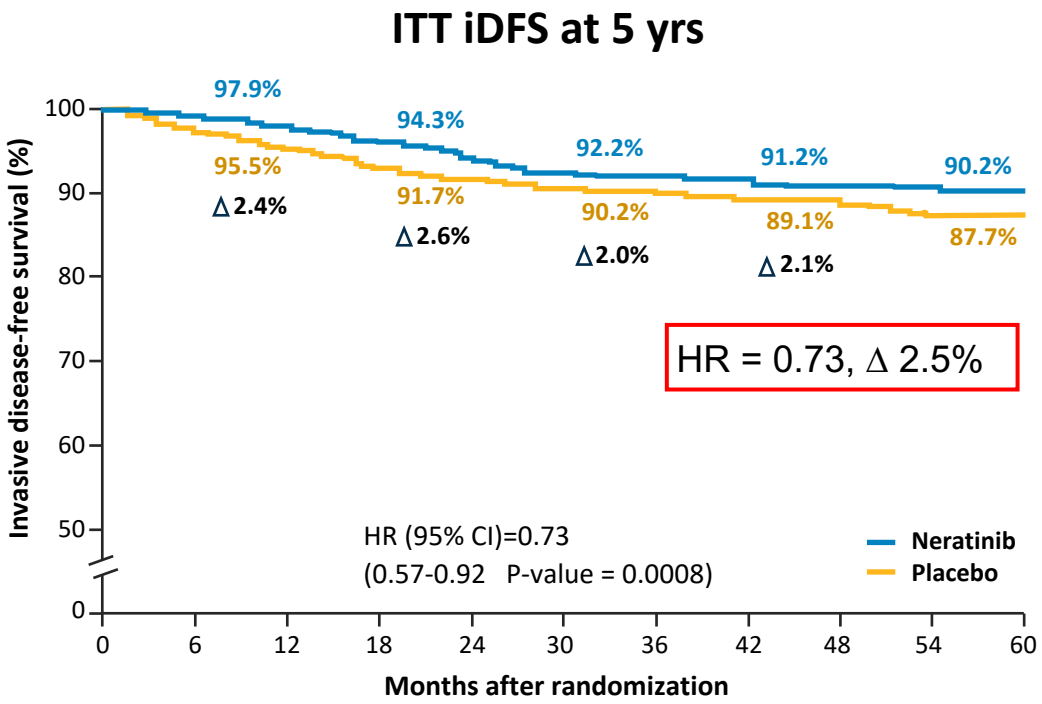
Primary endpoint: invasive disease-free survival (iDFS)[a]

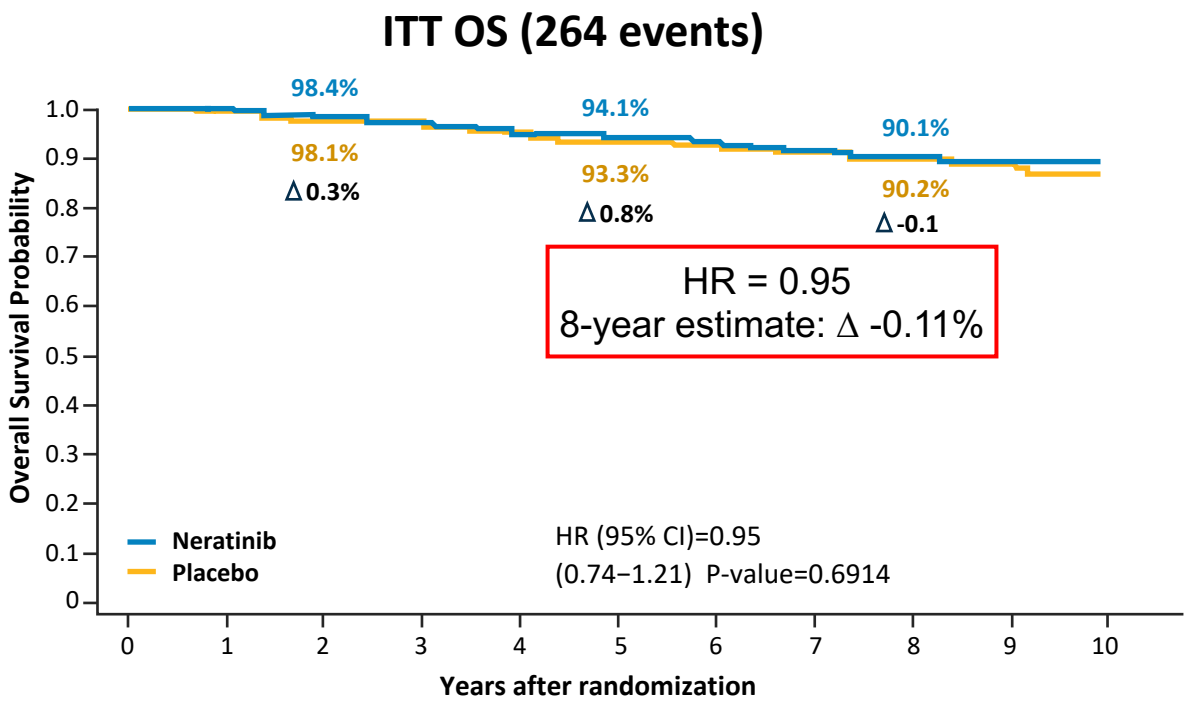
Secondary endpoints: overall survival, DFS-DCIS, distant DFS, time to distant recurrence, CNS metastases, safety,

Stratification: nodes 0, 1-3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab

Study blinded: Until primary analysis; OS remains blinded

ExteNET iDFS and OS Intent-To-Treat Population (N=2,840)





No. at risk

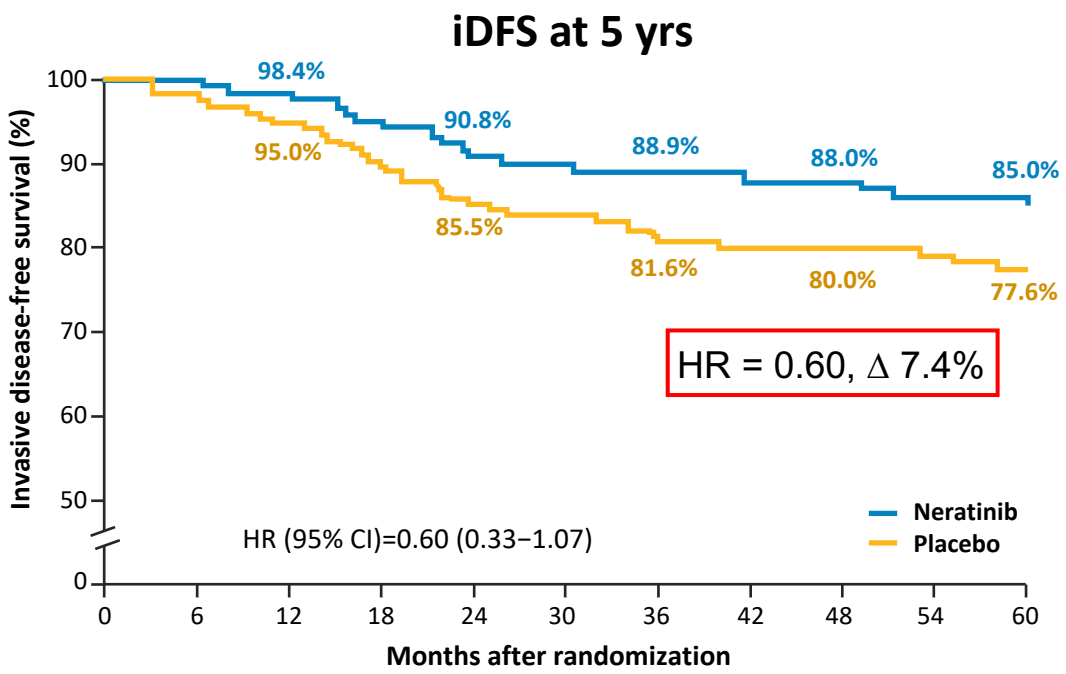
Neratinib	1420	1316	1272	1225	1106	978	965	949	938	920	885
Placebo	1420	1354	1298	1248	1142	1029	1011	991	978	958	927

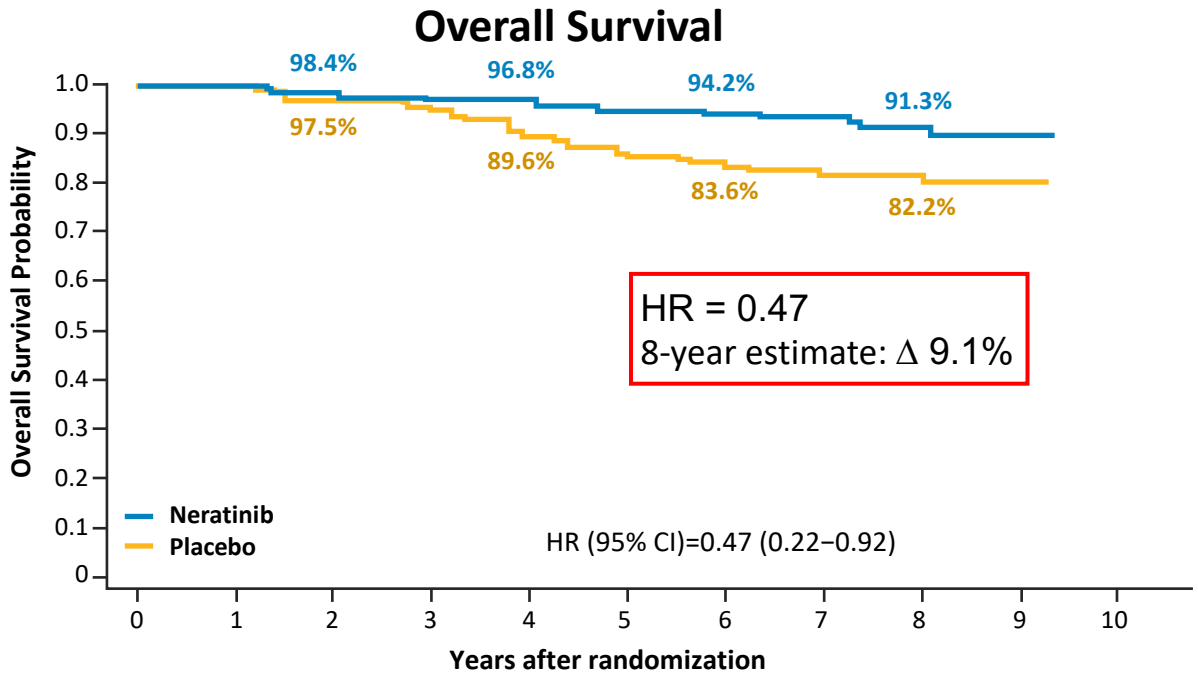
No. at risk

Neratinib	1420	1364	1309	1213	1118	1168	1123	1041	746	218	0
Placebo	1420	1384	1341	1249	1223	1199	1166	1086	796	221	0

Martin et al. *Lancet Oncol*. 2017;18(12):1688-1700.

ExteNET: No pCR Post Neoadjuvant Therapy HR+, ≤1 Year from Trastuzumab (N=295)





No. at risk

Neratinib	131	126	121	113	100	94	93	91	91	88	84
Placebo	164	159	151	143	125	107	103	99	99	98	94

No. at risk

Neratinib	131	126	121	116	113	110	106	100	60	14	0
Placebo	164	161	156	143	135	129	123	115	65	12	0

Chan A, et al. *Clin Breast Cancer*. 2021;21(1):80-91.e7.

WHEN SHOULD WE GIVE NERATINIB?

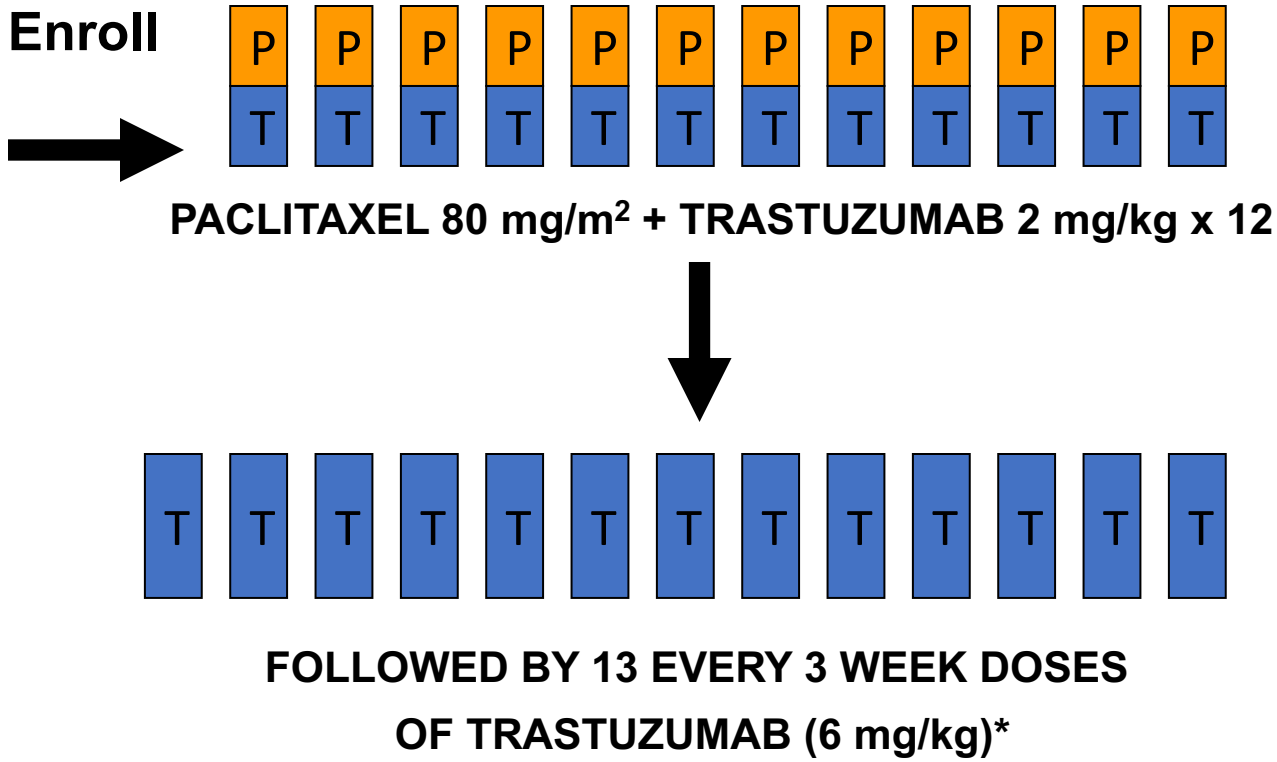
- Benefit seen in patients with high risk HR+ HER+ disease (larger benefit in patients with residual disease after preoperative therapy)
- Challenge is lack of data in patients who have previously received pertuzumab and/or T-DM1
- Must also weigh potential benefit with toxicity (~40% grade 3/4 diarrhea)
    - All patients should receive prophylactic anti-diarrheals (OR can consider a dose escalation approach)

CONSIDER NERATINIB IN HIGH RISK MULTI-NODE POSITIVE HR+ HER2+ PATIENTS AFTER COMPLETION OF HP or T-DM1

APT TRIAL: STUDY DESIGN

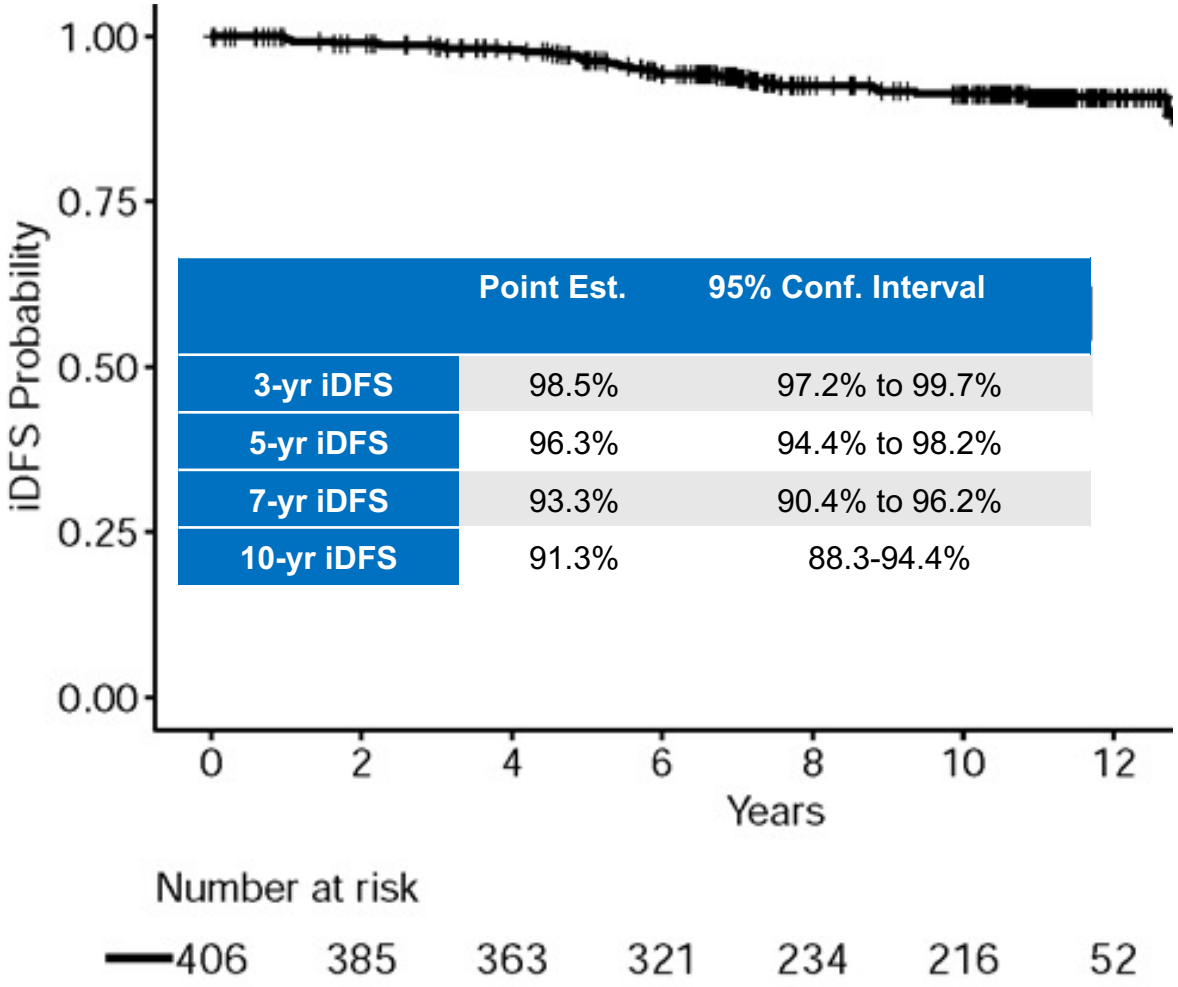
HER2+
ER+ or ER-
Node Negative
≤ 3 cm

Planned N=400



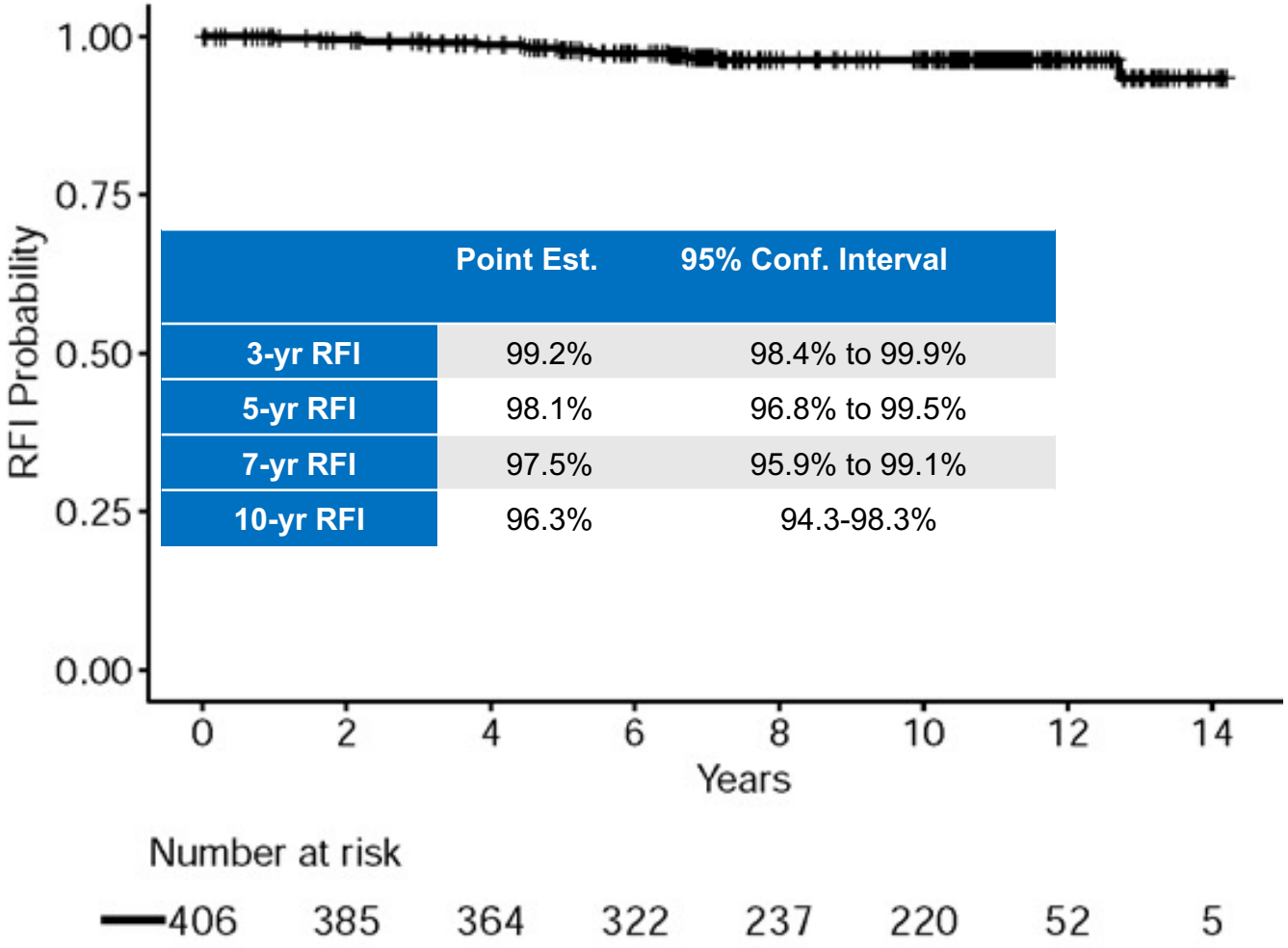
Tolaney SM et al. *N Engl J Med*. 2015;372(2):134-41.
Tolaney SM et al. *J Clin Oncol*. 2019;37(22):1868-1875.

APT: 10 year RESULTS



	Point Est.	95% Conf. Interval
3-yr iDFS	98.5%	97.2% to 99.7%
5-yr iDFS	96.3%	94.4% to 98.2%
7-yr iDFS	93.3%	90.4% to 96.2%
10-yr iDFS	91.3%	88.3-94.4%

6 Distant Events



	Point Est.	95% Conf. Interval
3-yr RFI	99.2%	98.4% to 99.9%
5-yr RFI	98.1%	96.8% to 99.5%
7-yr RFI	97.5%	95.9% to 99.1%
10-yr RFI	96.3%	94.3-98.3%

RFI Events=
- **Invasive Local/Regional Recurrence**
- **Distant Recurrence**
- **Death from Breast Cancer**

Tolaney SM et al SABCS 2022

Does T-DM1 have a role for Stage I HER2+ Disease? ATEMPT Trial

Key Eligibility Criteria

- Stage 1 HER2+ breast cancer
  - HER2 centrally tested (ASCO CAP 2013 guidelines)
- N0 or N1mic
- Left Ventricular EF ≥ 50%
- No prior invasive breast cancer
- ≤90 days from last surgery

N = 497

R 3:1

3

1

N = 383

T-DM1

3.6 mg/kg IV q3 wks x 17

N = 114

TH

Paclitaxel 80 mg/m^2 IV + Trastuzumab 2 mg/kg IV wkly x12 → Trastuzumab 6 mg/kg every 3 wks x13

Stratification factors:

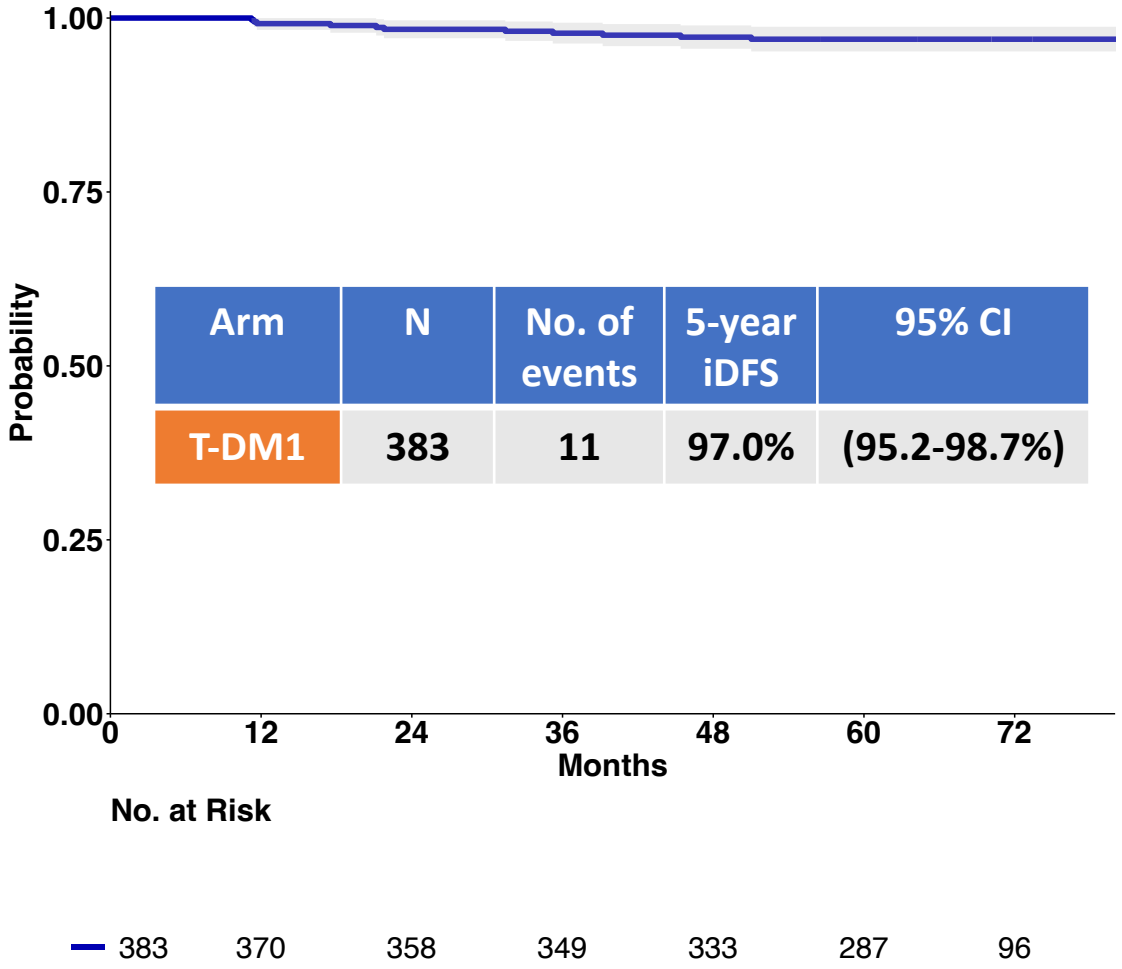
- Age (<55, ≥55)
- Planned radiation (Yes/No)
- Planned hormonal therapy (Yes/No)

*Radiation and endocrine therapy could be initiated after 12 weeks on study therapy

Tolaney S et al. SABCS 2019. GS1-05.

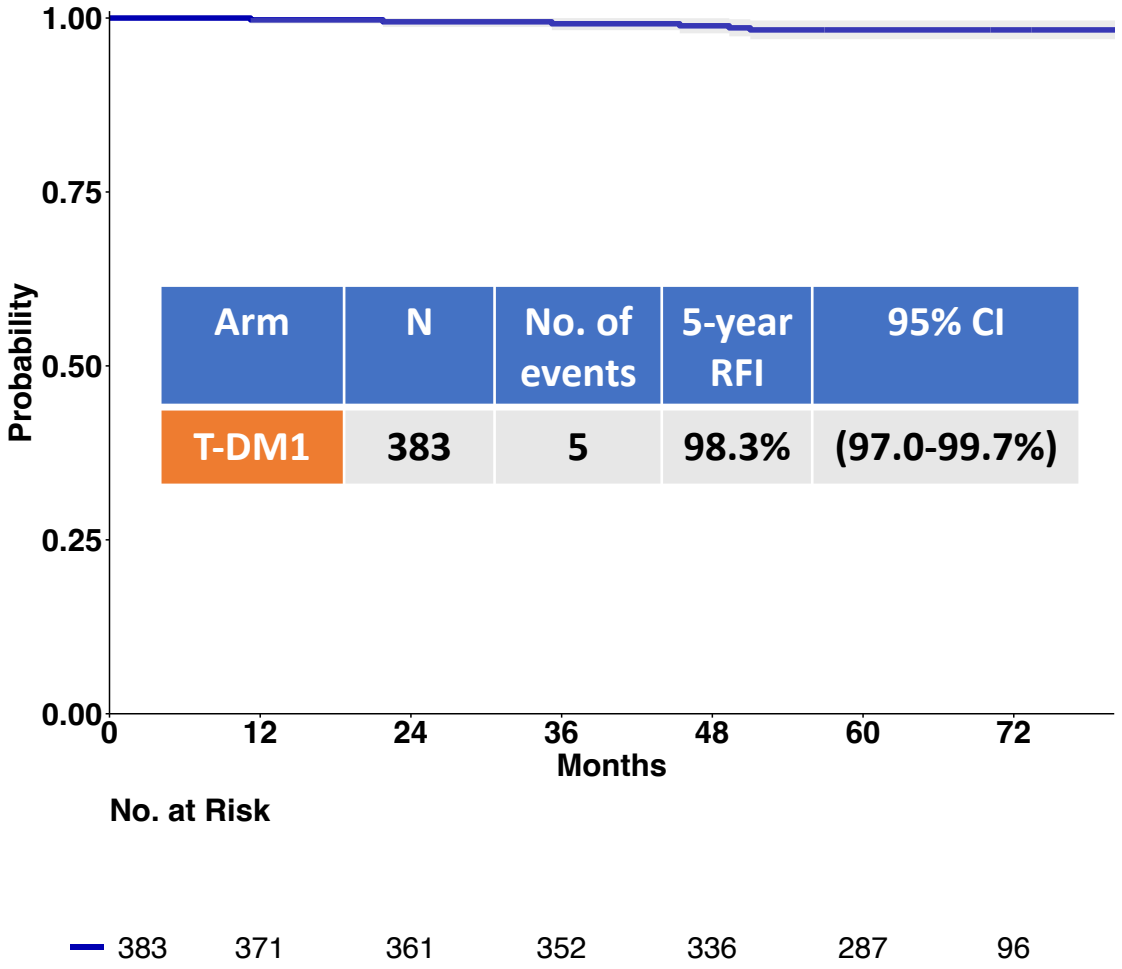
5-year outcomes with T-DM1: iDFS and RFI

5-year iDFS



Arm	N	No. of events	5-year iDFS	95% CI
T-DM1	383	11	97.0%	(95.2-98.7%)

5-year RFI



Arm	N	No. of events	5-year RFI	95% CI
T-DM1	383	5	98.3%	(97.0-99.7%)

3 Distant Events

ATEMPT: CLINICALLY RELEVANT TOXICITY

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

p=0.91

Tolaney S et al. SABCS 2019. GS1-05.

WHICH PATIENTS WITH STAGE I HER2+ DISEASE SHOULD GET T-DM1?

- **T-DM1 for 1 year was associated with very few recurrences in patients with Stage I HER2+ disease**
  - **3 year DFS 97.7% (95% CI: 96.2-99.3), RFI 99.1% (95% CI: 98.1-100)**
- **T-DM1 was not associated with significantly fewer clinically relevant toxicities than TH**
- **Not all toxicities are captured in the CRT endpoint, including alopecia, and patient reported outcomes (PROs) should be considered when assessing tolerability (generally favored T-DM1)**
- **Given the low event rate seen in this trial, T-DM1 may be an alternative to TH**

Which stage I HER2+ breast cancer patients should get systemic therapy (TH or T-DM1)?

Hormone Receptor Status	<0.5 cm	0.5-1.0cm	>1.0-2.0cm
HR+	NO	YES	YES
HR-	Sometimes*	YES	YES

*if high risk features (high grade with LVI), and relatively larger size

Should small HER2+ tumors get preop therapy?

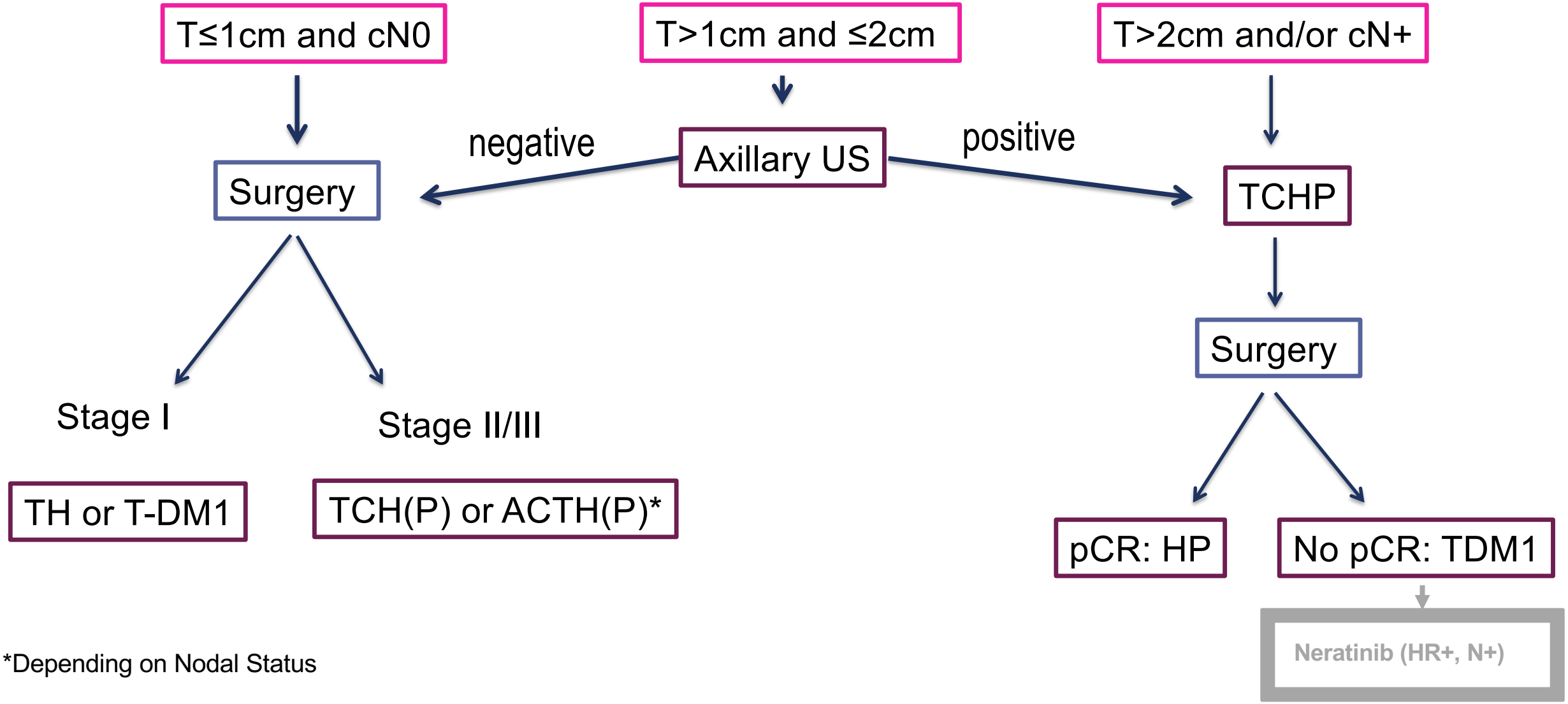
DFCI SERIES: Pathologic nodal status with upfront surgery in HER2+ cancers

	pN+ N= 73	pN0 N= 295	P value*
Clinical T category			**< 0.001**
1mic	6 (10.4%)	42 (89.6%)	
1a	3 (11.5%)	23 (88.5%)	
1b	7 (8.0%)	80 (92.0%)	
1c	**38 (24.7%)**	116 (75.3%)	
2	**19 (35.8%)**	34 (64.2%)	

- Up to 25% of T1c tumors will be node positive, and therefore should be getting preoperative therapy
- Should we do axillary US upfront on all clinically node-negative patients and if negative, then take to surgery, and give adjuvant TH, or give preop TH for these pts?
  - RFI 97.5% suggests may not need more than TH for almost all pts, so could lead to overtreatment

Axillary Ultrasound for clinically node-negative stage I patients is critical for decision-making

HER2+ Early Breast Cancer Algorithm



*Depending on Nodal Status

- Thank You!

Appendix

Editorial Review

- Selection of neoadjuvant and adjuvant systemic therapy for HER2-positive localized breast cancer
  - Slides 8-20, 25-33
- Available data from clinical trials exploring the feasibility of chemotherapy de-escalation in the setting of dual HER2 blockade for localized disease (eg, ADAPT HER2+/HR-, TRAIN-2)
  - Slides 3-6
- Long-term findings, including rates of CNS recurrence, with the use of postadjuvant neratinib for HER2-positive localized breast cancer
  - Slides 21-24

Appendix Slides – None