2025 DEBATES AND DIDACTICS in Hematology and Oncology

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center
Where Science Becomes Hope

JULY 24 - 27, 2025 • SEA ISLAND, GEORGIA

This activity is jointly provided by Partners for Advancing Clinical Education and Bio Ascend

Treatment Approaches in HER2 Positive Breast Cancer

Jane Lowe Meisel, MD

Professor of Hematology/Medical Oncology

Co-Director, Breast Medical Oncology

Associate Vice-Chair of Faculty Development and Promotions

Winship Cancer Institute at Emory University

Outline

Early-Stage HER2+ Breast Cancer: High-Risk

- New considerations for neoadjuvant therapy
- Optimizing adjuvant therapy

Early-Stage HER2+ Breast Cancer: Low Risk

- When to opt for adjuvant treatment (no NACT)
- Ongoing trials/further de-escalation

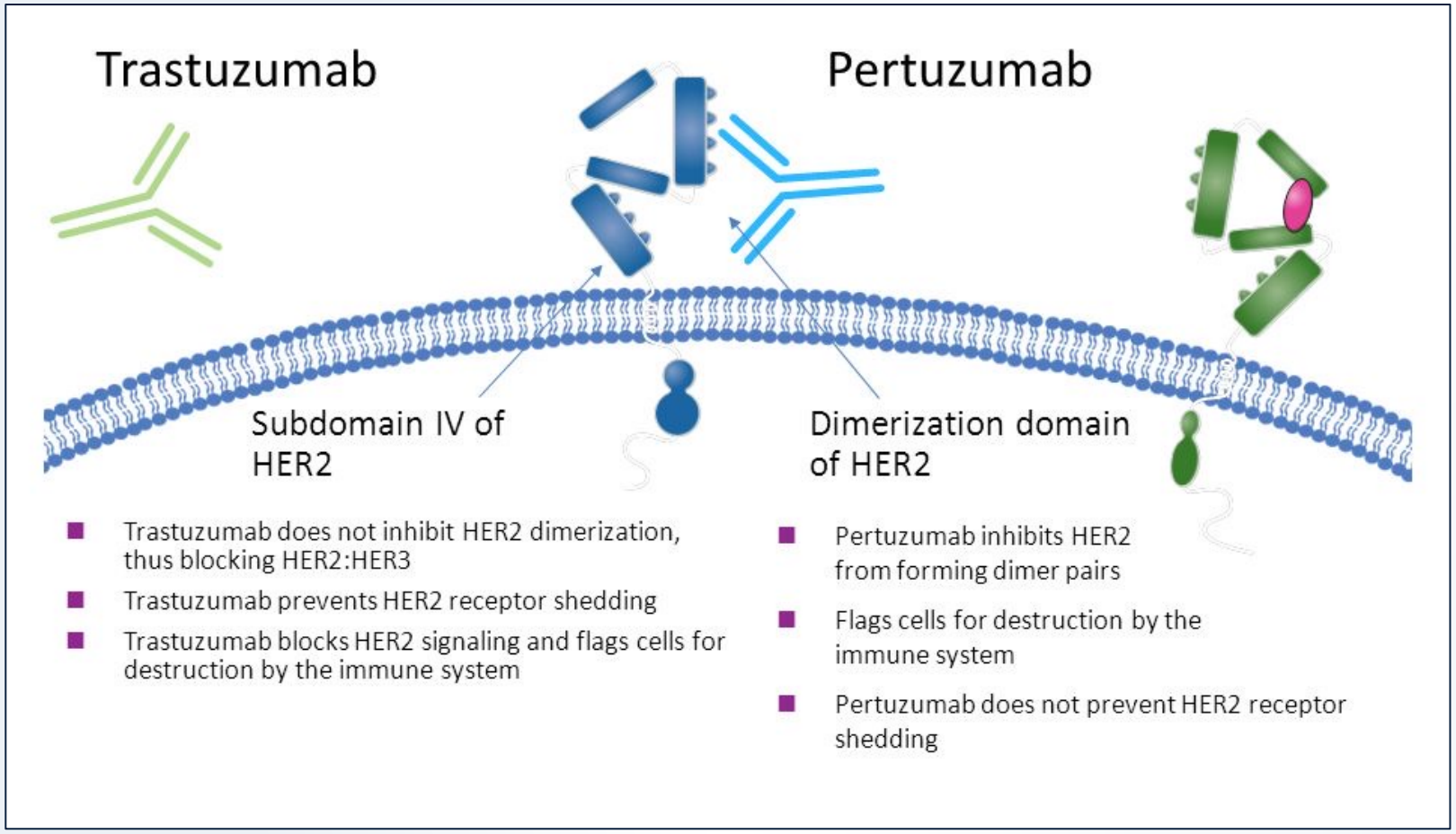
Advanced HER2+ Breast Cancer

- Potentially changing paradigms for 1L treatment
- Upcoming trials and future possibilities

Early-Stage HER2+ Breast Cancer

High-risk disease

Dual anti-HER2 therapy



Neoadjuvant Trastuzumab + Pertuzumab

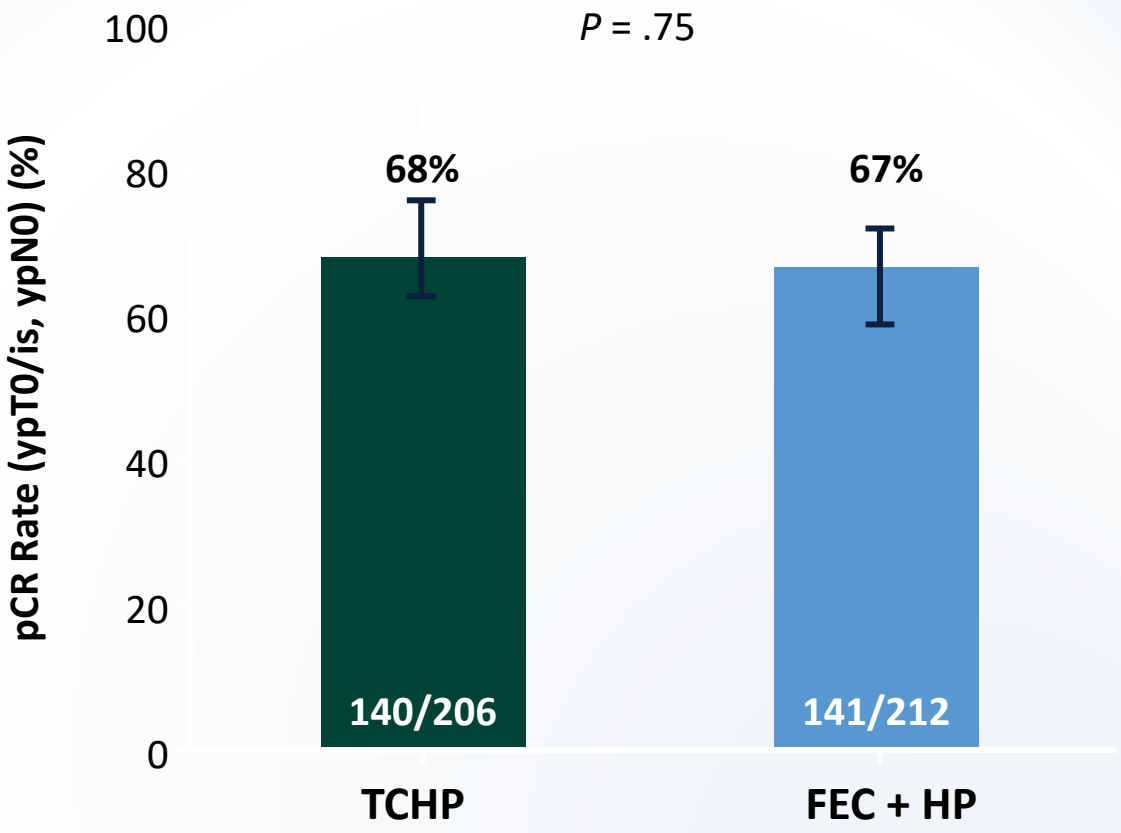
	Regimen	Duration	pCR	P value
NEOSPHERE (N=417)	TH		29%	
	TP	12 w	24%	
	THP		45.8%	0.0141
	HP		16.8%	
TRYPHAENA (N=225)	FECHP → THP		61.6%	
	FEC → THP	24 w	57.3%	
	TCbHP		66.2%	

E=epirubicin; C=cyclophosphamide;
F=fluorouracil; T=docetaxel;
Cb=carboplatin; H=trastuzumab; P=pertuzumab

Slide courtesy of Dr. Chau Dang.

TRAIN-2: TCHP vs FEC + HP in stage II-III HER2+ BC

- High rate of pCR with or without anthracyclines (68% in TCHP groups, 67% in FEC-HP—>TCHP)
- pCR was consistent across prespecified subgroups
  - -Clinical T stage (0-2 vs 3-4)
  - -Nodal status (- vs +)
  - -HR status (- vs +)
  - -Age (<50 yr vs ≥50 yr)
- There was no difference in EFS or OS



van der Voort. JAMA Oncol. 2021;7:978.

Patient Case

62F with no past medical history presents with a newly diagnosed breast cancer measuring 4.2cm on mammogram/US that is ER 56% PR 0% Her2 2+/FISH positive. She is clinically node negative.

Do you recommend:

A) go straight to surgery and decide on systemic therapy adjuvantly

B) neoadjuvant TCHP (taxotere/carboplatin/trastuzumab/pertuzumab)

C) neoadjuvant AC->THP

D) neoadjuvant paclitaxel/trastuzumab x 4 cycles

Patient Case

62F with no past medical history presents with a newly diagnosed breast cancer measuring 4.2cm on mammogram/US that is ER 56% PR 0% Her2 2+/FISH positive. She is clinically node negative.

Do you recommend:

A) go straight to surgery and decide on systemic therapy adjuvantly

B) neoadjuvant TCHP (taxotere/carboplatin/trastuzumab/pertuzumab)

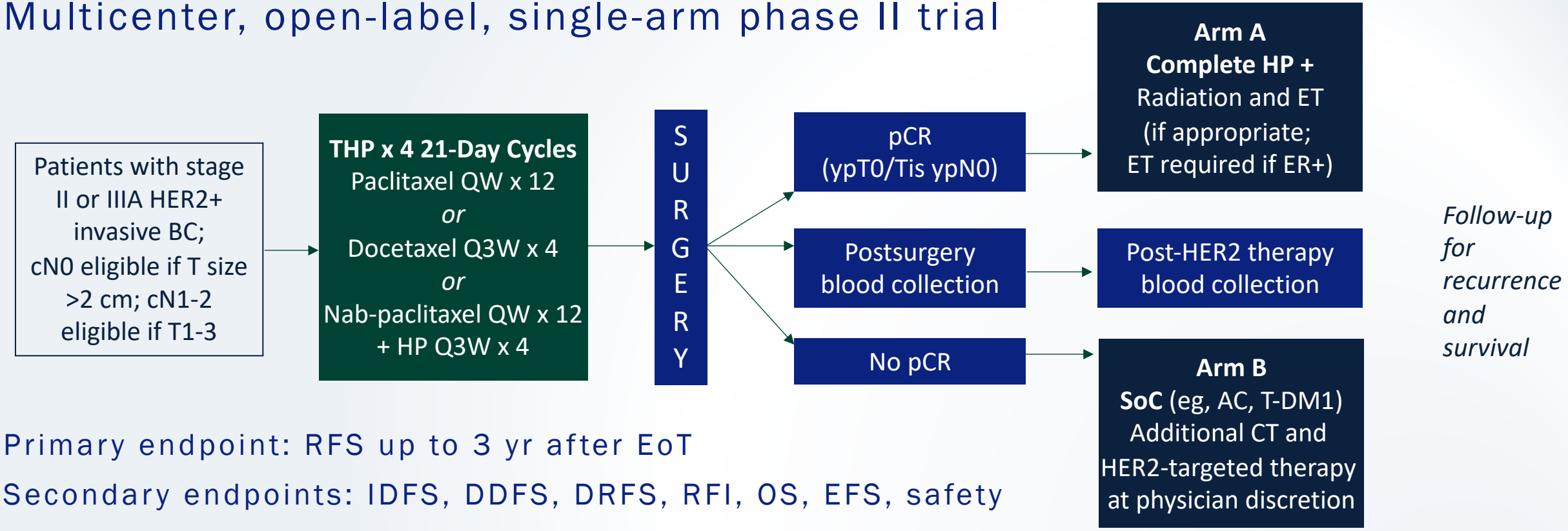
C) neoadjuvant AC->THP

D) neoadjuvant paclitaxel/trastuzumab x 4 cycles

*Less long-term toxicity than AC-THP, but still not an easy regimen. Can we de-escalate further for certain patients?

COMPASS-HER2

Multicenter, open-label, single-arm phase II trial



Primary endpoint: RFS up to 3 yr after EoT

Secondary endpoints: IDFS, DDFS, DRFS, RFI, OS, EFS, safety

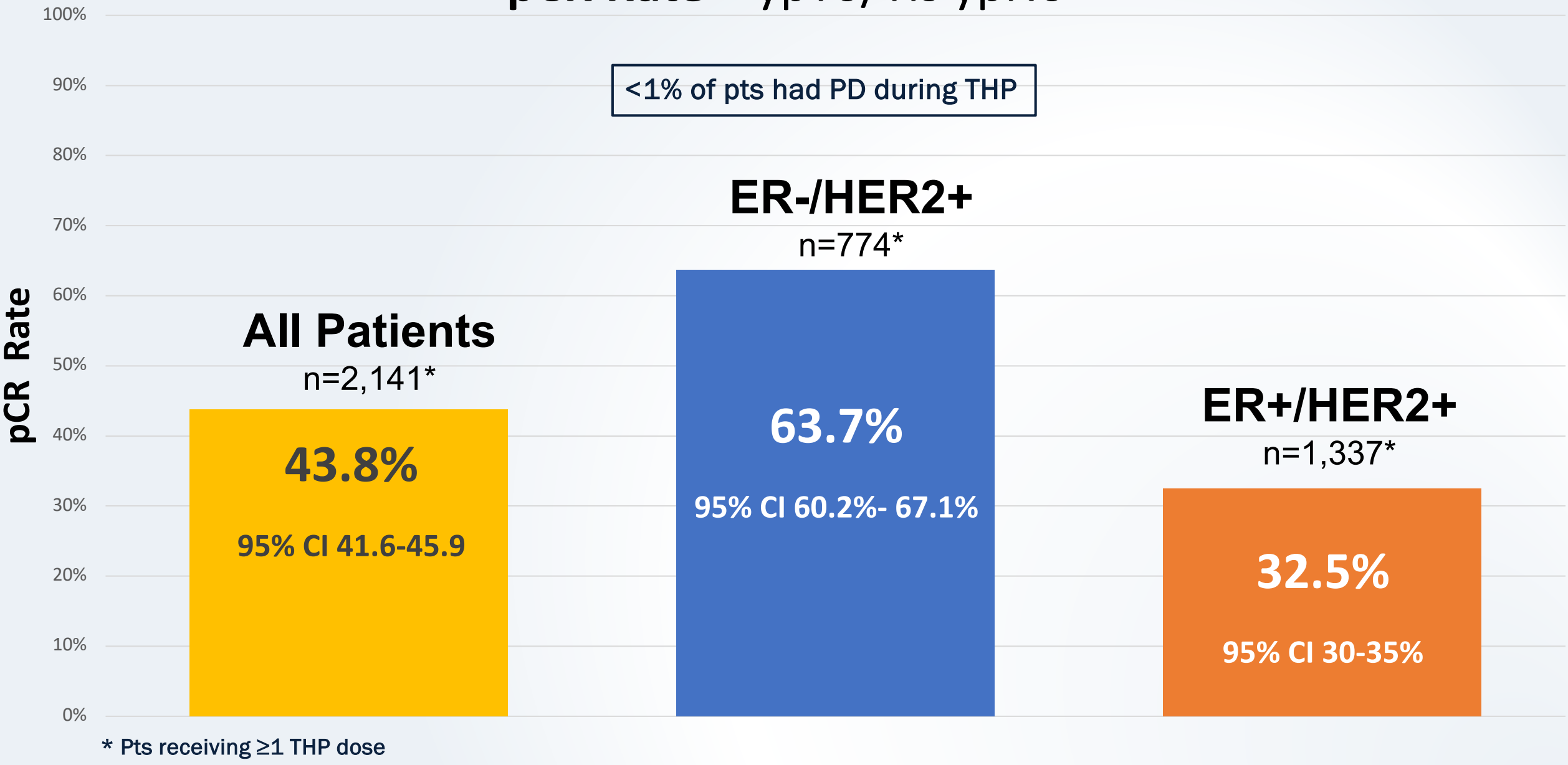
Baseline tumor characteristics

Ductal: 93%
Grade 3: 56%
ER-: 36%
ER+: ~2/3 >70% expression
HER2 IHC 3+: 79%

ER+ compared to ER- tumors
Fewer grade 3
More HER2 IHC 2+/ISH+

	All pts (%) n= 2,175	ER- (%) n=781	ER+ (%) n= 1,394
Histologic type			
Ductal	93%	94%	92%
Lobular/Mixed	5%	2%	6%
Other	3%	3%	2%
Grade			
1	3%	1%	4%
2	40%	29%	45%
3	56%	69%	49%
% cells ER+			
0%	36%	100%	
1-10%	6%	------	10%
11-70%	13%	------	21%
> 70%	44%		69%
HER2 IHC (local)			
3+	79%	85%	75%
2+ (ISH ratio)	17%	10%	20%
≤3	61%	56%	62%
>3- 4	16%	20%	15%
>4	23%	22%	23%
IHC 0/1/unknown ISH+	4%	5%	4%

pCR Rate* ypT0/Tis ypN0



* Pts receiving ≥1 THP dose

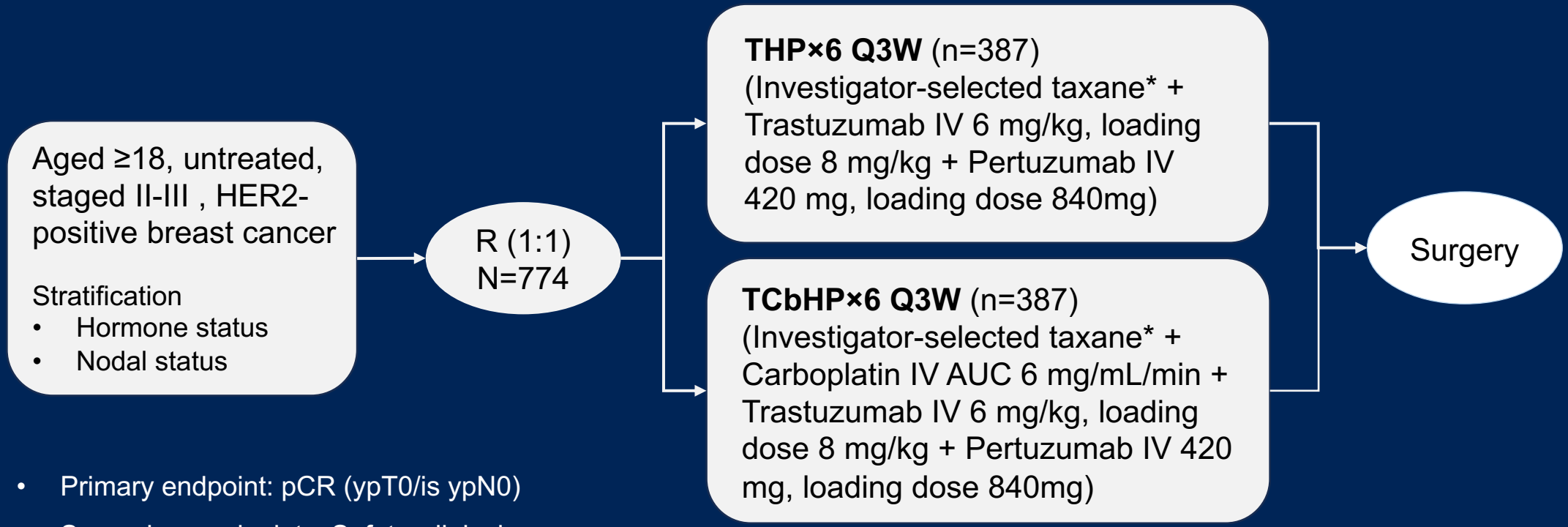
3 Clinicopathologic factors significant for predicting pCR (multivariable analysis)

All patients n=2141*		
Clinical factor	**OR for pCR (95% CI)**	**# of patients**
ER status		
ER+ >70%	1.0	950
ER+ 11-70%	3.35 (2.5-4.49)	281
ER+ 1-10%	4.75 (3.2-7.06)	136
ER- 0%	5.44 (2.5-4.49)	774
HER2 IHC		
2+/ISH+	1.0	353
3+	6.25 (4.39-8.89)	1691
Taxane		
docetaxel	1.0	735
paclitaxel	1.48 (1.2-1.81)	1355

T stage, N stage, clinical stage, age, ECOG PS, race and histologic grade did not contribute to the prediction of pCR in the multivariable model

* n=patients who received ≥ 1 dose THP

neoCARHP Study Design (NCT04858529)



- Primary endpoint: pCR (ypT0/is ypN0)
- Secondary endpoints: Safety, clinical response during neoadjuvant therapy, EFS, DFS, OS

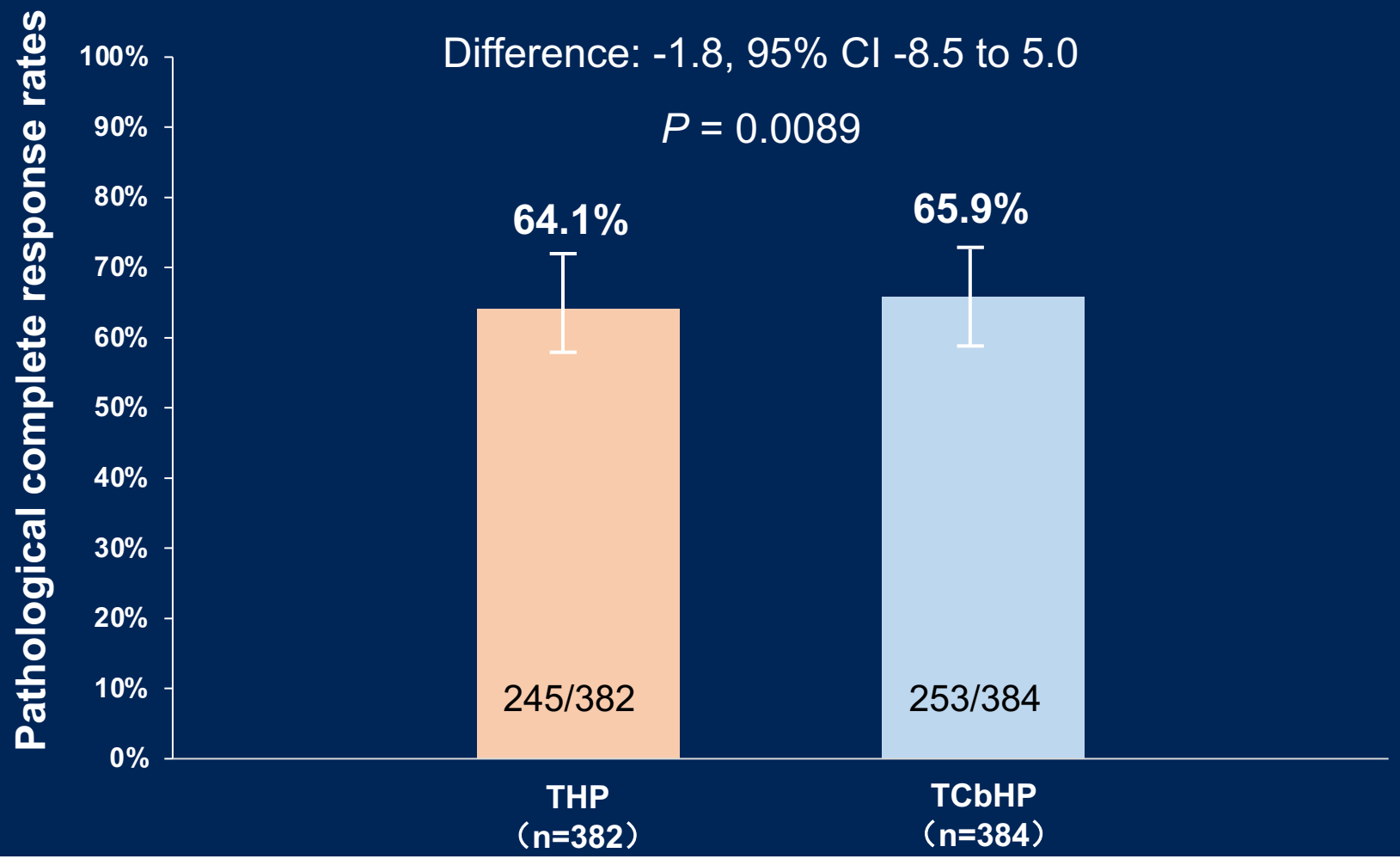
* Docetaxel, Paclitaxel or Nab-paclitaxel

Baseline Patient Characteristics

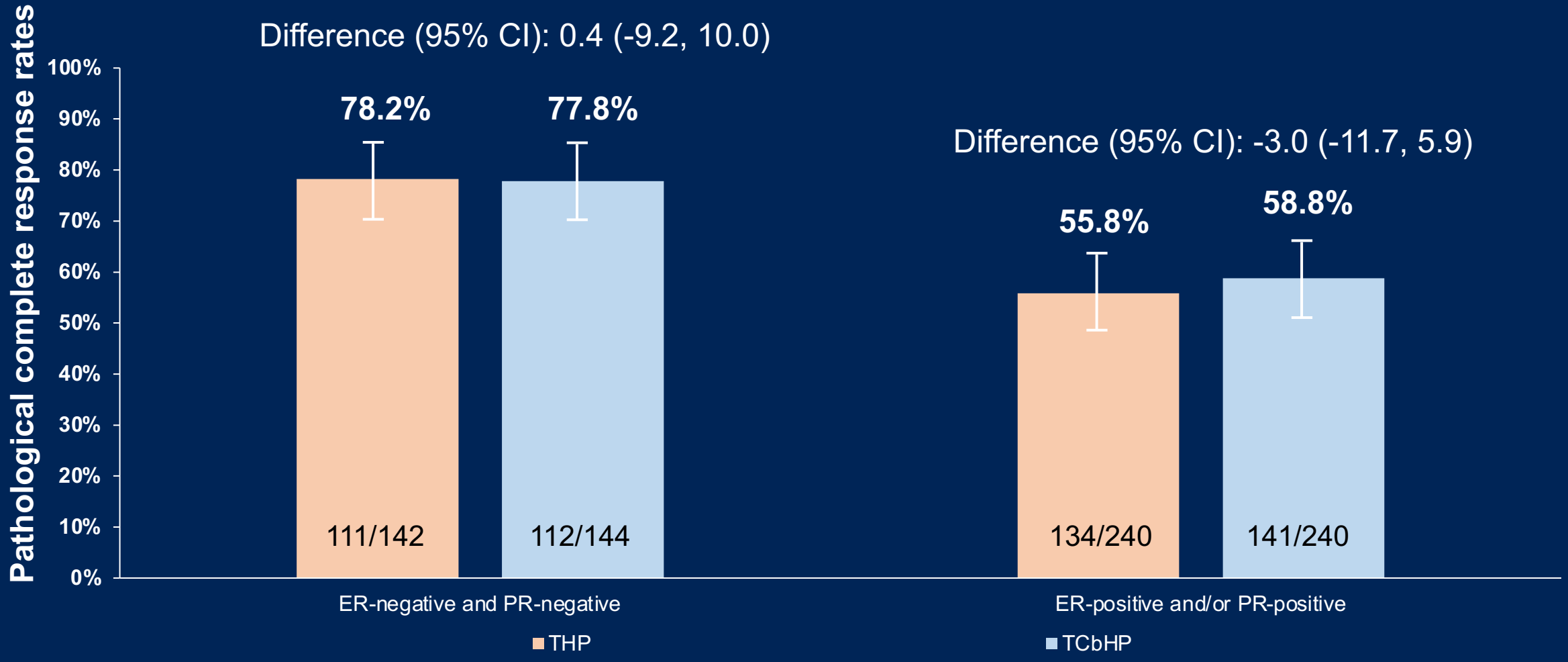
	THP (n=382)	TCbHP (n=384)
Age (median [IQR], years)	52 (45-58)	51 (44-56)
Menopausal status, n (%)		
Premenopausal	191 (50.0%)	200 (52.1%)
Postmenopausal	191 (50.0%)	184 (47.9%)
T stage, n (%)		
T1-2	311 (81.4%)	302 (78.6%)
T3-4	71 (18.6%)	82 (21.4%)
Nodal status, n (%)		
Negative	137 (35.9%)	138 (35.9%)
Positive	245 (64.1%)	246 (64.1%)
Disease stage, n (%)		
Stage II	294 (77.0%)	275 (71.6%)
Stage III	88 (23.0%)	109 (28.4%)
Histological type, n (%)		
Ductal	375 (98.2%)	376 (97.9%)
Lobular	1 (0.3%)	2 (0.5%)
Others	6 (1.6%)	6 (1.6%)

	THP (n=382)	TCbHP (n=384)
Hormone receptor status, n (%)		
ER-negative andPR-negative	142 (37.2%)	144 (37.5%)
ER-positive and/orPR-positive	240 (62.8%)	240 (62.5%)
HER2 status, n (%)		
Immunohistochemistry 3+	338 (88.5%)	348 (90.6%)
Immunohistochemistry 2+ and ISH-positive	44 (11.5%)	36 (9.4%)
Ki67, n (%)		
≤30%	163 (42.7%)	172 (44.8%)
>30%	219 (57.3%)	212 (55.2%)
Taxane therapy, n (%)		
Nab-paclitaxel	170 (44.5%)	171 (44.5%)
Docetaxel	137 (35.9%)	141 (36.7%)
Paclitaxel	75 (19.6%)	72 (18.8%)

Efficacy Analysis: pCR



Efficacy Analysis: pCR by hormone receptor status



Patient Case

73F with no past medical history presents with a newly diagnosed breast cancer measuring 2.2cm on mammogram, and has one biopsy-proven involved node. Her cancer is ER 30% PR 60% Her2 3+ with Ki67 65%. She has a history of significant nausea with medications and is concerned about receiving chemotherapy.

Do you recommend:

A) go straight to surgery and decide on systemic therapy adjuvantly

B) neoadjuvant TCHP (taxotere/carboplatin/trastuzumab/pertuzumab)

C) neoadjuvant AC->THP

D) neoadjuvant paclitaxel/trastuzumab/pertuzumab x 4-6 cycles

Patient Case

73F with no past medical history presents with a newly diagnosed breast cancer measuring 2.2cm on mammogram, and has one biopsy-proven involved node. Her cancer is ER 30% PR 60% Her2 3+ with Ki67 65%. She has a history of significant nausea with medications and is concerned about receiving chemotherapy.

Do you recommend:

A) go straight to surgery and decide on systemic therapy adjuvantly

B) neoadjuvant TCHP (taxotere/carboplatin/trastuzumab/pertuzumab)

C) neoadjuvant AC->THP

D) **neoadjuvant paclitaxel/trastuzumab/pertuzumab x 4-6 cycles**

Neoadjuvant chemotherapy in clinical practice

- Appropriate to offer for patients with node-positive disease or tumors >2cm
  - Often, we use TCHP rather than AC-THP since no improvement in outcomes with anthracyclines and usually more short- and long-term toxicity
  - AC-THP in select situations (when diarrhea is a big concern; or with more tumor heterogeneity)
  - Could we now think about THP alone in other select situations, such as smaller ER-HER2+ tumors?

- Questions:

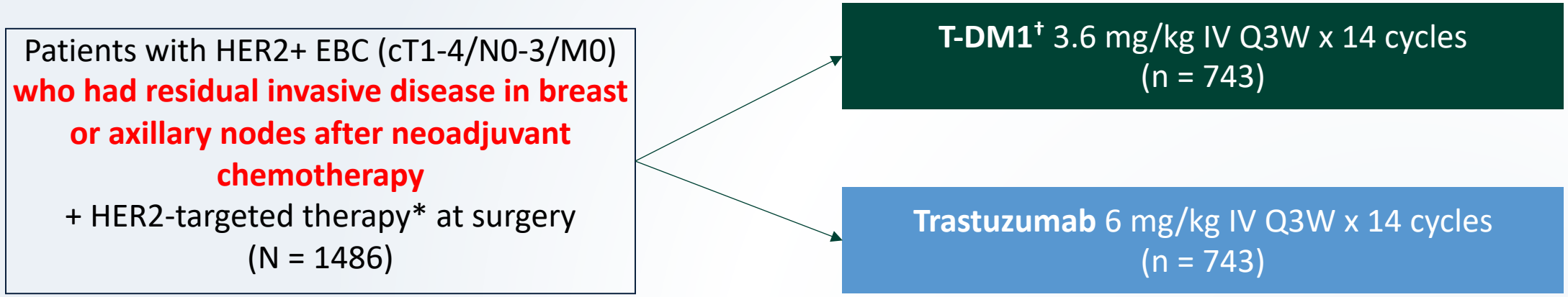
  -How will things change in the future?

  *DESTINY-Breast 11: press release announced that T-DXd followed by THP showed an improved pCR rate compared to ddAC-THP. Will this become an option for patients?

  -How do we use pCR to help us make decisions about adjuvant therapy?

KATHERINE trial

- Phase III randomized controlled trial

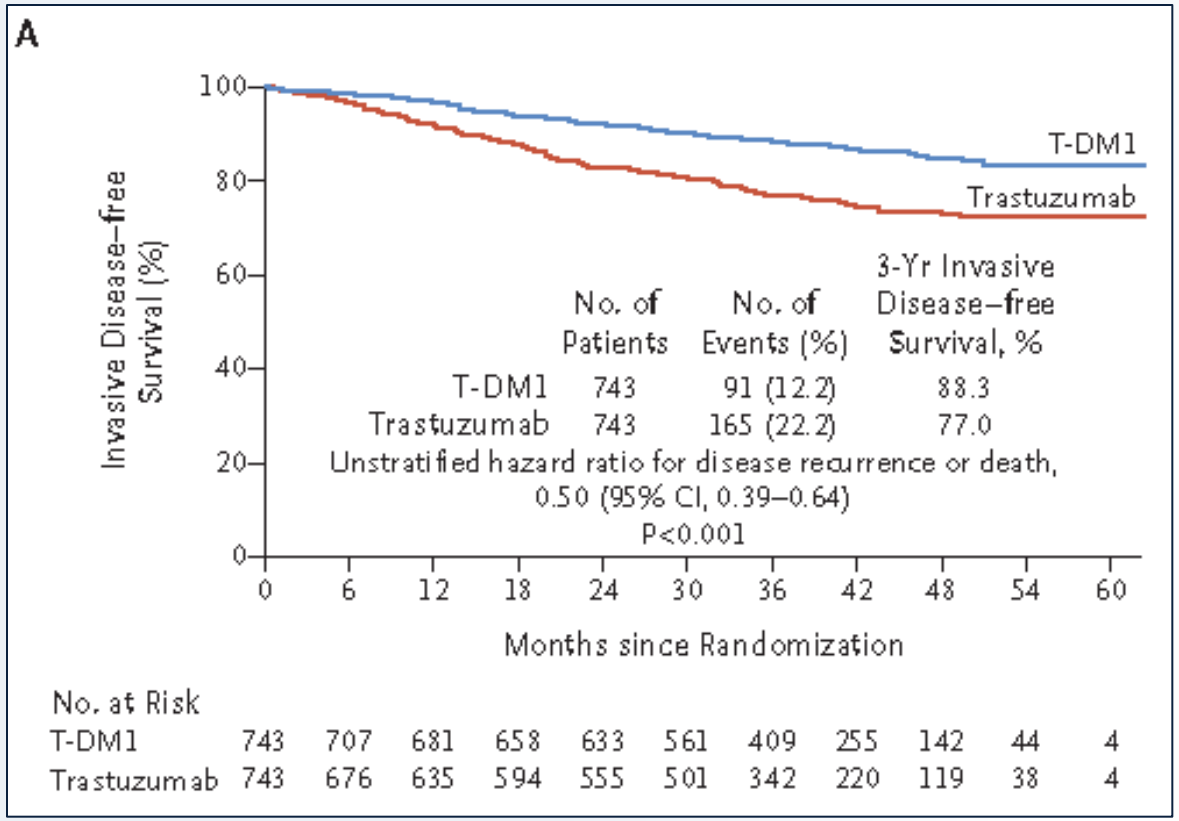


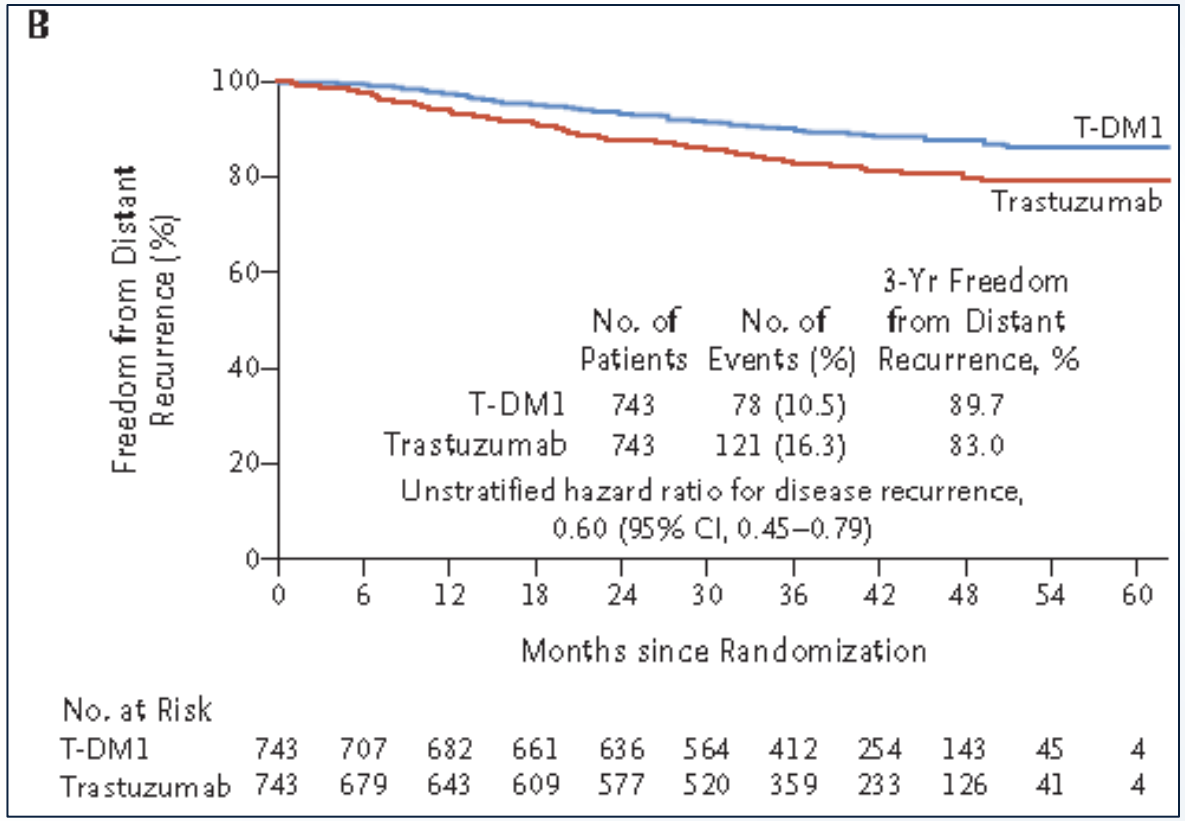
Randomization occurred within 12 wk of surgery; **radiotherapy and/or endocrine therapy given per local standards**.
*Minimum of 9 wk of taxane and trastuzumab. †Patients who d/c T-DM1 for toxicity allowed to switch to trastuzumab to complete 14 cycles.

- Primary endpoint: IDFS
- Secondary endpoints: distant recurrence-free survival, OS, safety

N Engl J Med. 2019;380(7):617.

KATHERINE: Results





N Engl J Med. 2019;380(7):617.

Current standard of care

- For node-positive patients who get a pCR to NACT, HP x 1 year has become the standard of care
- For non-pCR, T-DM1 is the standard
- What does the future hold?

  - Trials:
    - DESTINY-Breast 05: T-DXd vs T-DM1 for patients with non-pCR after NACT
    - CompassHER2 RD: T-DM1 + tucatinib vs placebo for patients with non-pCR after NACT

Early-Stage HER2+ Breast Cancer

Lower-risk disease

Neoadjuvant chemotherapy for all? Defining standards for our smallest tumors

- Most neoadjuvant trials limited eligibility to either node-positive or high-risk node negative tumors (>1cm or in many cases >2cm)
- Therefore, how much HER2 directed adjuvant treatment is indicated for patients with node-negative, smaller HER2+ breast cancers has not been not entirely clear

- On the one hand, these earliest-stage patients appear to be at higher risk, stage for stage, compared with patients with small HER2- tumors…
- But on the other hand, what about overtreatment?

De-escalating therapy in HER2+ breast cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Sara M. Tolaney, M.D., M.P.H., William T. Barry, Ph.D., Chau T. Dang, M.D., Denise A. Yardley, M.D., Beverly Moy, M.D., M.P.H., P. Kelly Marcom, M.D., Kathy S. Albain, M.D., Hope S. Rugo, M.D., Matthew Ellis, M.B., B.Chir., Ph.D., Iuliana Shapira, M.D., Antonio C. Wolff, M.D., Lisa A. Carey, M.D., Beth A. Overmoyer, M.D., Ann H. Partridge, M.D., M.P.H., Hao Guo, M.S., Clifford A. Hudis, M.D., Ian E. Krop, M.D., Ph.D., Harold J. Burstein, M.D., Ph.D., and Eric P. Winer, M.D.

APT trial: design and patient population

Single-arm study of weekly paclitaxel x trastuzumab x 12 weeks followed by trastuzumab q3 weeks x 1 year

Primary endpoint: DFS

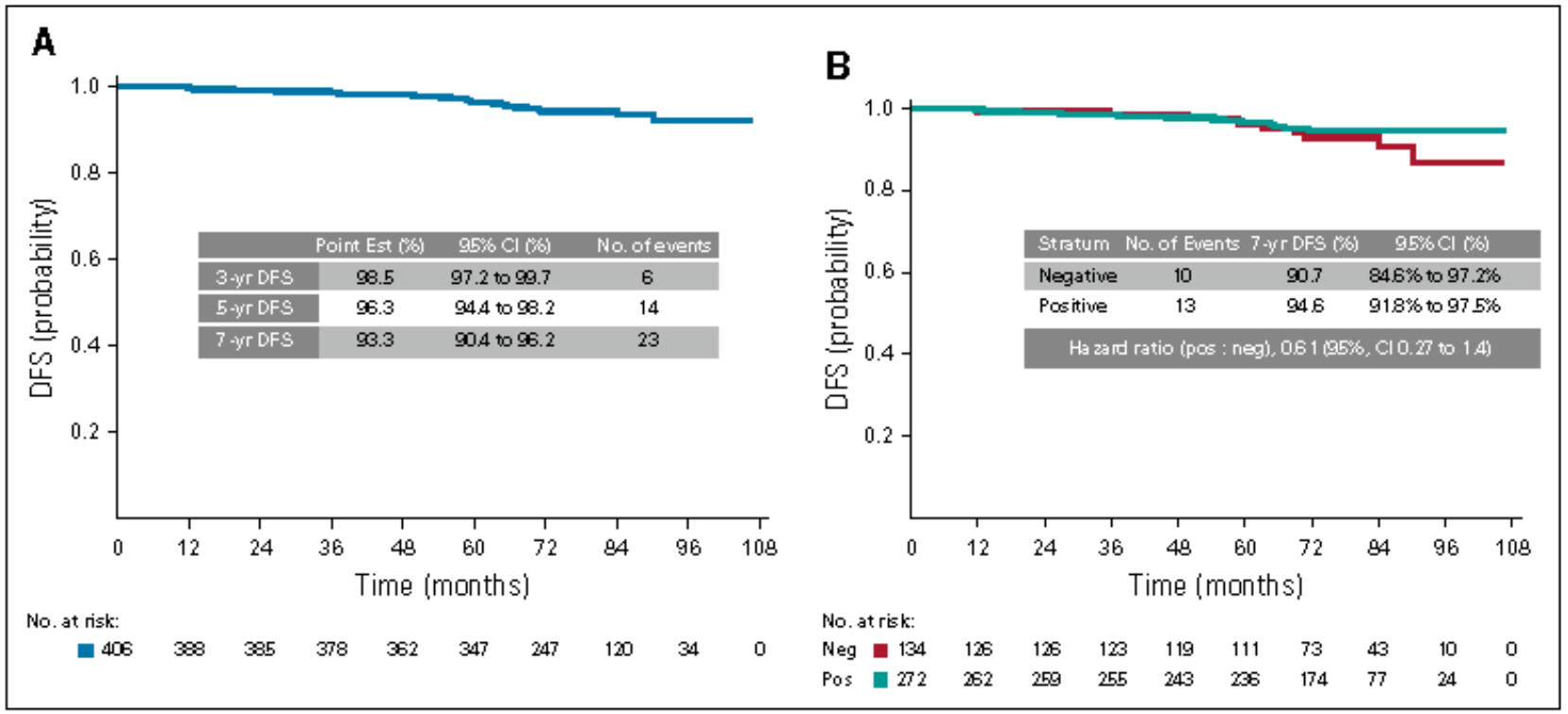
Secondary endpoints: recurrence-free survival, OS, breast-cancer specific survival

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Patients (N = 406)
	no. (%)
Age group	
<50 yr	132 (32.5)
50–59 yr	137 (33.7)
60–69 yr	96 (23.6)
≥70 yr	41 (10.1)
Sex	
Female	405 (99.8)
Male	1 (0.2)
Race†	
White	351 (86.5)
Black	28 (6.9)
Asian	11 (2.7)
Other	16 (3.9)
Primary tumor	
Size	
T1mic: ≤0.1 cm	9 (2.2)
T1a: >0.1 to ≤0.5 cm	68 (16.7)
T1b: >0.5 to ≤1.0 cm	124 (30.5)
T1c: >1.0 to ≤2.0 cm	169 (41.6)
T2: >2.0 to ≤3.0 cm	36 (8.9)
Nodal status	
N0	400 (98.5)
N1mic	6 (1.5)
Histologic grade	
I: well-differentiated	44 (10.8)
II: moderately differentiated	131 (32.3)
III: poorly differentiated	228 (56.2)
Unknown	3 (0.7)
HER2-positive status	406 (100)
Estrogen-receptor status	
Positive	260 (64.0)
Negative	141 (34.7)
Borderline	5 (1.2)
Progesterone-receptor status	
Positive	201 (49.9)
Negative	196 (48.3)
Borderline	8 (2.0)
Unknown	1 (0.2)
Hormone-receptor status	
Positive	272 (67.0)
Negative	134 (33.0)

N Engl J Med 2015: 372: 134-141. January 8, 2015.

APT trial: 7-year follow-up



This has become a new standard-of-care for stage I patients

J Clin Oncol 2019; 37: 1868-1875.

*3y-rate of survival free from invasive disease was 98.7%

*3y RFS was 99.2%

*There was no difference seen when patients were stratified by tumor size (≤1 versus >1 cm).

*7-year DFS of 93 percent and OS of 95 percent.

Patient case

40F presents to your office after having her first screening mammogram. An 8mm mass is identified and biopsy reveals ER 98% PR 80% HER 2 3+, grade 3 IDC. She undergoes lumpectomy and sentinel node biopsy, with final pathology showing a 9mm tumor with the same characteristics as the biopsy, and 0/3 negative nodes (pT1bN0).

Do you offer:

a) AC x 4 followed by paclitaxel/trastuzumab x 12 weeks, followed by trastuzumab for one year (plus endocrine therapy)

b) Taxotere/carboplatin/trastuzumab/pertuzumab (TCHP) x 6 cycles, followed by trastuzumab/pertuzumab for one year (plus endocrine therapy)

c) Paclitaxel + trastuzumab x 12 weeks, followed by trastuzumab for one year (plus endocrine therapy)

Patient case

40F presents to your office after having her first screening mammogram. An 8mm mass is identified and biopsy reveals ER 98% PR 80% HER 2 3+, grade 3 IDC. She undergoes lumpectomy and sentinel node biopsy, with final pathology showing a 9mm tumor with the same characteristics as the biopsy, and 0/3 negative nodes (pT1bN0).

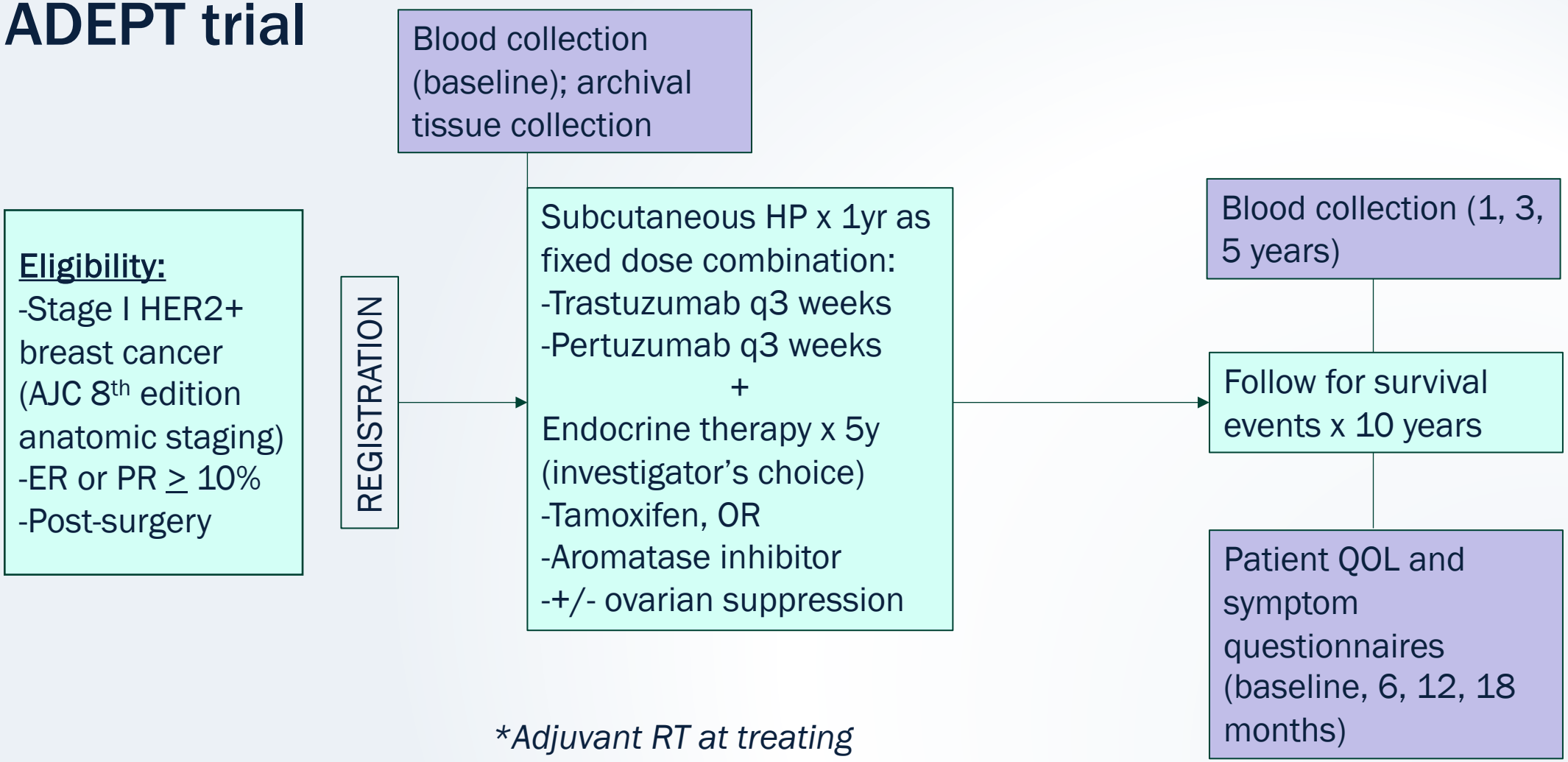
Do you offer:

a) AC x 4 followed by paclitaxel/trastuzumab x 12 weeks, followed by trastuzumab for one year (plus endocrine therapy)

b) Taxotere/carboplatin/trastuzumab/pertuzumab (TCHP) x 6 cycles, followed by trastuzumab/pertuzumab for one year (plus endocrine therapy)

c) Paclitaxel + trastuzumab x 12 weeks, followed by trastuzumab for one year (plus endocrine therapy)

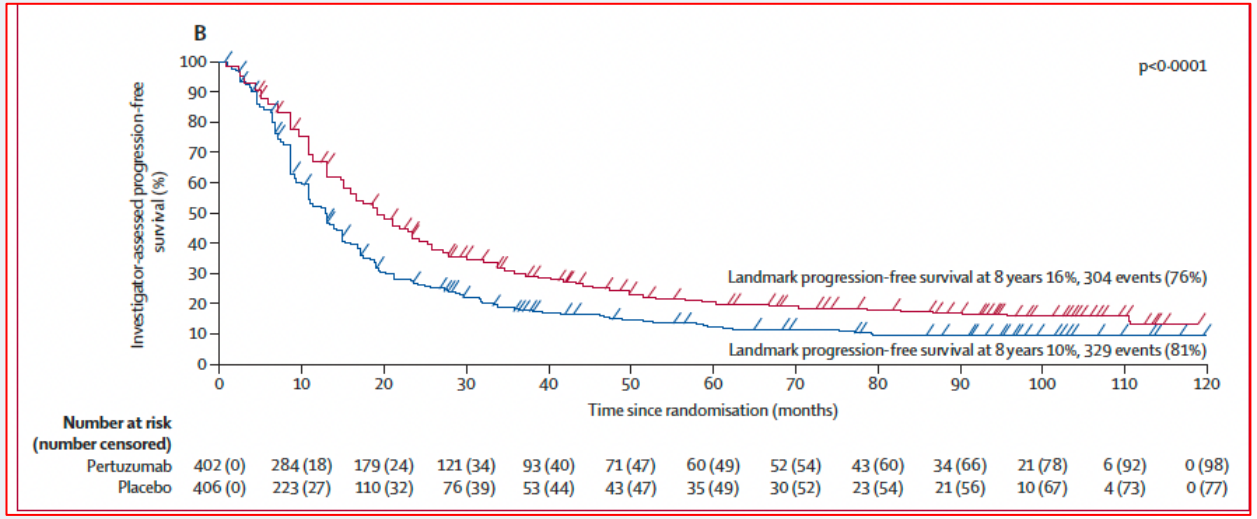
ADEPT trial

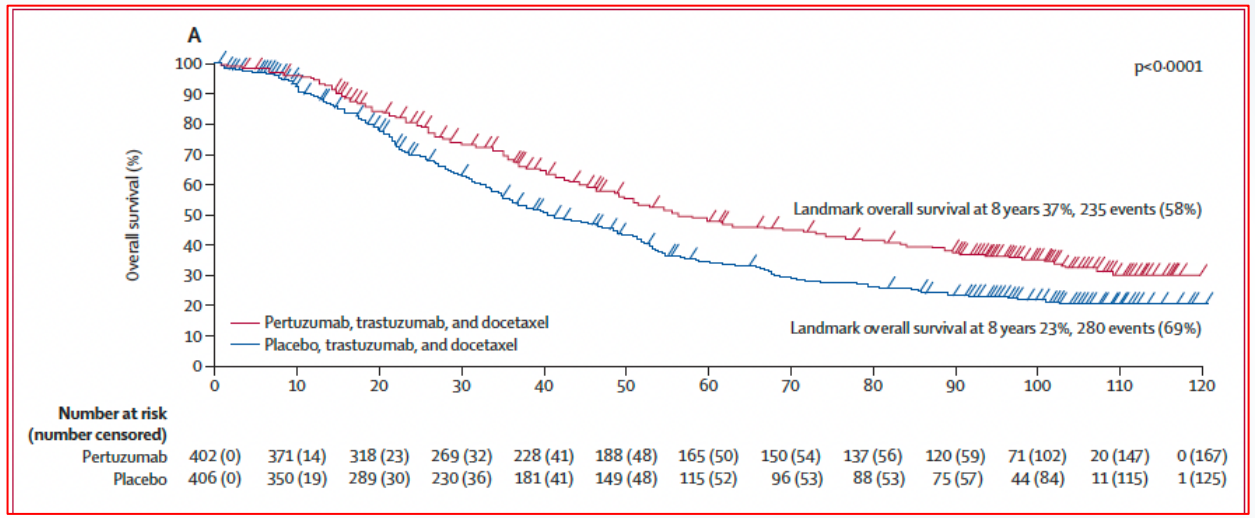


**Adjuvant RT at treating team's discretion*

Metastatic HER2+ Breast Cancer

Summer 2024
First-Line Standard of Care= Taxane + HP
CLEOPATRA





mPFS: 18.7 vs 12.4 mos

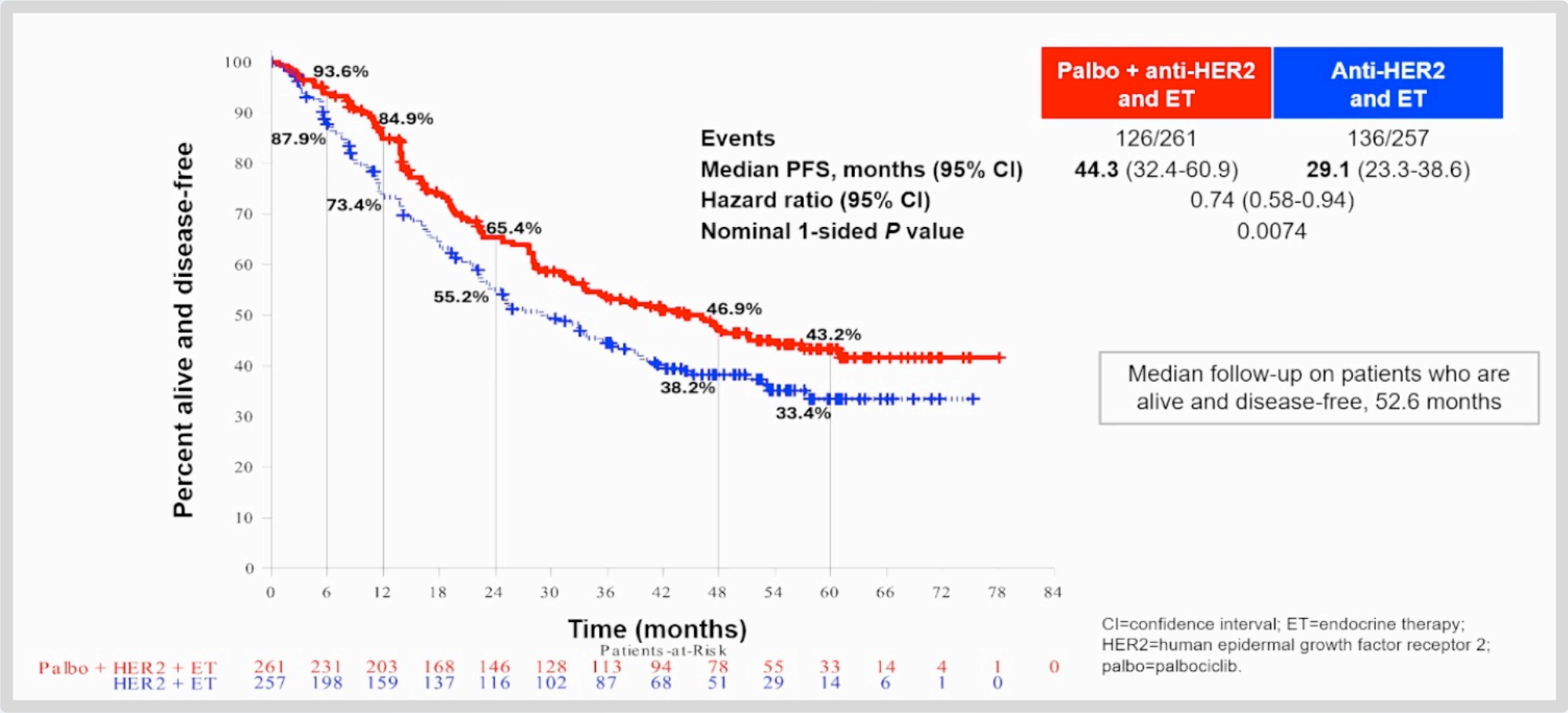
Landmark PFS at 8 yrs: 16% vs 10%

c

Landmark OS at 8 yrs: 37% vs 23%

Swain S et al. *Lancet Oncol* 2020; 21: 519-30. Courtesy of Claudine Isaacs, MD

PATINA

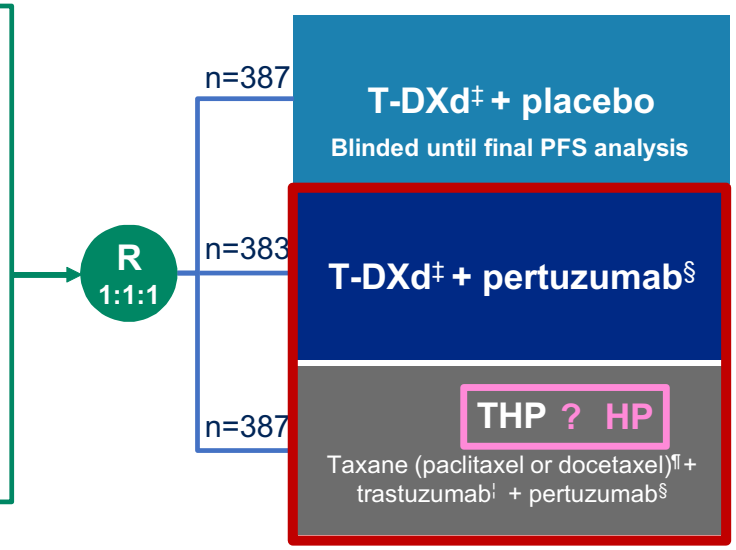


Metzger, O, *et al*. SABCS 2024; GS2-12

DESTINY-Breast09 – 1L HER2+ mBC

Eligibility criteria

- HER2+ a/mBC
- Asymptomatic/inactive brain mets allowed
- DFI >6 mo from last chemotherapy or HER2-targeted therapy in neoadjuvant/ adjuvant setting
- One prior line of ET for mBC permitted
- **No other prior systemic treatment for mBC†**



Endpoints

Primary

- PFS (BICR)

Key secondary

- OS

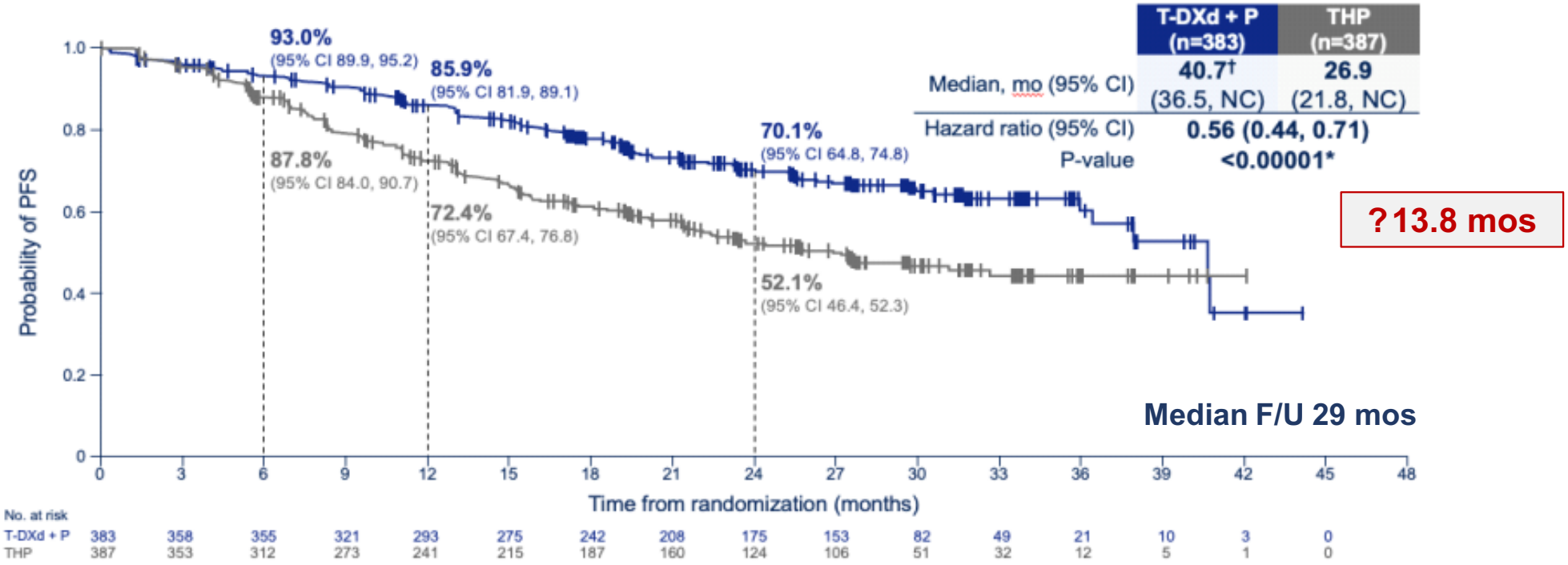
Secondary

- PFS (INV)
- ORR (BICR/INV)
- DOR (BICR/INV)
- PFS2 (INV)
- Safety and tolerability

- **<u>Key participant characteristics</u>:**
  - 51% de novo mBC; 54% HR+; ~82% IHC 3+
  - Of those initially diagnosed with ESB: ~ 80-85% received (neo)adjuvant chemo; **~ 58% trastuzumab**; **~15% pertuzumab**; **2% T-DM1**
  - Concurrent use of **ET in HR+**: **13.5% in T-DXd + P arm**; **38.3% in THP arm**

PRESENTED BY: Claudine Isaacs, MD, FRCPC

DESTINY-Breast09: Primary Endpoint PFS (BICR)



? 13.8 mos

Median F/U 29 mos

Generally consistent benefit across subgroups

PRESENTED BY: Claudine Isaacs, MD, FRCPC

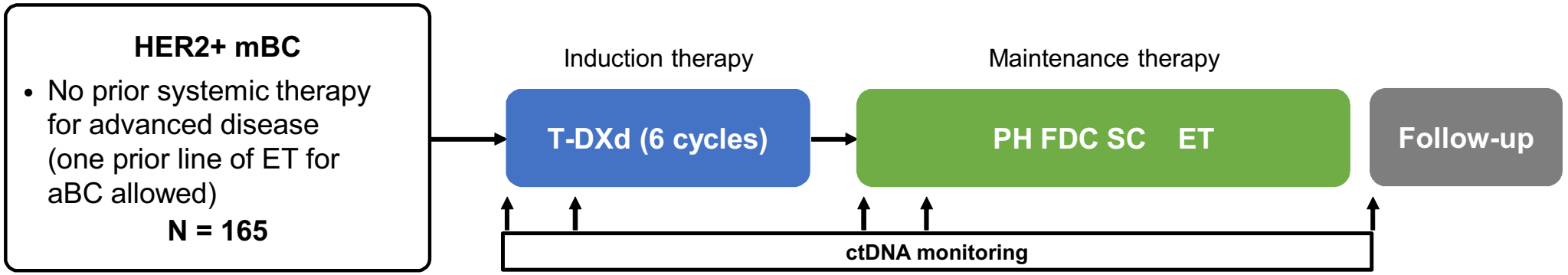
Destiny-Breast 09: a new standard of care?

Food for thought

- T-DXd performed impressively in this population, but is much more toxic than HP maintenance
- Should we wait for PFS2 data before making this standard of care?
- Can we predict which patients might benefit from this strategy versus other strategies?
  - Some patients might benefit from endocrine therapy +/- CDK 4/6i + HP
  - Some may do just as well with T-DXd induction followed by HP (+/- endocrine) maintenance
  - Biomarkers….

What about T-DXd + P induction followed by HP maintenance?

DEMETHER: Phase II study of 1L T-DXd induction followed by maintenance PH FDC SC[1]



Primary endpoints
- 1-year PFS, 3-year OS

- Single arm P2 trial limited by lack of control
- 8.7% on T-DXd + P switched to HP due to AEs

PRESENTED BY: Claudine Isaacs, MD, FRCPC

Cortés J, *et al*. SABCS 2024; P5-03-11

Changing standards of care for metastatic HER2+ breast cancer

- Several important considerations now when choosing 1L therapy
  - Goal: to help people live as well as possible, as long as possible – and this means different things to different people

- For second-line therapy and beyond – much depends on what has come before
  - HER2CLIMB regimen (capecitabine/tucatinib/trastuzumab)
  - Trastuzumab +/- additional endocrine therapies and/or chemotherapy
  - Margetuximab

- Trials of new ADCs and combination therapies
  - T-DXd + endocrine therapy
  - ARX-788, Disitimab vedotin, trastuzumab duocarmazine

Thank you!

Q&A