HER2-positive Breast Cancer: Recent Advances

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Objectives

To discuss advances in:

1. Adjuvant breast cancer: de-escalating or switching therapies

2. Metastatic breast cancer: optimal sequencing

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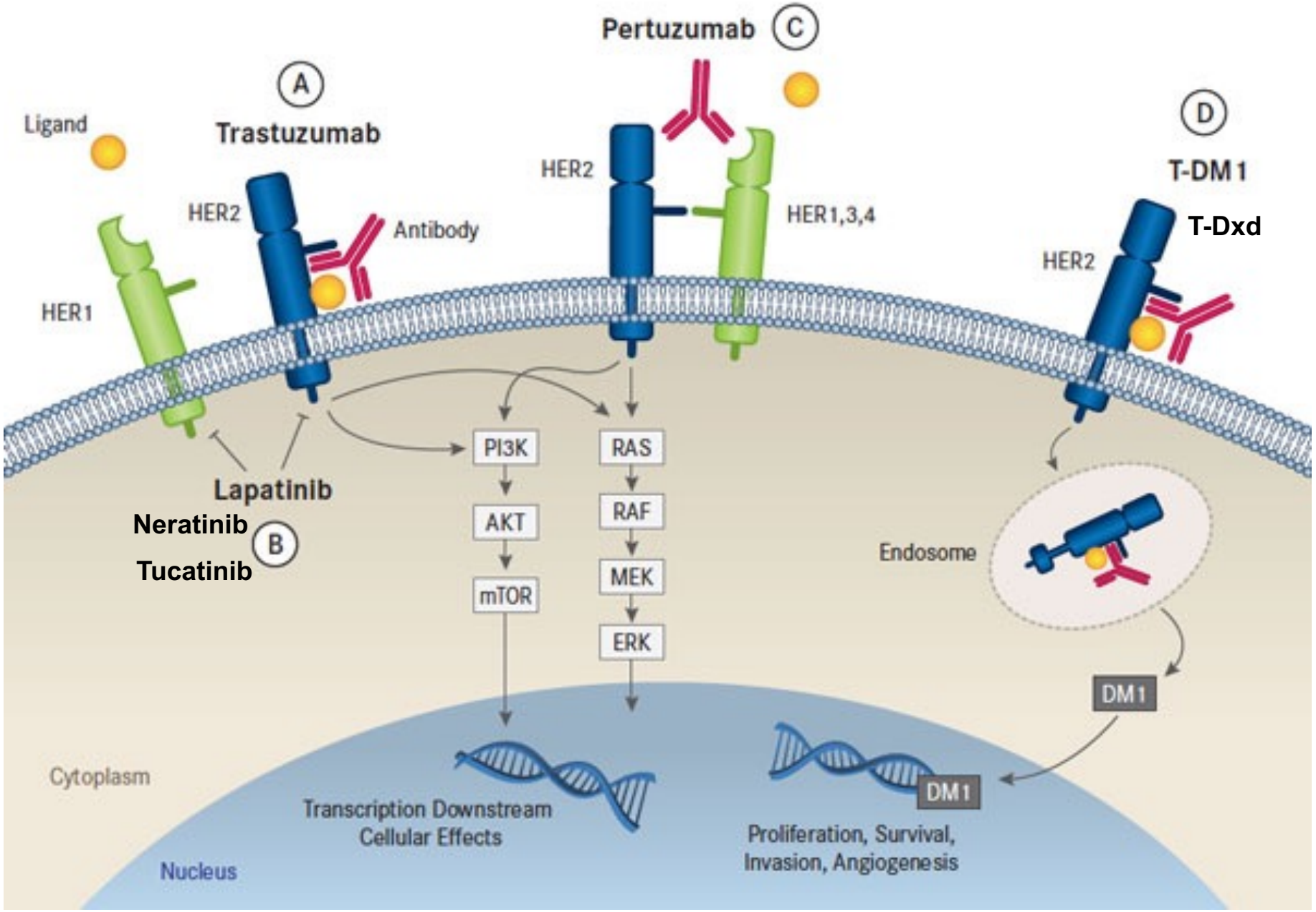

Pertuzumab
C
A
Trastuzumab
Ligand
HER2
Antibody
HER1
HER2
HER1,3,4
D
T-DM1
T-Dxd
HER2
PI3K
RAS
AKT
RAF
MEK
mTOR
ERK
Lapatinib
Neratinib
B
Tucatinib
Endosome
DM1
Cytoplasm
Transcription Downstream
Cellular Effects
DM1
Proliferation, Survival,
Invasion, Angiogenesis
Nucleus

Case 1

- 51 y/o woman presents with a clinical T2 N1 left breast mass.
- Biopsy of the breast reveals a grade 3 invasive carcinoma NOS. Tumor is ER 70%, PgR 2%, HER2 3+ and amplified. Biopsy of axillary LN benign but suspicious.

Case 2

- A healthy 85 y/o woman has an abnormal screening mammogram of her right breast.
- Biopsy reveals a grade 2 invasive lobular carcinoma with pleomorphic features, ER 100%, PgR 50%. HER2 3+ and amplified.

Neoadjuvant vs adjuvant approach?

Neoadjuvant

- Locally advanced
- Node positive

Adjuvant

- Potential to de-escalate therapy

Adjuvant HER2 therapy

Trial	Design	N	DFS
NCCTG 9831 and NSABP B-31[1]	AC→T +/- H	4046	HR 0.48, p<0.0001
HERA[2]	Ch→ +/- H x 1 year or 2 years	3401	HR 0.54, p<0.0001
BCIRG-006[3]	AC→T AC→TH TCH	3222	 HR 0.64, p<0.001 HR 0.75, p=0.04

A=doxorubicin; C=cyclophosphamide; T=paclitaxel; H=trastruzumab; Ch=anthracycline-based chemotherapy; T=docetaxel; C=carboplatin

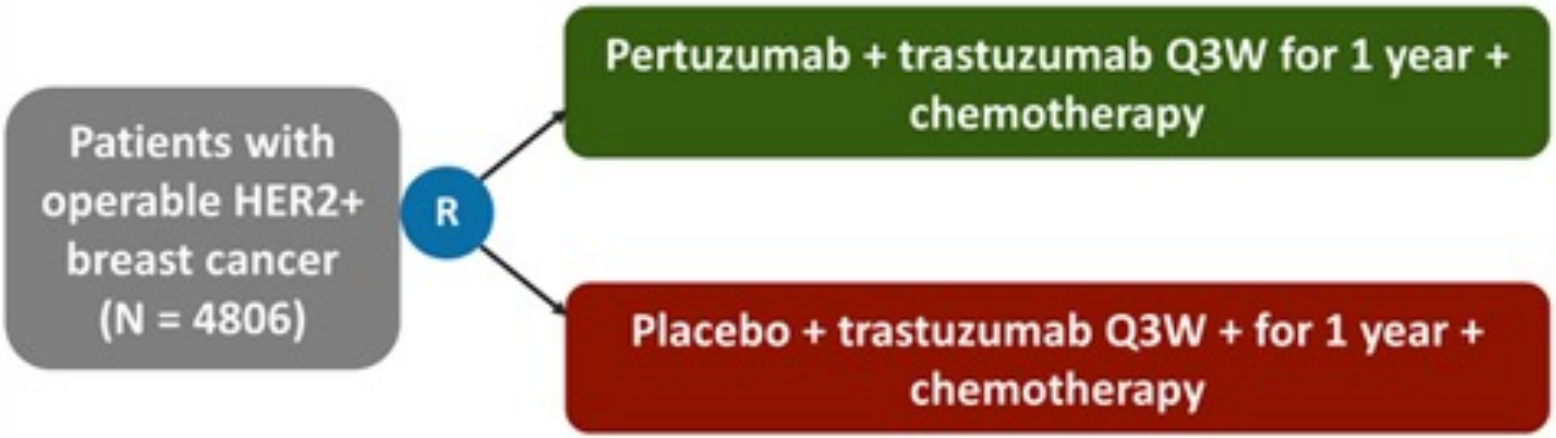
1. Romand, et al, NEJM, 2005; 2. Piccart-Gebhart, et al, NEJM 2005; 3. Slamon, et al, NEJM 2011

Additional HER2 therapies

- Pertuzumab
- Neratinib
- Trastuzumab-emtansine

APHINITY: Phase 3 Trial of Adjuvant Pertuzumab and Trastuzumab + Chemotherapy

- Randomized, double-blind, placebo-controlled trial



- Primary endpoints: IDFS duration, percentage of patients with both HF (NYHA Class III or IV), and drop in LVEF of ≥ 10 points from baseline and to below 50%

Clinicaltrials.gov. NCT01358877.

Demographic and Baseline Disease Characteristics of the Patients.

Table 1. Demographic and Baseline Disease Characteristics of the Patients.

Characteristic	Pertuzumab Group (N = 2400)	Placebo Group (N = 2404)
Nodal status — no. of patients (%)		
0 positive nodes and tumor ≤1 cm*	90 (3.8)	84 (3.5)
0 positive nodes and tumor >1 cm*	807 (33.6)	818 (34.0)
1–3 positive nodes	907 (37.8)	900 (37.4)
≥4 positive nodes	596 (24.8)	602 (25.0)
Adjuvant chemotherapy regimen — no. of patients (%)†		
Anthracycline-containing regimen	1865 (77.7)	1877 (78.1)
Non–anthracycline-containing regimen	535 (22.3)	527 (21.9)
Hormone-receptor status — no. of patients (%)‡		
Negative	864 (36.0)	858 (35.7)
Positive	1536 (64.0)	1546 (64.3)
Protocol version — no. of patients (%)*		
Protocol A	1828 (76.2)	1827 (76.0)
Protocol B	572 (23.8)	577 (24.0)
Age — no. of patients (%)		
<40 yr	326 (13.6)	327 (13.6)
40–64 yr	1759 (73.3)	1784 (74.2)
≥65 yr	315 (13.1)	293 (12.2)
Pathological tumor size — no. of tumors/total no. (%)§		
0 to <2 cm	978/2400 (40.8)	948/2405 (39.4)
2 to <5 cm	1275/2400 (53.1)	1283/2405 (53.3)
≥5 cm	147/2400 (6.1)	174/2405 (7.2)

Minckwitz G et al. N Engl J Med ;377:122-131

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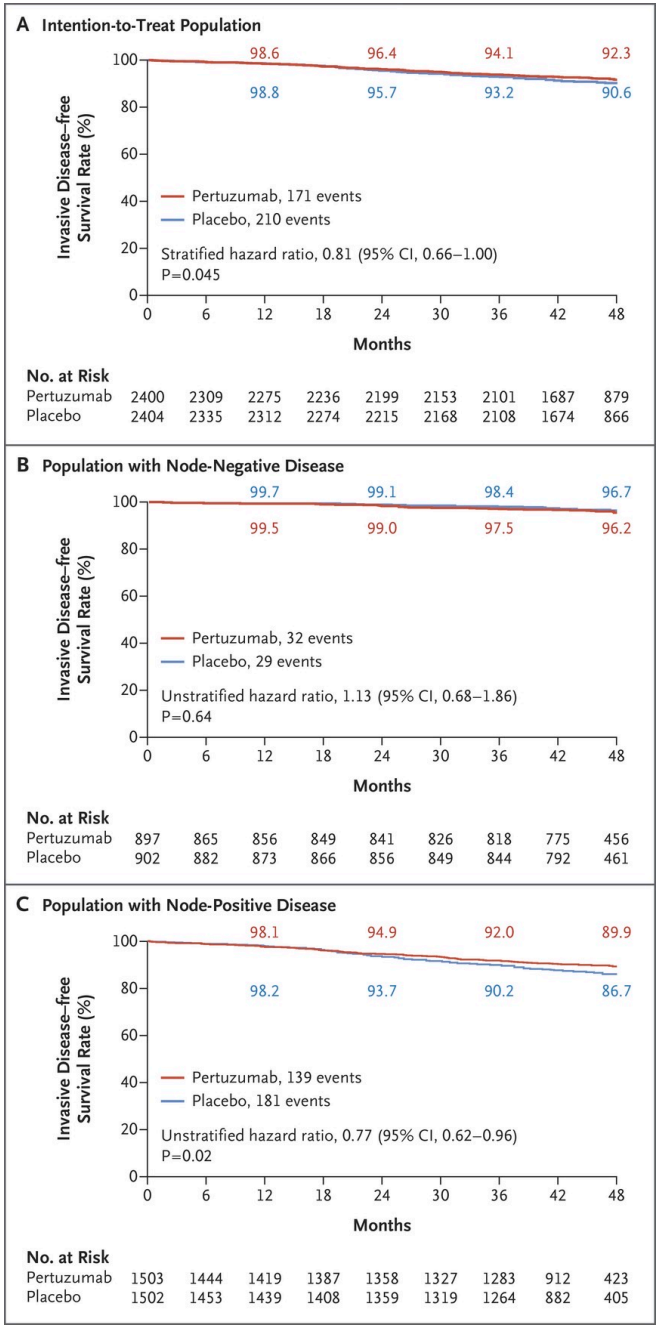
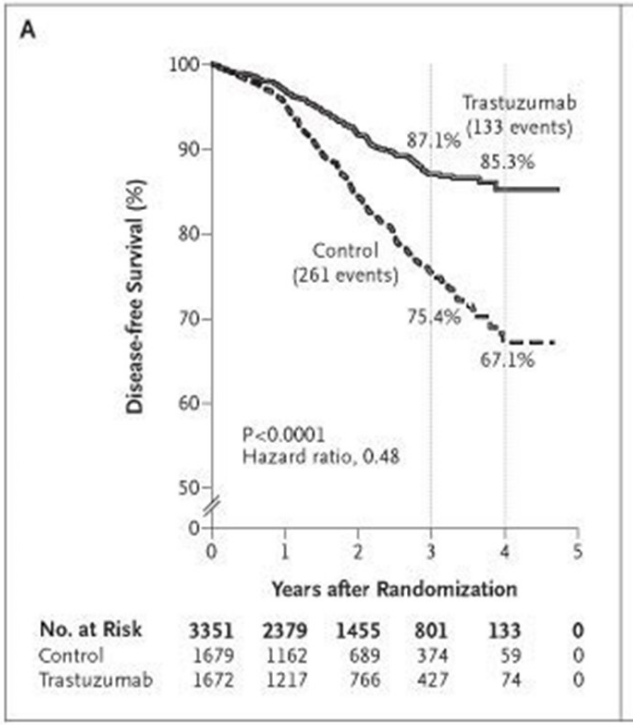
Kaplan–Meier Plot of Invasive-Disease–free Survival





Romand, et al NEJM 2005

von Minckwitz G et al. N Engl J Med ;377:122-131

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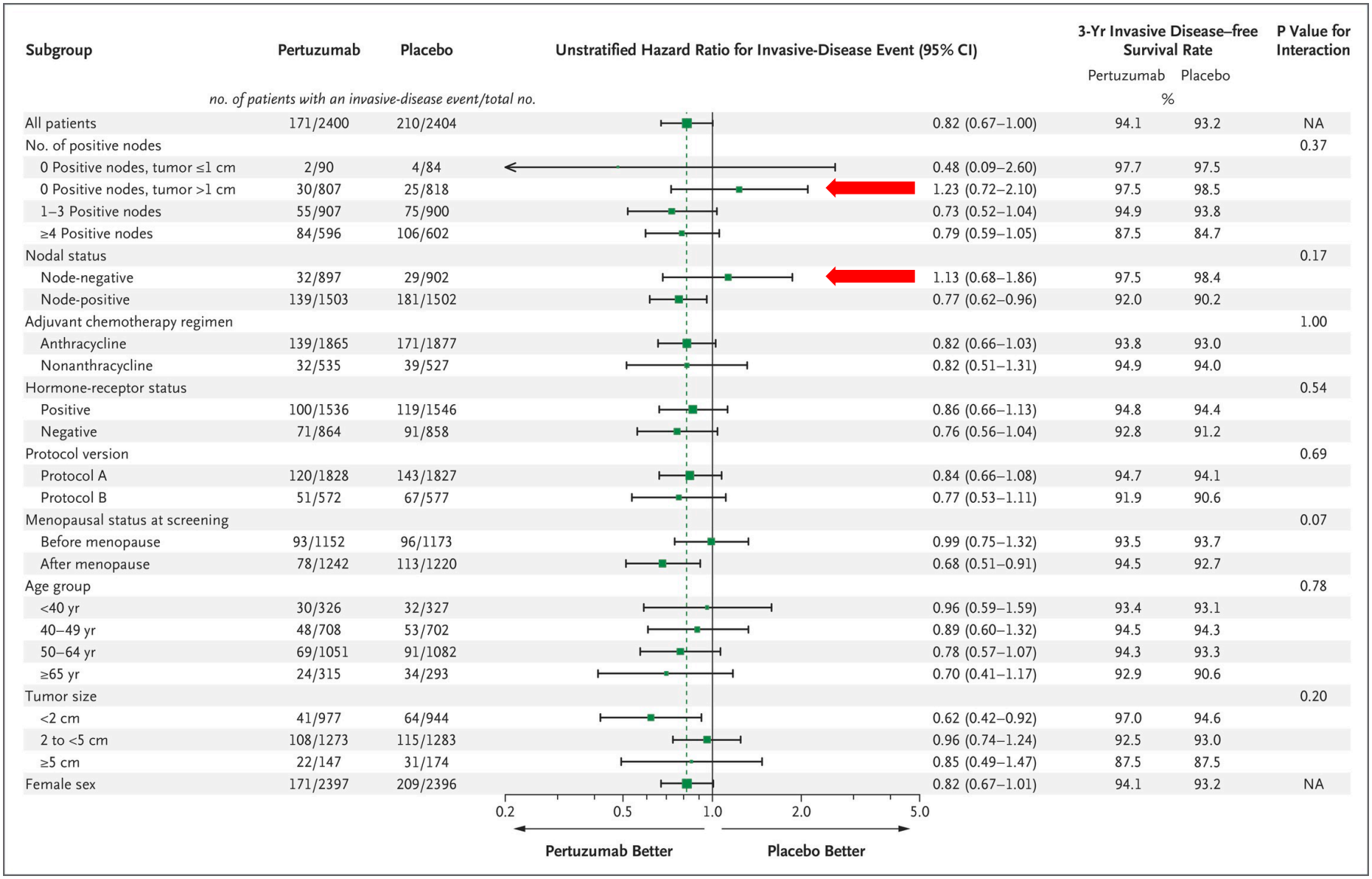
Forest Plot of Invasive-Disease–free Survival



Subgroup	Pertuzumab	Placebo	Unstratified Hazard Ratio for Invasive-Disease Event (95% CI)	3-Yr Invasive Disease–free Survival Rate		P Value for Interaction
				Pertuzumab	Placebo	
	no. of patients with an invasive-disease event/total no.			%		
All patients	171/2400	210/2404	0.82 (0.67–1.00)	94.1	93.2	NA
No. of positive nodes						0.37
0 Positive nodes, tumor ≤1 cm	2/90	4/84	0.48 (0.09–2.60)	97.7	97.5	
0 Positive nodes, tumor >1 cm	30/807	25/818	1.23 (0.72–2.10)	97.5	98.5	
1–3 Positive nodes	55/907	75/900	0.73 (0.52–1.04)	94.9	93.8	
≥4 Positive nodes	84/596	106/602	0.79 (0.59–1.05)	87.5	84.7	
Nodal status						0.17
Node-negative	32/897	29/902	1.13 (0.68–1.86)	97.5	98.4	
Node-positive	139/1503	181/1502	0.77 (0.62–0.96)	92.0	90.2	
Adjuvant chemotherapy regimen						1.00
Anthracycline	139/1865	171/1877	0.82 (0.66–1.03)	93.8	93.0	
Nonanthracycline	32/535	39/527	0.82 (0.51–1.31)	94.9	94.0	
Hormone-receptor status						0.54
Positive	100/1536	119/1546	0.86 (0.66–1.13)	94.8	94.4	
Negative	71/864	91/858	0.76 (0.56–1.04)	92.8	91.2	
Protocol version						0.69
Protocol A	120/1828	143/1827	0.84 (0.66–1.08)	94.7	94.1	
Protocol B	51/572	67/577	0.77 (0.53–1.11)	91.9	90.6	
Menopausal status at screening						0.07
Before menopause	93/1152	96/1173	0.99 (0.75–1.32)	93.5	93.7	
After menopause	78/1242	113/1220	0.68 (0.51–0.91)	94.5	92.7	
Age group						0.78
<40 yr	30/326	32/327	0.96 (0.59–1.59)	93.4	93.1	
40–49 yr	48/708	53/702	0.89 (0.60–1.32)	94.5	94.3	
50–64 yr	69/1051	91/1082	0.78 (0.57–1.07)	94.3	93.3	
≥65 yr	24/315	34/293	0.70 (0.41–1.17)	92.9	90.6	
Tumor size						0.20
<2 cm	41/977	64/944	0.62 (0.42–0.92)	97.0	94.6	
2 to <5 cm	108/1273	115/1283	0.96 (0.74–1.24)	92.5	93.0	
≥5 cm	22/147	31/174	0.85 (0.49–1.47)	87.5	87.5	
Female sex	171/2397	209/2396	0.82 (0.67–1.01)	94.1	93.2	NA

Minckwitz G et al. N Engl J Med ;377:122-131

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Summary of Adverse Events (Safety Analysis Population).

Table 3. Summary of Adverse Events (Safety Analysis Population).*

Event	Pertuzumab Group (N = 2364)	Placebo Group (N = 2405)
	no. of patients (%)	
Grade ≥3 adverse event	1518 (64.2)	1379 (57.3)
Neutropenia	385 (16.3)	377 (15.7)
Febrile neutropenia	287 (12.1)	266 (11.1)
Neutrophil count decreased	228 (9.6)	230 (9.6)
Diarrhea†	232 (9.8)	90 (3.7)
Anemia	163 (6.9)	113 (4.7)
Fatal adverse event‡	18 (0.8)	20 (0.8)
Primary cardiac event§	17 (0.7)	8 (0.3)
NYHA class III or IV heart failure and substantial decrease in LVEF¶	15 (0.6)	6 (0.2)
Definite or probable cardiac death	2 (0.1)	2 (0.1)
Secondary cardiac event‖	64 (2.7)	67 (2.8)
Identified automatically from LVEF assessments	50 (2.1)	47 (2.0)
Identified by cardiac advisory board	14 (0.6)	20 (0.8)

Minckwitz G et al. N Engl J Med ;377:122-131

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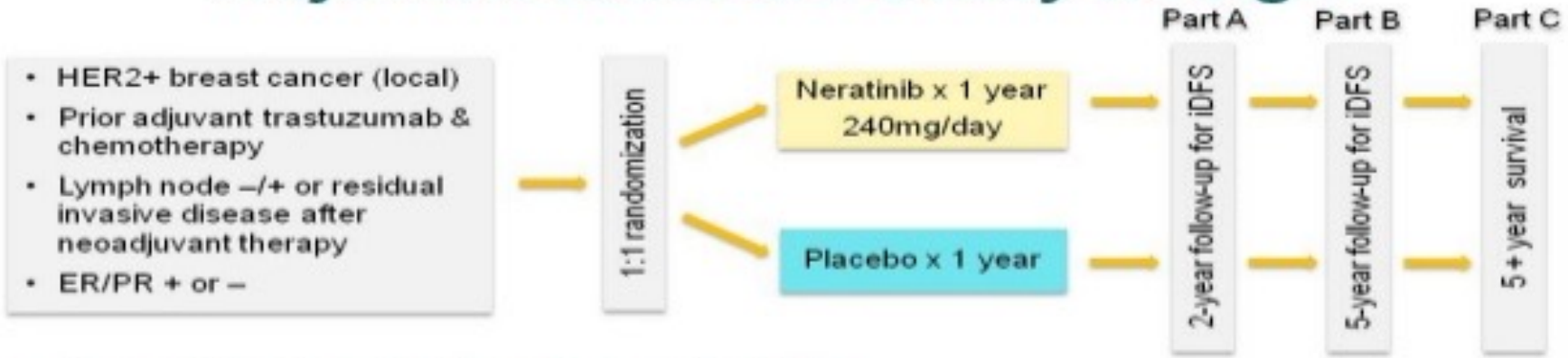
Adjuvant ExteNET Study Design

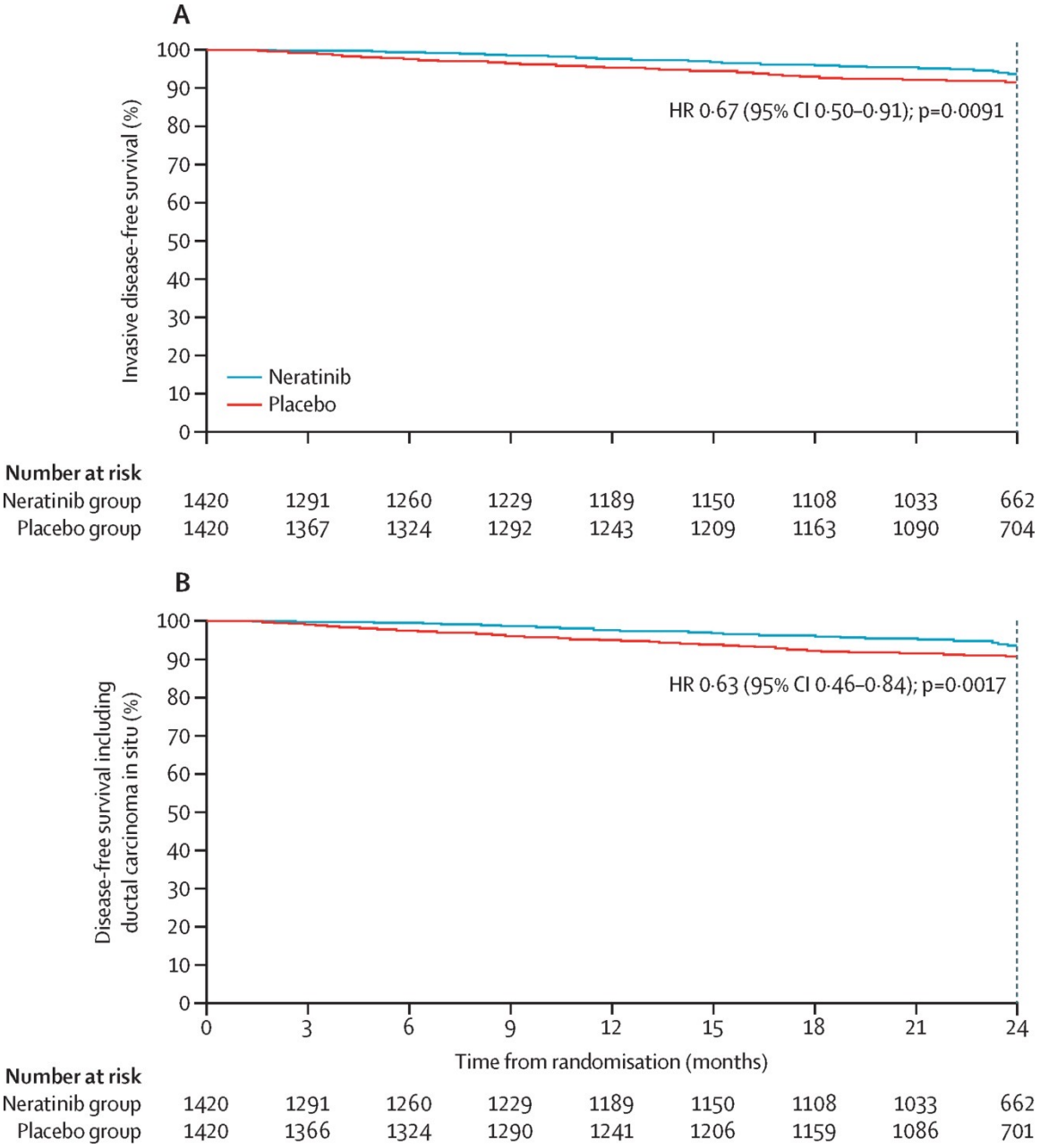


- Primary endpoint: invasive disease-free survival (iDFS)
- Secondary endpoints: DFS-DCIS, time to distant recurrence, distant DFS, CNS metastases, overall survival, safety
- Other analyses: biomarkers, health outcome assessment (FACT-B, EQ-5d)
- Stratified by: nodes 0, 1–3 vs 4+, ER/PR status, concurrent vs sequential trastuzumab

Chan A , ASCO 2015 ASCO Annual '15 Meeting

Presented By Shanu Modi at 2015 ASCO Annual Meeting

Figure 2



Chan, et al
Lancet Oncology 2016

Table 3 Treatment-emergent adverse events occurring in at least 10% of patients in the safety population

	Neratinib group (n=1408)			Placebo group (n=1408)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Diarrhoea	781 (55%)	561 (40%)	1 (<1%)	476 (34%)	23 (2%)	0
Nausea	579 (41%)	26 (2%)	0	301 (21%)	2 (<1%)	0
Fatigue	359 (25%)	23 (2%)	0	276 (20%)	6 (<1%)	0
Vomiting	322 (23%)	47 (3%)	0	107 (8%)	5 (<1%)	0
Abdominal pain	314 (22%)	24 (2%)	0	141 (10%)	3 (<1%)	0
Headache	269 (19%)	8 (1%)	0	269 (19%)	6 (<1%)	0
Upper abdominal pain	201 (14%)	11 (1%)	0	93 (7%)	3 (<1%)	0
Rash	205 (15%)	5 (<1%)	0	100 (7%)	0	0
Decreased appetite	166 (12%)	3 (<1%)	0	40 (3%)	0	0

Chan, et al
Lancet Oncology 2016

KATHERINE

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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*

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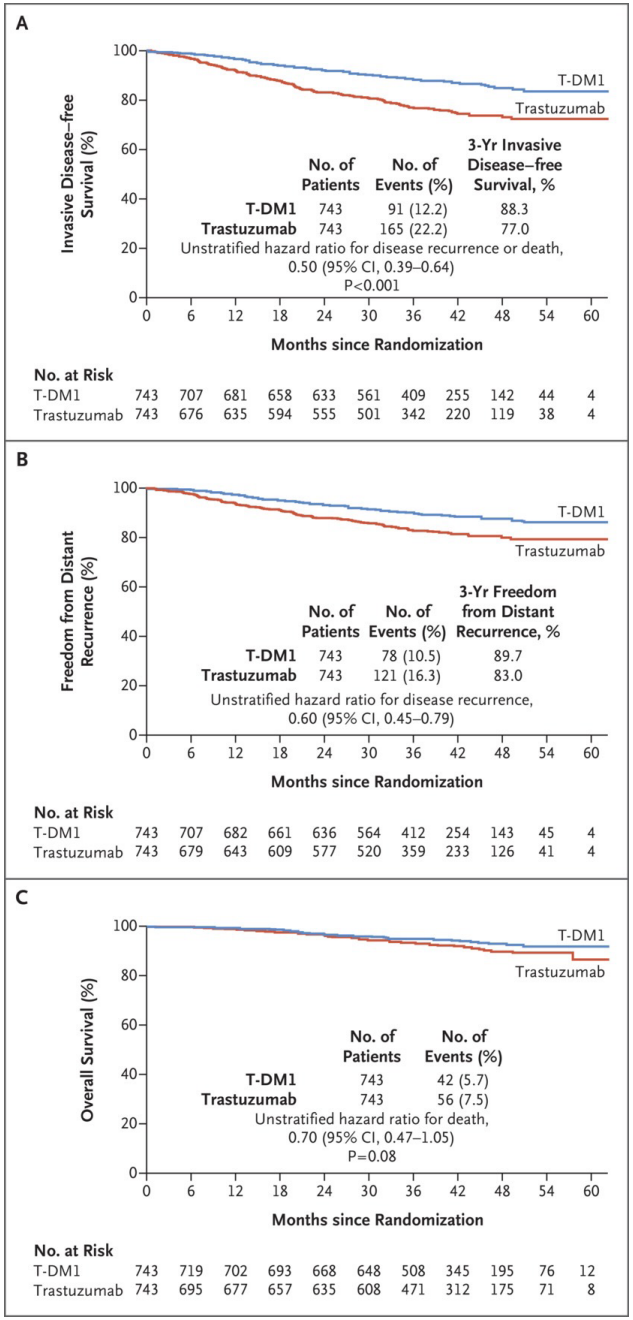
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Trastuzumab Group (N=743)	T-DM1 Group (N=743)
Median age (range) — yr	49 (23–80)	49 (24–79)
Race or ethnic group — no. of patients (%)†		
White	531 (71.5)	551 (74.2)
Asian	64 (8.6)	65 (8.7)
Black	19 (2.6)	21 (2.8)
American Indian or Alaska Native‡	50 (6.7)	36 (4.8)
Multiple or unknown	79 (10.6)	70 (9.4)
Clinical stage at presentation — no. of patients (%)		
Inoperable breast cancer§	190 (25.6)	185 (24.9)
Operable breast cancer¶	553 (74.4)	558 (75.1)
Hormone-receptor status — no. of patients (%)		
Estrogen-receptor–negative and progesterone-receptor–negative or status unknown	203 (27.3)	209 (28.1)
Estrogen-receptor–positive, progesterone-receptor–positive, or both	540 (72.7)	534 (71.9)
Previous use of anthracycline — no. of patients (%)	564 (75.9)	579 (77.9)
Neoadjuvant HER2-targeted therapy — no. of patients (%)		
Trastuzumab alone	596 (80.2)	600 (80.8)
Trastuzumab plus pertuzumab	139 (18.7)	133 (17.9)
Trastuzumab plus other HER2-targeted therapy‖	8 (1.1)	10 (1.3)

Kaplan–Meier Estimates of Survival in the Interim Analysis.



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

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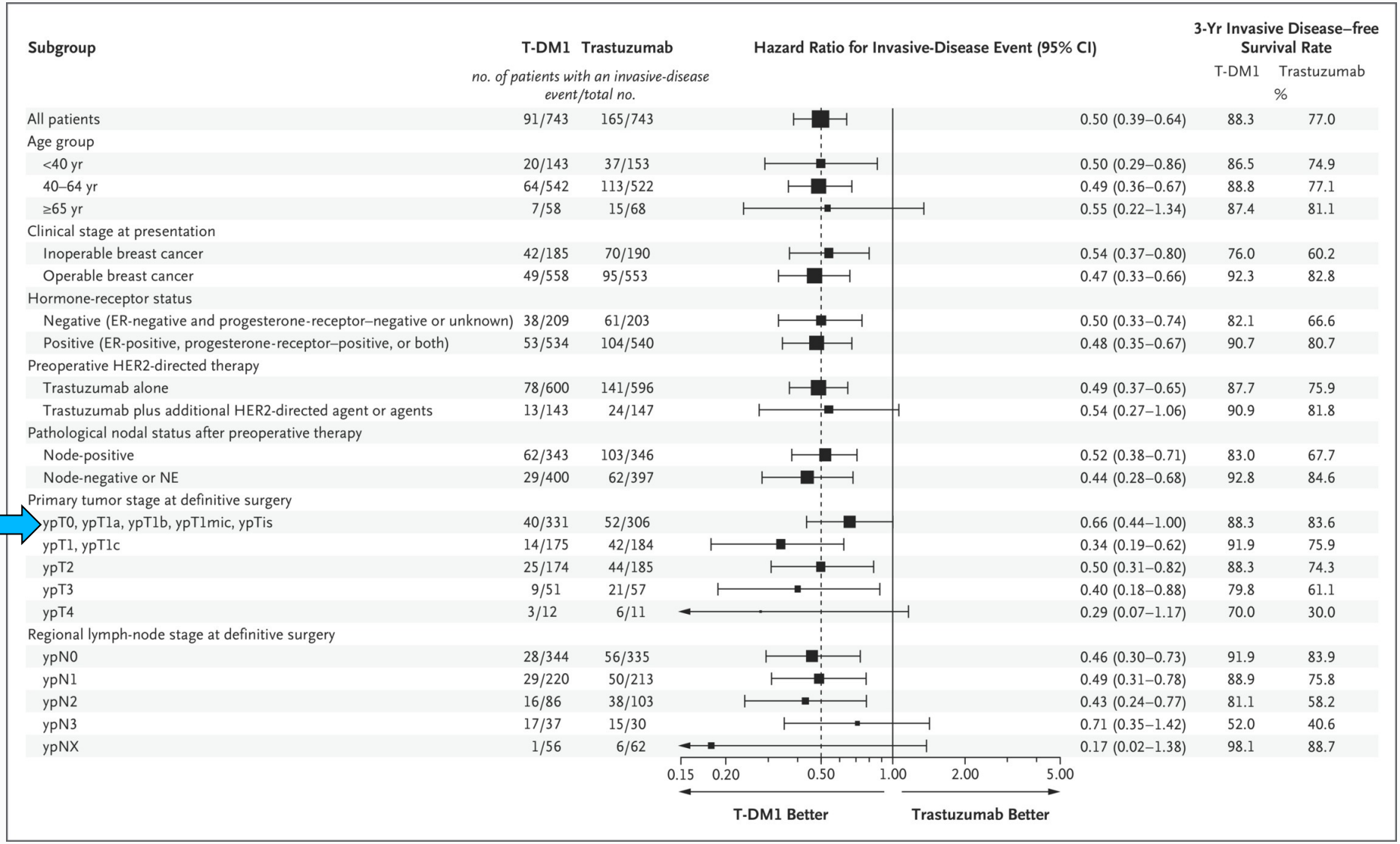
Subgroup Analysis of Invasive Disease–free Survival.



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

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Summary of Adverse Events in the Safety Population.

Table 2. Summary of Adverse Events in the Safety Population.*

Event	Trastuzumab Group (N = 720)	T-DM1 Group (N = 740)
	no. of patients (%)	
Any adverse event	672 (93.3)	731 (98.8)
Grade ≥3 adverse event	111 (15.4)	190 (25.7)
Adverse event leading to death†	0	1 (0.1)
Serious adverse event	58 (8.1)	94 (12.7)
Adverse event leading to discontinuation of trial drug‡	15 (2.1)	133 (18.0)
Grade ≥3 adverse event that occurred in ≥1% of patients in either group		
Decreased platelet count	2 (0.3)	42 (5.7)
Hypertension	9 (1.2)	15 (2.0)
Radiation-related skin injury	7 (1.0)	10 (1.4)
Peripheral sensory neuropathy	0	10 (1.4)
Decreased neutrophil count	5 (0.7)	9 (1.2)
Hypokalemia	1 (0.1)	9 (1.2)
Fatigue	1 (0.1)	8 (1.1)
Anemia	1 (0.1)	8 (1.1)

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

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How does this change clinical practice?

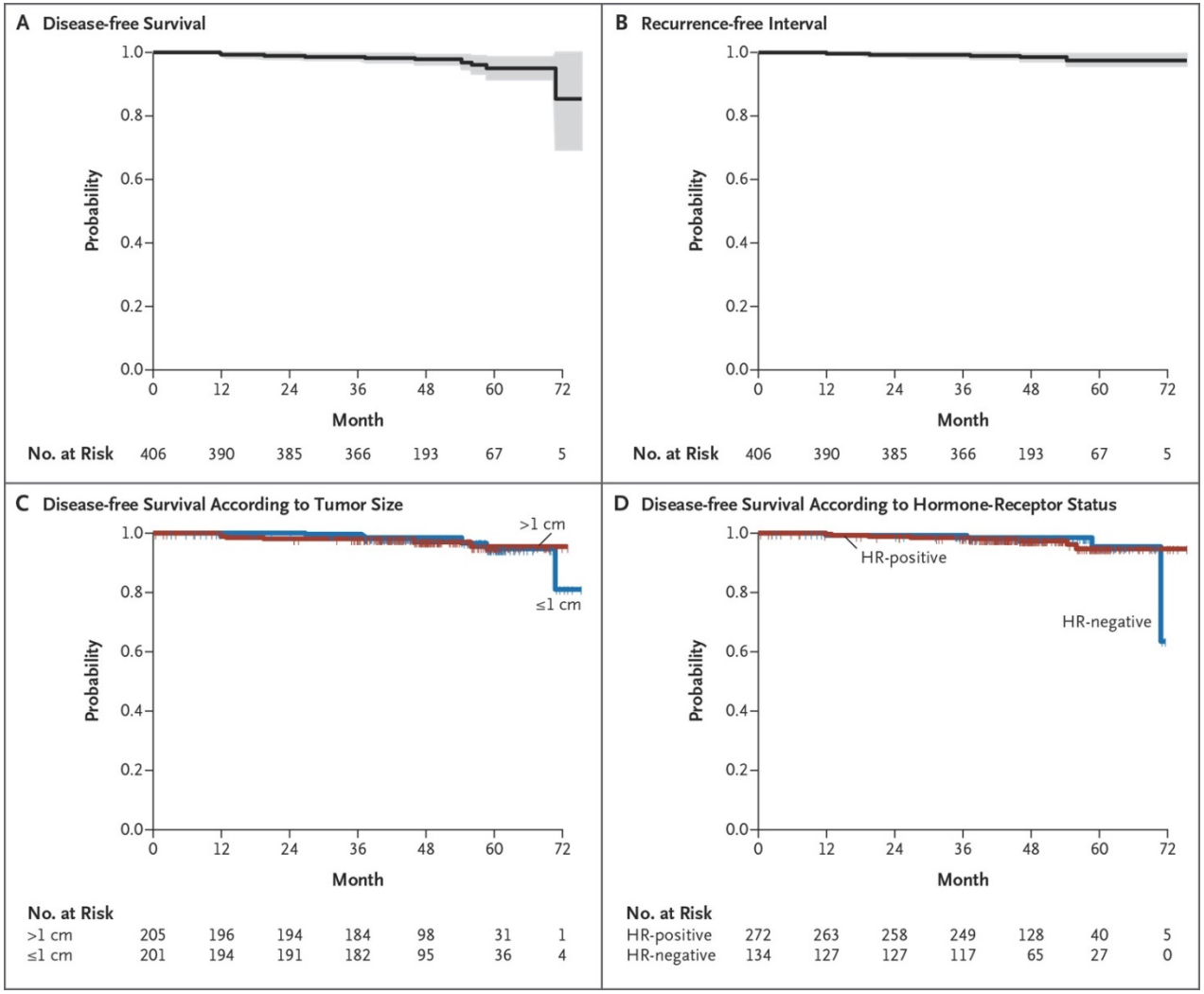
- Additional HER2 directed therapies come at cost, both in side effects and dollars.
- Post-operative trastuzumab emtansine should be offered for residual disease

How does this change clinical practice?

- Consider a year of adjuvant pertuzumab in high-risk patients:
  - –Node positive
  - –HR negative

- Unclear role for adjuvant neratinib

De-escalating chemotherapy



- ≤ 3 cm
- Node negative

- Weekly paclitaxel x 12 + 1 year of trastuzumab

Tolaney, et al, NEJM 2015

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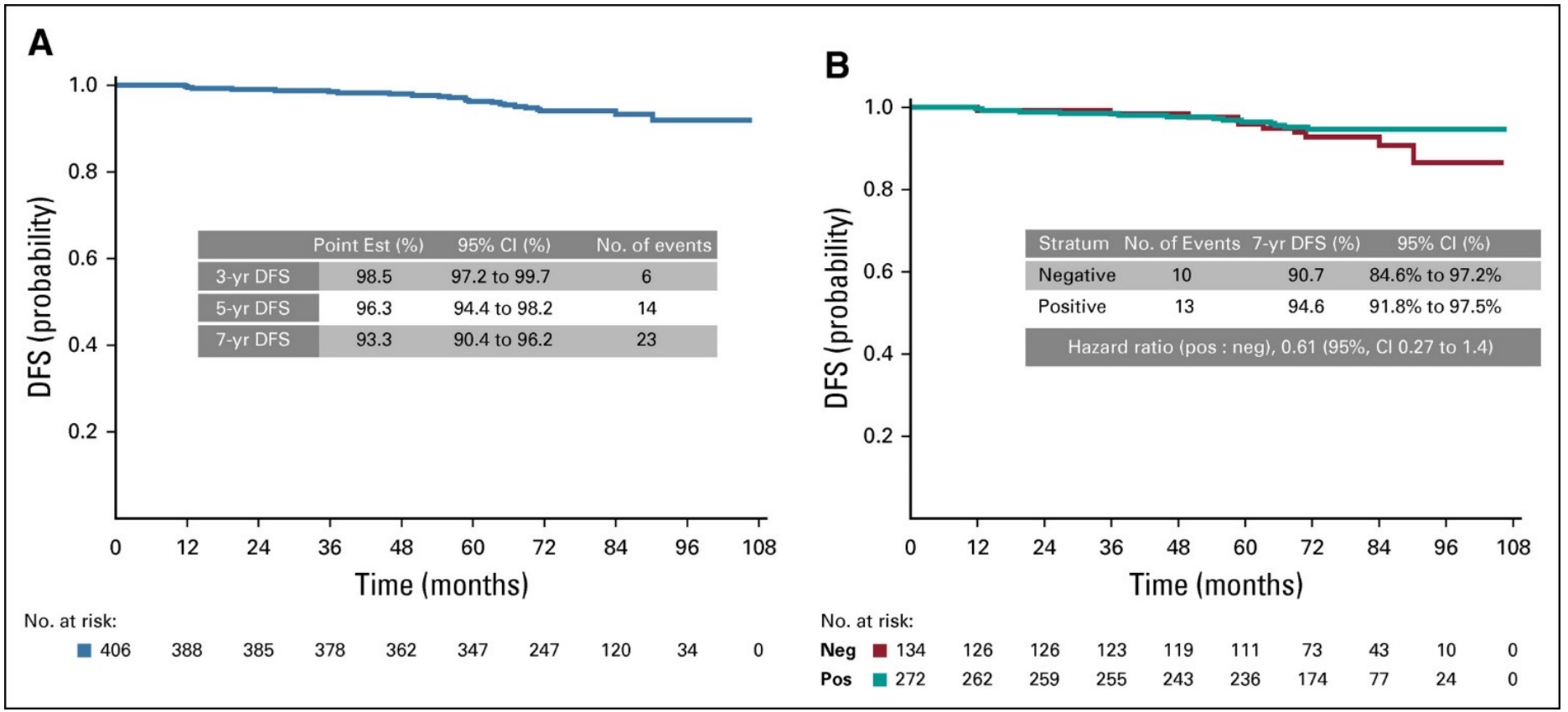

FIG 2. Disease-free survival (DFS). (A) Kaplan-Meier plot of DFS in the intention-to-treat population. (B) DFS according to hormone-receptor status. Abbreviations: neg, negative; Point est, point estimate; pos, positive.

Published in: Sara M. Tolaney; Hao Guo; Sonia Pernas; William T. Barry; Deborah A. Dillon; Lauren Ritterhouse; Bryan P. Schneider; Fei Shen; Kit Fuhrman; Michele Baltay; Chau T. Dang; Denise A. Yardley; Beverly Moy; P. Kelly Marcom; Kathy S. Albain; Hope S. Rugo; Mathew J. Ellis; Iuliana Shapira; Antonio C. Wolff; Lisa A. Carey; Beth Overmoyer; Ann H. Partridge; Clifford A. Hudis; Ian E. Krop; Harold J. Burstein; Eric P. Winer; *Journal of Clinical Oncology* 2019 371868-1875.
DOI: 10.1200/JCO.19.00066

TABLE 2. DFS Events Observed

DFS Event	No. (%)	Time to Event (months), Median (range)
Any recurrence or death	23 (5.7)	
Local/regional recurrence	5 (1.2)	
Ipsilateral axilla (HER2 positive)	3	20 (12-54)
Ipsilateral breast (HER2 positive)	2	51 (37-65)
New contralateral primary breast cancer	6 (1.5)	
HER2 positive	1	56
HER2 negative	3	36 (12-59)
Unknown	2	87 (84-90)
Distant recurrence	4 (1.0)	53 (27-63)
Death		
Non–breast-cancer related	8 (2.0)	66 (13-71)

Abbreviations: DFS, disease-free survival; HER2, human epidermal growth factor receptor 2.

TABLE 2. DFS Events Observed

Published in: Sara M. Tolaney; Hao Guo; Sonia Pernas; William T. Barry; Deborah A. Dillon; Lauren Ritterhouse; Bryan P. Schneider; Fei Shen; Kit Fuhrman; Michele Baltay; Chau T. Dang; Denise A. Yardley; Beverly Moy; P. Kelly Marcom; Kathy S. Albain; Hope S. Rugo; Mathew J. Ellis; Iuliana Shapira; Antonio C. Wolff; Lisa A. Carey; Beth Overmoyer; Ann H. Partridge; Clifford A. Hudis; Ian E. Krop; Harold J. Burstein; Eric P. Winer; *Journal of Clinical Oncology* 2019 371868-1875.
DOI: 10.1200/JCO.19.00066

TABLE 3. Estimated 3-Year, 5-Year, and 7-Year Rates for RFI, BCSS, and OS

	RFI			BCSS			OS		
Time (years)	No. of Events	No. at Risk	Rate (95% CI)	No. of Events	No. at Risk	Rate (95% CI)	No. of Events	No. at Risk	Rate (95% CI)
3	3	378	99.2 (98.4 to > 99.9)	0	386	—	1	386	99.7 (99.2 to > 99.9)
5	7	347	98.1 (96.8 to 99.5)	1	362	99.7 (98.1 to > 99.9)	5	362	98.7 (97.5 to 99.8)
7	9	120	97.5 (95.9 to 99.1)	3	127	98.6 (97.0 to > 99.9)	14	127	95.0 (92.4 to 97.7)

Abbreviations: BCSS, Breast Cancer-Specific Survival; OS, overall survival; RFI, Recurrence-Free Interval.

TABLE 3. Estimated 3-Year, 5-Year, and 7-Year Rates for RFI, BCSS, and OS

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DOI: 10.1200/JCO.19.00066

Adjuvant trials of trastuzumab duration

Trial	Non-inferiority DFS HR	Experimental duration vs 12 m	N	Results	Cardiac toxicity?
PHARE[1]	1.15	6 months	3384	HR 1.21	Yes
HORG[2]	1.53	6 months	481	HR 1.57	No difference
Short HER[3]	1.29	9 weeks	1254	1.15 (0.9-1.46)	Yes
SOLD[4]	1.3*	9 weeks	2176	1.39	Yes
PERSEPHONE[5]	1.3	6 months	4000	1.07 (0.93-1.24)	Yes

1. Pivot, et al, Lancet Oncology 2103; 2. Mavroudis, et al, Ann Onc 2015; 3. Conte, et al, ASCO 2017;
4. Joensuu, et al, JAMA Onc 2018; 5. Earl, et al, ASCO 2018.

How does this change clinical practice?

- For select patients, weekly paclitaxel and a year of trastuzumab are associated with excellent outcomes
- Duration of adjuvant trastuzumab remains 1 year; can be reassured if patient cannot complete a year

Case 1

- 51 y/o presents with a clinical T2 N1 left breast mass.
- Biopsy of the breast reveals a grade 3 invasive carcinoma NOS. Tumor is ER 70%, PgR 2%, HER2 3+ and amplified. Biopsy of axillary LN benign but suspicious.

Case 2

- A healthy 85 y/o woman has an abnormal screening mammogram of her right breast.
- Biopsy reveals a grade 2 invasive lobular carcinoma with pleomorphic features, ER 100%, PgR 50%. HER2 3+ and amplified.

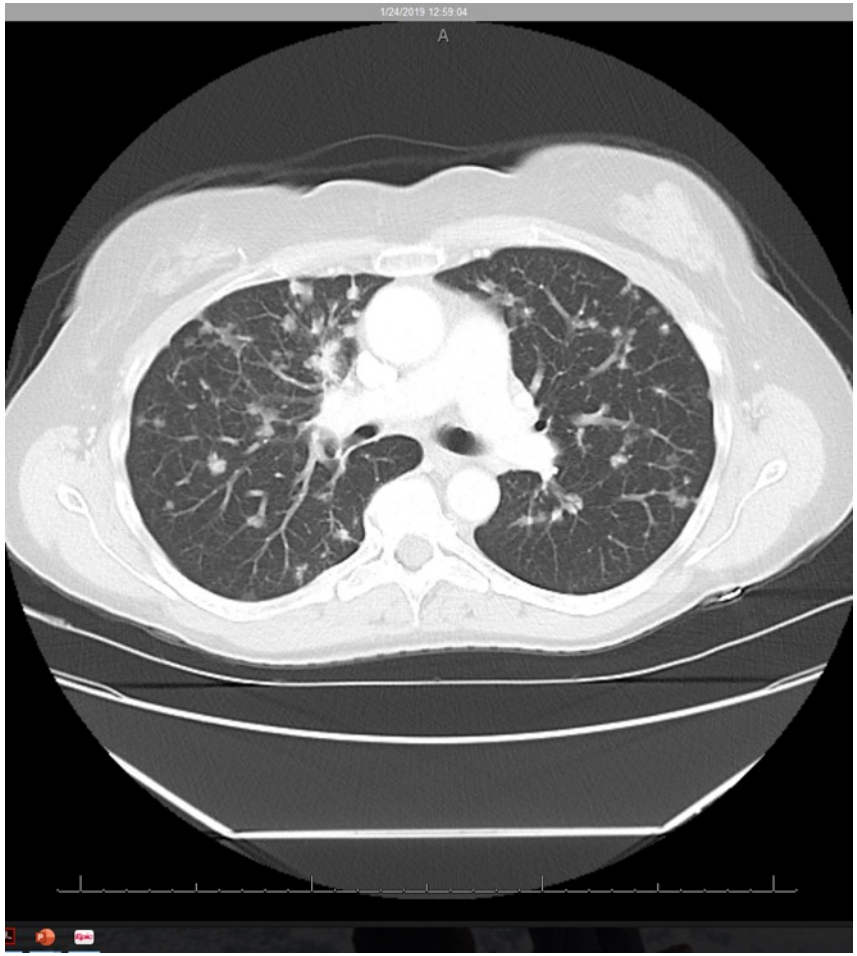
Case 3

- A 62 y/o woman presents with a URI that won't resolve.

- 8 years earlier, she had a stage I, T1BN0, HR+, HER2 amplified breast cancer.
- She received adjuvant docetaxel and cyclophosphamide and a year of trastuzumab and 5 years of exemestane.

Case 3

- Biopsy of a lung nodule confirms HR+, HER2 amplified MBC
- She is started on paclitaxel, trastuzumab and pertuzumab



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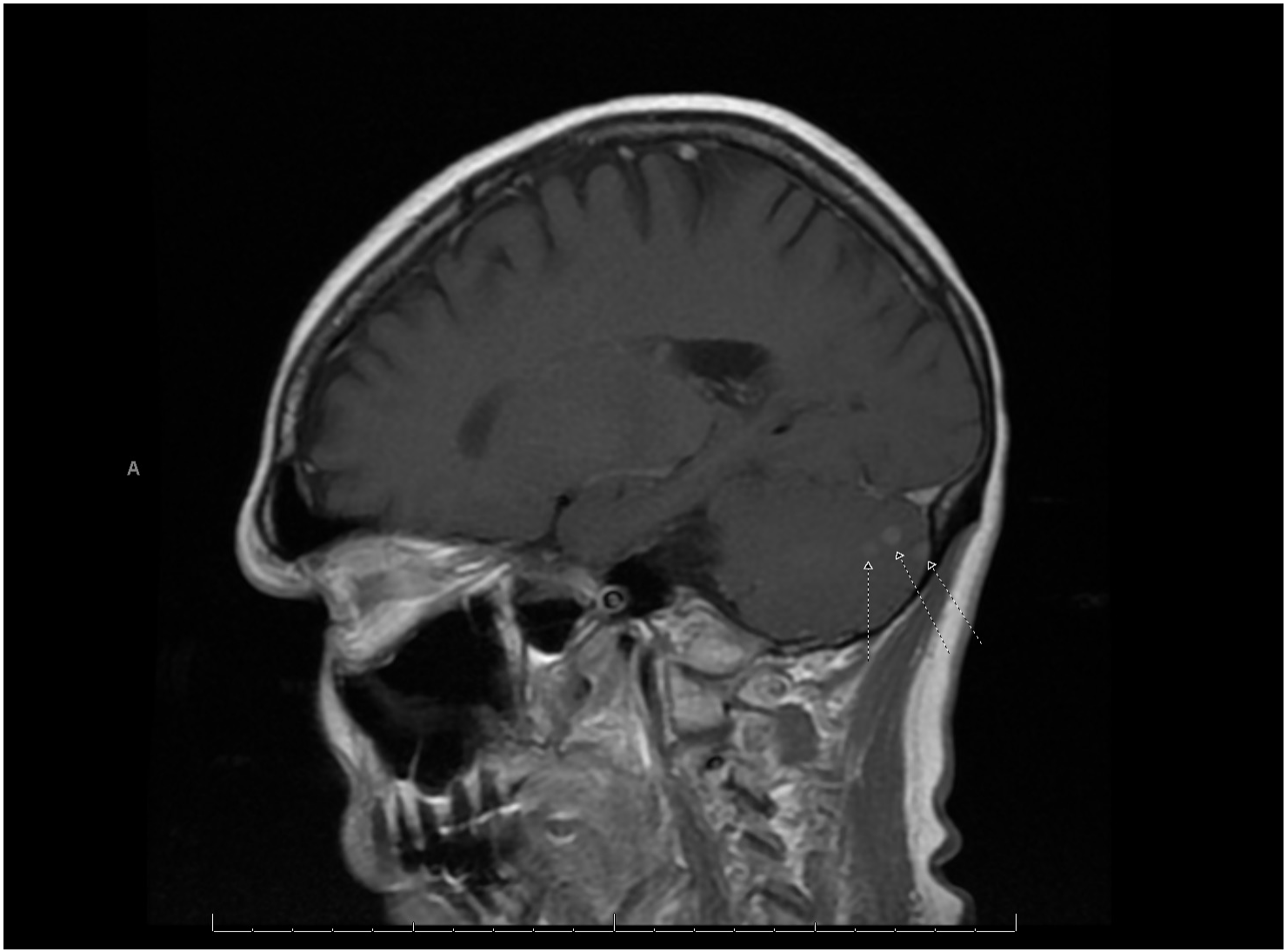
A

Phase III trials in HER2+ MBC

Trial	Design	Median OS	Population
CLEOPATRA[1]	1st line THP vs TH	56.5 vs 40.8 months	10% prior H
EMILIA[2]	2nd line T-DM1 vs CL	29.9 vs 25.4 months	100% prior H, taxanes
TH3RESA[3]	3rd line T-DM1 vs TPC	22.7 vs 15.8 months	100% prior H, L and taxane
EGF 104900[4]	3rd/4th line HL vs L	14 vs 9.8 months	Prior anthracyclines, taxane, H; Median 3 prior txs

T=docetaxel; H=trastuzumab; P=pertuzumab, C=capectabine; L=lapatinib;
TPC=treatment of physician's choice

1. Swain, et al, NEJM 2015; 2. Dieras, et al, Lancet Onc 2017; 3. Krop, et al, Lancet Onc 2017; 4. Blackwell, et al, JCO 2012

HER2CLIMB

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 13, 2020 VOL. 382 NO. 7

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

R.K. Murthy, S. Loi, A. Okines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.U. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S.S. Shachar, V. Müller, S. Braga, F.P. Duhoux, R. Greil, D. Cameron, L.A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Walker, W. Feng, and E.P. Winer

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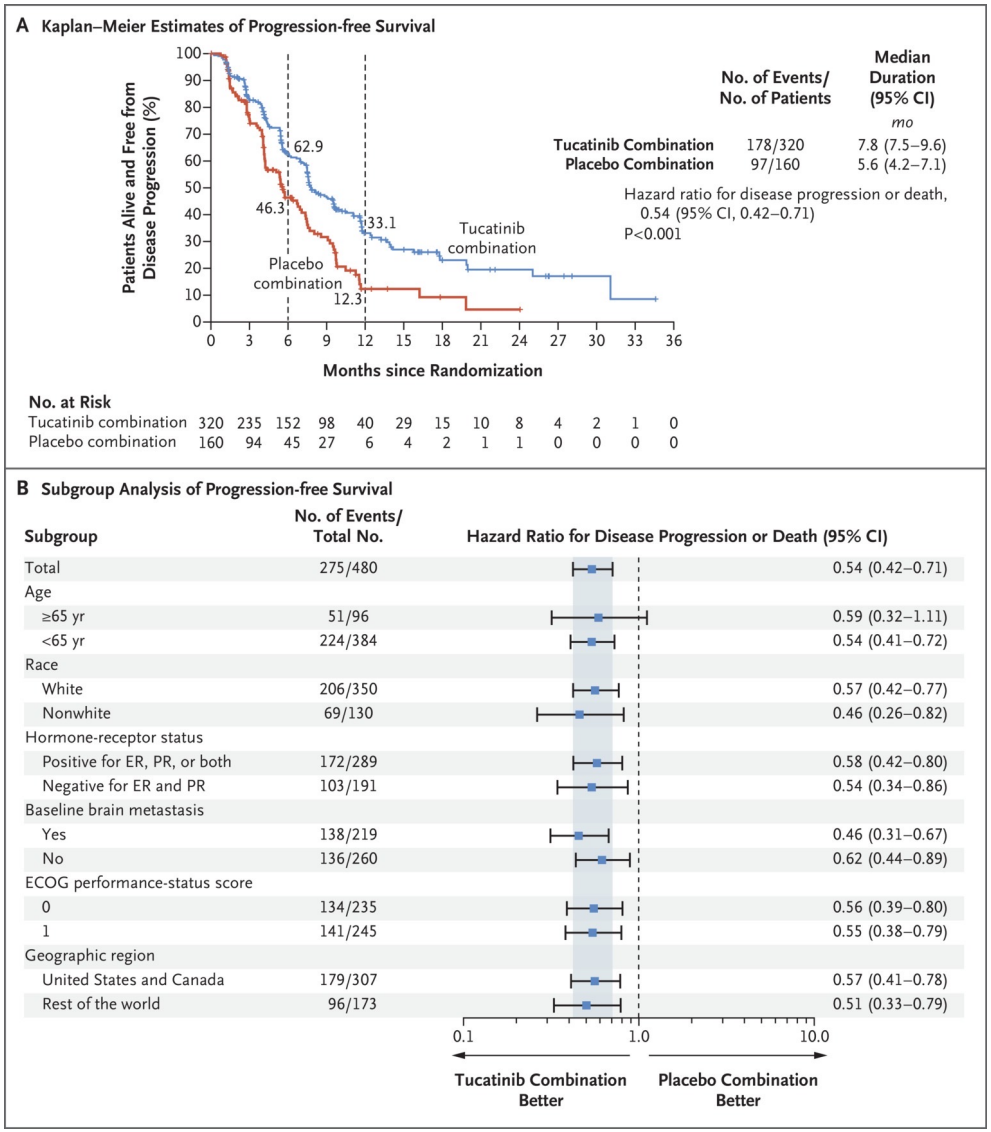
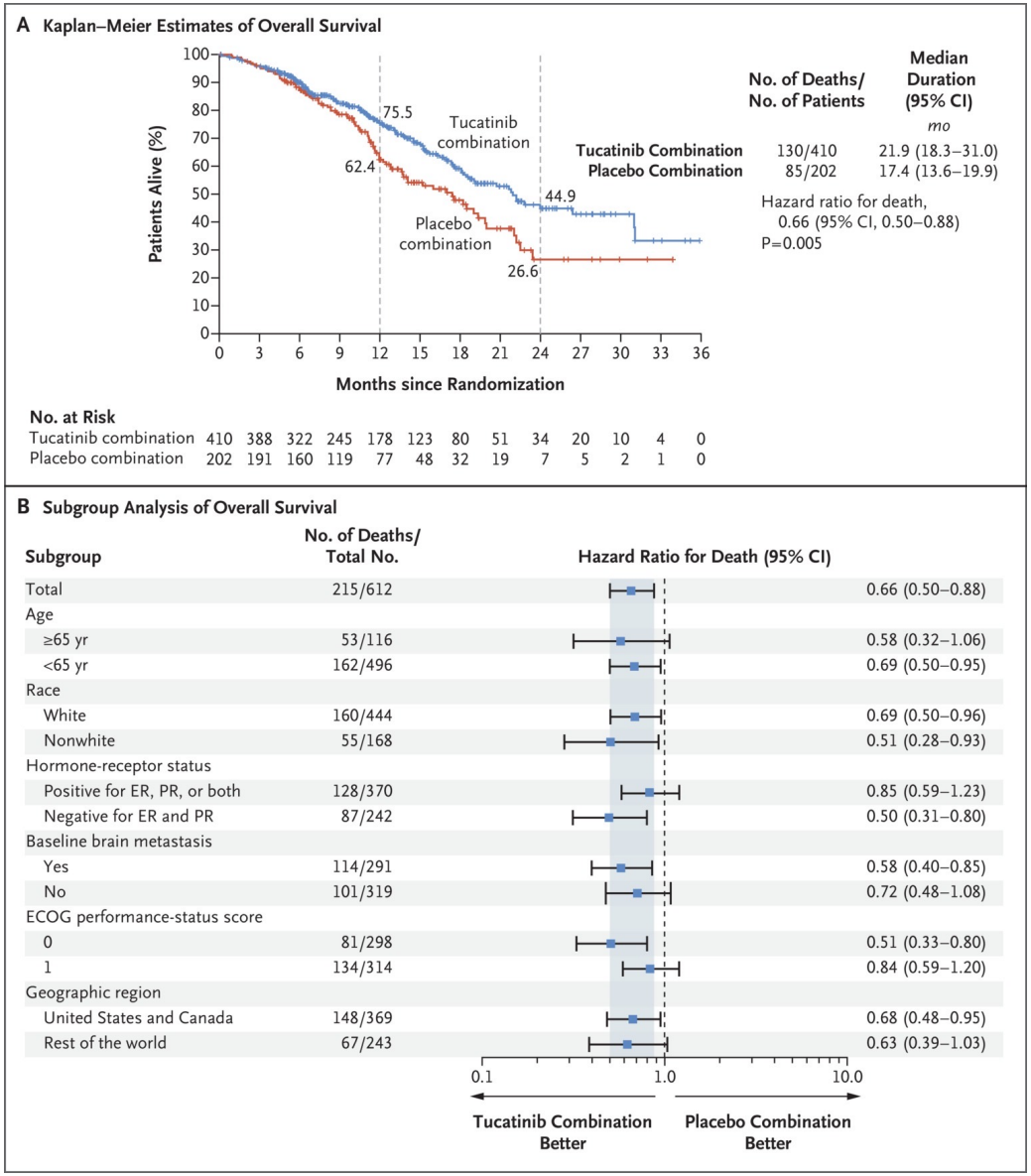
Kaplan–Meier Estimates of Progression-free Survival in the Primary End-Point Analysis Population and Prespecified Subgroups.



Murthy RK et al. N Engl J Med 2020;382:597-609

The NEW ENGLAND JOURNAL of MEDICINE

Kaplan–Meier Estimates of Overall Survival in the Total Population and Prespecified Subgroups



Murthy RK et al. N Engl J Med 2020;382:597-609

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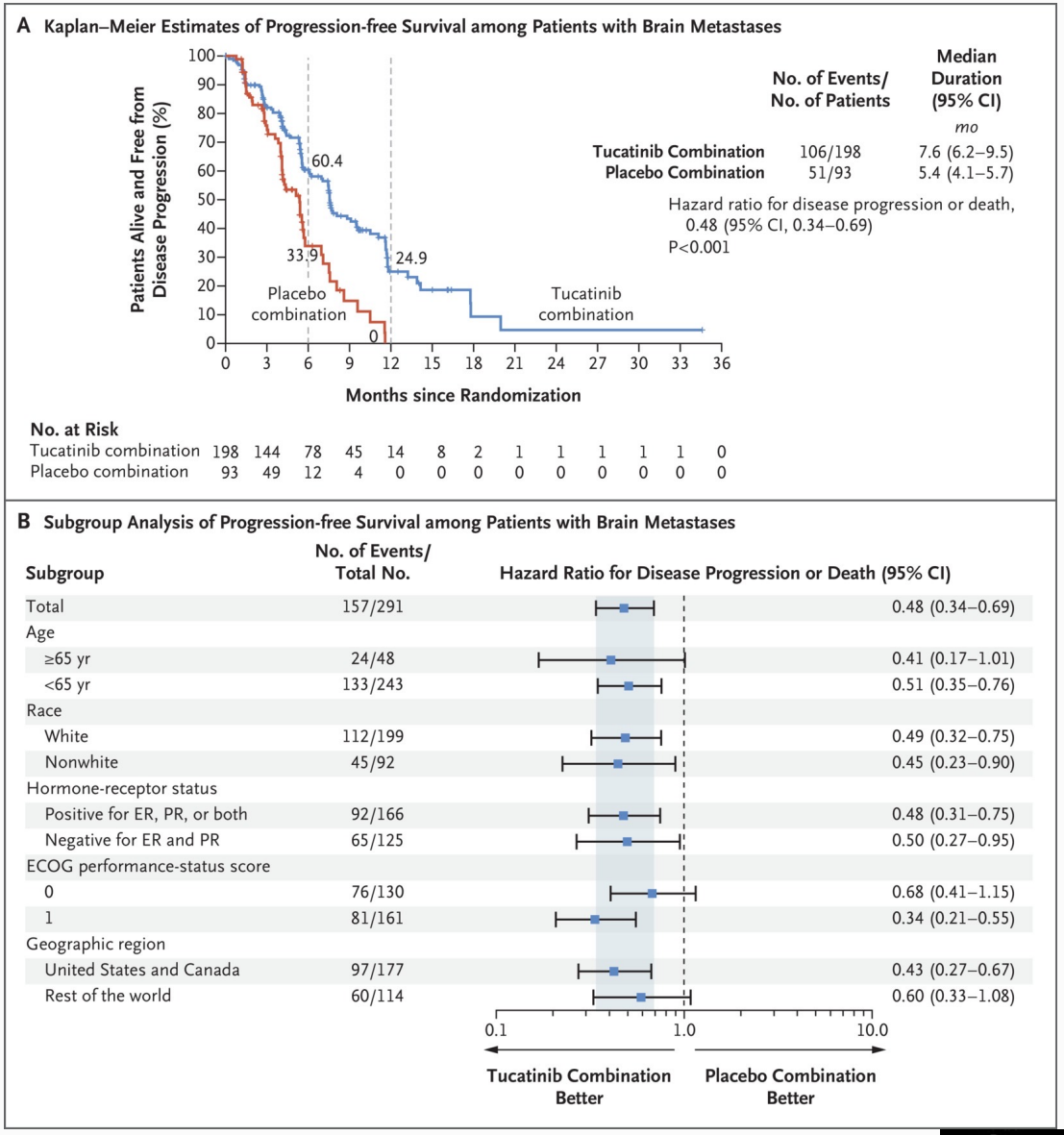
Kaplan–Meier Estimates of Progression-free Survival among the Patients with Brain Metastases in the Total Population and Prespecified Subgroups.



Murthy RK et al. N Engl J Med 2020;382:597-609

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Patient Demographic and Disease Characteristics in the Primary End-Point Analysis Population and the Total Population.

Table 1. Patient Demographic and Disease Characteristics in the Primary End-Point Analysis Population and the Total Population.*

Characteristic	Primary End-Point Analysis Population (N=480)		Total Population (N=612)	
	Tucatinib Combination (N=320)	Placebo Combination (N=160)	Tucatinib Combination (N=410)	Placebo Combination (N=202)
Female sex — no. (%)	317 (99.1)	158 (98.8)	407 (99.3)	200 (99.0)
Age — no. (%)				
<65 yr	252 (78.8)	132 (82.5)	328 (80.0)	168 (83.2)
≥65 yr	68 (21.2)	28 (17.5)	82 (20.0)	34 (16.8)
Median age — yr	54.0	54.0	55.0	54.0
Race — no. (%)†				
Asian	17 (5.3)	3 (1.9)	18 (4.4)	5 (2.5)
Black	30 (9.4)	13 (8.1)	41 (10.0)	14 (6.9)
White	225 (70.3)	125 (78.1)	287 (70.0)	157 (77.7)
Unknown or other	48 (15.0)	19 (11.9)	64 (15.6)	26 (12.9)
Geographic region — no. (%)				
United States and Canada	204 (63.8)	103 (64.4)	246 (60.0)	123 (60.9)
Rest of the world	116 (36.2)	57 (35.6)	164 (40.0)	79 (39.1)
Hormone-receptor status — no. (%)				
Positive for ER or PR or both	190 (59.4)	99 (61.9)	243 (59.3)	127 (62.9)
Negative for ER and PR	126 (39.4)	61 (38.1)	161 (39.3)	75 (37.1)
Other	4 (1.2)	0	6 (1.5)	0
ECOG performance-status score — no. (%)‡				
0	159 (49.7)	76 (47.5)	204 (49.8)	94 (46.5)
1	161 (50.3)	84 (52.5)	206 (50.2)	108 (53.5)
Stage IV at initial diagnosis — no. (%)	108 (33.8)	67 (41.9)	143 (34.9)	77 (38.1)
Presence or history of brain metastases — no. (%)	148 (46.2)	71 (44.4)	198 (48.3)	93 (46.0)
Location of other metastases — no. (%)				
Lung	160 (50.0)	82 (51.2)	200 (48.8)	100 (49.5)
Liver	108 (33.8)	64 (40.0)	137 (33.4)	78 (38.6)
Bone	178 (55.6)	85 (53.1)	223 (54.4)	111 (55.0)
Previous lines of therapy, median no. (range)	4 (2–14)	4 (2–17)	4 (2–14)	4 (2–17)
Previous lines of therapy for metastatic cancer, median no. (range)	3 (1–14)	3 (1–13)	3 (1–14)	3 (1–13)
Previous therapies — no. (%)				
Trastuzumab	320 (100)	160 (100)	410 (100)	202 (100)
Pertuzumab	320 (100)	159 (99.4)	409 (99.8)	201 (99.5)
Trastuzumab emtansine	320 (100)	160 (100)	410 (100)	202 (100)
Lapatinib	22 (6.9)	10 (6.2)	24 (5.9)	10 (5.0)

Murthy RK et al. N Engl J Med 2020;382:597-609

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Most Common Adverse Events.

Table 2. Most Common Adverse Events.*

Event	Tucatinib-Combination Group (N = 404)		Placebo-Combination Group (N = 197)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	401 (99.3)	223 (55.2)	191 (97.0)	96 (48.7)
Diarrhea	327 (80.9)	52 (12.9)	105 (53.3)	17 (8.6)
PPE syndrome	256 (63.4)	53 (13.1)	104 (52.8)	18 (9.1)
Nausea	236 (58.4)	15 (3.7)	86 (43.7)	6 (3.0)
Fatigue	182 (45.0)	19 (4.7)	85 (43.1)	8 (4.1)
Vomiting	145 (35.9)	12 (3.0)	50 (25.4)	7 (3.6)
Stomatitis	103 (25.5)	10 (2.5)	28 (14.2)	1 (0.5)
Decreased appetite	100 (24.8)	2 (0.5)	39 (19.8)	0
Headache	87 (21.5)	2 (0.5)	40 (20.3)	3 (1.5)
Aspartate aminotransferase increased	86 (21.3)	18 (4.5)	22 (11.2)	1 (0.5)
Alanine aminotransferase increased	81 (20.0)	22 (5.4)	13 (6.6)	1 (0.5)

Murthy RK et al. N Engl J Med 2020;382:597-609

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DESTINY

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ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

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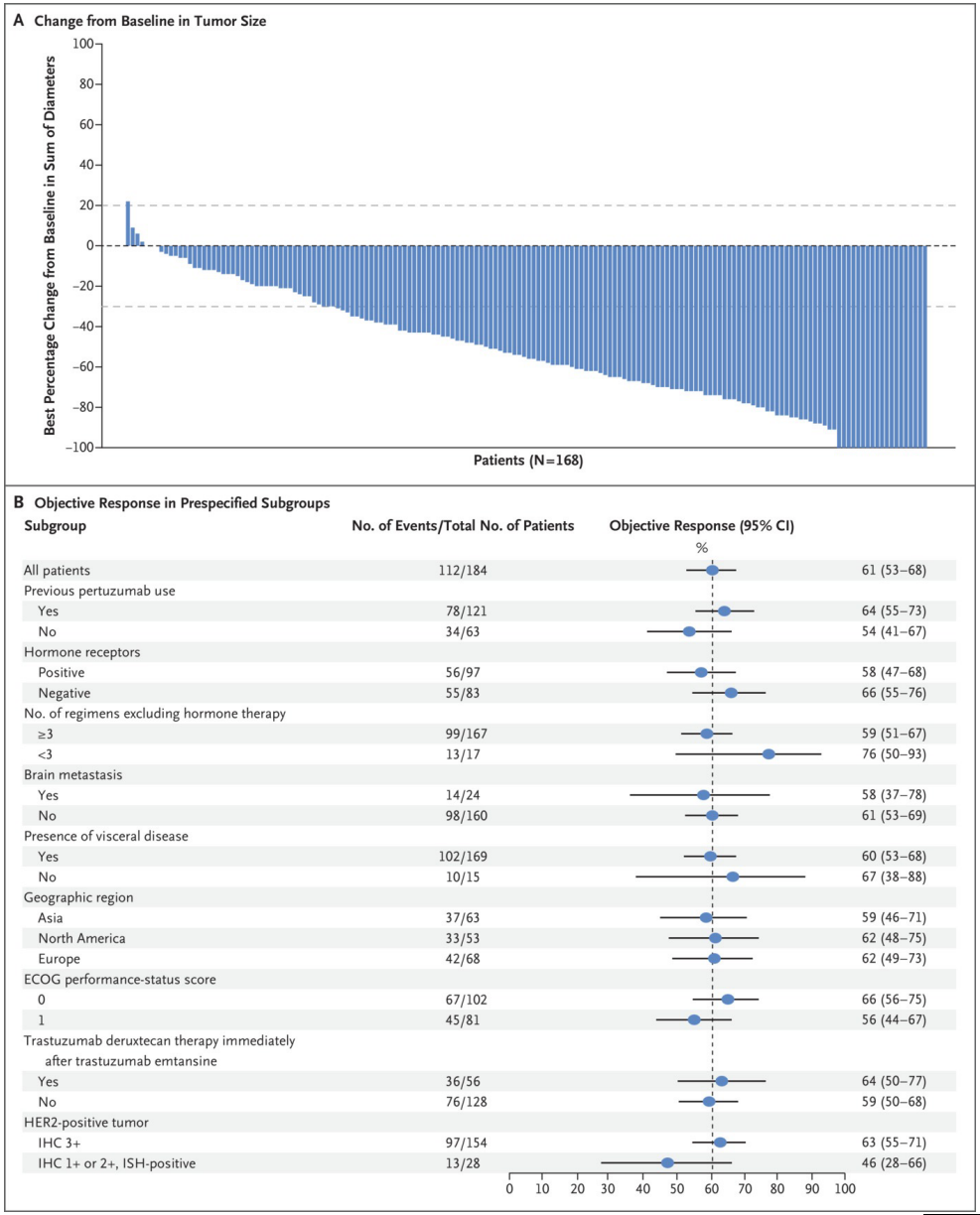
Response to Trastuzumab Deruxtecan, According to Tumor Size and Subgroup Analyses.



Modi S et al. N Engl J Med 2020;382:610-621

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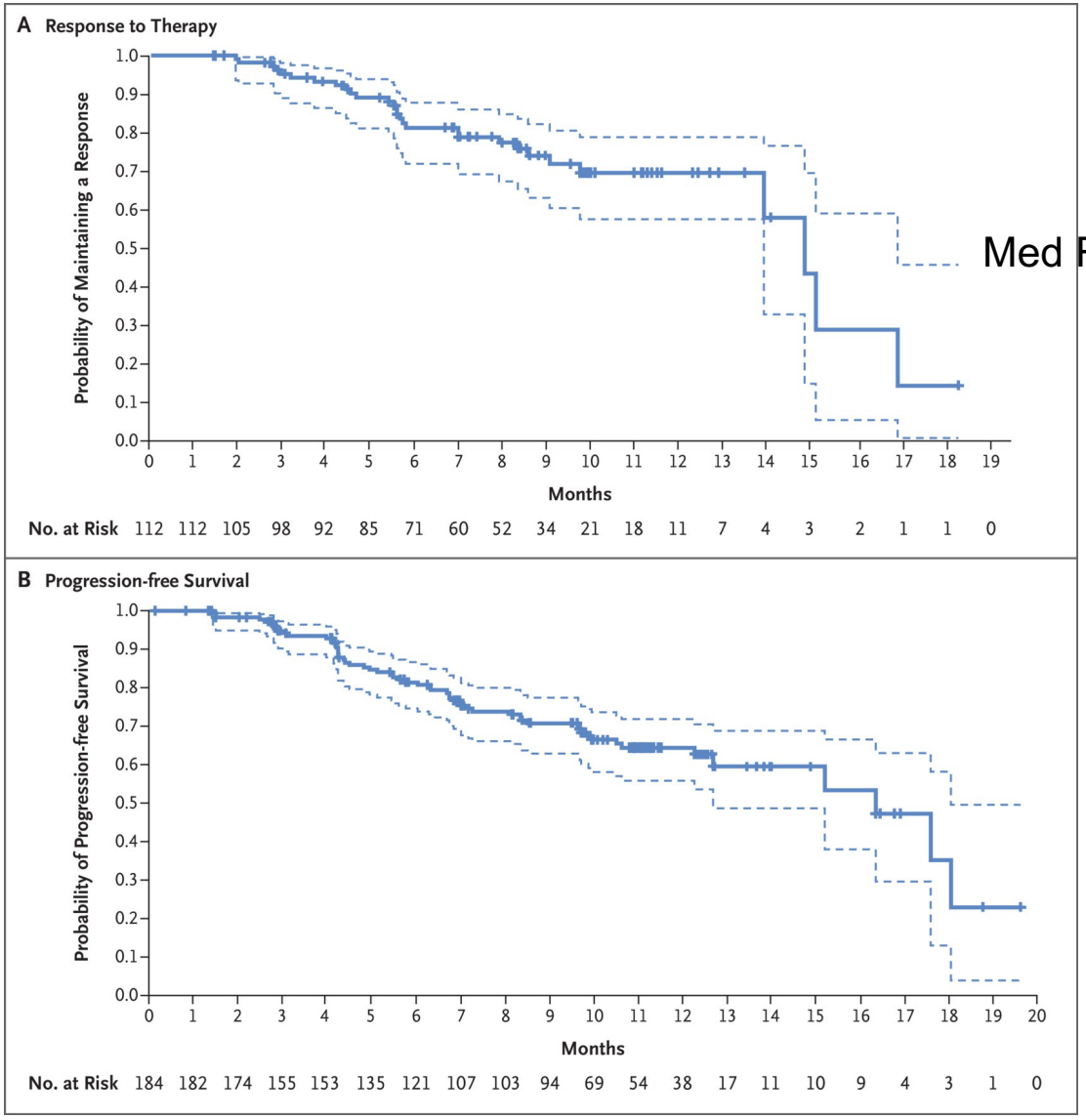
Kaplan–Meier Analysis of Response Duration and Progression-free Survival.



Med Resp Dur 14.8 mos

Med PFS 16.4 mos

Modi S et al. N Engl J Med 2020;382:610-621

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Adverse Events in the Overall Population of 184 Patients.

Table 2. Adverse Events in the Overall Population of 184 Patients.*

Adverse Events	Any Grade	Grade 3	Grade 4
	number of patients (percent)		
Any adverse event†	183 (99.5)	89 (48.4)	7 (3.8)
Nausea	143 (77.7)	14 (7.6)	0
Fatigue	91 (49.5)	11 (6.0)	0
Alopecia	89 (48.4)	1 (0.5)	0
Vomiting	84 (45.7)	8 (4.3)	0
Constipation	66 (35.9)	1 (0.5)	0
Decreased neutrophil count‡	64 (34.8)	36 (19.6)	2 (1.1)
Decreased appetite	57 (31.0)	3 (1.6)	0
Anemia§	55 (29.9)	15 (8.2)	1 (0.5)
Diarrhea	54 (29.3)	5 (2.7)	0
Decreased white-cell count¶	39 (21.2)	11 (6.0)	1 (0.5)
Decreased platelet count‖	39 (21.2)	7 (3.8)	1 (0.5)
Headache	36 (19.6)	0	0
Cough	35 (19.0)	0	0
Abdominal pain**	31 (16.8)	2 (1.1)	0
Decreased lymphocyte count††	26 (14.1)	11 (6.0)	1 (0.5)
Adverse events of special interest			
Interstitial lung disease‡‡	25 (13.6)	1 (0.5)	0
Prolonged QT interval	9 (4.9)	2 (1.1)	0
Infusion-related reaction	4 (2.2)	0	0
Decreased left ventricular ejection fraction§§	3 (1.6)	1 (0.5)¶¶	0

Modi S et al. N Engl J Med 2020;382:610-621

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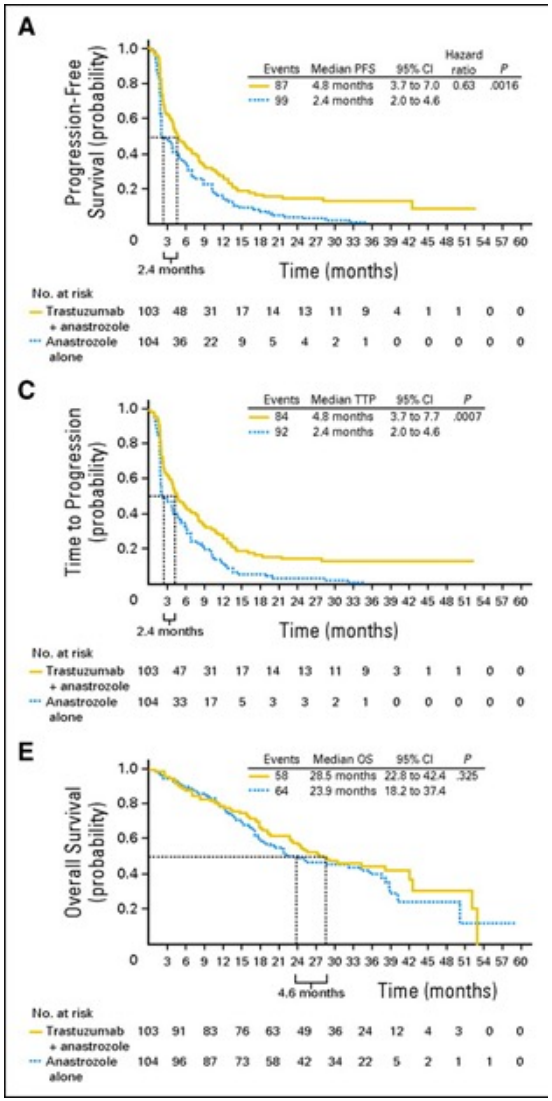
How does this change clinical practice?

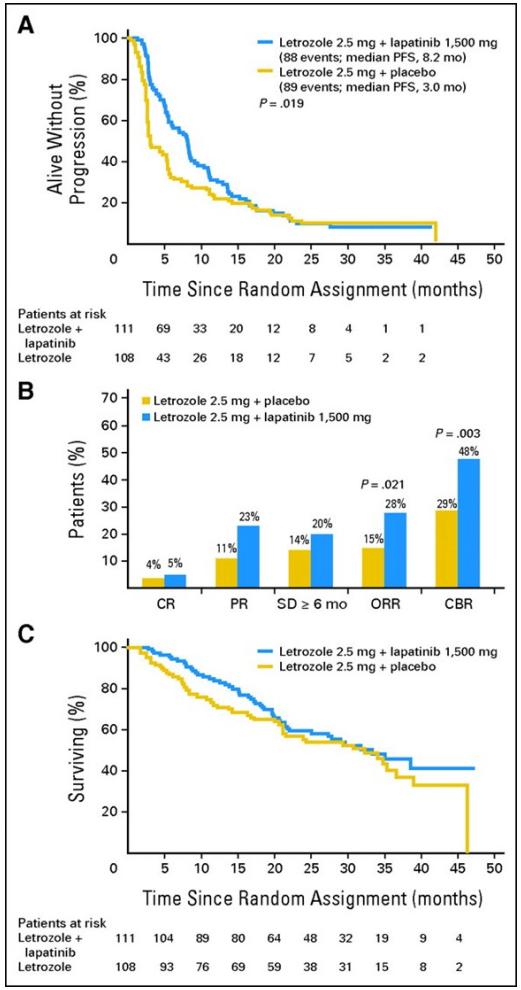
- Trastuzumab deruxtecan was FDA-approved in Dec 2019, followed by tucatinib in April 2020.

- Patients have increasing options in the metastatic setting.

What about endocrine therapy?



Kaufman, et al, JCO 2009



Johnston, et al, JCO 2009

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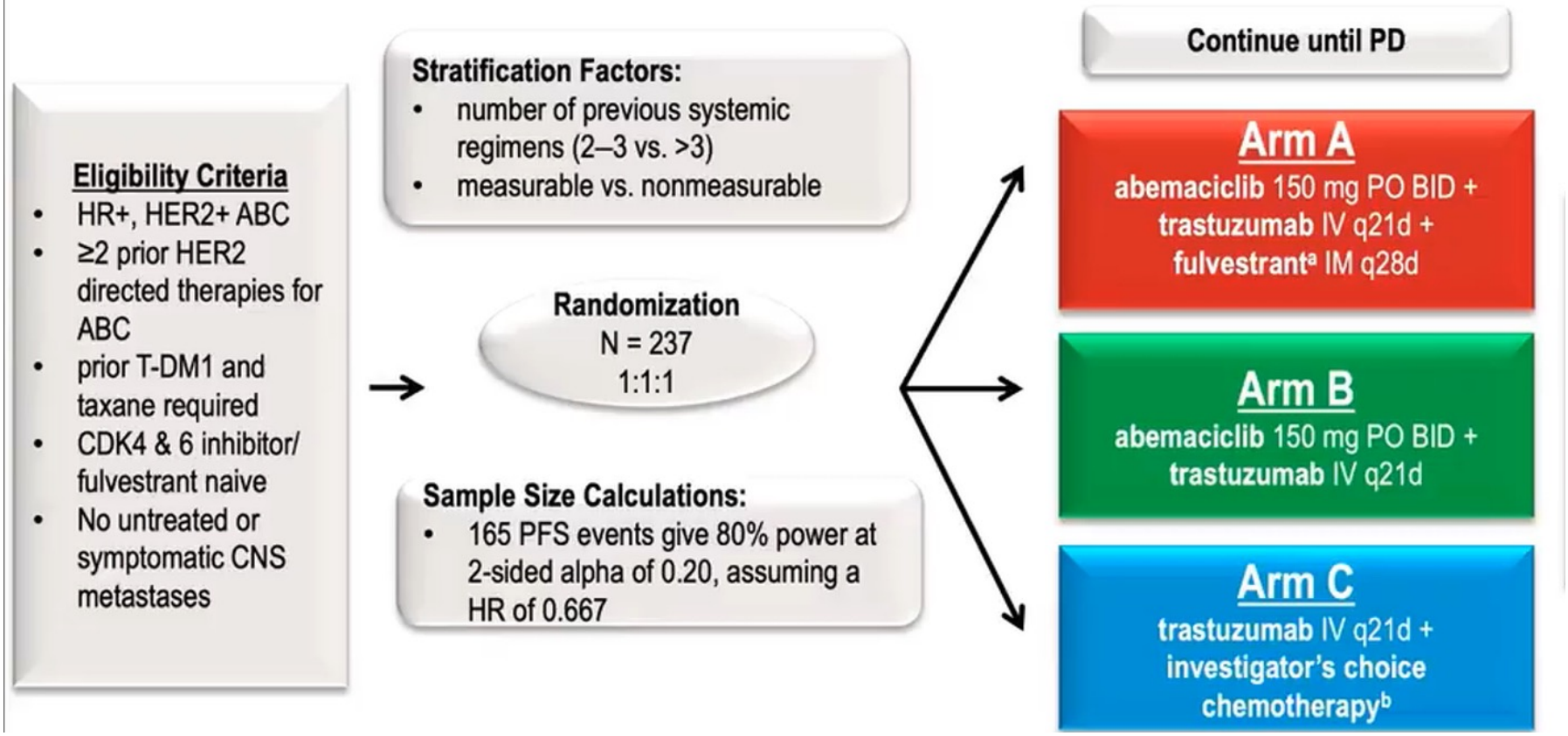
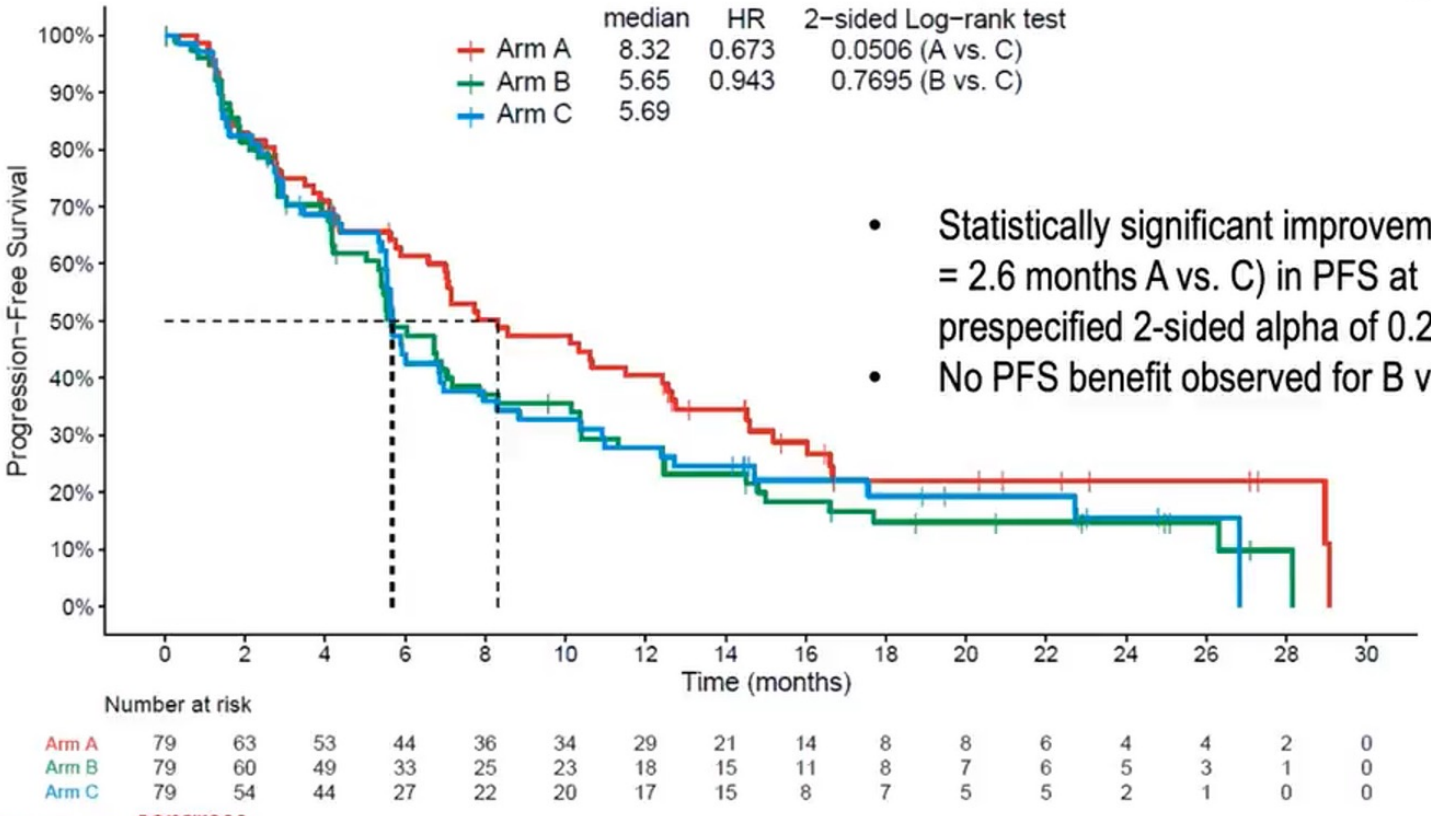
monarcHER STUDY DESIGN



Tolaney, et al, Lancet Onc 2020

PRIMARY ENDPOINT: PFS

Arm A= abemaciclib + trastuzumab + fulv
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy



- Statistically significant improvement = 2.6 months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

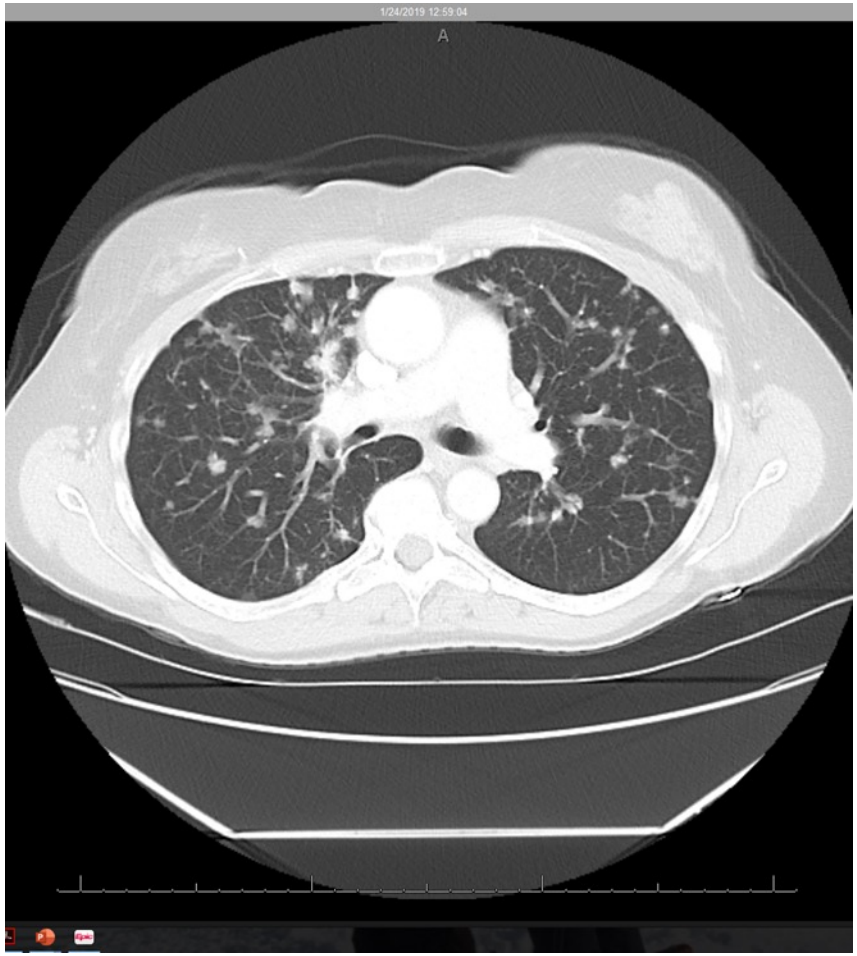
Tolaney, et al, Lancet Onc 2020

How does this change clinical practice?

- Many effective HER2-directed therapies as continued HER2 blockade necessary
- Tucatinib with impressive CNS activity
- Non-chemotherapy options are promising
- Unknown efficacy of pertuzumab after trastuzumab exposure

Case 3

- Biopsy of a lung nodule confirms HR+, HER2 amplified MBC
- She is started on paclitaxel, trastuzumab and pertuzumab



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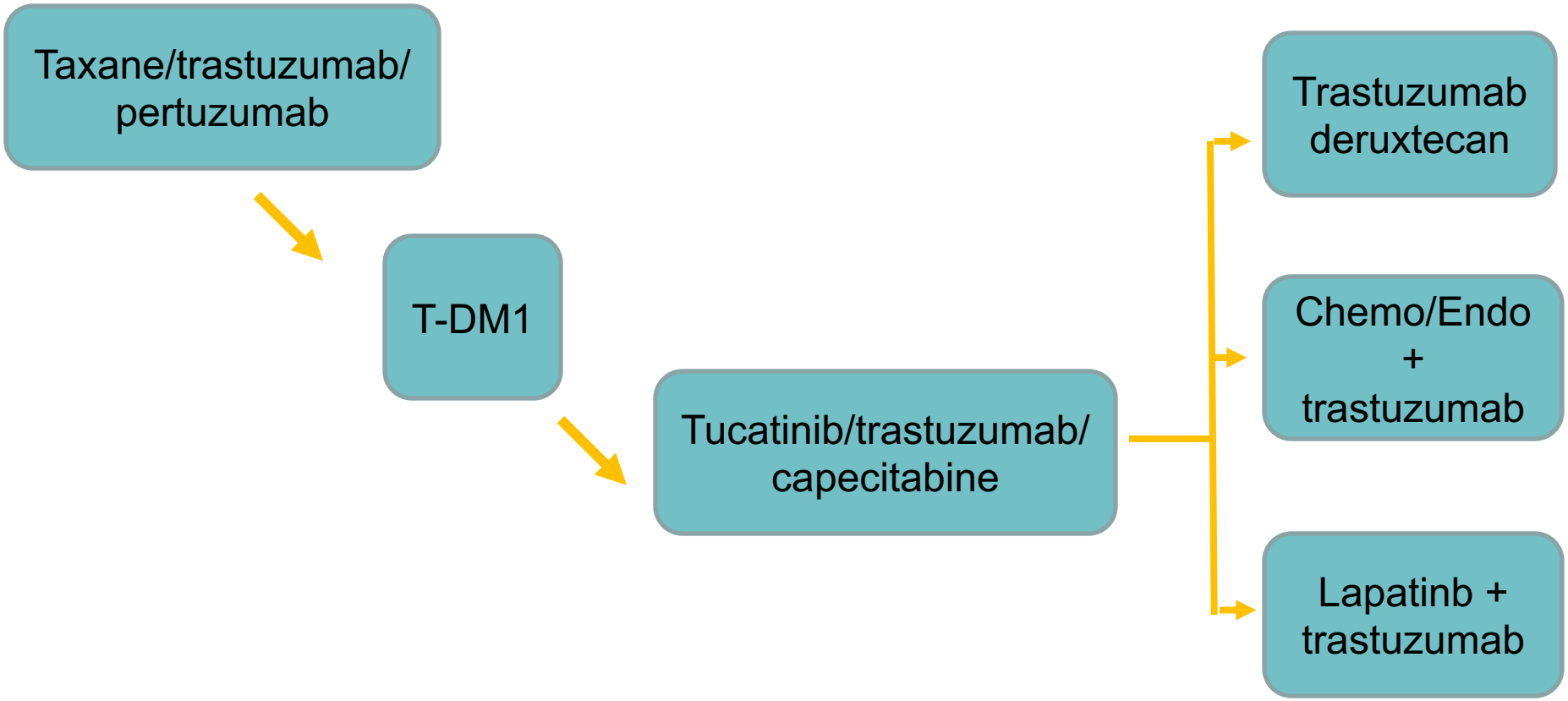
Optimal sequencing?



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Thank you.
Questions?

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