Memorial Sloan Kettering
Cancer Center

Treatment of Early-Stage HER2+ Breast Cancer

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Memorial Sloan Kettering Cancer Center

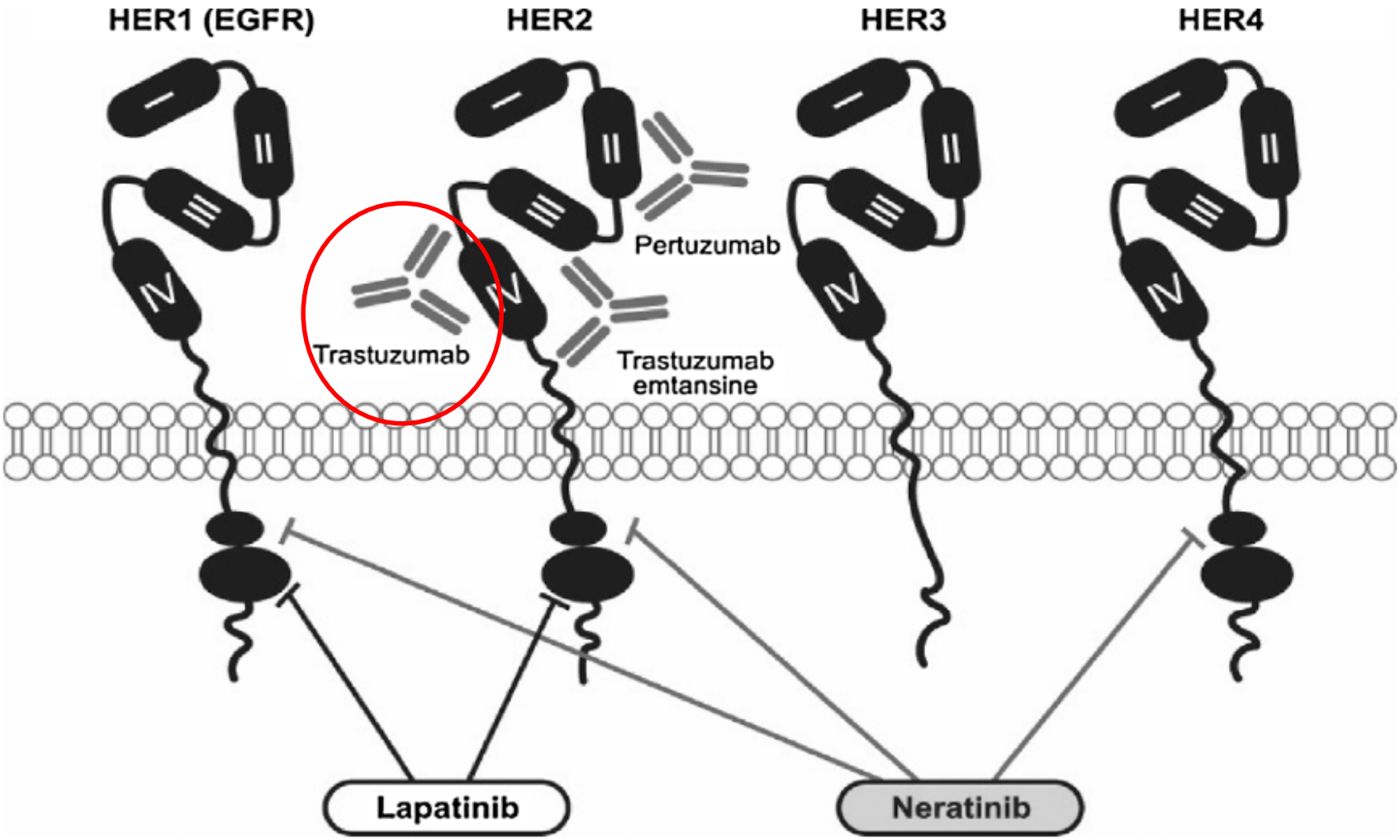
Disclosures

- I have research funding from
  - Roche/Genentech
  - PUMA

Objectives

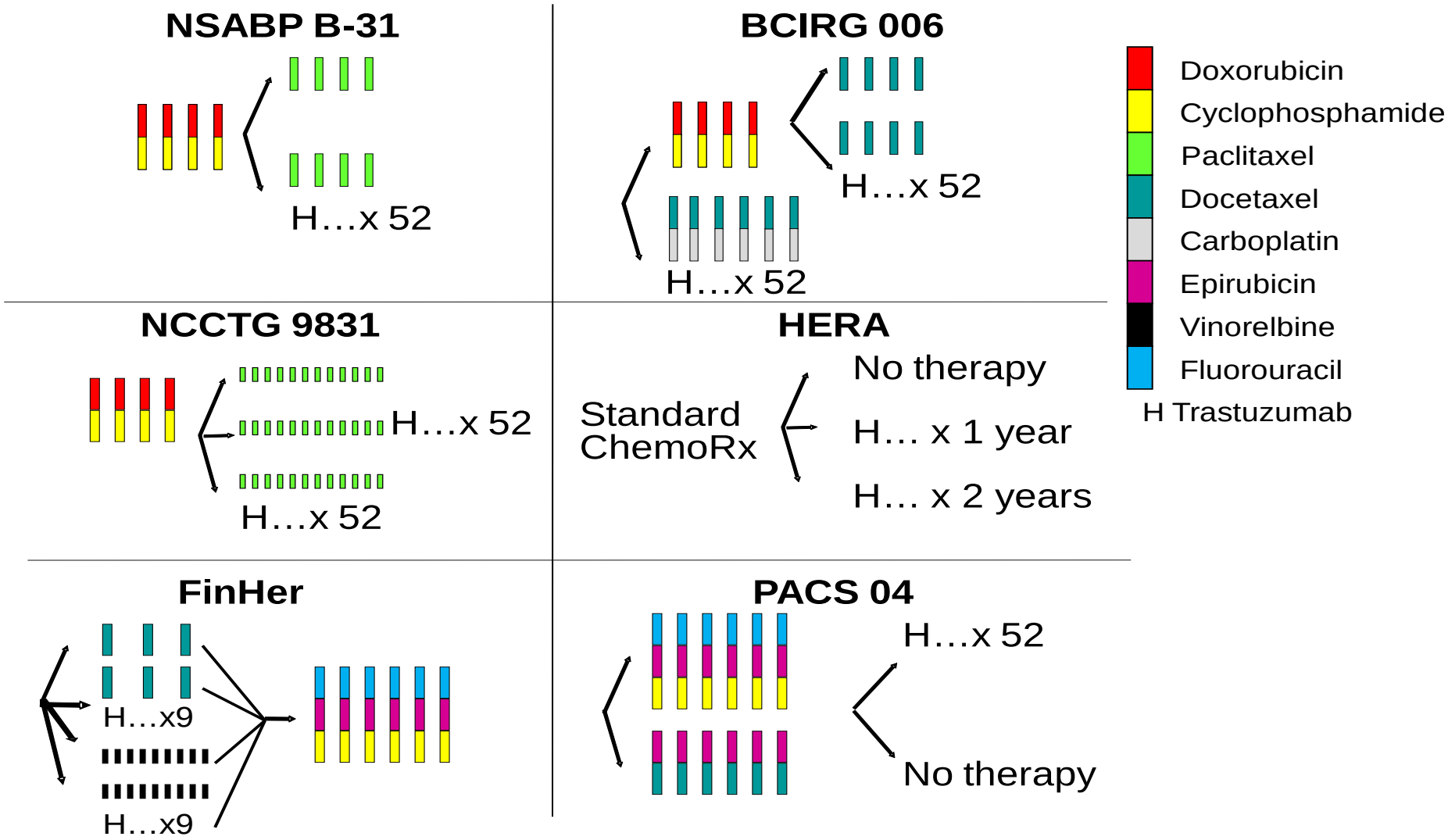
- Trastuzumab
  - Historical adjuvant data
- Neoadjuvant
  - NEOSPHERE
  - TRYPHAENA
  - BERENICE
- Adjuvant
  - APHINITY
  - ExteNET
  - APT, US Oncology

Trastuzumab



Baselga et al. Crit Rev In Onc/Hem 2017

Trastuzumab in Adjuvant Setting



Persistent Benefit of Adjuvant Trastuzumab

Study	Rx	Med FU	DFS	OS
HERA [1] (x-over 52%)	Chemo Chemo → H x 1 yr Chemo → H x 2 yr	11yrs	63% 69% 69%	73% 79% 80%
B-31[2,3] (x-over 20%)	ACT AC → TH→ H	8.4 yrs*	62.2% 73.7%	75.2% 84.0%
N 9831[2,3] (x-over 20%)	AC → w T AC → w TH→ H AC → w T→ H	8.4 yrs*	62.2% 73.7%	75.2% 84.0%
BCIRG 006 [4] (x-over 3.1%)	AC → D DCbH→ H AC → DH→ H	10 yrs	67.9% 73.0% 74.6%	78.7% 83.3% 85.9%

A=doxorubicin, C=cyclophosphamide
T=pac;itaxel, D=docetaxel, Cb=carboplatin
H=trastuzumab, N=not reported
*Combined analysis of B-31/N9831

1. Cameon et al. Lancet 2017
2. Perez et al. JCO 2014
3. Slamon et al. SABC 2015

Adjuvant Trastuzumab, Asymptomatic LVEF Decline and Heart Failure, and Treatment Interruption

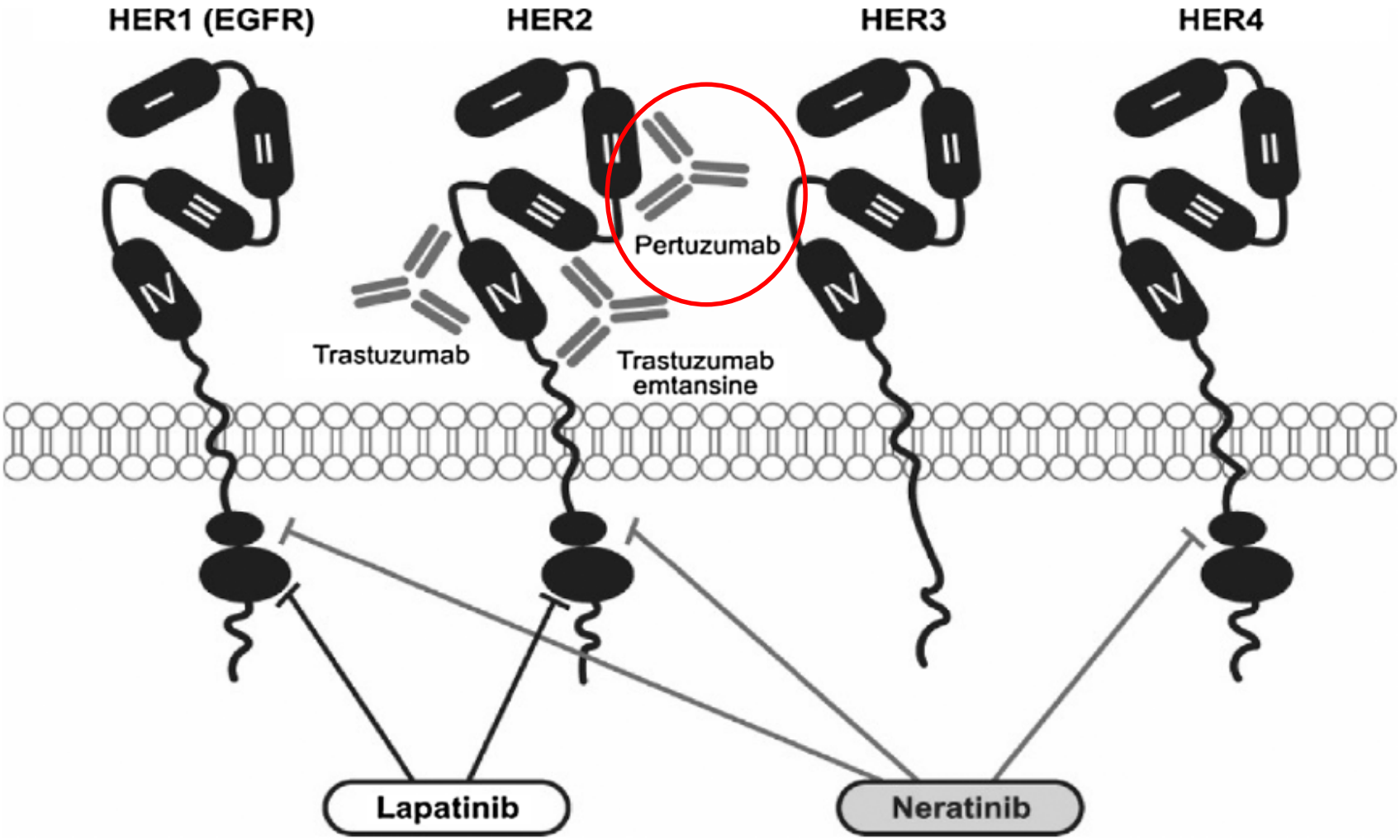
Study	Rx	Med FU (yrs)	Asx LVEF ↓≥ 10% to < 50%	NYHA Class III-IV	Med FU (yrs)	NYHA Class III-IV	Trastuzumab Discontinuation-Cardiac causes
HERA [1-2]	Chemo Chemo → H x 1 yr Chemo → H x 2 yr	3.6	0.9% 4.1% 7.2%	0.0 % 0.8 % NR	11	0.1 % 1.0 % 1.0 %	NA 5.2% 9.4%
B-31 [3-5]	ACT AC → TH→ H	2	NR 14%	0.8% 4.1%	7	1.0% 4.0%	NA 18%
N 9831 [3,6-7]	AC → w T AC → w T→ H AC → w TH→ H	3.75	4%-5.1% 4%-7.8% 5.8%-10.4%	0.3% 2.8% 3.3%	9	0.6% 2.8% 3.4%	NA NR 18%
BCIRG 006 [8-9]	AC → D AC → DH→ H DCbH→ H	5	11.2% 18.6% 9.4%	0.7% 2.0% 0.4%	10	0.7% 2.0% 0.4%	NA 5.7% 2.9%

A=doxorubicin, C=cyclophosphamide
T=pac;itaxel, D=docetaxel, Cb=carboplatin
H=trastuzumab
NR=not reported, NA=not applicable

1. Procter et al. JCO 2010
2. Cameron et al. Lancet 2017
3. Romond et al. NEJM 2005
4. Tan-Chiu et al. JCO 2005
5. Romond et al. JCO 2012
6. Perez et al. JCO 2008
7. Advani et al. JCO 2015
8. Slamon et al. NEJM 2011
9. Slamon et al. SABC 2015

Neoadjuvant and Adjuvant Anti-HER2 Therapy

Pertuzumab

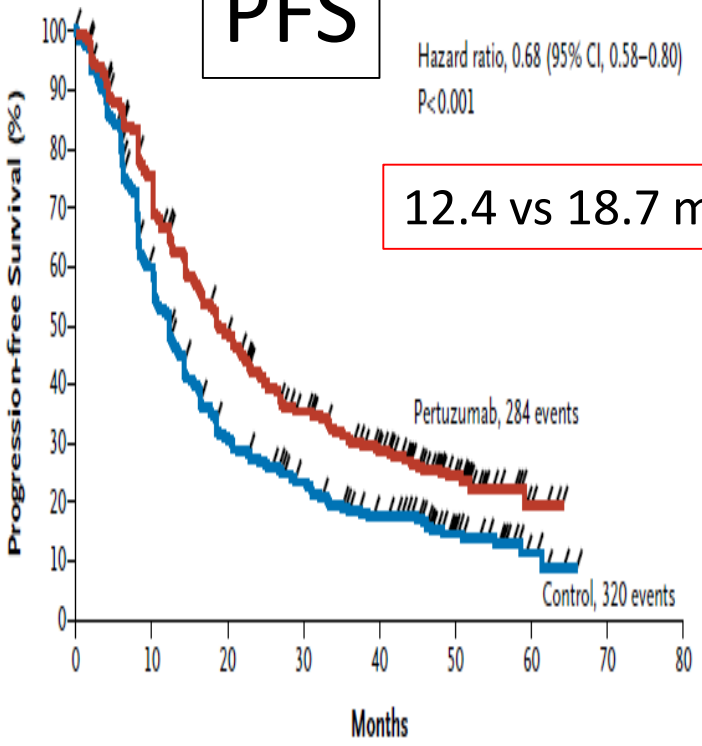


Baselga et al. Crit Rev In Onc/Hem 2017

CLEOPATRA

Docetaxel/Trastuzumab/Pertuzumab > Docetaxel/Trastuzumab/Placebo

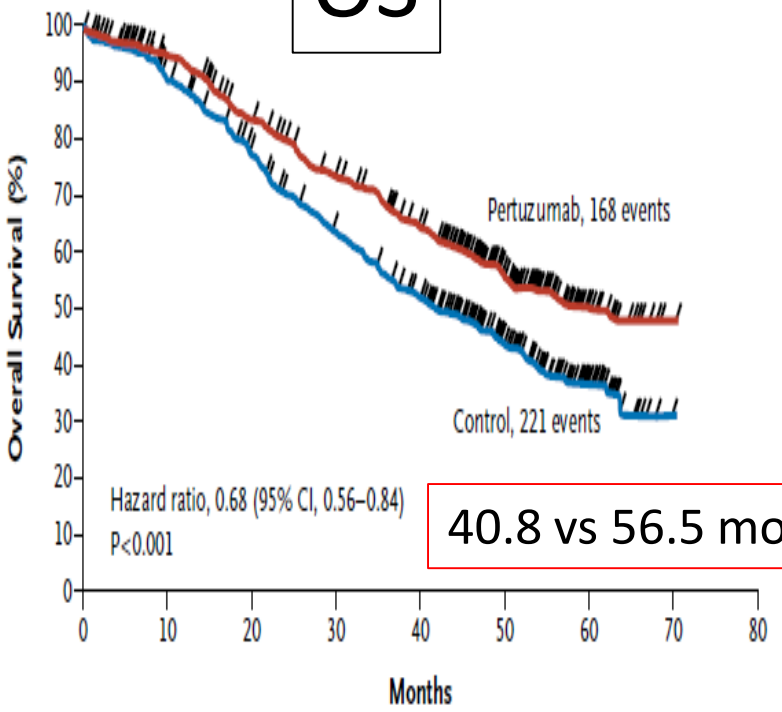
PFS



12.4 vs 18.7 mo

No. at Risk									
Pertuzumab	402	284	179	121	87	37	6	0	0
Control	406	223	110	75	51	21	6	0	0

OS



40.8 vs 56.5 mo

No. at Risk									
Pertuzumab	402	371	318	268	226	104	28	1	0
Control	406	350	289	230	179	91	23	0	0

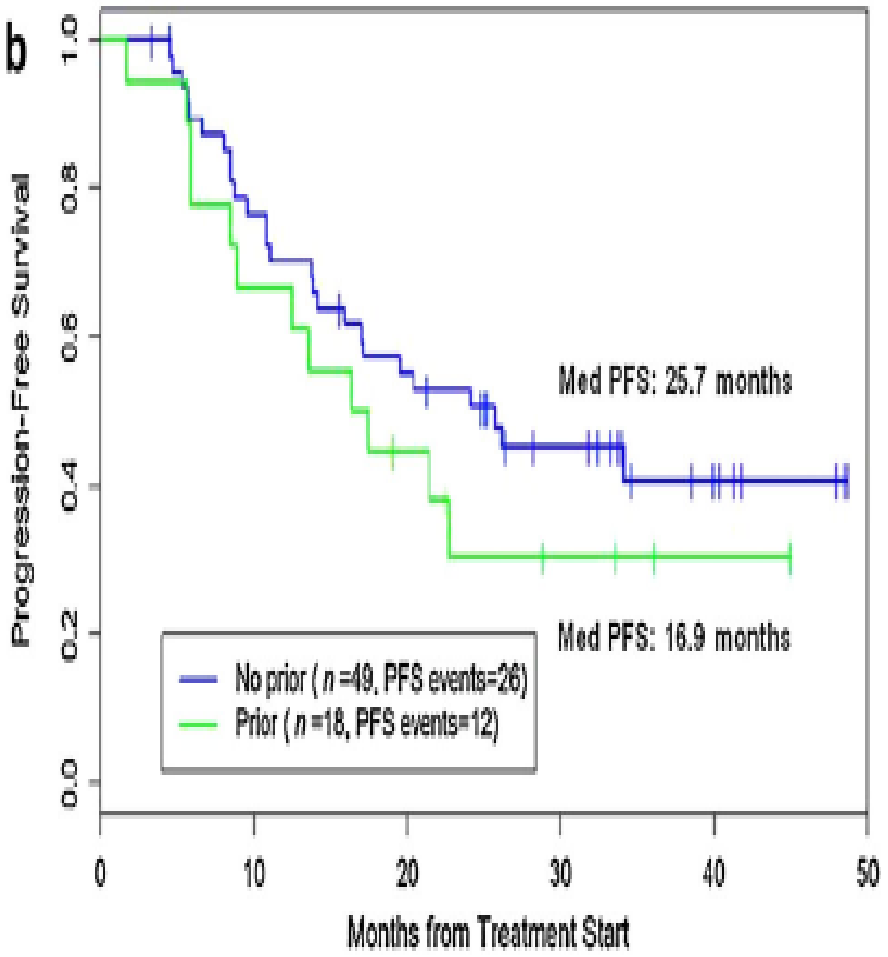
1. Baselga et al. NEJM 2012
2. Swain et al. NEJM 2015

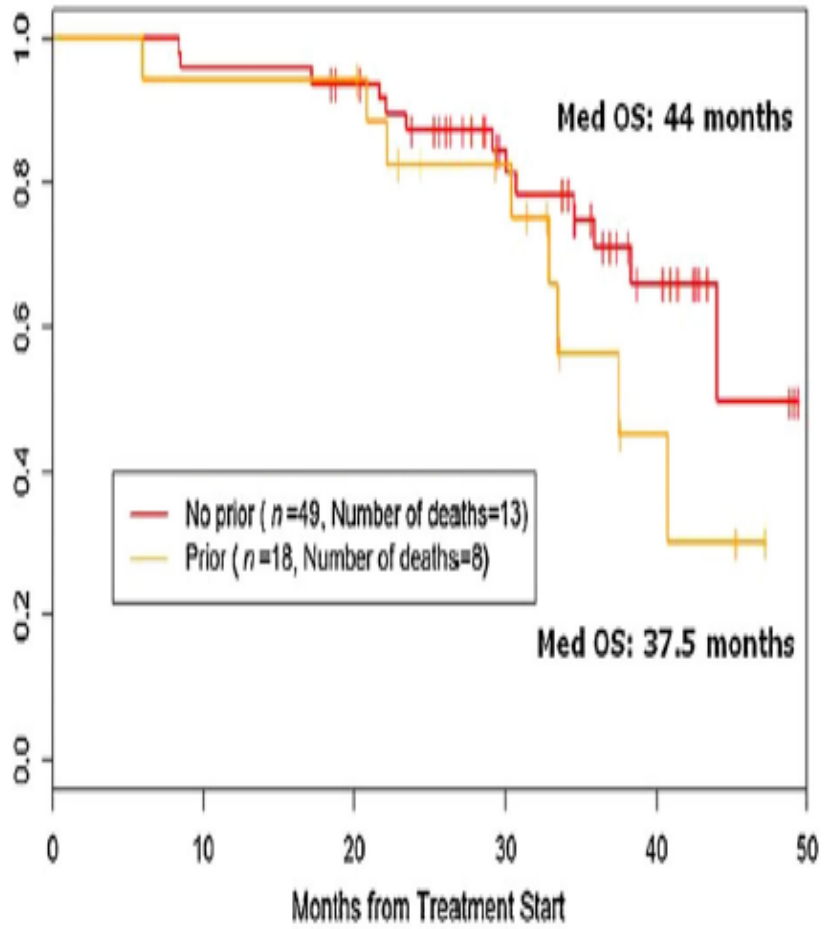
MSKCC Study
Paclitaxel, Trastuzumab, Pertuzumab (THP)

PFS

Med FU of 33 mo

OS



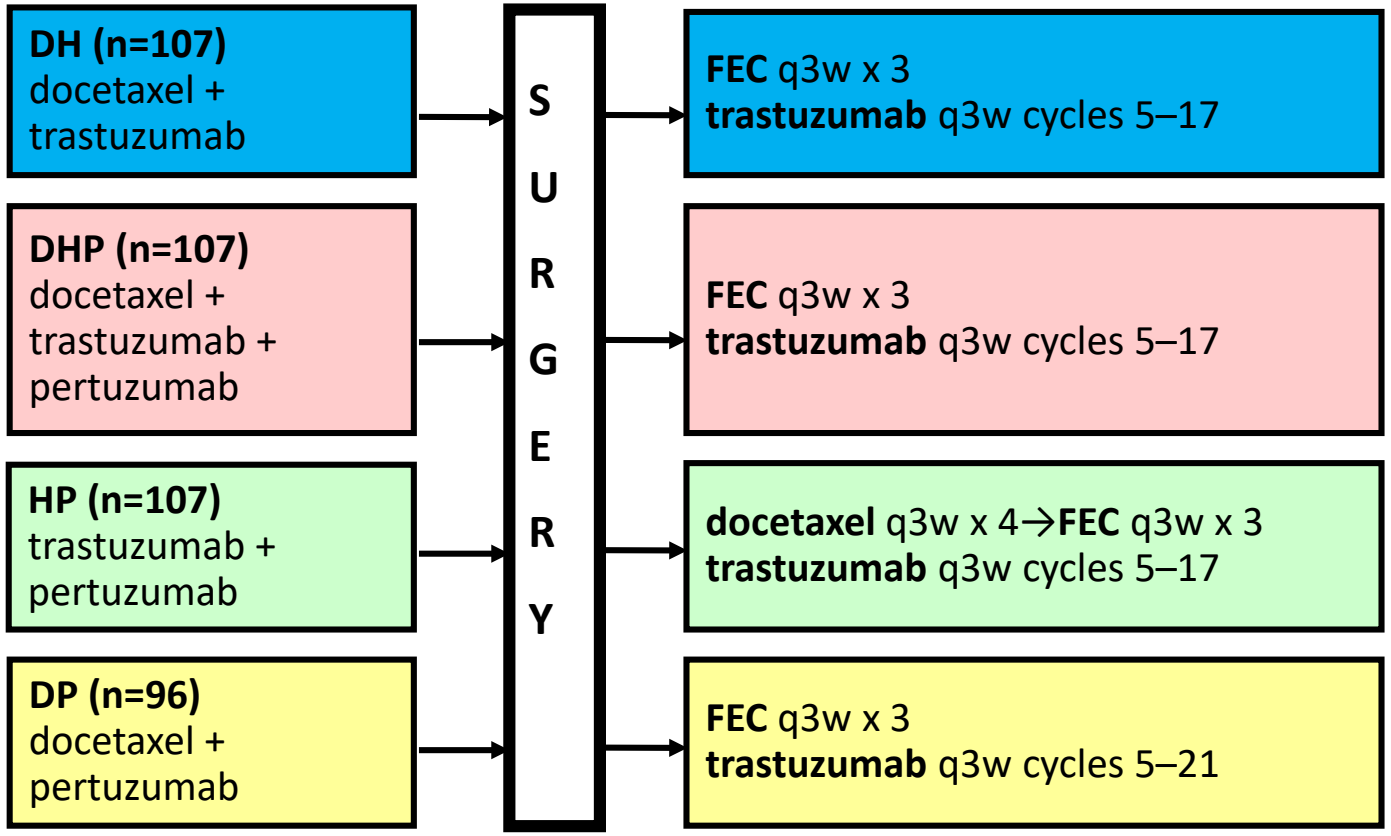


1. Dang et al. JCO 2015
2. Smyth et al. Breast Can Res Tr 2016

NeoSphere
N=417

Patients with operable or locally advanced /inflammatory* HER2-positive BC

Chemo-naïve & primary tumors >2cm



Study dosing: q3w x 4

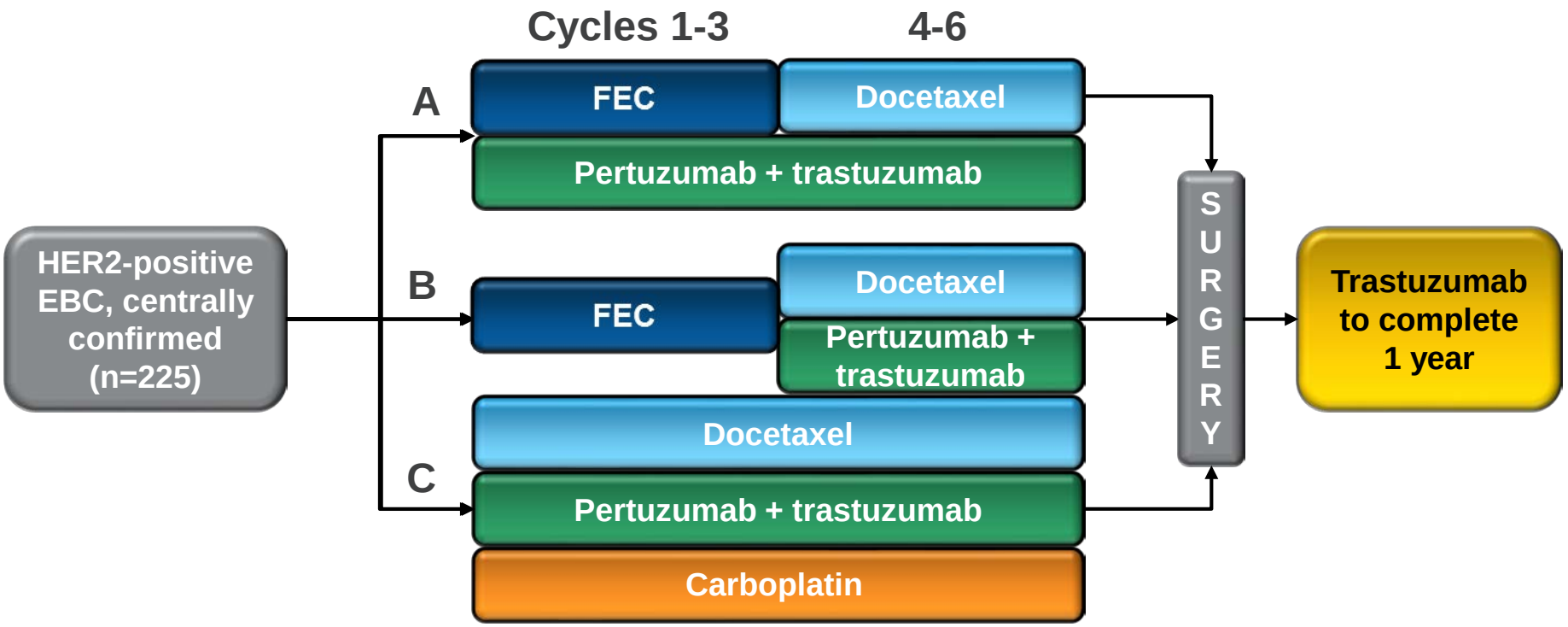
BC, breast cancer; FEC, 5-fluorouracil, epirubicin and cyclophosphamide

*Locally advanced=T2–3, N2–3, M0 or T4a–c, any N, M0; operable=T2–3, N0–1, M0; inflammatory = T4d, any N, M0

H, trastuzumab; P, pertuzumab; D, docetaxel

Gianni et al. Lancet Oncol 2012

TRYPHAENA* Phase II Neoadjuvant Trastuzumab and Pertuzumab in HER2-Positive Early Breast Cancer



- All 3 arms were experimental
- Study dosing q3w:
  - FEC: 500 mg/m^2, 100 mg/m^2, 600 mg/m^2
  - Carboplatin: AUC 6
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Pertuzumab: 840 mg loading dose, 420 mg maintenance
  - Docetaxel: 75 mg/m^2 (escalating to 100 mg/m^2 if tolerated, in Arms A and B only)
- Stratification:
  - Operable, locally advanced, and inflammatory breast cancer
  - Hormone receptor positivity

EBC=early-stage breast cancer; FEC=5-fluorouracil, epirubicin, cyclophosphamide

Schneeweiss et al. Ann Oncol. 2013

Neoadjuvant Trastuzumab + Pertuzumab

	Regimen	Duration	pCR	P value
NEOSPHERE (N=417)	DH		29%	
	DP	12 w	24%	
	DHP		45.8%	0.0141
	HP		16.8%	
TRYPHAENA (N=225)	FECHP → DHP		61.6%	
	FEC → DHP	18 w	57.3%	
	DCbHP		66.2%	

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

FDA Approval
"Neoadjuvant" Setting

- Based on significant PFS/OS benefit of pertuzumab in MBC and pCR gain in neoadjuvant setting, pertuzumab was granted accelerated approval in neoadjuvant setting

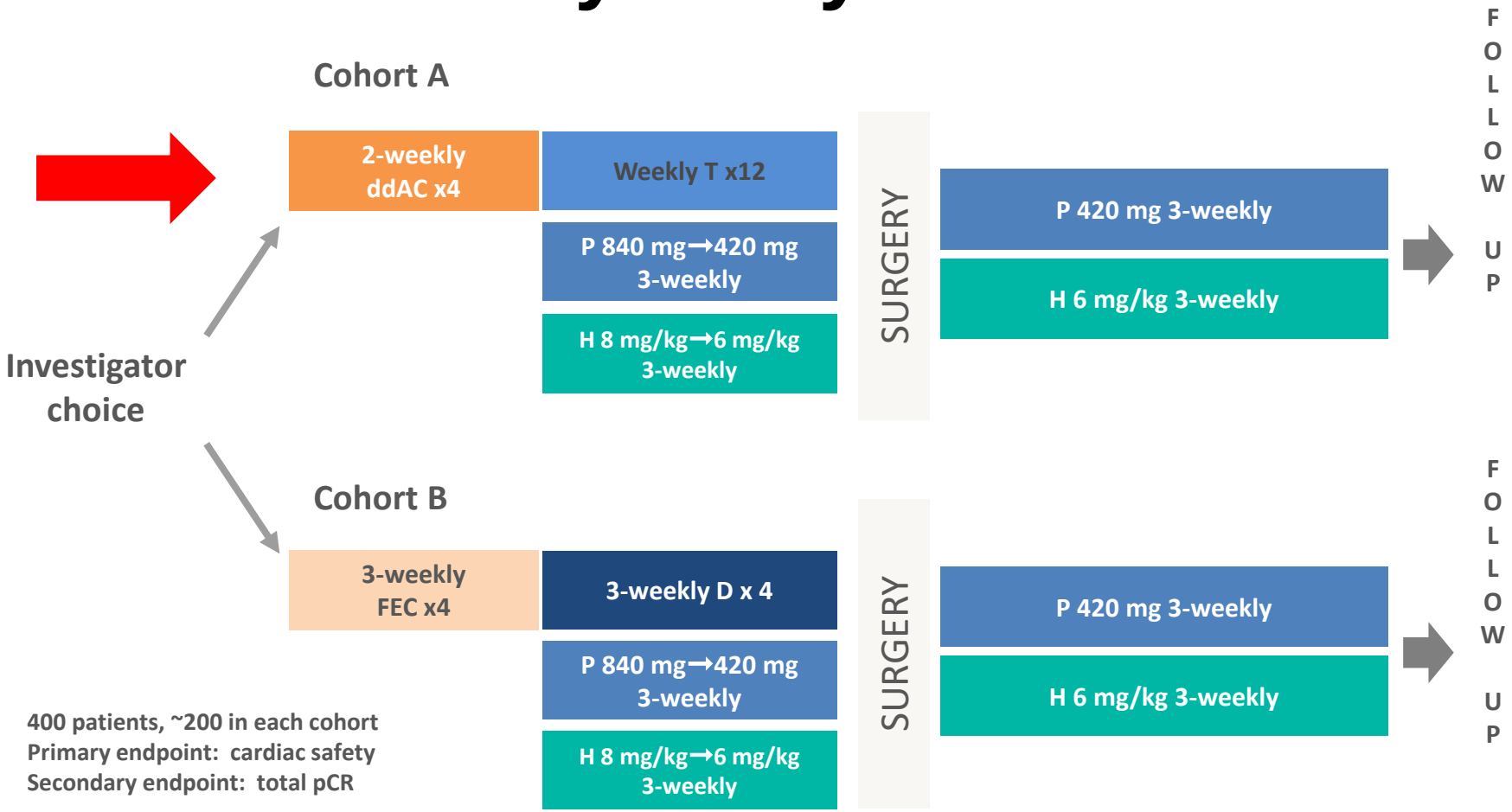
- Eligible pts are those w/ stage II-III
  - Size > 2 cm
  - Node (+)
  - Locally advanced breast cancer
  - Inflammatory breast cancer

- Up to 6 cycles of pertuzumab allowed

- Safety of pertuzumab with doxorubicin containing regimen not established

www.fda.org

Cardiac safety study – BERENICE



ddAC= dose-dense doxorubicin and cyclophosphamide;
FEC=5-fluorouracil, epirubicin, cyclophosphamide; T=paclitaxel;
D=docetaxel; P=pertuzumab; H=trastuzumab

Swain, Dang et al. Ann Oncol 2018

BERENICE

Cohort	tpCR (ypT0/is ypN0)	NYHA Class III-IV Heart Failure
ddAC-THP	61.8%	1.5%
FEC-DHP	60.7%	0%

ddAC= dose-dense doxorubicin and cyclophosphamide;
FEC=5-fluorouracil, epirubicin, cyclophosphamide;
T=paclitaxel;
D=docetaxel; P=pertuzumab; H=trastuzumab

NYHA=New York Heart Association

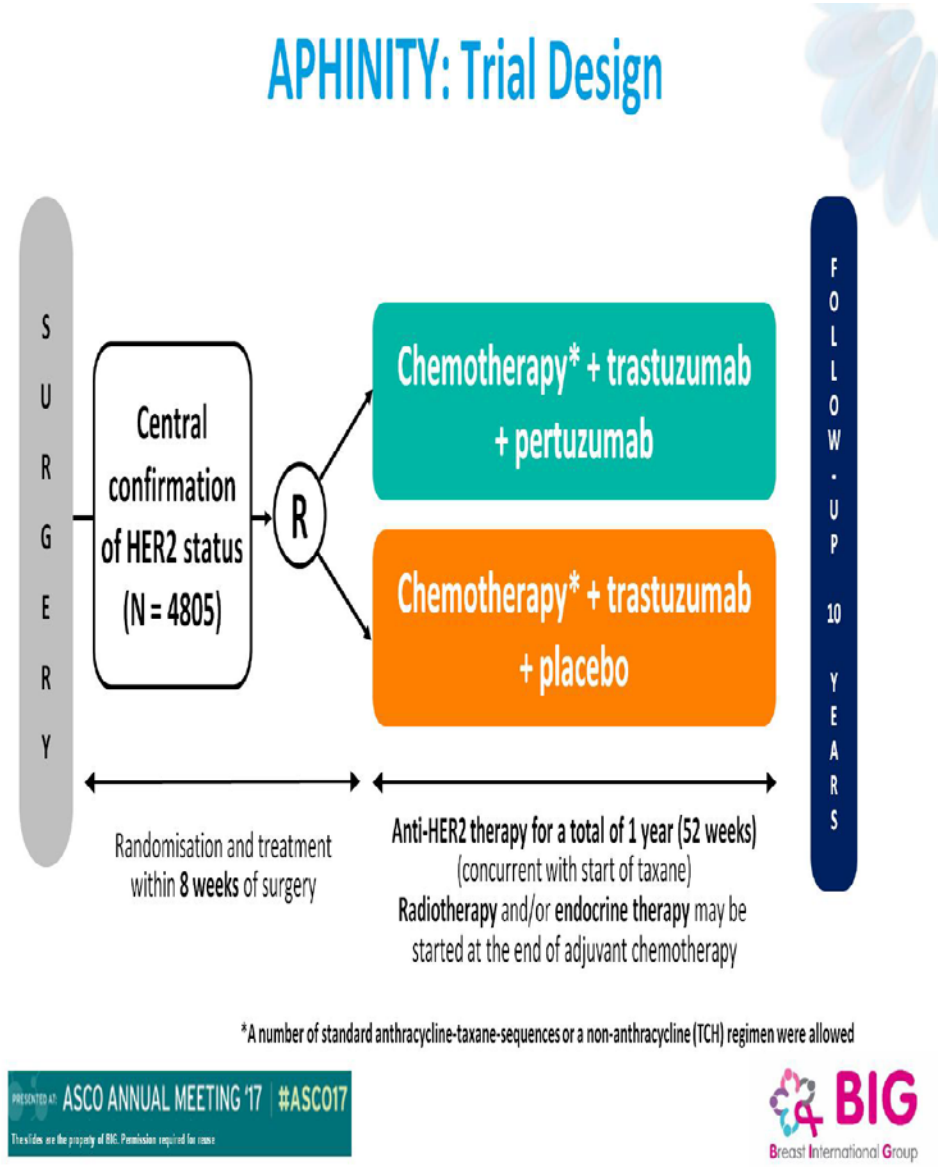
Swain, Dang et al. Ann Oncol 2018

Neoadjuvant Use Trastuzumab/Pertuzumab

- Stage II-III: Yes
  - Downstage (primary tumor and/or axilla)
  - HP-based therapy

- Stage I: No

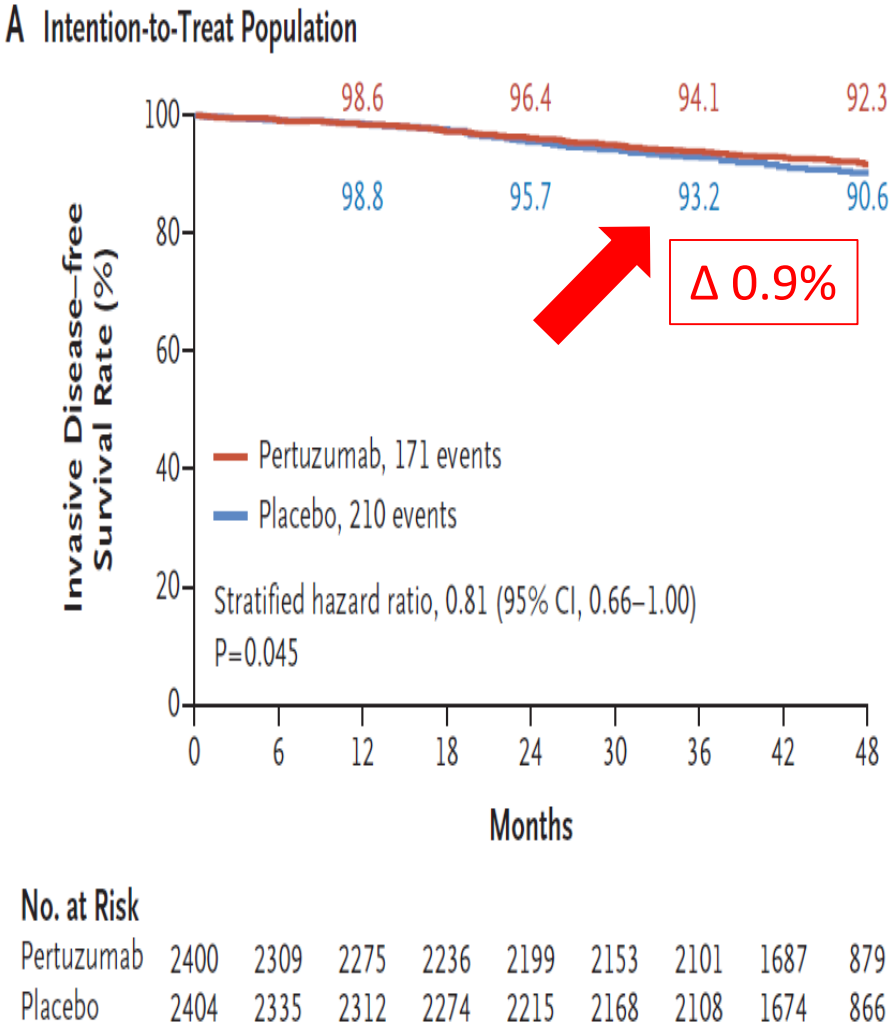
Adjuvant Pertuzumab



- Eligibility
  - Stage I-III
  - HER2 (+)
  - LVEF $\geq$ 55%
- 1°-3 yr iDFS, 2°-OS, safety
- Demographics
  - Node (-) 38%
  - HR (+) 64%
  - Anthracycline 78%

von Minckwitz et al. NEJM 2017

Primary Endpoint
3-year iDFS



- Preplanned analysis
  - **LN- (97.5% vs 98.4%, p=0.64)**
  - **LN+ (92% vs 90.2%, HR 0.77, p=0.02)**
  - **ER- (92.8% vs 91.2%, p=0.08)**
  - **ER+ (94.8% vs 94.4%, p=0.28)**
- Adjuvant Pertuzumab FDA approved 2017
  - For pts at “high risk of recurrence”
- Note:
  - Pertuzumab appropriate for LN+
  - Less clear in other subgroups

von Minckwitz et al. NEJM 2017
www.fda.org

APHINITY: Cardiac Endpoints

N (%)	Pertuzumab n=2364	% Treatment difference (95% CI)	Placebo n=2405
Primary cardiac endpoint	**17 (0.7)**	**0.4 (0.0, 0.8)**	**8 (0.3)**
• Heart failure NYHA III/IV + LVEF drop* • Cardiac death**	15 (0.6) 2 (0.08)		6 (0.2) 2 (0.08)
• Recovered according to LVEF	7		4
Secondary cardiac endpoint Asymptomatic or mildly symptomatic LVEF drop*	**64 (2.7)**	**-0.1 (-1.0, 0.9)**	**67 (2.8)**

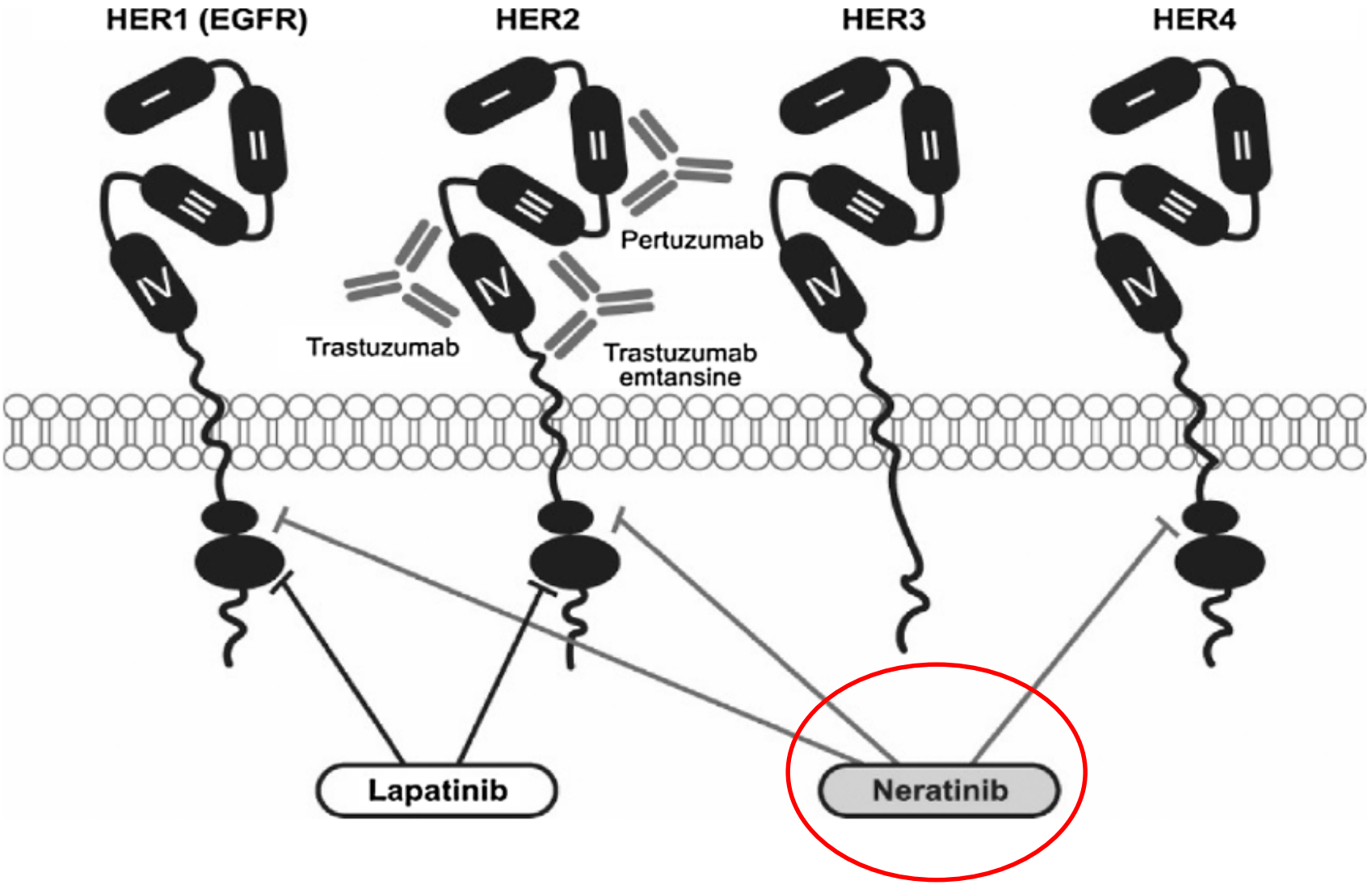
*LVEF drop = ejection fraction drop ≥10% from baseline AND to below 50%;
**Identified by the Cardiac Advisory Board for the trial according to a prospective definition

BIG
Breast International Group

APHINITY: Common Grade ≥ 3 Adverse Events

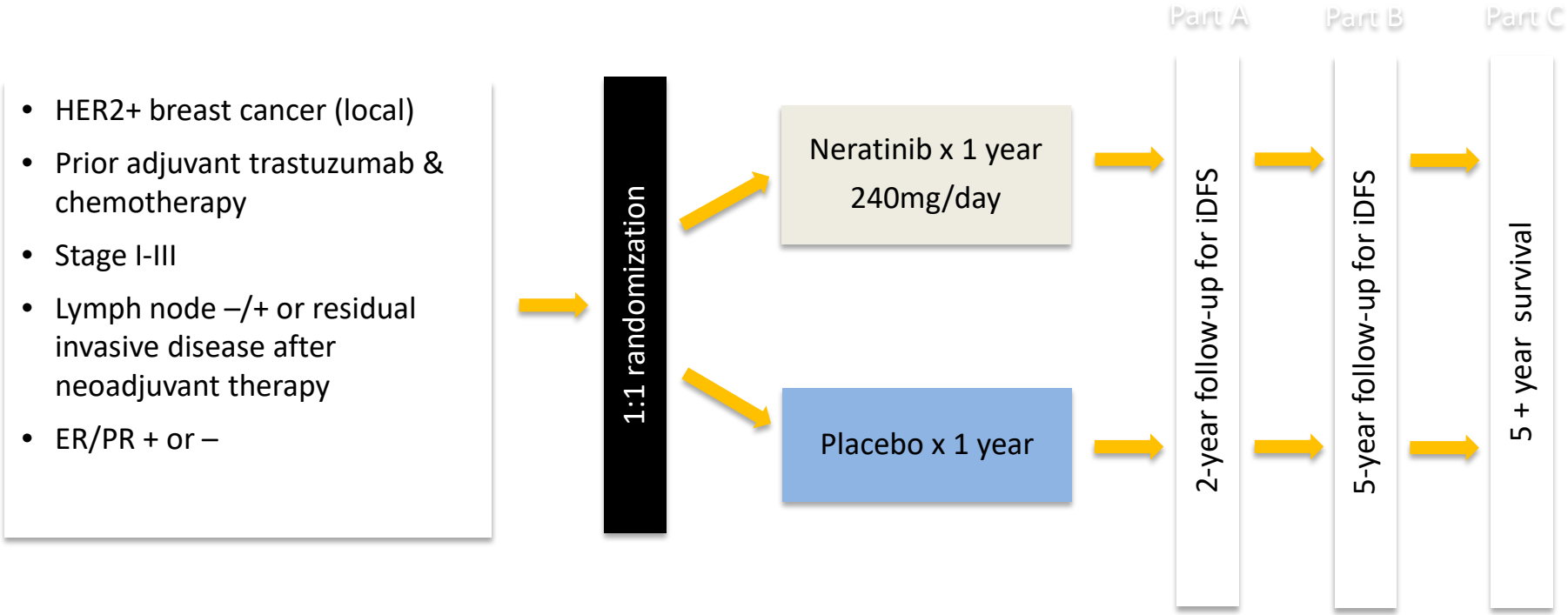
	Pertuzumab n=2364	Placebo n=2405
Neutropenia	385 (16.3%)	377 (15.7%)
Febrile Neutropenia	287 (12.1%)	266 (11.1%)
Anaemia	163 (6.9%)	113 (4.7%)
Diarrhoea	232 (9.8%)	90 (3.7%)
- with chemotherapy and targeted therapy	232 (9.8%)	90 (3.7%)
- with targeted therapy (post-chemotherapy)	12 (0.5%)	4 (0.2%)
- with AC->T (N=1834; 1894)	137 (7.5%)	59 (3.1%)
- with TCH (N= 528; 510)	95 (18.0%)	31 (6.1%)

Neratinib



Baselga et al. Crit Rev In Onc/Hem 2017

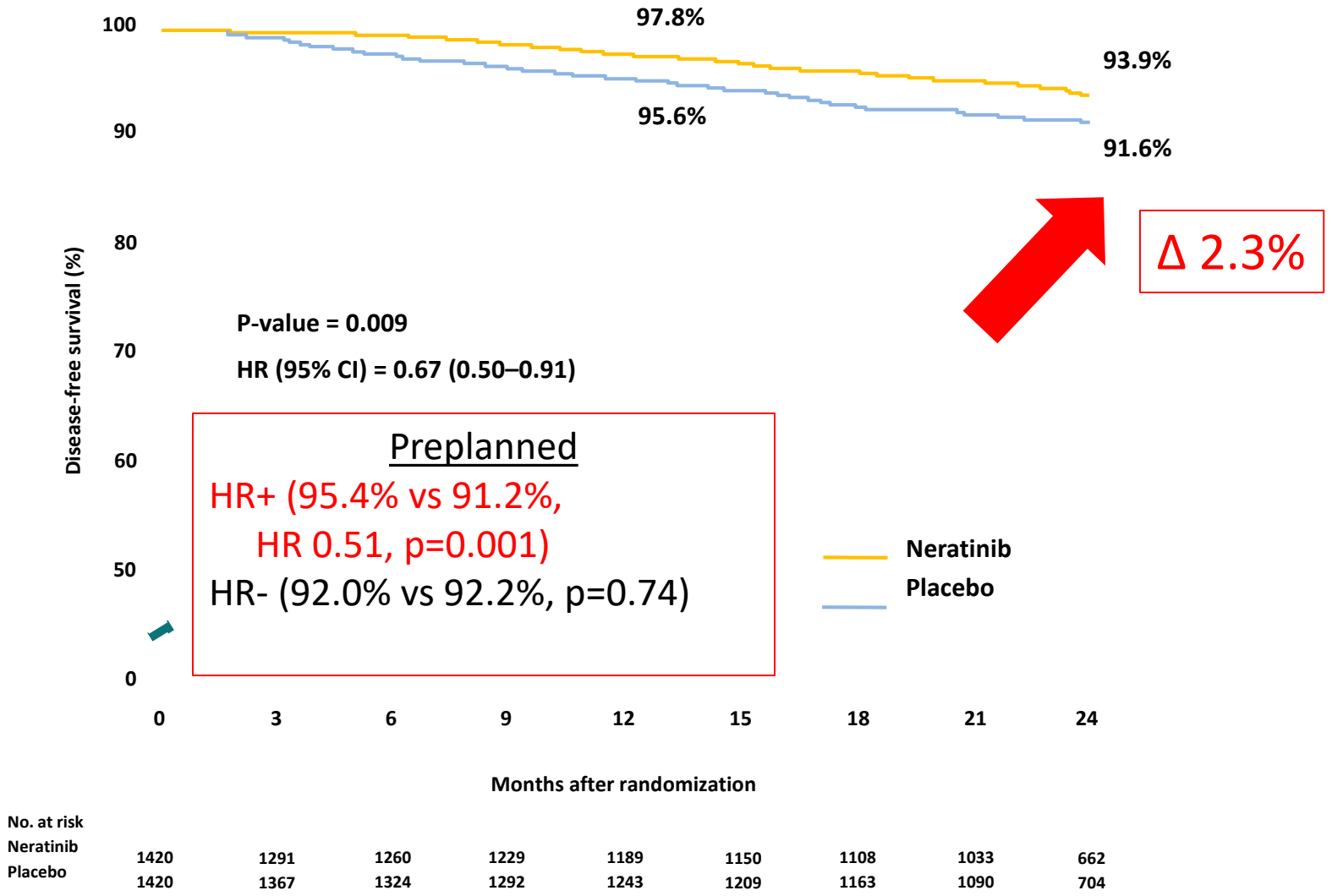
ExteNET



- 1°-2 yr iDFS
- 2°-DCIS-DFS, OS, safety
- Demographics
  - Node (-) 24%
  - HR (+) 57%
  - Anthracycline 78%

Chan et al. Lancet Onc 2016

Primary Endpoint: Invasive DFS (ITT)



Chan et al. Lancet Onc 2016

Safety (Adverse Events ≥10%)

n (%)	Neratinib (n=1408)		Placebo (n=1408)	
	All grades	Grade 3–4	All grades	Grade 3–4
Diarrhea	1343 (95.4)	562 (39.9)	499 (35.4)	23 (1.6)
Nausea	605 (43.0)	26 (1.8)	303 (21.5)	2 (0.1)
Fatigue	382 (27.1)	23 (1.6)	283 (20.1)	6 (0.4)
Vomiting	369 (26.2)	47 (3.3)	113 (8.0)	5 (0.4)
Abdominal pain, general	340 (24.1)	24 (1.7)	144 (10.2)	3 (0.2)
Headache	278 (19.7)	8 (0.6)	275 (19.5)	6 (0.4)
Abdominal pain, upper	212 (15.1)	11 (0.8)	96 (6.8)	3 (0.2)
Rash	211 (15.0)	5 (0.4)	100 (7.1)	0
Decreased appetite	170 (12.1)	3 (0.2)	40 (2.8)	0
Muscle spasms	159 (11.3)	1 (0.1)	45 (3.2)	1 (0.1)
Dizziness	146 (10.4)	3 (0.2)	128 (9.1)	3 (0.2)
Arthralgia	86 (6.1)	2 (0.1)	162 (11.5)	4 (0.3)

Neratinib

- FDA approved
  - As extended Rx in HER2+ pts after trastuzumab based Rx
- NCCN
  - "Consider" neratinib in pts w/ HR (+) dz "perceived" to be at high risk of recurrence
- Note:
  - Stage II-III (node+) →HP-based Rx (ie: AC-THP or DCbHP)
  - No data on neratinib after HP-based Rx

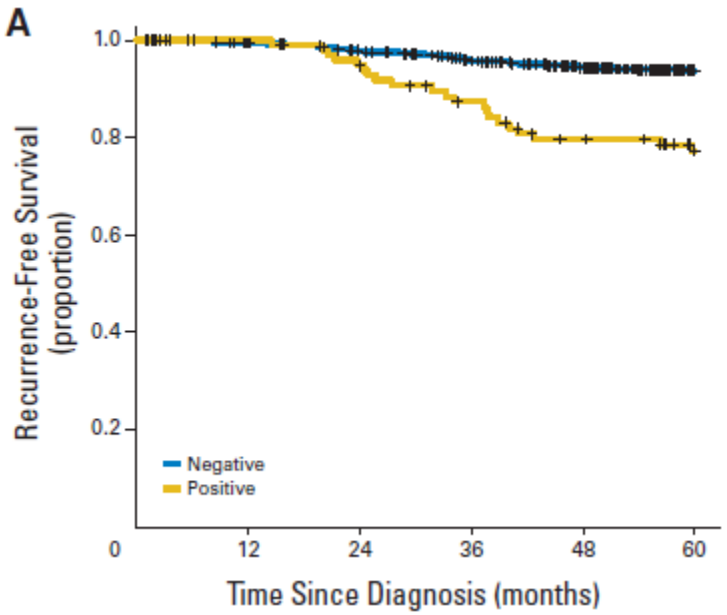
www.fda.org
http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Stage I HER2+

Outcomes for T1a/bN0 HER2+ Tumors

MDACC Series (N=98)

HER2 status	N	5 yr RFS
HER2+	98	77.1%
HER2-	867	93.7%



Gonzalez-Angulo et al. JCO 2009

NCCN Series (N=520)

	No Rx	Chemo +/- tras
For HR+ HER2+	↓	↓
5-yr DRFS		
T1a	96%	vs 100%
T1b	94%	vs 96%
5-yr OS		
T1a	95%	vs 100%
T1b	95%	vs 99%
For HR-HER2+		
5-yr DRFS		
T1a	93%	vs 100%
T1b	94%	vs 94%
5-yr OS		
T1a	93%	vs 100%
T1b	100%	vs 95%

Vaz-Luiz et al. JCO 2014

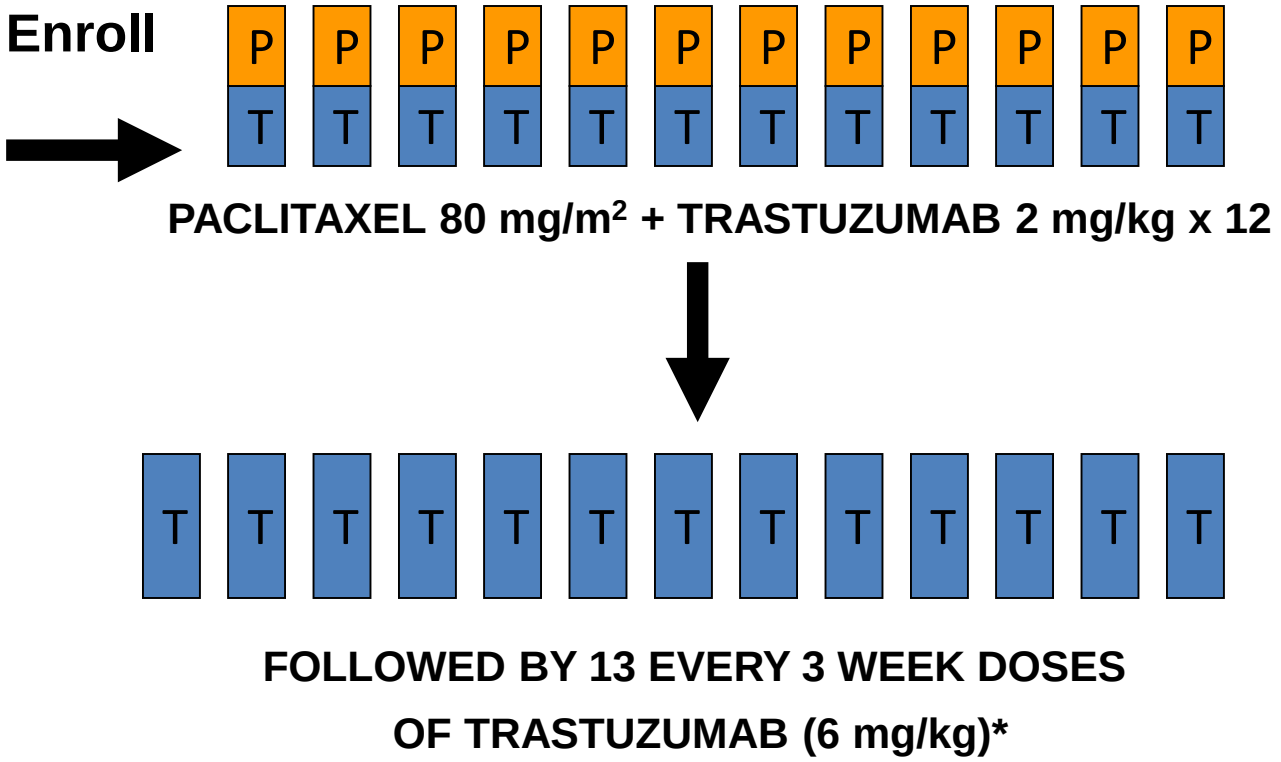
Adjuvant Paclitaxel and Trastuzumab (APT)

HER2+
ER+ or ER-
Node Negative
≤ 3 cm

Planned N=400

T1a-19%
1b-31%
1c-42%
T2 - 9%

Enroll



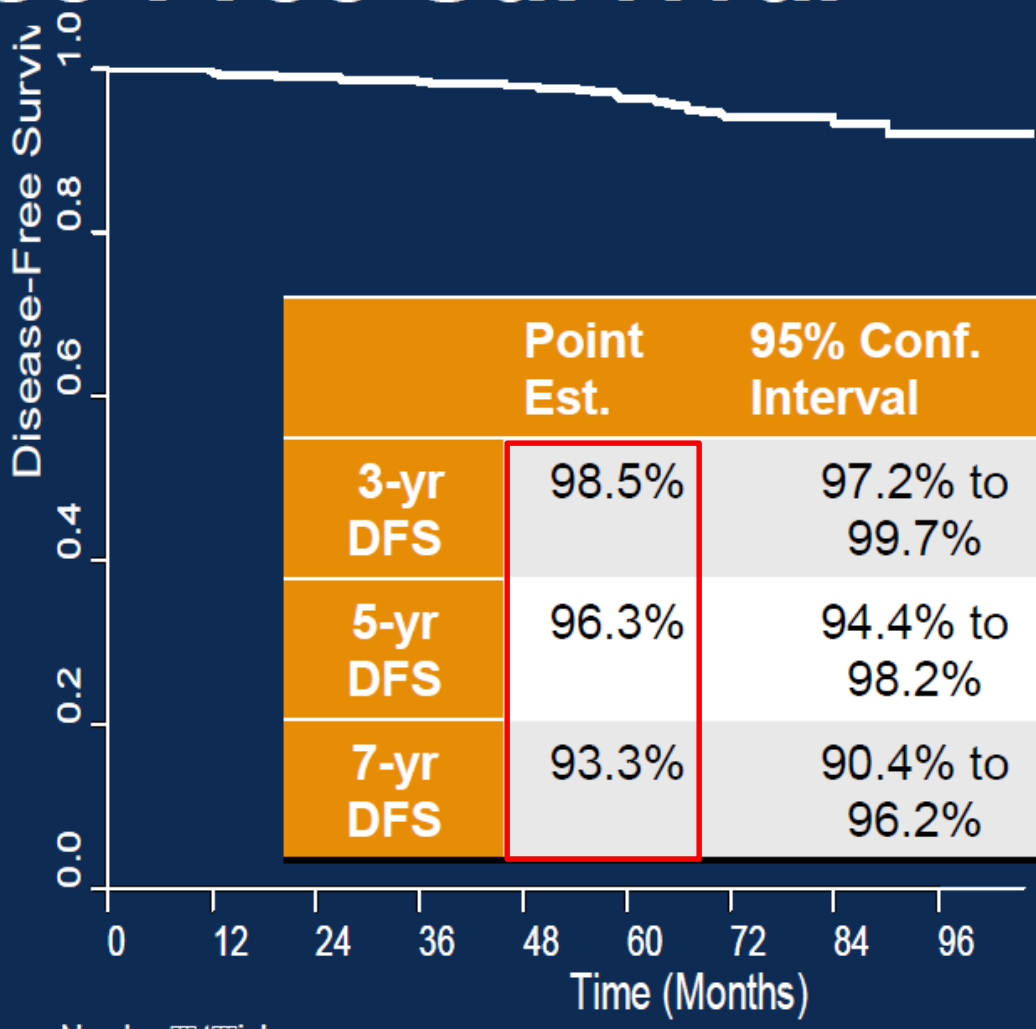
***Dosing could alternatively be 2 mg/kg IV weekly for 40 weeks**
****** Radiation and hormonal therapy was initiated after completion of paclitaxel**

Tolaney et al. NEJM 2015

Patient Characteristics

	N	%	
Age			
<50	132	33	
50-70	233	57	
≥70	41	10	
Size of Primary Tumor			
T1a ≤0.5 cm	77	19	50%
T1b >0.5-≤1.0	124	31	
T1c >1.0-≤2.0	169	42	50%
T2 >2.0-≤3.0	36	9	
Histologic Grade			
I Well differentiated	44	11	
II Moderately differentiated	131	32	
III Poorly differentiated	228	56	
HR Status (ER and/or PR)			
Positive	272	67	
Negative	134	33	

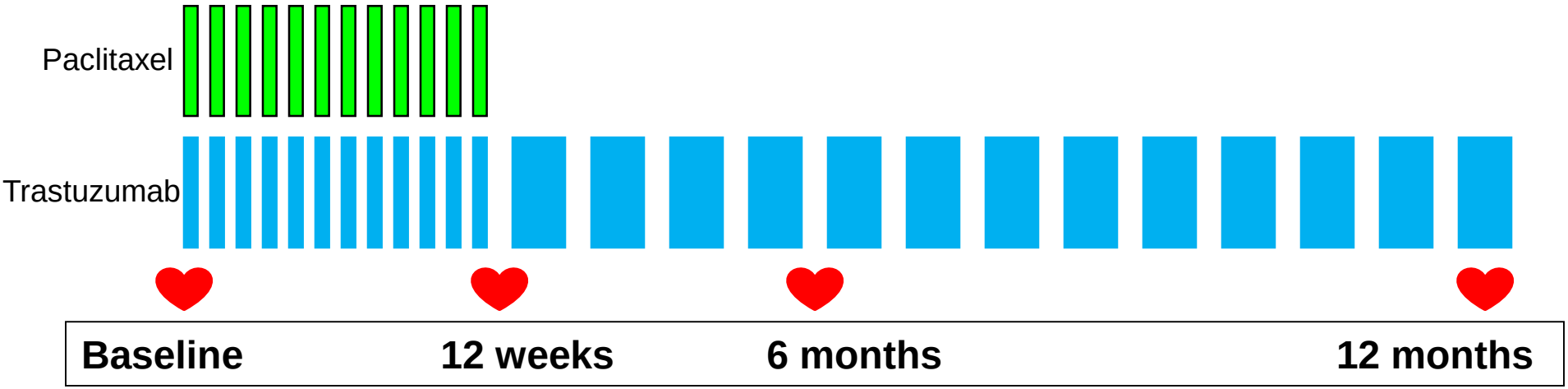
Disease-Free Survival



	Point Est.	95% Conf. Interval	No. of events
3-yr DFS	98.5%	97.2% to 99.7%	6
5-yr DFS	96.3%	94.4% to 98.2%	14
7-yr DFS	93.3%	90.4% to 96.2%	23

Tolaney et al. ASCO 2017

Non-Anthracycline + Trastuzumab Cardiac Toxicity



ECHO or MUGA

Cardiac event	N	% (95% CI)
Symptomatic Congestive Heart Failure*	2	0.5 (0.1-18)
Asymptomatic Declines in LVEF**	13	3.2 (1.7-5.4)

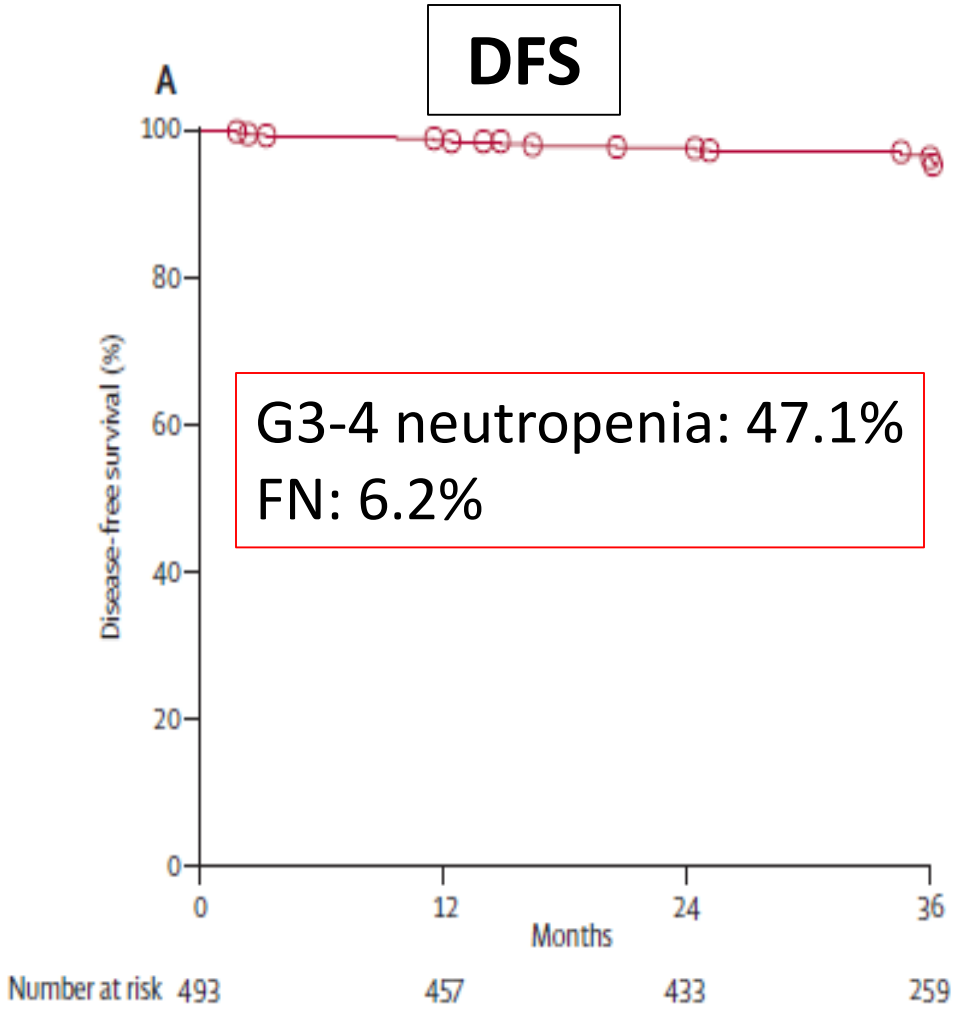
*Both patients had normalization of LVEF after discontinuation of trastuzumab

**11 of 13 were able to resume trastuzumab therapy after an interruption of trastuzumab

Dang et al. JAMA Oncol 2016

Phase II Study of Docetaxel, Cyclophosphamide, and Trastuzumab

- N = 493, med FU of 3 yrs
- Node Status
  - Node (-): 79.3%
  - Node (+): 20.7%
- Stage: I (57.6%), II (41.2%)
  III (1.2%)
- Outcomes:
  - 2 year DFS: 97.8%
  - 3 year DFS: 96.9%
    - Node (-): 97.8%
    - Node (+): 93.5%
- Symptomatic heart failure: 0.4%



G3-4 neutropenia: 47.1%
FN: 6.2%

Jones et al. Lancet Oncol 2014

Putting it together

- Node (+)
  - Stage 2-3 → HP-based (ie: ddAC-THP or DCbHP)
  - No data on neratinib after HP (cost, QOL)
- Node (-)
  - Stage 2-3 → HP-based (≥T2) ?
    - No significant benefit of HP in node (-) tumors in APHINITY
    - If pts have received H-based Rx (ie: ddAC-TH, DCbH), can consider neratinib (ie: in HR+ pts)
  - Stage 1 → TH (T1, N1mi) or DCH
    - Pts in APT did well with TH alone

A=doxorubicin, C=cyclophosphamide, T=paclitaxel, D=docetaxel, Cb=carboplatin, H=trastuzumab, P=pertuzumab

NCCN
HER2 (+)

- Node (-) or N1mi:
  - ≤ 0.5 cm: “Consider” Chemo + trastuzumab
  - ≤ 0.5 cm N1mi: “Consider” Chemo + trastuzumab
  - ≥ 0.6 - 1.0 cm: “Consider” Chemo + trastuzumab
  - > 1.0 cm: Chemo + trastuzumab
- Node (+): Chemo + trastuzumab

Add endocrine Rx hormone receptor (+) disease

http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

NCCN HER2-Positive (Neoadjuvant/Adjuvant)

- Preferred
  - AC → TH+/-P
  - DCbH+/-P
  - TH
- Other
  - AC → DH+/-P
  - DCH

Stage II-III

-AC → TH+/-P

-DCbH+/-P

(Consider neratinib in pts w/ HR+ "perceived" to have high-risk of recurrence after trastuzumab; no data after HP)

Stage I

-TH

-DCH

A=doxorubicin, E=epirubicin, C=cyclophosphamide, T=paclitaxel, D=docetaxel, Cb=carboplatin, H=trastuzumab, P=pertuzumab

http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Summary
Anti-HER2 Rx

- Neoadjuvant
  - Downstage tumor and/or axilla (ie: Stage II-III)
  - Same Rx as adjuvant
- Stage II-III HER2 (+)
  - Chemo + HP (ie: LN+)
    - ie: AC →THP, DCbHP
    - no data on neratinib after HP
  - Chemo + H (no P), consider neratinib in pts w/ HR+ disease “perceived” to be high-risk
- Stage I HER2 (+)
  - Taxane + trastuzumab (ie: TH or DCH)

Thank You!