The Role of Biomarkers in Early HER2+ Breast Cancer and the Management of Early HER2+ Breast Cancer in the Adjuvant Setting

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Considerations in decision making for stage II- III HER2+ breast cancer

- **Stage II-III disease**
  - What is the role of anthracyclines?
  - Can we de-escalate following pCR to an abbreviated neoadjuvant regimen?
    - How abbreviated can that neoadjuvant regimen be?
  - Biomarkers: which are promising and how should we use them?
  - How should we escalate for those patients without pCR?

Predictive markers and biomarkers at baseline for pCR

- Clinical: Stage
- ER positivity
- HER2 expression
  - Intrinsic subtype (HER2E); ERBB2 expression; HER2 heterogeneity
- TILs/immune activation
- PIK3CA mutations
- ctDNA
- Other expression profiles (HER2Dx)
- Imaging: MRI (TNBC) or MRI radiomics

pCR rates are lower for ER+ HER2-Positive (vs ER- HER2+) after chemotherapy and dual HER2+-targeted Rx

Trial	pCR in ER+ HER2-Positive	pCR in ER-Negative HER2-Positive
NeoALTTO[a]	42%	61%
CALGB 40601[b]	41%	79%
NSABP B-41[c]	56%	73%
NeoSphere[d]	26%	63%
NOAH[e]	30%	51%
Kristine[f]	45%	60%
TRYPHAENA[g]	46%	65%
TRAIN-2[h]	52%	86%

a. Baselga J, et al. Lancet 2012; 379: 633-640 ; b. Carey L, et al. J Clin Oncol. 2016;34:542-549 ; c. Robidoux A, et al. Lancet Oncol. 2013;14:1183-1192 (in THL arms) ; d. Gianni L, et al. Lancet Oncol. 2012;13:25-32; e. Gianni L, et al. Lancet. 2010;375:377-384; f. Hurvitz S, et al. Lancet Oncol. 2018;19:115-126; g. Schneeweiss A, et al. Ann Oncol. 2013;24:2278-2284;h. van Ramshorst et al. Lancet Oncol 2018; 19:P1630-1640.

HER2-enriched subtype (HER2E) has higher rate of pCR after HER2-based preoperative chemotherapy

	NOAH[a]	Neo ALTTO[b]	CALGB 40601[c]	CherLOB [d]	ICO+ CLINIC[e]	OPTIHER[f]	KRISTINE [g]	KRISTINE [g]	BERENICE [h]
Therapy	**AT** +H	**T** +L/H/LH	**T** +L/H/LH	**AT** +L/H/LH	**AT** +H	**AT** +H+P	**T-DM1** +P	**DC** +H+P	**A T** +H+P
N	63	254	265	64	154	58	183	171	294
Variable	pCR_{BA}	pCR_{B}	pCR_{B}	pCR_{BA}	pCR_{BA}	pCR_{BA}	pCR_{BA}	pCR_{BA}	pCR_{BA}
pCR in HER2E (mean, 63.9%)	52.9%	52.0%	65.8%	50.0%	63.4%	83.3%	62.2%	72.1%	74.2%
pCR in non-HER2E (mean, 29.3%)	34.5%	21.5%	31.1%	17.0%	26.2%	46.43%	26.9%	32.8%	26.9%
P-value	.014	< .001	< .001	.008	< .001	.003	< .001	< .001	< .001

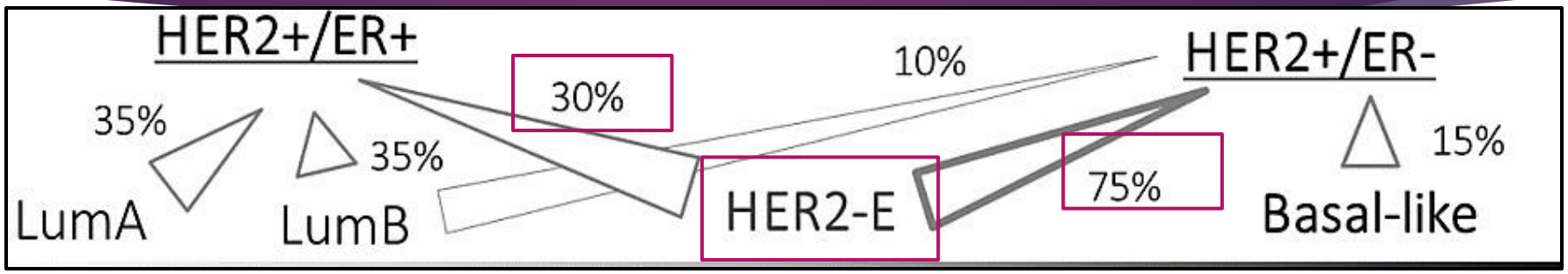
slide courtesy of Lisa Carey MD

AT, anthracycline/taxane; C, carboplatin; D, docetaxel; H, herceptin; L, lapatinib; P, pertuzumab; T, paclitaxel. B, breast; A, axilla

a. Prat A, et al. Clin Cancer Res. 2014;20:511-521; b. Fumagalli D, et al. JAMA Oncol. 2017;3:227-234; c. Carey LA, et al. J Clin Oncol. 2016;34:542-549; d. Dieci MV, et al. Ann Oncol 2019;30:418-423. e. Pernas S, et al. Cancer Res. 2018;78(4 Suppl):P2-09-11; f. Gavilá J, et al. Cancer Res. 2018;78(4 Suppl): P2-09-04. g. Prat A, et al. Cancer Res. 2018;78(4 Suppl):PD3-06; h. Swain SM, Ann Oncol. 2018 ;29:646-653

ER+ HER2+ breast cancer is less often HER2E

[a]



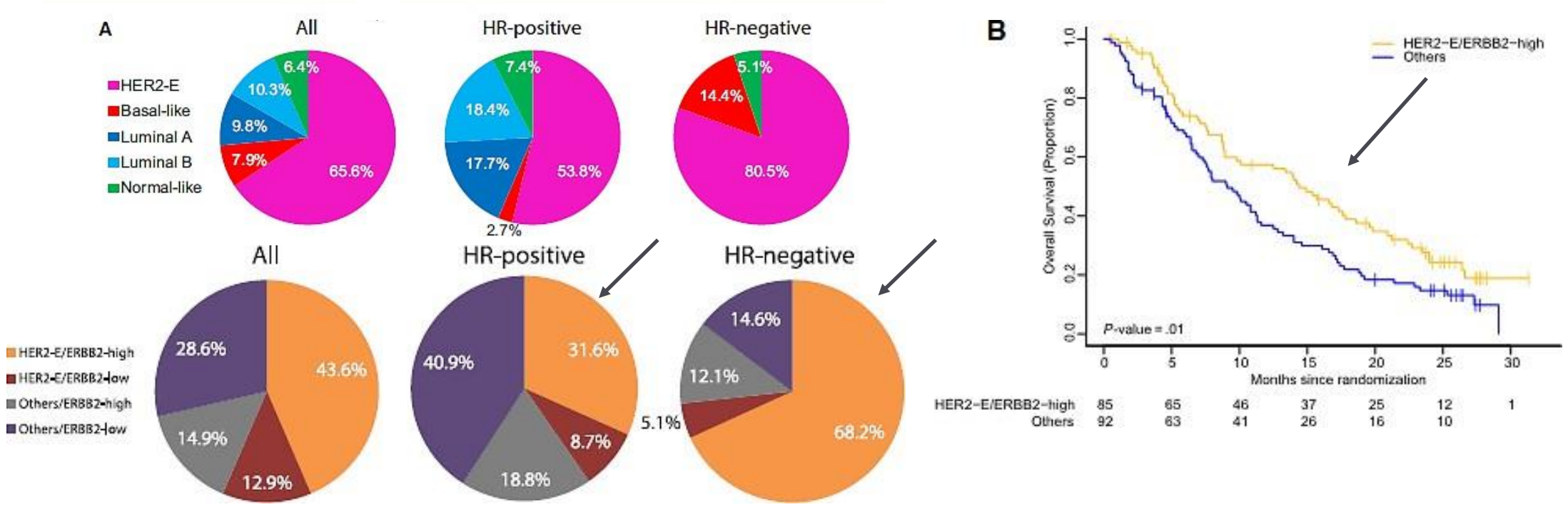
- HER2-E has highest activation of EGFR/HER2 signaling
- In a recent meta-analysis, the HER2-enriched subtype was significantly associated with pCR after HER2-targeted therapy, irrespective of ER status, with or without chemotherapy[b]
- 75% of ER-negative HER2-positive are HER2-E vs 30% of ER-positive
- HER-positive are HER2E [a]

a. Brandao M, et al. Clin Cancer Res. 2020;26:2783-2788; b. Schettini F, et al. Cancer Treat Rev. 2020;84:101965.

HER2E subtype plus high ERBB2 expression predicts response to anti-HER2 therapy

422 HER2-positive tumors

(TBCRC 006, TBCRC 023, SOLTI-PAMELA, PER-ELISA, EGF104090)

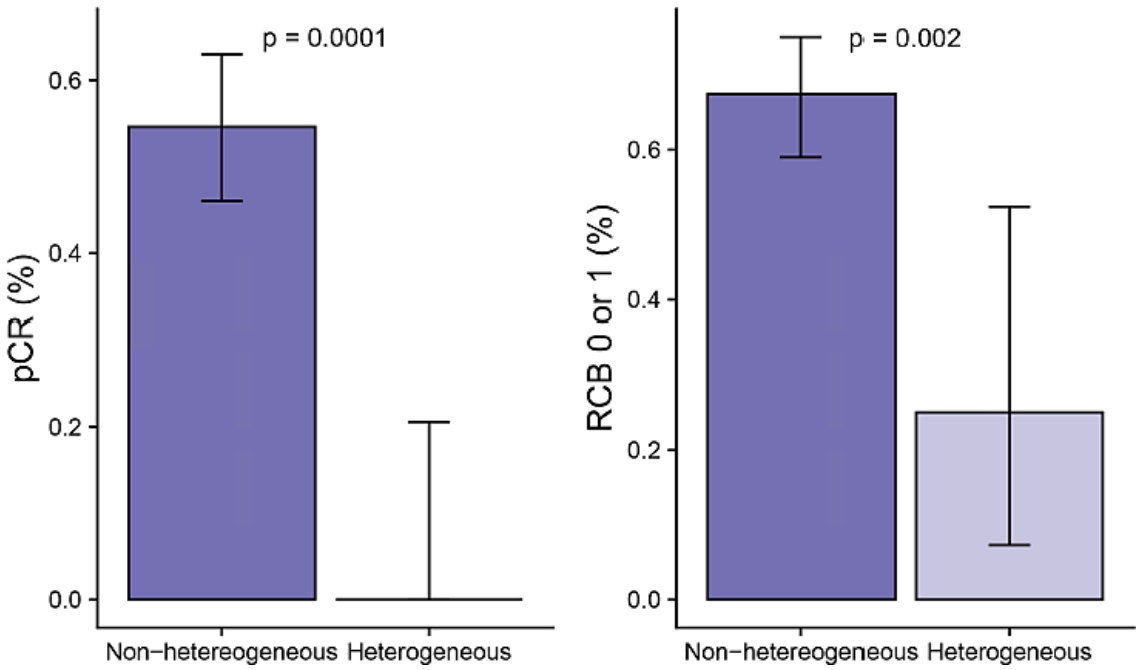


Prat et al. J Natl Cancer Inst. 2020;112:46-54.

Intratumoral HER2 heterogeneity is associated with less response to anti-HER2 therapy

Neoadjuvant T-DM1 + pertuzumab

- Heterogeneity defined as:
  - HER2-positive (FISH) in > 5% to < 50% tumor cells or
  - An area of tumor that was HER2-negative
- 10% (16/157) tumors had HER2 heterogeneity
- 81% of tumors (N = 13) with heterogeneity were
  - ER+
  - pCR:
  - 0% for heterogeneous tumors
  - 55% for tumors without HER2 heterogeneity[a]



Metzger Filho O, et al. Cancer Discovery. 2021;11:2474-2487.

Higher TILs Predict for pCR in HER2-Positive Breast Cancer

Various meta-analyses of neoadjuvant randomized studies investigating TIL in HER2-positive breast cancer[a,b]

- High baseline TIL are associated with increased probability of pCR
- No interaction with various anti-HER2 therapy
- No interaction with the chemotherapy backbone (anthracyclines or not)

NeoALTTO and CALGB 40601: immune signatures predicted for pCR [c, d]

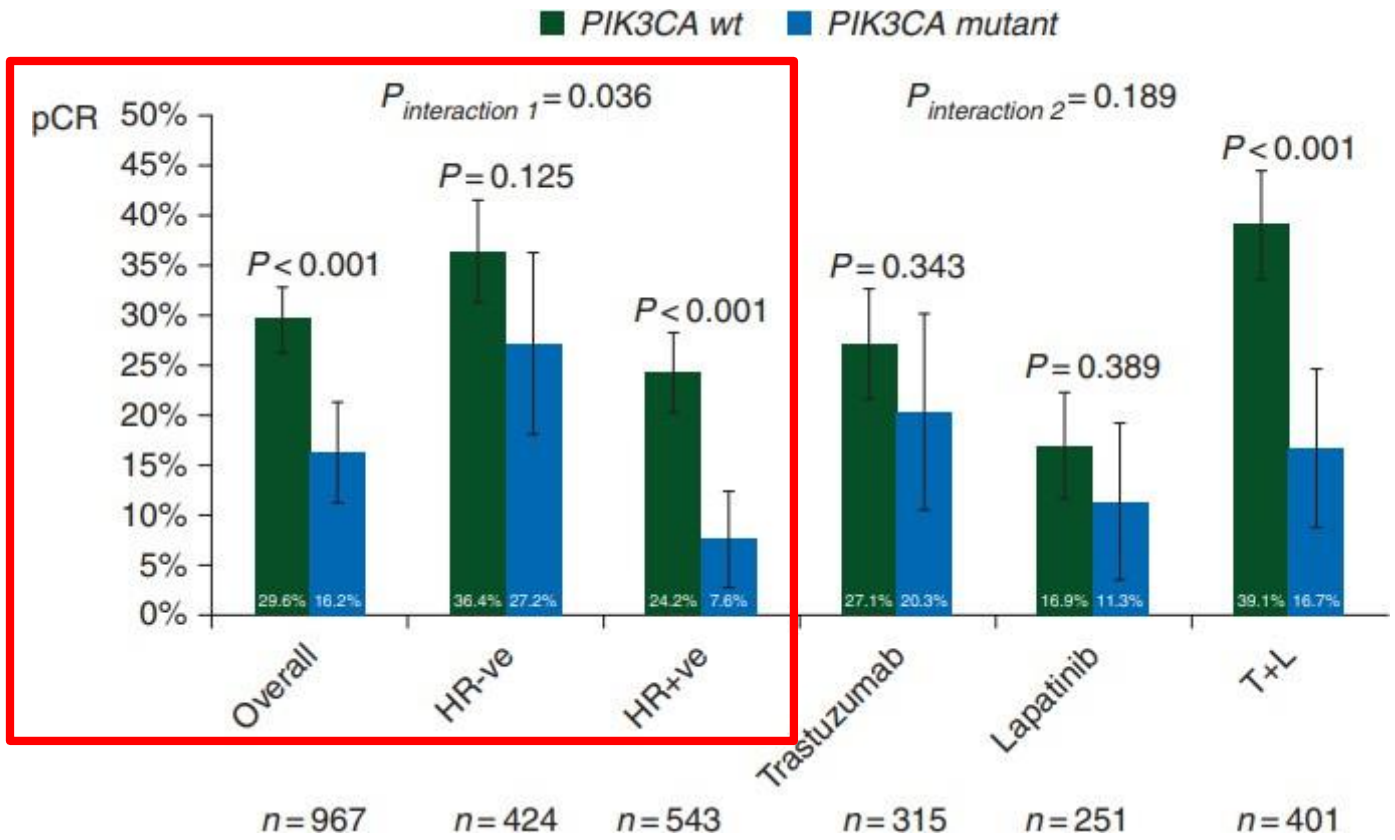
However, relationship of TILs & pCR not as consistent as with TNBC

- Some trials did not find improved pCR with ↑ TILs: Tryphena; NeoSphere, GeparSepto [e,f,g,h]

a. Denkert C, et al. Lancet Oncol. 2018;19:40-50; b. Solinas C, et al. Breast. 2017;35:142-150; c. Fumagalli et al. JAMA Oncol 2016; 3:227. d. Fernandaz-Martinez et al. JCO 2020; 38:4184-93 e. Ignatiadis M, et al. Ann Oncol. 2018;29:1777-1783; f. Bianchini G, et al. Ann Oncol. 2015;26:2429-2436; g. Bidard et al. JNCI 2018: 110, 560-567 h. Hamy A, et al. Clin Cancer Res. 2019;25:6731-6741;

PIK3CA mutations are associated with lower pCR

- Overall ~22% of HER2-positive BC have a PIK3CA mutation[a]
- In pooled analysis of 5
  - RCT using taxane, trastuzumab and lapatinib, PIK3CA mutation predicted for lower pCR, mainly among ER-positive HER2-positive[b]



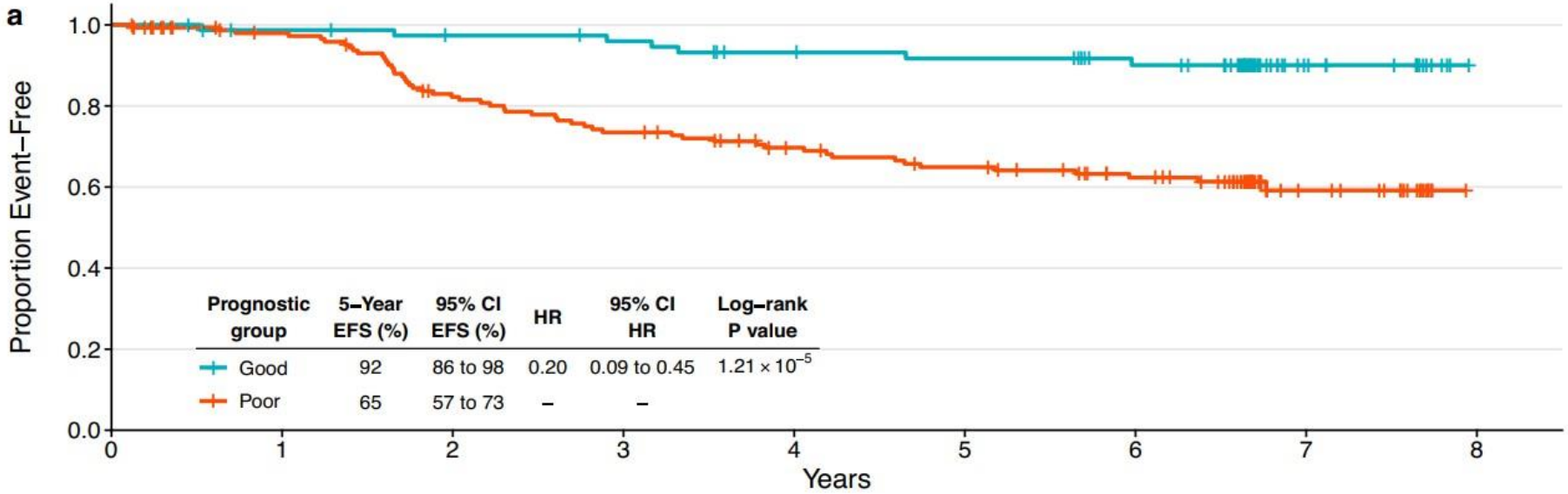
a. Zardavas D, et al. J Clin Oncol. 2018;36:981-990; b. Loibl S, et al. Ann Oncol. 2016;27:1519-1525

ER-Positive HER2-Positive: Why Lower pCR?

- Less often HER2E
- Lower TILs/ immune activation
- More HER2 heterogeneity
- More often PIK3CA mutated
- But despite lower pCR compared with ER-negative HER2-positive tumors, the HR-positive HER2-positive tumors have better outcomes

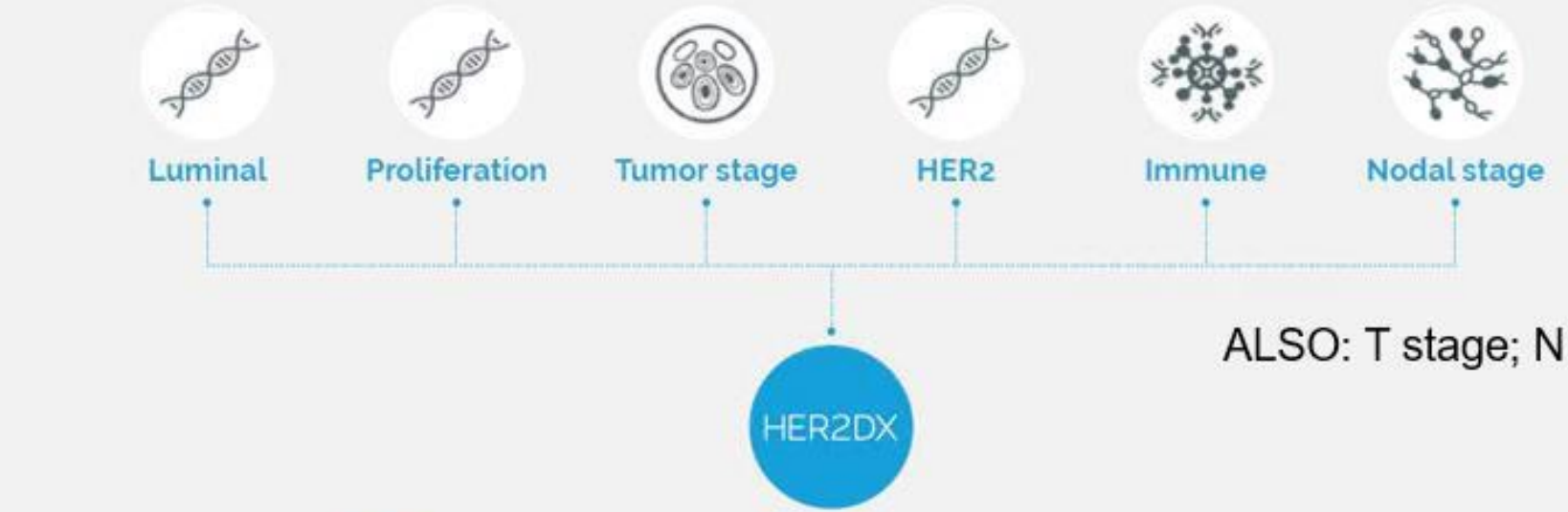
Clinicopathologic and immune factors combined predict:

- HER2 EveNT score (cN stage, ER, breast pCR, sTILs, immune scores: B cell receptor)
- Developed in NeoALTTO, validated in CALGB 40601
- 5 yr EFS: Good prognostic group 93% vs poor prognostic group 75%



Rediti et al. Nature Communications 2023; 14:7053

HER2Dx combines gene expression and clinical data:



ALSO: T stage; N stage

27 genes

- Immune infiltration (14 genes)
- Luminal differentiation (5 genes)
- Tumor cell proliferation (4 genes)
- HER2 amplicon (4 genes, including ERBB2)

Prat et al. EBioMedicine 2022

HER2Dx algorithm produces a 1) pCR score & 2) a risk score

Test Report v1.1
Report Date: August 25, 2021

Patient ID: B21-06780-A6
Sample external ID:

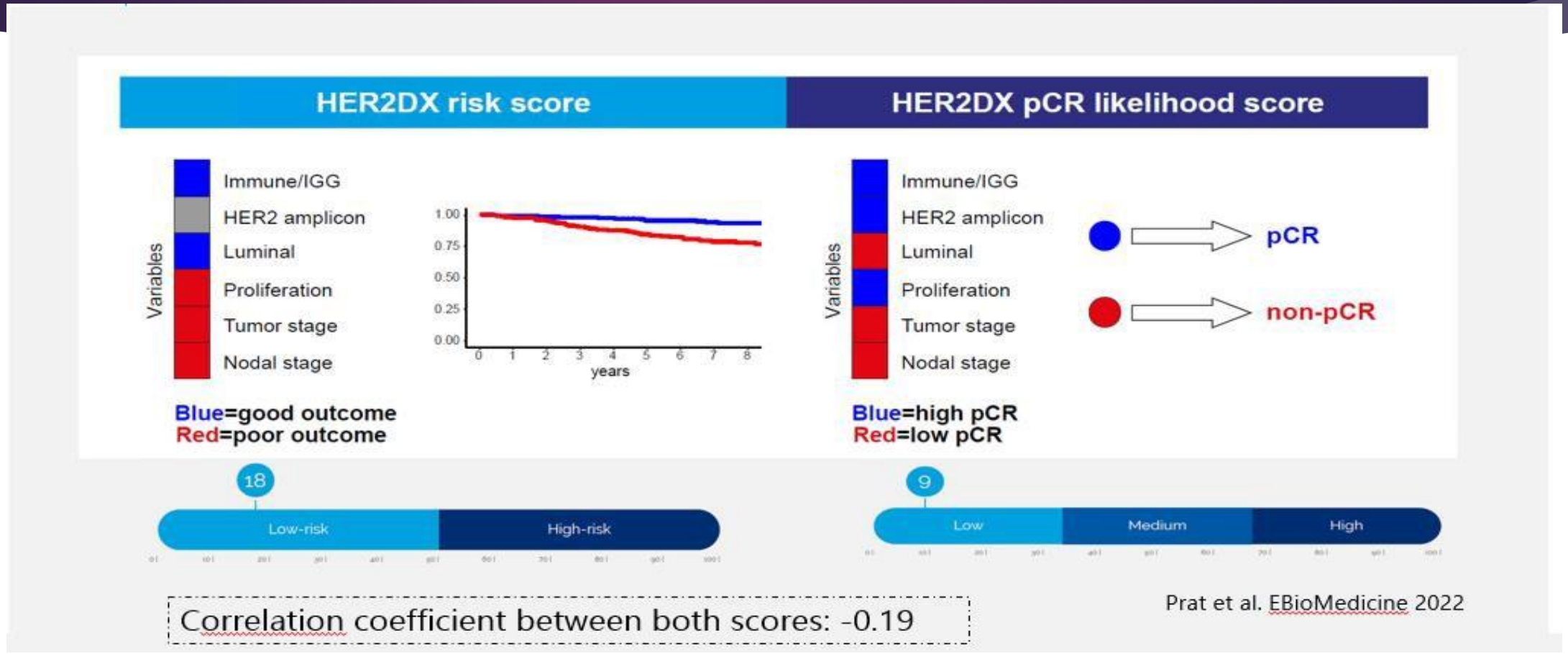
Tumor stage: ○ T1 ○ T2 ○ T3 ○ T4
Nodal stage: ○ N0 ○ N1 ○ N2-3

SUMMARY

HER2DX	RELAPSE RISK	pCR LIKELIHOOD SCORE	ERBB2 EXPRESSION
Score	18	9	25
Result	Low	Low	Low
Description	**94%** disease-free survival at 7-years when treated with chemotherapy and trastuzumab	**23%** pCR rate when treated with trastuzumab-based chemotherapy	Similar expression as in HER2-negative disease

Slide courtesy of Aleix Prat

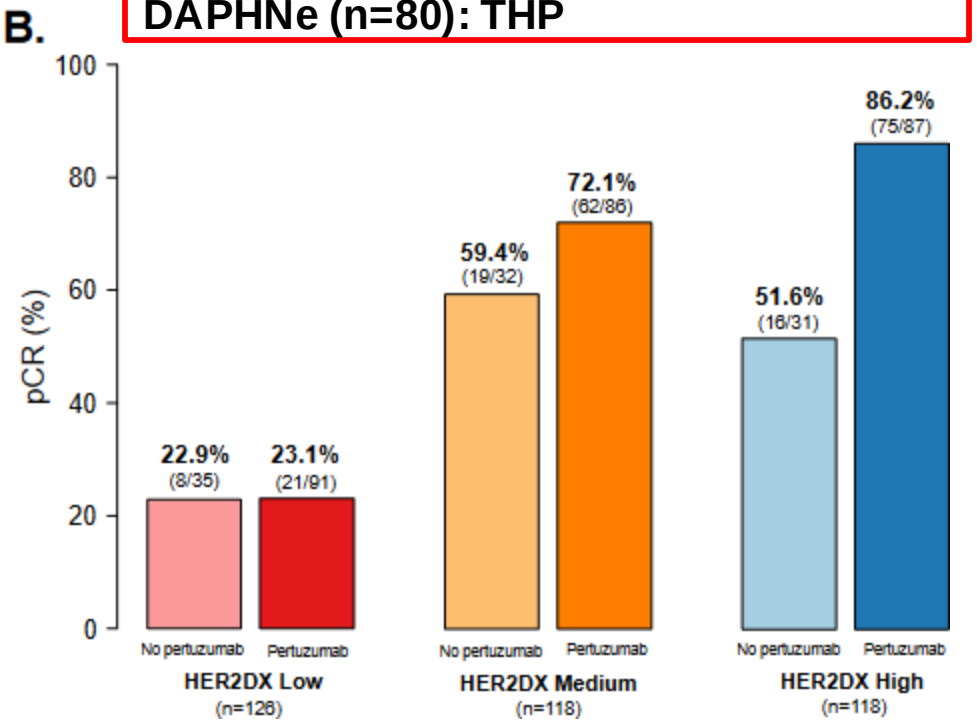
HER2Dx pCR and risk score



HER2Dx pCR score: likelihood of pCR and pertuzumab benefit

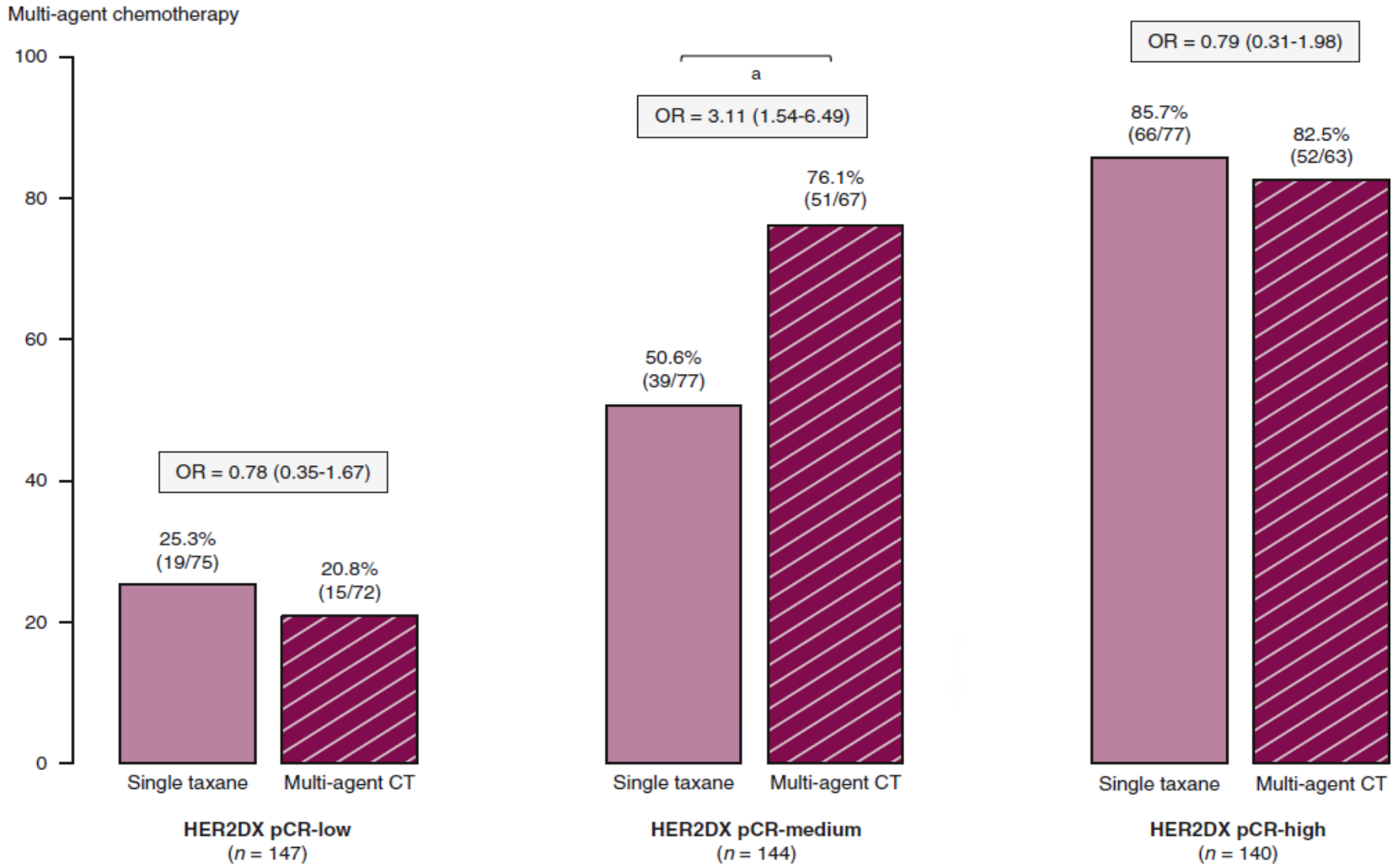
Group	Patients, No.	OR (95% CI)
Low		
GOM	53	0.88 (0.25-3.02)
I-SPY2	42	0.81 (0.11-6.08)
Overall	95	0.86 (0.30-2.46)
Heterogeneity: I^2 = 0%, P = .95		
Medium		
GOM	54	2.06 (0.61-6.94)
I-SPY2	42	4.05 (0.53-30.92)
Overall	96	2.46 (0.87-6.98)
Heterogeneity: I^2 = 0%, P = .58		
High		
GOM	48	4.00 (0.97-16.46)
I-SPY2	43	7.59 (1.63-35.41)
Overall	91	5.36 (1.89-15.20)
Heterogeneity: I^2 = 0%, P = .55		

GOM (n=155): TCHP vs TCH
ISPY2 (n=127): TH vs THP vs T-DM1+P
DAPHNe (n=80): THP



Bueno-Muiño et al. JAMA Oncol 2023

HER2Dx pCR score and benefit of multi-agent chemotherapy



Villacampa et al. Ann Oncol 2023

EA1181: CompassHER2 pCR HER2Dx is a secondary objective

Eligibility
- HER2+ BC
- T>2 cm or N+

N = 2152
Enrollment completed

Registration → **THP × 4 (12 weeks)**
(nab)/paclitaxel qwk or
docetaxel q3w (T)
+
trastuzumab (H) and
pertuzumab (P)
→ Surgery

EA1181 if pCR (expect 40%)
Complete 1 y of HP
with no further chemo
ET/RT if indicated

Overall PI: Tung

Tissue block collection
Blood collection for ctDNA, CTCs at several timepoints

Co-primary Objectives; in patients with pCR:
ER-positive HER2-positive: 3y RFS > 92% *(3y RFS H_0 = 92%, $H_1 \geq$ 95%)*
ER-negative HER2-positive: 3y RFS > 92% *(3y RFS H_0 = 92%, $H_1 \geq$ 95%)*

Clinicaltrials.gov. Accessed July 30, 2024 . https://clinicaltrials.gov/ct2/show/results/NCT04266249?view=results.

Clinical validation of **HER2DX risk score** in stage 1 HER2+ disease

Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer: final 10-year analysis of the open-label, single-arm, phase 2 APT trial

Sara M Tolaney, Paolo Tarantino, Noah Graham, Nabihah Tayob, Laia Parè, Guillermo Villacampa, Chau T Dang, Denise A Yardley, Beverly Moy, P Kelly Marcom, Kathy S Albain, Hope S Rugo, Matthew J Ellis, Iuliana Shapira, Antonio C Wolff, Lisa A Carey, Romualdo Barroso-Sousa, Patricia Villagrasa, Michelle DeMeo, Molly DiLullo, Jorge Gomez Tejeda Zanudo, Jakob Weiss, Nikhil Wagle, Ann H Partridge, Adrienne G Waks, Clifford A Hudis, Ian E Krop, Harold J Burstein, Aleix Prat, Eric P Winer

N=284 HER2DX

Relapse-free interval

HER2DX low-risk and high-risk

10-year 97.1% vs 90.0%

p=0.030

Tolaney et al. Lancet Oncol 2023

original reports

Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT): A Randomized Clinical Trial

Sara M. Tolaney, MD, MPH[1,2]; Nabihah Tayob, PhD[1]; Chau Dang, MD[3]; Denise A. Yardley, MD[4]; Steven J. Isakoff, MD, PhD[5]; Vicente Valero, MD[6]; Meredith Faggen, MD[1]; Therese Mulvey, MD[5]; Ron Bose, MD, PhD[7]; Jiani Hu, MSc[1]; Douglas Weckstein, MD[1]; Antonio C. Wolff, MD[8]; Katherine Reeder-Hayes, MD, MBA, MSc[9]; Hope S. Rugo, MD[10]; Bhuvaneswari Ramaswamy, MD[11]; Dan Zuckerman, MD[12]; Lowell Hart, MD[13]; Vijayakrishna K. Gadi, MD, PhD[14]; Michael Constantine, MD[1]; Kit Cheng, MD[15]; Frederick Briccetti, MD[1]; Bryan Schneider, MD[16]; Audrey Merrill Garrett, MD[17]; Kelly Marcom, MD[18]; Kathy Albain, MD[19]; Patricia DeFusco, MD[20]; Nadine Tung, MD[2,21]; Blair Ardman, MD[22]; Rita Nanda, MD[23]; Rachel C. Jankowitz, MD[24]; Mothaffar Rimawi, MD[25]; Vandana Abramson, MD[26]; Paula R. Pohlmann, MD, PhD, MSc[27]; Catherine Van Poznak, MD[28]; Andres Forero-Torres, MD[29]; Minetta Liu, MD[30]; Kathryn Ruddy, MD[30]; Yue Zheng, MSc[1]; Shoshana M. Rosenberg, ScD, MPH[1,2]; Richard D. Gelber, PhD[1,2]; Lorenzo Trippa, PhD[1,2]; William Barry, PhD[1]; Michelle DeMeo, BS[1]; Harold Burstein, MD, PhD[1,2]; Ann Partridge, MD, MPH[1,2]; Eric P. Winer, MD[1,2]; and Ian Krop, MD, PhD[1,2]

N=187 HER2DX

Relapse-free interval

HER2DX low-risk and high-risk

5-year 98.1% vs 81.8%

p=0.010

Tarantino et al. JCO 2024

Slide courtesy of Aleix Prat

Considerations in decision making for stage II- III HER2+ breast cancer

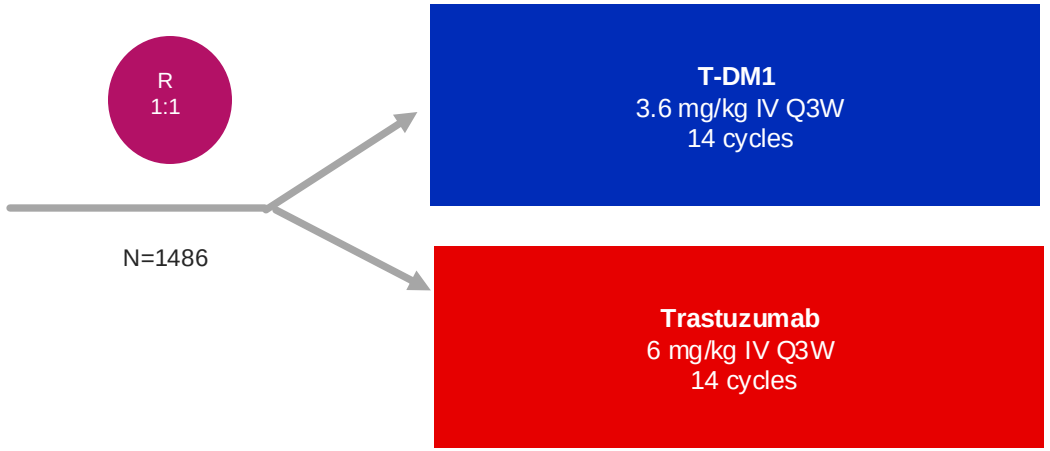
- **Stage II-III disease**
  - What is the role of anthracyclines?
  - Can we de-escalate following pCR to an abbreviated neoadjuvant regimen?
    - How abbreviated can that neoadjuvant regimen be?
  - Biomarkers: which are promising and how should we use them?
  - How should we escalate for those patients without pCR?

Adjuvant treatment of HER2+ early breast cancer

- KATHERINE trial
- ShortHER trial
- ExteNET
- CompassHER2 RD (*actively recruiting*)
- DESTINY-Breast 05 (*active, not recruiting*)

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

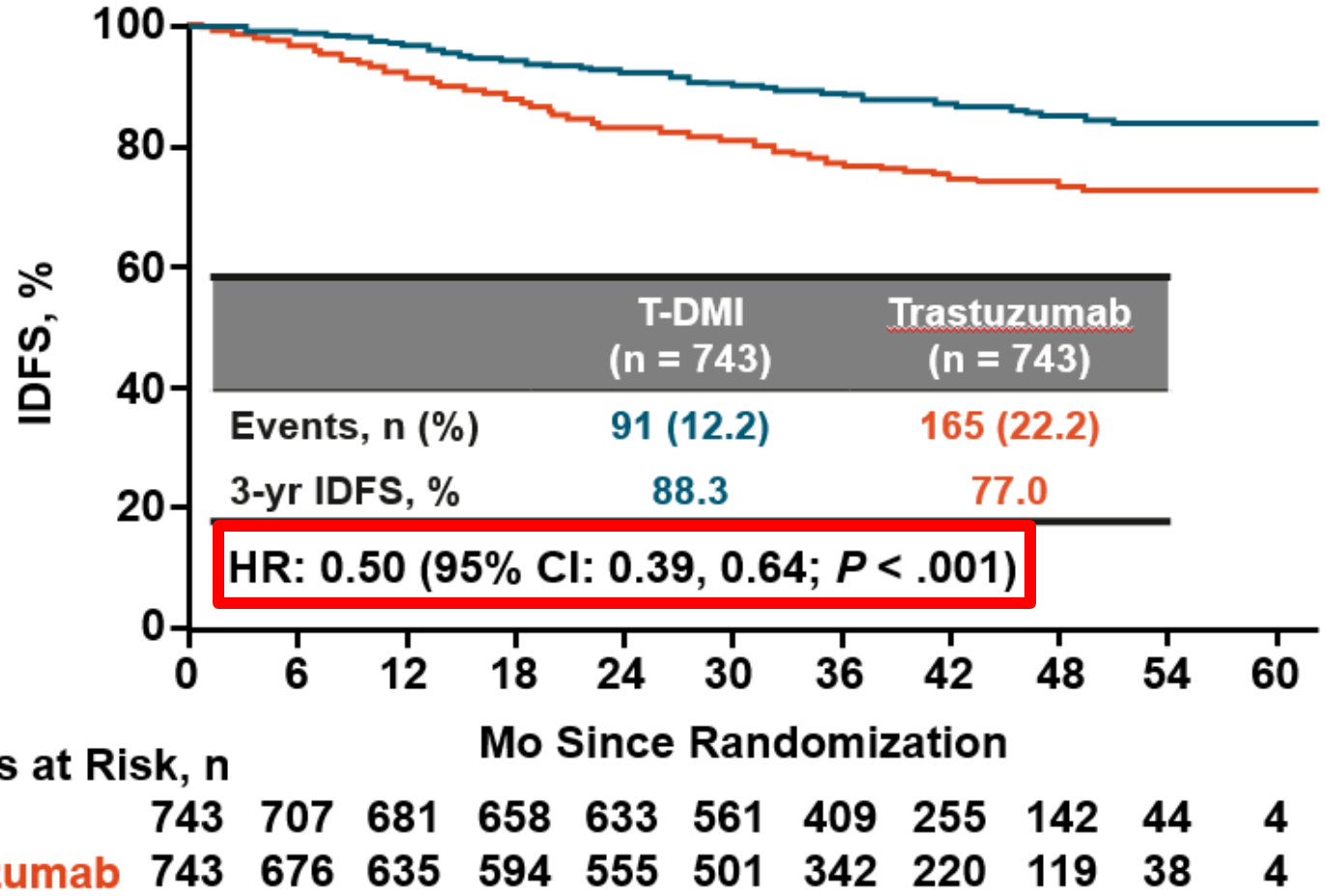


Radiation and endocrine therapy per protocol and local guidelines

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.

KATHERINE: 3 yr iDFS significantly improved with T-DM1



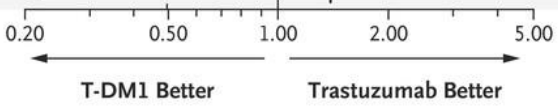
First IDFS Event, %	T-DM1	T
Any	12.2	22.2
Distant recurrence	10.5*	15.9†
Locoregional recurrence	1.1	4.6
Contralateral breast cancer	0.4	1.3
Death without prior event	0.3	0.4

CNS events: *5.9% vs †4.3%.

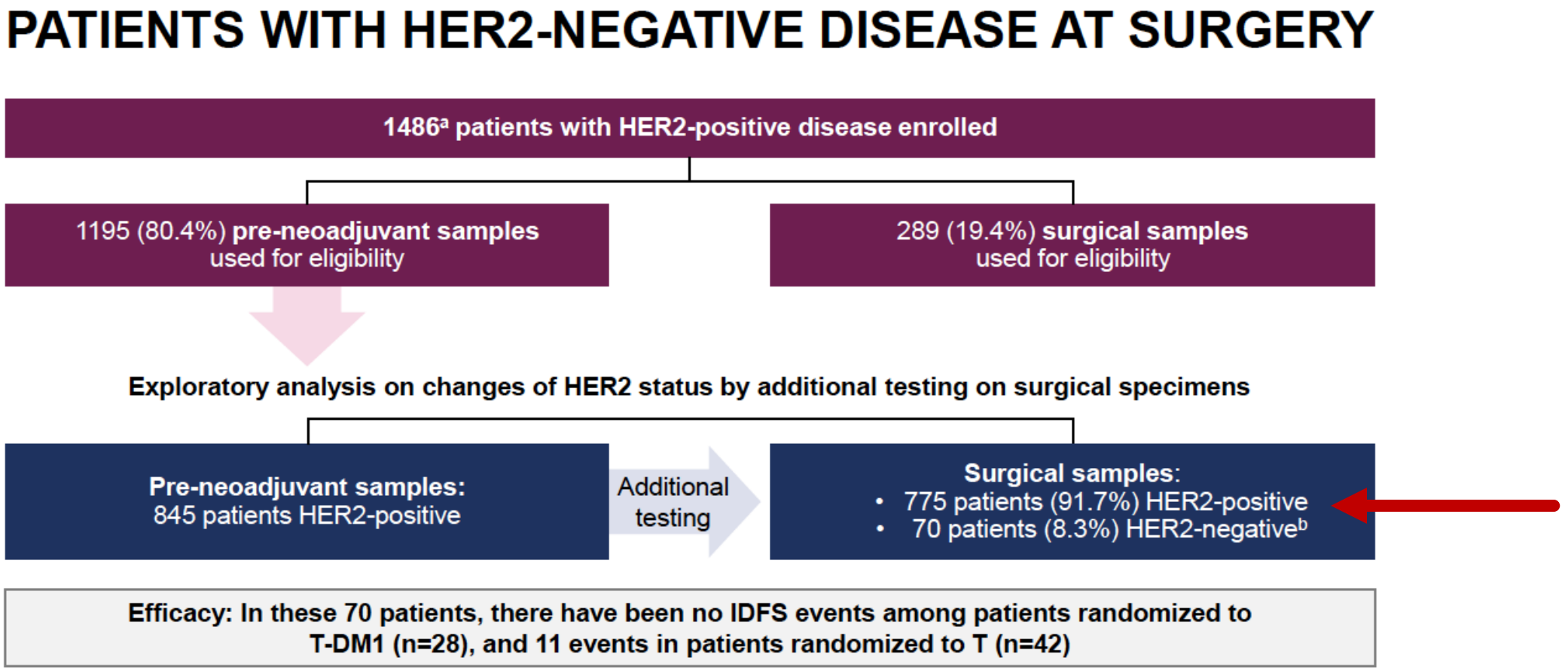
Geyer C et al. SABCS 2018. Abstract GS1-10;
von Minckwitz et al. N Engl J Med. 2019;380(7):617-628.

KATHERINE: even patients with small amounts of residual tumor benefit

Subgroup	T-DM1	Trastuzumab	Hazard Ratio for Invasive-Disease Event (95% CI)	3-Yr Invasive Disease–free Survival Rate	
	no. of patients with an invasive-disease event/total no.			T-DM1 %	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



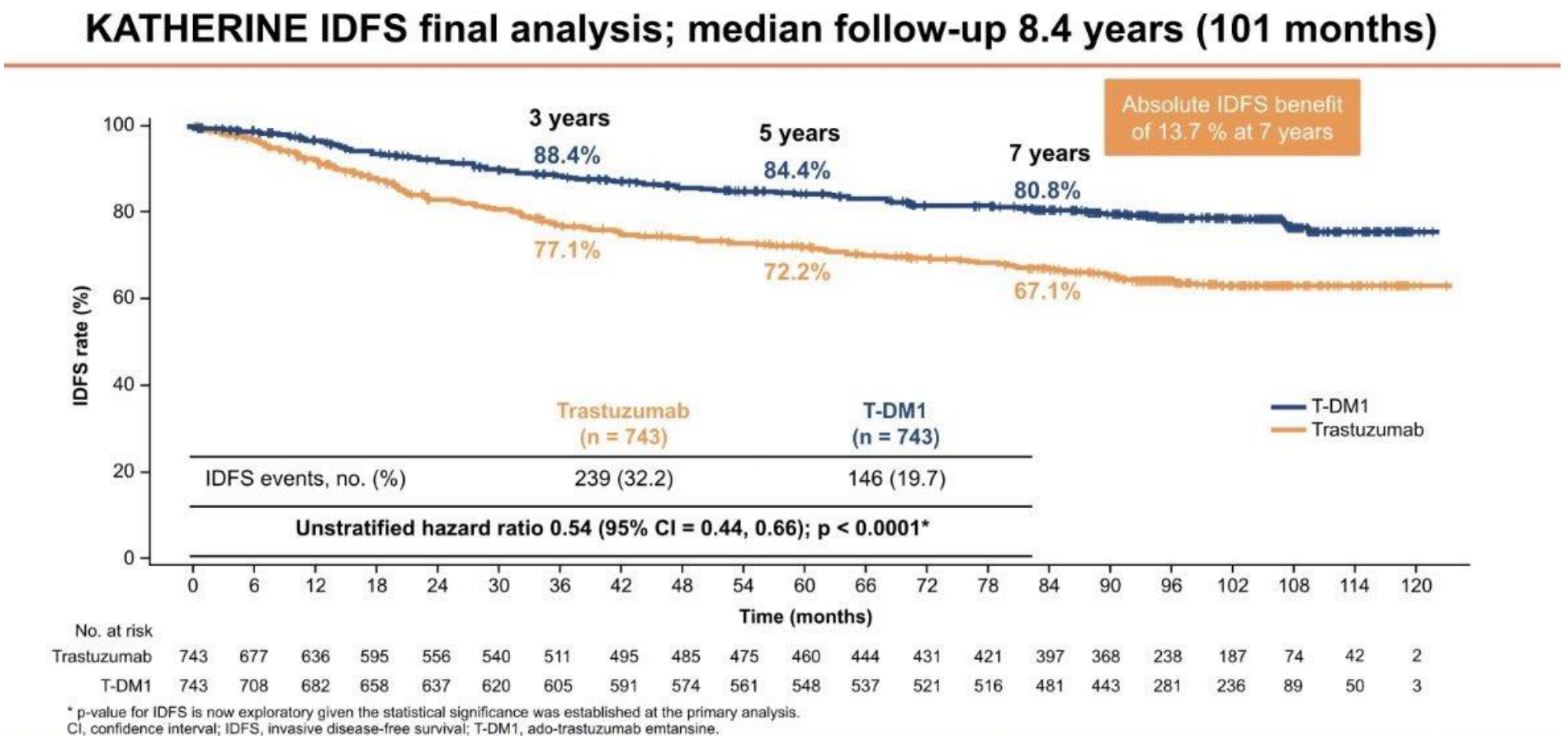
KATHERINE: even patients with HER2-negative residual tumor may benefit



SUPPORTS THE USE OF ADJUVANT T-DM1 EVEN IF RESIDUAL DISEASE IS HER2-NEGATIVE

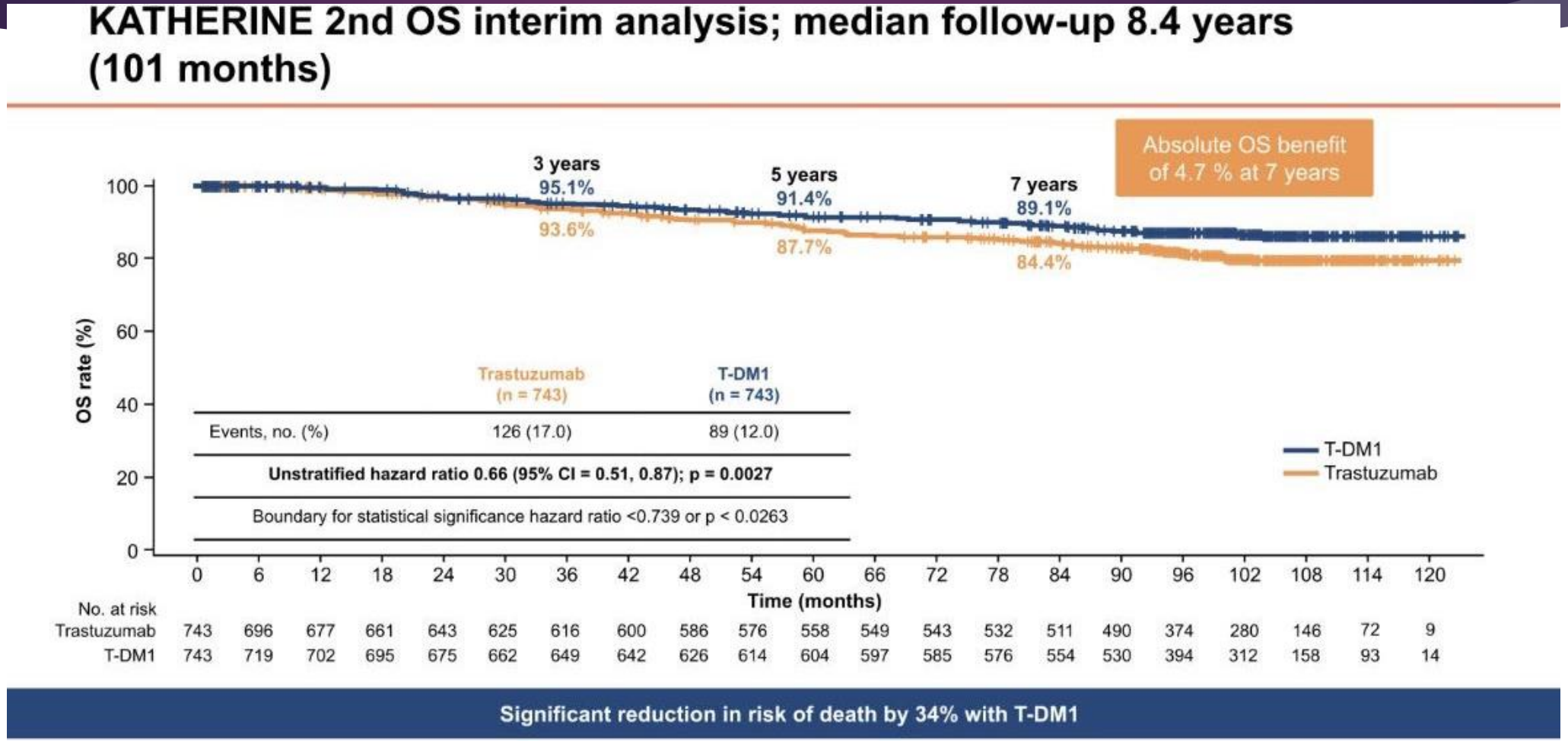
Loibl S et al. ESMO Breast 2020. Abstract 960.

KATHERINE trial long term follow up



Sibylle Loibl, MD, PhD, et al San Antonio Breast 2023

KATHERINE trial long term follow up



Sibylle Loibl, MD, PhD et al, San Antonio Breast 2023

ShortHER2 trial: Evaluating the length of trastuzumab therapy in adjuvant setting

- Phase III non-inferiority trial comparing 9 weeks (short arm) vs 1 year (long arm) of adjuvant trastuzumab combined with chemotherapy in HER2+ early breast cancer
- Patient characteristics (1254 HER2+ early breast cancer patients stratified)
  - Median age 55
  - 54% node negative, 30% 1-3 positive nodes, 16% with 4 or more positive nodes
- First primary endpoint: disease free survival (2017 ASCO)
  - Non-inferiority could not be claimed, HR 1.13 (90% CI 0.89-1.42)

- Pier Franco Cont
- e et al.,

1. Nine-weeks versus one-year trastuzumab for early-stage HER2+ breast cancer: 10-year update of the Short-HER phase III randomized trial.. *JCO* **41**, LBA637-LBA637(2023).DOI:10.1200/JCO.2023.41.17_suppl.LBA637

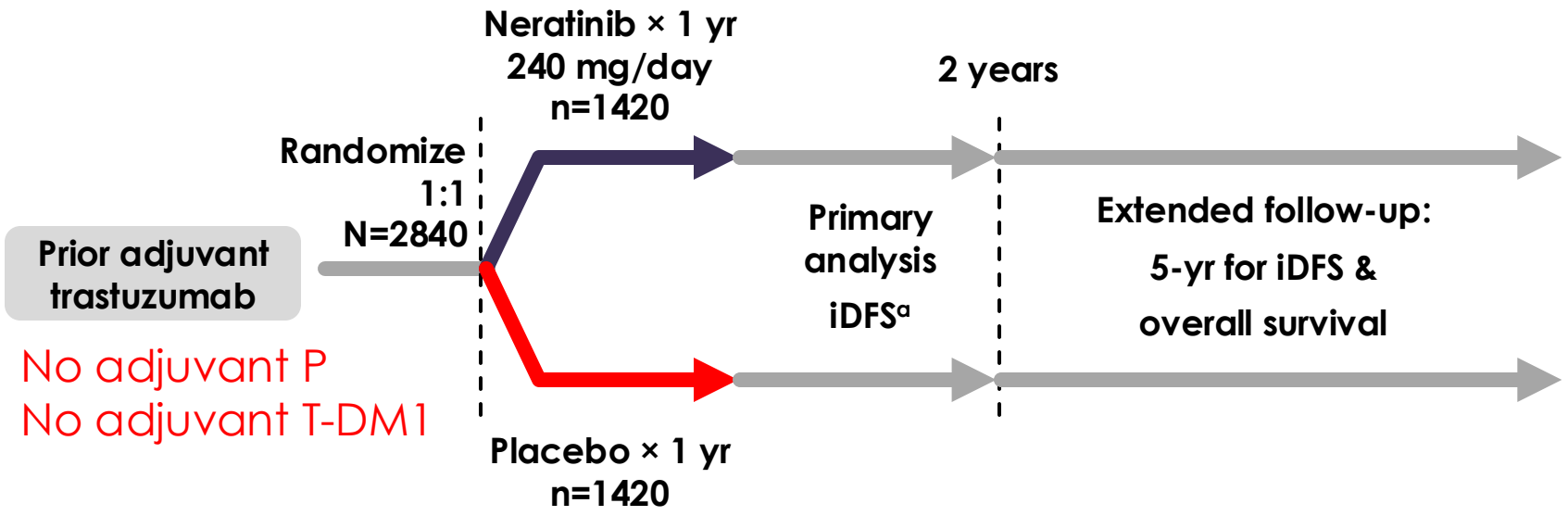
ShortHER trial, 10 year follow up

	10 year OS			10 year DFS		
Subgroups (n)	**Long arm**	**Short arm**	**Hazard ratio (90% CI)**	**Long arm**	**Short arm**	**Hazard ratio (90% CI)**
ITT (1254	89%	88%	HR 1.06 (0.86-1.31)	77%	78%	HR 1.15 (0.85-1.56)
N0 (672)	81%	85%	0.74 (0.54-1.04)	89%	95%	0.57 (0.33-0.99)
N 1-3 (383)	77%	79%	1.11 (0.76-1.64)	92%	89%	1.37 (0.77-2.44)
N > 4(198)	63%	53%	1.84 (1.24-2.75)	84%	64%	1.87 (1.11-3.14)

- **At 9 years, 248 DFS events and 116 deaths reported**
- **1 year of trastuzumab remains SOC for HER2 early breast cancer at the 10 year follow up**

Pier Franco Conte et al., Nine-weeks versus one-year trastuzumab for early-stage HER2+ breast cancer: 10-year update of the Short-HER phase III randomized trial.. *JCO* **41**, LBA637-LBA637 (2023). DOI: 10.1200/JCO.2023.41.17_suppl.LBA637

ExteNET study: Adding neratinib



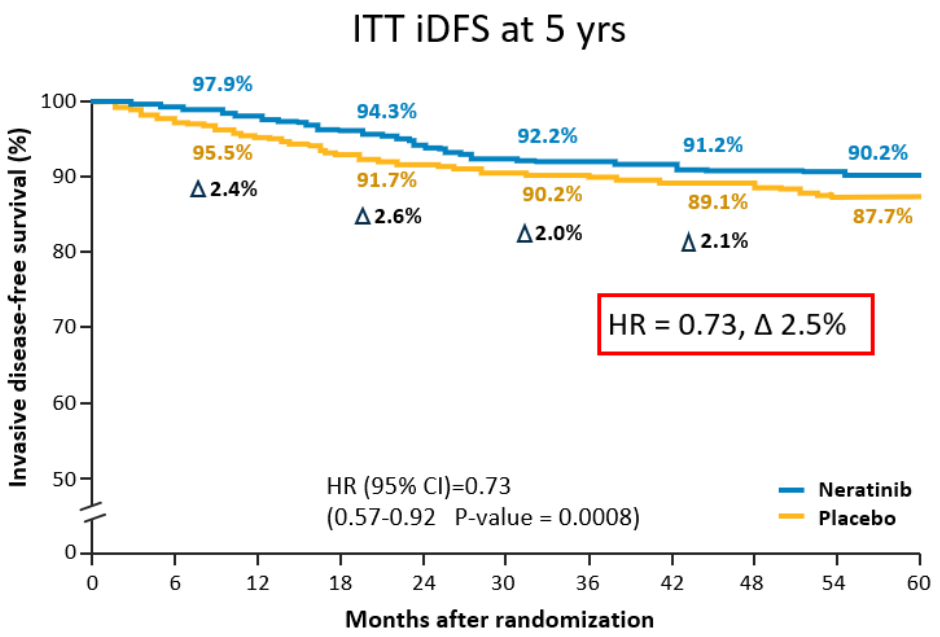
Primary endpoint: invasive disease-free survival (iDFS)[a]

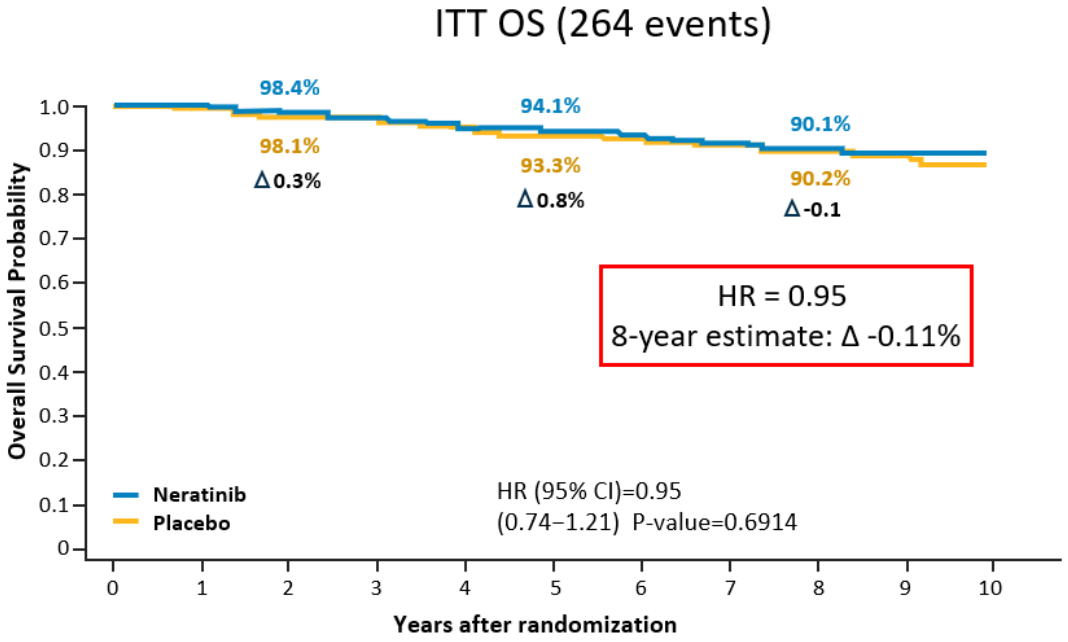
Secondary endpoints: overall survival, DFS-DCIS, distant DFS, time to distant recurrence, CNS metastases, safety,

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 for ITT 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

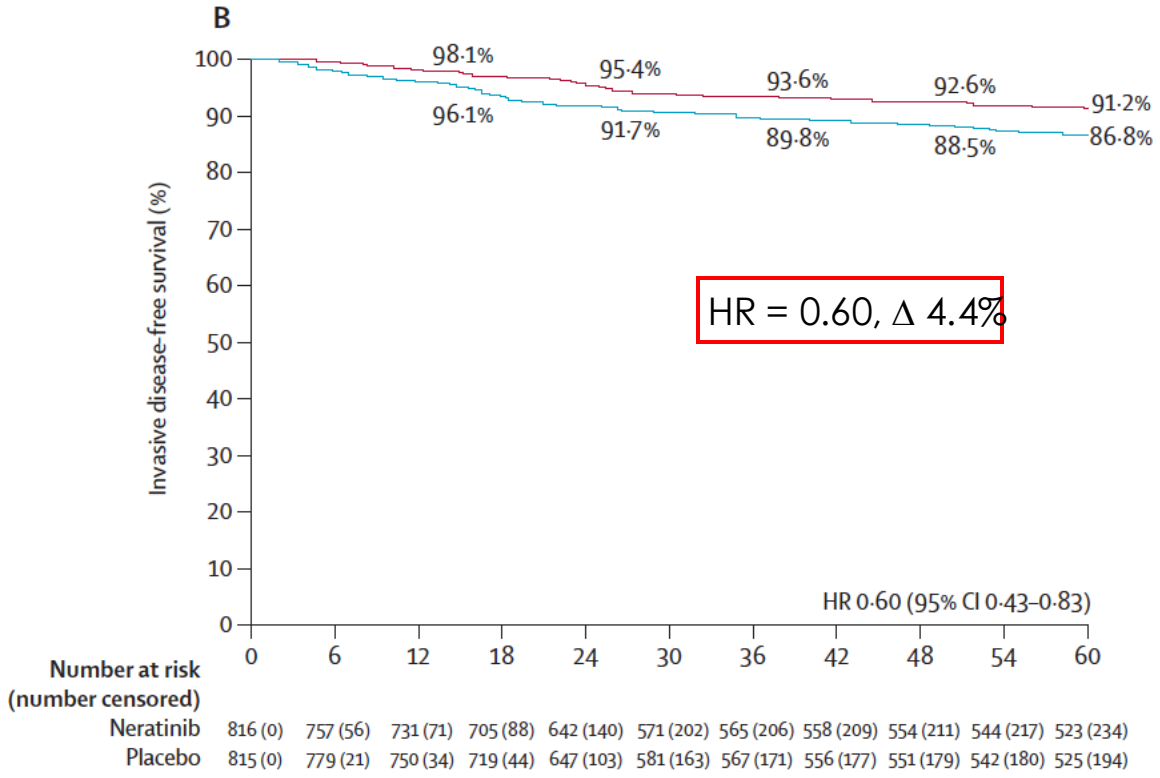
No. at risk

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.

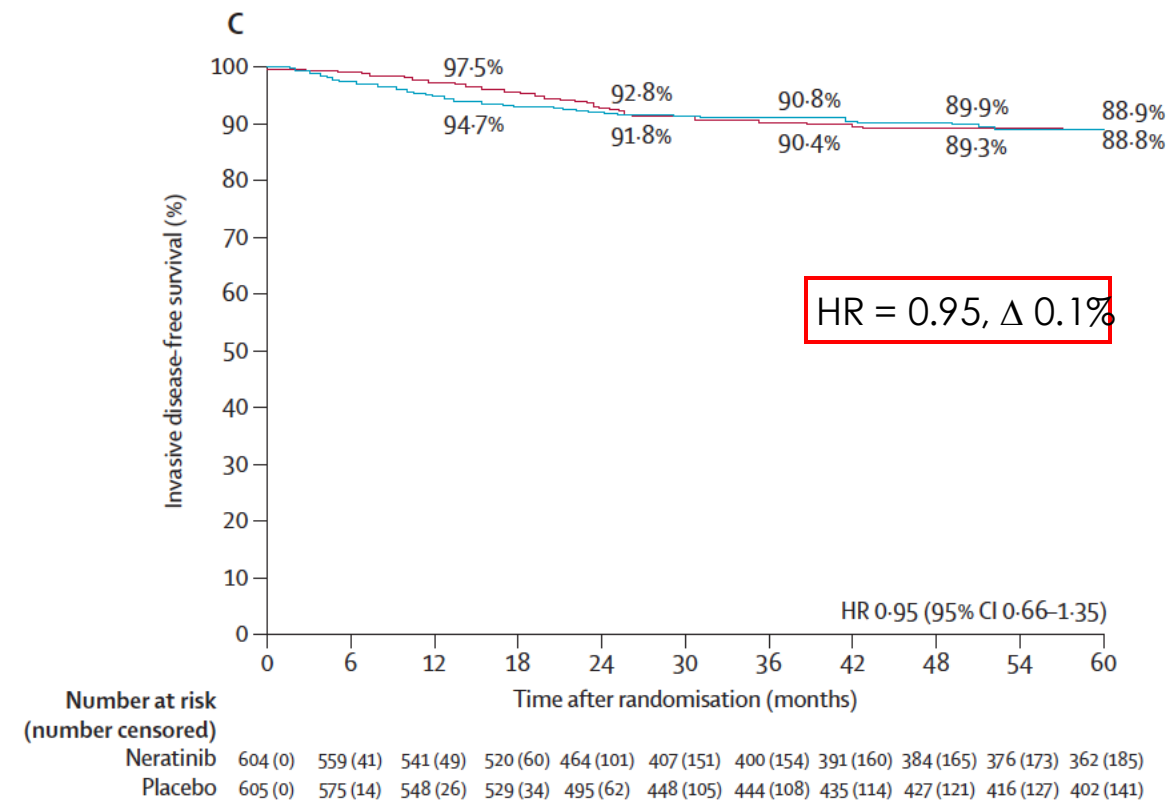
ExteNET: iDFS by HR status

HR+ iDFS at 5 yrs



HR = 0.60, Δ 4.4%

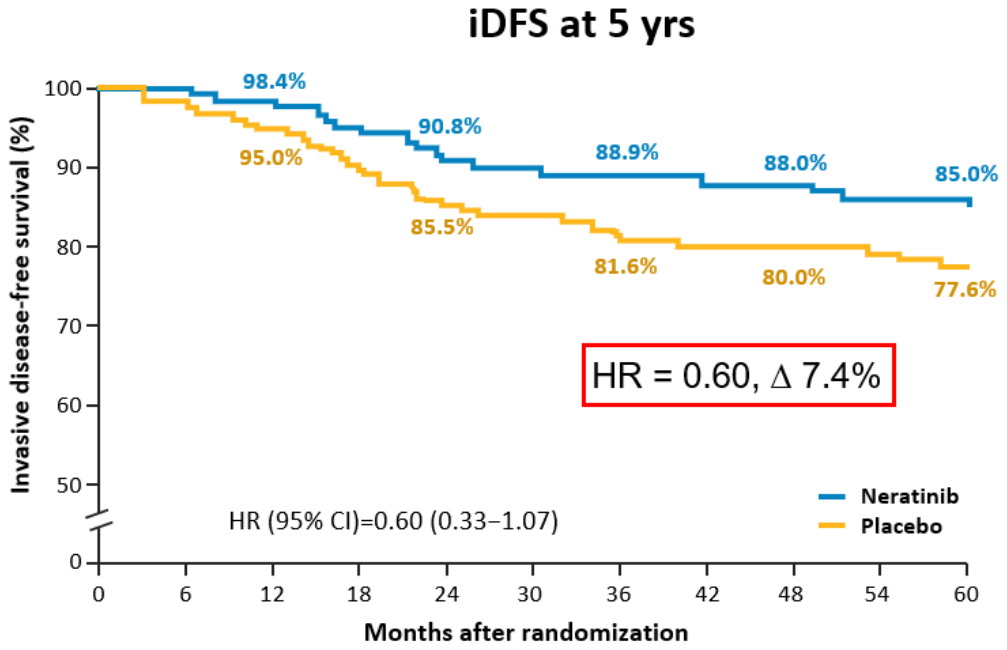
HR- iDFS at 5 yrs

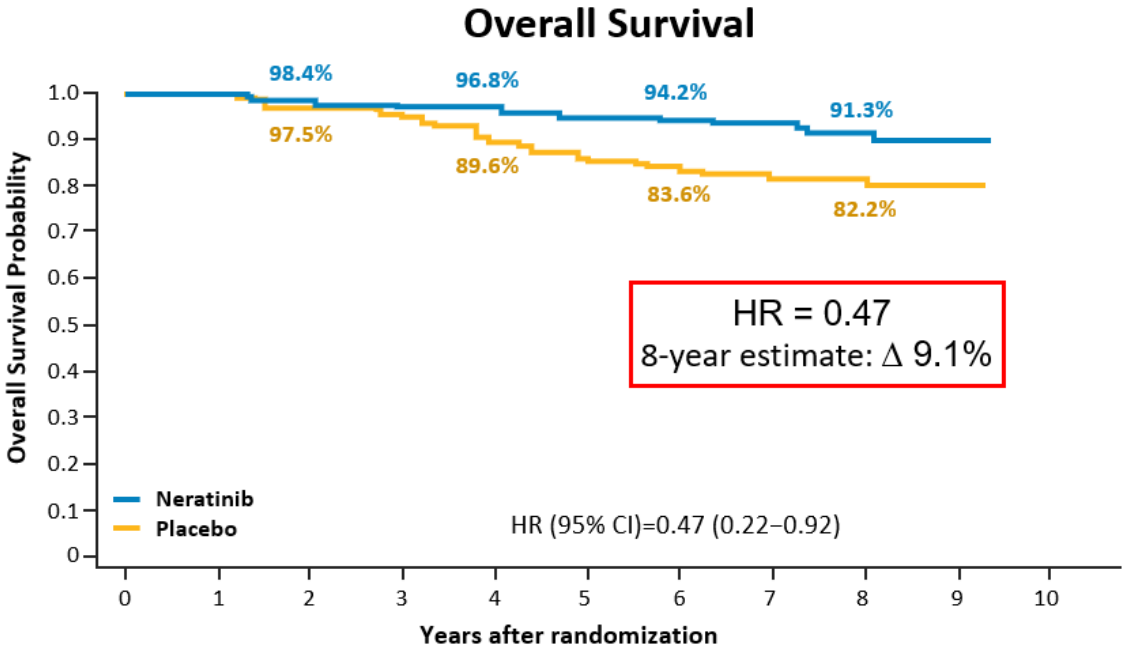


HR = 0.95, Δ 0.1%

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

ExteNET: Greater benefit among non-pCR, HR+, <1 yr from adjuvant trastuzumab patients (N=295) *subgroup analysis





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

A011801 CompassHER RD: An Escalation Trial

- CompassHER2 EA1181: Neoadjuvant de-escalation of THP in stage II-III HER2+ early breast cancer
- CompassHER2 A011801: **Escalation trial, HER2+ residual disease after neoadjuvant therapy**
  - Trial actively recruiting, NCT04457596

A011801 CompassHER2 RD

Key Inclusion Criteria (yes to all)

- *HER2*+ invasive residual BC, ER+, and ER-
- cT1-4,N0-3 *at diagnosis*
- ER-: any amount of residual disease
- ER+: lymph node positive disease post op
- Received ≥6 cycles of chemotherapy (preop ± postop; including ≥9 weeks neoadjuvant taxane and trastuzumab) prior to registration

Residual invasive HER2+ disease after neoadjuvant chemotherapy and HER2 therapy

R
1:1

TDM1 and placebo x 14 cycles

T-DM1 and tucatinib x 14 cycles

Primary objective: iDFS HER2+

O'Sullivan, C. C., Ballman, K. V., McCall, L., Kommalapati, A., Zemla, T., Weiss, A., ... Partridge, A. H. (2021). Alliance A011801 (compassHER2 RD): Postneoadjuvant T-DM1 + Tucatinib/Placebo in Patients with Residual HER2-Positive Invasive Breast Cancer. *Future Oncology*, *17*(34), 4665–4676. https://doi-org.kumc.idm.oclc.org/10.2217/fon-2021-0753

DESTINY-Breast 05

Phase III, multicenter, randomized , open label, active-controlled study of trastuzumab deruxtecan vs trastuzumab emtansine in patients with high risk HER2+ breast cancer with residual disease in breast or axilla following NACT

*high risk defined based on inoperable cancer at disease presentation or operable with positive node status after NACT

Patients

- High risk HER2+ early breast cancer w/ residual disease after NACT and preoperative HER2 therapy

R
1:1

800 patients received:

T-Dxd 5.4 mg/kg q3w x 14 cycles

800 patients received:

T-DM1 3.6 mg/kg q3w x 14 cycles

Primary efficacy outcome: iDFS

Stratification:
- Operative status at presentation
- Tumor hormone receptor status
- Post-neo-adjuvant therapy pathologic nodal status
- HER2 targeted neo-adjuvant therapy approach (single vs double)

Dowling GP, Toomey S, Bredin P, Parker I, Mulroe E, Marron J, McLoughlin O, Teiserskiene A, Power C, O'Shea AM, Greally M, Morris PG, Duke D, Hill ADK, Hennessy BT. Neoadjuvant trastuzumab deruxtecan (T-DXd) with response-directed definitive therapy in early stage HER2-positive breast cancer: a phase II study protocol (SHAMROCK study). BMC Cancer. 2024 Jan 17;24(1):91. doi: 10.1186/s12885-024-11851-4. PMID: 38233810; PMCID: PMC10792949

Thank you!