What's new for HER2 positive Early Breast Cancer?

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- Review of recent clinical trial results of HER2 positive EBC

  - Escalation : KATHERINE

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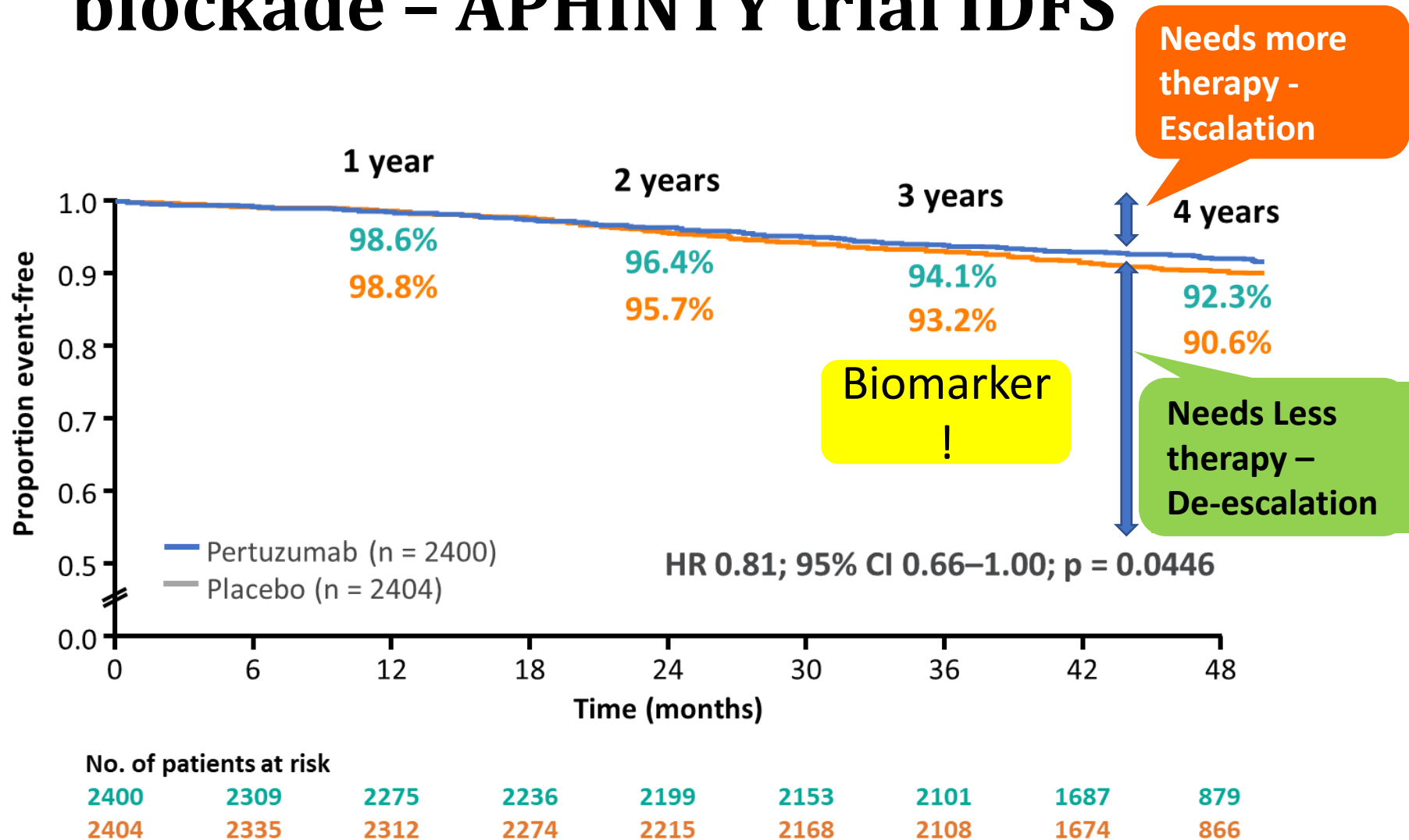# HER2 positive early breast cancer

• HR of relapse in patients with biopsy proven stage Ⅰ~Ⅲ breast cancer : improvement in HER2+ patients most striking
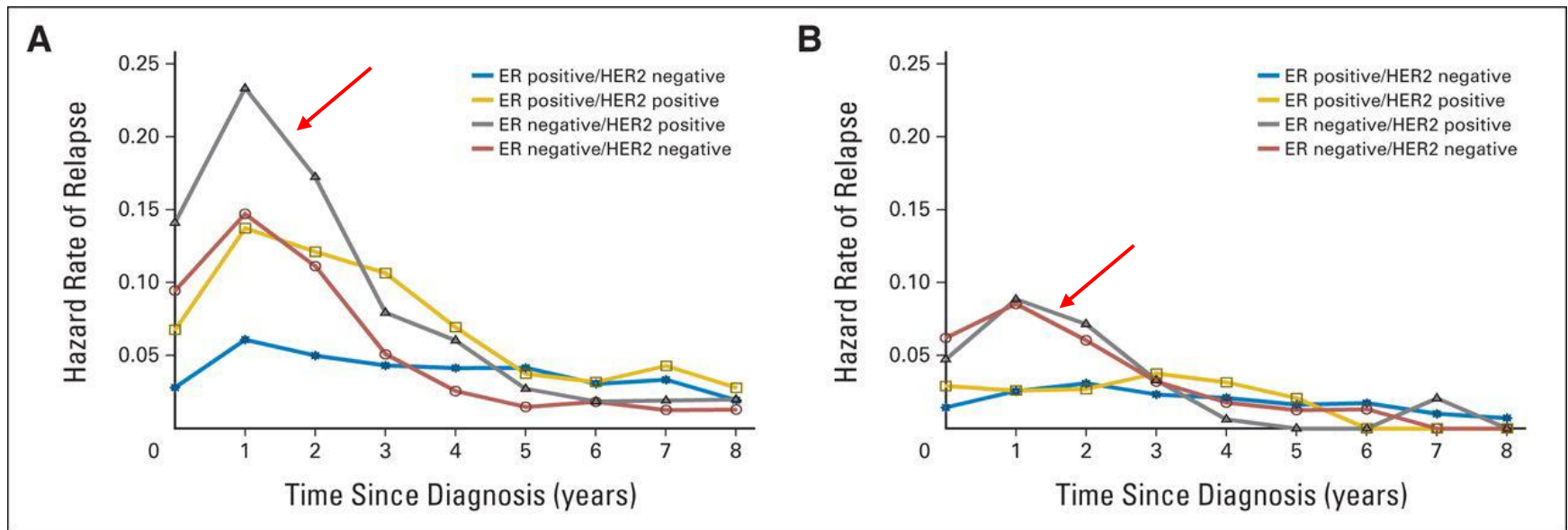
Between 1986 and 1992

Between 2004 and 2008

Cossetti RJ, et al. J Clin Oncol. 2015;33:65-73.

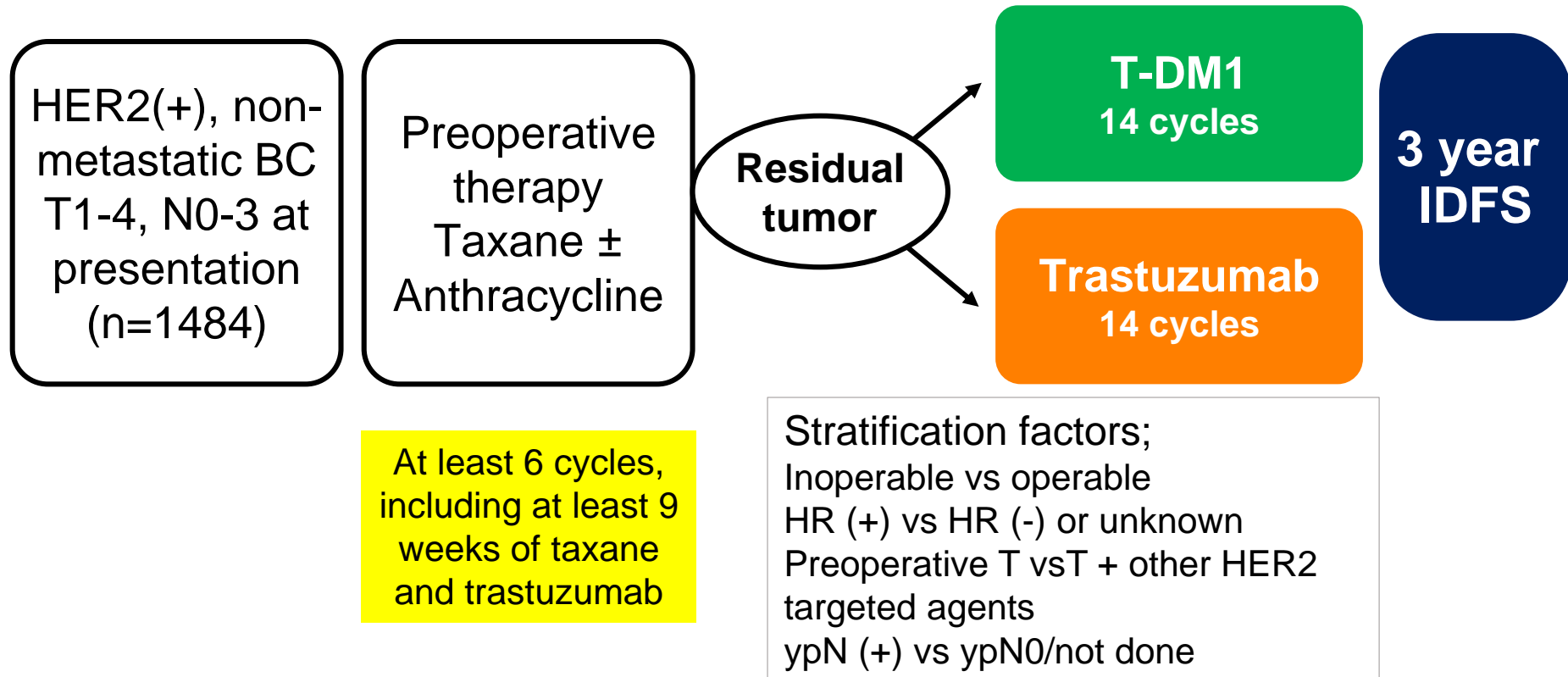# Even better outcome with dual blockade – APHINTY trial IDFS

non-pCR in HER2 positive BC
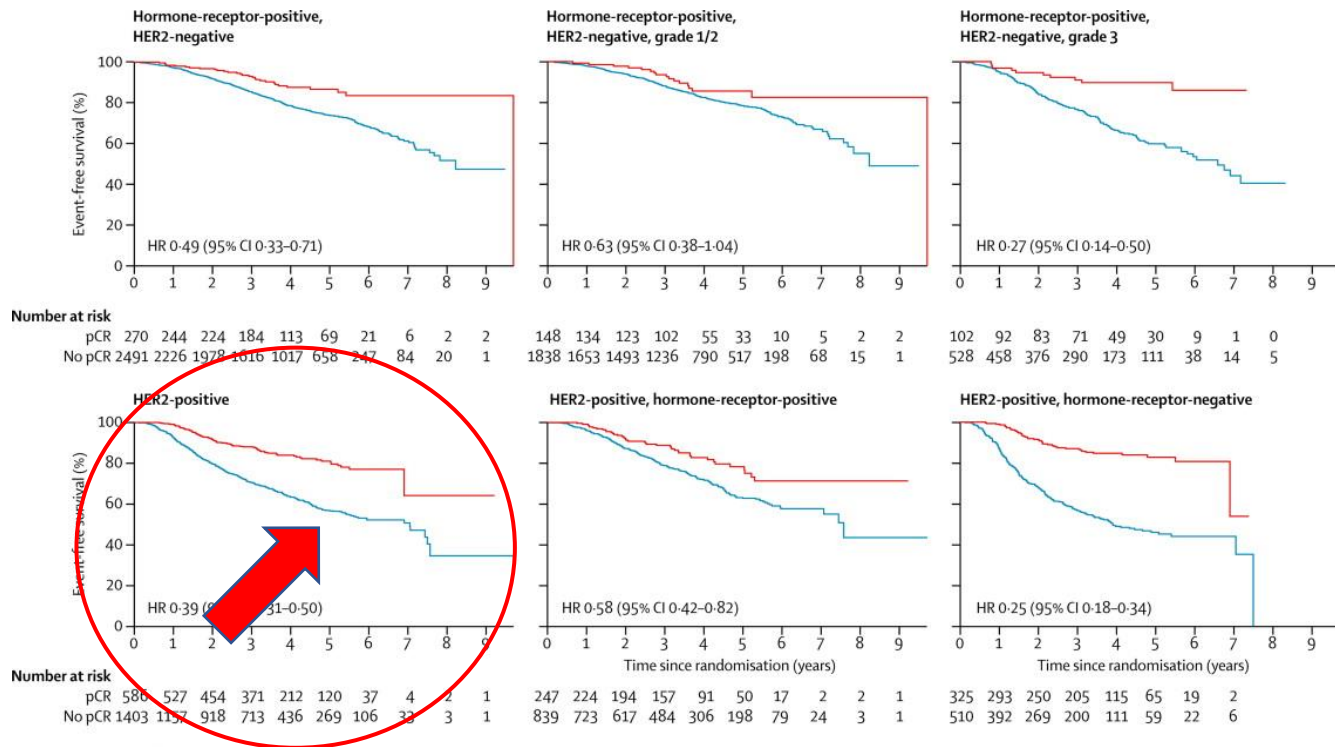
Association between pCR and long term outcomes strongest in TNBC & HER2+ BC who received trastuzumab
HR: 0.39 (95% CI: 0.31-0.50) : poor prognosis with non-pCR pts

Cortazar P et al, Lancet 2014;384: 164–72

Katherine : Phase III adjuvant study

HER2(+), non-metastatic BC T1-4, N0-3 at presentation (n=1484)

Preoperative therapy Taxane ± Anthracycline

Residual tumor

T-DM1
14 cycles

Trastuzumab
14 cycles

3 year IDFS

At least 6 cycles, including at least 9 weeks of taxane and trastuzumab

Stratification factors;
Inoperable vs operable
HR (+) vs HR (-) or unknown
Preoperative T vsT + other HER2 targeted agents
ypN (+) vs ypN0/not done

von Minckwitz G, et al. N Eng J Med 2018

Baseline demographics & clinical characteristics

	Trastuzumab Group	T-DM1 Group
Characteristic	N=743	N=743
Median Age (range) - yr	49 (23-80)	49 (24-79)
Clinical stage at presentation – no of pts (%)		
Inoperable breast cancer	190 (25.6)	185 (24.9)
Operable breast cancer	553 (74.4)	558 975.1)
HR status – no of patients (%)		
ER negative and PR negative	203 (27.3)	209 (28.1)
ER positive, PR positive or both	540 (71.7)	534 (71.9)
Previous use of anthracyclines – no of pts (%)	564 (75.9)	579 (77.9)
Neoadjuvant HER2 targeted therapy – no of pts (%)		
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)

KATHERINE: Invasive DFS
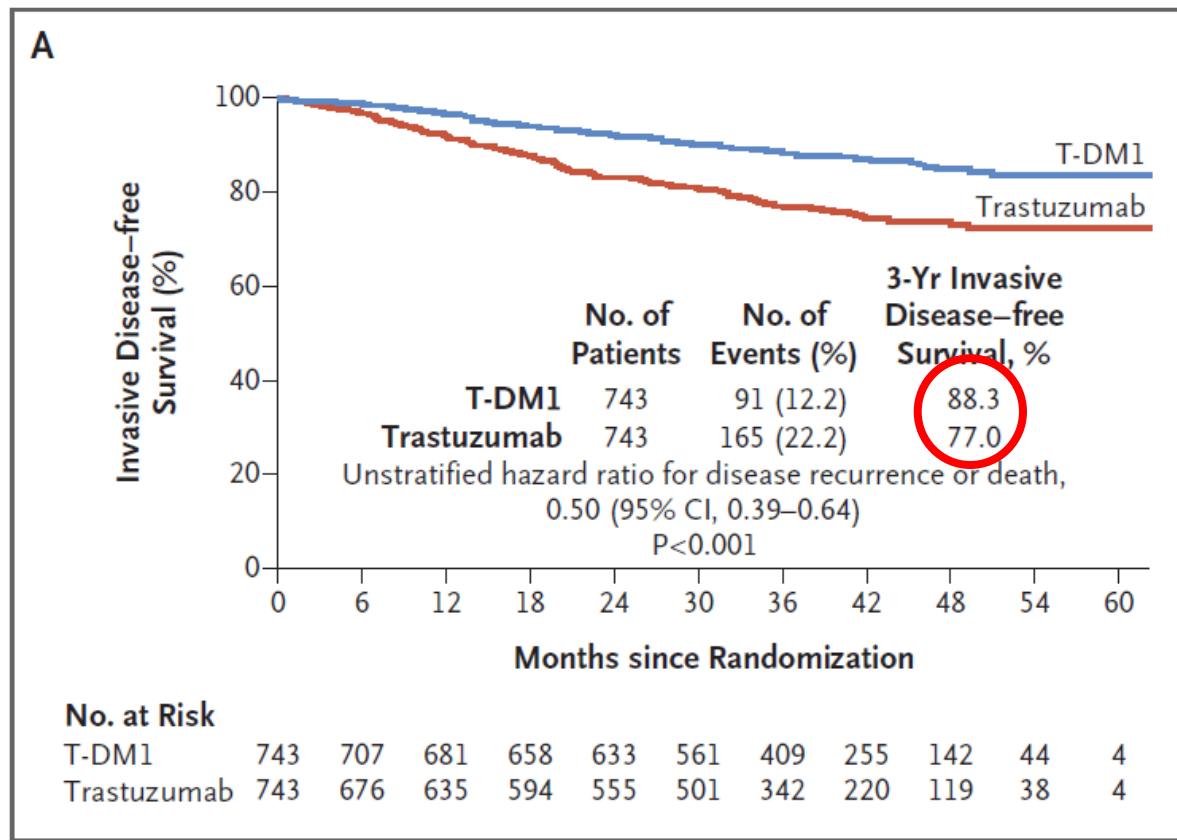
First IDFS Event, %	T-DM1	T
Any	12.2	22.2
Distant recurrence	10.5*	15.9†
Locoregional recurrence	1.1	4.6
Contralateral BC	0.4	1.3
Death without prior event	0.3	0.4
CNS event	5.9	4.3

HR : 0.50 (95% CI: 0.39-0.64; P < 0.001)

Subgroup analysis of IDFS

Subgroup	T-DM1	Trastuzumab	Hazard Ratio for Invasive-Disease Event (95% CI)		3-Yr Invasive Disease–free Survival Rate	
					T-DM1	Trastuzumab
	no. of patients with an invasive-disease event/total no.				%	
All patients	91/743	165/743		0.50 (0.39–0.64)	88.3	77.0
Age group						
<40 yr	20/143	37/153		0.50 (0.29–0.86)	86.5	74.9
40–64 yr	64/542	113/522		0.49 (0.36–0.67)	88.8	77.1
≥65 yr	7/58	15/68		0.55 (0.22–1.34)	87.4	81.1
Clinical stage at presentation						
Inoperable breast cancer	42/185	70/190		0.54 (0.37–0.80)	76.0	60.2
Operable breast cancer	49/558	95/553		0.47 (0.33–0.66)	92.3	82.8
Hormone-receptor status						
Negative (ER-negative and progesterone-receptor–negative or unknown)	38/209	61/203		0.50 (0.33–0.74)	82.1	66.6
Positive (ER-positive, progesterone-receptor–positive, or both)	53/534	104/540		0.48 (0.35–0.67)	90.7	80.7
Preoperative HER2-directed therapy						
Trastuzumab alone	78/600	141/596		0.49 (0.37–0.65)	87.7	75.9
Trastuzumab plus additional HER2-directed agent or agents	13/143	24/147		0.54 (0.27–1.06)	90.9	81.8
Pathological nodal status after preoperative therapy						
Node-positive	62/343	103/346		0.52 (0.38–0.71)	83.0	67.7
Node-negative or NE	29/400	62/397		0.44 (0.28–0.68)	92.8	84.6
Primary tumor stage at definitive surgery						
ypT0, ypT1a, ypT1b, ypT1mic, ypTis	40/331	52/306		0.66 (0.44–1.00)	88.3	83.6
ypT1, ypT1c	14/175	42/184		0.34 (0.19–0.62)	91.9	75.9
ypT2	25/174	44/185		0.50 (0.31–0.82)	88.3	74.3
ypT3	9/51	21/57		0.40 (0.18–0.88)	79.8	61.1
ypT4	3/12	6/11		0.29 (0.07–1.17)	70.0	30.0
Regional lymph-node stage at definitive surgery						
ypN0	28/344	56/335		0.46 (0.30–0.73)	91.9	83.9
ypN1	29/220	50/213		0.49 (0.31–0.78)	88.9	75.8
ypN2	16/86	38/103		0.43 (0.24–0.77)	81.1	58.2
ypN3	17/37	15/30		0.71 (0.35–1.42)	52.0	40.6
ypNX	1/56	6/62		0.17 (0.02–1.38)	98.1	88.7

0.20   0.50   1.00   2.00   5.00

T-DM1 Better ← → Trastuzumab Better

Risk of first invasive-disease event by neoadjuvant HER2-targeted therapy in the ITT population

%

Legend: ■ Trastuzumab ■ T-DM1

No prior pertuzumab
- Trastuzumab: 23.7
- T-DM1: 13

Unstratified HR = 0.489
(95% CI, 0.371-0.645)

Prior pertuzumab
- Trastuzumab: 17.3
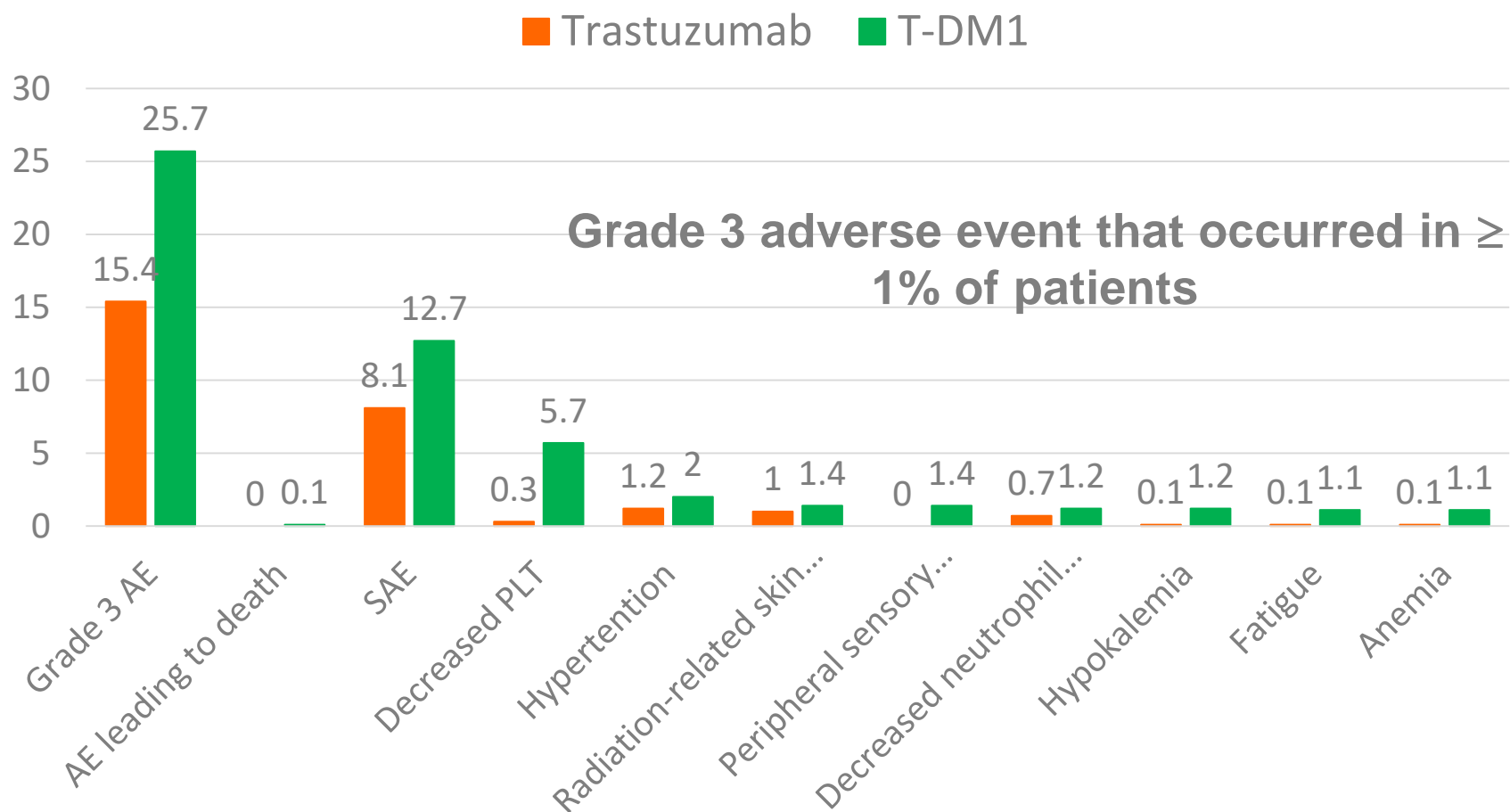- T-DM1: 9

Unstratified HR = 0.498
(95% CI, 0.249-0.995)
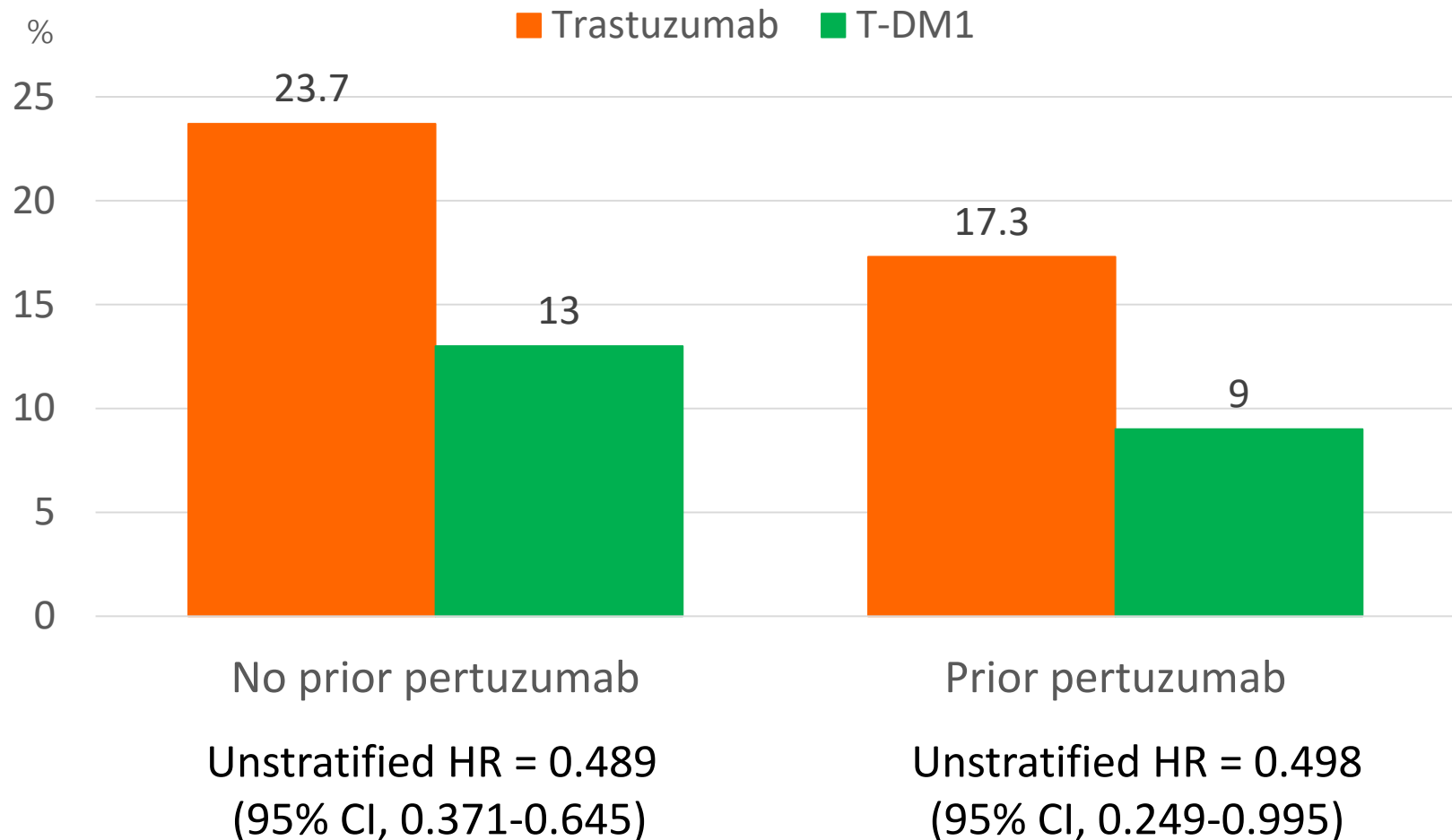
Secondary endpoints DRFS and OS
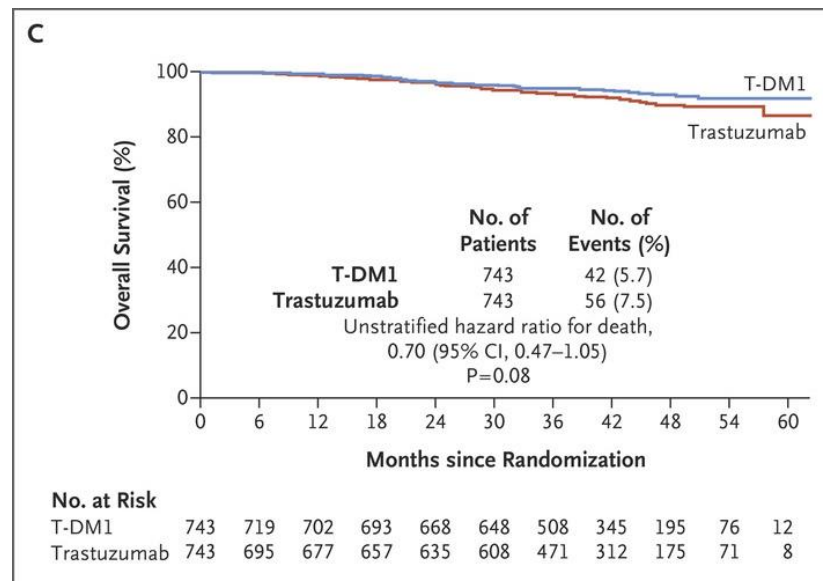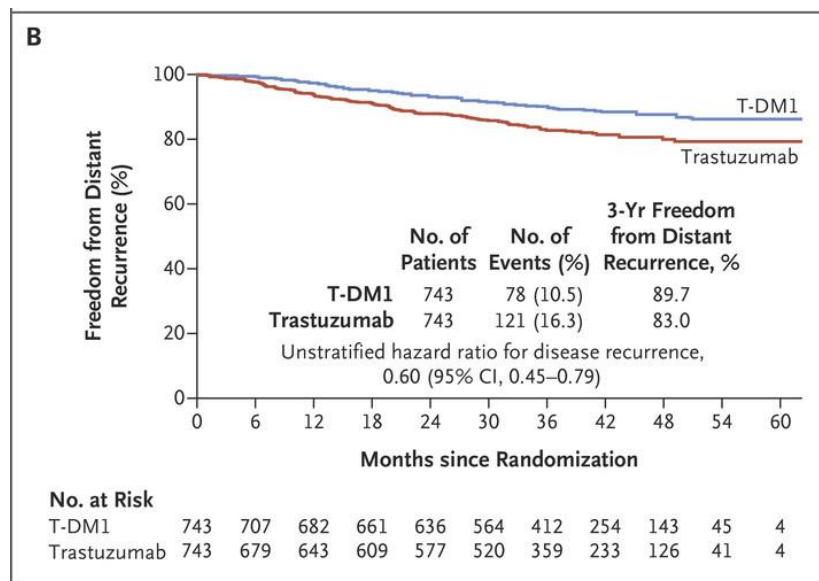
- HR : 0.60 (95% CI: 0.45-0.79)

- 3 year freedom from recurrence: 89.7% vs 83%

- HR: 0.70 (95% CI: 0.47–1.05)

Summary of AEs in the safety population

von Minckwitz G, et al. N Eng J Med 2018
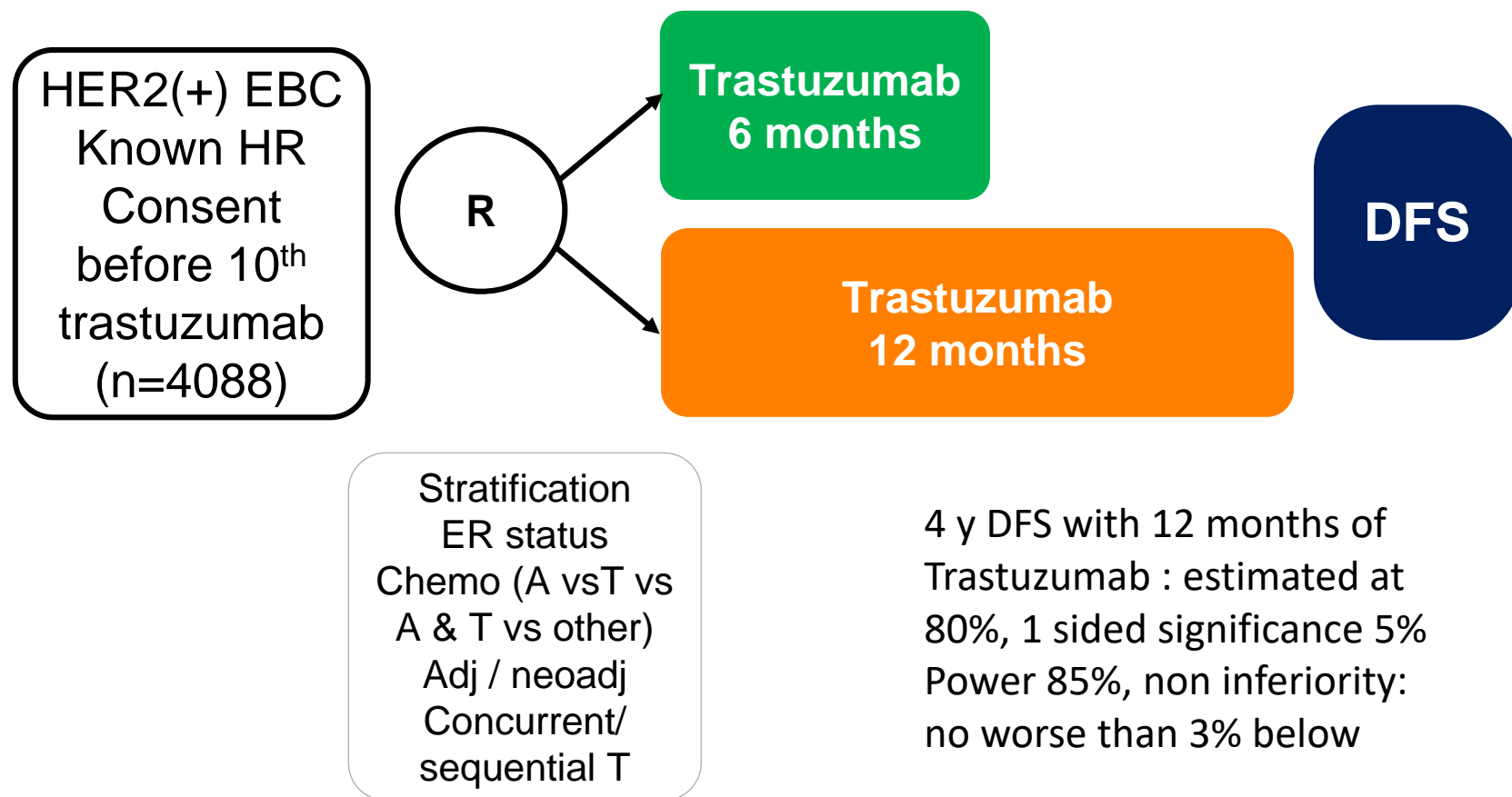
Summary & discussion

- T-DM1 significantly prolonged IDFS compared with trastuzumab in HER2+ EBC with residual invasive disease after neoadjuvant chemotherapy and HER2 targeted therapy
    - HR: 0.50 (95% CI: 0.39-0.64; P < 0.001)
    - Benefit with T-DM1 across all subgroups, including patients with prior pertuzumab in the neoadjuvant setting
- More AEs, SAEs, AE leading to discontinuation but no unexpected safety signals
- Recommended in NCCN guideline : "If HER-2 positive If residual disease: T-DM1 (Category 1) alone for 14 cycles. If ado-trastuzumab emtansine discontinued for toxicity, then trastuzumab (Category 1) ± pertuzumab to complete on year of therapy"

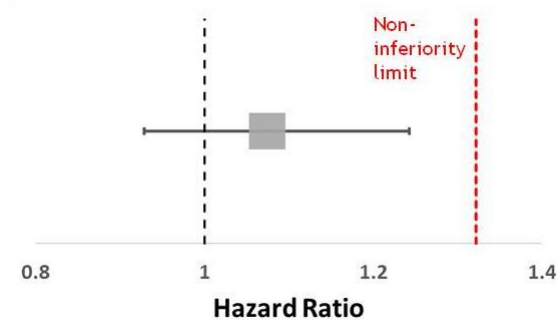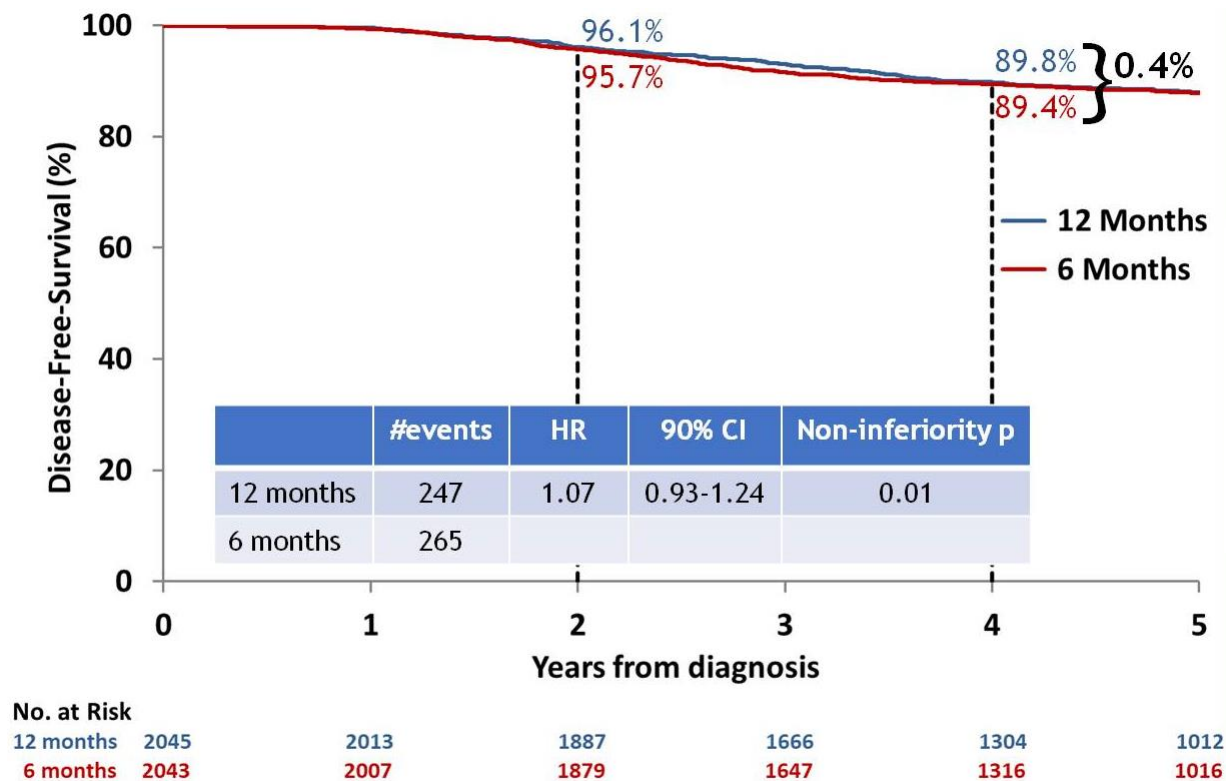# Shorter duration of anti-HER2 treatment

	Chemo Backbone	Duration	N	DFS	HR
PHARE[1]	Investigator choice	6 mos	1690	84.9% (48m)	1.28 (1.05-1.56)
		12 mos	1690	87.8%	
Short-HER[2]	TH#3-FEC#3	9 weeks	626	85.4%	1.15 (0.91-1.46)
	AC/FEC#4-TH#4-H	12 mos	627	87.5%	
SOLD[3]	TH#3-FEC#3	9 wks	1085	88.0% (5y)	1.39
	TH#3-FEC#3-H	12 mos	1089	90.5%	
Hellenic group[4]	ddFEC-T	6 vs 12 months	481	93.3% vs 95.7% (3yr)	1.57 (0.86-2.10)
Persephone[5]	Investigator choice	6 vs 12 months	4000	[?]	[?]

1. Pivot X, et al, Lancet Oncol 2013;14:741-8 2. NCT00629278. 3. SABCS 2017. 4. Mavroudis D, e al. Ann Oncol 2015. 5. NCT00712140

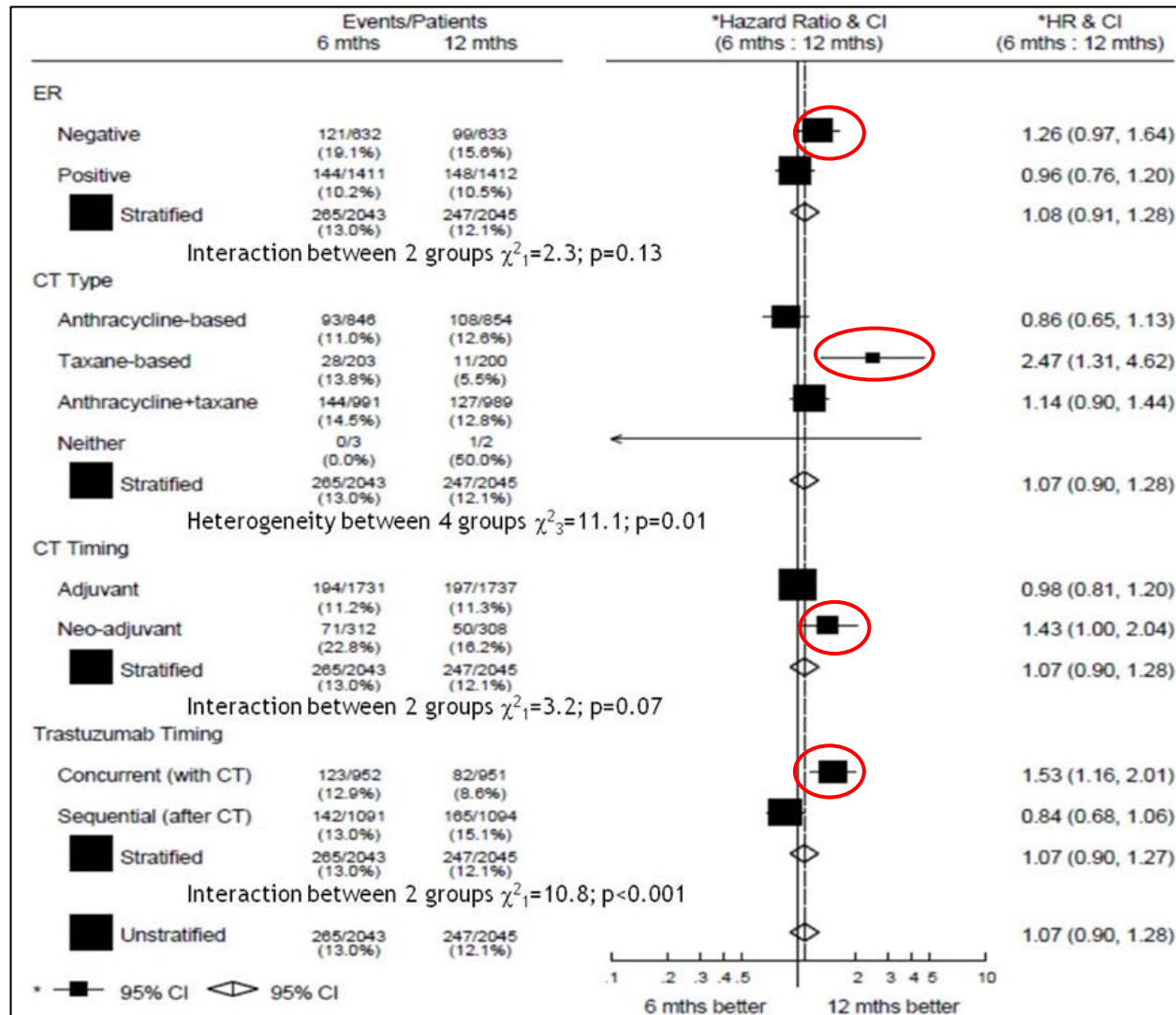# PERSEPHONE : 6 vs 12 mo of adjuvant trastuzumab, non-inferiority trial

HER2(+) EBC
Known HR
Consent
before 10th
trastuzumab
(n=4088)

R

Trastuzumab 6 months

Trastuzumab 12 months

DFS

Stratification
ER status
Chemo (A vsT vs
A & T vs other)
Adj / neoadj
Concurrent/
sequential T

4 y DFS with 12 months of Trastuzumab : estimated at 80%, 1 sided significance 5% Power 85%, non inferiority: no worse than 3% below

Earl H, et al. ASCO 2018

Disease free survival

Earl H, et al. ASCO 2018

DFS : Pre-defined subgroup analysis

	Events/Patients		*Hazard Ratio & CI	*HR & CI
	6 mths	12 mths	(6 mths : 12 mths)	(6 mths : 12 mths)
ER				
Negative	121/632 (19.1%)	99/633 (15.6%)		1.26 (0.97, 1.64)
Positive	144/1411 (10.2%)	148/1412 (10.5%)		0.96 (0.76, 1.20)
■ Stratified	265/2043 (13.0%)	247/2045 (12.1%)		1.08 (0.91, 1.28)
Interaction between 2 groups χ^2_1=2.3; p=0.13				
CT Type				
Anthracycline-based	93/846 (11.0%)	108/854 (12.6%)		0.86 (0.65, 1.13)
Taxane-based	28/203 (13.8%)	11/200 (5.5%)		2.47 (1.31, 4.62)
Anthracycline+taxane	144/991 (14.5%)	127/989 (12.8%)		1.14 (0.90, 1.44)
Neither	0/3 (0.0%)	1/2 (50.0%)		
■ Stratified	265/2043 (13.0%)	247/2045 (12.1%)		1.07 (0.90, 1.28)
Heterogeneity between 4 groups χ^2_3=11.1; p=0.01				
CT Timing				
Adjuvant	194/1731 (11.2%)	197/1737 (11.3%)		0.98 (0.81, 1.20)
Neo-adjuvant	71/312 (22.8%)	50/308 (16.2%)		1.43 (1.00, 2.04)
■ Stratified	265/2043 (13.0%)	247/2045 (12.1%)		1.07 (0.90, 1.28)
Interaction between 2 groups χ^2_1=3.2; p=0.07				
Trastuzumab Timing				
Concurrent (with CT)	123/952 (12.9%)	82/951 (8.6%)		1.53 (1.16, 2.01)
Sequential (after CT)	142/1091 (13.0%)	165/1094 (15.1%)		0.84 (0.68, 1.06)
■ Stratified	265/2043 (13.0%)	247/2045 (12.1%)		1.07 (0.90, 1.27)
Interaction between 2 groups χ^2_1=10.8; p<0.001				
■ Unstratified	265/2043 (13.0%)	247/2045 (12.1%)		1.07 (0.90, 1.28)

* —■— 95% CI   ◇ 95% CI

.1 .2 .3 .4 .5   2 3 4 5 10
6 mths better   12 mths better

ER (-)

taxane based

neo-adjuvant

concurrent

Overall survival

	#events	HR	90% CI	Non-inferiority p
12 months	156	1.14	0.95-1.37	0.0006
6 months	179			

No. at Risk

12 months	2045	2019	1939	1732	1376	106
6 months	2043	2014	1937	1731	1386	106

Earl H, et al. ASCO 2018
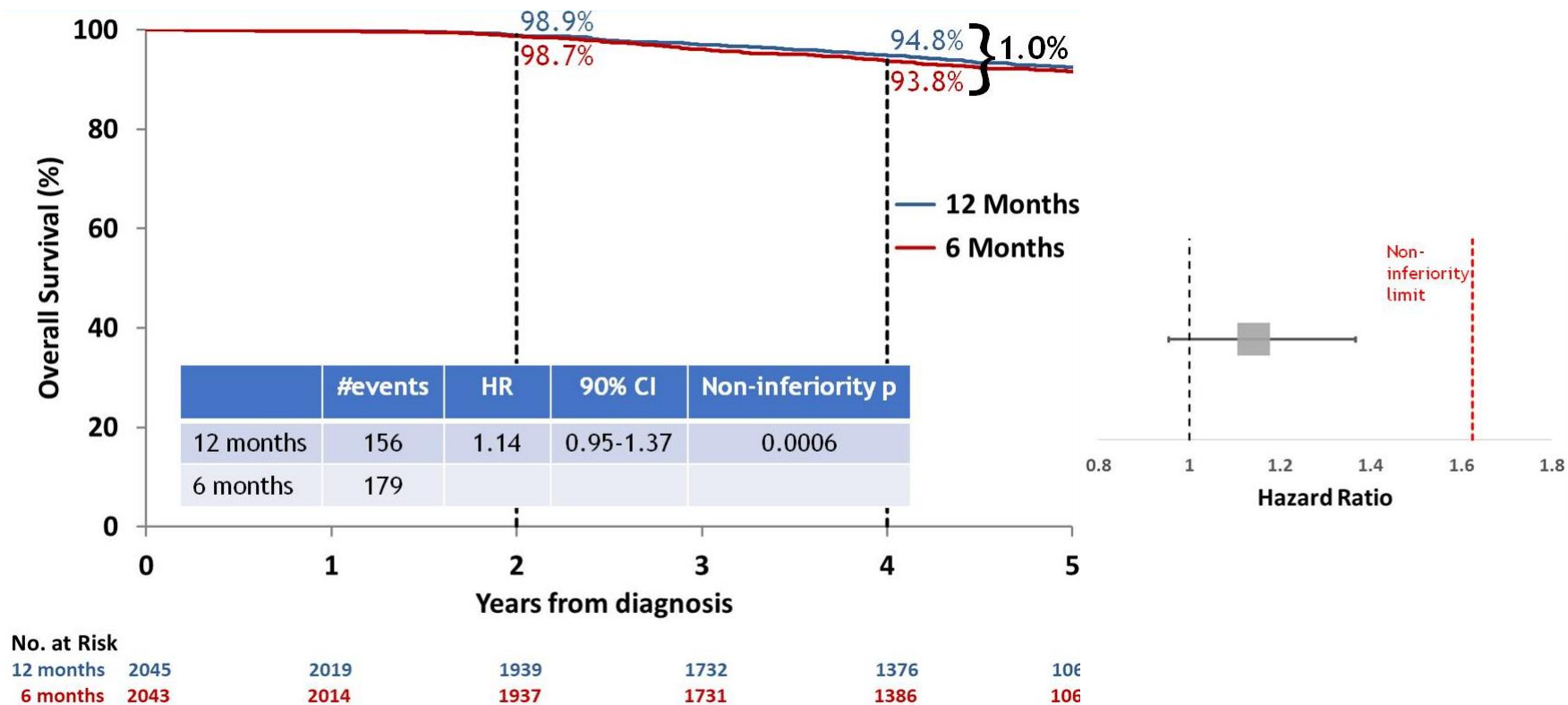
Summary of PERSEPHONE

- 6 months of adjuvant trastuzumab is non-inferior to 12 months (4yr DFS: 89.4% vs 89.8%; HR = 1.07)

- Reduced cardiac & other toxicities, and costs both to patients and healthcare systems

- Valuable results for low-resource countries

Random effects modelling predicted lines and 95%CIs

LVEF (%)

— 12 month patients   - - -6 month patients

MONTHS FROM START OF TRASTUZUMAB
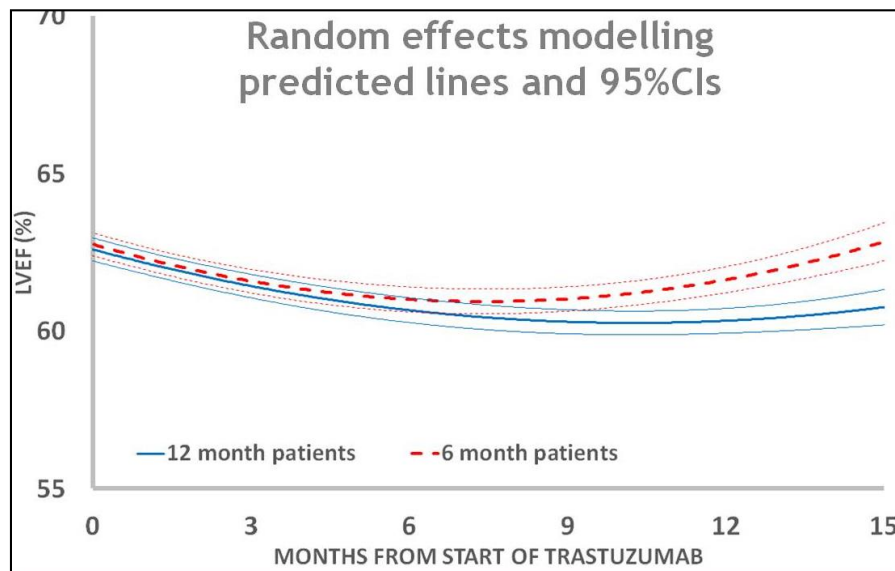
- stopped trastuzumab because of cardiotoxicity: 8% (12mo) vs 4% (6 mo), p < 0.0001

- 6 months group had more rapid recovery of cardiac function

Earl H, BJC 2016

RESPECT : adjuvant trastuzumab monotherapy in older patients

HER2(+) BC 70-80 yrs old Stage1 (pT > 0.5cm), 2A, 2B, 3A (n=274)

R

Trastuzumab

Trastuzumab + chemotherapy

Investigator's choice (PTx, DTx, AC,EC, FEC, CMF, TC, TcbH)

DFS
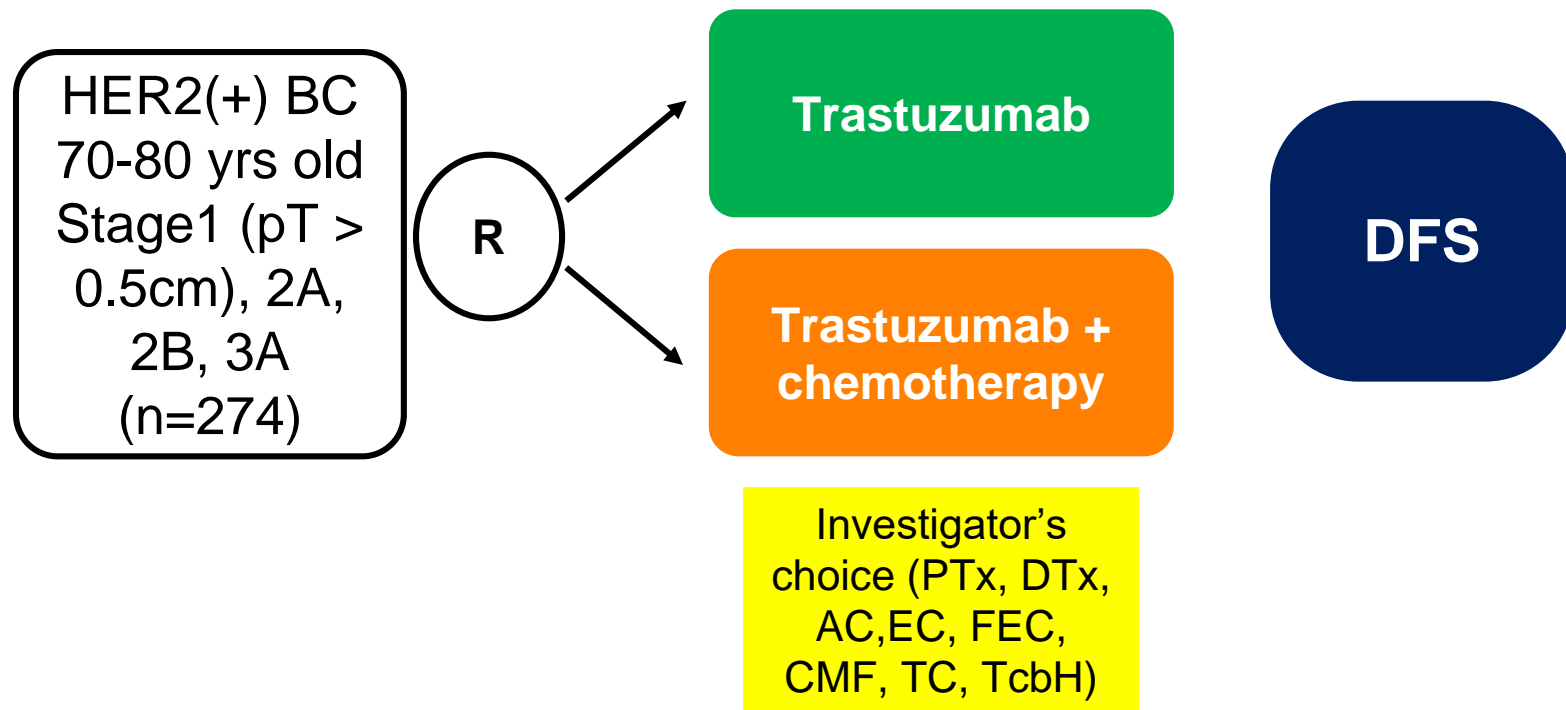
RESPECT
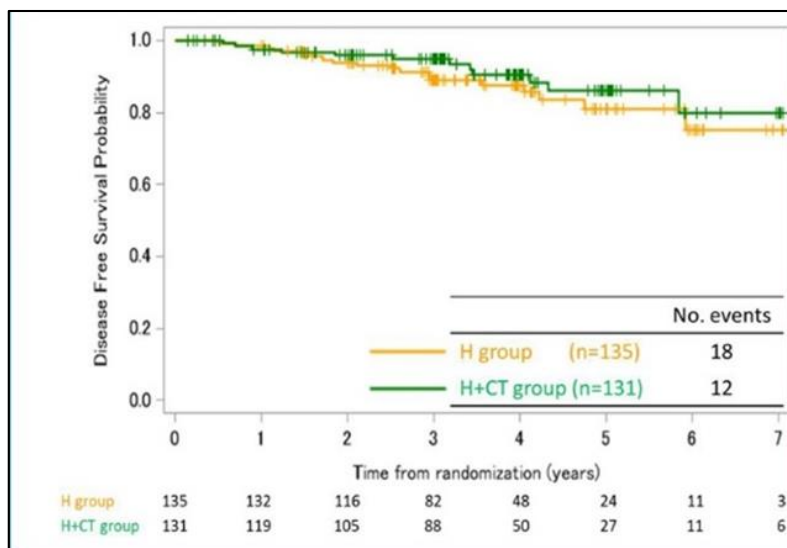
Fig. 2A. DFS (n=266)
DFS at 3 yrs was 94.8% in H+CT group vs 89.2% in H group (HR=1.42; 95% CI, 0.68 to 2.95, P=0.35). The difference in RMST between arms at 3 years was -0.45 months (95% CI, -1.71 to 0.80).
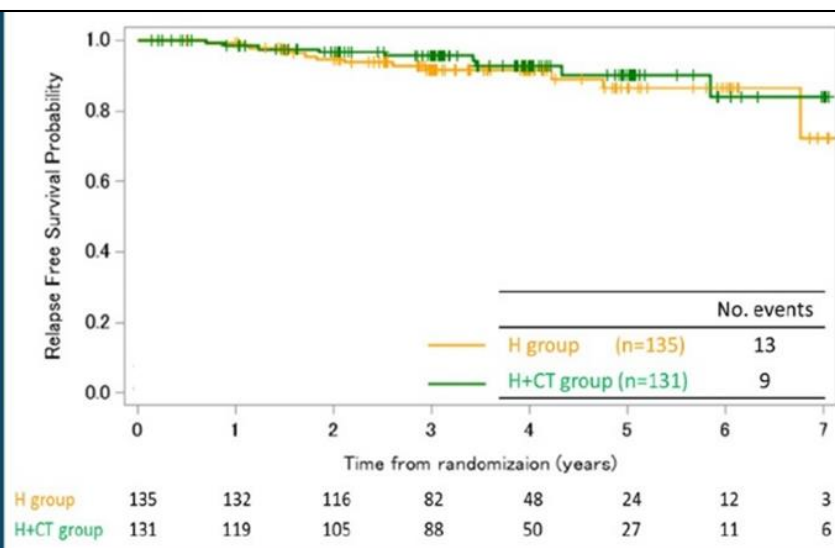
Fig. 2B. RFS (n=266)
RFS at 3 yrs was 95.6% (9 events with 4 deaths) in H+CT group vs 91.7% (13 events with 5 deaths) in H group.
The difference in RMST between arms at 3 years was -0.41 months (95% CI, -1.51 to 0.68).

DFS at 3 yrs : 94.8% in H+CT vs 89.2% in H arm (HR = 1.42; 95% CI, 0.68 to 2.95, P = 0.35). FACT-G score: H: 42.9% vs H+CT: 25.3%, P = 0.021

Sawaki M, et al. 2018 ASCO

RESPECT

- Older patients do benefit from standard treatment

- Attempt of de-escalation does not always succeed

- Inclusion of 'older patients' : not just based on chronologic age

- Still, there are patients who can do very well with even single agent trastuzumab : 3 year DFS 89.2% with trastuzumab alone – need robust biomarker to select candidates for de-escalation
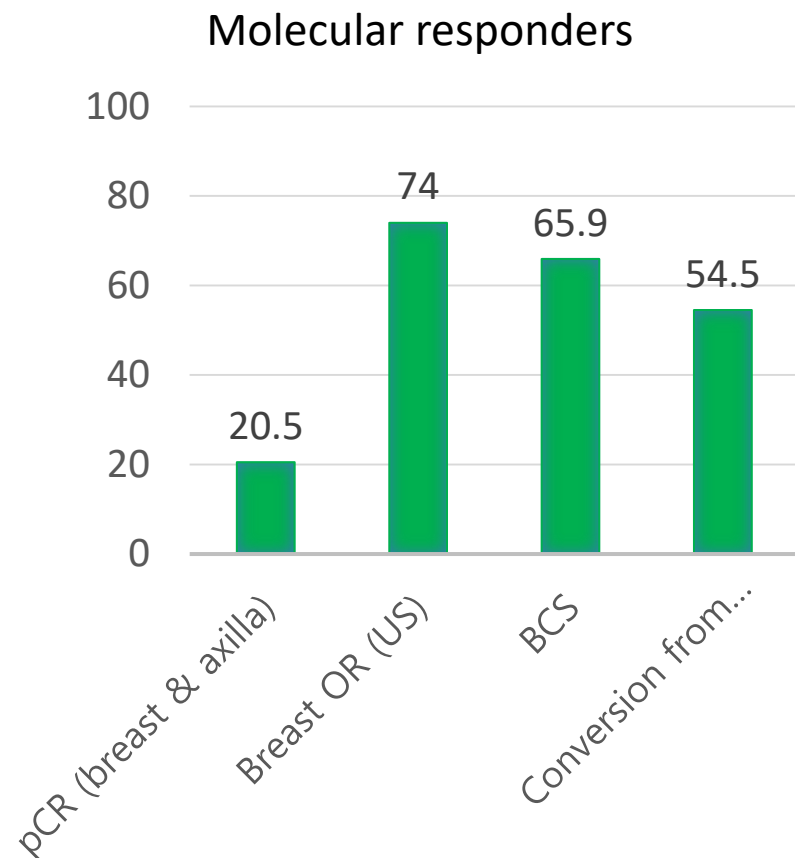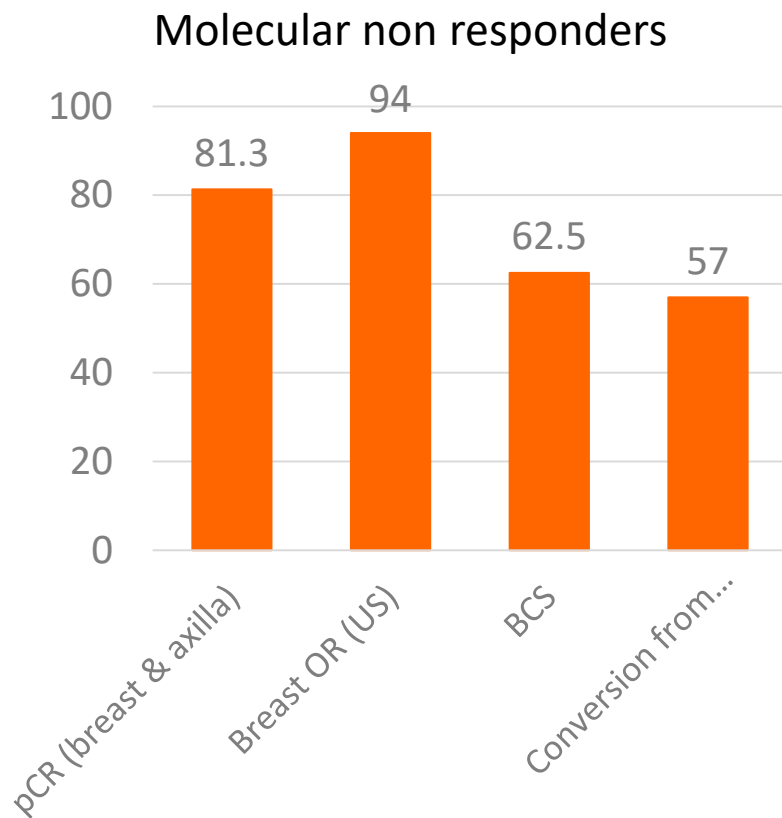
CALGB 49907: CMF or AC vs capecitabine in older women $\geq$ 65 y

Muss H et al, N Engl J Med 2009; 360:2055-2065
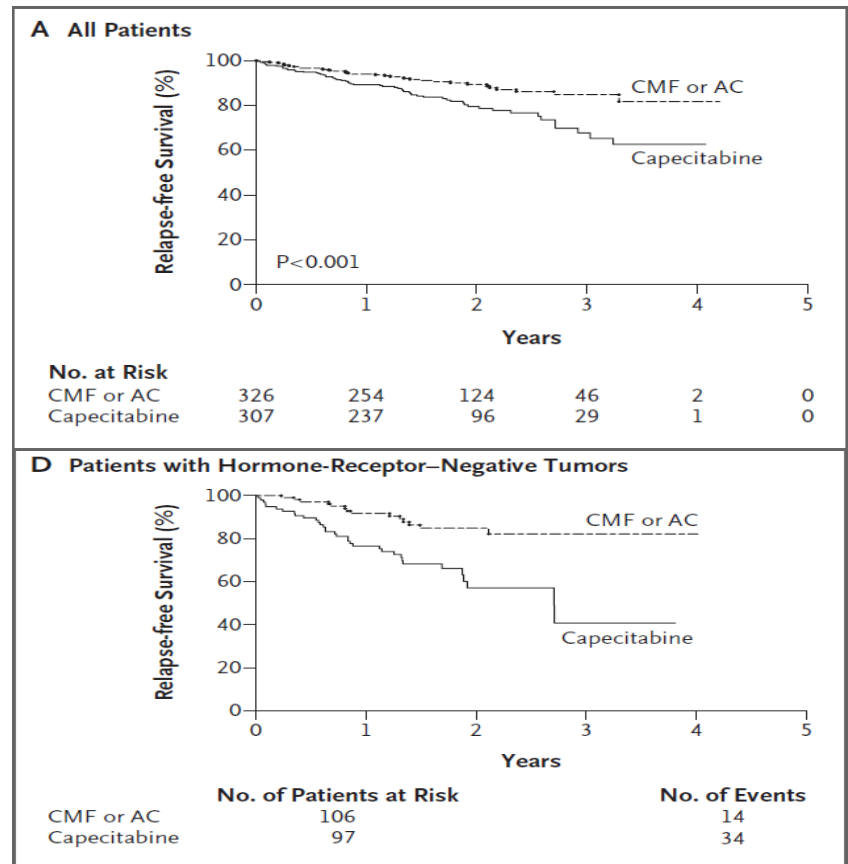
PerELISA neoadjuvant study
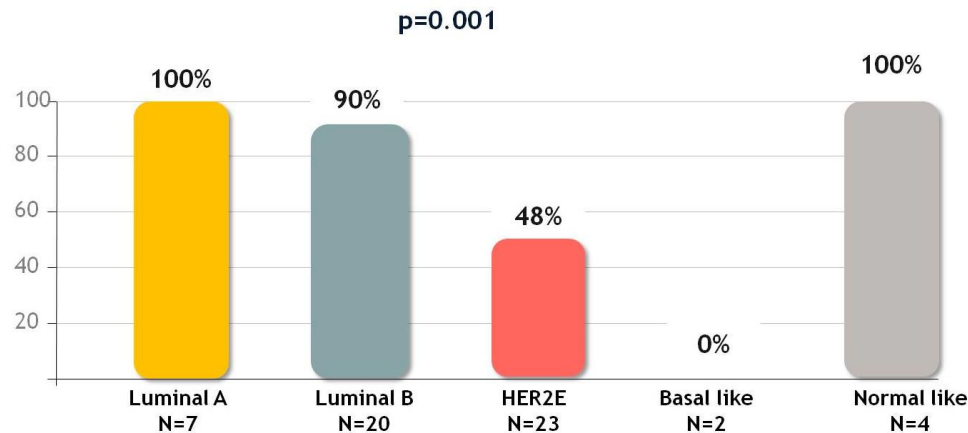
- Histologically confirmed, IDC, stage Ⅱ-ⅢA, HR positive (ER ≥ 10%), HER2 positive, postmenopausal, LVEF within normal range, adequate organ function)


Diagnostic Core Biopsy

2 wks

Letrozole

Core needle biopsy for molecular response

Molecular responders

Molecular non-responders

Letrozole Trastuzumab Pertuzumab

Pacliataxel Trastuzumab Pertuzumab

pCR

Molecular response: ↓ Ki67 > 20% from baseline

Guarneri V, et al. 2018 ASCO
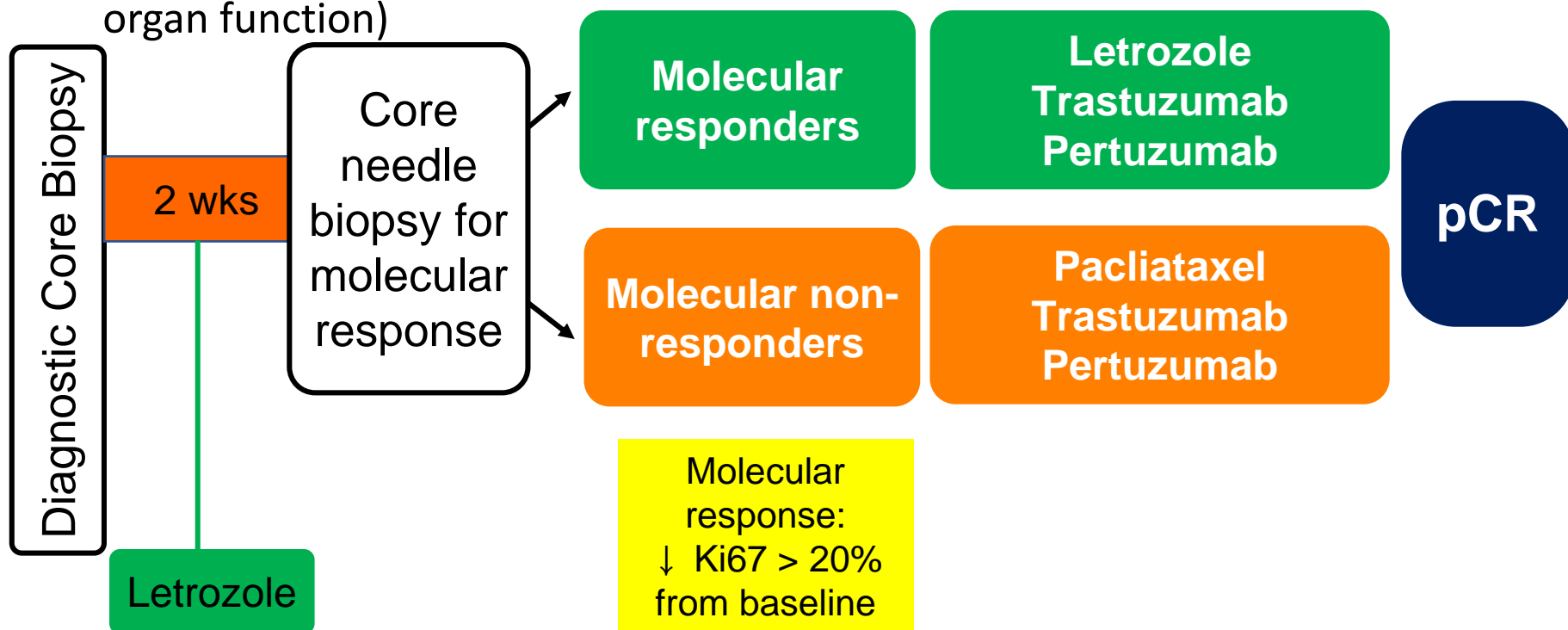
Outcome : pCR according to molecular response

Guarneri V, et al. 2018 ASCO

PAM50 and molecular response

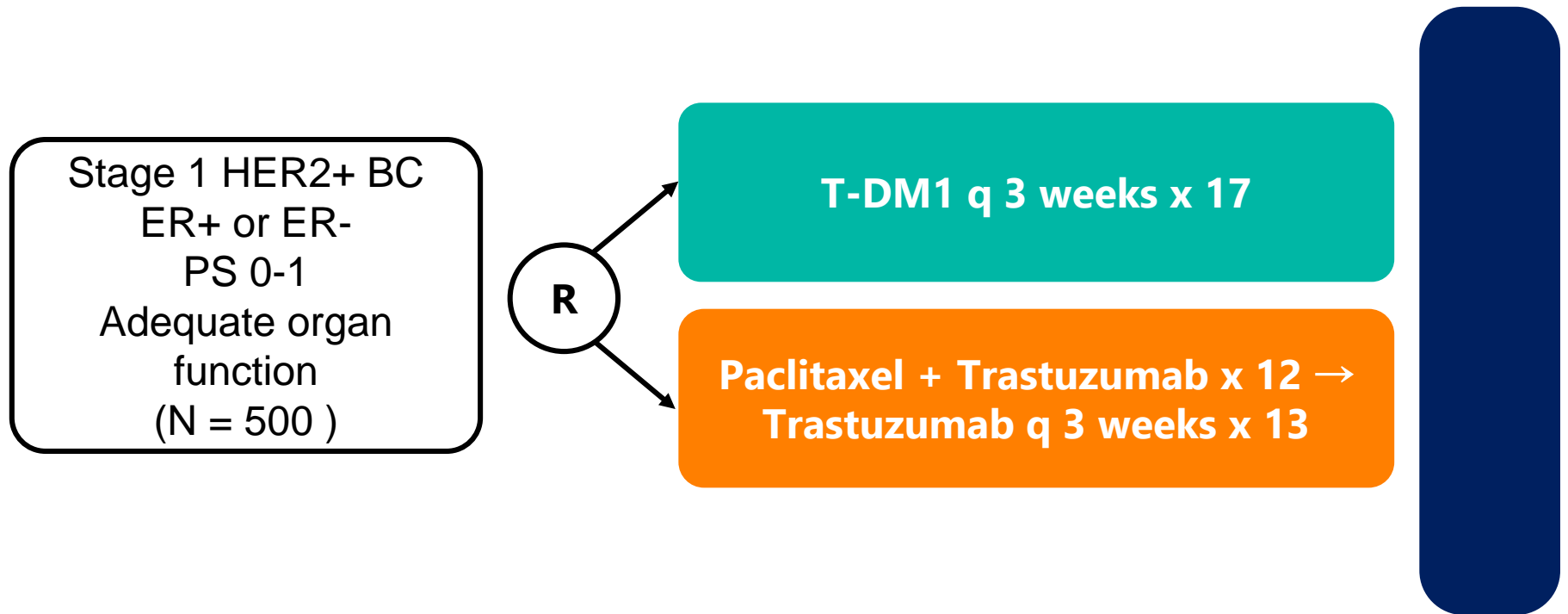PAM 50 analysis and molecular response
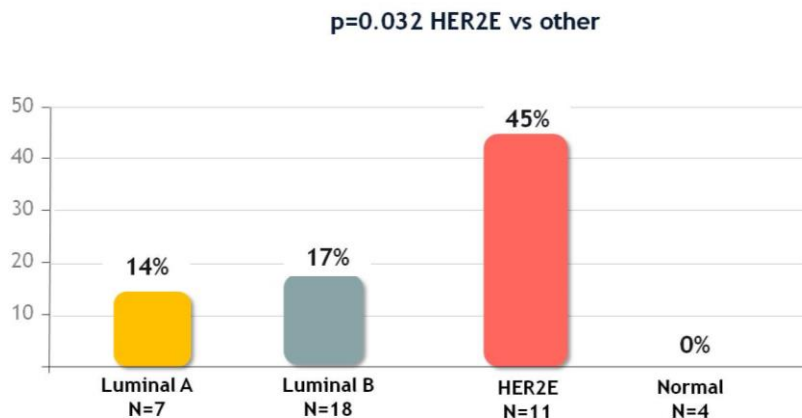
PAM 50 and pCR: molecular responders
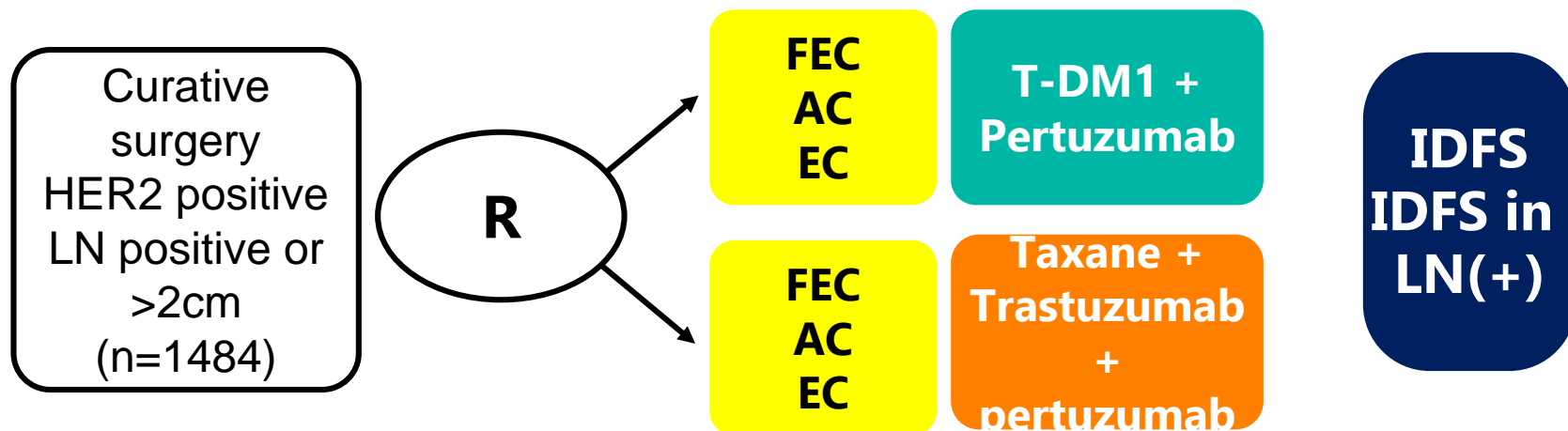
Guarneri V, et al. 2018 ASCO

Summary of PerELISA trial

- In molecular responding patients, letrozole + trastuzumab and pertuzumab resulted in 20% breast and axillary LN pCR

- Baseline TILs and PIK3CA mutational status were not associated with molecular response or pCR

- Intrinsic subtype by PAM50 was significantly associated with molecular response and response with pCR
  - HER2 enriched subtype further enriches for patients most likely benefit from the de-escalated approach.

Guarneri V, et al. 2018 ASCO

ATEMPT

Stage 1 HER2+ BC
ER+ or ER-
PS 0-1
Adequate organ
function
(N = 500)

R

T-DM1 q 3 weeks x 17

**Paclitaxel + Trastuzumab x 12 →
Trastuzumab q 3 weeks x 13**

KAITLIN

```
Curative surgery
HER2 positive
LN positive or
>2cm
(n=1484)
```
→ R →

FEC AC EC → **T-DM1 + Pertuzumab**

FEC AC EC → **Taxane + Trastuzumab + pertuzumab**

**IDFS
IDFS in
LN(+)**

Summary

- Excellent outcome of HER2 positive EBC with recent study results
  - Addition of adjuvant pertuzumab, extension of neratinib
  - T-DM1 in patients with residual invasive disease after neoadjuvant treatment
- Still escalation and de-escalation strategies are needed to further improve outcome & reduce toxicities in the treatment of HER2+ EBC
- 1 year of adjuvant anti-HER2 treatment still standard but 6 months treatment can be valuable option for resource limited settings & to reduce cardiotoxicities
- Biomarker to reliably identify those who need de-escalation strategies (such as endocrine plus anti-HER2 therapy or anti-HER2 therapy only) needed