HER2 Target Therapies: Recent Advances

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UCDAVIS
COMPREHENSIVE
CANCER CENTER

Today's Talk

- Early stage
- Advanced stage
- Future directions

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2023 ASCO ANNUAL MEETING

3-year invasive disease-free survival (iDFS) of the strategy-based, randomized phase II PHERGain trial evaluating chemotherapy (CT) de-escalation in human epidermal growth factor receptor 2-positive (HER2[+]) early breast cancer (EBC)

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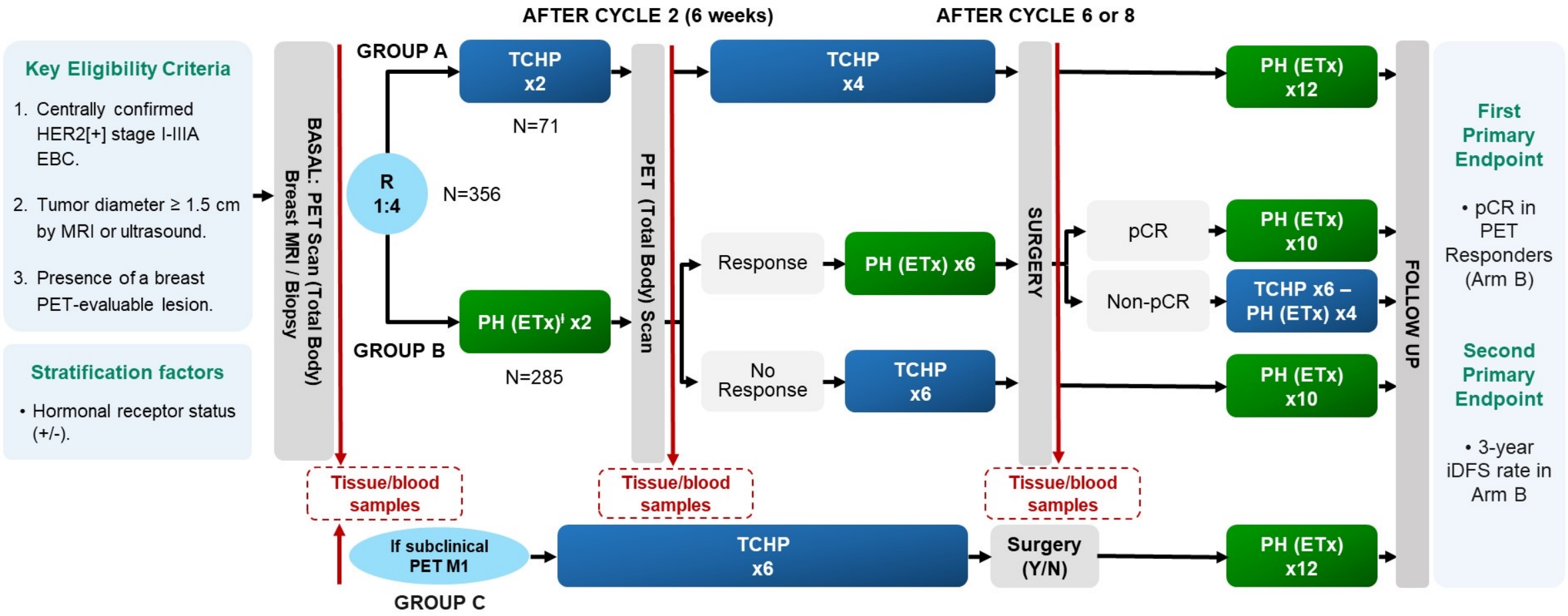
Background

- The introduction of HER2-directed therapies has dramatically improved the outcome of patients with HER2[+] EBC, leading to the investigation of different de-escalation strategies.[1, 2]
- Early metabolic evaluation using ^{18}F-FDG PET/CT helps to recognize patients with an increased probability of pathological complete response (pCR).[3]
- PHERGain trial assessed the opportunity of CT de-escalation with a response-adapted strategy in HER2[+] EBC based on i) an early metabolic response by ^{18}F-FDG PET/CT to neoadjuvant trastuzumab plus pertuzumab (HP) and ii) the pathological response.[4]

1. Bueno Muiño C, et al. (2022). *Cancers*, 14(3), 512.
2. Pernas S, et al. (2021). *JCO Oncol Pract*, 17(6), 320-330.
3. Gebhart G, et al. (2013). *J Nucl Med*, 54:1862-8
4. Pérez-García, JM, et al. (2021). *Lancet Oncol*, 22(6), 858-871

CT: chemotherapy; EBC: Early breast cancer; HER2: Human Epidermal Growth Factor Receptor 2; ^{18}F-FDG PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography

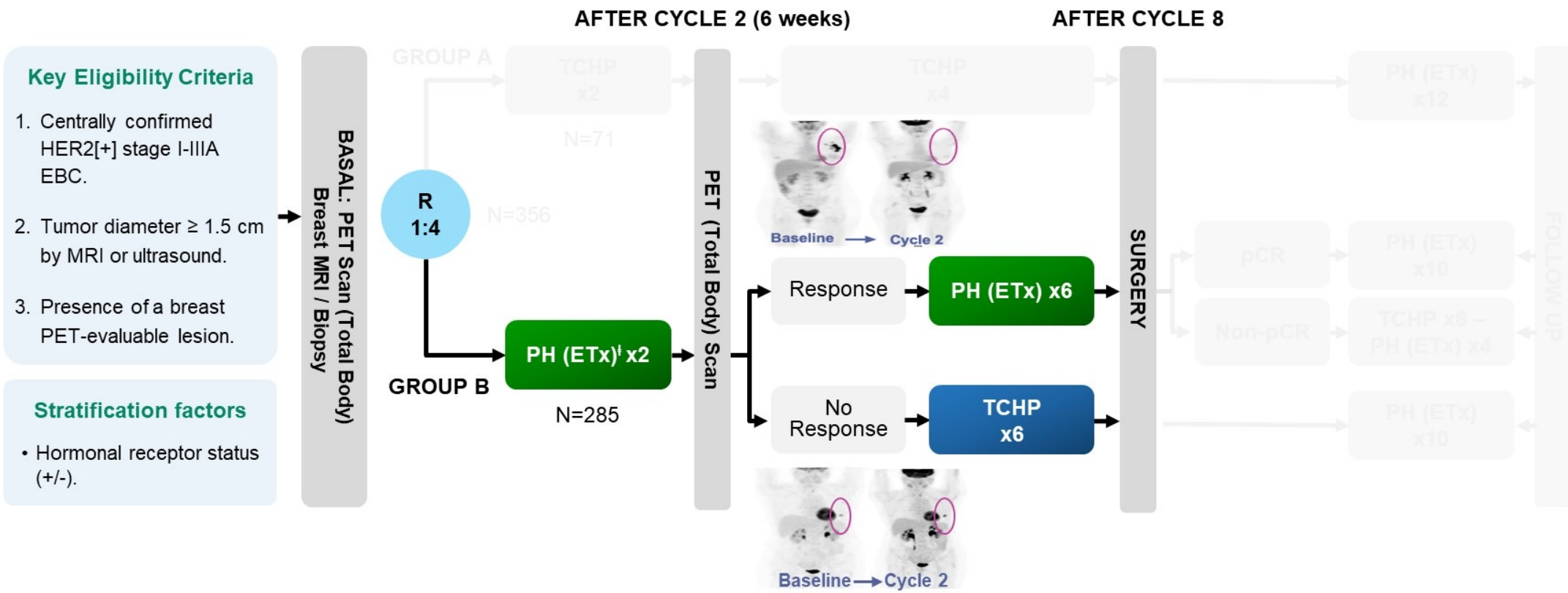
PHERGain Study Design



C: Carboplatin; D: Docetaxel; EBC: Early breast cancer; ETx: Endocrine therapy (letrozole post-menopausal/tamoxifen pre-menopausal), Adjuvant ETx up to 3 years from surgery; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; H: Trastuzumab SC; HER2: Human Epidermal Growth Factor Receptor 2; iDFS: Invasive disease-free survival; MRI: Magnetic resonance Imaging; P: Pertuzumab IV; R: Randomization; TCHP: Trastuzumab, pertuzumab, docetaxel, and carboplatin. [t] All hormonal receptor-positive patients received ETx concomitantly with PH (except on chemotherapy).

- PET RESPONDERS: RECIST responders after cycle 2 with SUV_{max} reduction ≥40%.
- pCR, Pathological complete response (ypT0/isN0)

PHERGain Study Design



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- PET RESPONDERS: RECIST responders after cycle 2 with SUV_{max} reduction ≥40%.
- pCR, Pathological complete response (ypT0/isN0).

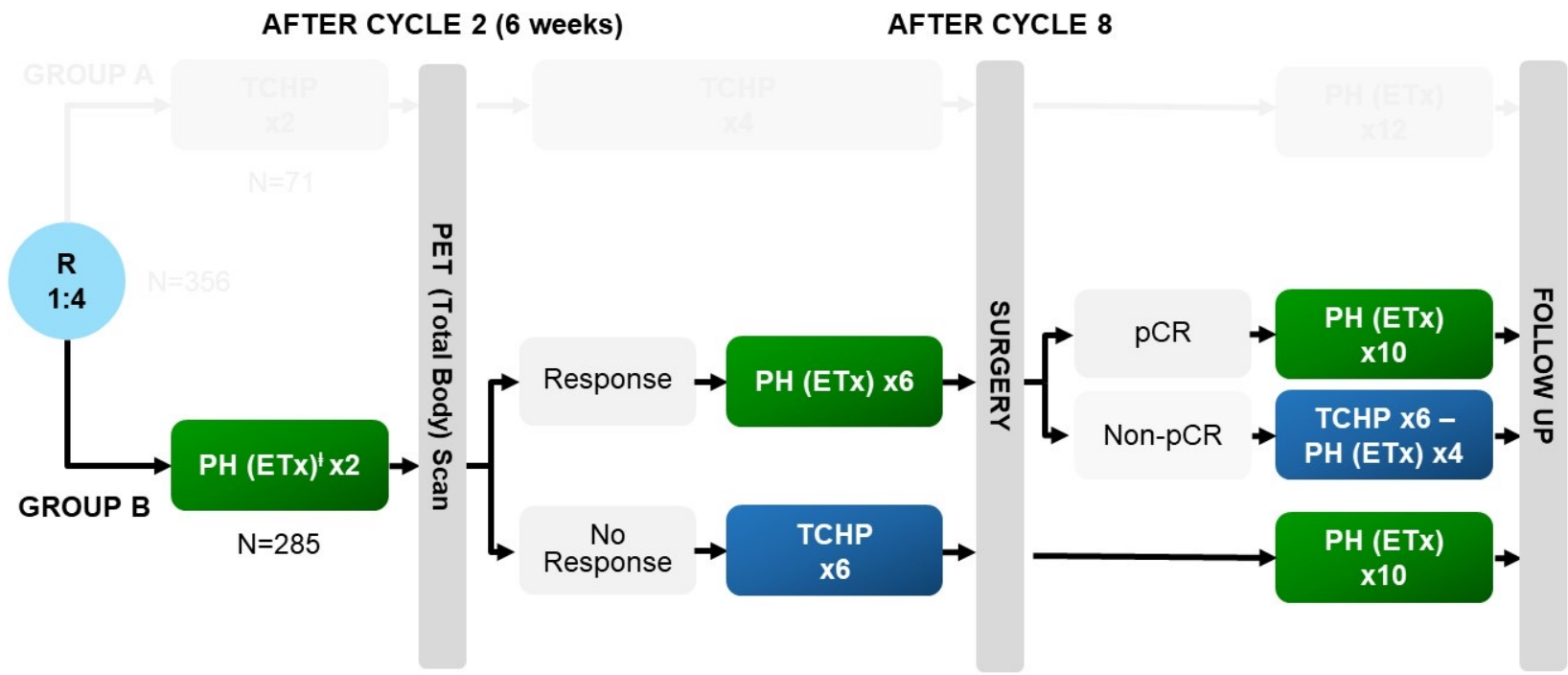
PHERGain Study Design

Key Eligibility Criteria

1. Centrally confirmed HER2[+] stage I-IIIA EBC.
2. Tumor diameter ≥ 1.5 cm by MRI or ultrasound.
3. Presence of a breast PET-evaluable lesion.

Stratification factors

- Hormonal receptor status (+/-).



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- PET RESPONDERS: RECIST responders after cycle 2 with SUV_{max} reduction ≥40%.
- pCR, Pathological complete response (ypT0/isN0).

Key eligibility criteria

Inclusion criteria

- Stage I-IIIA invasive breast cancer.
- Tumor diameter ≥ 1.5 centimeter by MRI or ultrasound.
- At least one PET-evaluable breast lesion (SUV_{max} ≥ 1.5 x SUV_{mean} liver + 2 SD).
- Centrally confirmed HER2[+] breast cancer.
- Patient must have ER and PR status locally determined.

Exclusion criteria

- Previous chemotherapy, anti-HER2, radiotherapy, or endocrine therapy for invasive breast cancer.
- Evidence of metastatic disease by routine clinical assessment. Patients with subclinical M1 detected by PET will be included into Group C.

ER: Estrogen receptor; HER2: Human Epidermal Growth Factor Receptor 2; M1: Metastases; MRI: Magnetic resonance imaging; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; PR: Progesterone receptor; SD: Standard deviation; SUVmax: The maximum Standardized Uptake Value; SUVmean: The mean standardized uptake value.

Study Endpoints

Primary endpoints

- pCR (ypT0/isN0) in PET Responders (Group B)
- 3-year iDFS rate in Group B

Secondary endpoints

- pCR in Group A and Group B
- pCR by PET response / Other definitions of pCR
- Breast-conserving surgery
- Tumor response by MRI
- Optimal PET cut-off SUV_{max} for pCR
- 3-year iDFS in Group A
- 3-year DDFS in Group A and Group B
- 3-year EFS in Group A and Group B
- 3-year OS in Group A and Group B
- Long term outcomes per group
- Health-related quality of life
- Toxicity (CTCAE v4.0)

CTCAE v4.0: Common Terminology Criteria for Adverse Events version 4.0; DDFS: Disease-free survival; EFS: Event-free survival; iDFS: Invasive disease-free survival; OS: Overall survival; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response; SUV_{max}: The maximum Standardized Uptake Value

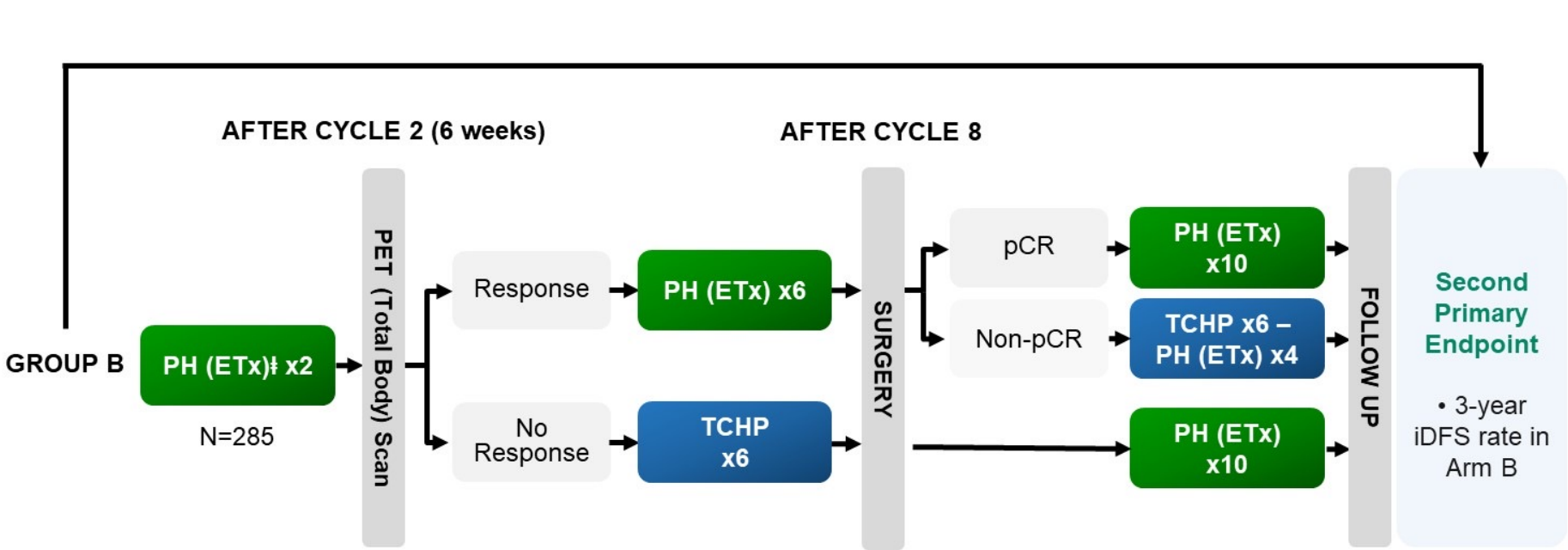
3-year iDFS Primary Endpoint

Key Eligibility Criteria

1. Centrally confirmed HER2[+] stage I-IIIA EBC.
2. Tumor diameter ≥ 1.5 cm by MRI or ultrasound.
3. Presence of a breast PET-evaluable lesion.

Stratification factors

- Hormonal receptor status (+/-).



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- PET RESPONDERS: RECIST responders after cycle 2 with SUV_{max} reduction ≥40%.
- pCR, Pathological complete response (ypT0/isN0).

Baseline Characteristics

ITT population	Group A (N = 71)	Group B (N = 285)
Menopausal status		
Premenopausal	37 (52.1%)	146 (51.2%)
Postmenopausal	34 (47.9%)	139 (48.8%)
ECOG Performance status		
0	69 (97.2%)	264 (92.6%)
1	2 (2.8%)	21 (7.4%)
Histologically confirmed lesions		
Unifocal	56 (78.9%)	217 (76.1%)
Multifocal	15 (21.1%)	68 (23.9%)
Stage		
I	9 (12.7%)	24 (8.4%)
II	50 (70.4%)	219 (76.8%)
III	12 (16.9%)	42 (14.7%)

Data are *n* (%), unless otherwise specified.

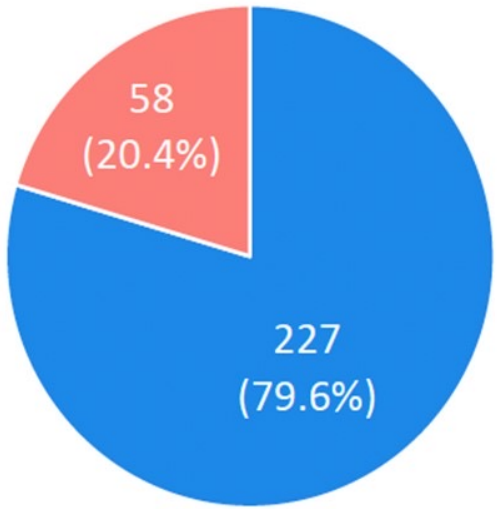
Baseline Characteristics (cont.)

ITT population	Group A (N = 71)	Group B (N = 285)
Nodal status		
Positive	32 (45.1%)	140 (49.1%)
Negative	39 (54.9%)	145 (50.9%)
Hormone receptor status		
ER-negative and PR-negative	27 (38.1%)	93 (32.6%)
ER-positive and/or PR-positive	44 (61.9%)	192 (67.4%)
HER2 IHC score and FISH analysis		
2+ and FISH-positive	13 (18.3%)	64 (22.5%)
3+	58 (81.7%)	221 (77.5%)

Data are *n* (%), unless otherwise specified.

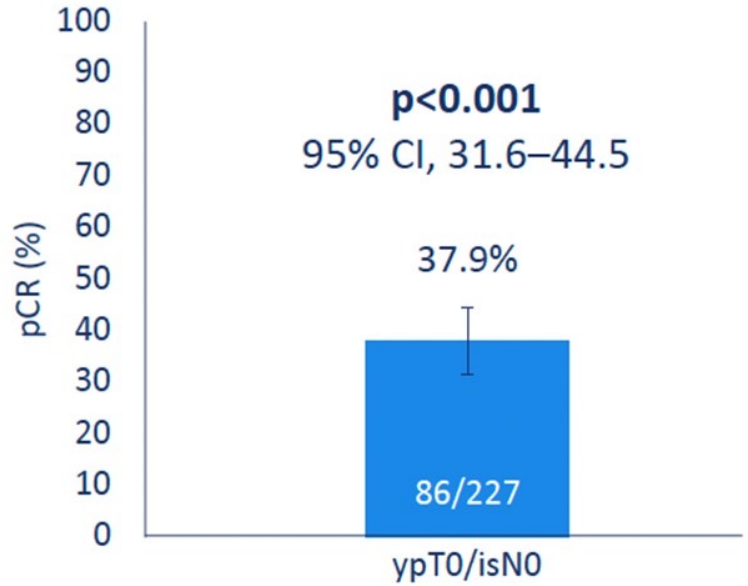
Primary Endpoint: pCR in ^{18}F-FDG-PET responders in group B

PET Responders and Non-Responders



PET Responder PET Non-Responder

pCR rate



Null hypothesis: pCR ≤20%

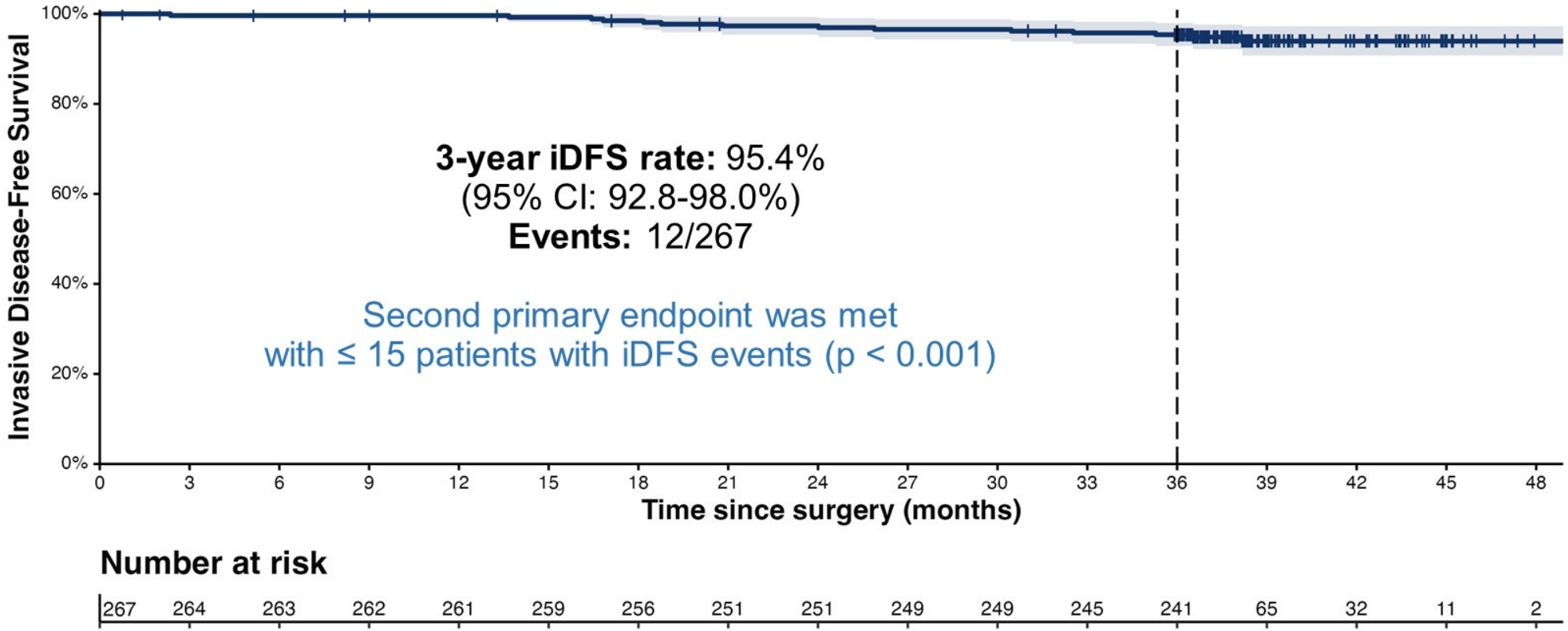
pCR was observed in patients with both HER2++ and HER2+++, pts with stage II and stage III, and pts ER+ and ER-.

Pérez-García, JM, et al. (2021). *Lancet Oncol*, 22(6), 858-871.

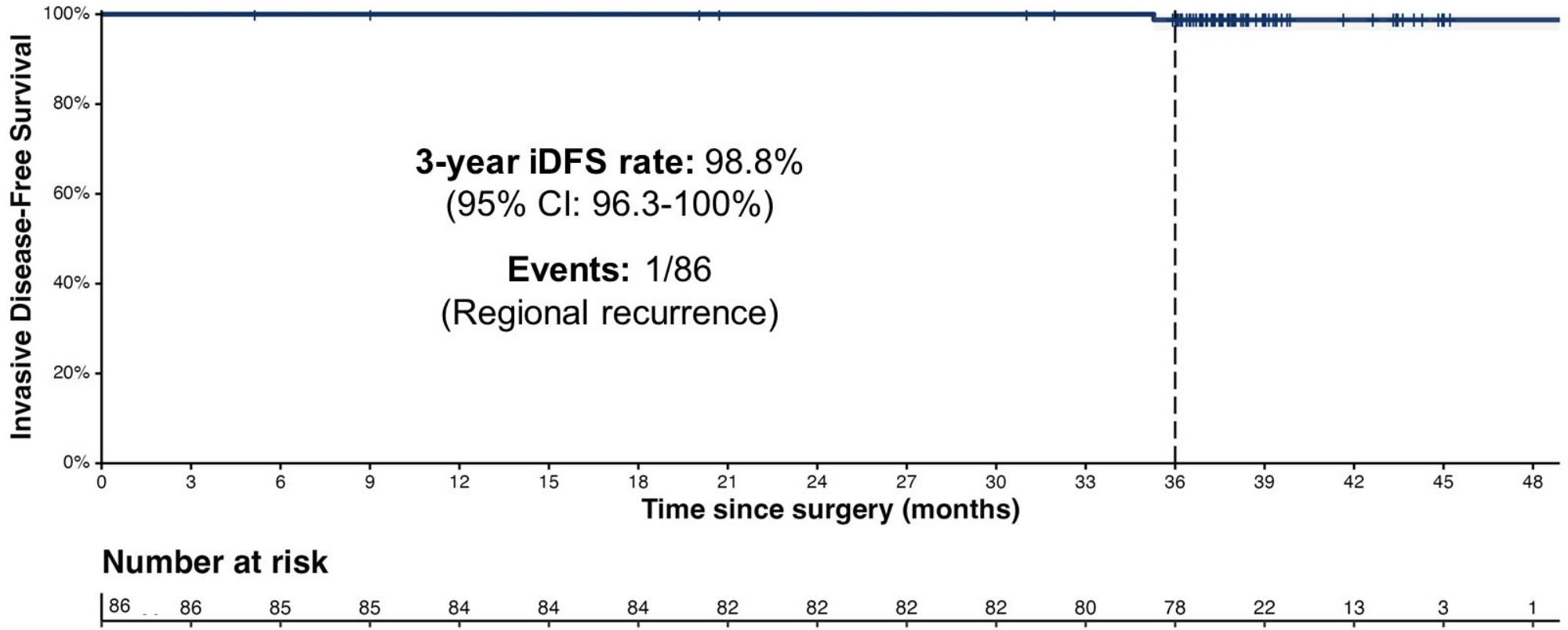
CI: Confidence interval; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; pCR: Pathological complete response (ypT0/isN0).

Primary Endpoint: 3-year iDFS rate in group B

ITT population



Subgroup analysis:
3-year iDFS rate without CT in PET responders with pCR (n=86)

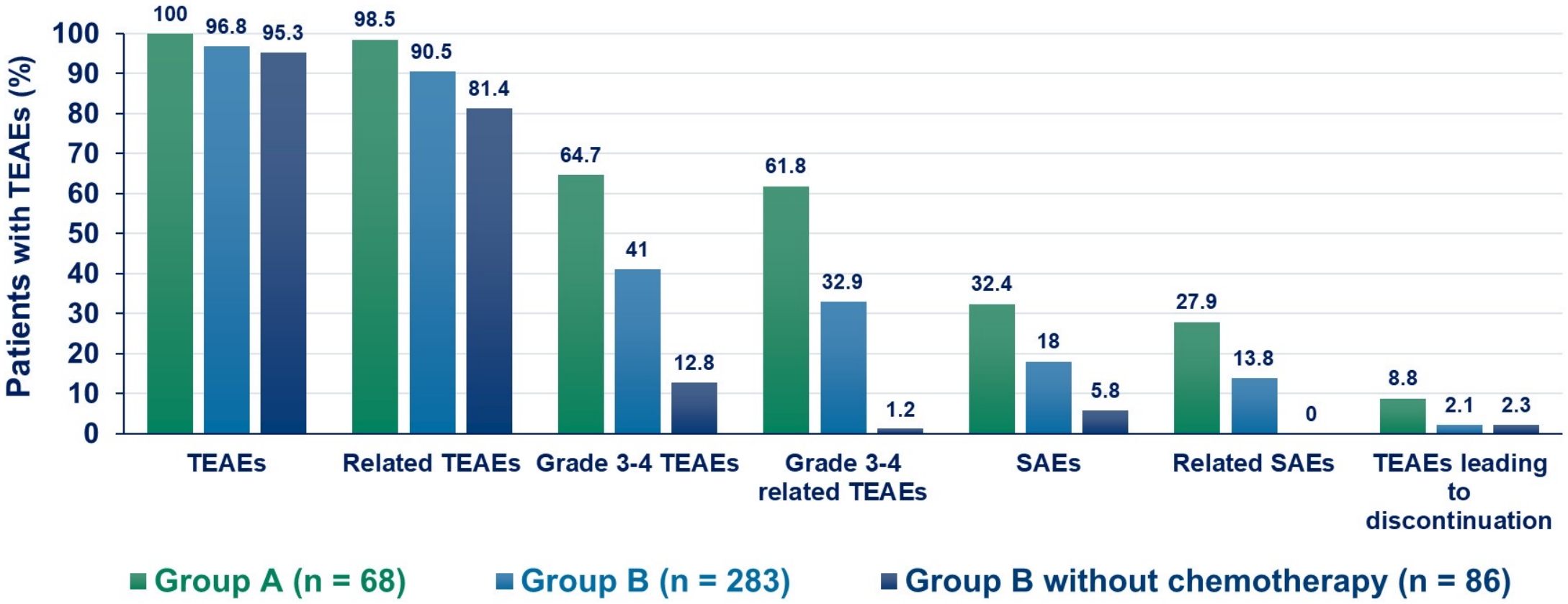


Efficacy Analysis: Summary of other efficacy endpoints

	Group A (n = 63)	Group B (n = 267)	Group B without CT (n = 86)
3-year iDFS	**98.3%**	**95.4%**	**98.8%**
(95% CI)	(95.1–100%)	(92.8–98.0%)	(96.3–100%)
3-year DDFS	**98.3%**	**96.5%**	**100%**
(95% CI)	(95.1–100%)	(94.3–98.8%)	(100–100%)
	(n = 71)	**(n = 285)**	**(n = 86)**
3-year EFS	**98.4%**	**93.5%**	**98.8%**
(95% CI)	(95.3–100%)	(90.7–96.5%)	(96.6–100%)
3-year OS	**98.4%**	**98.5%**	**100%**
(95% CI)	(95.3–100%)	(97.1–100%)	(100–100%)

None of these comparisons between the groups reached statistical significance.
iDFS and DDFS are defined from the time of surgery; EFS and OS are defined from randomization.

Safety Analysis: Summary of safety data



There was **no death** related to the study treatment.

How does this impact clinical care?

- This phase II noncomparative trial used a response-adaptive strategy to identify a group of patients who responded to preoperative HER2-directed therapy alone.
- The results are hypothesis-generating.
- Long-term follow up is needed.
- HER2-directed therapy alone may be an option for those who are not candidates for chemotherapy.

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

The Lancet Oncology
Volume 24 Issue 3 Pages 273-285 (March 2023)
DOI: 10.1016/S1470-2045(23)00051-7

Trial design

- Single-arm phase 2 trial of adjuvant paclitaxel (weekly x12) + trastuzumab
- T ≤3 cm, node negative
- Primary endpoint = 3-year invasive disease-free survival

Final 10-year results (n=406)

IDFS	31 events	N (%)
	Ipsilateral locoregional recurrences	6 (19.4)
	Contralateral breast cancer	9 (29)
	Distant recurrences	6 (19.4)
	All-cause deaths	10 (32.3)
10-year IDFS	91.3% (95% CI 88.3-94.4)	
Overall survival	94.3% (95% CI 91.8-96.8)	
10-year BCSS	98.8% (95% CI 97.6-100)	

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Exploratory studies (~270/406)

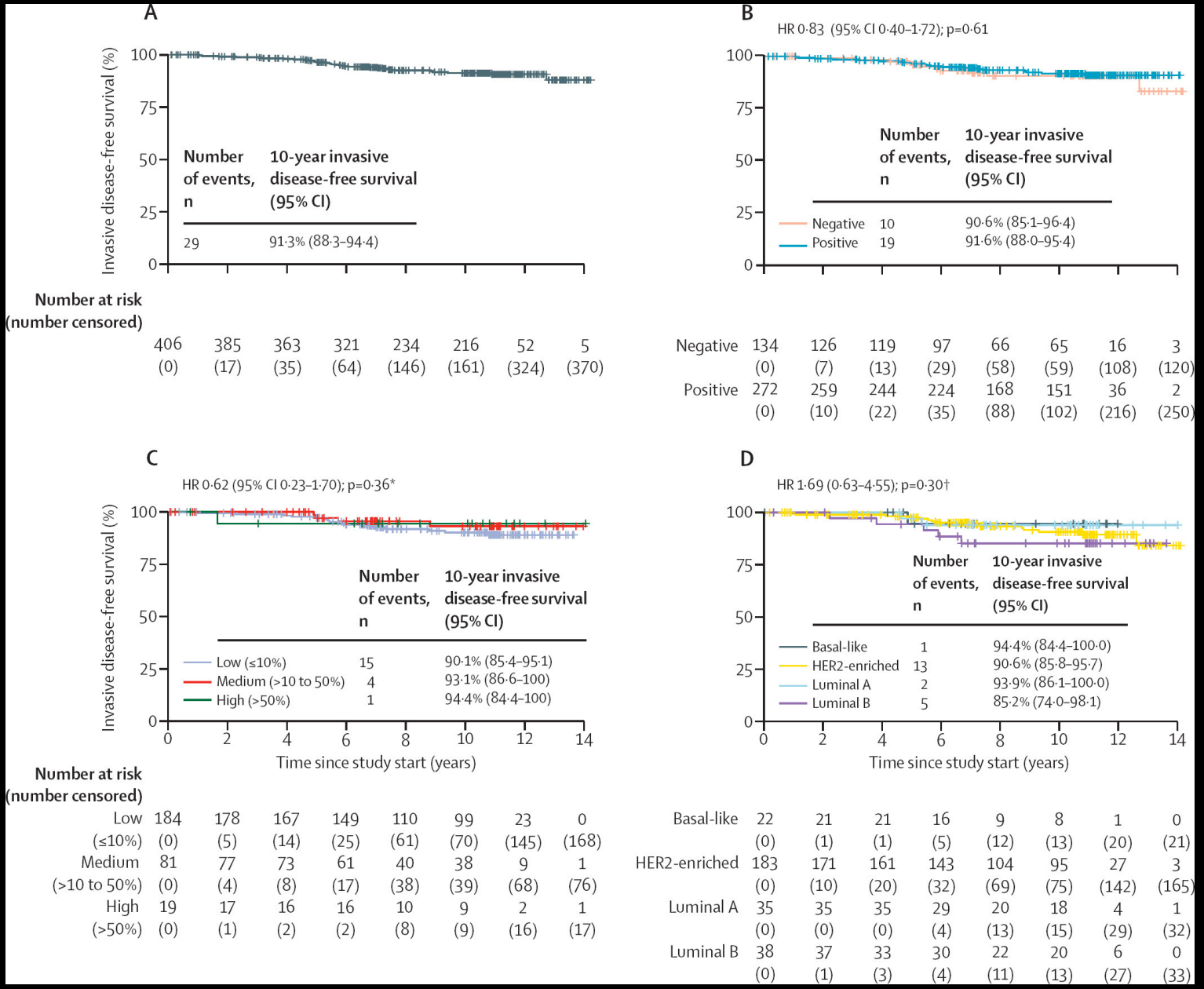
- Stromal tumor-infiltrating lymphocytes (sTILs)
- PAM50

- HER2DX risk score (0-100) to predict long-term relapse

  -27-gene expression and clinical feature classifier

  -3 gene signatures tracking immune features, tumor cell proliferation and luminal differentiation

Figure 1



The Lancet Oncology 2023 24273-285DOI: (10.1016/S1470-2045(23)00051-7)

Figure 3

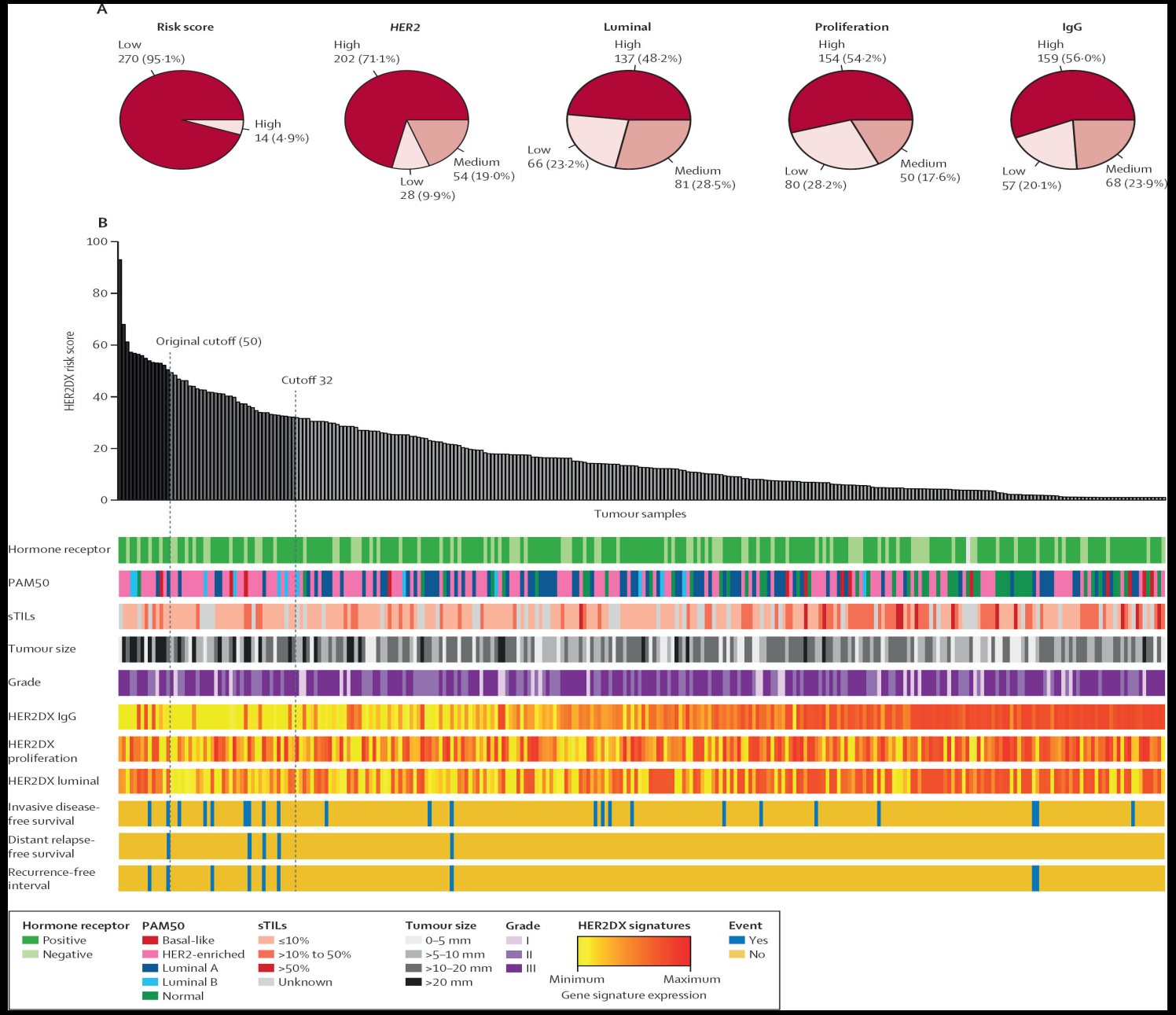


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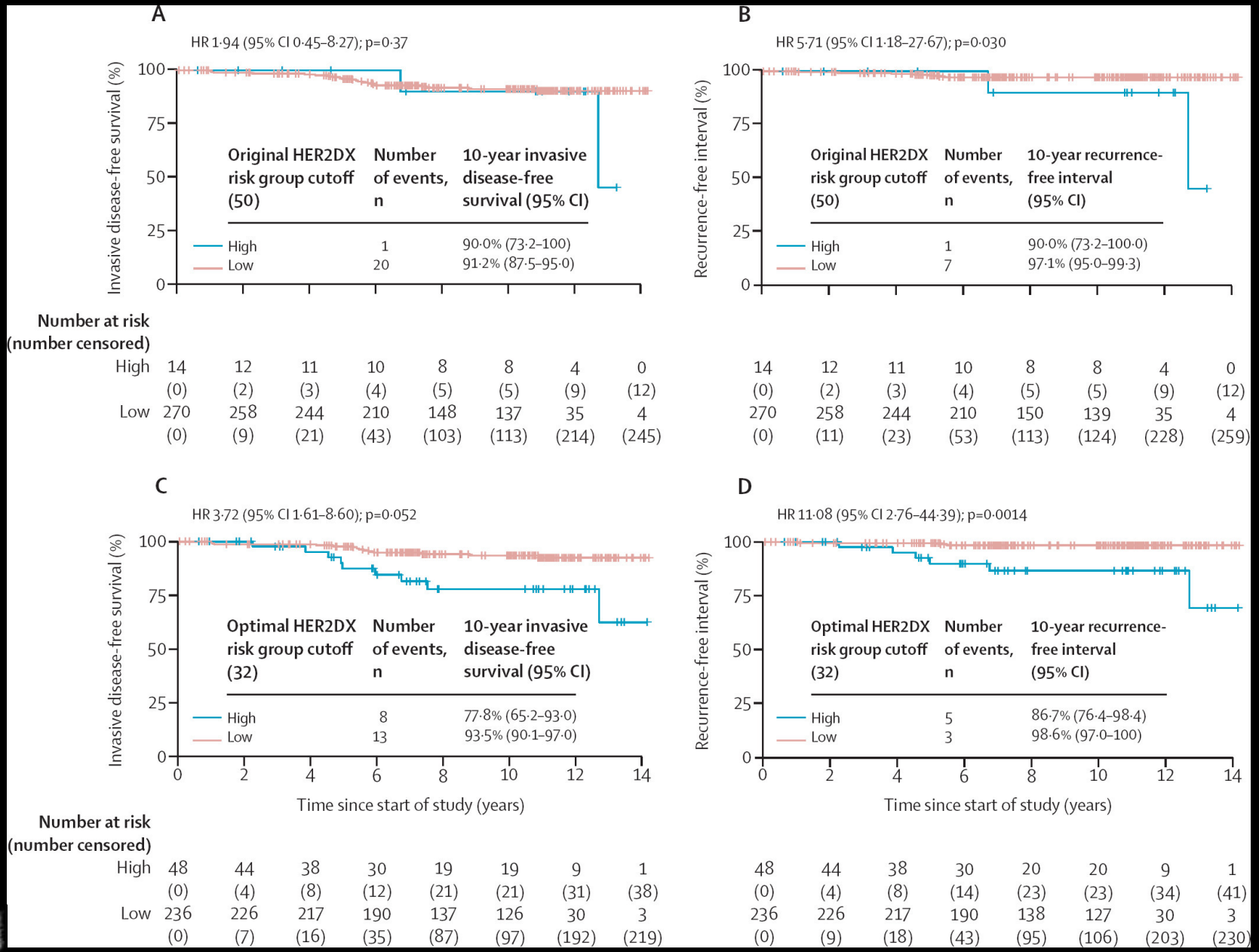
Figure 4



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How does this impact clinical care?

- Paclitaxel and trastuzumab are already a standard adjuvant option for small, node-negative, HER2 positive tumors.
- 10-year data is reassuring for a non-randomized phase II trial.

- HER2DX risk score is exploratory.

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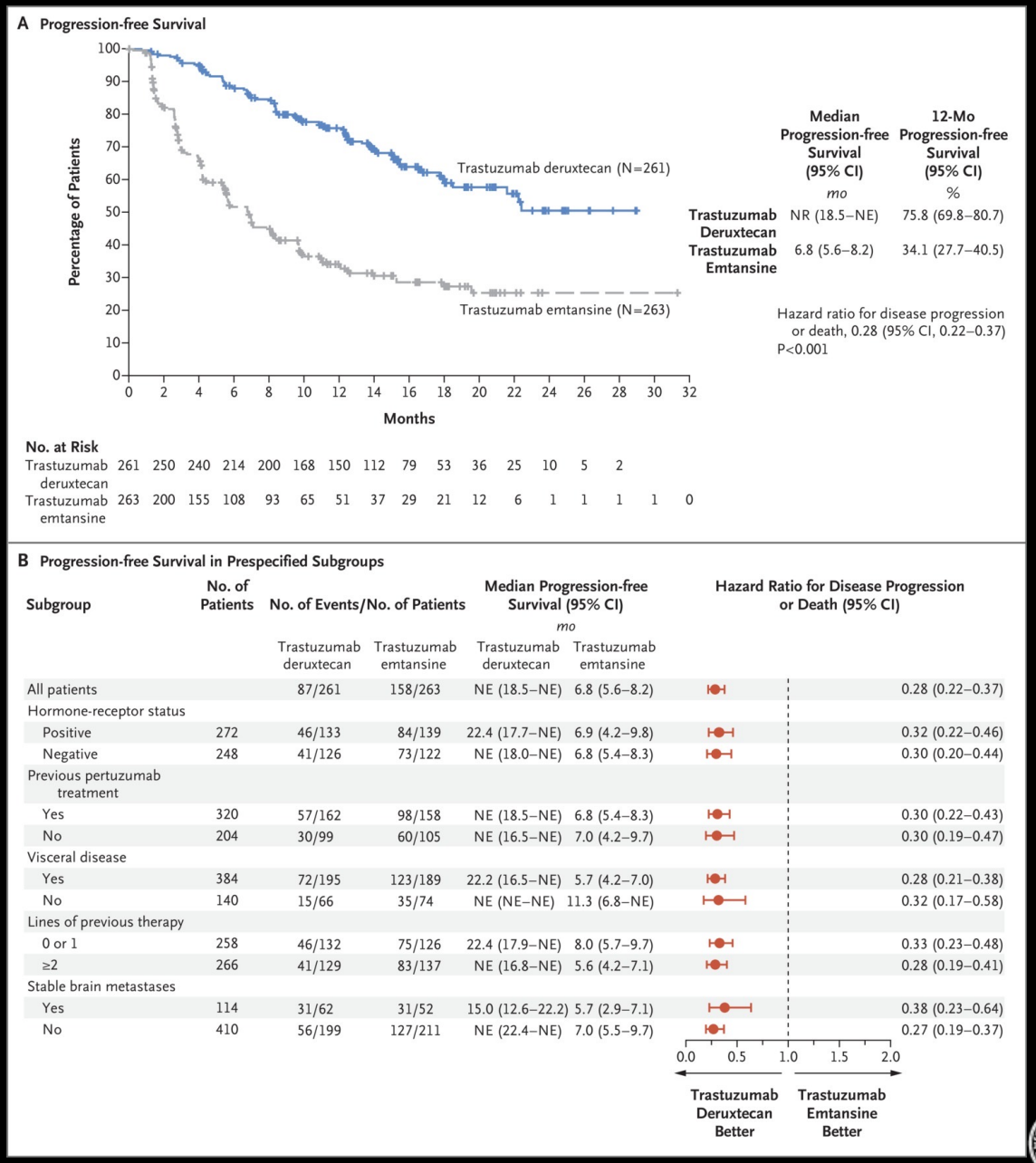
Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial

Sara A Hurvitz, MD, Roberto Hegg, MD, Wei-Pang Chung, MD PhD, Seock-Ah Im, MD PhD, William Jacot, MD PhD, Vinod Ganju, MD, Joanne Wing Yan Chiu, MB BS, Binghe Xu, MD PhD, Erika Hamilton, MD, Srinivasan Madhusudan, FRCP PhD, Hiroji Iwata, MD PhD, Sevilay Altintas, MD PhD, Jan-Willem Henning, MD, Giuseppe Curigliano, MD PhD, José Manuel Perez-Garcia, MD PhD, Sung-Bae Kim, MD PhD, Vanessa Petry, MD, Chiun-Sheng Huang, MD PhD, Wei Li, MD, Jean-Sebastien Frenel, MD PhD, Silvia Antolin, MD, Winnie Yeo, PhD, Giampaolo Bianchini, MD, Sherene Loi, MD, Junji Tsurutani, MD PhD, Anton Egorov, MD, Yali Liu, PhD, Jillian Cathcart, PhD, Shahid Ashfaque, MD, Javier Cortés, MD PhD

The Lancet
Volume 401 Issue 10371 Pages 105-117 (January 2023)
DOI: 10.1016/S0140-6736(22)02420-5

Kaplan–Meier Analysis and Subgroup Analysis of Progression-free Survival.

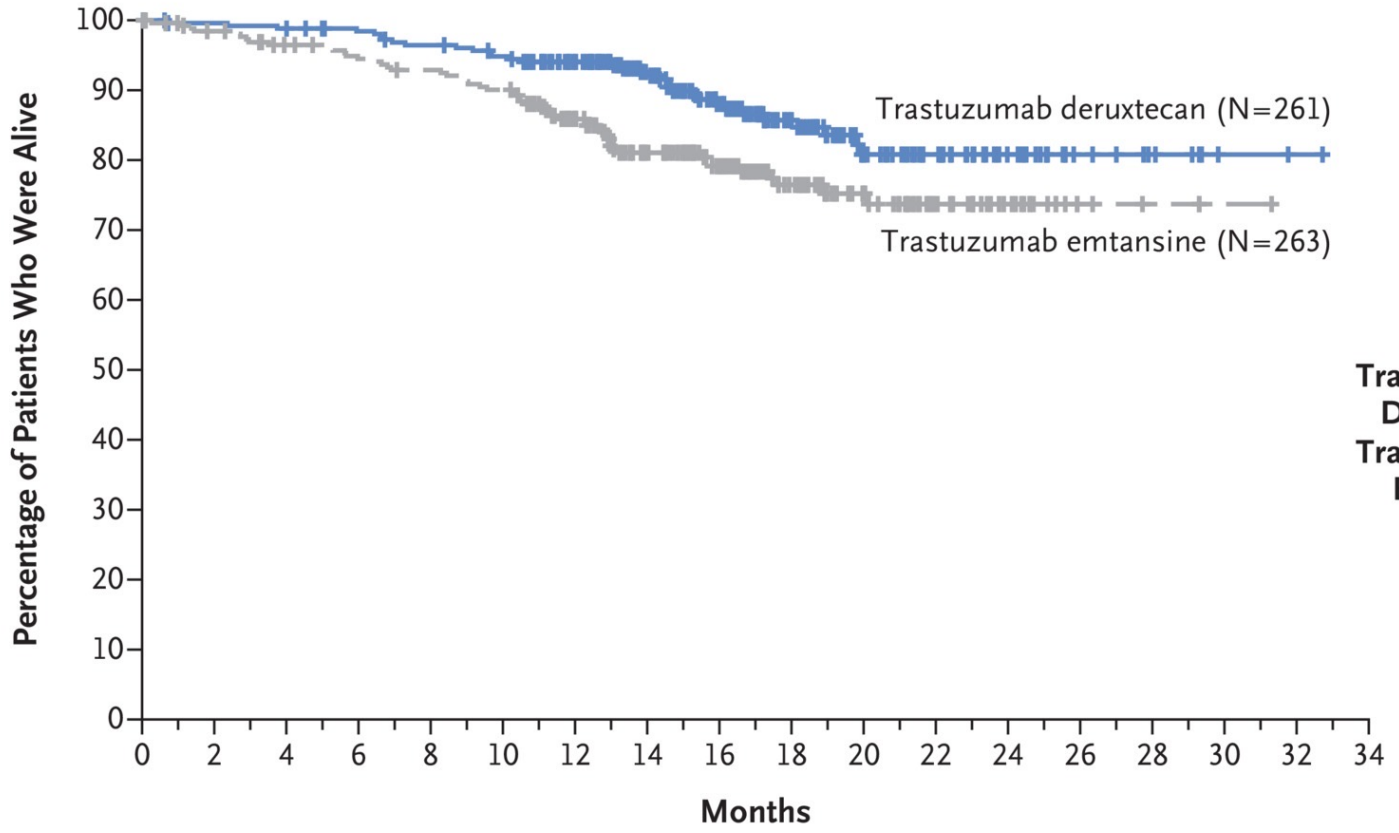
- MBC prior taxane and trastuzumab
- Controlled brain metastases allowed
- No interstitial lung dz



Cortés J et al. N Engl J Med 2022;386:1143-1154

The NEW ENGLAND JOURNAL of MEDICINE

First Interim Analysis of Overall Survival.



	Median Overall Survival (95% CI)	12-Mo Overall Survival (95% CI)
	mo	%
Trastuzumab Deruxtecan	NE (NE–NE)	94.1 (90.3–96.4)
Trastuzumab Emtansine	NE (NE–NE)	85.9 (80.9–89.7)

Hazard ratio for death, 0.55
(95% CI, 0.36–0.86)
P=0.007

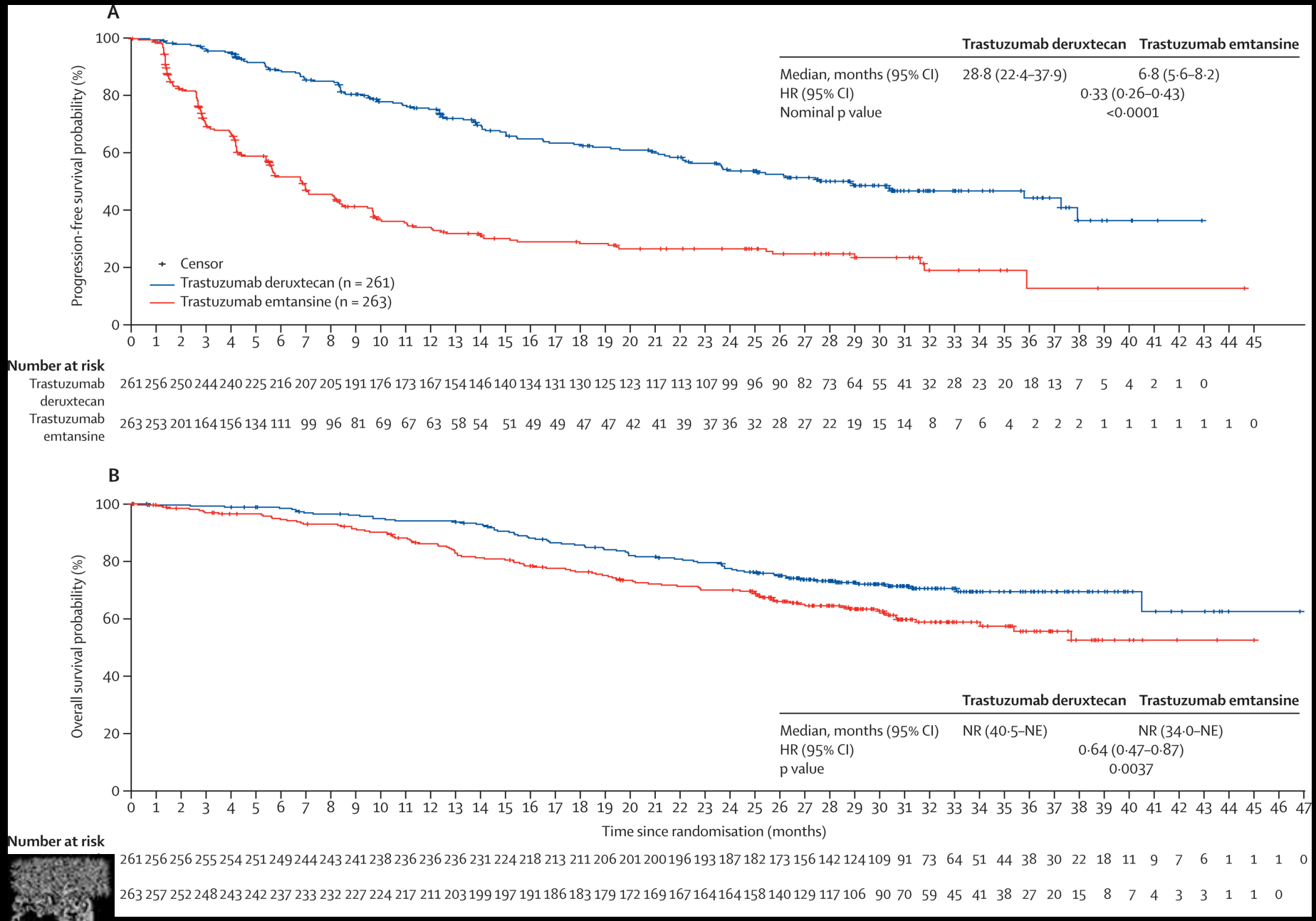
No. at Risk

Trastuzumab deruxtecan	261	256	254	249	243	237	218	180	133	86	56	42	24	11	7	6	2	2	1	0
Trastuzumab emtansine	263	253	243	236	231	224	188	151	120	75	52	32	18	5	3	3	1	1	0	

Cortés J et al. N Engl J Med 2022;386:1143-1154

The NEW ENGLAND JOURNAL of MEDICINE

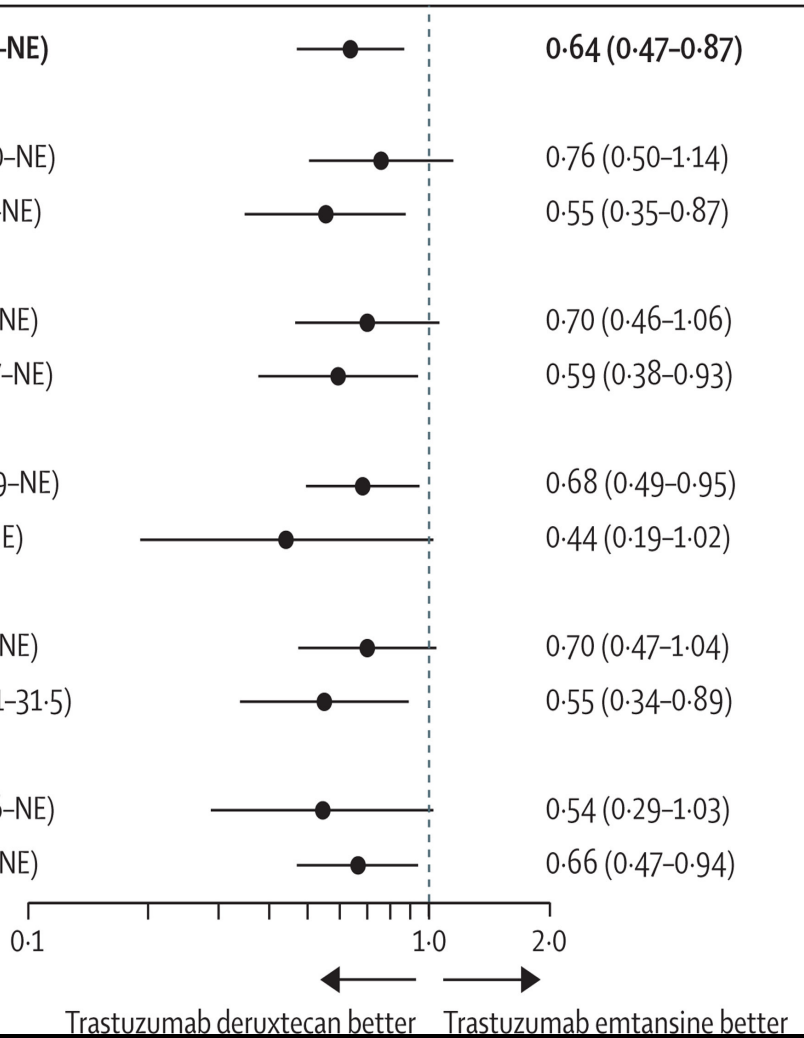
Figure 1



The Lancet 2023 401105-117DOI: (10.1016/S0140-6736(22)02420-5)

Figure 2

	Number of events		Median overall survival time, months (95% CI)		Hazard ratio for death (95% CI)
	Trastuzumab deruxtecan	Trastuzumab emtansine	Trastuzumab deruxtecan	Trastuzumab emtansine	
All patients	**72/261**	**97/263**	**NR (40·5–NE)**	**NR (34·0–NE)**	**0·64 (0·47–0·87)**
Hormone receptor status					
Positive	42/133	51/139	NR (40·5–NE)	37·7 (34·0–NE)	0·76 (0·50–1·14)
Negative	30/126	45/122	NR (NE–NE)	NR (28·5–NE)	0·55 (0·35–0·87)
Previous pertuzumab					
Yes	41/162	50/158	NR (40·5–NE)	NR (37·7–NE)	0·70 (0·46–1·06)
No	31/99	47/105	NR (NE–NE)	31·5 (22·7–NE)	0·59 (0·38–0·93)
Baseline visceral disease					
Yes	64/195	80/189	NR (40·5–NE)	35·4 (29·9–NE)	0·68 (0·49–0·95)
No	8/66	17/74	NR (NE–NE)	NR (NE–NE)	0·44 (0·19–1·02)
Previous lines of systemic therapy*					
<3	44/188	57/191	NR (40·5–NE)	NR (37·7–NE)	0·70 (0·47–1·04)
≥3	28/73	40/72	NR (27·4–NE)	22·8 (16·1–31·5)	0·55 (0·34–0·89)
Baseline brain metastases					
Yes	17/43	22/39	NR (23·8–NE)	25·1 (12·6–NE)	0·54 (0·29–1·03)
No	55/218	75/224	NR (40·5–NE)	NR (37·7–NE)	0·66 (0·47–0·94)



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HER2-positive MBC

Setting	Regimen	Trial
1st-line	Taxane + trastuzumab and pertuzumab	CLEOPATRA
2nd-line	Trastuzumab deruxtecan	DESTINY 03
3rd-line	Tucatinib, trastuzumab + capecitabine	HER2CLIMB
	Trastuzumab emtansine	EMILIA
4th line and beyond	Trastuzumab + chemotherapy	
	Lapatinib + capecitabine	
	Trastuzumab + lapatinib	
	Neratinib + capecitabine	NALA
	Margetuximab + chemotherapy	SOPHIA

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Future Directions

- Ongoing trials to move additional agents (trastuzumab deruxtecan, tucatinib, margetuximab) to the adjuvant setting.
- De-escalation of therapy (HER2 therapy alone, endocrine therapy)

- For MBC, moving trastuzumab deruxtecan, tucatinib, endocrine therapy + CDK 4/6is to first-line setting

Thank you

Questions?

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