How I treat HER2+ Breast Cancer in 2023

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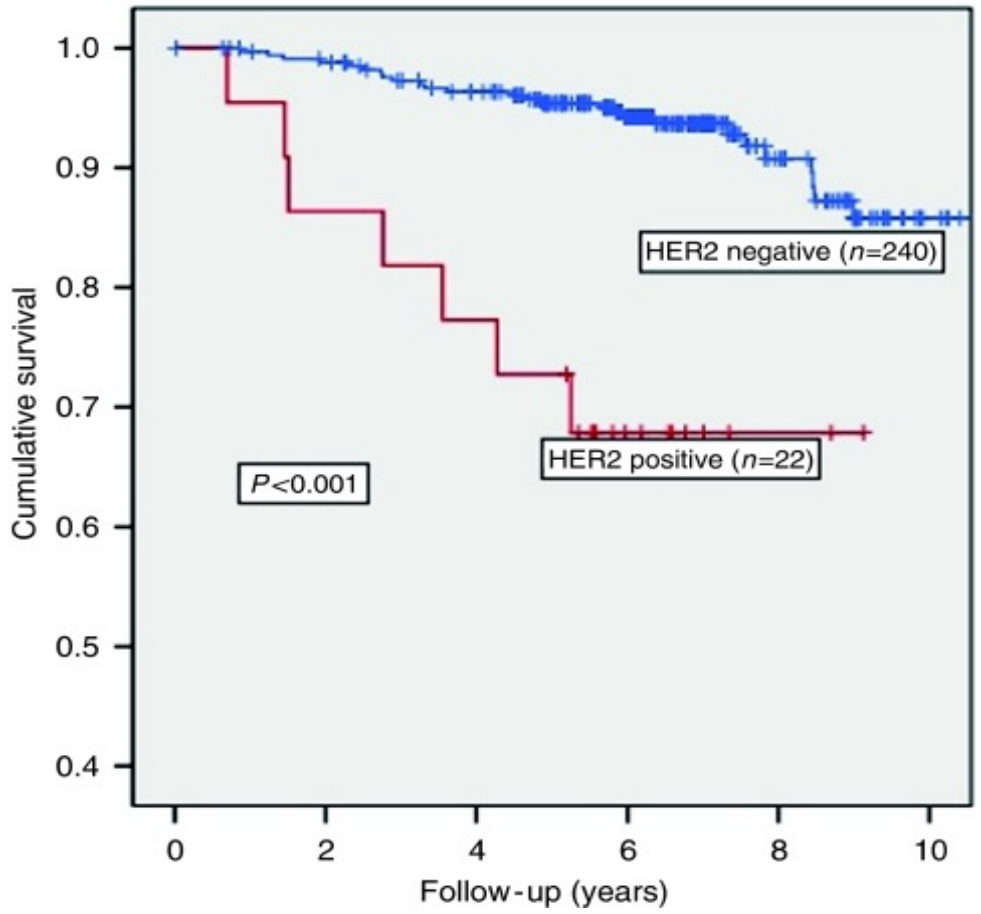
Outline

- Early Stage/Adjuvant
- Neoadjuvant/post-neoadjuvant
- Metastatic

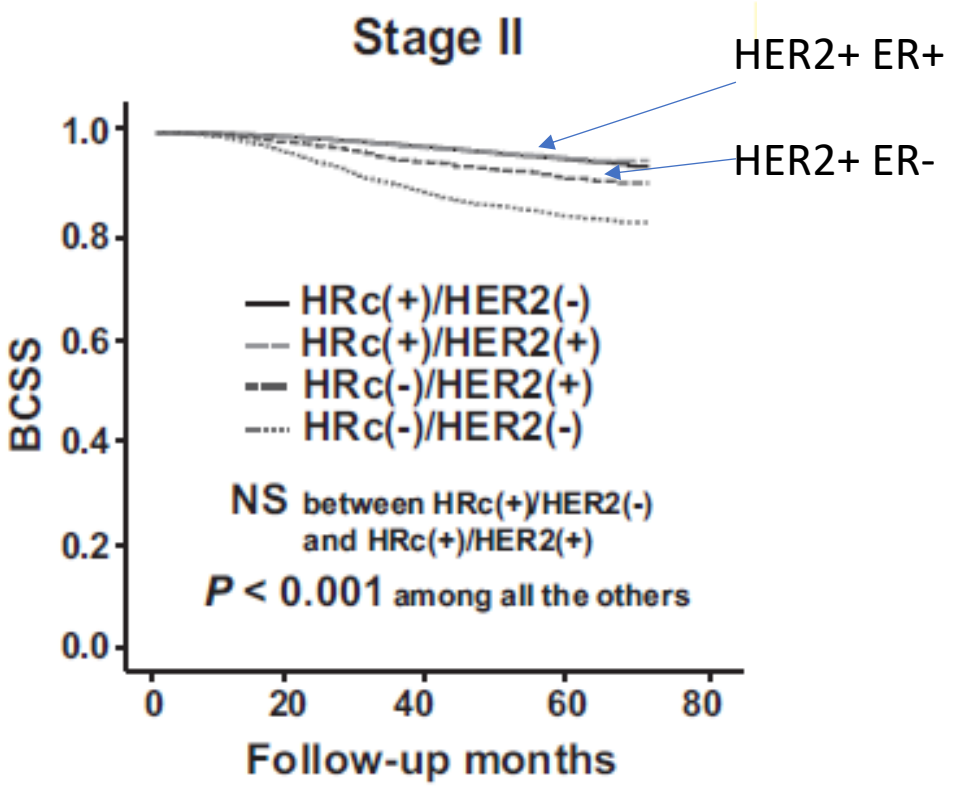
Impact of HER-2 Targeting Therapies on HER-2+ Breast Cancer

Before



SM Tovey. *British Journal of Cancer* (2009) 100(5), 680 – 683

After



Ki-Tae Hwang. *Clin Cancer Res*; 25(6) March 15, 2019

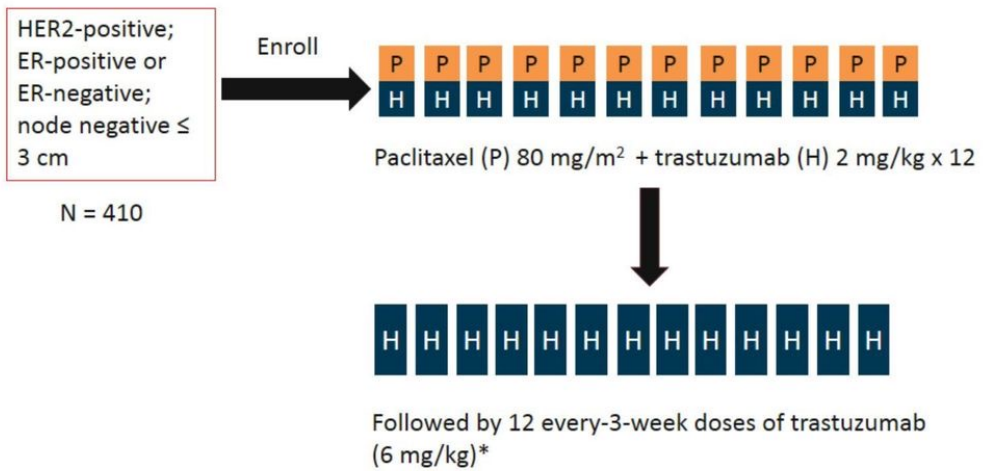
How I treat early stage HER2+ breast cancer

- Adjuvant Therapy

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

Study Design: APT Trial



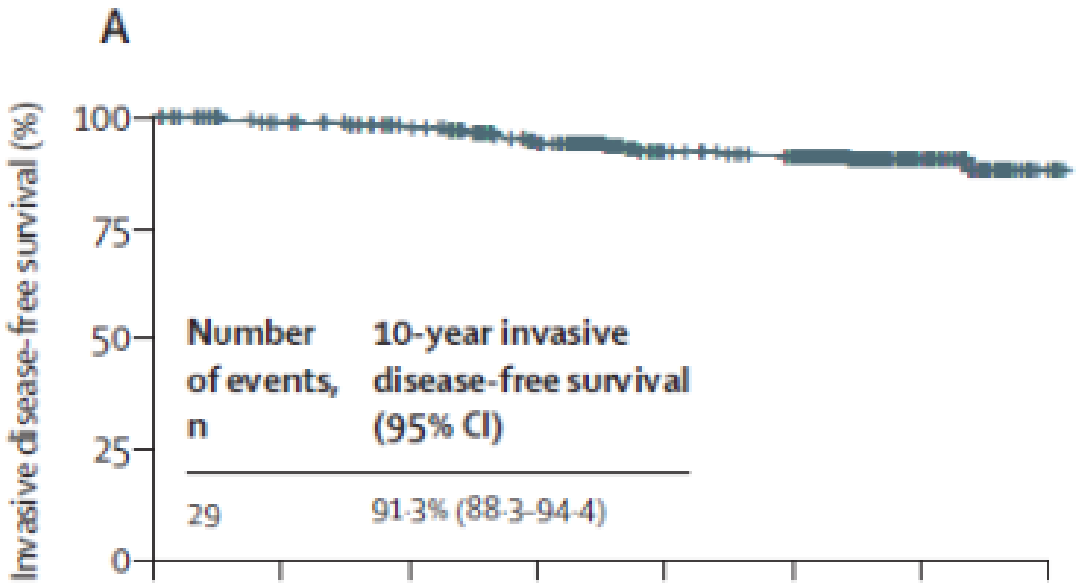
*Patients received paclitaxel (80 mg/m²) with trastuzumab x 12 weekly, followed by trastuzumab (weekly or every 3 weeks) x 39 weeks

Tolaney SM, et al. ASCO 2017. Abstract 511.

Lancet Oncol 2023; 24: 273–85

APT: Final 10 yr OS

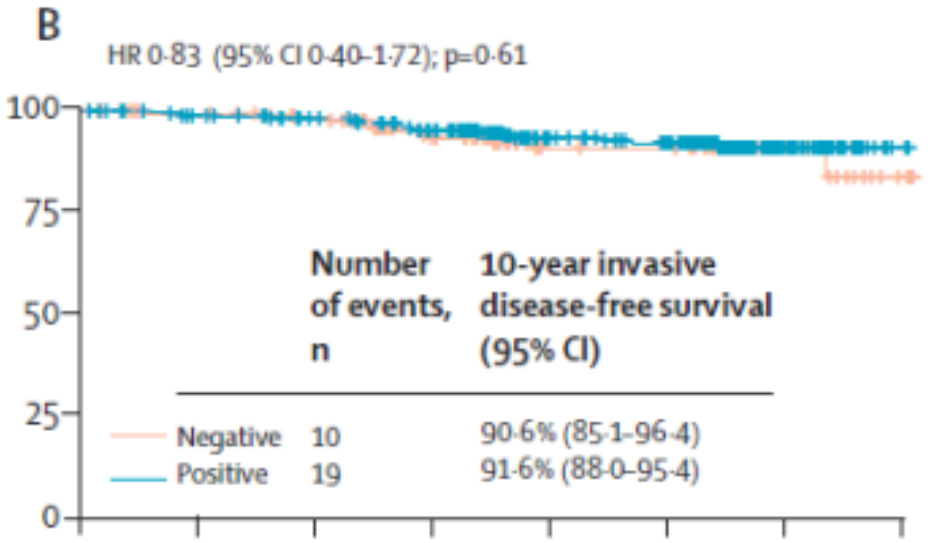
Overall



Number at risk (number censored)

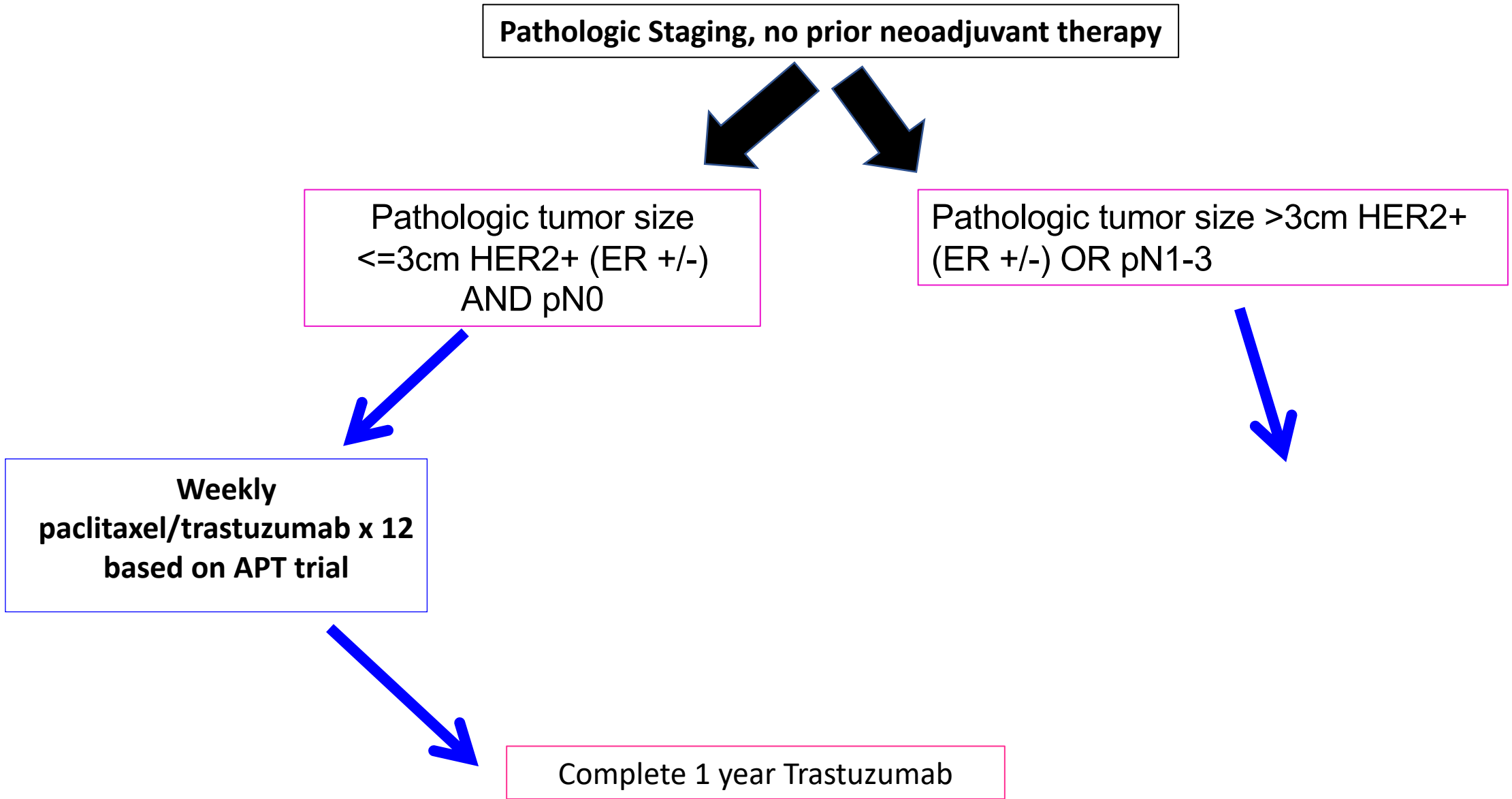
	406 (0)	385 (17)	363 (35)	321 (64)	234 (146)	216 (161)	52 (324)	5 (370)

HR+ vs. HR-



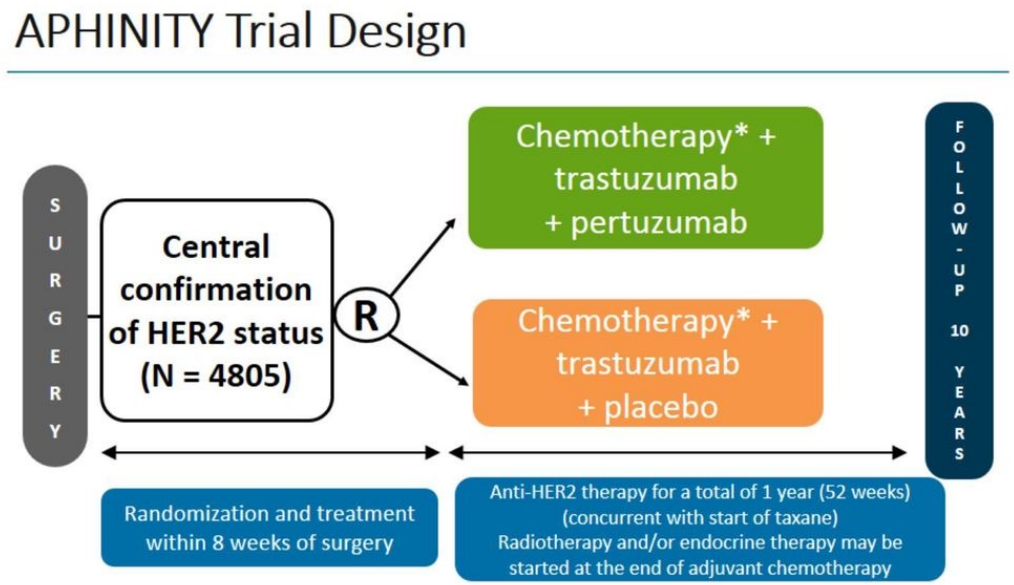
Negative	134 (0)	126 (7)	119 (13)	97 (29)	66 (58)	65 (59)	16 (108)	3 (120)
Positive	272 (0)	259 (10)	244 (22)	224 (35)	168 (88)	151 (102)	36 (216)	2 (250)

De-escalation of Adjuvant therapy in HER2+ Early Stage Breast Cancer:



Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer in the APHINITY Trial: 6 Years' Follow-Up

Martine Piccart, MD, PhD[1]; Marion Procter, PhD[2]; Debora Fumagalli, MD, PhD[3]; Evandro de Azambuja, MD, PhD[1]; Emma Clark, MSc[4]; Michael S. Ewer, MD, JD, PhD[5]; Eleonora Restuccia, MD[6]; Guy Jerusalem, MD, PhD[7]; Susan Dent, BSc, MD[8]; Linda Reaby, AM, PHD[9,10]; Hervé Bonnefoi, MD[11]; Ian Krop, MD, PhD[12]; Tsang-Wu Liu, MD[13]; Tadeusz Pieńkowski, MD, PhD[14]; Masakazu Toi, MD, PhD[15]; Nicholas Wilcken, PhD[16,17]; Michael Andersson, MD, DMSci[19,18]; Young-Hyuck Im, MD, PhD[19]; Ling Ming Tseng, MD[20]; Hans-Joachim Lueck, MD[21]; Marco Colleoni, MD[22]; Estefania Monturus, PhD[6]; Mihaela Sicoe, MSc[3]; Sébastien Guillaume, MSc[1]; José Bines, MD, PhD[23]; Richard D. Gelber, PhD[24]; Giuseppe Viale, MD[25]; and Christoph Thomssen, MD[26] for the APHINITY Steering Committee and Investigators

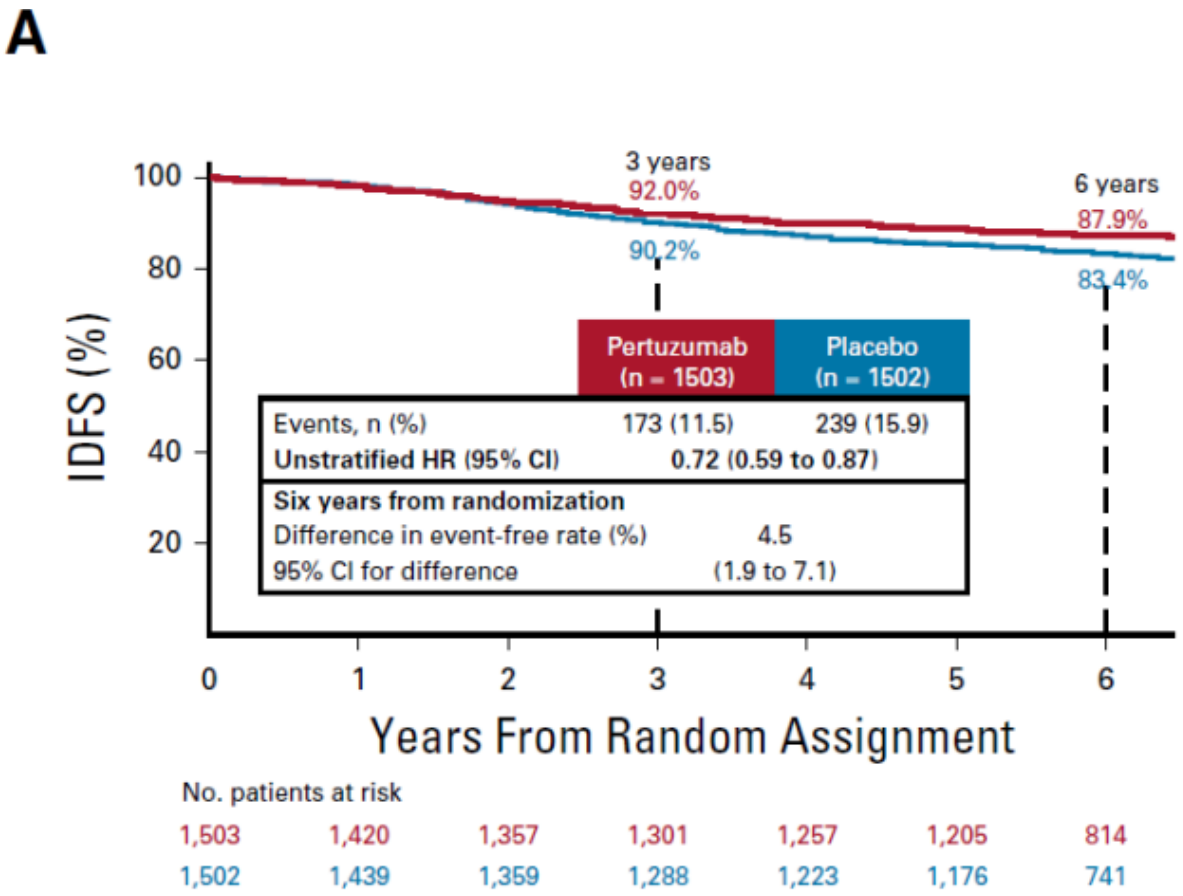


*A number of standard anthracycline-taxane-sequences or a non-anthracycline (TCH) regimen were allowed. von Minckwitz G, et al. *N Engl J Med*. 2017;377:122-131.

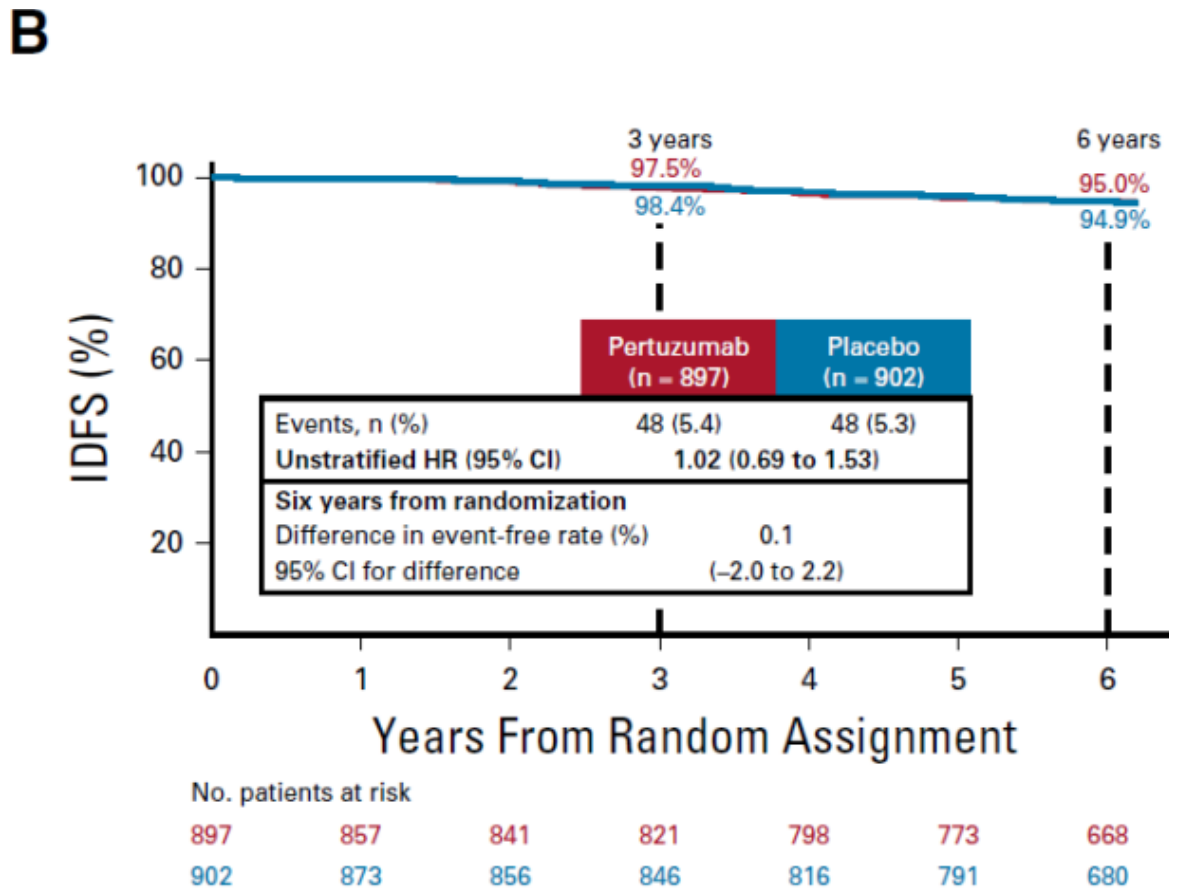
J Clin Oncol 39:1448-1457.

Aphinity: Adjuvant pertuzumab beneficial only for N+ dz

Node +

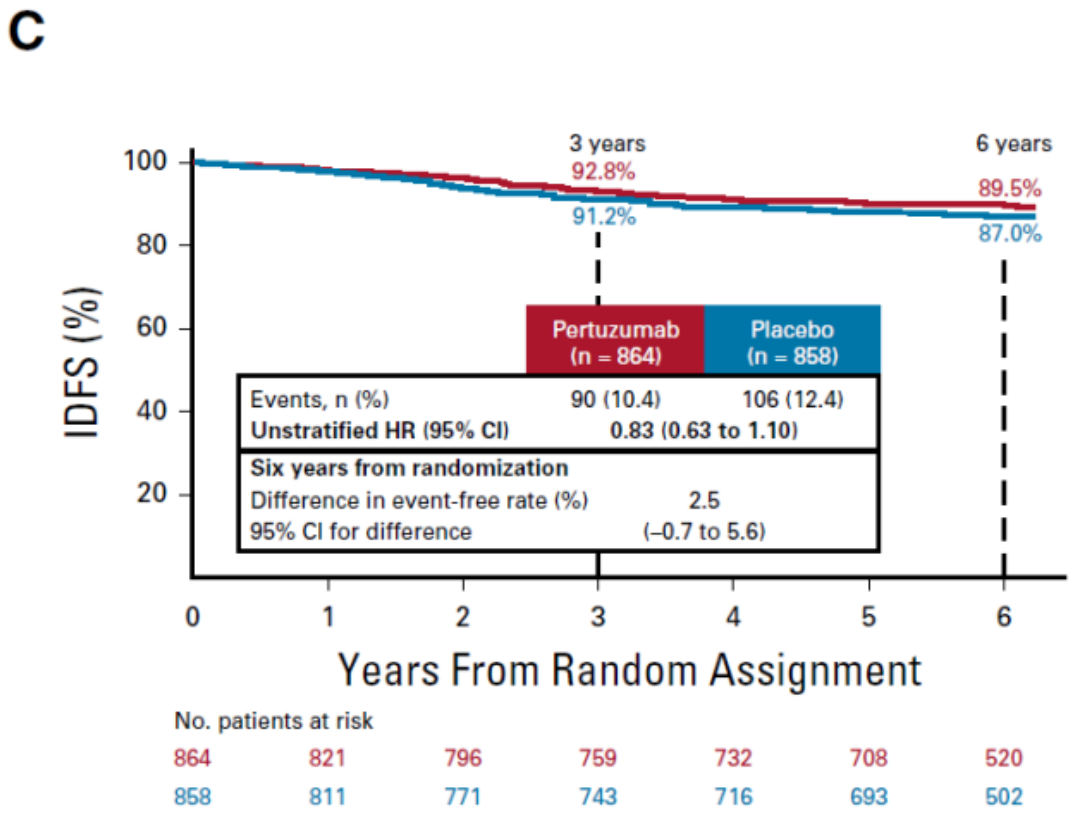


Node -

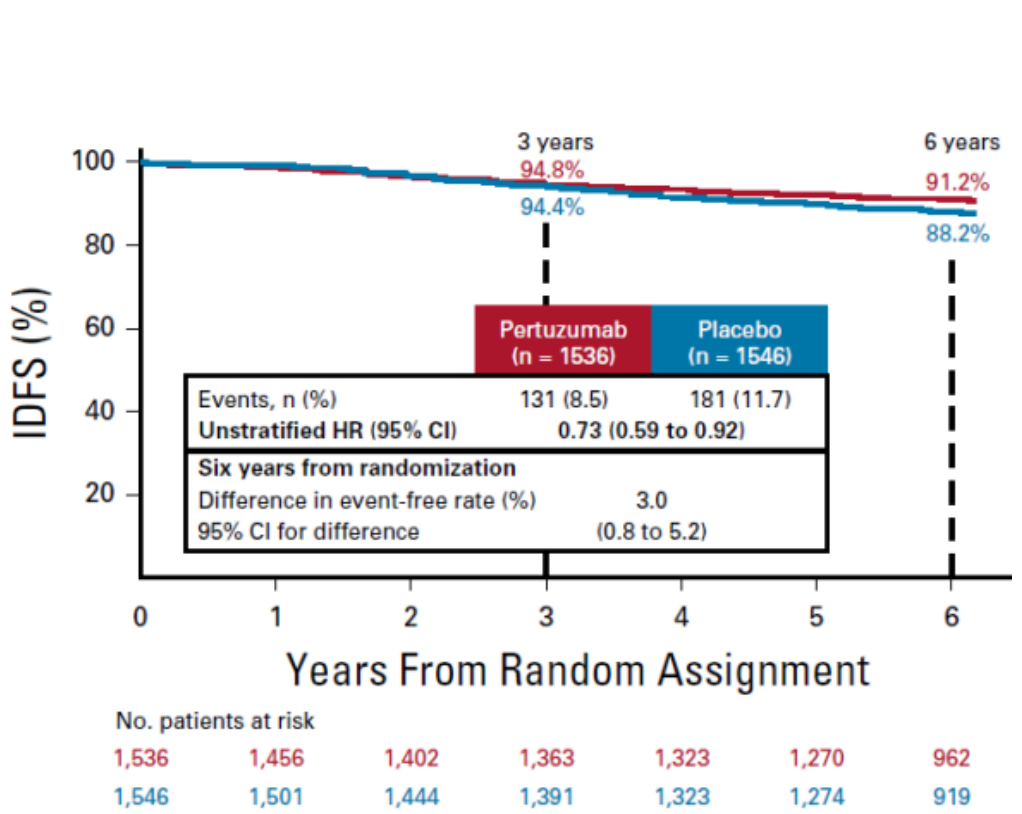


Aphinity: Adjuvant pertuzumab no difference by ER status

ER-



ER+



No advantage of adjuvant anthracyclines vs. non-anthracyclines: BCIRG-006

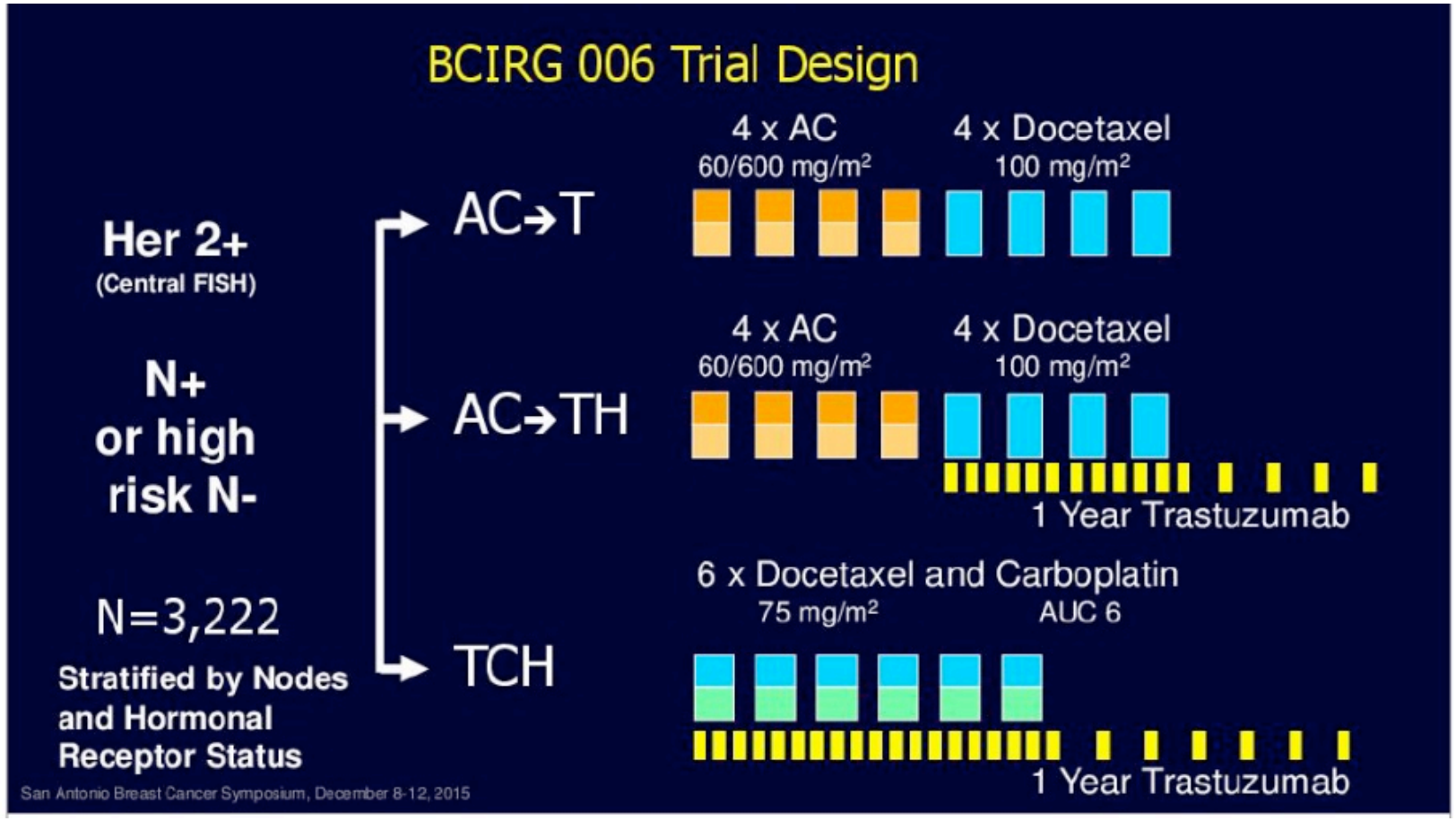
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 6, 2011 VOL. 365 NO. 14

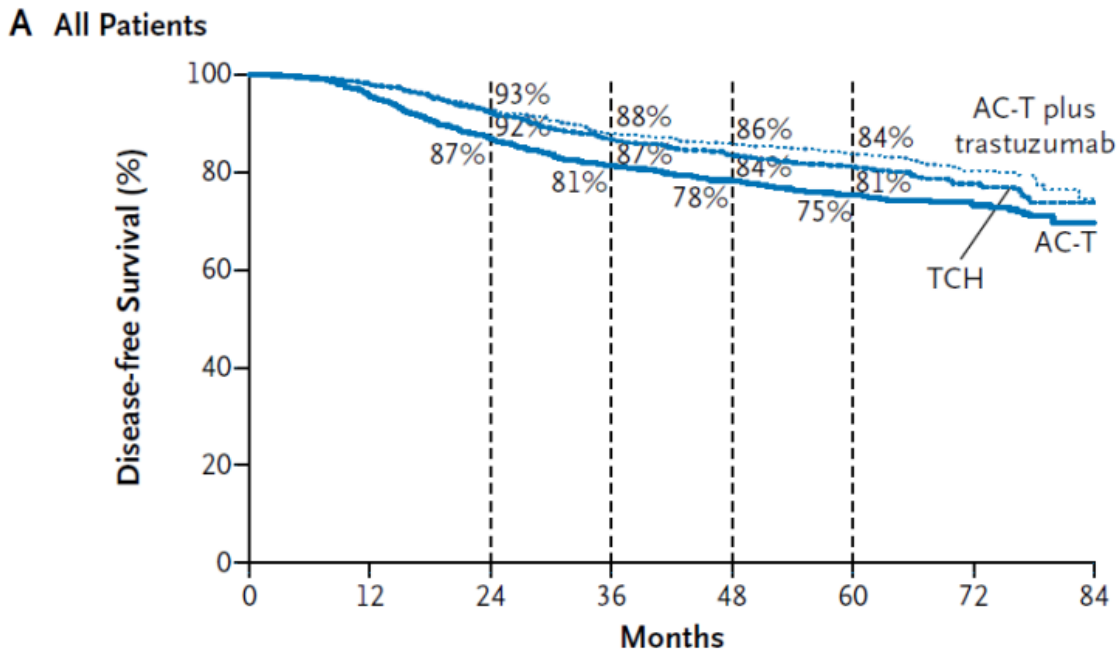
Adjuvant Trastuzumab in HER2-Positive Breast Cancer

Dennis Slamon, M.D., Ph.D., Wolfgang Eiermann, M.D., Nicholas Robert, M.D., Tadeusz Pienkowski, M.D., Miguel Martin, M.D., Michael Press, M.D., Ph.D., John Mackey, M.D., John Glaspy, M.D., Arlene Chan, M.D., Marek Pawlicki, M.D., Tamas Pinter, M.D., Vicente Valero, M.D., Mei-Ching Liu, M.D., Guido Sauter, M.D., Gunter von Minckwitz, M.D., Frances Visco, J.D., Valerie Bee, M.Sc., Marc Buyse, Sc.D., Belguendouz Bendahmane, M.D., Isabelle Tabah-Fisch, M.D., Mary-Ann Lindsay, Pharm.D., Alessandro Riva, M.D., and John Crown, M.D., for the Breast Cancer International Research Group*

BCIRG-006 study design

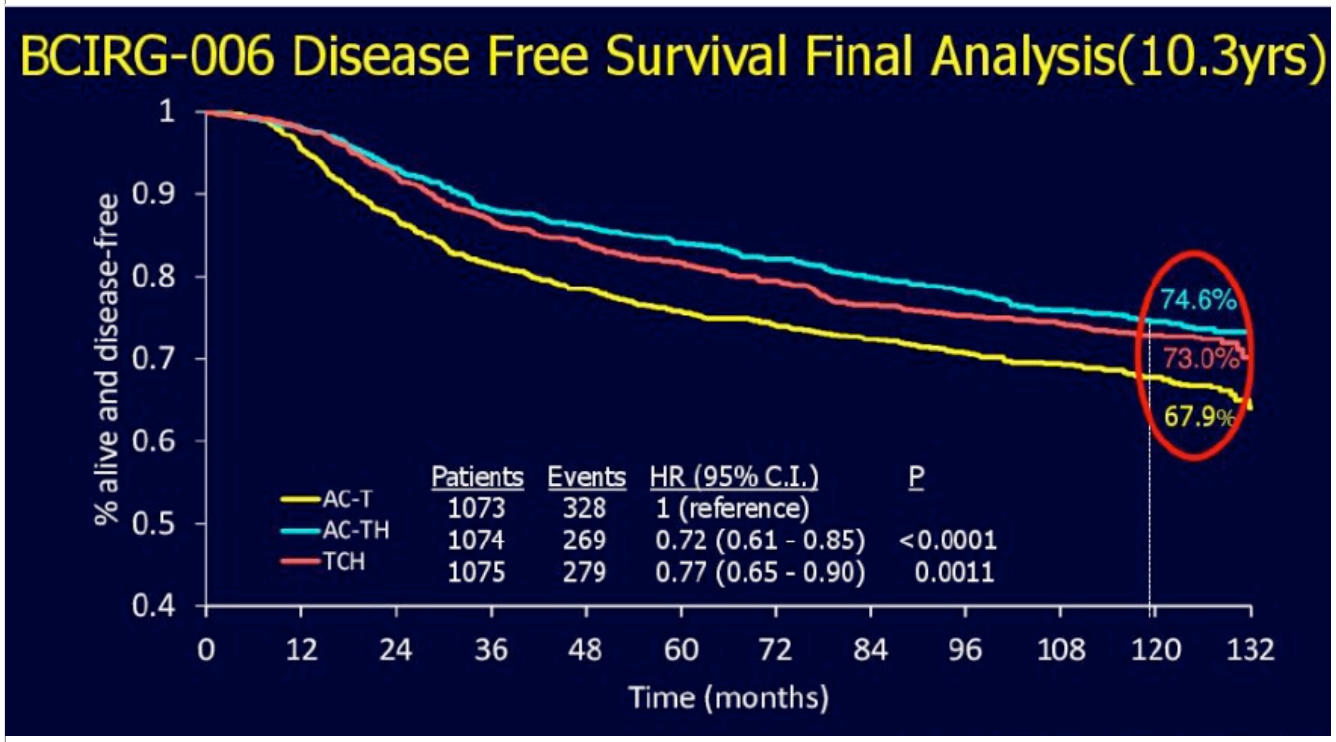


BCIRG-006 DFS (5 and 10 years)

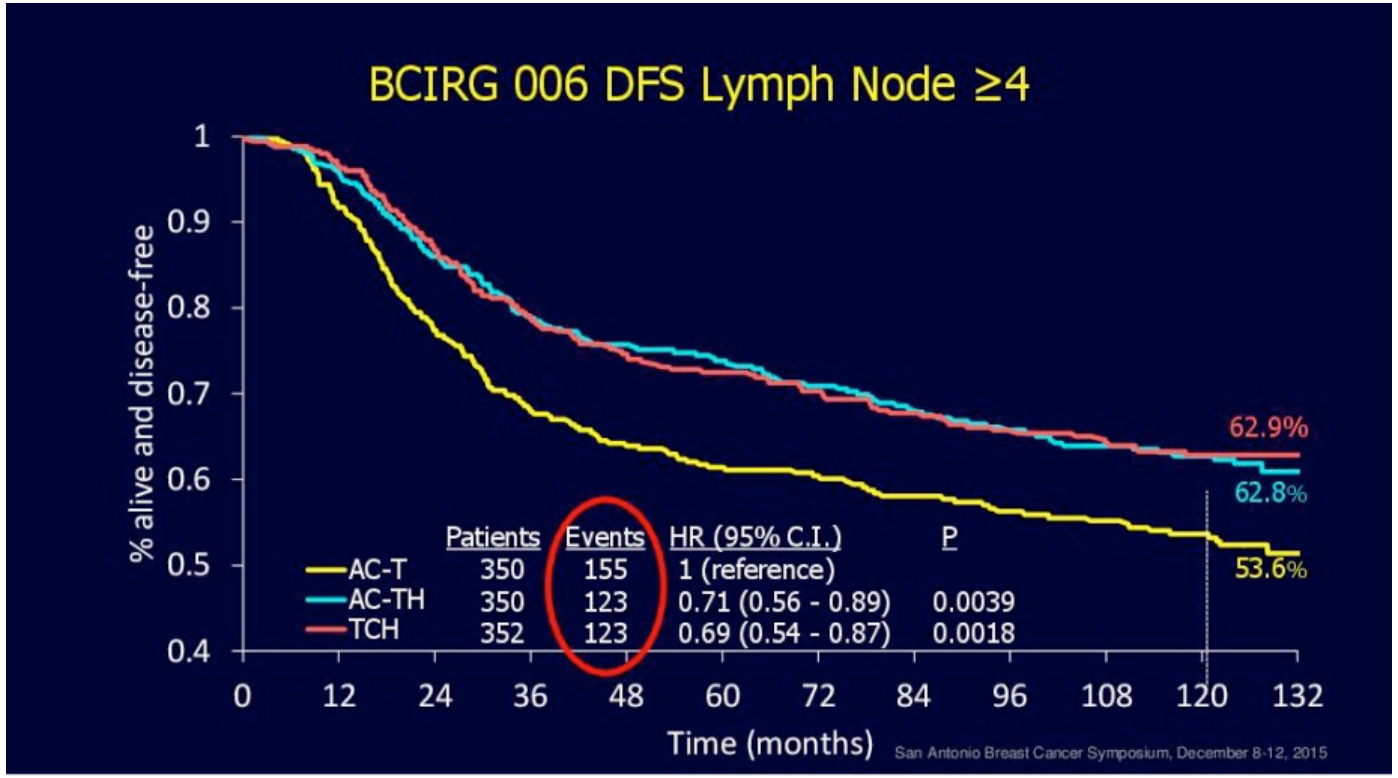


No. at Risk

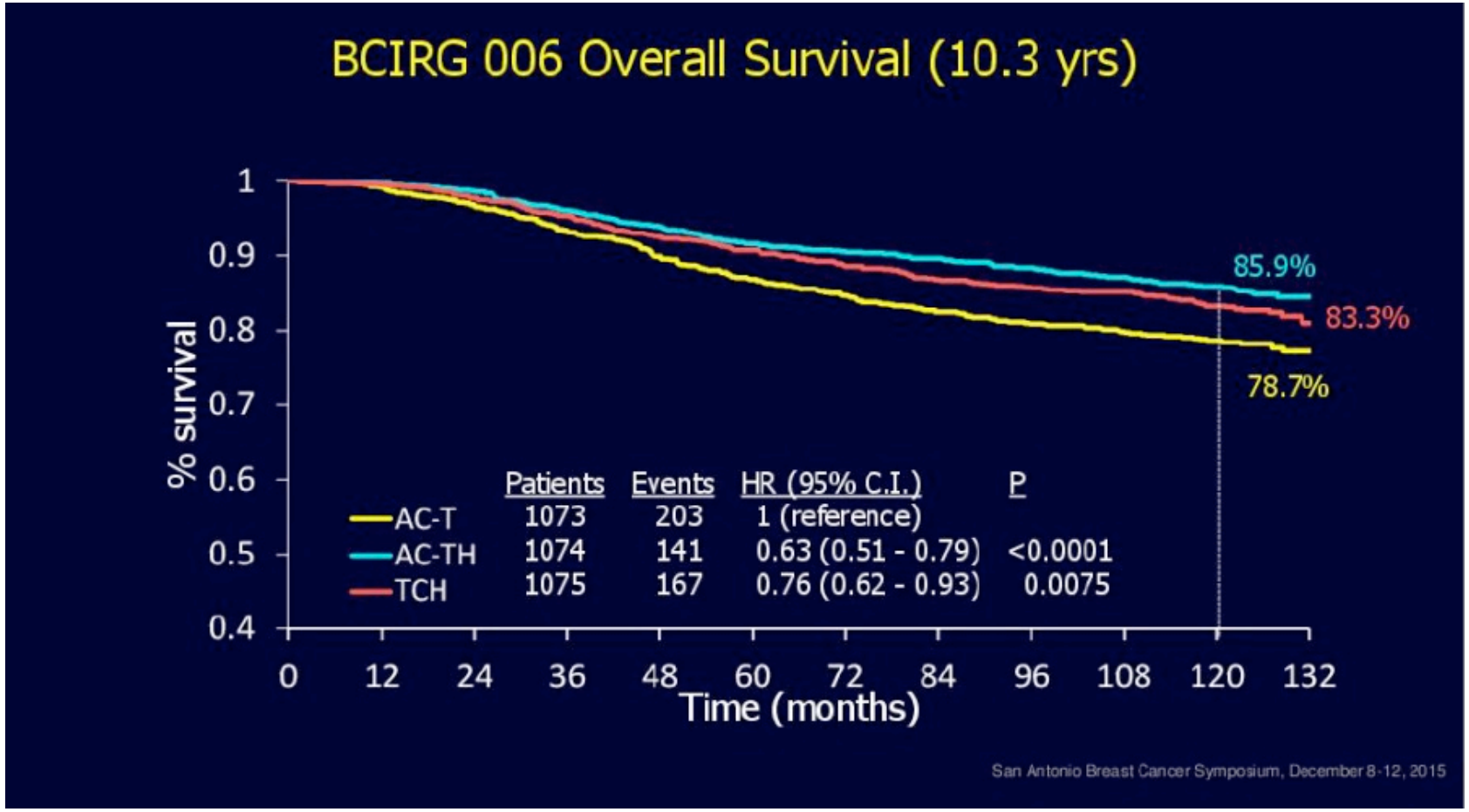
AC-T	1073	977	861	774	695	555	202	29
AC-T plus trastuzumab	1074	1028	951	861	774	620	226	37
TCH	1075	1021	939	848	770	606	208	33



BCIRG-006: anthracycline/trastuzumab combo is not superior to TCH even in >4+ nodes



BCIRG-006 OS: final analysis



Abstract S5-04. Presented December 11, 2015.

AC-TH: increased CHF, cardiac deaths, and AML

BCIRG 006 Cardiac Deaths and CHF

	AC→T n=1,050	AC→TH n=1,068	TCH n=1,056
Cardiac related death	0	0	0
Cardiac left ventricular function (CHF) Grade 3 / 4	8	21	4

p=0.0005

San Antonio Breast Cancer Symposium - December 8-12, 2015

BCIRG-006 Mean LVEF - All Observations (Final Analysis)

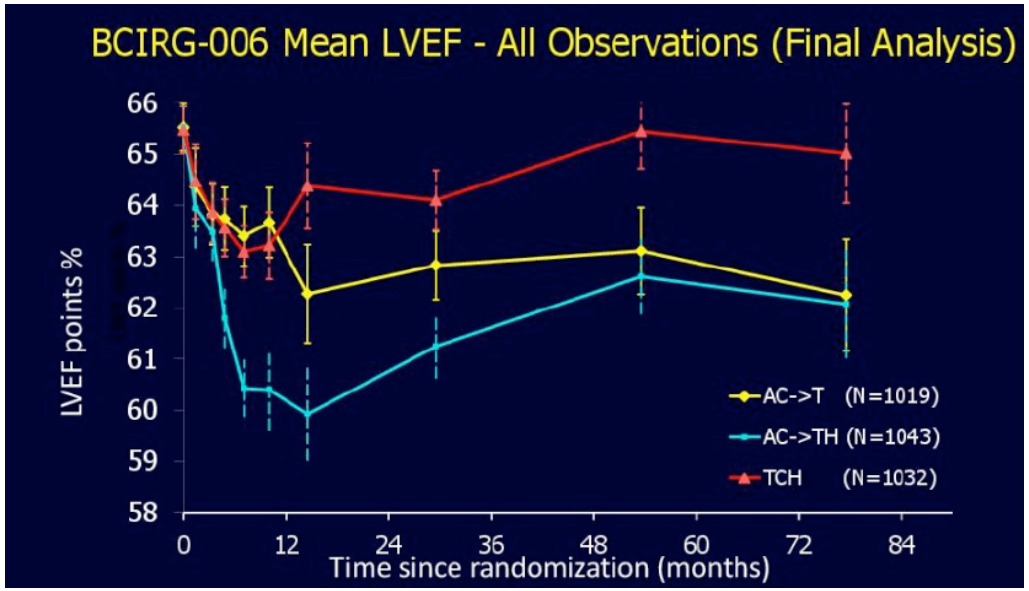


Table 1: BCIRG-006: Therapeutic Index, Final Analysis at 10 Years

	AC-TH	TCH
Disease-free survival events	269	279
Grade 3/4 congestive heart failure	21 (2%)	4 (0.4%)
Total disease-free survival events	290	283
Treatment-related leukemia	7	0
Sustained LVEF loss > 10%	200	97

AC-TH = doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab; TCH = docetaxel, carboplatin, and trastuzumab; LVEF = left ventricular ejection fraction.

Can chemo be omitted in older HER2+ pts or those unable to tolerate paclitaxel or docetaxel?

rapid communicatio

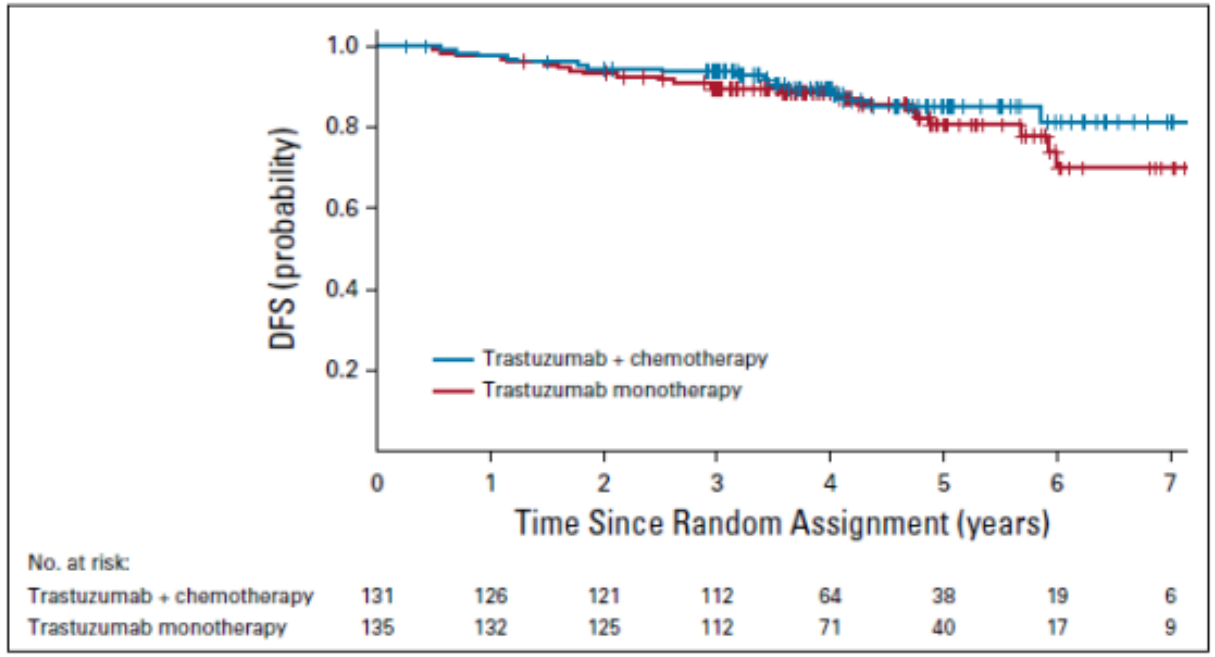
Randomized Controlled Trial of Trastuzumab Wit or Without Chemotherapy for HER2-Positive Early Breast Cancer in Older Patients

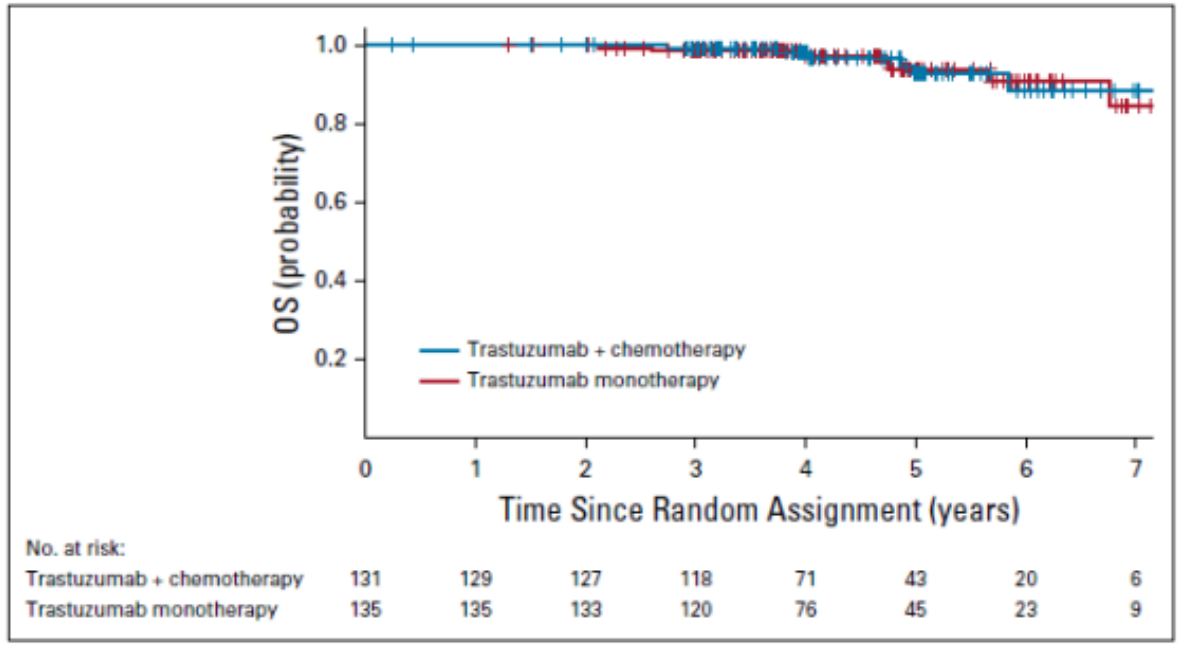
Masataka Sawaki, MD, PhD[1]; Naruto Taira, MD, PhD[2]; Yukari Uemura, PhD[3]; Tsuyoshi Saito, MD, PhD[4]; Shinichi Baba, MD[5]; Kokoro Kobayashi, MD[6]; Hiroaki Kawashima, MD, PhD[7]; Michiko Tsuneizumi, MD, PhD[8]; Noriko Sagawa, MD, PhD[9]; Hiroko Bando, MD, PhD[10]; Masato Takahashi, MD, PhD[11]; Miki Yamaguchi, MD, PhD[12]; Tsutomu Takashima, MD, PhD[13]; Takahiro Nakayama, MD, PhD[14]; Masahiro Kashiwaba, MD, PhD[5]; Toshiro Mizuno, MD, PhD[15]; Yutaka Yamamoto, MD, PhD[16]; Hiroji Iwata, MD, PhD[1]; Takuya Kawahara, PhD[17]; Yasuo Ohashi, PhD[18]; and Hirofumi Mukai, MD, PhD[19], for the RESPECT study group

J Clin Oncol 38:3743-3752

Sawaki et. al non-inferiority trial results:

- Non-inferiority not met, however:
- 3 yr DFS trastuz vs. trastuz/chemo: 92.4% vs 95.3% (HR, 1.33; 95% CI, 0.63 to 2.79; P =0.53).
- Observed loss of survival without chemotherapy ~1 month at 3 years





J Clin Oncol 38:3743-3752

How small is too small for systemic therapy in HER2+ breast cancer?

Original Article

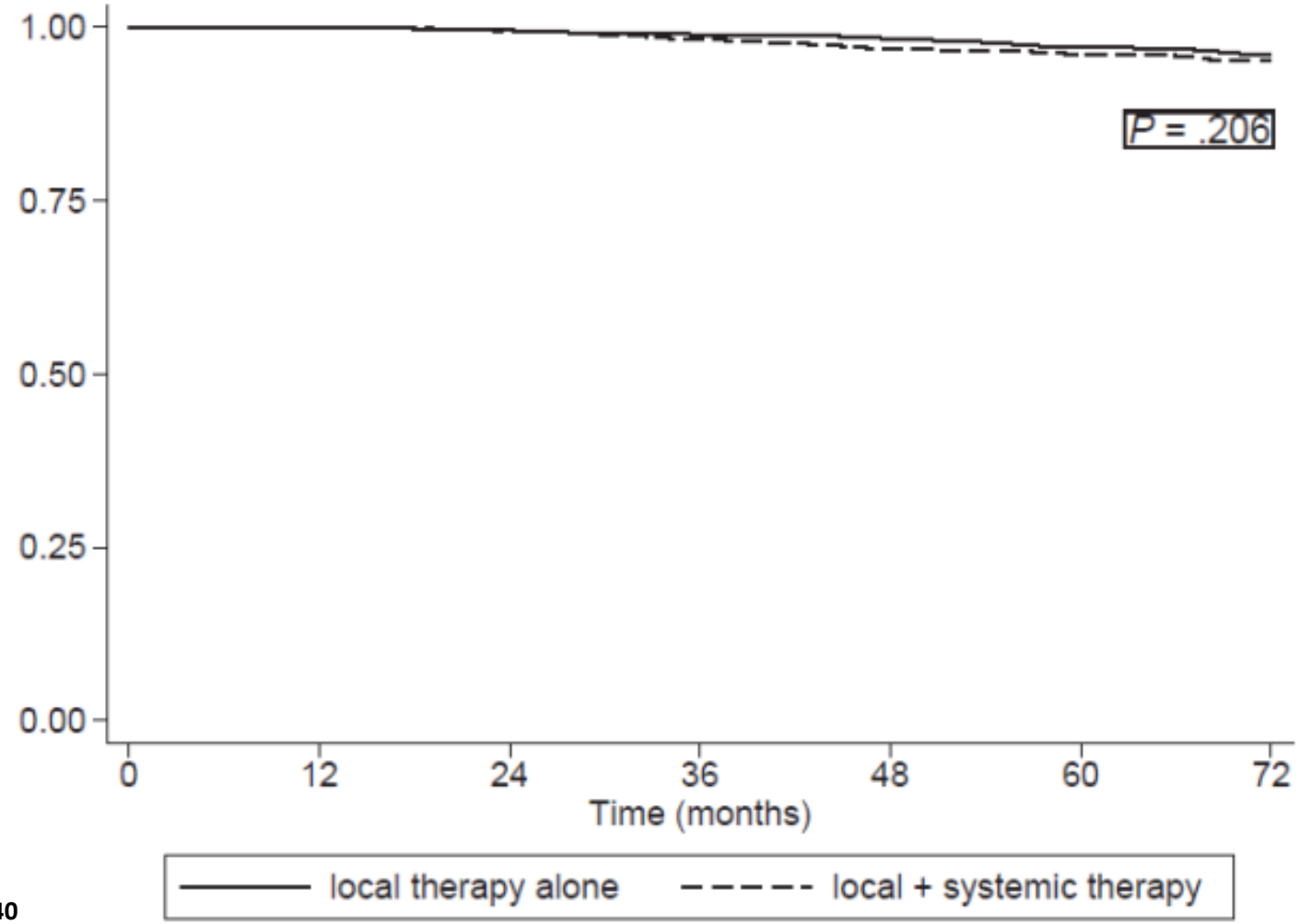
A comparison of local therapy alone with local plus systemic therapy for stage I pT1aN0M0 HER2+ breast cancer: A National Cancer Database analysis

Lifen Cao, MD, PhD [1]; Christopher W. Towe, MD[2]; Robert Shenk, MD[3,4]; Nickolas Stabellini, MS[5]; Amanda L. Amin, MD, MS [3,4]; and Alberto J. Montero, MD, MBA [1]

BACKGROUND: Small invasive breast cancers (BCs) with tumor sizes ≤5 mm (T1a) are associated with an excellent prognosis without systemic therapy. Although HER2 overexpression (HER2+) is associated with a higher risk of recurrence and poorer clinical outcomes, in the absence of HER2 directed therapy, it remains unclear whether adjuvant systemic therapy is necessary in node-negative patients diagnosed with HER2+ invasive BCs ≤5 mm (pT1aN0M0). **METHODS:** The National Cancer Database was searched to identify patients diagnosed with HER2+ pT1aN0M0 BCs from 2004 to 2017. The cohort was stratified by treatment status: local therapy alone or local plus adjuvant systemic therapy. A 1:1 propensity match was performed. Overall survival (OS) was analyzed using stratified multivariable Cox proportional hazards regression analyses. **RESULTS:** Of the 8948 patients found, 4026 (45.0%) underwent surgery alone, and 4922 (55.0%) received surgery plus systemic therapy. Patients with either moderately differentiated (odds ratio [OR], 2.053; $P < .001$) or poorly/undifferentiated tumors (OR, 3.780; $P < .001$) or with the presence of lymphovascular invasion (OR, 3.351; $P < .001$) were more likely to have received systemic therapy. Propensity matching generated 1162 pairs of patients who were hormone receptor positive (HR+) and 748 pairs who were hormone receptor negative (HR−). Propensity matching effectively reduced selection bias between study groups. In the matched cohort, the addition of systemic therapy was not associated with superior OS (hazard ratio for HR+, 1.613; $P = .107$, and hazard ratio for HR− 1.319; $P = .369$) compared with patients who received local therapy alone. **CONCLUSIONS:** In pT1aN0M0 HER2+ BC, the addition of adjuvant systemic therapy after surgical excision was not associated with improved OS compared with local therapy alone. ***Cancer* 2022;128:2433-2440**. © *2022 American Cancer Society*.

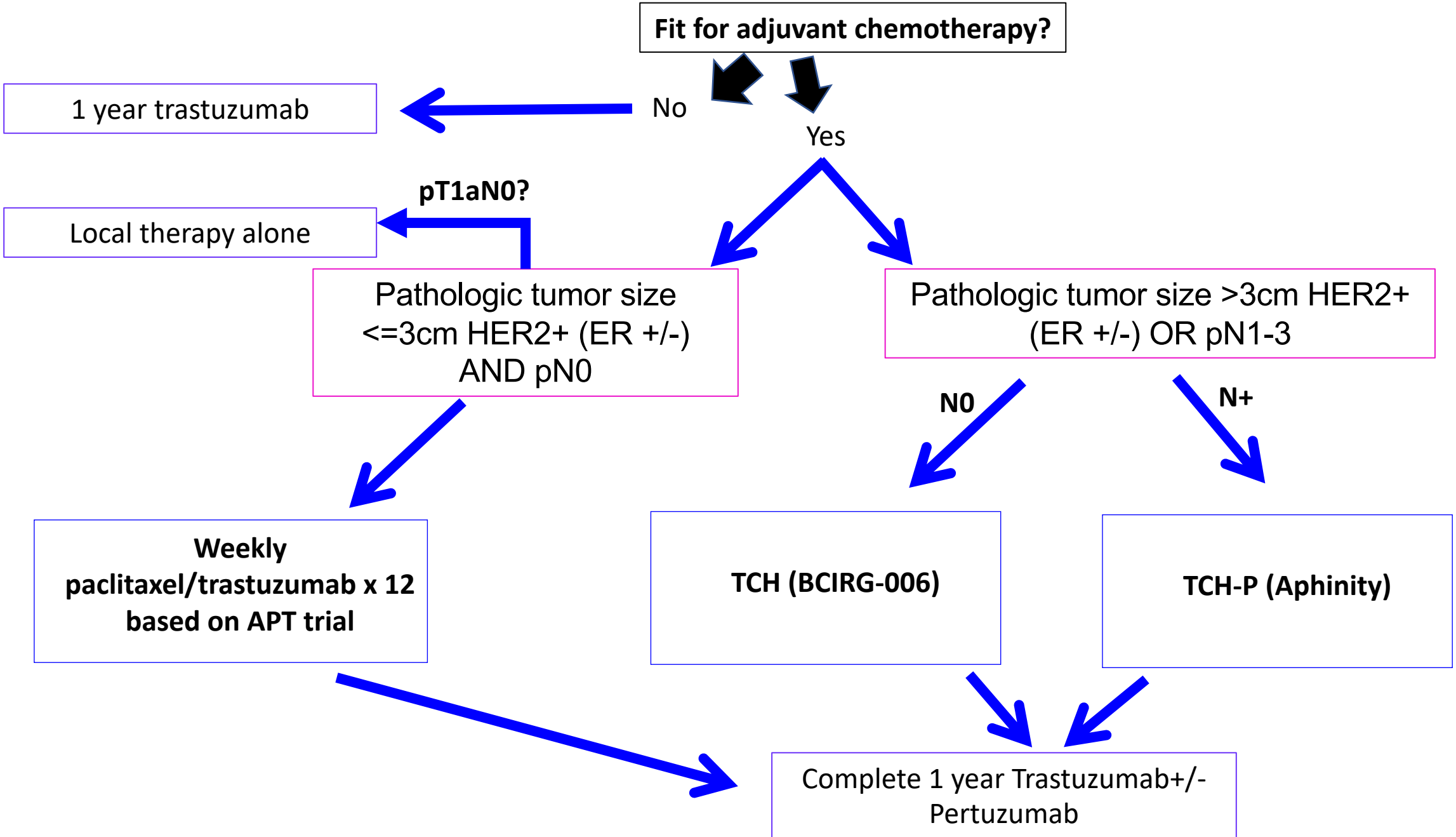
KEYWORDS: breast cancer, chemotherapy, HER2 positive, immunotherapy, T1a, trastuzumab.

For HER2+ pT1aN0 local therapy alone appears sufficient



Cao et al. Cancer 2022;128:2433-2440

Adjuvant therapy in HER2+ Early Stage Breast Cancer



How I treat early stage HER2+ breast cancer in 2023

- Neoadjuvant/post neoadjuvant therapy

The NEW ENGLAND JOURNAL of MEDICINE

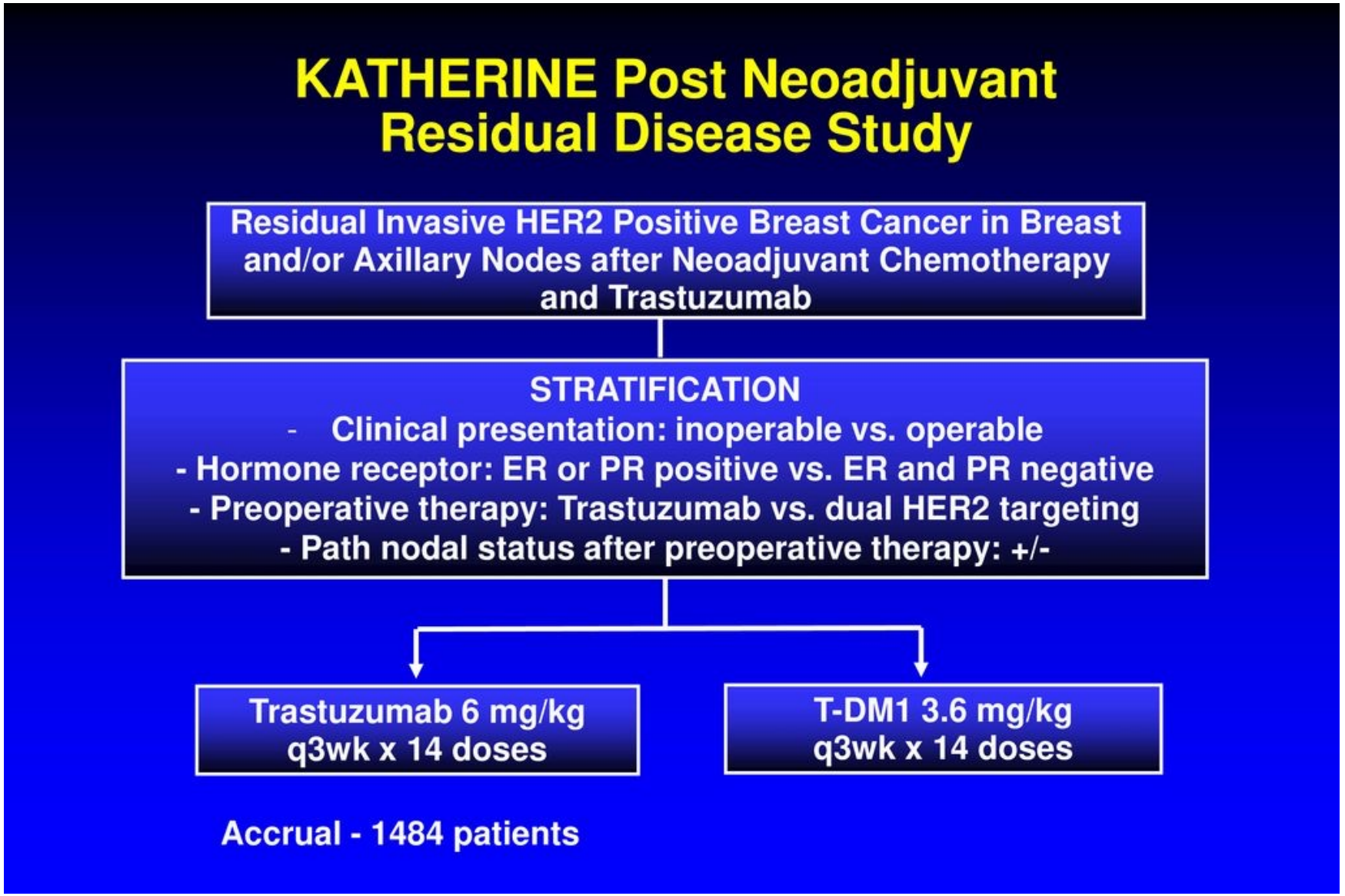
ESTABLISHED IN 1812 FEBRUARY 14, 2019 VOL. 380 NO. 7

Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer

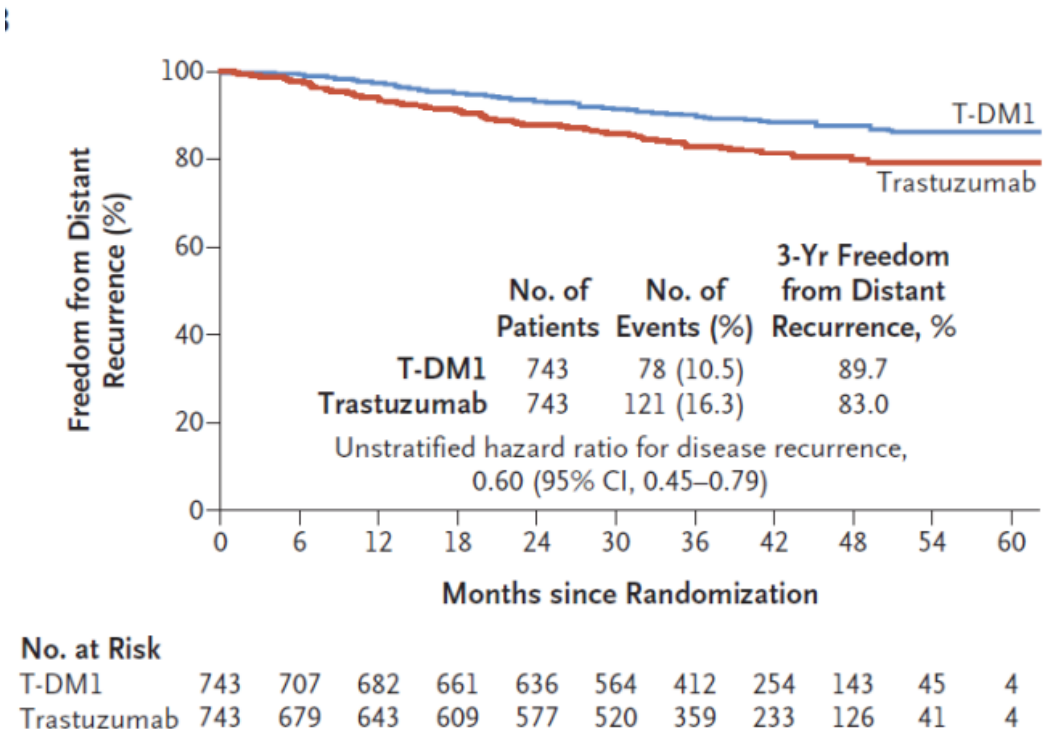
G. von Minckwitz, C.-S. Huang, M.S. Mano, S. Loibl, E.P. Mamounas, M. Untch, N. Wolmark, P. Rastogi, A. Schneeweiss, A. Redondo, H.H. Fischer, W. Jacot, A.K. Conlin, C. Arce-Salinas, I.L. Wapnir, C. Jackisch, M.P. DiGiovanna, P.A. Fasching, J.P. Crown, P. Wülfing, Z. Shao, E. Rota Caremoli, H. Wu, L.H. Lam, D. Tesarowski, M. Smitt, H. Douthwaite, S.M. Singel, and C.E. Geyer, Jr., for the KATHERINE Investigators*

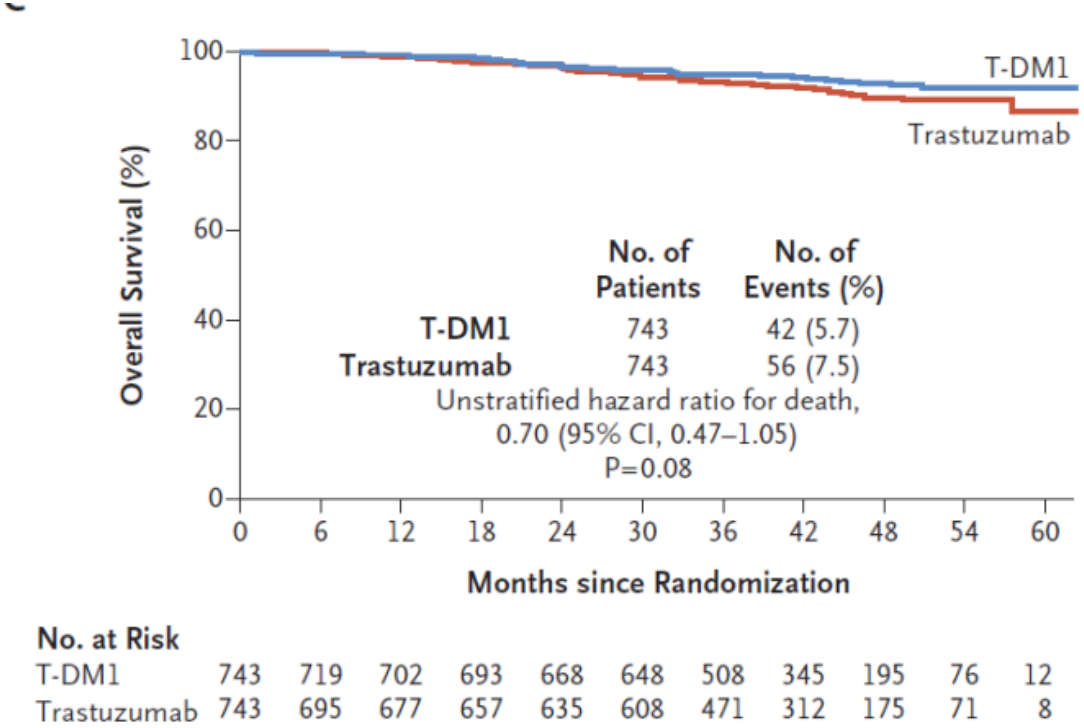
N Engl J Med 2019;380:617-28.

KATHERINE Post Neoadjuvant Residual Disease Study

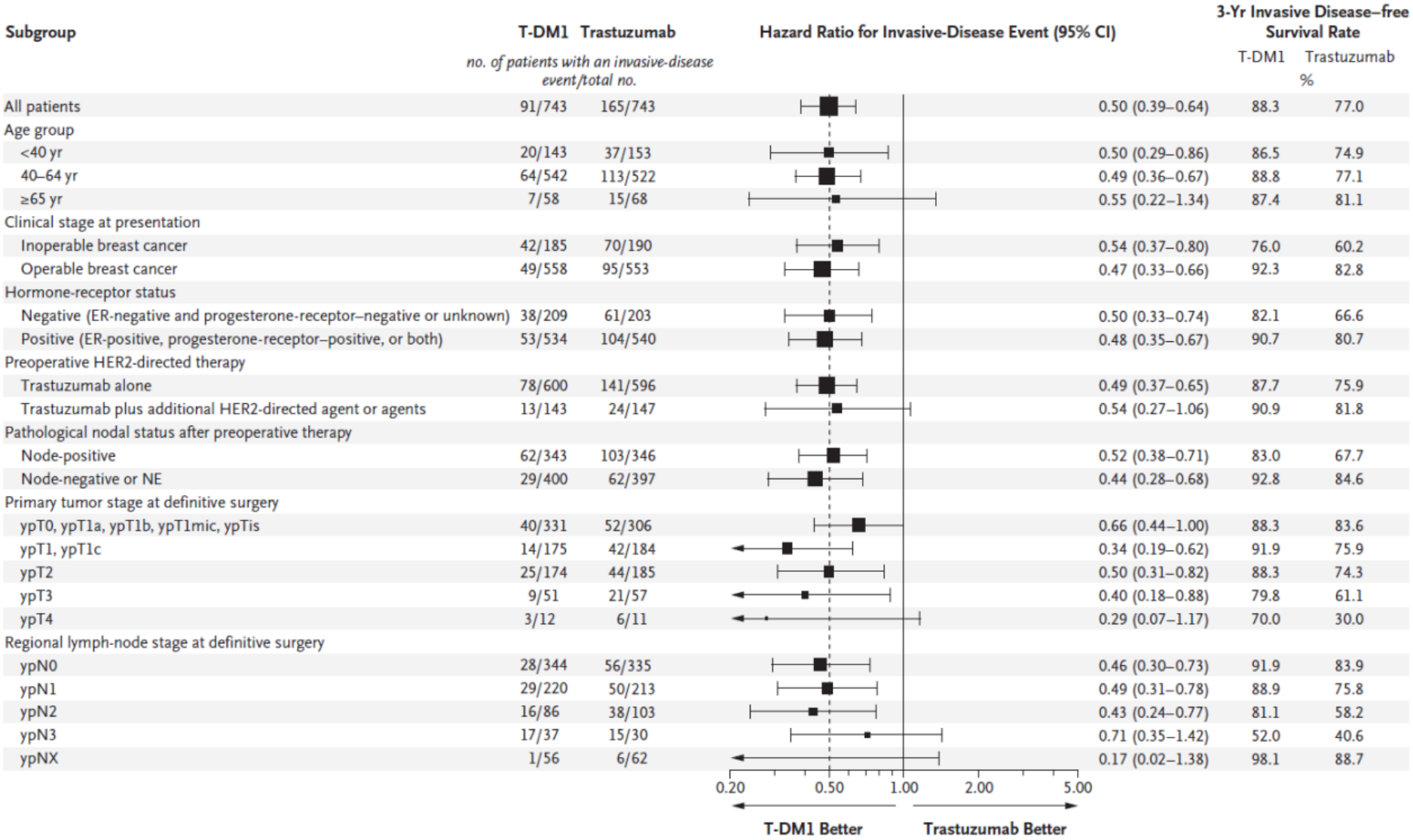


Adjuvant T-DM1: improved distant DFS and OS



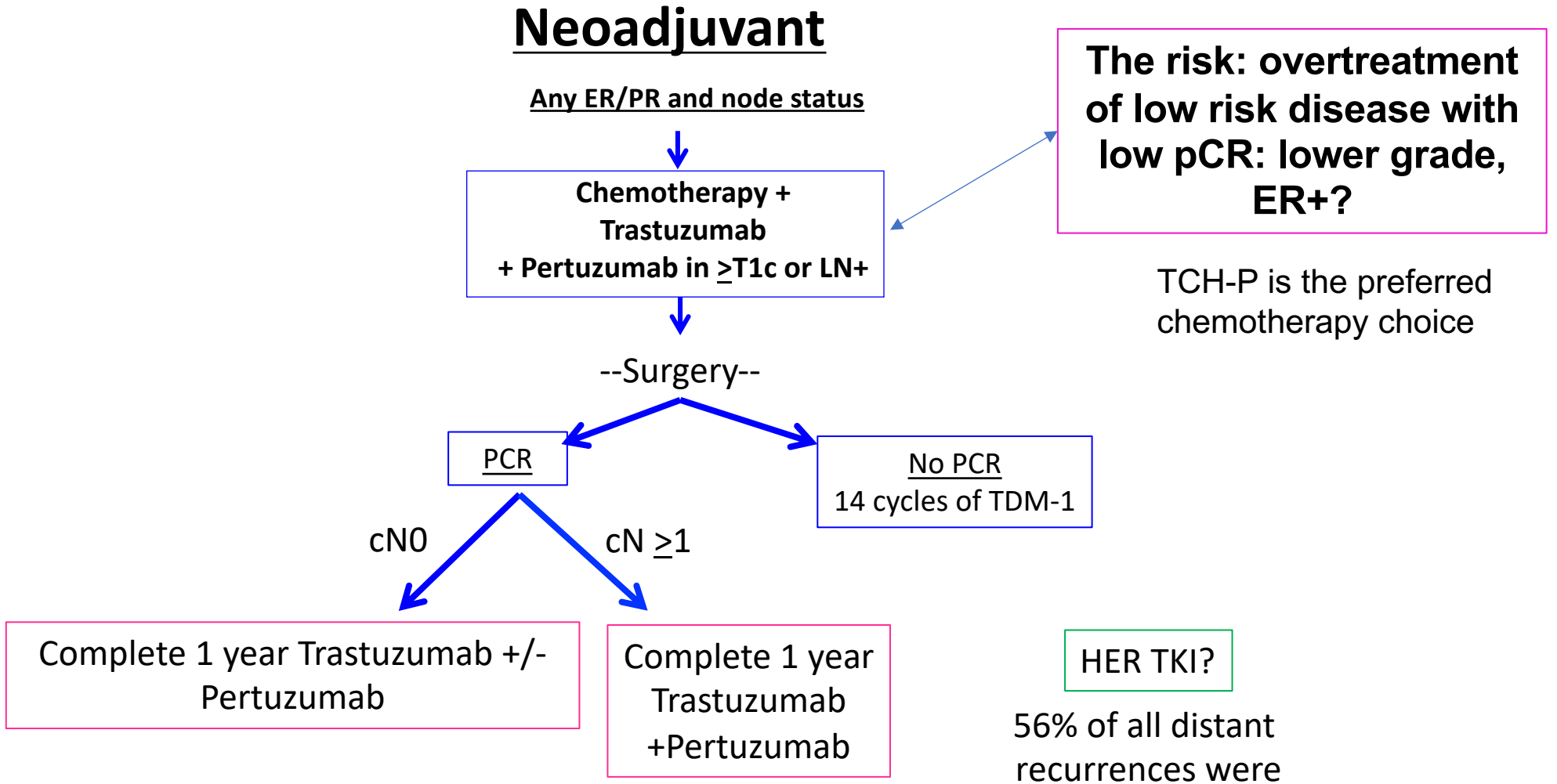


N Engl J Med 2019;380:617-28.



N Engl J Med 2019;380:617-28.

Neoadjuvant therapy is the treatment of choice in all but small (<2cm), node negative, HER2+ cancers



In HER2+ER+, yes to endocrine therapy, but what about neratinib?

[gg] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab is unknown.

NCCN Breast Guidelines **Version 4.2023 pg BINV-5**

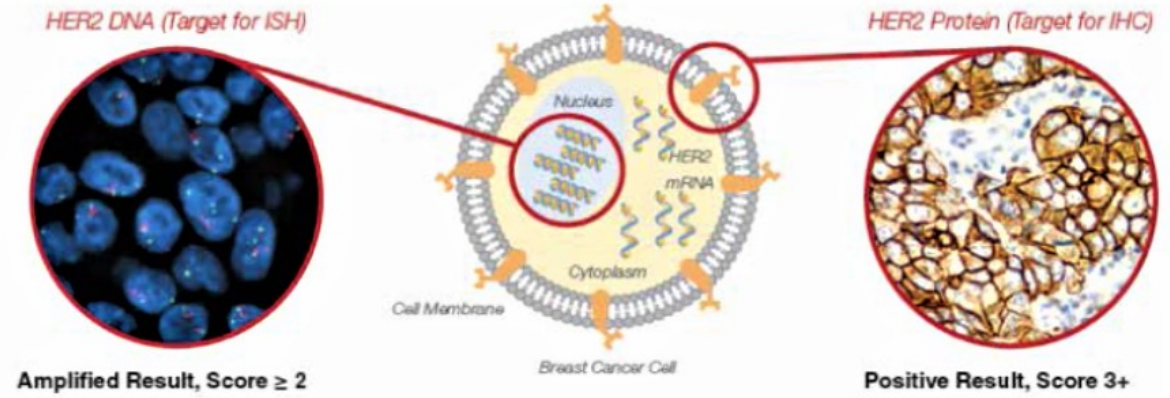
[i] Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab or ado-trastuzumab emtansine is unknown.

NCCN Breast Guidelines **Version 4.2023 pg BINV-L 2 of 9**

How I treat metastatic HER2+ breast cancer in 2023

2023: Remarkable Progress in the Treatment of HER2+ mBC

- Established therapies
  - Pertuzumab and T-DM1
- New oral tyrosine kinase inhibitors
  - Tucatinib
  - Neratinib
  - Pyrotinib
- Antibody drug conjugates
  - Trastuzumab deruxtecan
  - T-DM1
- Fc engineered antibodies
  - Margetuximab
- New directions



Recurrent HER2+ breast cancer: 1st line

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NCCN Guidelines Version 4.2023
Invasive Breast Cancer

NCCN Guidelines Index
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Discussion

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[k]

HR-Positive or -Negative and HER2-Positive[j,k]	
Setting	**Regimen**
First Line[l]	Pertuzumab + trastuzumab + docetaxel (Category 1, preferred)
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second Line[n]	Fam-trastuzumab deruxtecan-nxki[m] (Category 1, preferred)
Third Line	Tucatinib + trastuzumab + capecitabine[n] (Category 1, preferred)
	Ado-trastuzumab emtansine (T-DM1)[o]
Fourth Line and Beyond (optimal sequence is not known)[p]	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents[q,r]
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
	Additional Targeted Therapy Options see BINV-Q (6)

[j] See additional considerations for those receiving systemic HER2-targeted therapy (BINV-Q 4).
[k] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA-indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline mutation. There is lower-level evidence for HER2-positive tumors, therefore category 2A for this setting.
[l] Maintenance trastuzumab/pertuzumab after response (with concurrent endocrine therapy if ER+ and HER2+ metastatic breast cancer).
[m] Fam-trastuzumab deruxtecan-nxki may be considered in the first-line setting as an option for select patients (ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens]). Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.
[n] Tucatinib + trastuzumab + capecitabine is preferred in patients with both systemic and CNS progression in the third-line setting and beyond; and it may be given in the second-line setting.
[o] May be used as an option for third-line and beyond; the optimal sequence for third-line therapy and beyond is not known. If not a candidate fam-trastuzumab T-DM1 could be considered in the second-line.
[p] Multiple lines of concurrent chemotherapy with anti-HER2 therapy (trastuzumab or a TKI) offer clinical benefit for recurrent unresectable HER2+ metastatic breast cancer and have been studied in phase 2 or 3 trials. Clinical experience suggests frequent clinical benefit for such treatment. However, there are no meaningful data for use of any of these regimens among patients previously treated with pertuzumab-based chemotherapy, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, or trastuzumab/capecitabine/tucatinib regimens. Thus, the optimal sequence or true benefit of therapy is not known.
[q] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[r] Trastuzumab may be safely combined with all non-anthracycline–containing preferred and other single agents listed on (BINV-Q 5) for recurrent or metastatic breast cancer.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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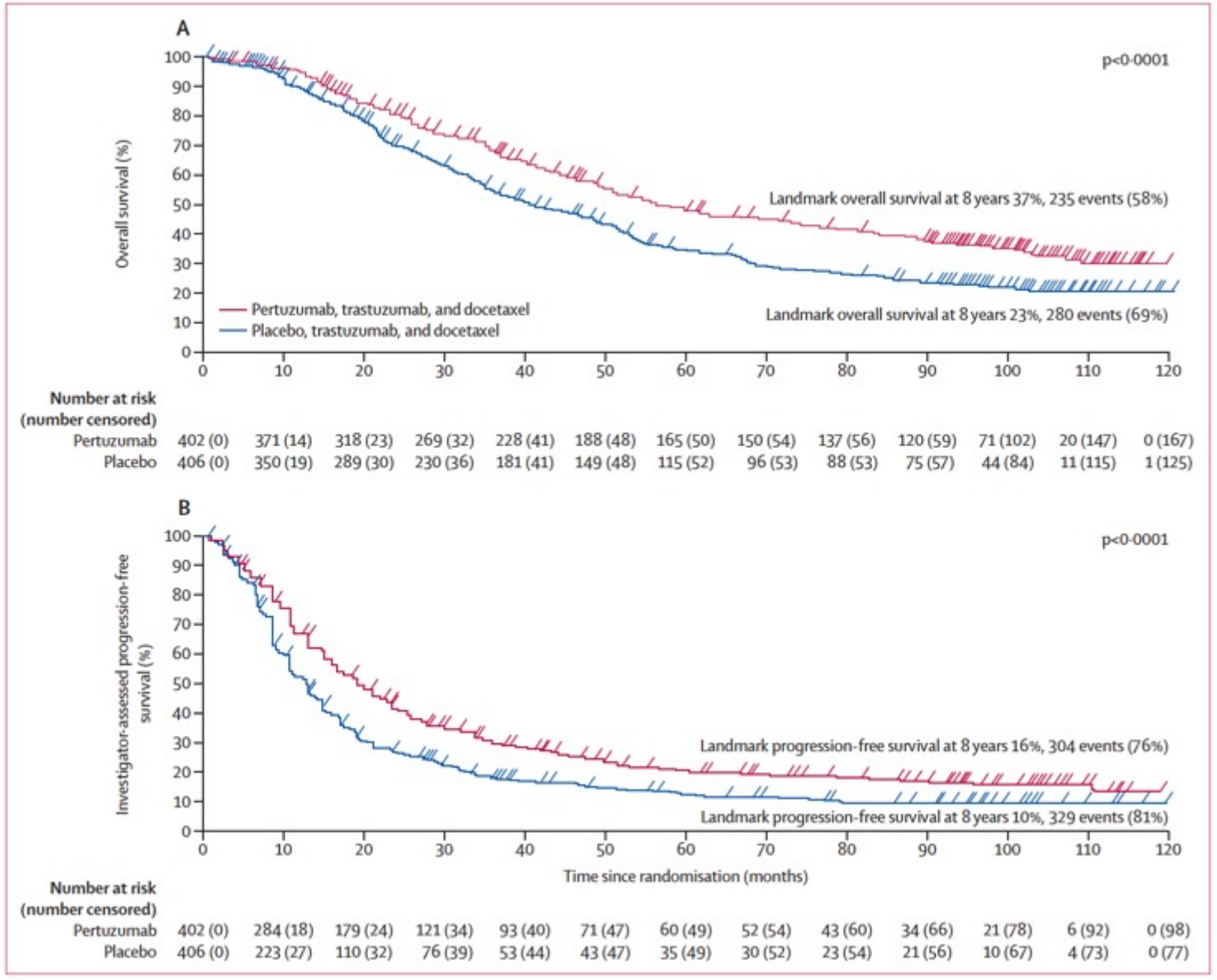
First-Line Pertuz/Trastuz: CLEOPATRA and Peruse

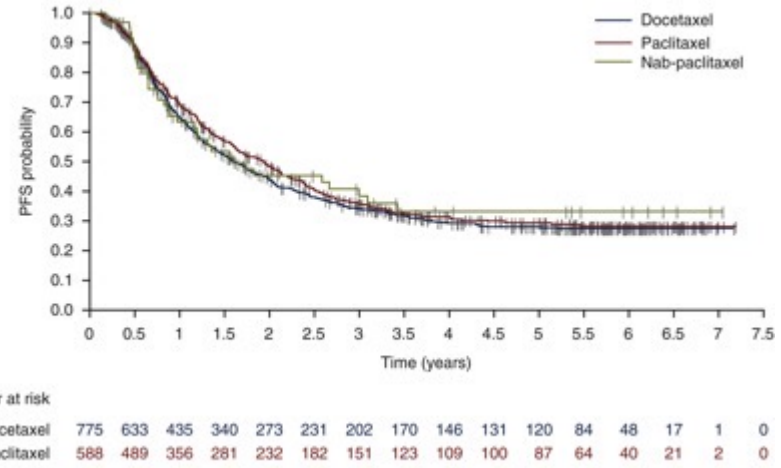


Swain et al. Lancet Oncol 2020, Miles et al. Ann Oncol 2021

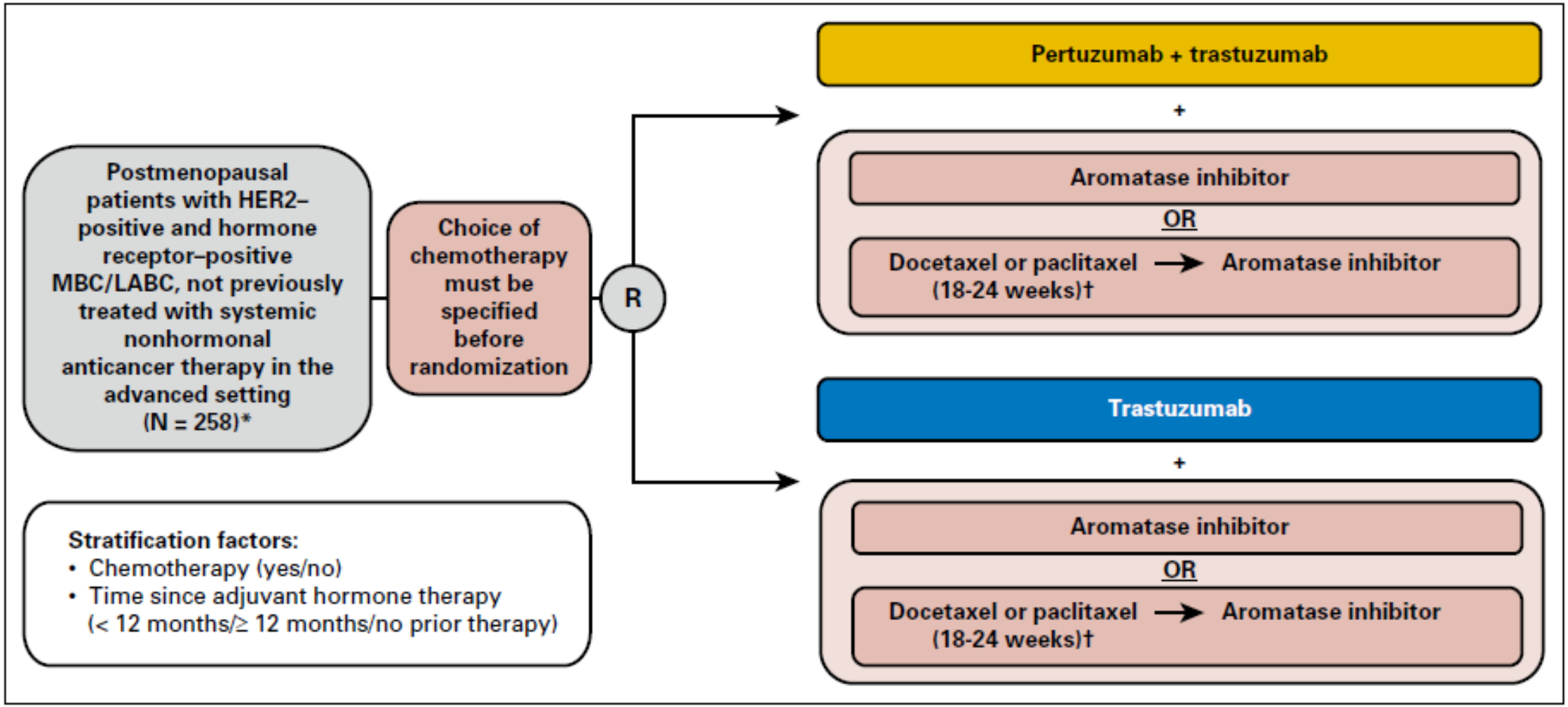
	Median PFS, mo	Median OS, mo
Pertuzumab + Trastuzumab/Doc	18.7	57.1
Placebo + Trastuzumab/Doc	12.4	40.8
HR	0.69	0.69

Peruse Study

- 1436 p\ts Rx with trastuzumab/pertuzumab + either paclitaxel, nab-paclitaxel or docetaxel.
- 41% received paclitaxel
- Median PFS/OS similar regardless of taxane



First-Line ET Plus Trastuzumab/Pertuzumab:
PERTAIN Trial

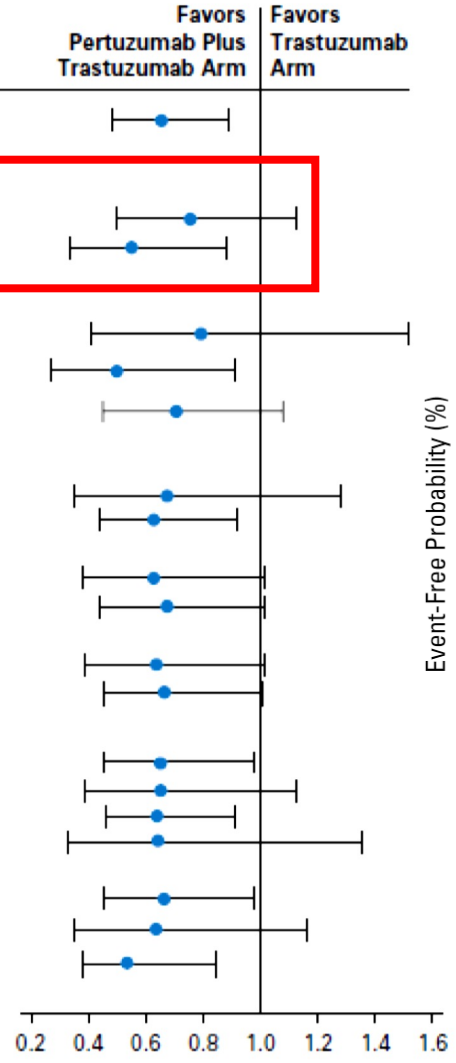


- Rimawi M, et al. J Clin Oncol. 2018;36:2826-2835.

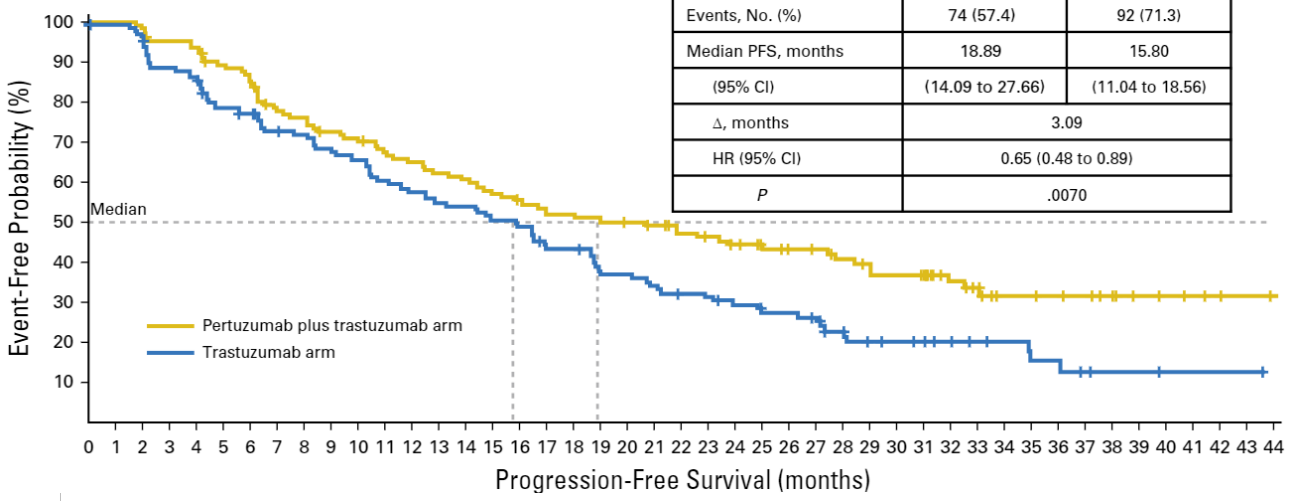
PERTAIN Trial: *Results*

B

Subgroup	No.	Events	HR	(95% CI)
ITT population	258	166	**0.66**	(0.48 to 0.89)
Chosen to receive induction chemotherapy				
Yes	148	94	**0.75**	(0.50 to 1.13)
No	110	72	**0.55**	(0.34 to 0.88)
Time since adjuvant hormone therapy				
< 12 months	48	37	**0.79**	(0.42 to 1.52)
≥ 12 months	84	45	**0.50**	(0.27 to 0.91)
No prior hormone therapy	126	84	**0.71**	(0.46 to 1.09)
Prior (neo)adjuvant treatment with trastuzumab				
Yes	59	40	**0.68**	(0.37 to 1.27)
No	199	126	**0.64**	(0.45 to 0.92)
Prior (neo)adjuvant chemotherapy				
Yes	115	71	**0.64**	(0.40 to 1.02)
No	143	95	**0.67**	(0.44 to 1.02)
Prior hormone therapy*				
Yes	110	70	**0.64**	(0.40 to 1.02)
No	148	96	**0.67**	(0.44 to 1.00)
Age category, years				
< 65	172	108	**0.66**	(0.45 to 0.97)
≥ 65	86	58	**0.66**	(0.39 to 1.12)
< 75	210	134	**0.65**	(0.47 to 0.92)
≥ 75	48	32	**0.65**	(0.31 to 1.35)
Disease type at screening				
Visceral	182	118	**0.67**	(0.47 to 0.97)
Nonvisceral	76	48	**0.65**	(0.36 to 1.16)
Centrally confirmed HER2–positive disease	180	117	**0.58**	(0.40 to 0.83)



	Pertuzumab Plus Trastuzumab Arm (n = 129)	Trastuzumab Arm (n = 129)
Events, No. (%)	74 (57.4)	92 (71.3)
Median PFS, months	18.89	15.80
(95% CI)	(14.09 to 27.66)	(11.04 to 18.56)
Δ, months	3.09	
HR (95% CI)	0.65 (0.48 to 0.89)	
P	.0070	



Rimawi M, et al. J Clin Oncol. 2018;36:2826-2835.

Recurrent HER2+ breast cancer: 2nd line

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SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[k]

HR-Positive or -Negative and HER2-Positive[j,k]	
Setting	**Regimen**
First Line[l]	Pertuzumab + trastuzumab + docetaxel (Category 1, preferred)
	Pertuzumab + trastuzumab + paclitaxel (preferred)
Second Line[n]	Fam-trastuzumab deruxtecan-nxki[m] (Category 1, preferred)
Third Line	Tucatinib + trastuzumab + capecitabine[n] (Category 1, preferred)
	Ado-trastuzumab emtansine (T-DM1)[o]
Fourth Line and Beyond (optimal sequence is not known)[p]	Trastuzumab + docetaxel or vinorelbine
	Trastuzumab + paclitaxel ± carboplatin
	Capecitabine + trastuzumab or lapatinib
	Trastuzumab + lapatinib (without cytotoxic therapy)
	Trastuzumab + other chemotherapy agents[q,r]
	Neratinib + capecitabine
	Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine)
	Additional Targeted Therapy Options see BINV-Q (6)

[j] See additional considerations for those receiving systemic HER2-targeted therapy (BINV-Q 4).
[k] Assess for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. While olaparib and talazoparib are FDA-indicated in HER2-negative disease, the panel supports use in any breast cancer subtype associated with a germline mutation. There is lower-level evidence for HER2-positive tumors, therefore category 2A for this setting.
[l] Maintenance trastuzumab/pertuzumab after response (with concurrent endocrine therapy if ER+ and HER2+ metastatic breast cancer).
[m] Fam-trastuzumab deruxtecan-nxki may be considered in the first-line setting as an option for select patients (ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens]). Fam-trastuzumab deruxtecan-nxki is associated with interstitial lung disease (ILD)/pneumonitis. Regular monitoring for this serious side effect is recommended. For patients with a history of ILD/pneumonitis, there are no data on managing safety or toxicity of this drug in a trial.
[n] Tucatinib + trastuzumab + capecitabine is preferred in patients with both systemic and CNS progression in the third-line setting and beyond; and it may be given in the second-line setting.
[o] May be used as an option for third-line and beyond; the optimal sequence for third-line therapy and beyond is not known. If not a candidate fam-trastuzumab T-DM1 could be considered in the second-line.
[p] Multiple lines of concurrent chemotherapy with anti-HER2 therapy (trastuzumab or a TKI) offer clinical benefit for recurrent unresectable HER2+ metastatic breast cancer and have been studied in phase 2 or 3 trials. Clinical experience suggests frequent clinical benefit for such treatment. However, there are no meaningful data for use of any of these regimens among patients previously treated with pertuzumab-based chemotherapy, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, or trastuzumab/capecitabine/tucatinib regimens. Thus, the optimal sequence or true benefit of therapy is not known.
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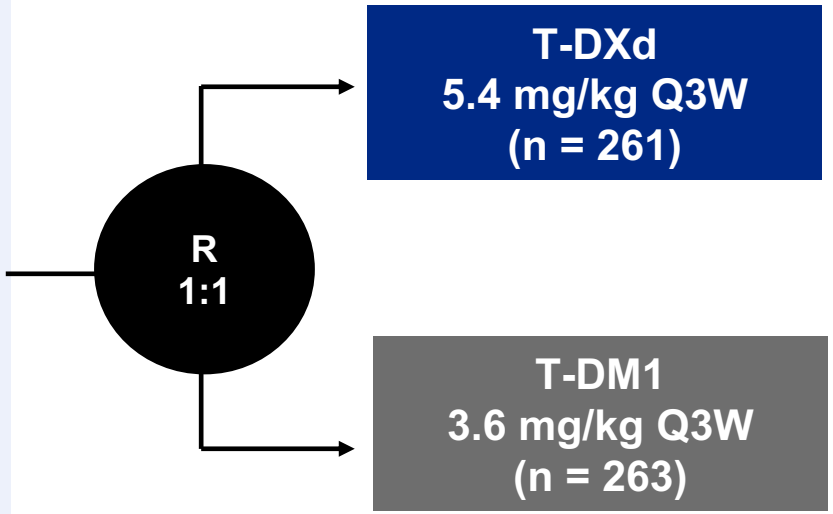
DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

An open-label, multicenter study (NCT03529110)

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

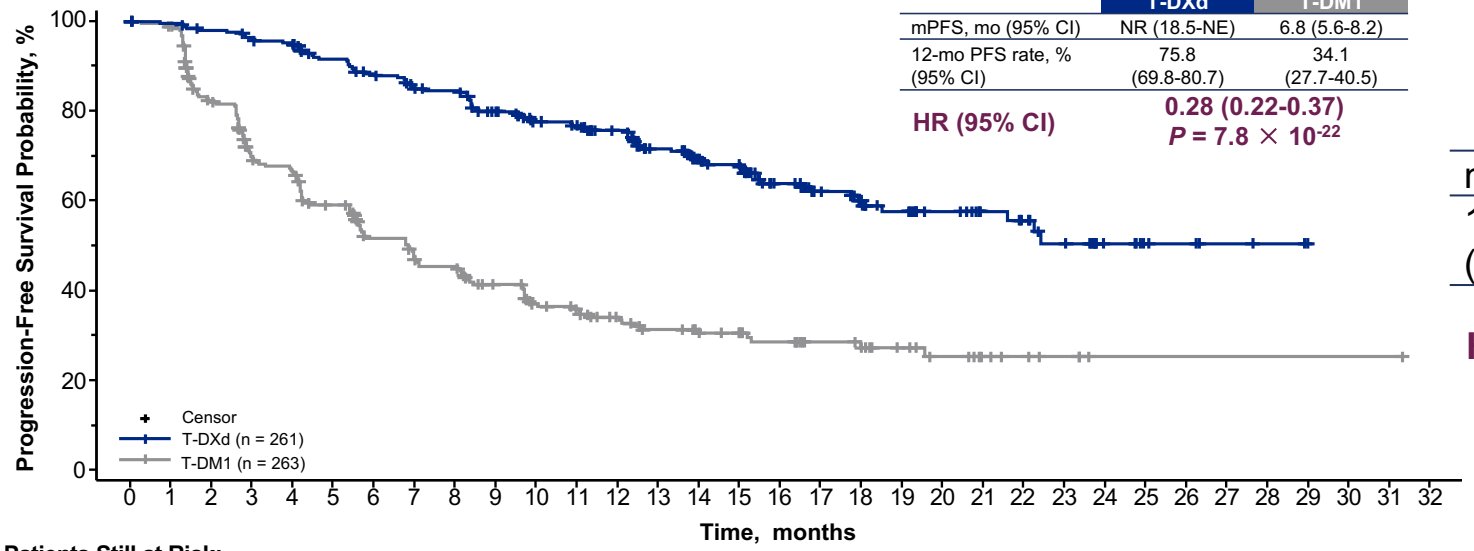
Details:
- HR+: 50%
- Brain mets: 24 vs 20%
- Prior pertuzumab: 61%
- One line of piror rx: 50 vs 47%

Cortes et al, ESMO 2021

2021 ESMO congress

BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Ph3, phase 3; Q3W, every 3 weeks.
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

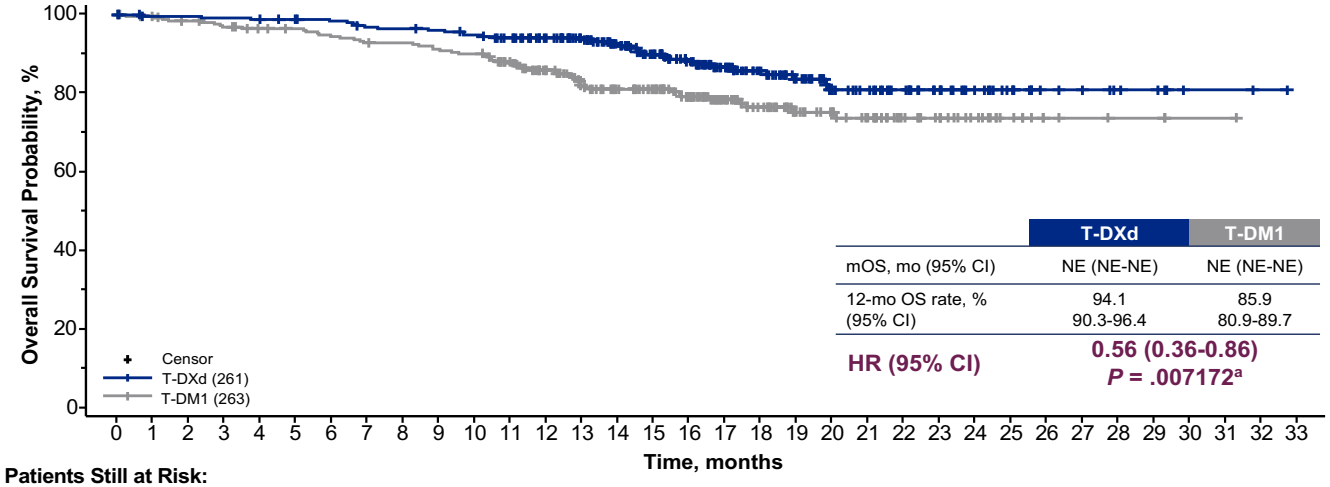
Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	0

PFS by Investigator Assessment

	T-DXd	T-DM1
mPFS, mo (95% CI)	25.1 (22.1-NE)	7.2 (6.8-8.3)
12-mo PFS rate, % (95% CI)	76.3 (70.4-81.2)	34.9 (28.8-41.2)
HR (95% CI)	0.26 (0.20-0.35)	
	$P = 6.5 \times 10^{-24}$	

Key Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 90.3-96.4	85.9 80.9-89.7
HR (95% CI)	0.56 (0.36-0.86)	
	$P = .007172$[a]	

Patients Still at Risk:

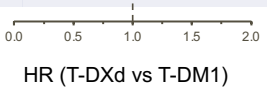
T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]$P = .007172$, but does not cross pre-specified boundary of $P < .000265$

PFS in Key Subgroups

		Number of Events		Median PFS (mo, 95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone Receptor Status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior Pertuzumab Treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral Disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior Lines of Therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
Brain Metastases	Yes (n = 114)	31/62	31/52	15.0 (12.6-22.2)	5.7 (2.9-7.1)	0.3796 (0.2267-0.6357)
	No (n = 410)	56/199	127/211	NE (22.4-NE)	7.0 (5.5-9.7)	0.2665 (0.1939-0.3665)

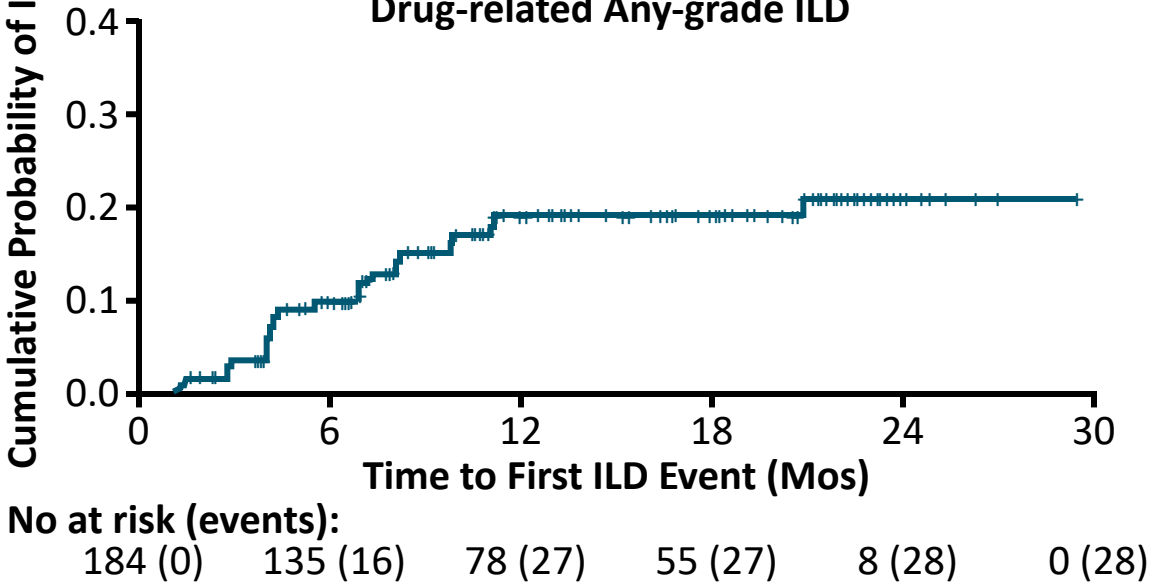


Warnings and Precautions: ILD/Pneumonitis Monitoring and Management

Interstitial lung disease, n (%)	T-Dxd 5.4 mg/kg (N = 184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	**28 (15.2)**

As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.

Cumulative Probability of Adjudicated Drug-related Any-grade ILD



Interrupt trastuzumab deruxtecan and initiate corticosteroid treatment if ILD/pneumonitis is suspected

Promptly Investigate Evidence of ILD

- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

For Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg prednisone or equivalent)
- Withhold trastuzumab deruxtecan until recovery to Grade 0
  - If resolved in ≤ 28 days from date of onset, maintain dose
  - If resolved in > 28 days from date of onset, reduce dose one level

For Symptomatic ILD (Grade ≥ 2)

- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan

Modi et al, SABCS 2020

ENHERTU [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo Inc and Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019.

Incidence of ILD after implementation of toxicity management guidelines

Updated toxicity management guidelines implemented (December 2019)

Incidence of ILD over time

	2016 (n=74)	2017 (n=168)	2018 (n=569)	2019 (n=179)	2020 (n=160)
Any Grade ILD, n (%)	18 (24.3)	33 (19.6)	87 (15.3)	28 (15.6)	11 (6.9)
Grade ≥3 ILD, n (%)	2 (2.7)	6 (3.6)	21 (3.7)	8 (4.5)	3 (1.9)
Grade 5 ILD, n (%)	1 (1.4)	5 (3.0)	12 (2.1)	5 (2.8)	2 (1.3)

Patients grouped by year of enrollment, based on a data snapshot from **December 2020**.

- Patients enrolled in 2020 (after implementation of toxicity management guidelines) appear to have had lower rates of all grade (6.9%), grade ≥3 (1.9%) and grade 5 ILD (1.3%) compared with those enrolled in previous years based on a December 2020 snapshot; however, this may be partly due to the shorter treatment duration

Powell, et al AACR 2021

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

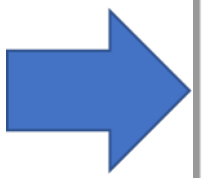
LVEF decrease, n (%)						
n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Any Grade**
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

Drug-Related TEAEs in ≥20% of Patients

	T-DXd		T-DM1	
Gastrointestinal disorders	All grade	grade >3	All grade	grade >3
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)

[a]Patients with prior history of ILD/pneumonitis requiring steroids were excluded. [b]Left ventricular dysfunction. [c]Decreased ejection fraction.



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NCCN Guidelines Version 2.2022
Invasive Breast Cancer

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Discussion

SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[h]

HER2-Positive			
Setting	**Regimen**	**NCCN Category of Preference**	**NCCN Category of Evidence**
First line[i]	Pertuzumab + trastuzumab + docetaxel[k]	Preferred Regimen	1
	Pertuzumab + trastuzumab + paclitaxel[k]	Preferred Regimen	2A
Second line[j]	Fam-trastuzumab deruxtecan-nxki[j,l,m]	Preferred Regimen	1
	Ado-trastuzumab emtansine (T-DM1)[j]	Other Recommended Regimen	2A
Third line and beyond (optimal sequence is not known)	Tucatinib + trastuzumab + capecitabine[k,n]	Other Recommended Regimen[n]	1
	Trastuzumab + docetaxel or vinorelbine[k,o]	Other Recommended Regimen	2A
	Trastuzumab + paclitaxel ± carboplatin[k,o]	Other Recommended Regimen	2A
	Capecitabine + trastuzumab or lapatinib[k,o]	Other Recommended Regimen	2A
	Trastuzumab + lapatinib[k,o] (without cytotoxic therapy)	Other Recommended Regimen	2A
	Trastuzumab + other agents[k,o,p,q]	Other Recommended Regimen	2A
	Neratinib + capecitabine[o]	Other Recommended Regimen	2A
	Margetuximab-cmkb + chemotherapy[o] (capecitabine, eribulin, gemcitabine, or vinorelbine)	Other Recommended Regimen	2A
Additional targeted therapy options (See BINV-R)			

[h] See additional considerations for those receiving systemic HER2-targeted therapy (BINV-Q 3 of 8).
[i] Maintenance trastuzumab/pertuzumab after response (with concurrent endocrine therapy if ER+ and HER2+ metastatic breast cancer).
[j] Regimens may also be used as an option for third-line and beyond; the optimal sequence for third-line therapy and beyond is not known.
[k] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[l] Fam-trastuzumab deruxtecan-nxki may be considered in the first-line setting as an option for select patients (ie, those with rapid progression within 6 months of neoadjuvant or adjuvant therapy [12 months for pertuzumab-containing regimens]).
[m] Fam-trastuzumab deruxtecan-nxki is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).
[n] Tucatinib + trastuzumab + capecitabine is preferred in patients with both systemic and CNS progression in the third-line setting and beyond; and it may be given in the second-line setting.
[o] Multiple lines of concurrent chemotherapy with anti-HER2 therapy (trastuzumab or a TKI) offer clinical benefit for recurrent unresectable HER2+ metastatic breast cancer and have been studied in phase 2 or 3 trials. Clinical experience suggests frequent clinical benefit for such treatment. However, there are no meaningful data for use of any of these regimens among patients previously treated with pertuzumab-based chemotherapy, ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, or trastuzumab/capecitabine/tucatinib regimens. Thus, the optimal sequence or true benefit of therapy is not known.
[p] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[q] Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed on BINV-Q (1 of 8) for recurrent or metastatic breast cancer.

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HER2CLIMB Primary Analysis Results

- The HER2CLIMB trial met all primary and alpha-controlled secondary endpoints at the first interim analysis.
- Importantly, the secondary endpoint of PFS in patients with brain metastases was met.

PFS by BICR
N=480*

Risk of progression or death was reduced by
46% (HR.54)
95% CI: 0.42 to 0.71, P<0.001
PFS 5.6 to 7.8 mo.

Overall Survival
N=612

Risk of death was reduced by
34% (HR .66)
95% CI, 0.50 to 0.88, P=0.005
OS 17.4 to 21.9 mo.

Updated OS: 19.2 vs 24.7 mo.

PFS by BICR in patients with brain metastases
N=291

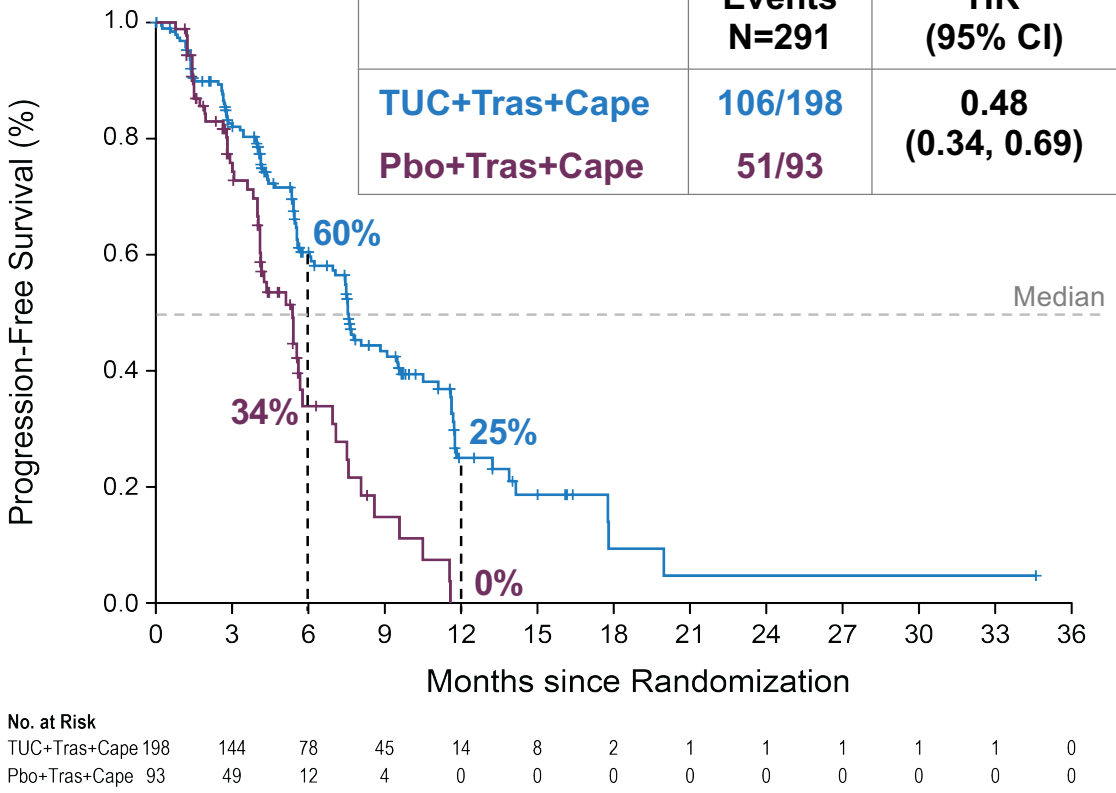
Risk of progression or death was reduced by
52% (HR .48)
95% CI, 0.34 to 0.69, P<0.001
PFS 5.4 to 7.6 mo.

*The primary endpoint of PFS was assessed in the first 480 patients enrolled.

Murthy RK, et al. *N Engl J Med* 2020;382:597-609.
Curigliano G et al. ASCO 2021. Abstract 1043.

PFS and OS for Patients with Brain Metastases

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	106/198	0.48 (0.34, 0.69)	<0.00001
Pbo+Tras+Cape	51/93		



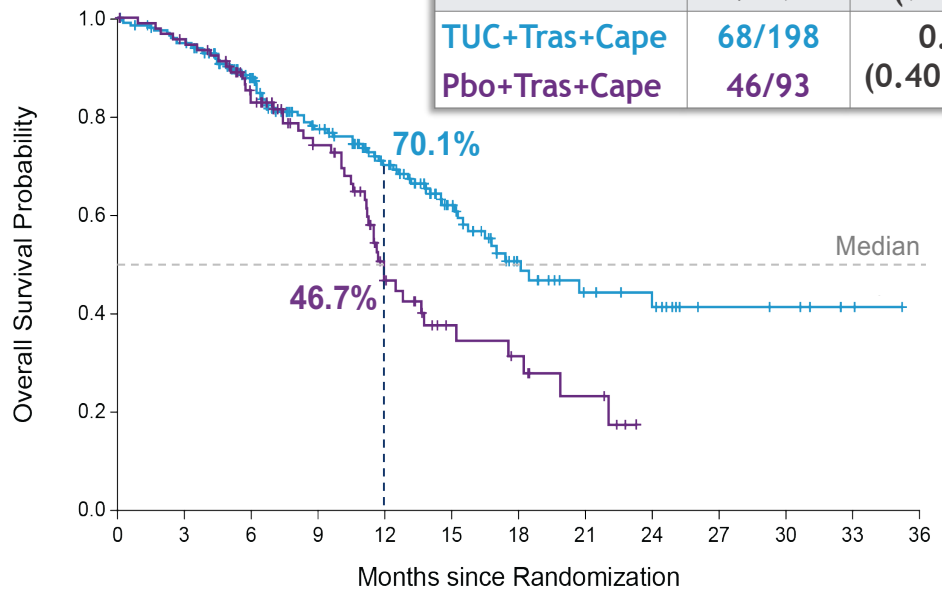
No. at Risk

TUC+Tras+Cape	198	144	78	45	14	8	2	1	1	1	1	1	0
Pbo+Tras+Cape	93	49	12	4	0	0	0	0	0	0	0	0	0

Risk of progression or death in patients with brain metastases was reduced by 52% in the total population

One-year PFS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
25% (17, 34)	0%
Median PFS (95% CI):	
7.6 months (6.2, 9.5)	5.4 months (4.1, 5.7)

	Events N=291	HR (95% CI)	P Value
TUC+Tras+Cape	68/198	0.58 (0.40, 0.85)	0.005
Pbo+Tras+Cape	46/93		



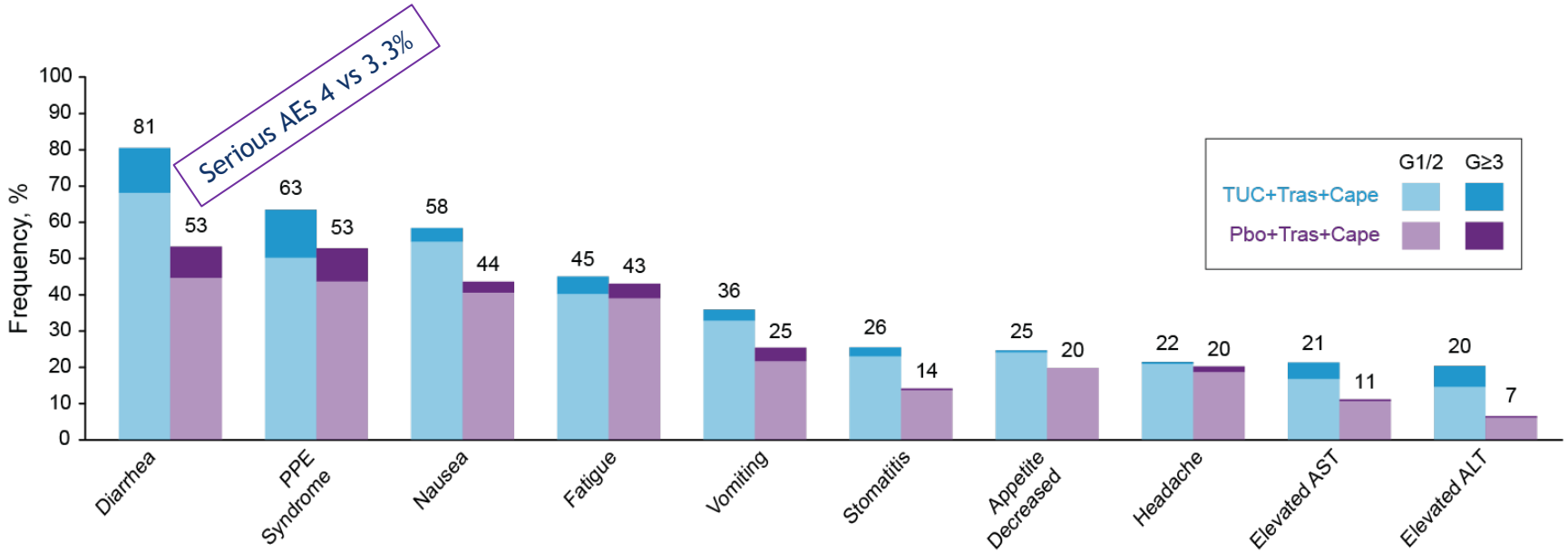
No. at Risk

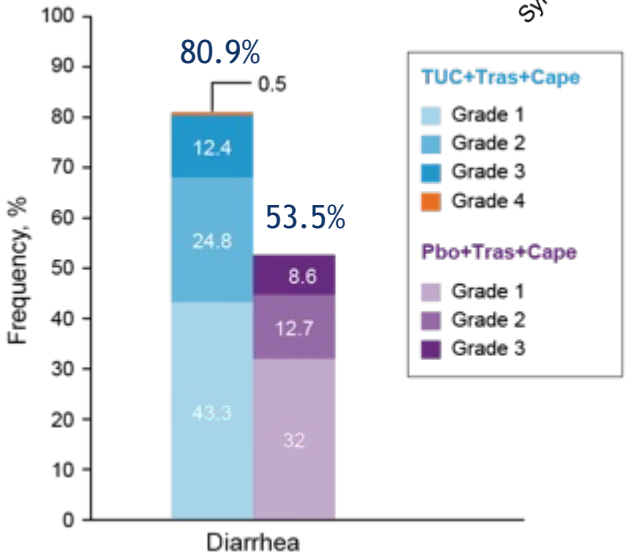
TUC+Tras+Cape	198	184	146	108	79	49	26	17	14	7	6	2	0
Pbo+Tras+Cape	93	87	67	49	23	12	9	5	0	0	0	0	0

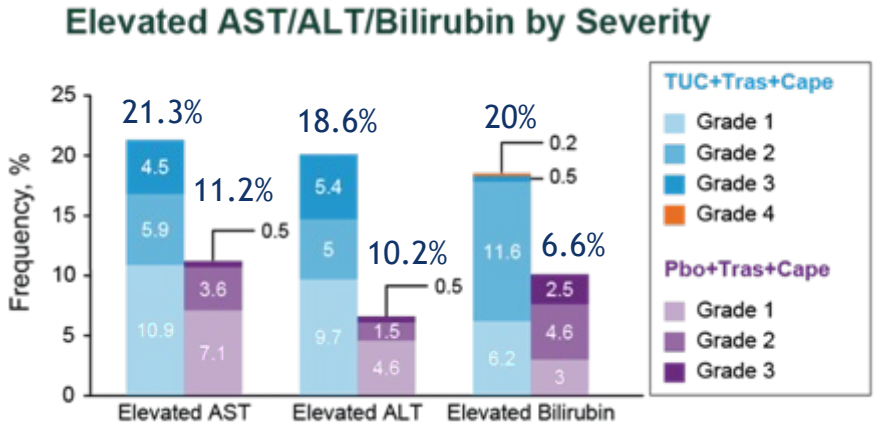
Risk of death was reduced by 42% in patients with brain metastases

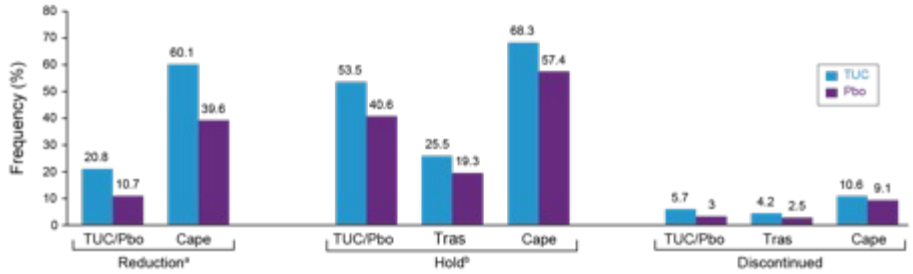
One-year OS (95% CI):	
TUC+Tras+Cape	Pbo+Tras+Cape
70.1% (62.1, 76.7)	46.7% (33.9, 58.4)
Median OS (95% CI):	
18.1 months (15.5, NE)	12.0 months (11.2, 15.2)

Safety: Most Common AEs (≥20% for Tucatinib)





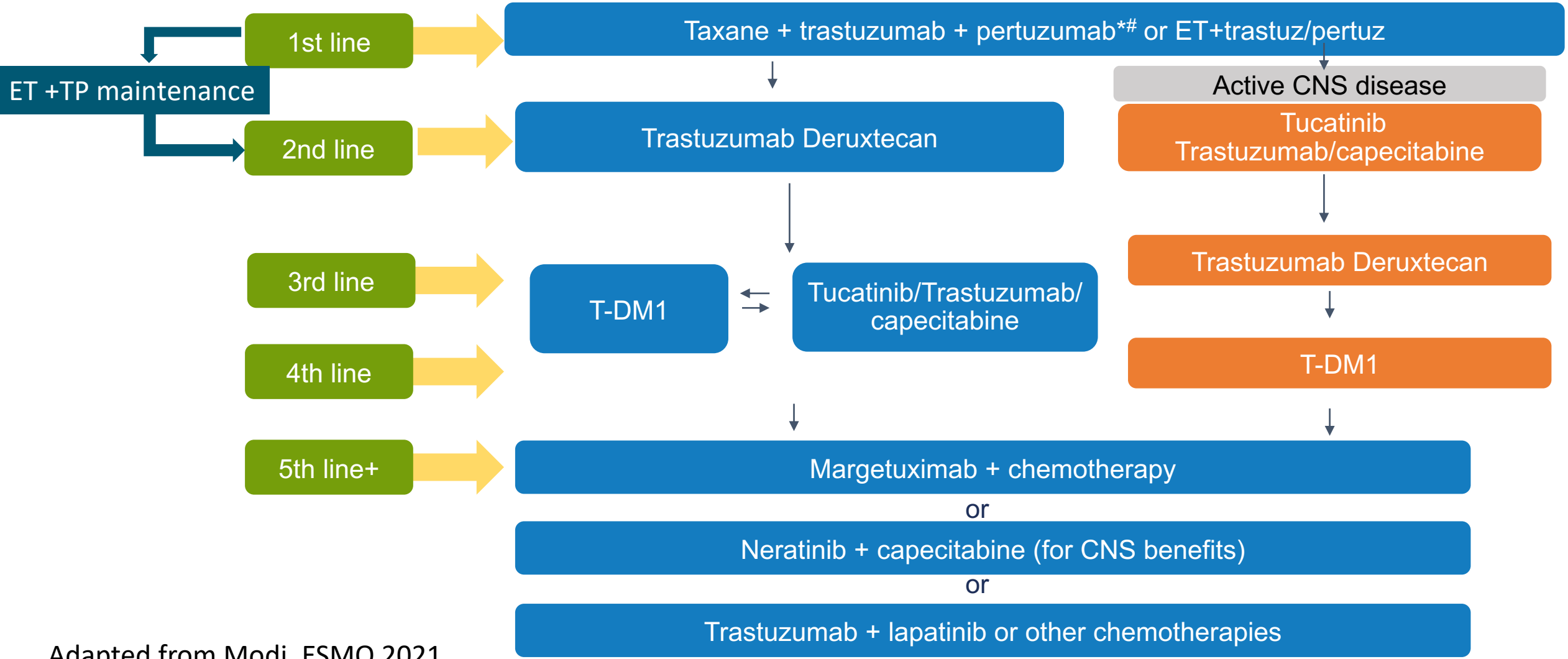




Capecitabine most commonly reduced, withheld, & discontinued drug due to AEs on both arms

Okines et al, ASCO 2020

2023 Approach to Therapy for HER2+ mBC



Adapted from Modi, ESMO 2021

*AI+TP in select cases and for maintenance in ER+ disease; # endocrine Tx + HER2 therapy at clinically appropriate points for ER+ MBC

Thank You!