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SABCS 2024 AHN Review
Updates in Her2+ Breast Cancer

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Disclosures

Consultant: Partners in Metastatic Breast Cancer clinic at JHU (2021-2023), Gilead, Curio Science

Advisory Board: Gilead, Biotheranostics, Astra Zeneca

Speakers Bureau: Astra Zeneca (2021), Daiichi Sankyo (2021)

Honoraria: CEA Clinical Education Alliance, Target Oncology. OncLive/MJH Life Sciences

Objectives

To briefly review updates in Her2+ breast cancer from SABCS 12/2024

- Overview of current treatment
- Touch Trial
- PATINA Trial

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The Herceptin Timeline

1985 HER2 gene discovered.

1987 Data published showing the link between HER2 overexpression and an aggressive type of breast cancer.

1990 Scientists humanize an antibody directed at HER2 that comes to be known as Herceptin.

Early 1990s Phase I and II trials conducted.

FDA.org, curetoday.com
SABCS.org

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The Herceptin Timeline

1997

Phase III trials for Herceptin completed.

Results show that Herceptin in combination with chemotherapy slows the progression of cancer and increases tumor shrinkage in metastatic disease.

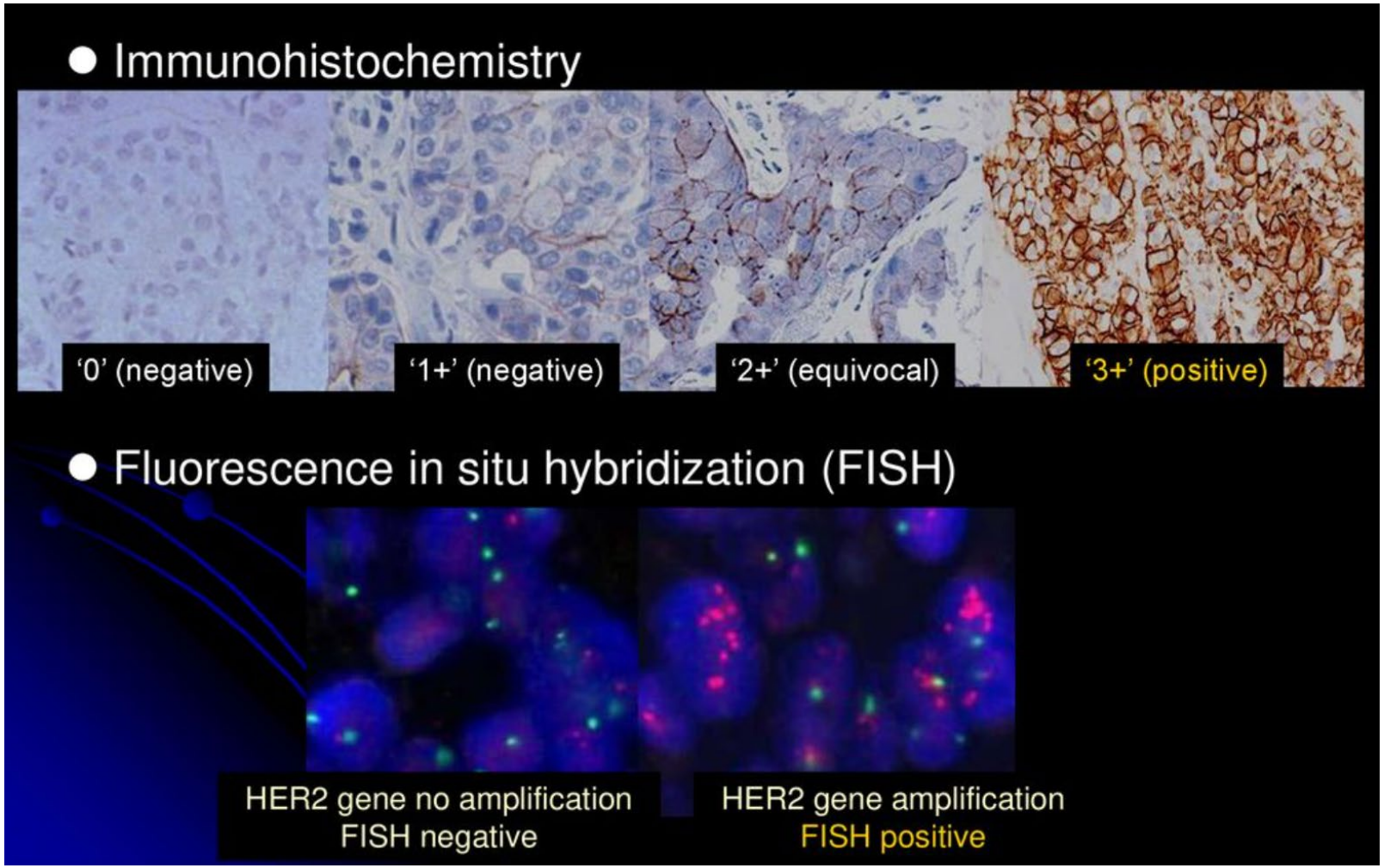
March 2001

Data from a phase III trial is published in *The New England Journal of Medicine* that shows a 25 percent increase in survival rate for women with HER2-positive metastatic breast cancer who receive Herceptin and chemotherapy compared with chemotherapy alone.

FDA.org, curetoday.com

The Herceptin Timeline

2002 FDA approves use of FISH (fluorescent in situ hybridization) gene amplification test for HER2 gene.



Pathologyoutlines.com
FDA.org, curetoday.com

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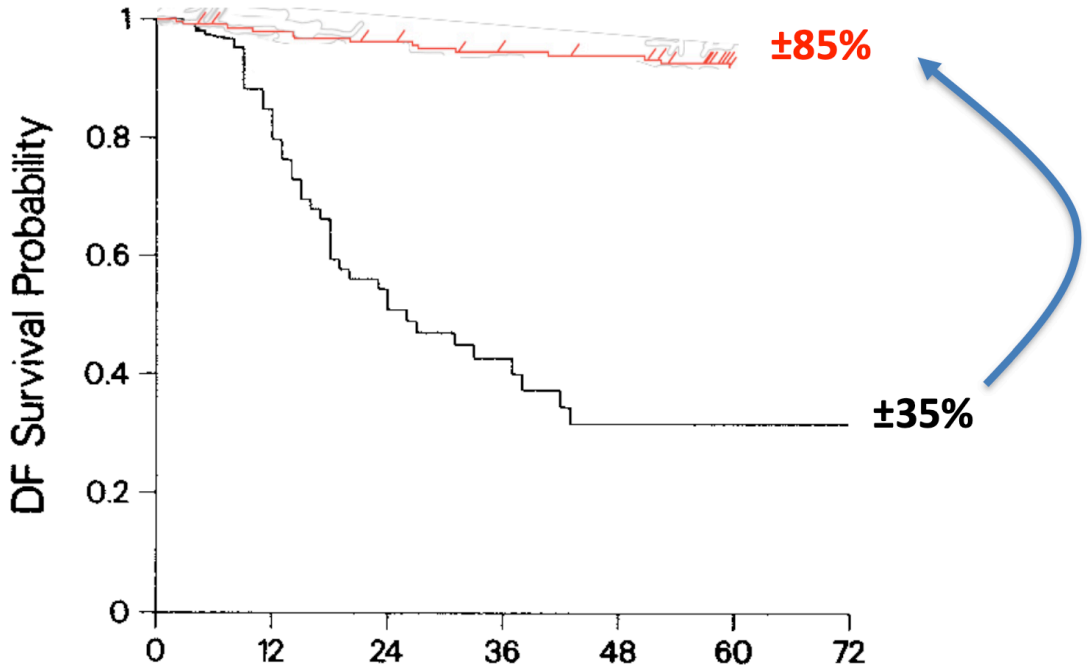
The Herceptin Timeline

2005

- Data from three large trials of Herceptin used in the adjuvant setting, presented at the annual meeting of the American Society of Clinical Oncology, show the drug reduces the risk of recurrence by 50 percent in HER2-positive breast cancer patients.

February 2006

- Application to the FDA for approval of Herceptin with chemotherapy in early-stage HER2-positive breast cancer in the adjuvant setting.



FDA.org, curetoday.com

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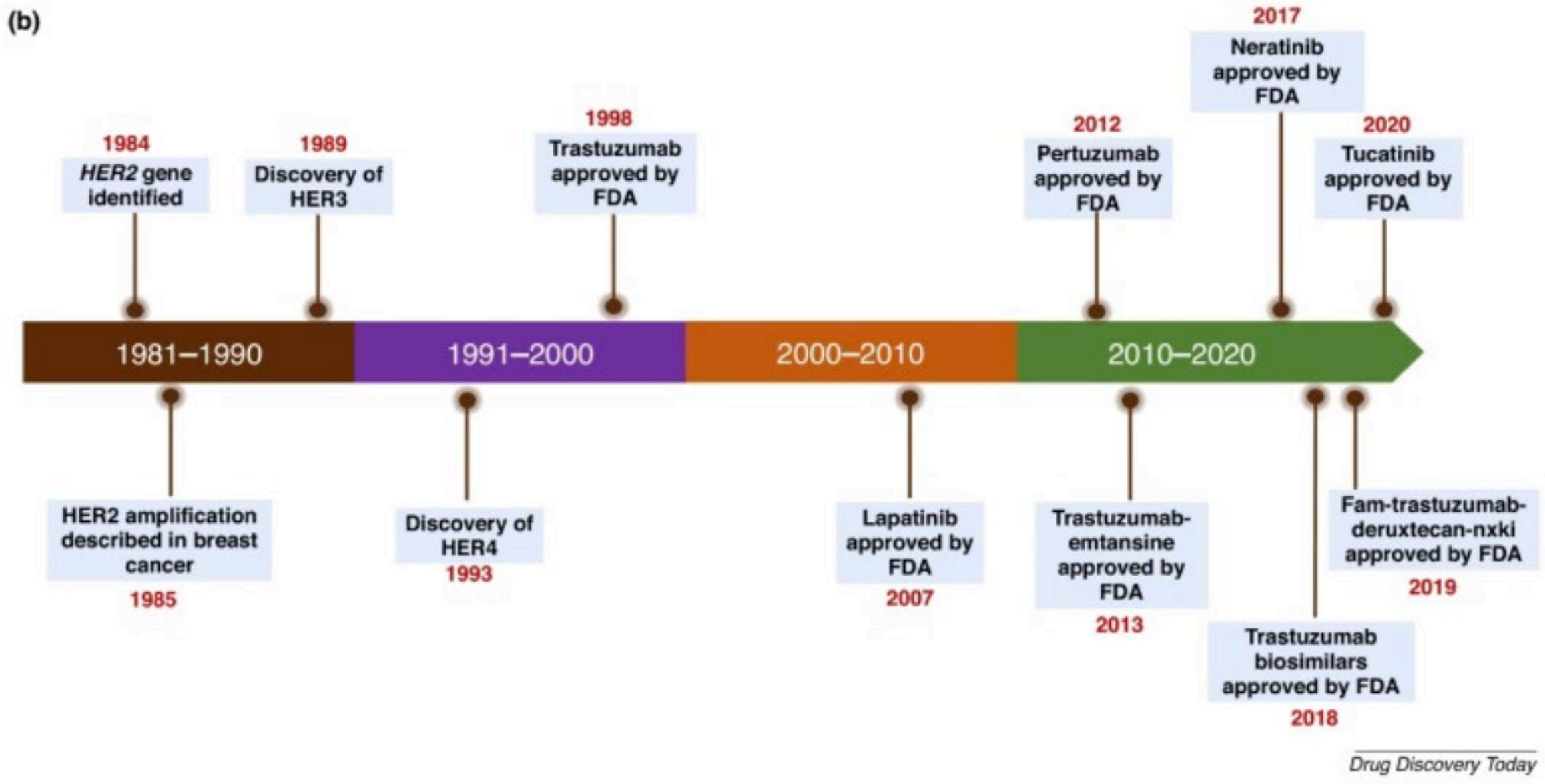
Her2 Treatment advances



Neoadjuvant Treatment for Her2+ Breast Cancer in 2025

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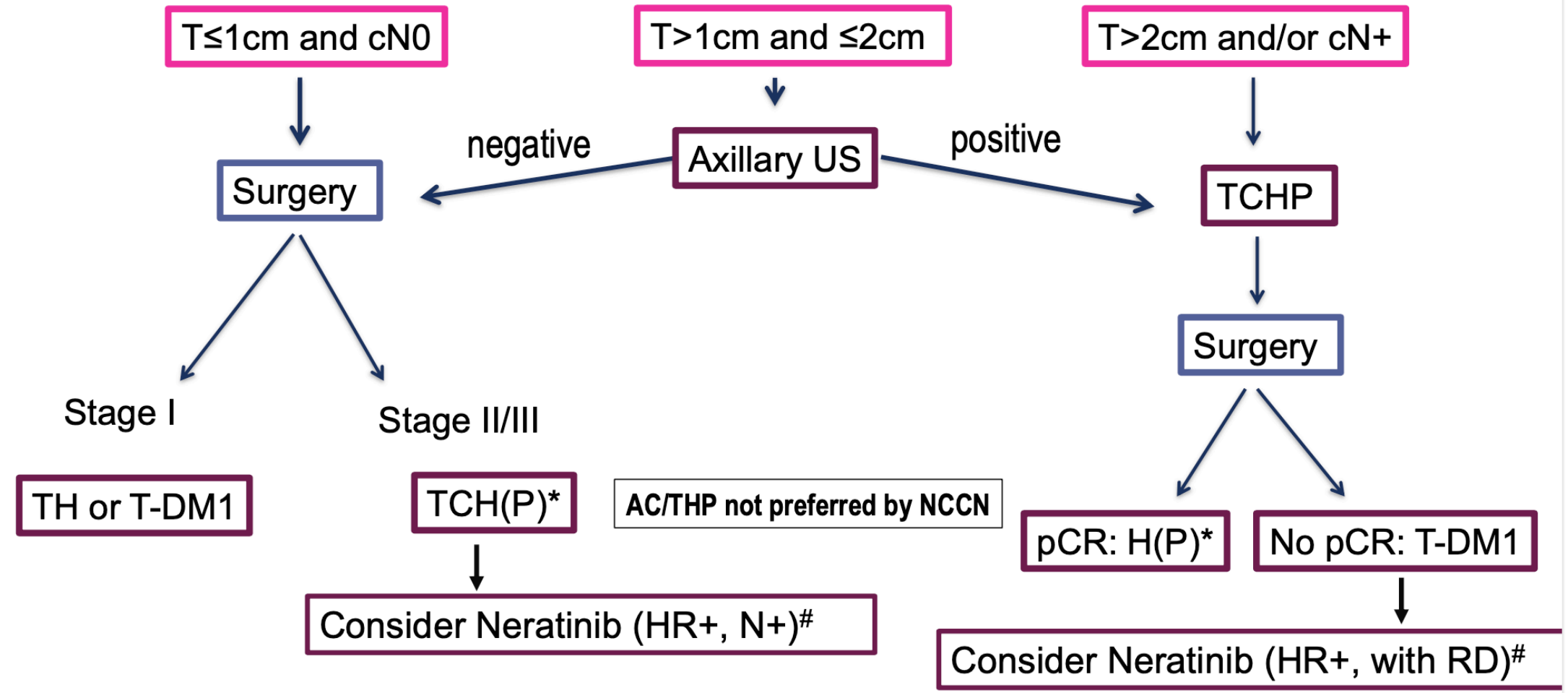
NCCN Guidelines HER2+ Early Breast Cancer



*Depending on Nodal Status; for pCR and N0, little benefit from P

#Adjuvant neratinib not evaluated post-pertuzumab and T-DM1

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Neoadjuvant Treatment for Her2+ Breast Cancer in 2025

- Increase breast preservation and axillary sparing surgery by decreasing tumor burden
- Assess the response to treatment
- Treatment of micro metastatic disease
- Guide adjuvant treatment decisions
- Early endpoints for clinical trials

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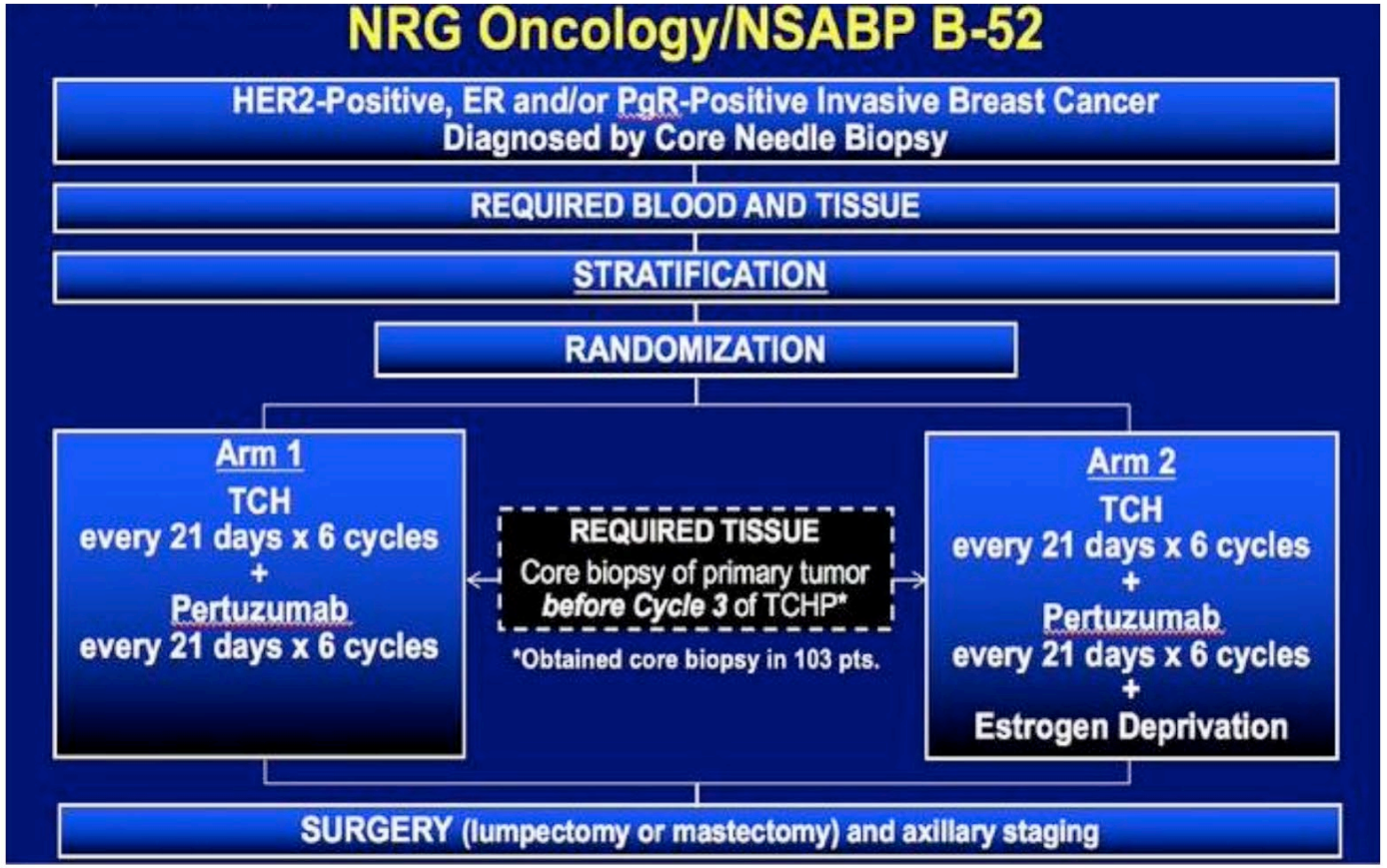
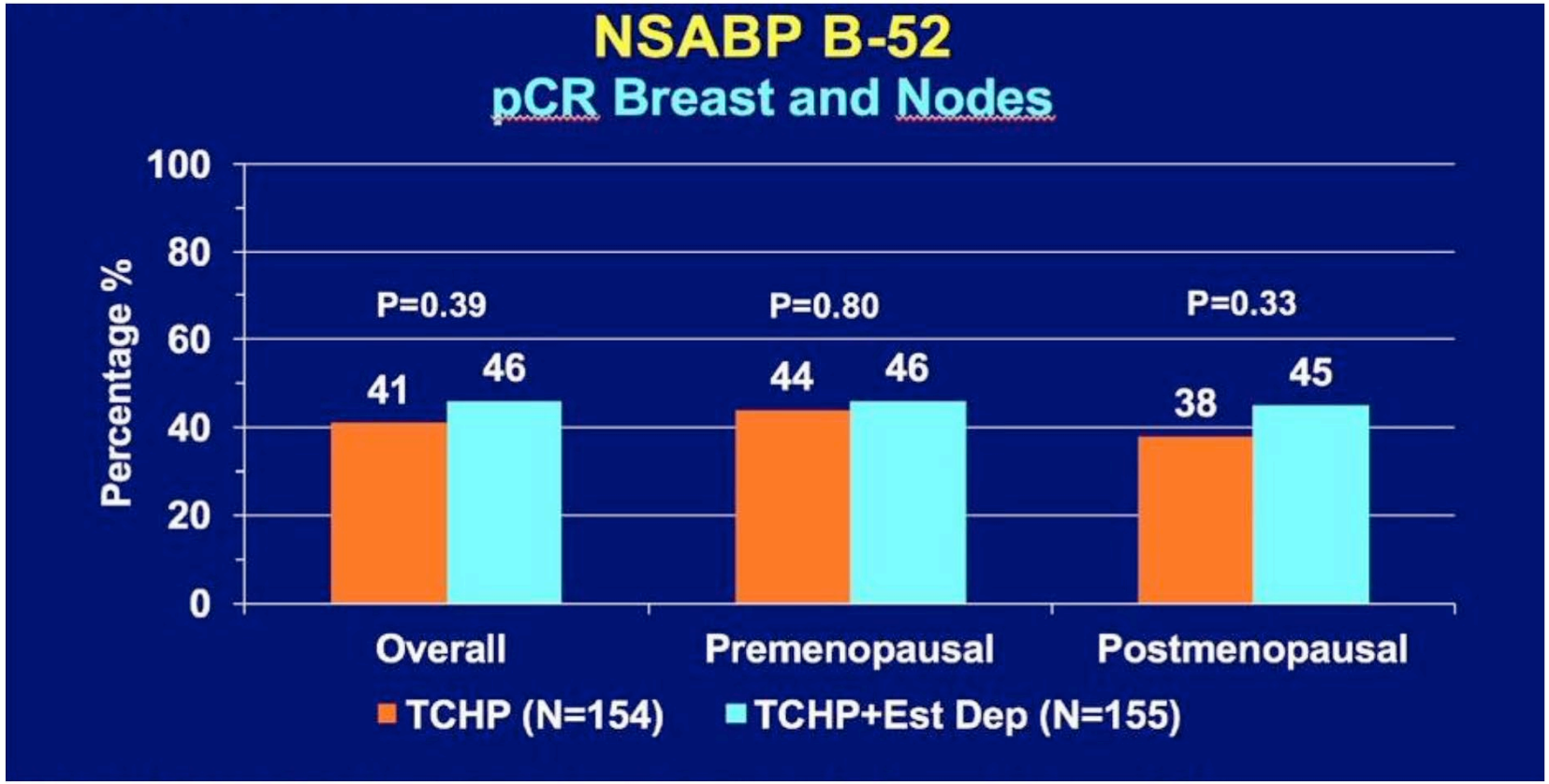
Some background worth mentioning…

NSABP B-52: concurrent estrogen deprivation



Rimawi; SABCS 2016

NSABP B-52: concurrent estrogen deprivation



Rimawi; SABCS 2016

Palbociclib plus letrozole versus weekly paclitaxel, both in combination with trastuzumab plus pertuzumab, as neoadjuvant treatment for patients with HR+/HER2+ early breast cancer

Primary results from the randomized phase II TOUCH trial (IBCSG 55-17)

Luca Malorni, MD, PhD on behalf of the TOUCH trial Investigators

L. Malorni, S. Tyekucheva, C. Zamagni, U. Hasler-Strub, A. Gombos, C. Chakiba-Brugère, M. Colleoni, A. Mueller, A.M. Minisini, D. Taylor, J.P. Salmon, E. Gallerani, A. Cariello, A. Fontana, H. Roschitzki-Voser, R. Kammler, B. Ruepp, S. Loi, G. Viale, M.M. Regan, E. Brain, L. Biganzoli

Background and hypothesis

- Patients with HR+ and HER2+ early breast cancer have an unmet clinical need due to lower pCR rates after neo-adjuvant chemotherapy+ anti-HER2 agents, and uncertainty regarding endocrine therapy response.
- Recently, pre-clinical [1-2] and clinical [3-4] data have suggested that the addition of CDK4/6 inhibitors to endocrine therapy and anti-HER2 agents in HR+/HER2+ breast cancer, might be a potential strategy for chemotherapy de-escalation. However, biomarkers to select patients are lacking.
- We have previously shown that high levels of RBsig, a gene-expression signature of functional loss of *RB1*, composed of E2F-1 and 2 associated genes, is associated with:
  - resistance to CDK4/6 inhibitors in ER+/HER2neg breast cancer models and clinical samples [5-6]
  - sensitivity to chemotherapy + anti-HER2 agents in patients with ER+/HER2+ early breast cancer [7-8]

Therefore, we hypothesized that RBsig status (HIGH or LOW) might show an interaction with therapy in patients treated with either:

- **a CDK4/6 inhibitor** in combination with **anti-HER2 therapy** and **endocrine therapy**
- **chemotherapy** and **anti-HER2 therapy**

1) Goel S. et al; Cancer Cell, 2016; 2) Viganò L. et al; Clin Can Res 2022; 3) Gianni L. et al; Lancet Oncol 2018; 4) Tolaney S.M. et al; Lancet Oncol 2020; 5) Guarducci C. et al; npj Breast Cancer 2018; 6) De Angelis C. et al; Clin Can Res 2021; 7) Risi E. et al, Breast Cancer Res Treat, 2018; 8) Risi E. et al, Ther Adv Med Oncol, 2019

Study design and statistical assumptions

37 sites in Belgium, Italy, Switzerland, France (Unicancer)

Post-menopausal(*) ER+/HER2+ early BC T>1cm(**); cN 0-1

n=145

R

Paclitaxel x 4 cycles + HP x 5 cycles (n=73)

Palbociclib + Letrozole x 4 cycles HP x 5 cycles (n=72)

FFPE

16 weeks

≤4 weeks

Surgery

FFPE

Primary Objective:
Explore the interaction between treatment activity (**pCR: ypT0/ypTis ypN0**) and **RBsig status** (HIGH or LOW) measured on pre-treatment biopsies by RNA-sequencing

Stratification:
Age and G8-score:
< 65y/ ≥ 65 y & G8 ≤14 /≥ 65 y & G8 > 14
Clinical node involvement: cN0/cN1

Treatment:

Paclitaxel: 80 mg/m2 iv; day 1,8,15 q28d x 4 cycles

HP:
Trastuzumab (H) 600 mg sc q21d x 5 cycles
Pertuzumab (P) 420 mg iv q 21 d (+loading dose 840 mg) x 5 cycles

Palbociclib (Palbo): 125 mg po STD schedule x 4 cycles
Letrozole (Let): 2.5 mg/day po x 16 weeks

* As for clinical examination, mammography, or ultrasonography
** Originally eligible pts ≥65y; amended after 35 pts had been randomized.

Hypothesis and assumptions:

- **Palbociclib+ Letrozole** expected better in **RBsig LOW**
- **Paclitaxel** expected better in **RBsig HIGH**

	A: Paclitaxel + HP	B: Palbo+ Let + HP	Odds Ratio (B:A)
	pCR rate		
RBsig HIGH	50%	10%	0.111
RBsig LOW	15%	30%	2.429

80% power with 110 pts; 86% power with 120 pts (alpha 0.05)

Baseline characteristics (treatment population)

		Paclitaxel + HP n = 73	Palbo + Let + HP n = 72	Overall n = 145
Age- Median (IQR)		69 (64, 74)	69 (59, 72)	69 (63, 73)
Age and G8 score*	< 65 years	21 (28%)	25 (34%)	46 (31%)
	≥65 years and G8 ≤14	19 (26%)	16 (22%)	35 (24%)
	≥65 years and G8 > 14	34 (46%)	32 (44%)	66 (45%)
ECOG PS: 0/1		65 (89%)/8 (11%)	67 (93%)/5 (7%)	132 (91%)/13 (9%)
Tumor size- Median (IQR)**		25 mm (20, 32)	25 mm (20, 30)	25 mm (20, 31)
N status*: N0/N1		54 (73%)/20 (27%)	56 (77%)/17 (23%)	110 (75%)/37 (25%)
Invasive ductal NST		69 (94.5%)	61 (84.7%)	130 (89.6%)
Grade 3		37 (55%)	39 (57%)	76 (56%)
ER + (≥10%)		73 (100%)	72 (100%)	145 (100%)
PgR + (≥1%)		57 (78%)	55 (76%)	112 (77%)
HER2+		73 (100)	72 (100)	145 (100)

* stratification factor ** by mammography (Max diam.)

Treatment administration (treatment population)

Drug / Compliance	Paclitaxel + HP n = 73	Palbo + Let + HP n = 72
Paclitaxel		
Completed 4 cycles of treatment	58 (79.5%)	--
Early discontinuation due to AE	12 (16.4%)	--
Early discontinuation due to other reasons	3 (4.1%)	
Palbociclib		
Completed 4 cycles of treatment	--	68 (94.4%)
Early discontinuation due to AE	--	2 (2.8%)
Early discontinuation due to other reason		2 (2.8%)
Trastuzumab + pertuzumab		
Completed 5 doses of treatment	68 (93.2%)	70 (97.2%)
Early discontinuation due to AE	5 (6.8%)	1[1] (2.8%)

[1] One additional pt skipped one dose of pertuzumab due to G3 diarrhea

Reasons for early discontinuation :

Paclitaxel

AE: infusion reaction (n=5), G2-3 neuropathy (n=3), other AE (n=4)
Other reasons: COVID (n=1), patient's/physician's decision (n=2)

Palbociclib

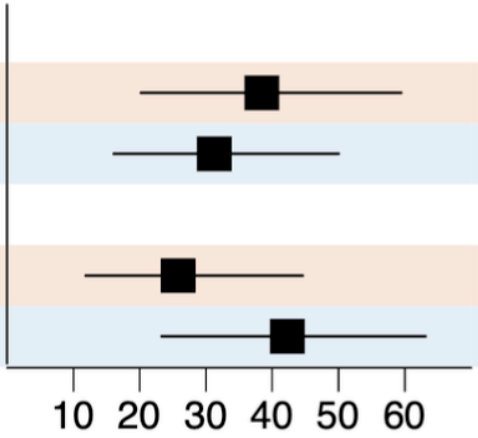
AE: G3 ALT/AST increase (n=2)
Other reasons: COVID (n=1), surgeon's decision (n=1)

pCR rate by treatment arm (treatment population)

	Paclitaxel + HP, n = 73	Palbo + Let + HP, n = 72	Overall, n = 145
pCR, n	24	24	48
% (95% CI)	**32.9%** (22.3- 44.9)	**33.3%** (22.6- 45.4)	**33.1%** (25.5, 41.4)

Primary objective: pCR by RBsig status (assessable population)

RBsig	Group	n pCR	Total	pCR rate (95% CI)	OR (95% CI)
HIGH					1.4 (0.5 – 4.1)
	Palbo + Let + HP	10	26	38.5 (20.2 – 59.4)	
	Paclitaxel + HP	10	32	31.2 (16.1 – 50.0)	
LOW					0.5 (0.2 – 1.4)
	Palbo + Let + HP	8	31	25.8 (11.9 – 44.6)	
	Paclitaxel + HP	11	26	42.3 (23.4 – 63.1)	



RBsig-by-treatment interaction OR 0.34, 95% CI (0.07, 1.63);
p-value for the interaction test 0.18

- RNA-sequencing was performed from pre-treatment FFPE biopsies (NEBNext® UltraTM II Directional RNA Library Prep Kit with the Twist Human Core Exome + Custom IntegraGen Enrichment V2 capture System, Paired End 100b reads).
- RNA-seq was successful in 119 pre-treatment biopsies (88%), 115 of whom met the criteria for primary endpoint assessment (assessable population)
- RBsig score was dichotomized at the median.

Conclusions

- TOUCH is the first trial randomizing post-menopausal patients with ER+/HER2+ early breast cancer to receive dual anti-HER2 blockade in combination with either a de-escalated chemo-free backbone of palbociclib+ letrozole or weekly paclitaxel.
- The primary hypothesis that RBsig status may predict a differential benefit of the two treatment arms was not supported by the study data.
- Additional translational studies are ongoing.
- Interestingly, a pCR rate of about 30% was reported in both treatment arms.
- The good treatment compliance observed within the LET+PALBO arm together with the activity of this combination support further investigation of this strategy in dedicated clinical trials.

Treatment of Her2+ Metastatic disease

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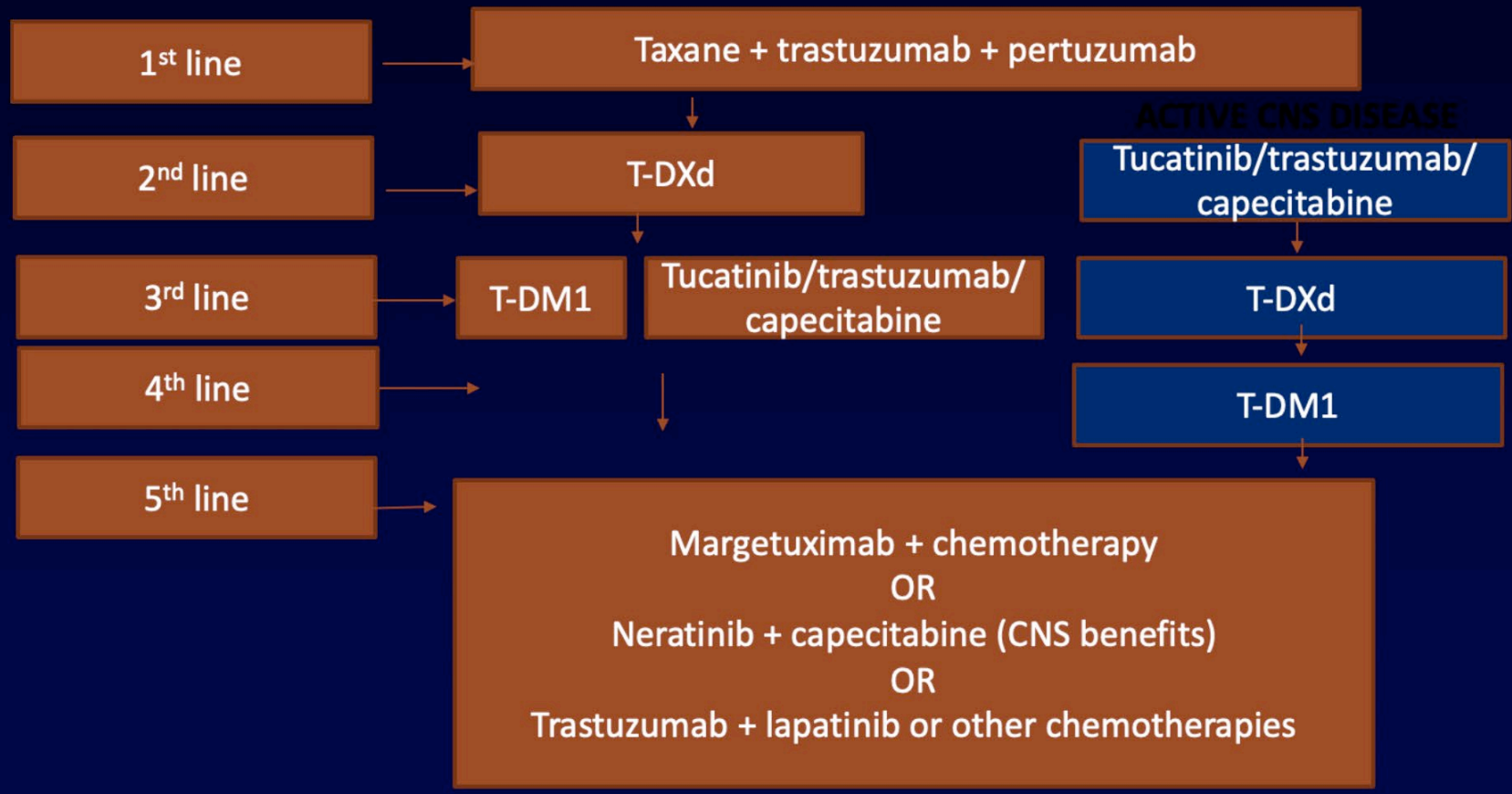
Current Treatment Algorithms for HER2+ MBC:
Almost exclusively based on HER2, no other biomarker selection for treatment



Adapted from Modi ESMO 2021; Gennari A et al Ann Oncol 2021.

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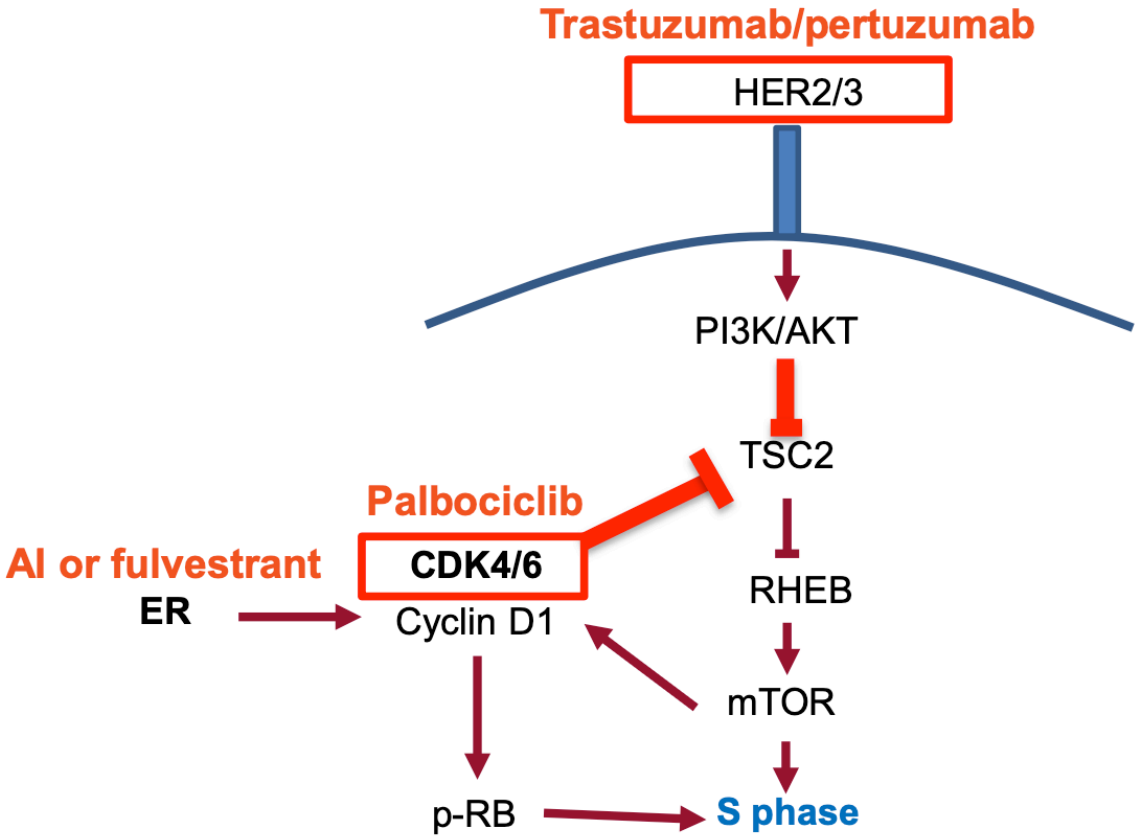
Treatment of Her2+ Metastatic disease

Escalation Trials

De-escalation trials

Development of biomarkers to help us who needs more and who can do well with less.

Background:
Rationale for Blocking HER2 and CDK4/6 Pathways



The HER2 and CDK4/6 pathways converge at the tumor suppressor protein TSC2

When CDK4/6 and HER2 inhibitors are combined, potent suppression of RB phosphorylation and mTORC1 activity, enhancing anti-proliferative effects in tumor cells

AI=aromatase inhibitor; AKT=protein kinase B; CDK4/6=cyclin-dependent kinase 4/6; HER2=human epidermal growth factor receptor 2; HER3=human epidermal growth factor receptor 3; CDK4/6=cyclin-dependent kinase 4/6; ER=estrogen receptor; mTOR=mammalian target of rapamycin; mTORC1=mammalian target of rapamycin complex 1; PI3K=phosphoinositide 3-kinase; p-RB=retinoblastoma protein; RHEB=ras homolog enriched in brain; S phase=synthesis phase; TSC2=tuberous sclerosis complex 2.

Goel S, et al. *Cancer Cell*. 2016;29(3):255-269.

AFT-38 PATINA Study Design

Registration

- Histologically confirmed HR+,HER2+ mBC
- No prior treatment in the advanced setting beyond induction treatment
- 6-8 cycles of treatment, including trastuzumab ± pertuzumab and taxane/vinorelbine

Key eligibility criteria

- Completion of induction chemotherapy and no evidence of disease progression (i.e., CR, PR, or SD)

N=518

R 1:1

- **Palbociclib (125 mg PO QD D1-D21) + Trastuzumab ± pertuzumab + endocrine therapy***
- **Trastuzumab ± pertuzumab + endocrine therapy***

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors

- Pertuzumab use (yes vs no)
  - The non-pertuzumab option is limited to up to 20% of the population
- Prior anti-HER2 therapy in the (neo)adjuvant setting (yes vs no, including de novo)†
- Response to induction therapy (CR or PR vs SD) by investigator assessment†
- Type of endocrine therapy (fulvestrant vs aromatase inhibitor)

97% were treated with Pertuzumab and Trastuzumab

Prior trastuzumab 71%

*Trastuzumab and pertuzumab were administered per SOC. Endocrine therapy options include an aromatase inhibitor or fulvestrant. †Factors used in stratified analyses.
CR=complete response; D=day; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; mBC=metastatic breast cancer; PD=progressive disease; PO=orally; PR=partial response; QD=once a day; R=randomization; SD=stable disease; SOC=standard of care.

Statistical Analysis

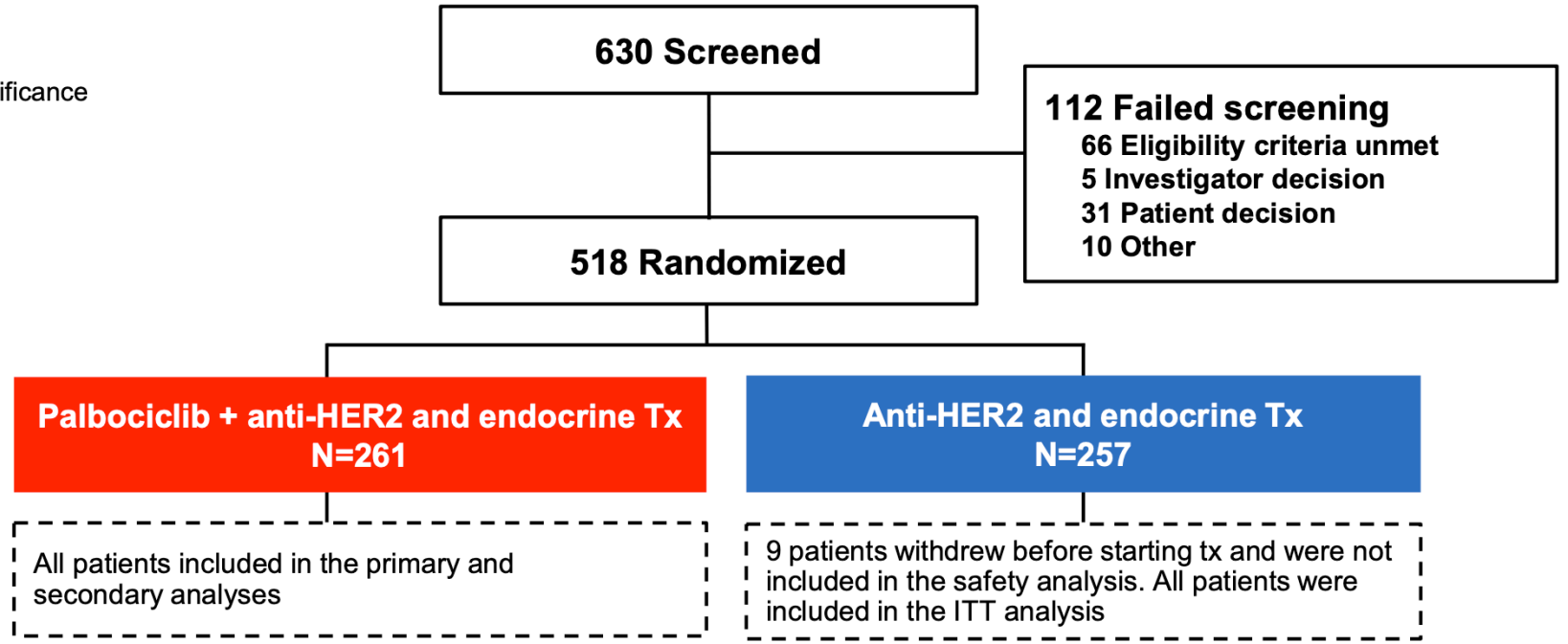
Primary endpoint (investigator-assessed PFS)

- 90% power for a minimum detectable hazard ratio of 0.667
- One-sided log-rank test at the 0.025 level of significance
- Final analysis planned after 269 events
  - Two planned interim analyses at 50% and 60% of PFS events

Key secondary objective (OS)

- OS is hierarchically tested at the interim and final PFS analysis
  - Pre-specified boundary (α=0.0002, and 0.025, 1-sided)
- Final OS analysis planned after 247 events
  - 80% power to detect a hazard ratio of 0.70
  - One-sided log-rank test at the 0.05 level of significance

OS=overall survival; PFS=progression-free survival.



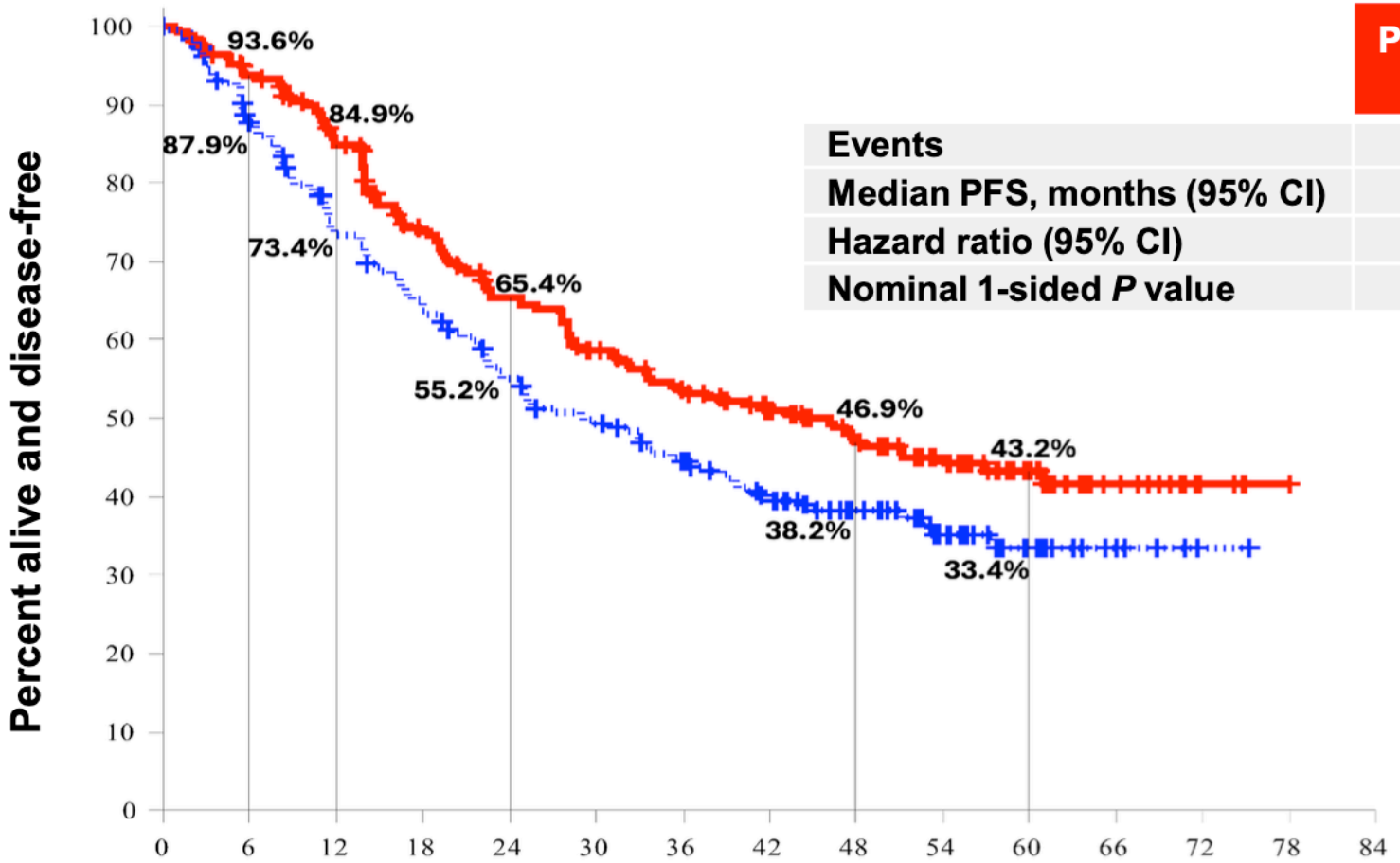
Patient Demographic and Key Characteristics

	Palbociclib + anti-HER2 and ET (N=261)	Anti-HER2 therapy and ET (N=257)	Total (N=518)
Age (years)			
Median (IQR)	53.5 (43.6, 60.4)	53.0 (45.1, 62.8)	53.4 (44.2, 61.4)
Race, n (%)			
White	205 (91.9)	192 (91.4)	397 (91.7)
Asian Indian + Chinese + other Asian	8 (3.1)	3 (1.2)	11 (2.1)
Black or African American	4 (1.8)	11 (5.2)	15 (3.5)
Other	6 (2.3)	4 (1.6)	10 (1.9)
Gender, n (%)			
Female	259 (99.2)	256 (99.6)	515 (99.4)
Male	2 (0.8)	1 (0.4)	3 (0.6)
Number of cycles of induction Tx			
Median (range)	6 (4-8)	6 (4-8)	

Patient Demographic and Key Characteristics (cont.)

	Palbociclib + anti-HER2 and ET (N=261)	Anti-HER2 therapy and ET (N=257)	Total (N=518)
Pertuzumab use, n (%)			
No	8 (3.1)	6 (2.3)	14 (2.7)
Yes	253 (96.9)	251 (97.7)	504 (97.3)
Type of endocrine therapy, n (%)			
Aromatase inhibitor	237 (90.8)	234 (91.1)	471 (90.9)
Fulvestrant	24 (9.2)	23 (8.9)	47 (9.1)
Prior anti-HER2 therapy in the (neo)adjuvant setting,* n (%)			
No	71 (27.2)	75 (29.2)	146 (28.2)
Yes	190 (72.8)	182 (70.8)	372 (71.8)
Best response to induction therapy by investigator assessment,* n (%)			
CR or PR	179 (68.6)	176 (68.5)	355 (68.5)
SD	82 (31.4)	81 (31.5)	163 (31.5)

Primary Endpoint: PFS (Investigator-Assessed)



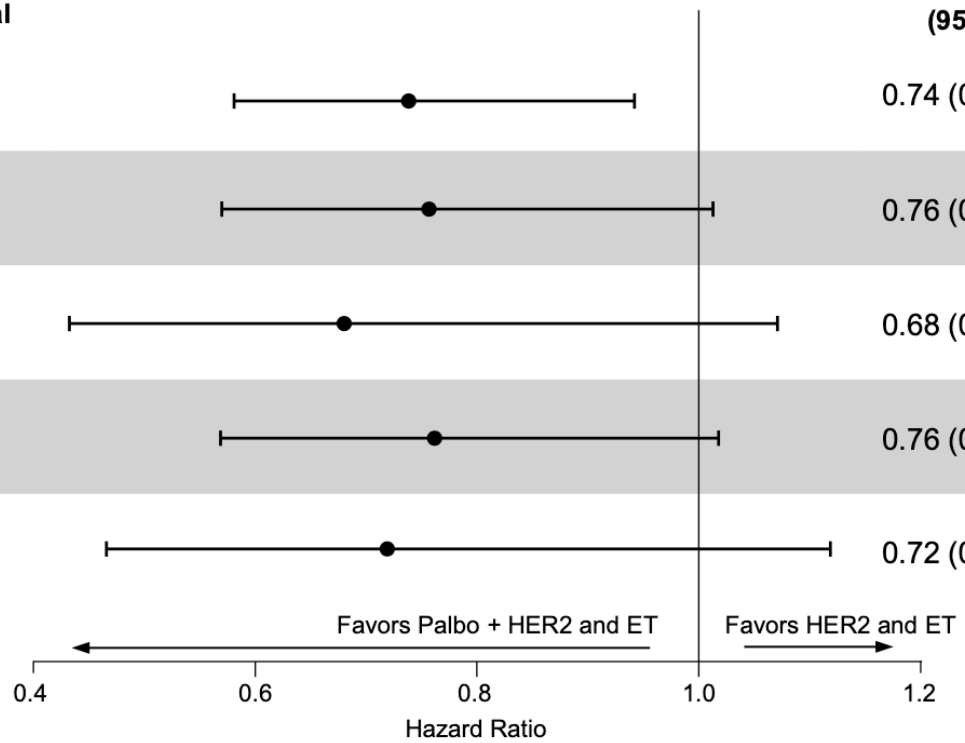
	Palbo + anti-HER2 and ET	Anti-HER2 and ET
Events	126/261	136/257
Median PFS, months (95% CI)	**44.3** (32.4-60.9)	**29.1** (23.3-38.6)
Hazard ratio (95% CI)	0.74 (0.58-0.94)	
Nominal 1-sided *P* value	0.0074	

Median follow-up on patients who are alive and disease-free, 52.6 months

CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; palbo=palbociclib.

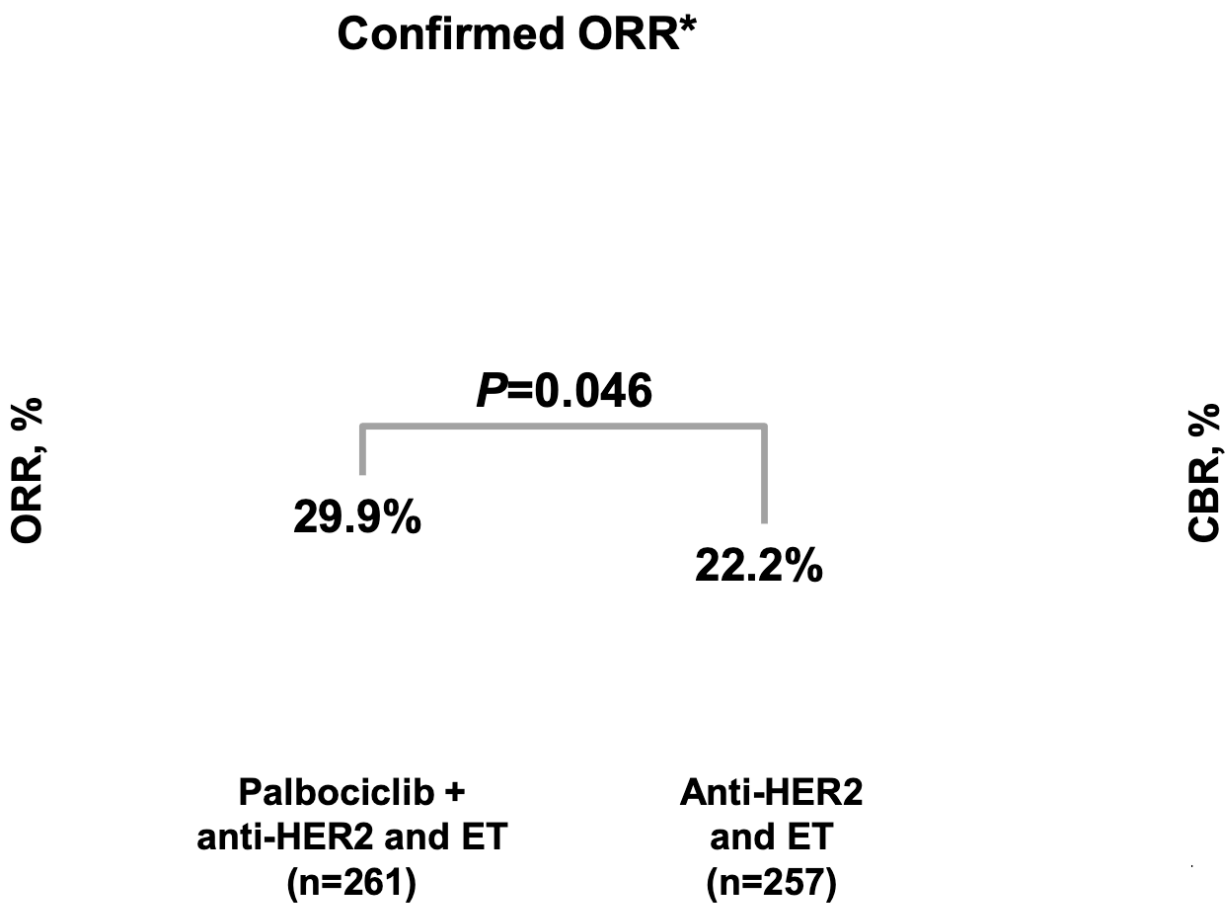
PFS by Stratification Subgroups

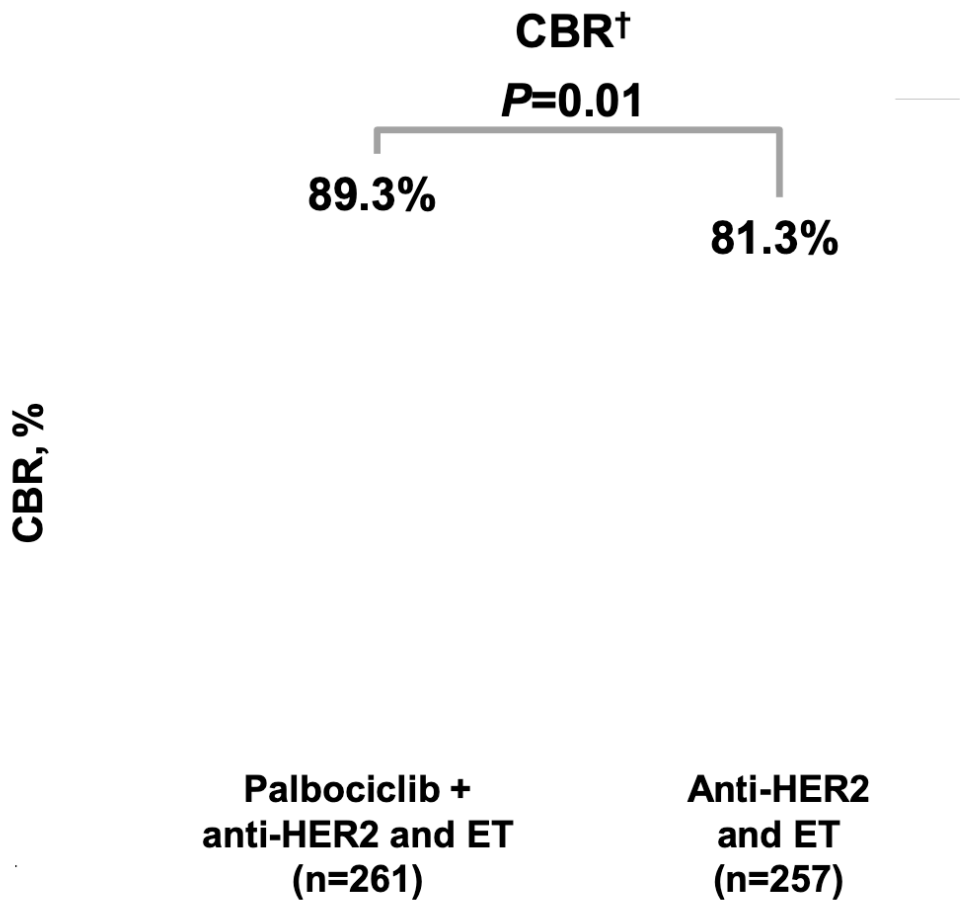
	Events/Total	Hazard Ratio (95% CI)
Overall	262/518	0.74 (0.58-0.94)
Prior anti-HER2 therapy	186/372	0.76 (0.57-1.01)
No prior anti-HER2 therapy	76/146	0.68 (0.543-1.07)
Best response to induction (CR* or PR*)	182/355	0.76 (0.57-1.02)
Best response to induction (SD*)	80/163	0.72 (0.47-1.12)



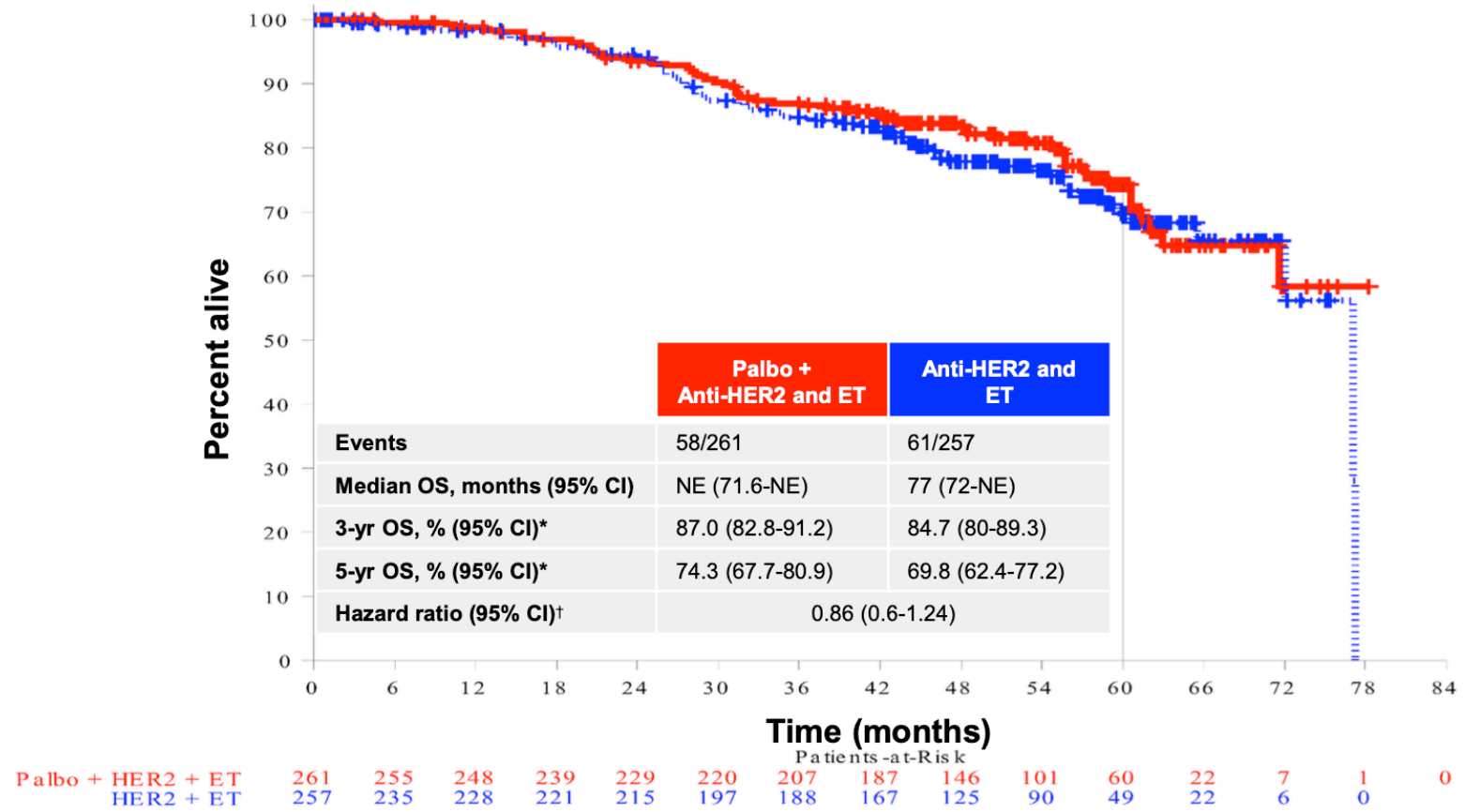
*Factors used in stratified analyses.
CR=Complete Response; Palbo=palbociclib; PR=Partial Response; SD=Stable Disease

Secondary Endpoints: ORR and CBR (Investigator-Assessed)





Secondary Endpoint: Overall Survival (Interim Analysis)



	Palbo + Anti-HER2 and ET	Anti-HER2 and ET
Events	58/261	61/257
Median OS, months (95% CI)	NE (71.6-NE)	77 (72-NE)
3-yr OS, % (95% CI)*	87.0 (82.8-91.2)	84.7 (80-89.3)
5-yr OS, % (95% CI)*	74.3 (67.7-80.9)	69.8 (62.4-77.2)
Hazard ratio (95% CI)†	0.86 (0.6-1.24)	

*Kaplan-Meier method.
†Unstratified Cox model.
CI=confidence interval; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; NE=not evaluable; OS=overall survival; palbo=palbociclib.

Adverse Events (Grade ≥2 in ≥10% of Patients)

Adverse Events, n (%)*	**Palbociclib + anti-HER2 and ET (N=261)**			**Anti-HER2 and ET (N=248)**		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Neutropenia	52 (19.9)	165 (63.2)	12 (4.6)	10 (4.0)	11 (4.4)	0 (0.0)
White blood cell count decreased	30 (11.5)	30 (11.5)	1 (0.4)	2 (0.8)	0 (0.0)	0 (0.0)
Fatigue	60 (22.9)	14 (5.4)	0 (0.0)	32 (12.9)	0 (0.0)	0 (0.0)
Stomatitis	45 (17.2)	11 (4.2)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)
Diarrhea	69 (26.4)	29 (11.1)	0 (0.0)	26 (10.5)	4 (1.6)	0 (0.0)
Upper respiratory tract infection	30 (11.5)	1 (0.4)	0 (0.0)	16 (6.5)	0 (0.0)	0 (0.0)
Urinary tract infection	26 (10.0)	2 (0.8)	0 (0.0)	19 (7.7)	1 (0.4)	0 (0.0)
Arthralgia	23 (8.8)	4 (1.5)	0 (0.0)	44 (17.7)	3 (1.2)	0 (0.0)
Ejection fraction decreased	22 (8.4)	1 (0.4)	0 (0.0)	21 (8.5)	8 (3.2)	0 (0.0)
Cardiac heart failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)

- The incidence of grade ≥4 adverse events regardless of treatment attribution was similar across study arms (12.3% vs 8.9% for palbociclib-containing arm vs control; *P*=0.21)
- Treatment discontinuation due to AEs were reported in 14 (7.5%) of patients in the palbociclib arm
- No treatment-related deaths were reported in either arm of the study

*Adverse events were assessed per Common Terminology Criteria for Adverse Events, version 4.0 regardless of treatment attribution. Stomatitis, mouth ulceration, mucosal inflammation, and mucositis were assessed as medical concepts using grouped terms. Fatigue and asthenia were assessed as medical concepts using grouped terms. Cardiac safety data were also included in the table above. AE=adverse events.

Conclusions

- Our results reinforce the strong scientific rationale for overcoming resistance to anti-HER2 therapy and endocrine therapy by adding CDK4/6 inhibition

- The addition of palbociclib to anti-HER2 and endocrine therapy demonstrated a statistically significant improvement in PFS in patients diagnosed with HR+,HER2+ advanced breast cancer in the first-line metastatic setting

- Palbociclib added to anti-HER2 and endocrine therapy had a manageable toxicity profile and without new safety signals

Implications to Clinical Practice

- The AFT-38 PATINA phase III study demonstrates a **clinically meaningful** improvement in PFS among patients diagnosed with HR+,HER2+ breast cancer
  - Median PFS increased from 29.1 to 44.3 months (Δ15.2 months)
  - Manageable toxicity

Palbociclib added to anti-HER2 and endocrine therapy may represent a new standard of care for patients diagnosed with HR+,HER2+ advanced breast cancer

What is the future of treatment of Her2+ breast cancer

The paradigm of treatment of ER+ / Her2+ early stage and metastatic breast cancer is now more nuanced and in the future.

Thank you

Allegheny Health Network