Otimizando a terapia HER2 no cenário adjuvante: impacto dos estudos Aphinity e ExteNET

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Instituto Nacional de Câncer
Clínica São Vicente

Disclosures

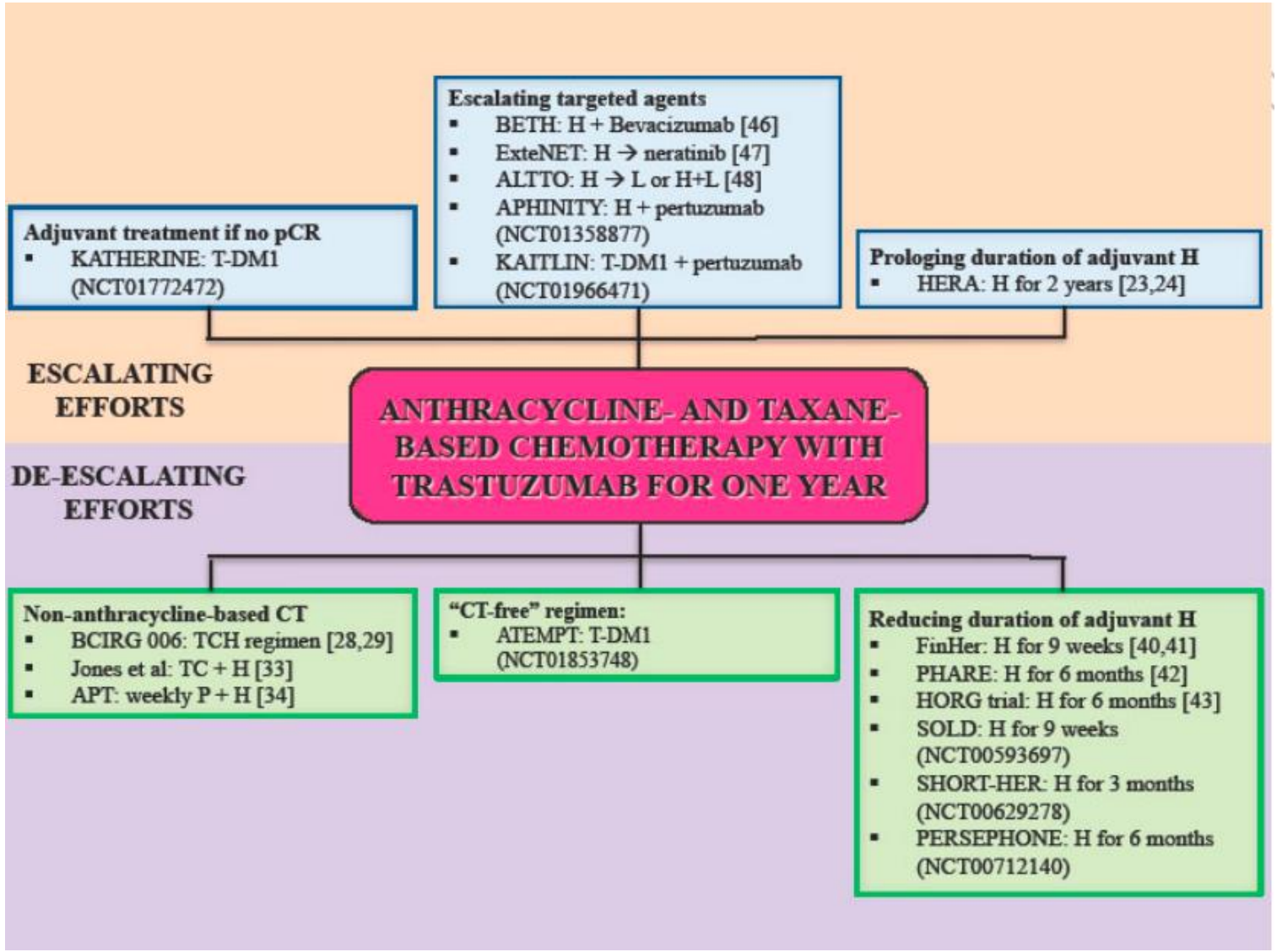
Clinical study: Roche

Travel expenses: AstraZeneca

Consultant: Abbvie, Genomic Health, Libbs, Pfizer, Roche

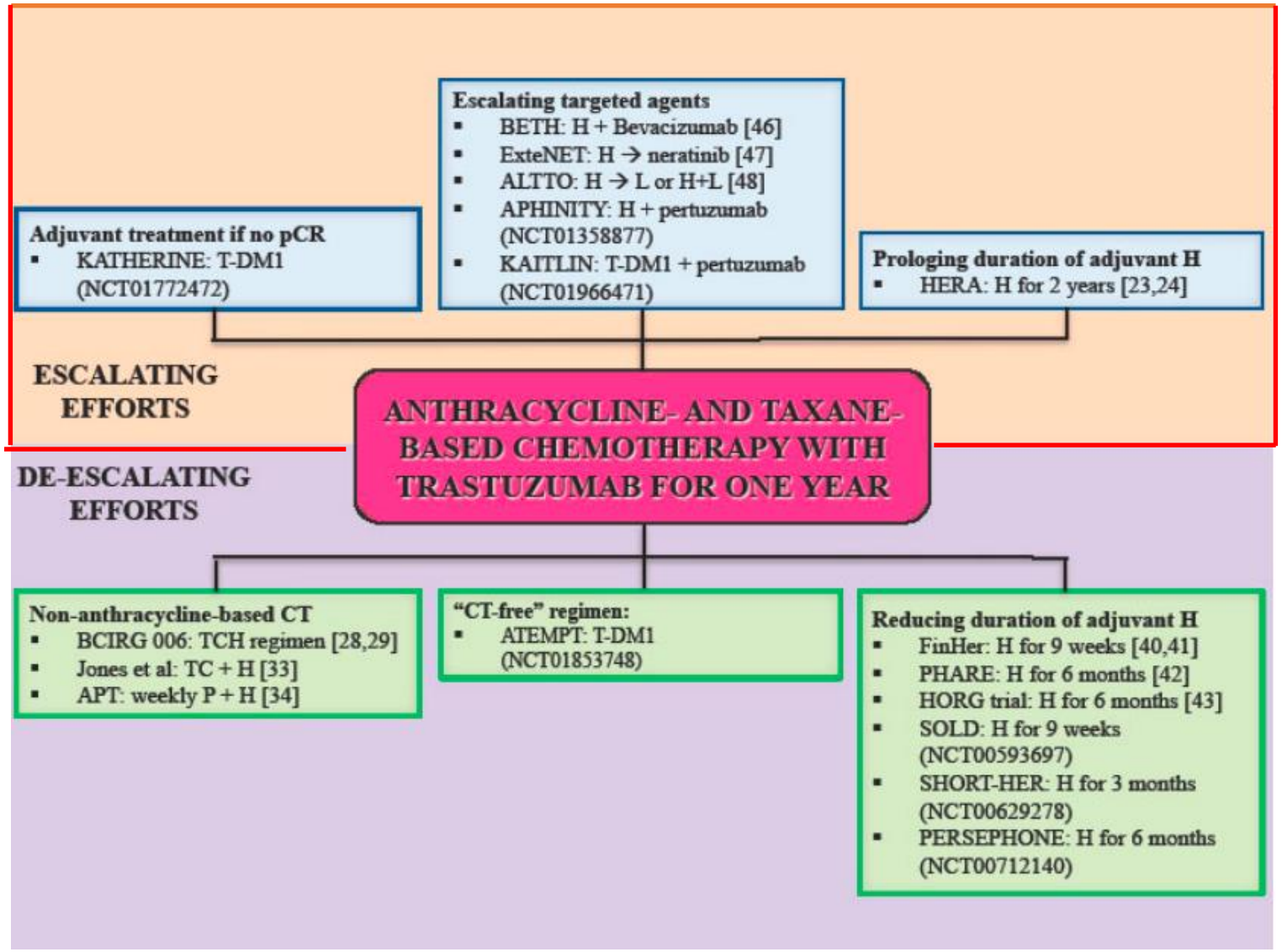
Personal opinion may not reflect the Instituto Nacional de Cancer orientation

Efforts in the adjuvant treatment of HER2-positive breast cancer



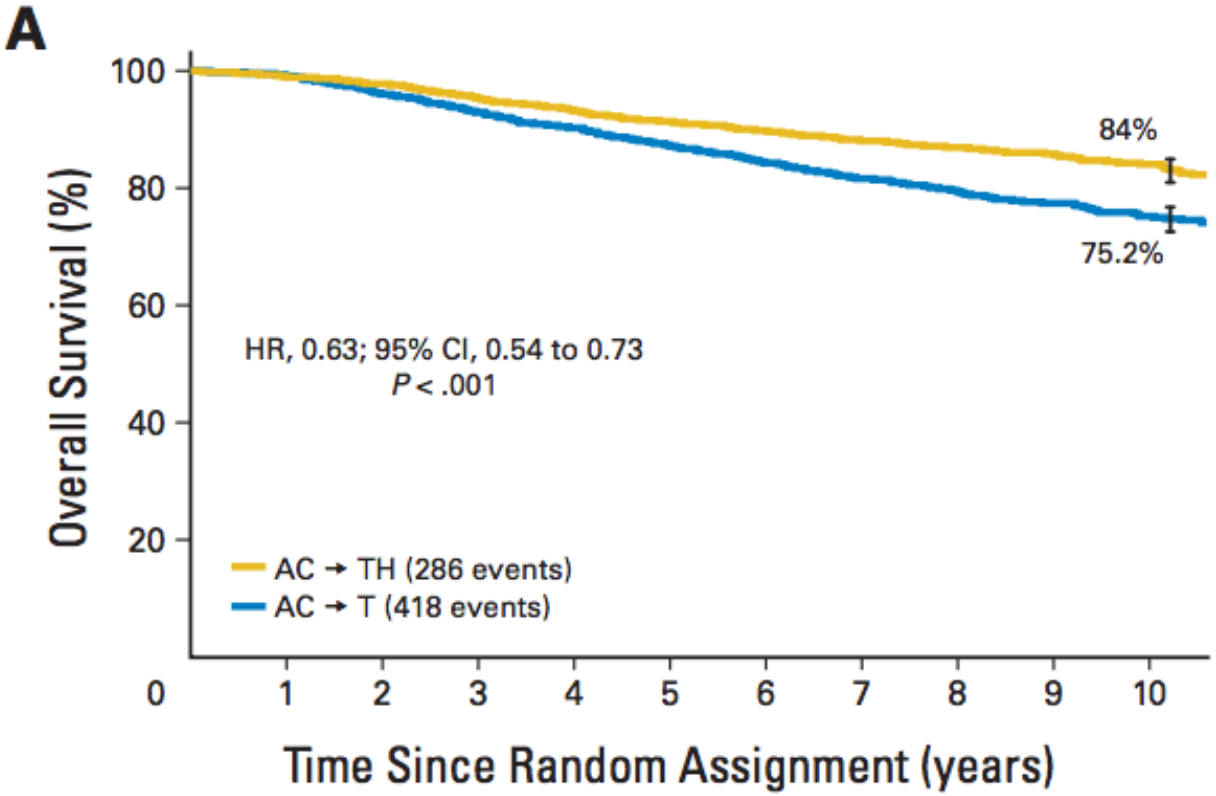
Lambertini M. Expert Rev Anticancer Ther 2017

Efforts in the adjuvant treatment of HER2-positive breast cancer



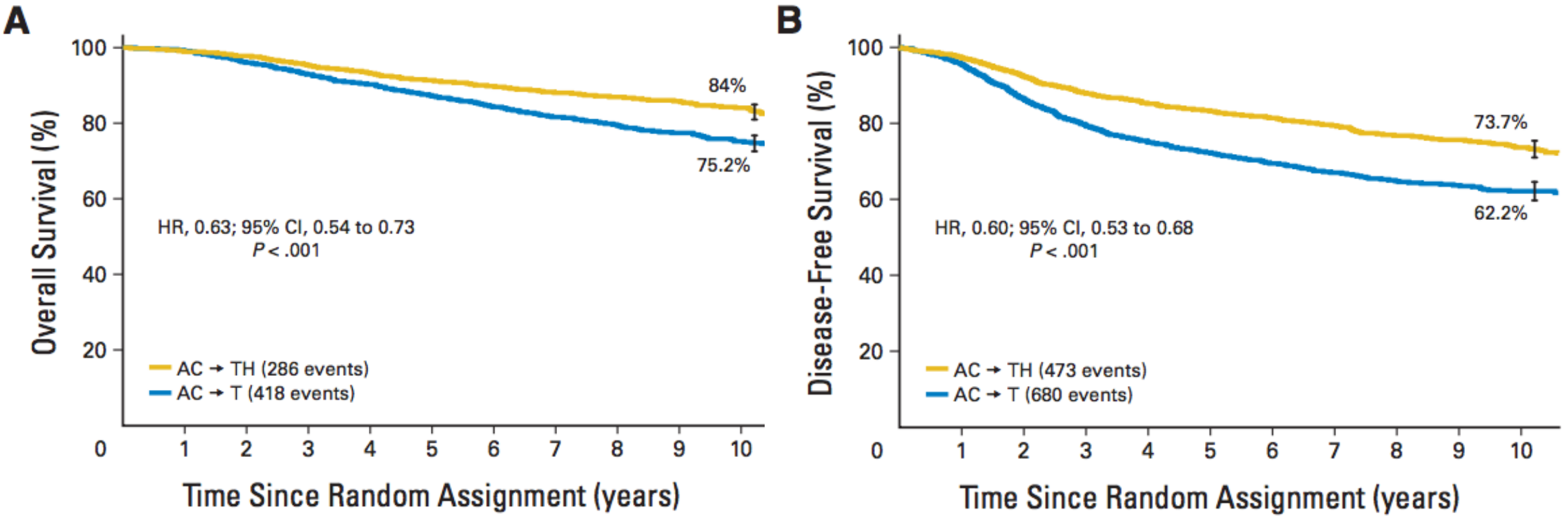
Lambertini M. Expert Rev Anticancer Ther 2017

Benefit of adjuvant trastuzumab extends long-term



Perez EA. J Clin Oncol 2014

Benefit of adjuvant trastuzumab extends long-term but disease continues to recur



Perez EA. J Clin Oncol 2014

Despite the enormous benefits from trastuzumab, patients at high risk continue to relapse

Trial	N + lymphnodes	10y DFS Control	10y DFS Trastuzumab
NCCTG 9831/ NSABP B-31	4-9 10	56% 38%	71% 62%
BCIRG 006	4	54%	63%
HERA	4	49%	55%

Perez EA. J Clin Oncol 2014
Slamon D. SABCS 2015
Cameron D. Lancet 2017

ExteNet Adjuvant Trial

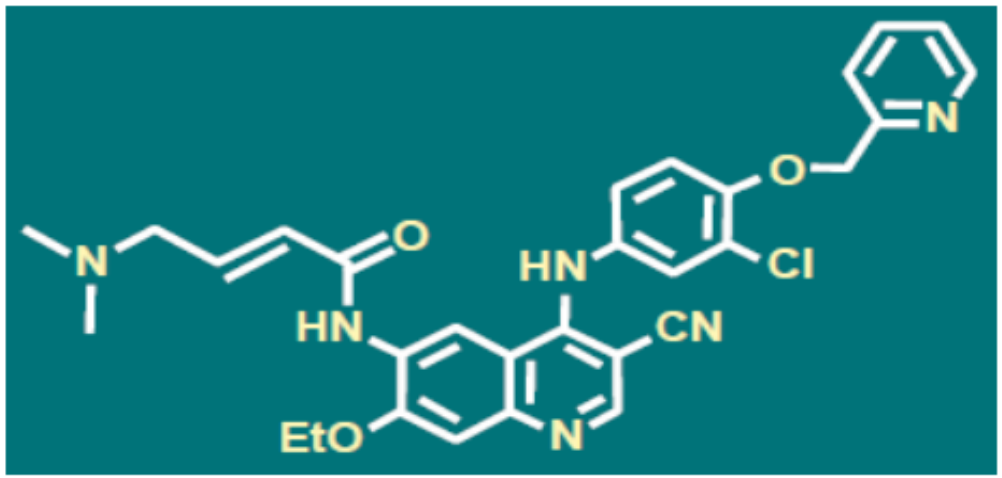
- Stage II/III HER2+ BC
- Treated with standard trastuzumab-based Rx
- Residual Dz if NeoAdj

N = 2840

1:1 Randomization

Placebo x 1 year

Neratinib 240 mg po daily x 1 year



Baseline characteristics of the intention-to-treat population

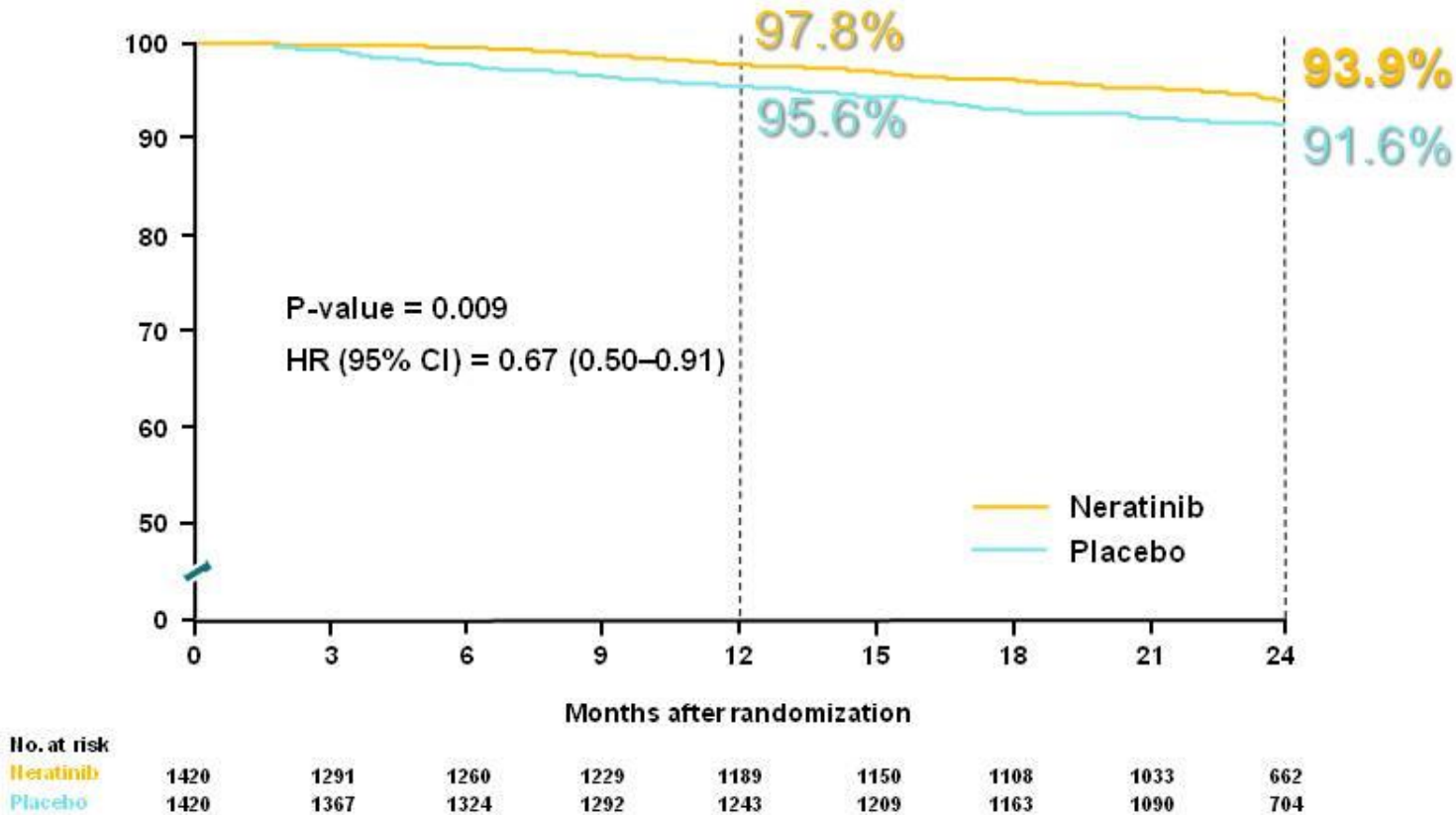
	Neratinib group (n=1420)	Placebo group (n=1420)
Nodal status*		
Negative	335 (24%)	336 (24%)
1–3 positive nodes	664 (47%)	664 (47%)
≥4 positive nodes	421 (30%)	420 (30%)
Hormone receptor status*		
Positive (ER positive, PR positive, or both)	816 (57%)	815 (57%)
Negative (ER and PR negative)	604 (43%)	605 (43%)
Previous trastuzumab regimen*		
Concurrent	884 (62%)	886 (62%)
Sequential	536 (38%)	534 (38%)
T stage		
T1	440 (31%)	459 (32%)
T2	585 (41%)	555 (39%)
≥T3	144 (10%)	117 (8%)
Unknown	250 (18%)	288 (20%)
Missing	1 (<1%)	1 (<1%)
Histological grade of tumour		
Undifferentiated or poorly differentiated	670 (47%)	689 (49%)
Moderately differentiated	461 (32%)	416 (29%)
Well differentiated	76 (5%)	65 (5%)
Unknown	213 (15%)	241 (17%)

3/4 LN +

>1/2 HR +

Chan A. Lancet Oncol 2016

ExteNET Trial: Invasive DFS, N=2840



Chan A , ASCO 2015

PRESENTED AT: ASCO Annual '15 Meeting

ExteNET: IDFS events

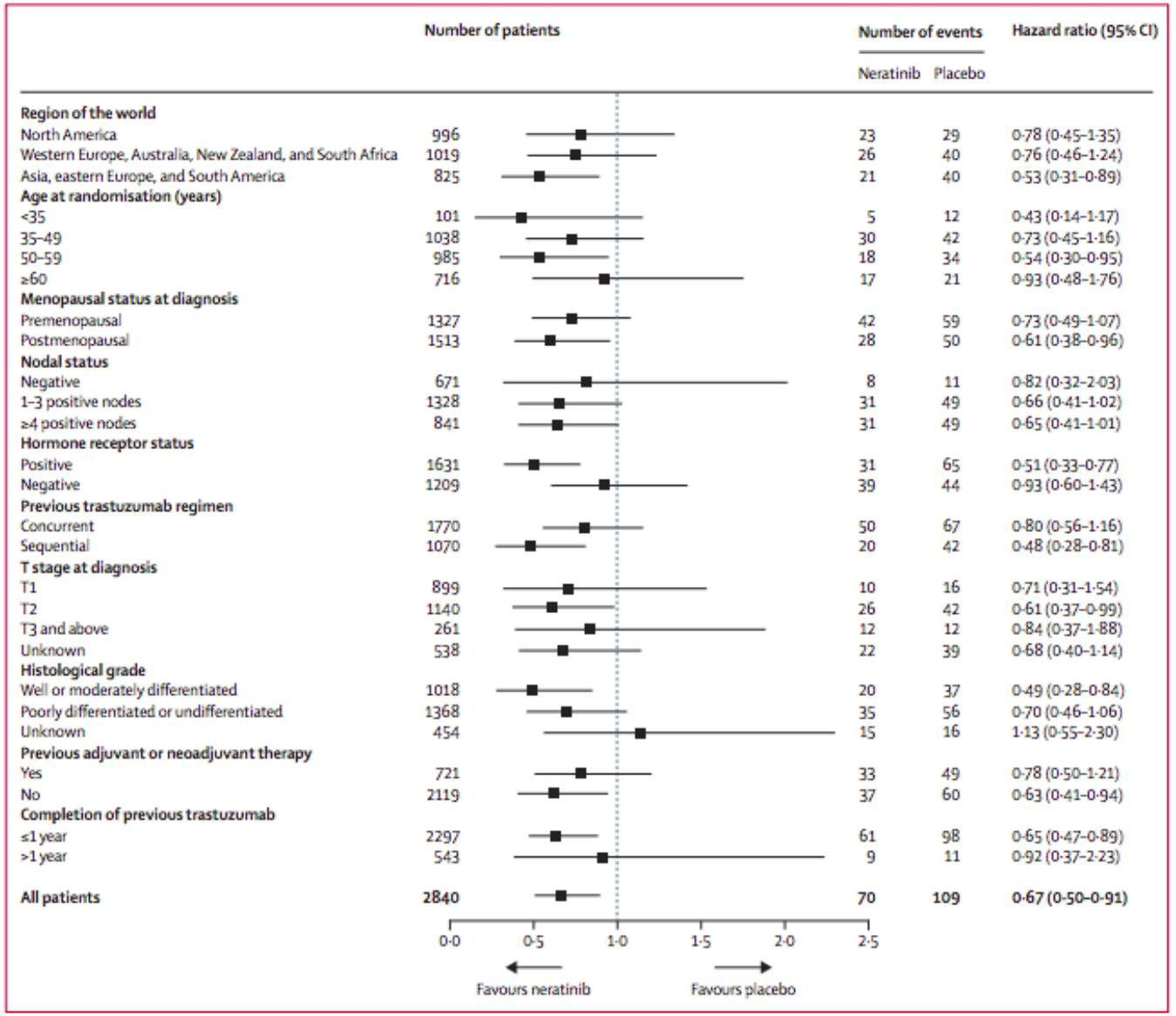
	Neratinib group (n=1420)	Placebo group (n=1420)
Any event	70 (5%)	109 (8%)
Local or regional invasive recurrence	8 (1%)	25 (2%)
Invasive ipsilateral breast tumour recurrence	4 (<1%)	4 (<1%)
Invasive contralateral breast cancer	2 (<1%)	5 (<1%)
Distant recurrence*	52 (4%)	73 (5%)
Bone	21 (1%)	21 (1%)
Brain	11 (1%)	15 (1%)
Distant lymph node	6 (<1%)	10 (1%)
Liver	13 (1%)	21 (1%)
Lung	5 (<1%)	12 (1%)
Other	5 (<1%)	2 (<1%)
Other abdominal viscera	0	2 (<1%)
Pleura	1 (<1%)	3 (<1%)
Subcutaneous tissue	1 (<1%)	1 (<1%)
Unknown	1 (<1%)	0
Death without previous recurrence	4 (<1%)	2 (<1%)

Data are n (%). *Patients might have had more than one distant site of recurrence.

***Table 2:* Invasive disease-free survival events in the intention-to-treat population**

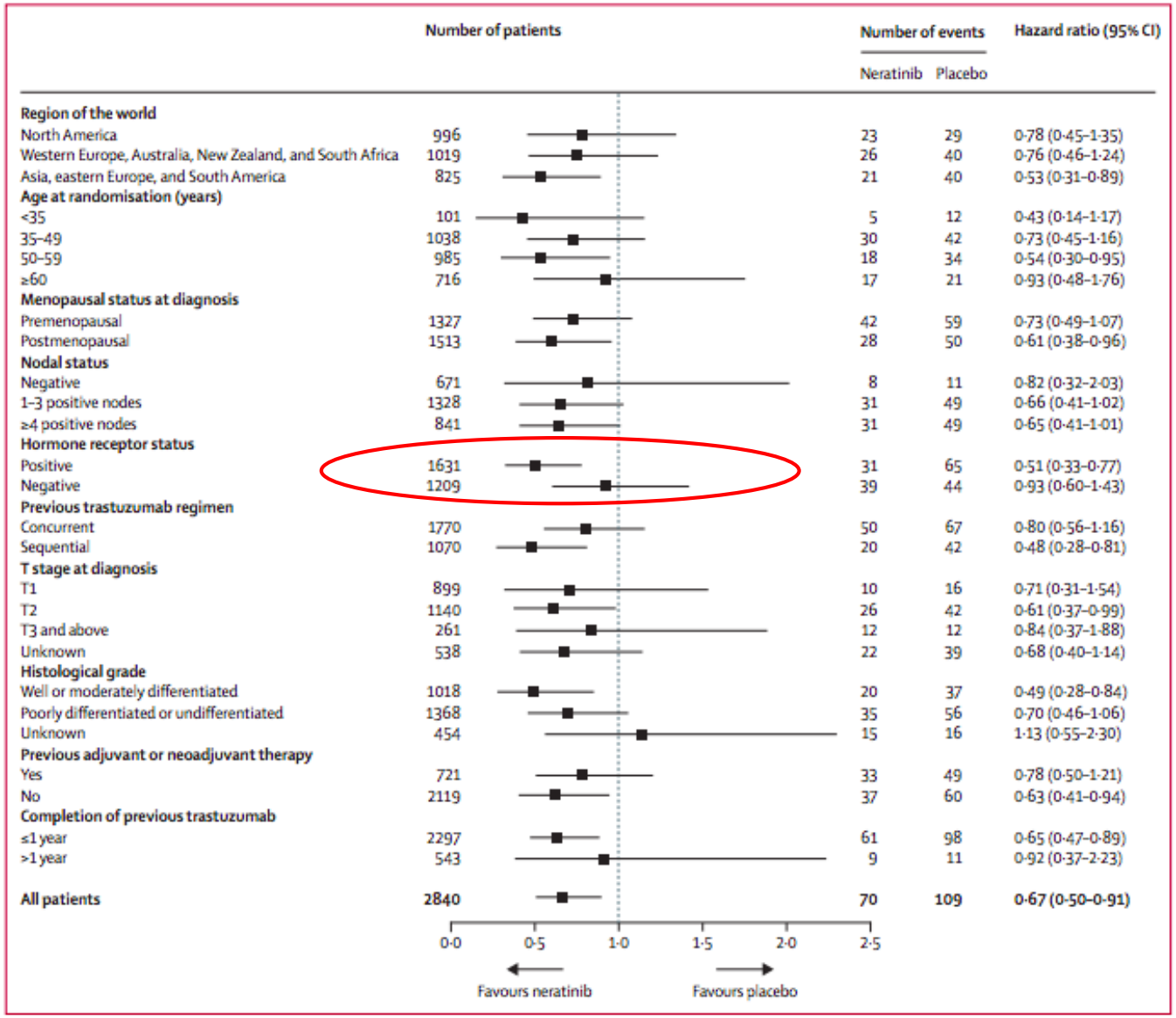
Chan A. Lancet Oncol 2016

ExteNET: IDFS by subgroups



Chan A. Lancet Oncol 2016

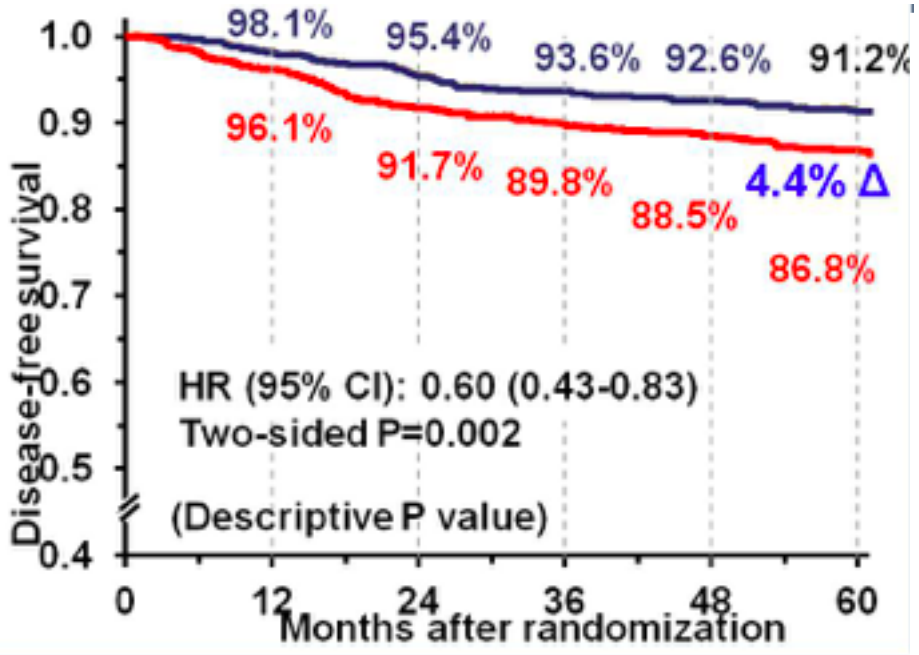
ExteNET: IDFS by subgroups



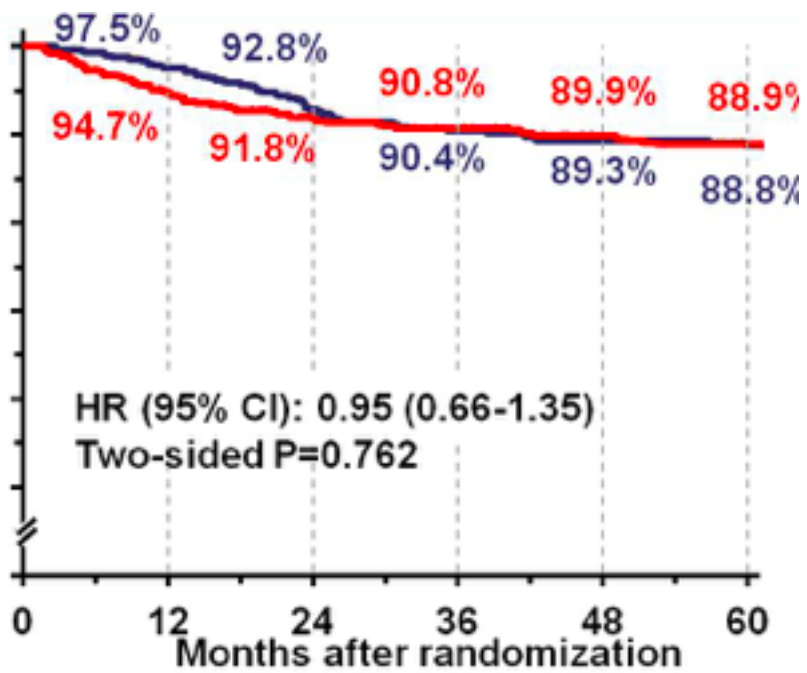
Chan A. Lancet Oncol 2016

ExteNET
IDFS improvement more evident in hormone receptor positive

Hormone receptor positive



Hormone receptor negative



ODAC Website

Adverse events occurring in at least 10% of patients in the safety population

	Neratinib group (n=1408)			Placebo group (n=1408)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Diarrhoea	781 (55%)	561 (40%)	1 (<1%)	476 (34%)	23 (2%)	0
Nausea	579 (41%)	26 (2%)	0	301 (21%)	2 (<1%)	0
Fatigue	359 (25%)	23 (2%)	0	276 (20%)	6 (<1%)	0
Vomiting	322 (23%)	47 (3%)	0	107 (8%)	5 (<1%)	0
Abdominal pain	314 (22%)	24 (2%)	0	141 (10%)	3 (<1%)	0
Headache	269 (19%)	8 (1%)	0	269 (19%)	6 (<1%)	0
Upper abdominal pain	201 (14%)	11 (1%)	0	93 (7%)	3 (<1%)	0
Rash	205 (15%)	5 (<1%)	0	100 (7%)	0	0
Decreased appetite	166 (12%)	3 (<1%)	0	40 (3%)	0	0
Muscle spasms	157 (11%)	1 (<1%)	0	44 (3%)	1 (<1%)	0
Dizziness	143 (10%)	3 (<1%)	0	125 (9%)	3 (<1%)	0
Arthralgia	84 (6%)	2 (<1%)	0	158 (11%)	4 (<1%)	0

Chan A. Lancet Oncol 2016

Adjuvant Neratinib

FDA approval on July 17, 2017:

"... Extended adjuvant treatment of early-satge HER2 overexpressed/amplified breast cancer, to follow trastuzumab adjuvant-based therapy."

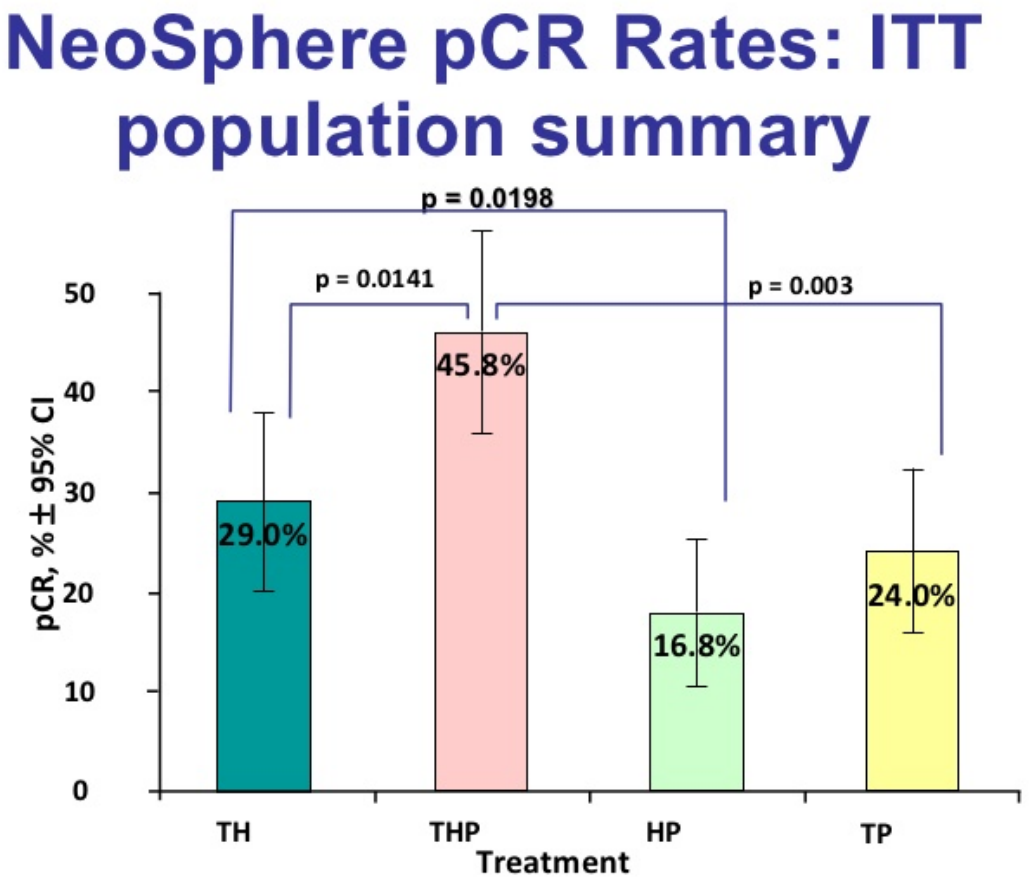
"...subgroup analysis were exploratory"

EMA/EMEA refusal on 22 February 2018:

Adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Nerlynx, intended for the treatment of breast cancer.

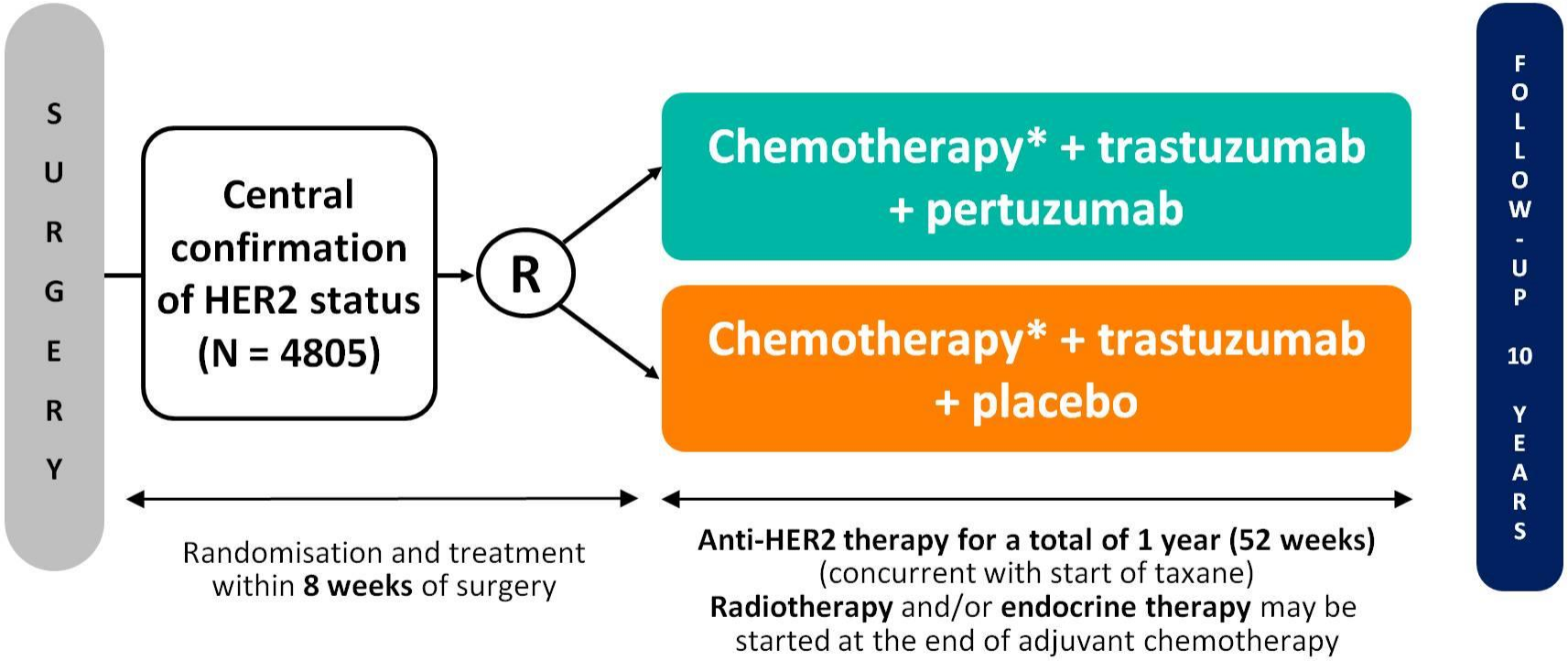
Combination of chemotherapy + trastuzumab + pertuzumab Improves OS in the advanced setting and increases pCR as neoadjuvant Rx

Swain S. N Engl J Med 2015



Gianni L. Lancet Oncol 2016

APHINITY: Trial Design



*A number of standard anthracycline-taxane-sequences or a non-anthracycline (TCH) regimen were allowed

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Von Minckwitz G. N Engl J Med 2017

APHINITY: Randomization Stratification Factors by Treatment

	Pertuzumab n=2400	Placebo n=2404*
Nodal status, n (%)		
0 positive nodes and T ≤1 cm*	90 (3.8)	84 (3.5)
0 positive nodes and T >1 cm*	807 (33.6)	818 (34.0)
1–3 positive nodes	907 (37.8)	900 (37.4)
≥ 4 positive nodes	596 (24.8)	602 (25.0)
Adjuvant chemotherapy regimen (randomised), n (%)		
Anthracycline-containing regimen	1865 (77.7)	1877 (78.1)
Non-anthracycline-containing regimen	535 (22.3)	527 (21.9)
Hormone receptor status (central), n (%)		
Negative (ER- and PgR-negative)	864 (36.0)	858 (35.7)
Positive (ER- and/or PgR-positive)	1536 (64.0)	1546 (64.3)
Geographical region, n (%)		
USA	296 (12.3)	294 (12.2)
Canada/Western Europe/Australia – New Zealand/South Africa	1294 (53.9)	1289 (53.6)
Eastern Europe	200 (8.3)	200 (8.3)
Asia Pacific	550 (22.9)	557 (23.2)
Latin America	60 (2.5)	64 (2.7)
Protocol Version, n (%)		
Protocol A	1828 (76.2)	1827 (76.0)
Protocol Amendment B	572 (23.8)	577 (24.0)

2/3 LN +

3/4 anthracycline

2/3 HR +

* One patient was excluded from the ITT population due to her falsification of personal information

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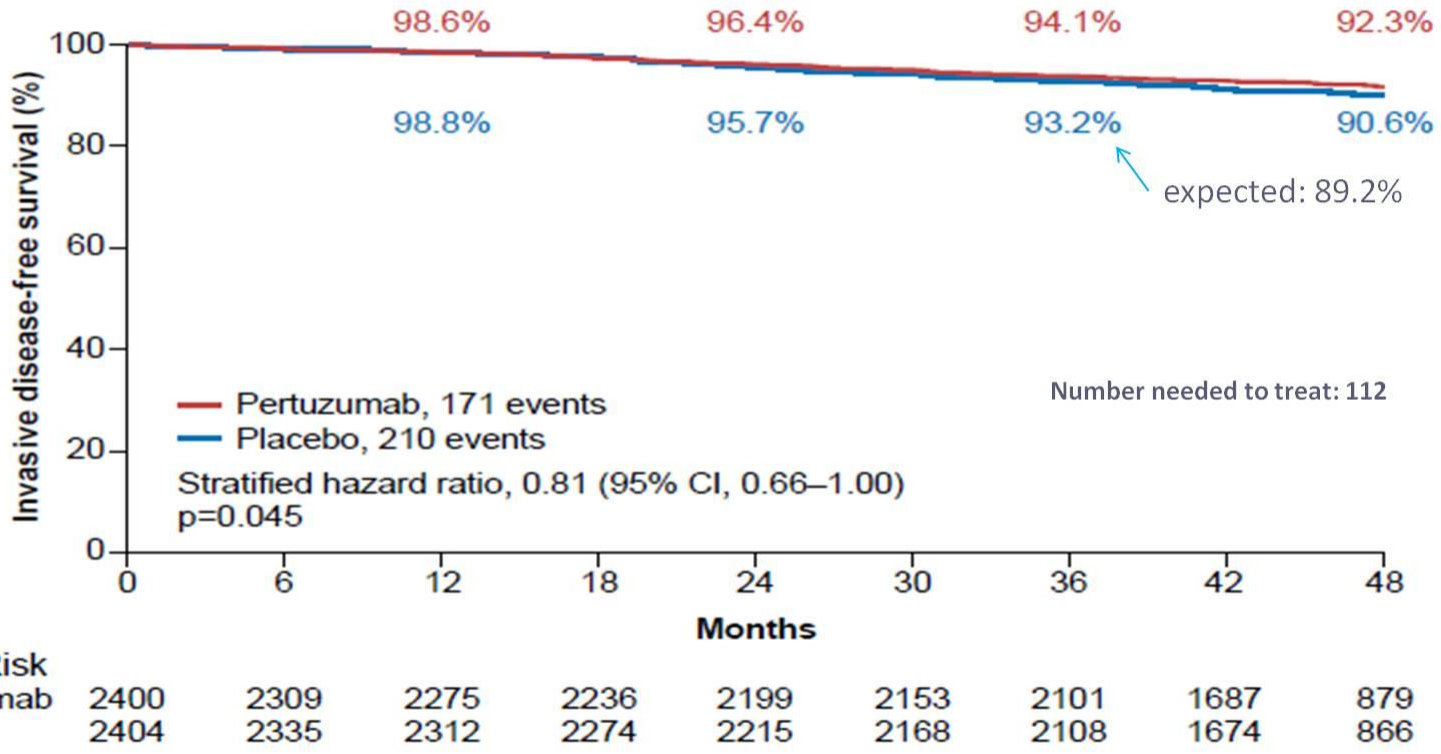
APHINITY: Intent-to-Treat Primary Endpoint Analysis Invasive Disease-free Survival



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APHINITY: Summary of first Occurrence of an IDFS Event

	Pertuzumab n=2400	Placebo n=2404
Total patients with IDFS event, n (%)	171 (7.1)	210 (8.7)
Category of first IDFS event, n (%)		
Distant recurrence	112 (4.7)	139 (5.8)
Locoregional recurrence	26 (1.1)	34 (1.4)
Contralateral breast cancer	5 (0.2)	11 (0.5)
Death without prior event	28 (1.2)	26 (1.1)
Site of first distant recurrence n (%)		
Lung/liver/pleural effusion	43 (1.8)	61 (2.5)
CNS	46 (1.9)	45 (1.9)
Other	9 (0.4)	9 (0.4)
Bone	21 (0.9)	30 (1.2)

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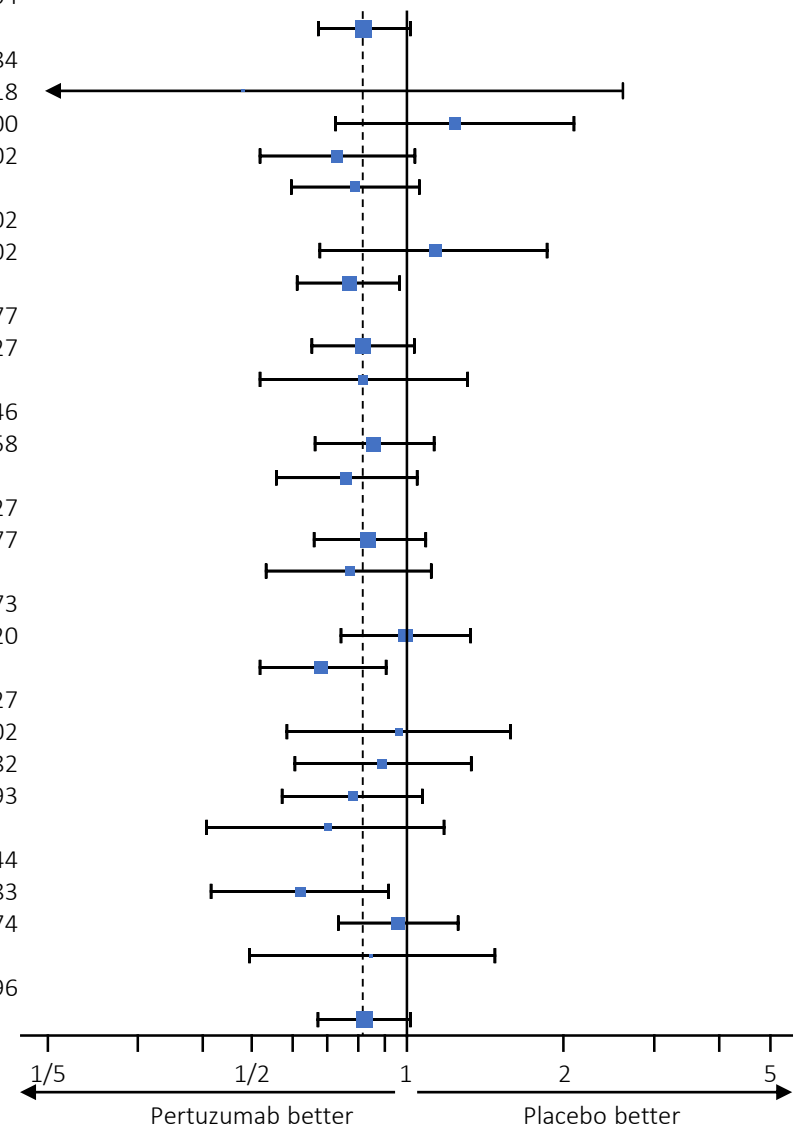
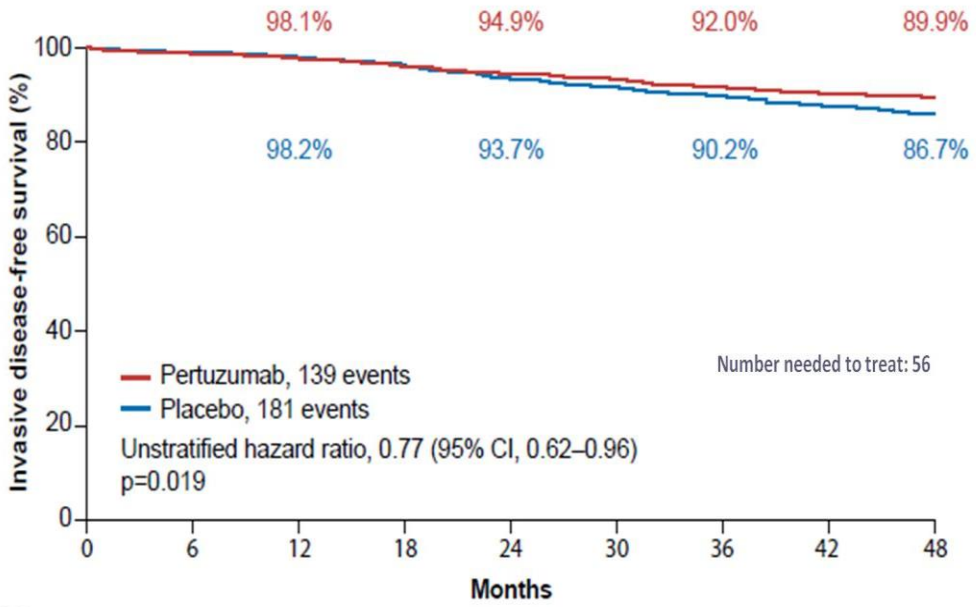
APHINITY: IDFS Forest Plot by Subgroups

Subgroup	No. of Events / No. of Patients: Pertuzumab	No. of Events / No. of Patients: Placebo	Unstratified Hazard Ratio (95%CI)	3-year IDFS Rate, %: Pertuzumab	3-year IDFS Rate, %: Placebo	Interaction test p-value
All patients	171 / 2400	210 / 2404	0.82 (0.67–1.00)	94.1	93.2	NA
Nodal status						
0 positive nodes, tumor ≤1cm	2 / 90	4 / 84	0.48 (0.09–2.60)	97.7	97.5	
0 positive nodes, tumor >1cm	30 / 807	25 / 818	1.23 (0.72–2.10)	97.5	98.5	0.374
1–3 positive nodes	55 / 907	75 / 900	0.73 (0.52–1.04)	94.9	93.8	
≥4 positive nodes	84 / 596	106 / 602	0.79 (0.59–1.05)	87.5	84.7	
0 positive nodes	32 / 897	29 / 902	1.13 (0.68–1.86)	97.5	98.4	0.169
≥1 positive nodes	139 / 1503	181 / 1502	0.77 (0.62–0.96)	92.0	90.2	
Adjuvant chemotherapy regimen						
Anthracycline	139 / 1865	171 / 1877	0.82 (0.66–1.03)	93.8	93.0	0.996
Non-anthracycline	32 / 535	39 / 527	0.82 (0.51–1.31)	94.9	94.0	
Central hormone receptor status						
Positive (ER- and/or PgR-positive)	100 / 1536	119 / 1546	0.86 (0.66–1.13)	94.8	94.4	0.543
Negative (ER- and PgR-negative)	71 / 864	91 / 858	0.76 (0.56–1.04)	92.8	91.2	
Protocol version						
Protocol A	120 / 1828	143 / 1827	0.84 (0.66–1.08)	94.7	94.1	0.686
Protocol Amendment B	51 / 572	67 / 577	0.77 (0.53–1.11)	91.9	90.6	
Menopausal status at screening						
Pre-menopausal	93 / 1152	96 / 1173	0.99 (0.75–1.32)	93.5	93.7	0.069
Post-menopausal	78 / 1242	113 / 1220	0.68 (0.51–0.91)	94.5	92.7	
Age group (years)						
<40	30 / 326	32 / 327	0.96 (0.59–1.59)	93.4	93.1	
40–49	48 / 708	53 / 702	0.89 (0.60–1.32)	94.5	94.3	0.781
50–64	69 / 1051	91 / 1082	0.78 (0.57–1.07)	94.3	93.3	
≥65	24 / 315	34 / 293	0.70 (0.41–1.17)	92.9	90.6	
Tumor size (cm)						
<2	41 / 977	64 / 944	0.62 (0.42–0.92)	97.0	94.6	
2–<5	108 / 1273	115 / 1283	0.96 (0.74–1.24)	92.5	93.0	0.203
≥5	22 / 147	31 / 174	0.85 (0.49–1.47)	87.5	87.5	
Sex						
Female	171 / 2397	209 / 2396	0.82 (0.67–1.01)	94.1	93.2	NA



Subgroups with more pronounced benefit

APHINITY: Node-positive Subgroup



No. at Risk

Pertuzumab	1503	1444	1419	1387	1358	1327	1283	912	423
Placebo	1502	1453	1439	1408	1359	1319	1264	882	405

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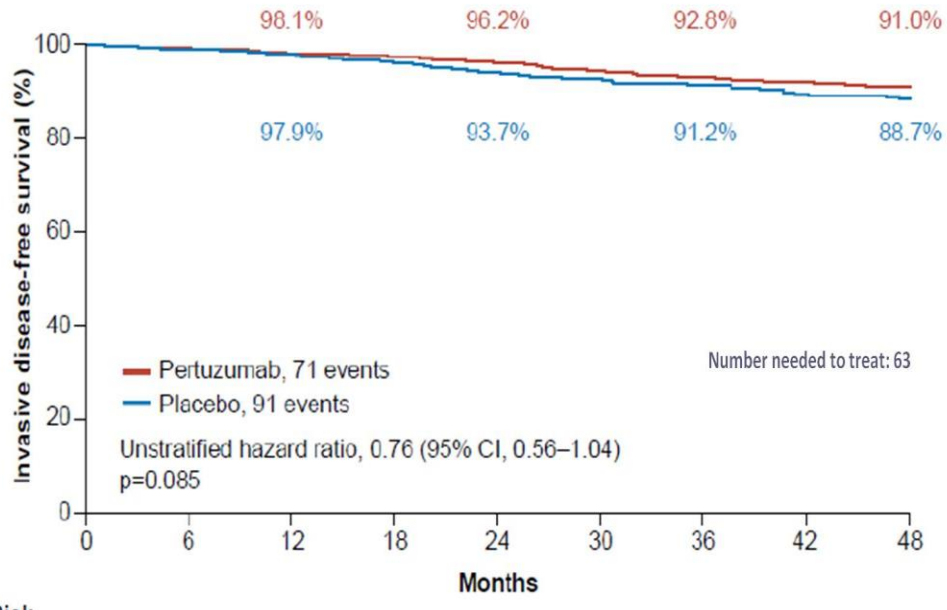
APHINITY: Hormone Receptor-negative Subgroup



No. at Risk

Pertuzumab	864	836	821	813	797	774	755	600	314
Placebo	858	827	811	793	771	758	730	569	302

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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

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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%)

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Tumor characteristics BCIRG 006 & APHINITY

Study	BCIRG 006	APHINITY
n	3222	4805
T1	40%	40%
LN positive	61%	64%
(> 4 positive LN)	33%	25%
HR positive	54%	64%

Slamon D. N Engl J Med 2011
Von Minckwitz G. N Engl J Med 2017

Tumor characteristics BCIRG 006 & APHINITY

Study	BCIRG 006	APHINITY
n	3222	4805
T1	40%	40%
LN positive	61%	64%
(> 4 positive LN)	33%	25%
HR positive	54%	64%

Slamon D. N Engl J Med 2011
Von Minckwitz G. N Engl J Med 2017

Adjuvant Pertuzumab

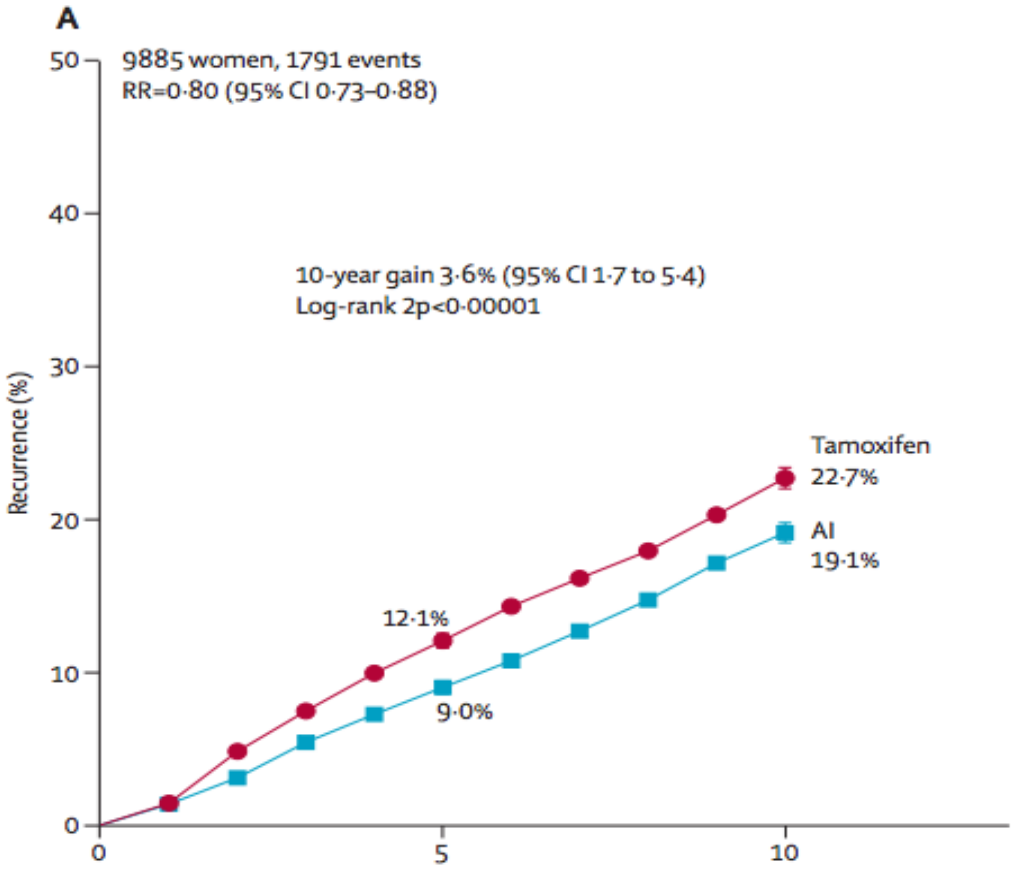
FDA approval on Dec 20, 2017:

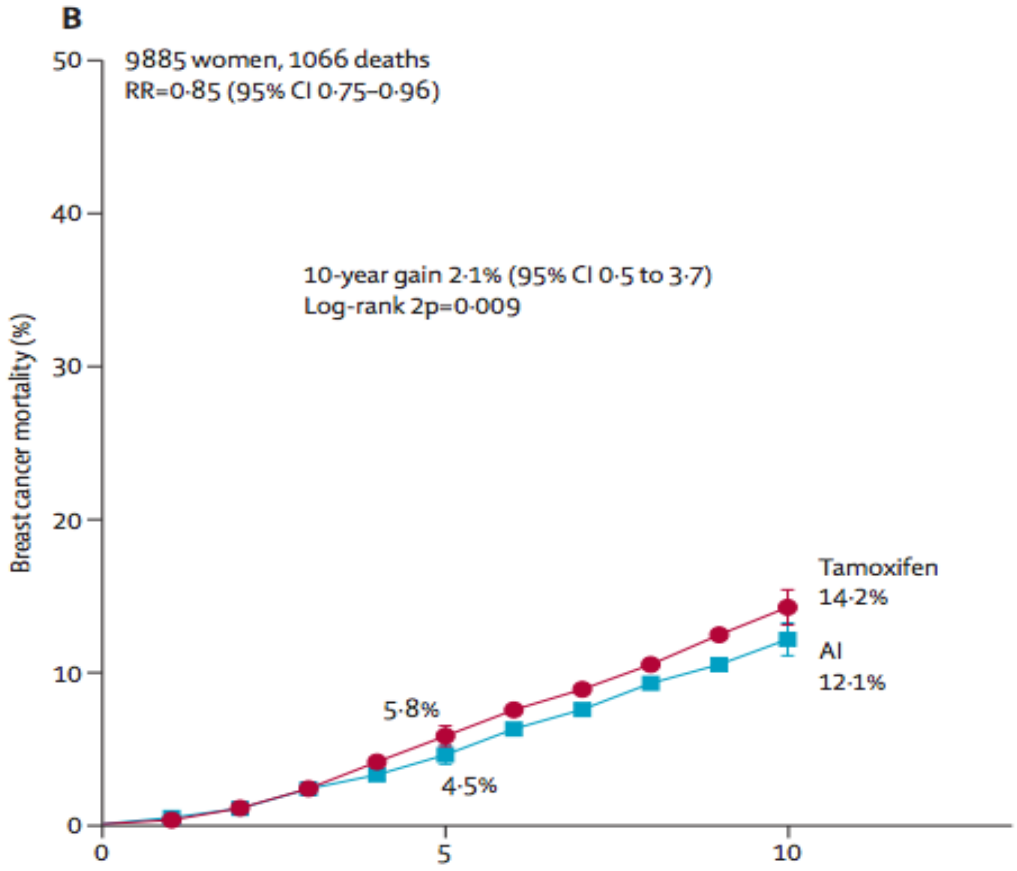
"... For use in combination with trastuzumab and chemotherapy as adjuvante treatment of adult patients with HER2 positive early breast cancer at high risk of recurrence."

"High risk patients included: patients such as those with hormone receptor negative or those with node positive breast cancer."

Anvisa aprova em 26 de fevereiro, 2018:

The benefits of Aromatase Inhibitors (AI) vs Tamoxifen
DFS(RR 0,80) and OS(RR 0,85)





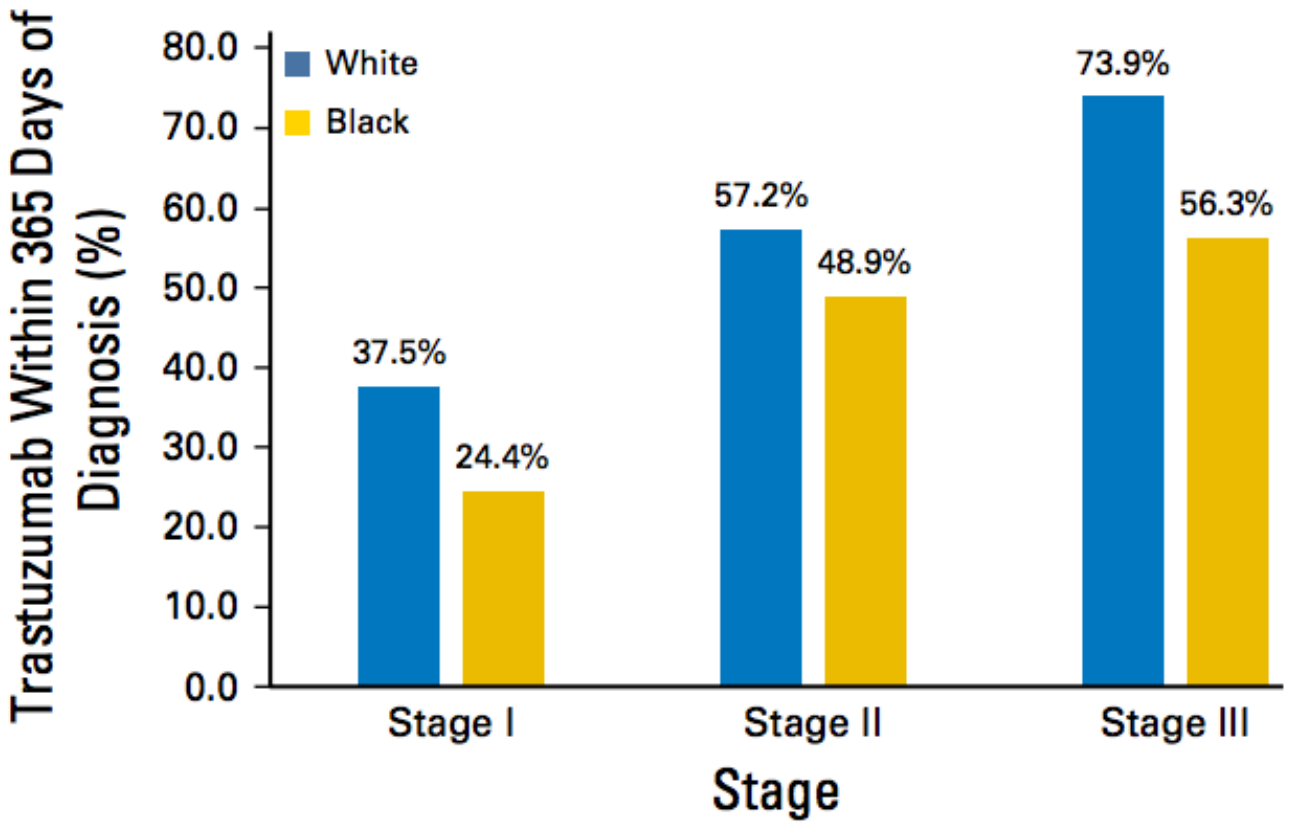
Early Breast Cancer Trialists' Collaborative Group. Lancet 2015

Access to adjuvant anti-HER2 treatment

SEER Medicare data
2010-2011
Stage I-III HER2-positive breast cancer
n=1362

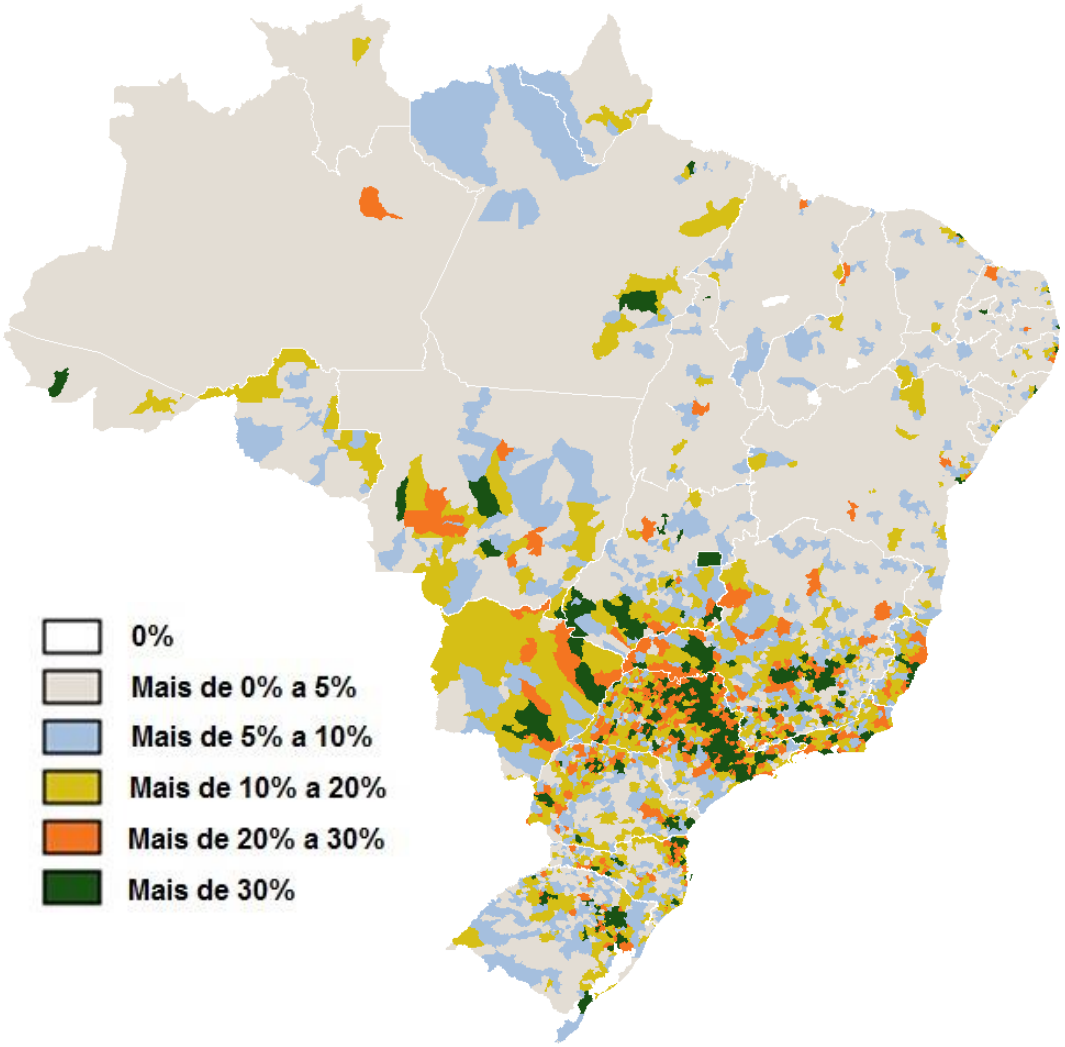
50% of women >65 years of age do not receive trastuzumab

Poverty, comorbidities and black women are independent risk factors to underRx



Reeder-Hayes. J Clin Oncol 2016

Brazilian health system: public SUS (all) and private (25%) depicted below
Trastuzumab available for early-stage breast cancer only after 2012 at SUS



Fonte: SIB/ANS/MS - 03/2017 e População - IBGE/20

Early-stage HER2 positive breast cancer
Take home messages

Talk to the Pathologist to ensure adequate HER2 testing

Adjuvant Trastuzumab leads to remarkable improvement with decrease in recurrence and death

Less treatment (less chemotherapy) is a good option for low-risk patients

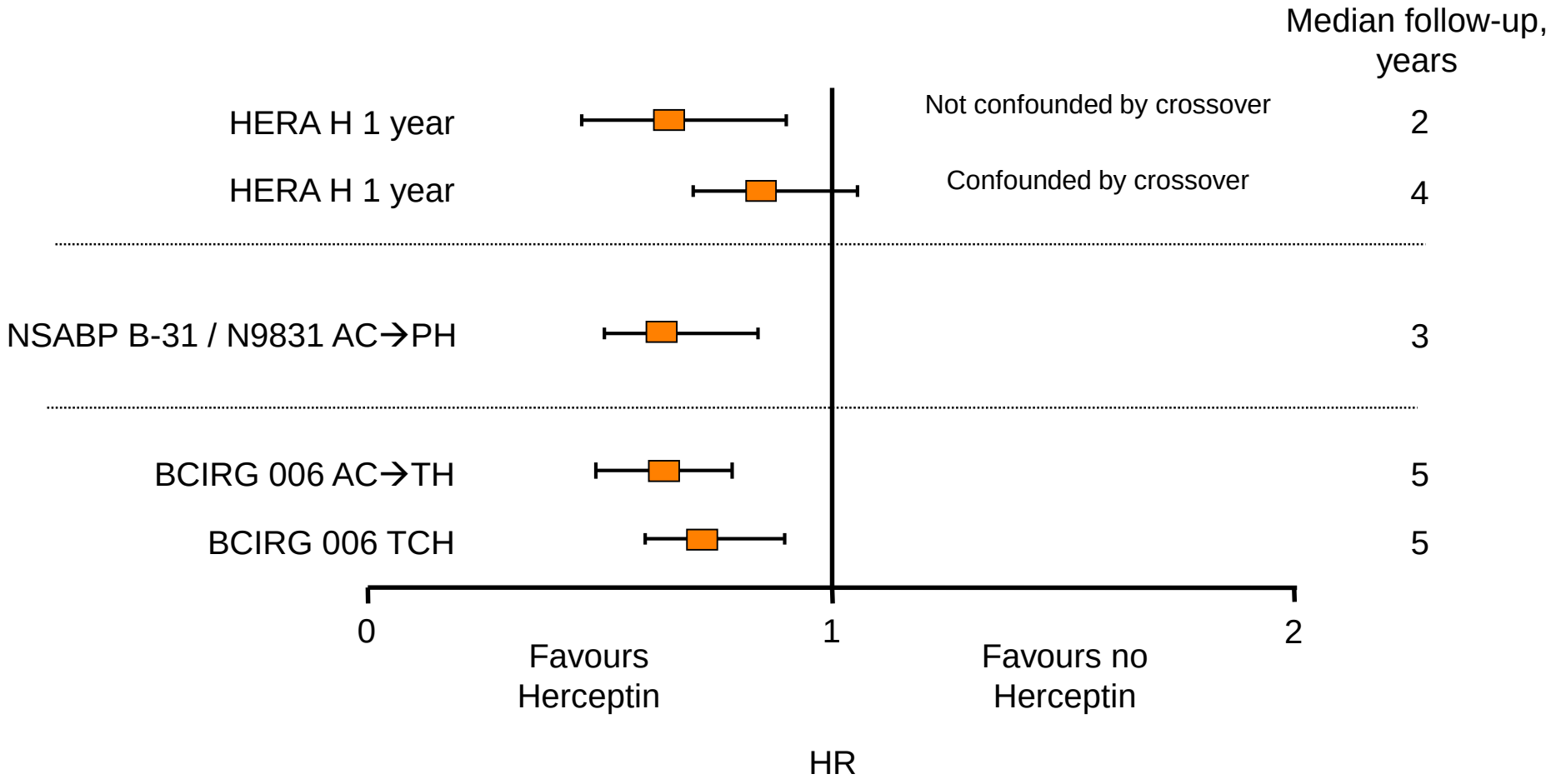
New agents (Pertuzumab and Neratinb) ameliorate the outcome in early-stage breast cancer

Efforts are ongoing to better select treatment (identify biomarkers beyond HER2)

Hopeful to provide these achievements to all those who need them

Extra

Improved outcome in HER2 positive early-stage breast cancer with adjuvant trasuzumab



Garnock-Jones et al 2010

Early-stage HER2-positive breast cancer

Attention to good quality HER2 testing

Should we give more treatment

Providing access

Early-stage HER2-positive breast cancer

Attention to good quality HER2 testing

Should we give more treatment

Provide access

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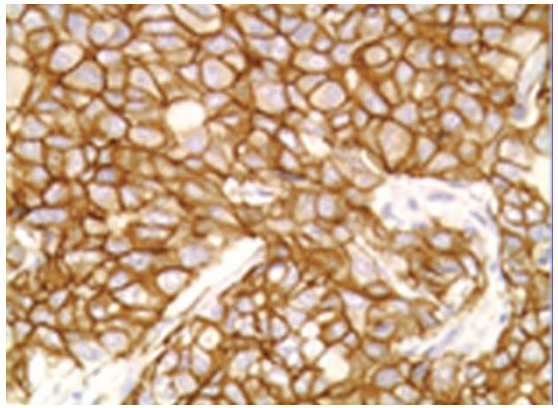
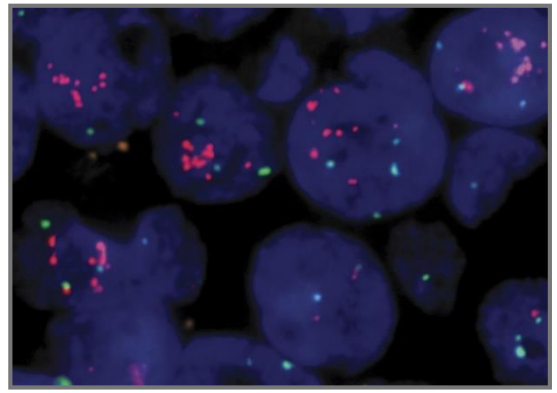
ASCO SPECIAL ARTICLE



Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update

Antonio C. Wolff, M. Elizabeth H. Hammond,* David G. Hicks,* Mitch Dowsett,* Lisa M. McShane,* Kimberly H. Allison, Donald C. Allred, John M.S. Bartlett, Michael Bilous, Patrick Fitzgibbons, Wedad Hanna, Robert B. Jenkins, Pamela B. Mangu, Soonmyung Paik, Edith A. Perez, Michael F. Press, Patricia A. Spears, Gail H. Vance, Giuseppe Viale, and Daniel F. Hayes**



- > 10% intense overexpressing cells
- HER2 to CEP17 ratio $\geq$ 2
- HER2 gene copy number $\geq$ 6

ASCO
CAP

How are we testing for HER2?

RESEARCH ARTICLE

HER2 Testing in Breast Carcinoma

Very Low Concordance Rate Between Reference and Local Laboratories in Brazil

Sheila Cristina Lordelo Wludarski, MD,† Lisandro Ferreira Lopes, MD, PhD,* Tácio R. Berto e Silva, MD,* Filomena M. Carvalho, MD, PhD,† Lawrence M. Weiss, MD,‡ and Carlos E. Bacchi, MD, PhD*†*

Concordance rate of only 34% (171/500)

Wludarski SC. Appl Immunohistochem Mol Morphol. 2011

Discordance in ER and HER2 testing (CIBOMA clinical trial)

1.441 “triple negative” specimens from NCT00130533 trial → central review

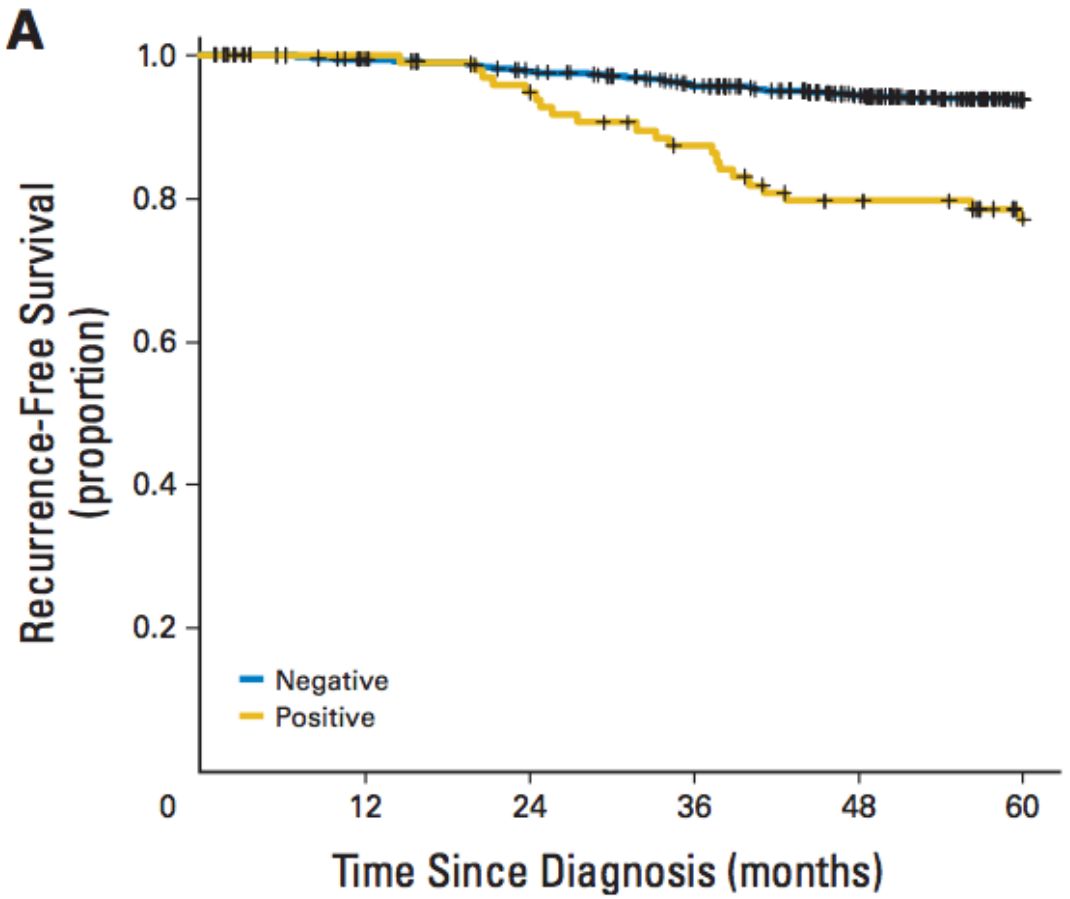
130 cases (9%) were not “triple negative”!!

- 74 Latin America(13%)
- 56 Spain (7%)

discrepancy ER or PgR > HER-2

Ruiz-Borrego M. ASC0 2011 abstract #78250

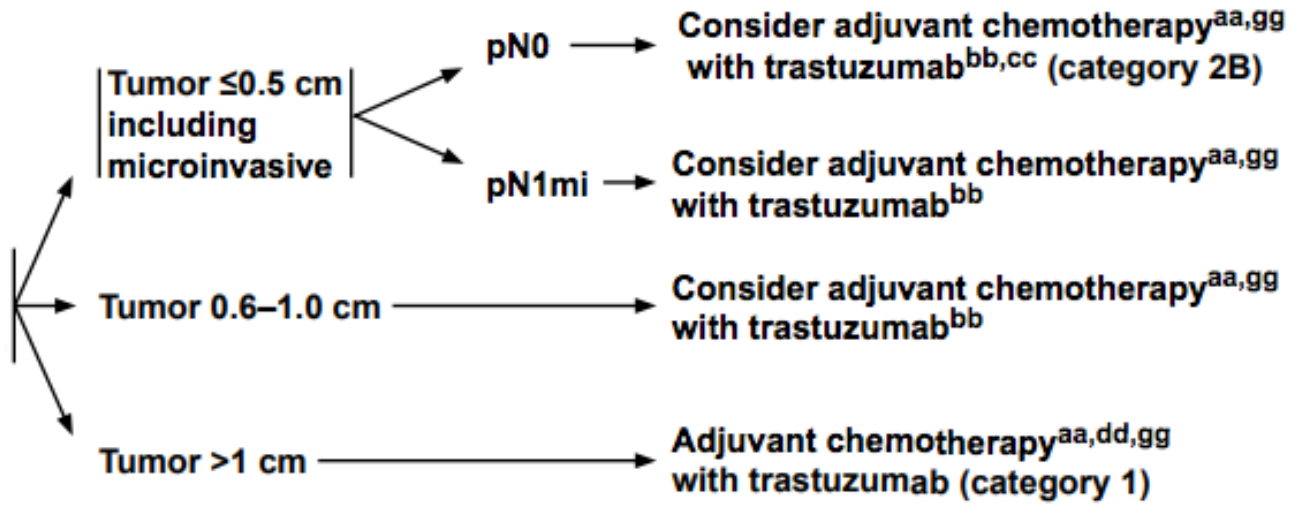
Outcome of small HER2 positive T1a/bN0 breast cancer without chemotherapy or trastuzumab



MDACC series

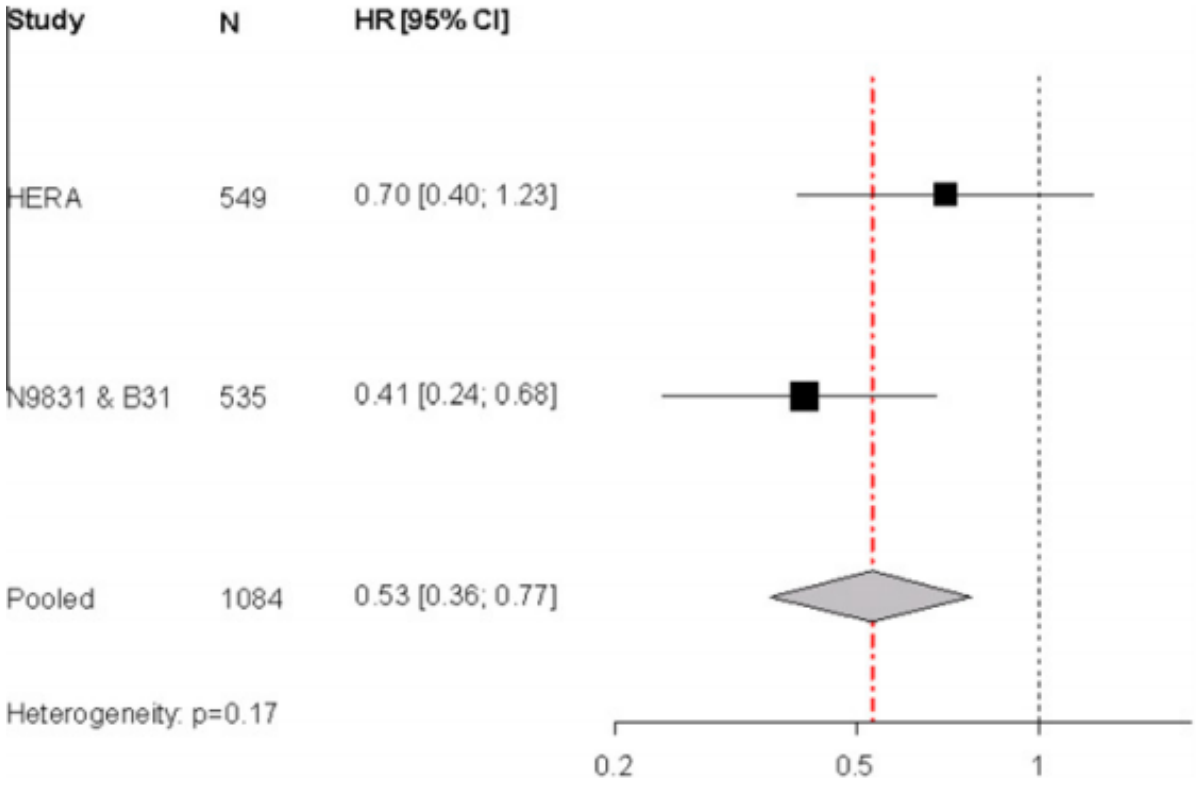
	n	RFS
HER2+	98	77%
HER2-	867	94%

Gonzalez-Angulo AM. J Clin Oncol 2009

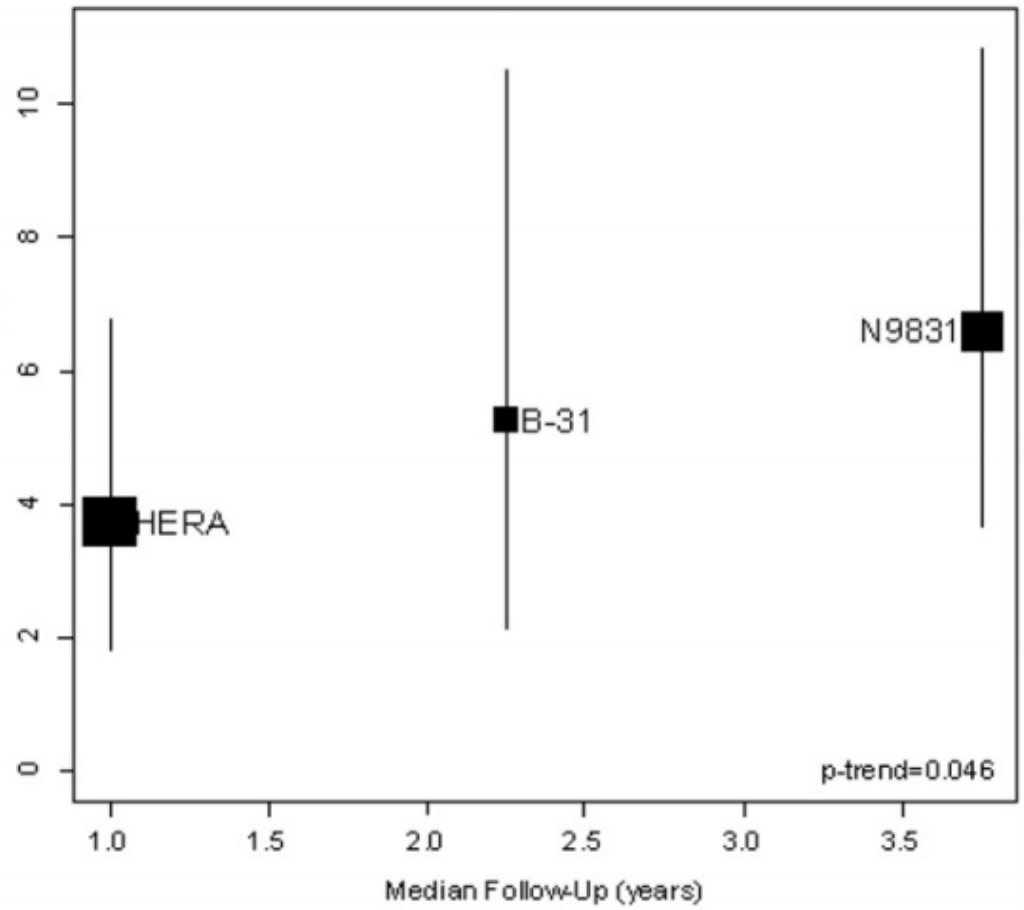


[bb]The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.

Adjuvant trastuzumab in elderly patients



47% relative risk reduction was observed in elderly patients treated with trastuzumab + chemotherapy



5% pooled cardiac events in elderly patients treated with trastzumab

Brollo J. Cancer Treat Rev 2013

Adjuvant trastuzumab in elderly patients: treatment considerations

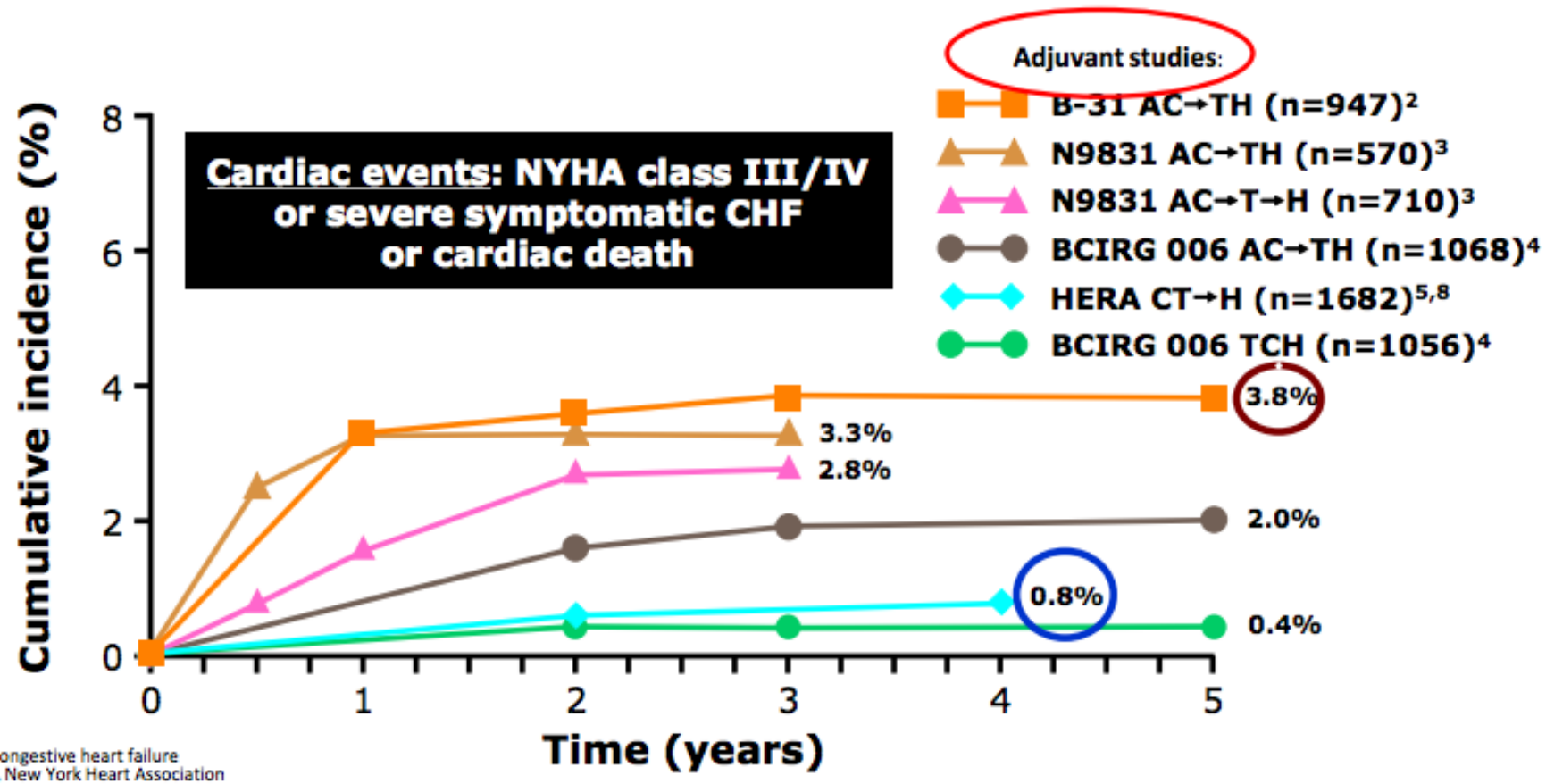
After assessing the patients's functional status, treatment options include:

TCH(P)(docetaxel, carboplatin and trastuzumab)(pertuzumab) is a treatment option for elderly patients, due to lower cardiac toxicity

Weekly paclitaxel and trastuzumab is an option for elderly patients at lower risk

Herceptin has a consistent safety profile based on experience in ~1,000,000 patients[1]

- Herceptin is well tolerated with a consistent safety and tolerability profile[2–7]
- Low cumulative incidence of cardiac events after long-term follow-up[2–7]



CHF, congestive heart failure
NYHA, New York Heart Association

1. PSUR 03/2011; 2. Rastogi P, *et al.* 2007; 3. Perez EA, *et al.* 2008; 4. Slamon D, *et al.* 2011
5. Procter M, *et al.* 2010; 6. Gianni L, *et al.* 2011; 7. Perez EA, *et al.* 2011; 8. Suter T, *et al.* 2007

CARDIAC EVENTS IN «EARLY BREAST CANCER TRIALS»

EBC trials (1-yr trastuzumab)	Therapy	Number of patients	% Asymptomatic LVEF decline	% Severe CHF	Cardiac death
HERA	H (1 year)	1678	3	0.6	0
NSABP B-31	AC--PH	947	NR	3.8 cumulative 5yr incidence	0
NCCTG N9831	AP--PH	570	NR	3.3 cumulative 3yr incidence	0
BCIRG 006	AC--DH	1068	18	1.9	0
BCIRG 006	DCarboH	1056	8.6	0.4	0

Slamon 2006; Rastogy 2007; Smith 2007; Perez 2008

	Recovery (% of patients)	Median Time (days)
Cardiac death	-	-
Severe CHF	80	124
Symptomatic CHF	67	151
Confirmed significant LVEF drop	69	192

CARDIAC ADVERSE EVENTS IN HERA trial

Trastuzumab and cardiac toxicity

Trastuzumab-associated cardiac toxicity is reversible, distinct form anthracycline-based (irreversible)

No cardiac deaths

Potential risk factors for trastuzumab-associated cardiac toxicity include

- anthracycline use
- age >50
- BMI> 25

Cardiac monitoring: echocardiogram (left ventricular ejection fraction)

- at baseline, 3, 6, 9 and 12 months

Guidelines for treatment modifications if needed

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Docetaxel or Vinorelbine with or without Trastuzumab for Breast Cancer

Heikki Joensuu, M.D., Pirkko-Liisa Kellokumpu-Lehtinen, M.D., Petri Bono, M.D., Tuomo Alanko, M.D., Vesa Kataja, M.D., Raija Asola, M.D., Tapio Utriainen, M.D., Riitta Kokko, M.D., Akseli Hemminki, M.D., Maija Tarkkanen, M.D., Taina Turpeenniemi-Hujanen, M.D., Sirkku Jyrkkiö, M.D., Martti Flander, M.D., Leena Helle, M.D., Seija Ingalsuo, M.D., Kaisu Johansson, M.D., Anna-Stina Jääskeläinen, M.D., Marjo Pajunen, M.D., Mervi Rauhala, M.D., Jaana Kaleva-Kerola, M.D., Tapio Salminen, M.D., Mika Leinonen, M.Sci., Inkeri Elomaa, M.D., and Jorma Isola, M.D., for the FinHer Study Investigators*

6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial

*Xavier Pivot, Gilles Romieu, Marc Debled, Jean-Yves Pierga, Pierre Kerbrat, Thomas Bachelot, Alain Lortholary, Marc Espié, Pierre Fumoleau, Daniel Serin, Jean-Philippe Jacquin, Christelle Jouannaud, Maria Rios, Sophie Abadie-Lacourtoisie, Nicole Tubiana-Mathieu, Laurent Cany, Stéphanie Catala, David Khayat, Iris Pauporté, Andrew Kramar, and the PHARE trial investigators**

original articles

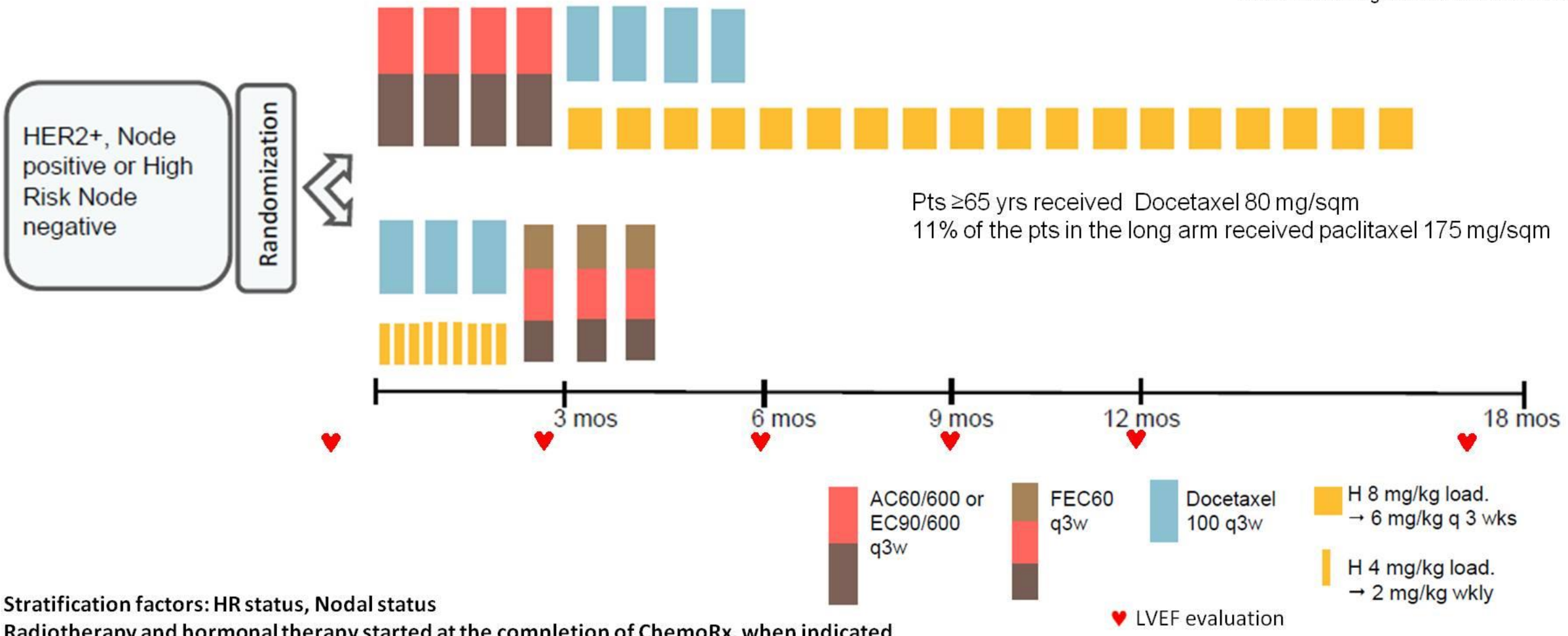
Annals of Oncology 26: 1333–1340, 2015
doi:10.1093/annonc/mdv213
Published online 1 May 2015

Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG)

D. Mavroudis[1]*, E. Saloustros[2], N. Malamos[3], S. Kakolyris[4], I. Boukovinas[5], P. Papakotoulas[6], N. Kentepozidis[7], N. Ziras[8] & V. Georgoulias[9], on behalf of the Breast Cancer Investigators of the Hellenic Oncology Research Group (HORG), Athens, Greece

Short-HER: Study Design

EUDRACT number: 2007-004326-25
NCI ClinicalTrials.gov number: NCT00629278



Stratification factors: HR status, Nodal status
Radiotherapy and hormonal therapy started at the completion of ChemoRx, when indicated

Presented By Pier Conte at 2017 ASCO Annual Meeting

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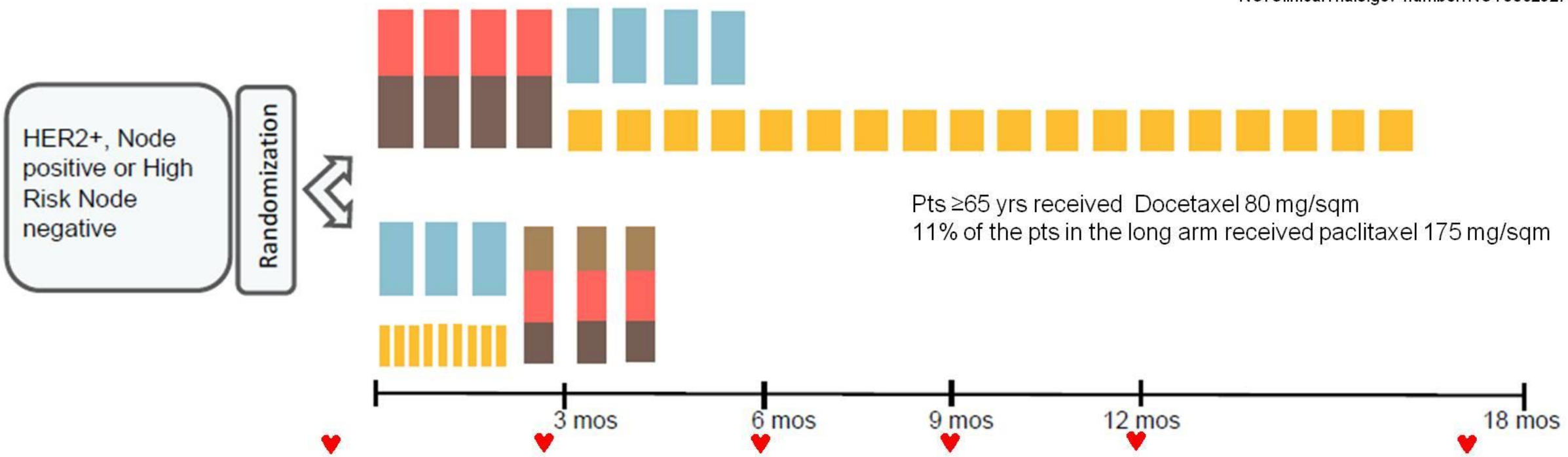


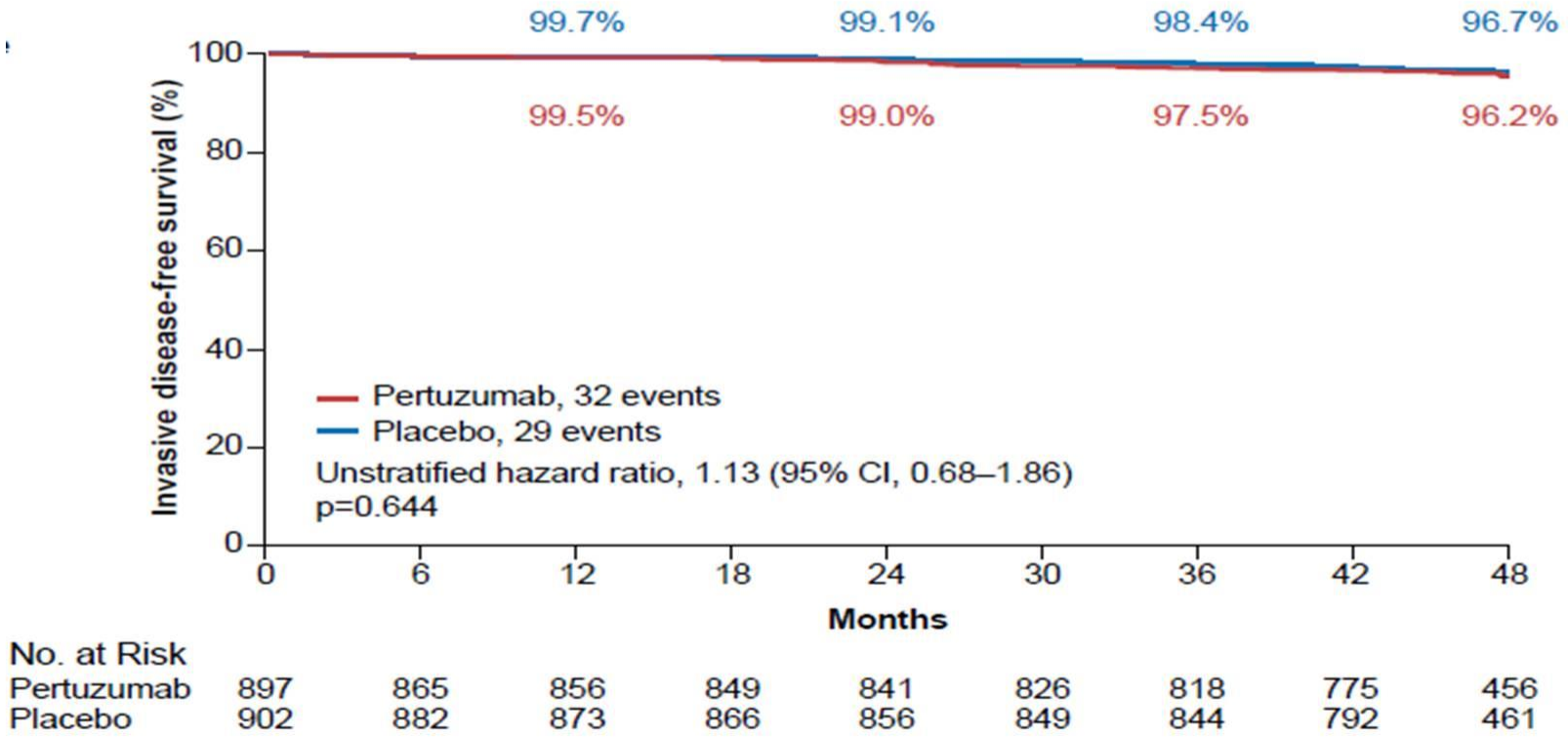
Did not demonstrate non-inferiority

Less cardiac toxicity

Stratification Factors: HR status, Nodal status

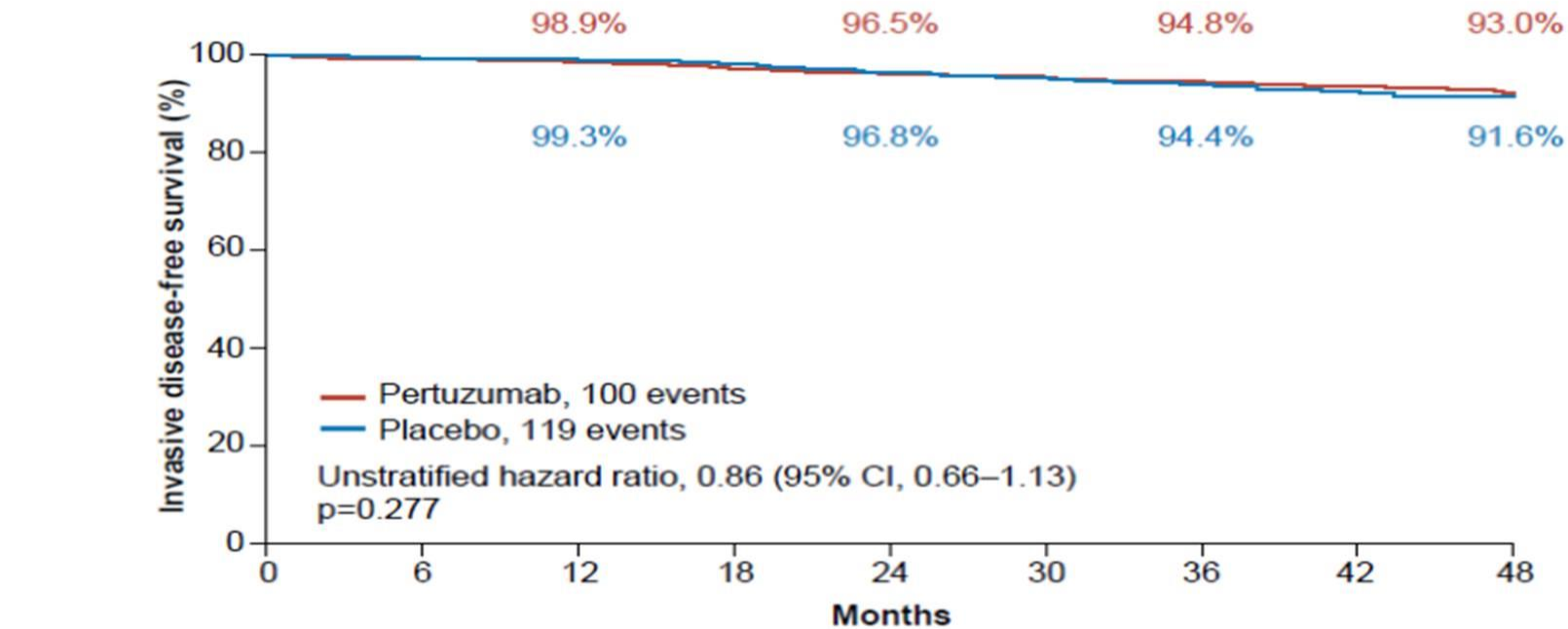
Radiotherapy and hormonal therapy started at the completion of ChemoRx, when indicated

APHINITY: Node-negative Subgroup



BIG
Breast International Group

APHINITY: Hormone Receptor-positive Subgroup



No. at Risk									
Pertuzumab	1536	1473	1454	1423	1402	1379	1346	1087	565
Placebo	1546	1508	1501	1481	1444	1410	1378	1105	564

BIG
Breast International Group

APHINITY: Conclusions

- **The APHINITY study met its primary objective**
  - **Pertuzumab reduced the risk of an IDFS event by 19% compared with placebo (HR 0.81; 95% CI 0.66, 1.00; p=0.045) at a median follow up of 45.4 months (3 years IDFS of 94.1% with pertuzumab and 93.2% with placebo)**
- Treatment effect was homogenous throughout all subgroups, however the N+ and HR-negative cohorts appeared to derive most benefit at the current point of time
  - with a relative risk reduction of 23% and 24%, respectively and
  - a 3-year IDFS absolute increase of 1.8% and 1.6% respectively
- Cardiac toxicity was low and not different between the two arms.
- The incidence of diarrhea was increased in the pertuzumab arm and occurred predominantly during chemotherapy and with TCH.
- Continued follow up for up to 10 years is important for overall survival, longer-term IDFS and safety analyses. Next analysis will be time-driven in 2.5 years.

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

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Breast International Group

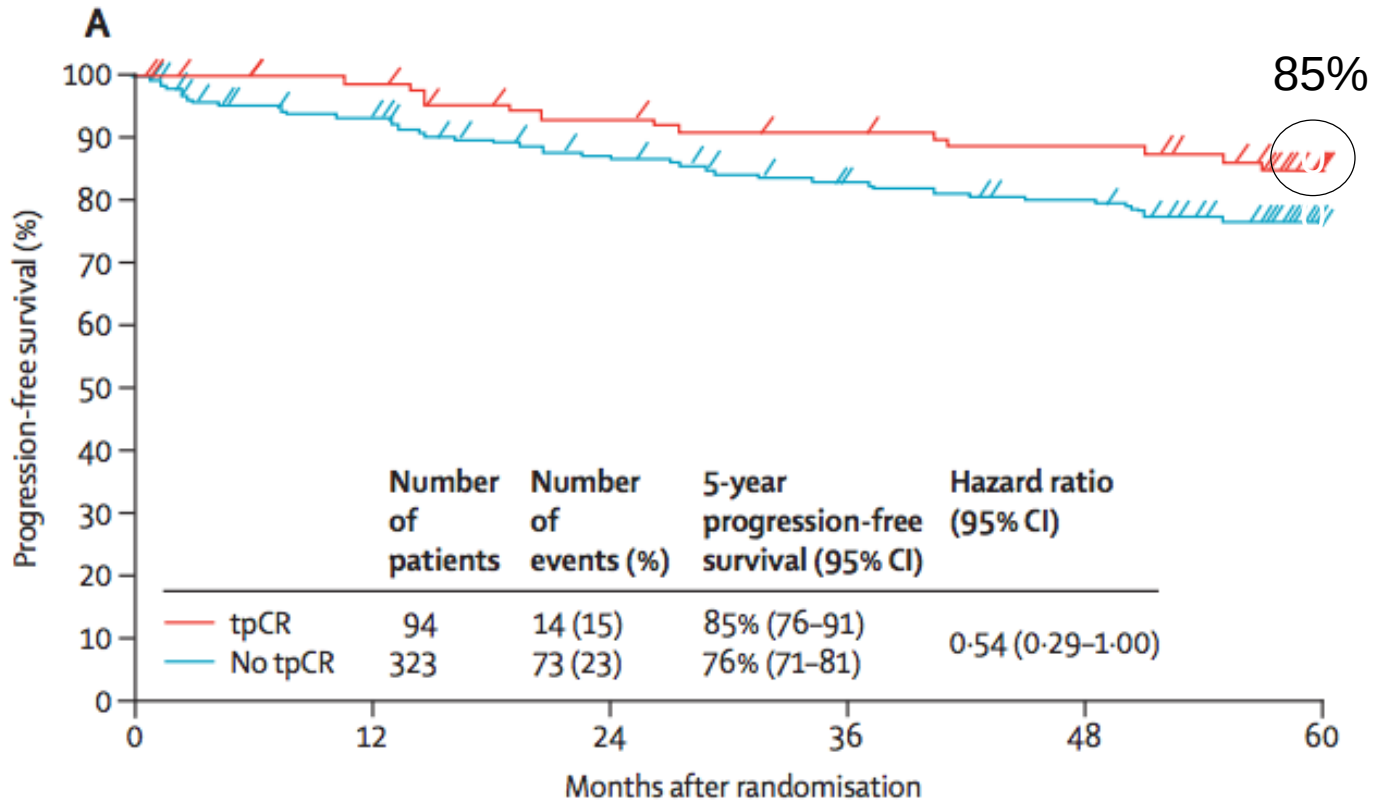
Proposed approach to early-stage HER2-positive breast cancer

Low risk Ex: T1N0, ER+	Higher risk Ex: LN+, ER neg
Surgery Paclitaxel + trastuzumab	Neoadjuvant Rx ChemoRx + trastuzumab + pertuzumab

Anti-HER2 Rx duration remains one year

Neratinib afterwards?

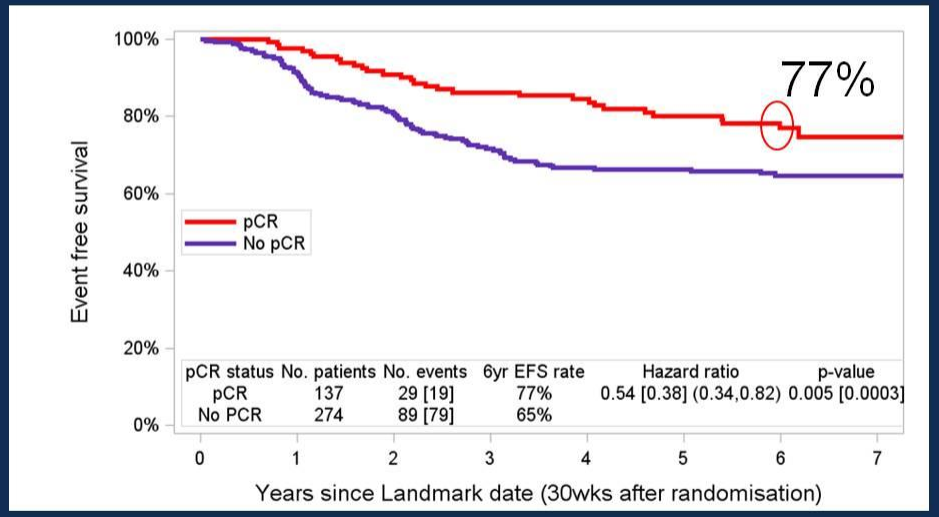
15% das pacientes com pCR apresentam recorrência em 5 anos (NeoSphere)



Gianni L. Lancet Oncol 2016.

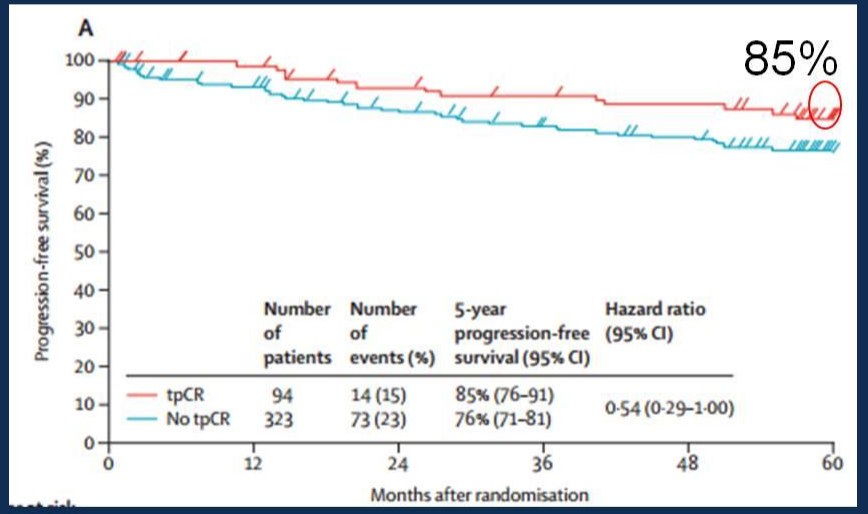
Clinical value of achieving a pCR following CT+anti-HER2 in Stage II-III

NeoALTTO (Huober et al. Abst#512)



42% T>5cm ; 16% N2+

NeoSphere (Gianni et al. Lancet Oncol 2016)



50% T>5cm ; ~25% N2+

Financial Implications

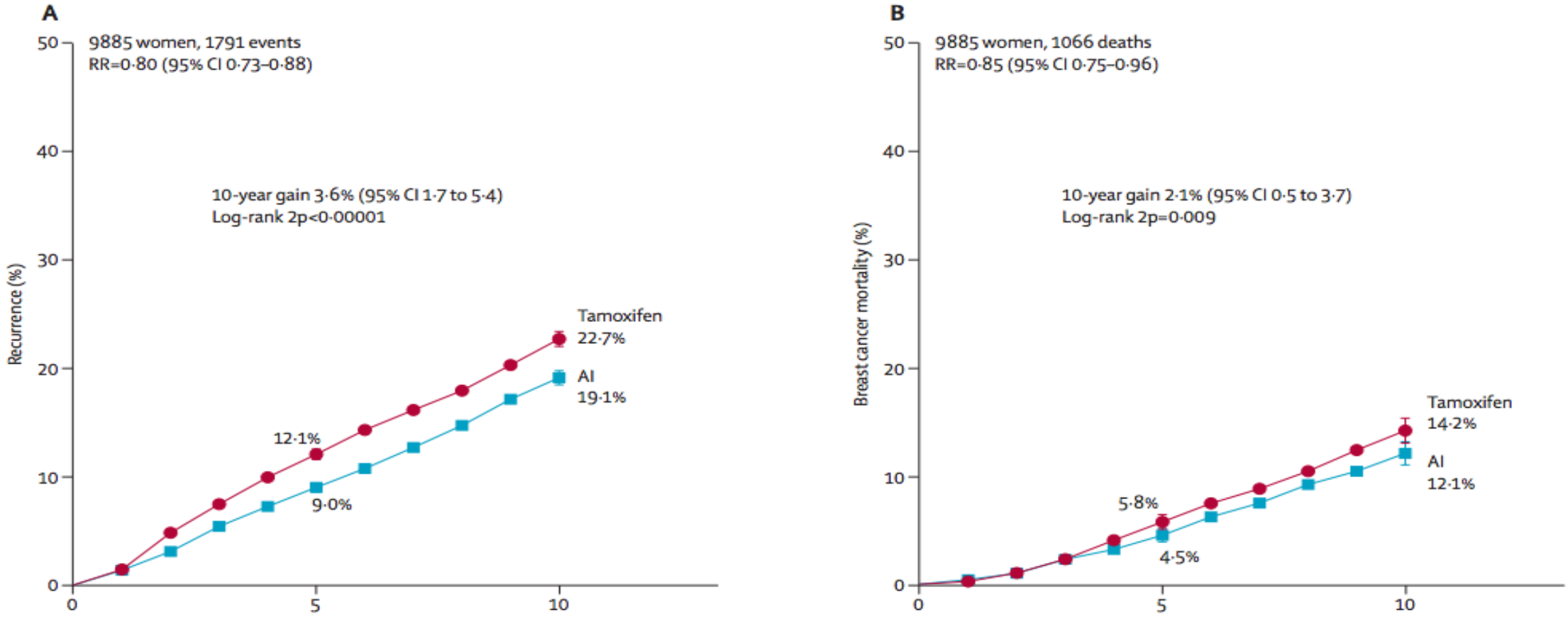
REGIMEN	Cost (USD)	Difference from 1 yr Trastuzumab
Trastuzumab (1yr)	$55,908	-
Tras + Pertuzumab (1 yr)	$150,504	+ $94,596
Tras + Lapatinib (1 yr)	$98,712	+ $42,804
9 weeks Trastuzumab	$9,676	- $46,232

Frame of reference: Letrozole (Δ 5 vs. 10 yrs) → $15,000 USD

Addition of paclitaxel to AC → $12,

Bach PB. NEJM 2009

Meta-análise: Tamoxifeno versus Inibidor de aromatase (AI)
Benefício em SLD (RR 0,80) e SG (RR 0,85)



Early Breast Cancer Trialists' Collaborative Group. Lancet 2015

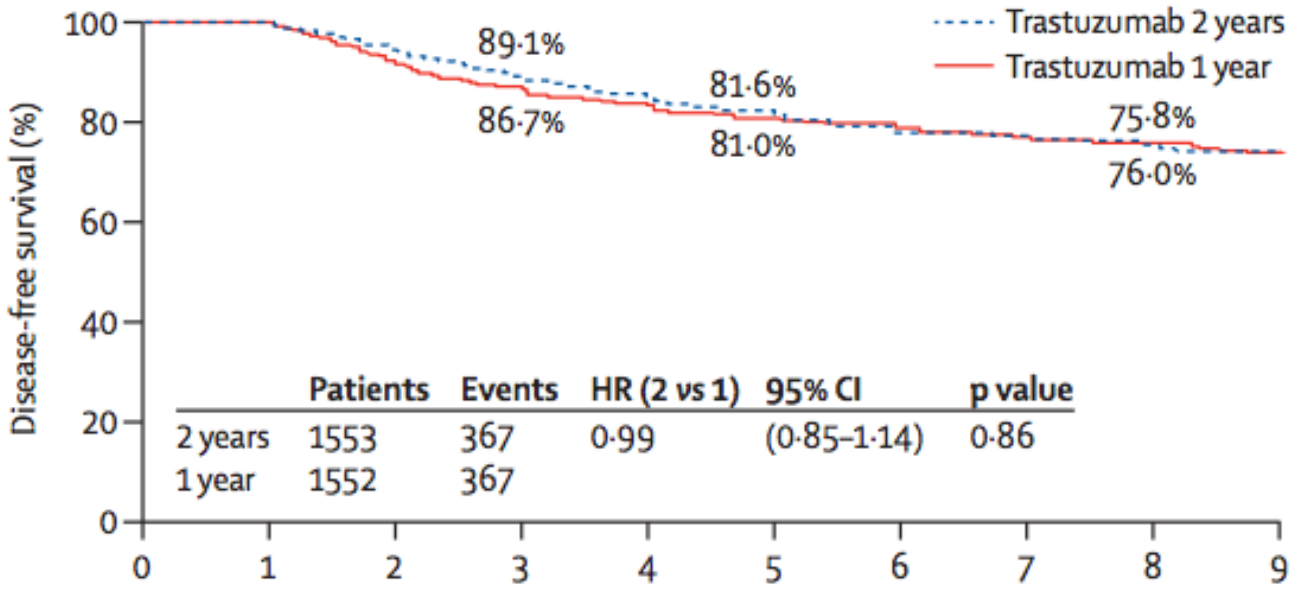
	"1st generation"	"2nd generation"
Chemotherapy	RR=0.70 (95%CI 0.63-0.77)[1]	RR=0.84 (95% CI 0.78-0.91)[2]
Hormonal Rx	RR=0.63 (95% CI 0.58-0.68)[3]	RR=0.8 (95% CI 0.73-0.88)[4]
Anti-HER2 Rx	RR=0.63 (95% CI 0.56-0.68)[5]	HR=0.81* (95% CI 0.66-1.00)[6]

* Single study

1- CMF polychemotherapy versus No chemotherapy. EBCTCG. Lancet 2005
2- Taxane + anthracycline versus Anthracycline. EBCTCG. Lancet 2012
3- Tamoxifen versus No hormone treatment. EBCTCG. Lancet 2011
4- Aromatase inhibitor versus Tamoxifen. EBCTCG. Lancet 2015
5- Trastzumab + chemotherapy versus Chemotherapy alone. Dahabreh IJ. Oncologist 2008
6- Pertuzumab + trastuzumab + chemotherapy versus trastuzumab + chemotherapy. von Minckwitz. N Engl J Med 2017

No benefit for extending trastuzumab beyond 1 year

HERA trial



Goldhisch A. Lancet 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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Adjuvant trastuzumab for 1 year remains the standard of care

original articles

Annals of Oncology 26: 1333–1340, 2015
doi:10.1093/annonc/mdv213
Published online 1 May 2015

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9 weeks vs 1 year adjuvant trastuzumab in combination with chemotherapy: results of the phase III multicentric Italian Short-HER study

PF Conte, G. Bisagni, A. Frassoldati, A. Brandes, E. Anselmi, F. Giotta, M. Aieta, V. Gebbia, A. Musolino, O. Garrone, C. Taverniti, G. Cavazzini, A. Turletti, D. Rubino, A. Ferro, E. Picardo, F. Piacentini, S. Balduzzi, R. D'Amico, V. Guarneri

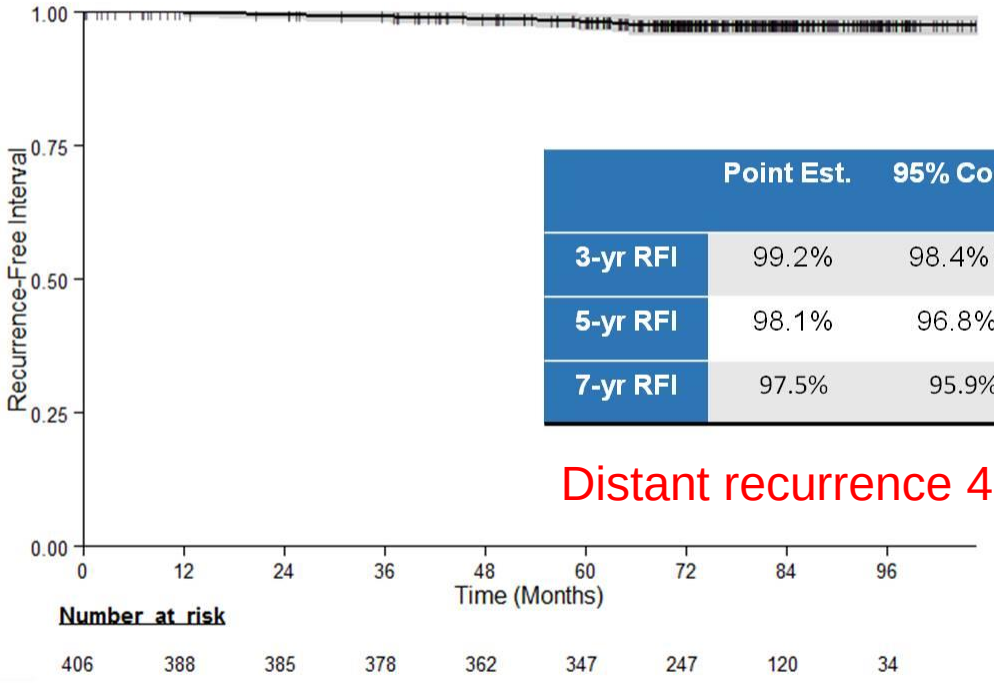
Medical Oncology 2, Istituto Oncologico Veneto IRCCS
DiSCOG-University of Padova, Italy
On behalf of the Short-HER Study Team

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

APT trial
Weekly paclitaxel x 12 + Trastuzumab (1 year) with excelent outcome

RFI Events

- **Invasive Local/Regional Recurrence**
- **Distant Recurrence**
- **Death from Breast Cancer**



	Point Est.	95% Conf. Interval	No. of events
3-yr RFI	99.2%	98.4% to >99.9%	3
5-yr RFI	98.1%	96.8% to 99.5%	7
7-yr RFI	97.5%	95.9% to 99.1%	9

Distant recurrence 4 (1%)

T1 = 91%
N0 = 99%
HR + = 67%

Tolaney et al, ASCO 2017

Presented By Eric Winer at 2017 ASCO Annual Meeting

Early-stage HER2-positive breast cancer

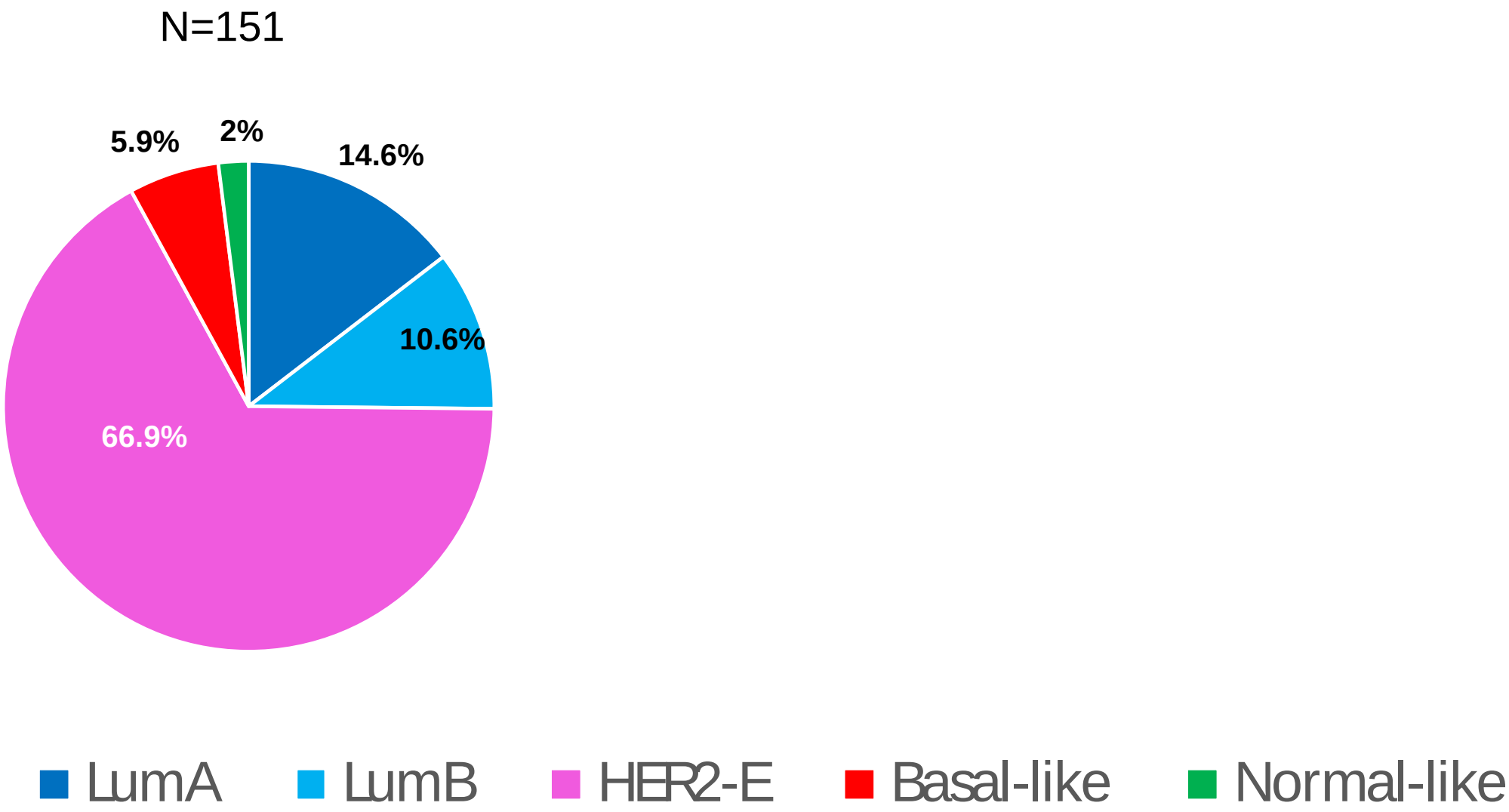
Attention to good quality HER2 testing

Should we give more treatment

Where do we go from here

Provide access

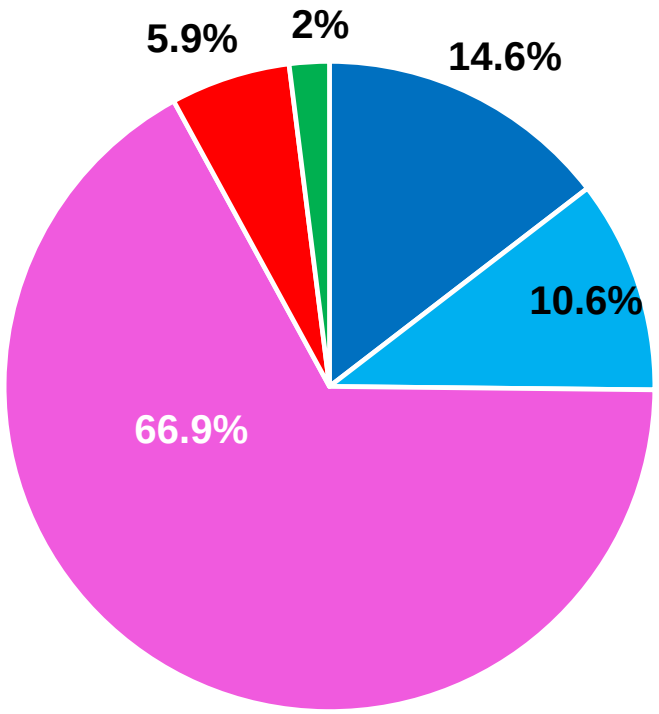
Attempts to identify biomarkers: PAM50 molecular panel
PAMELA trial: neoadjuvant trastuzumab + lapatinib

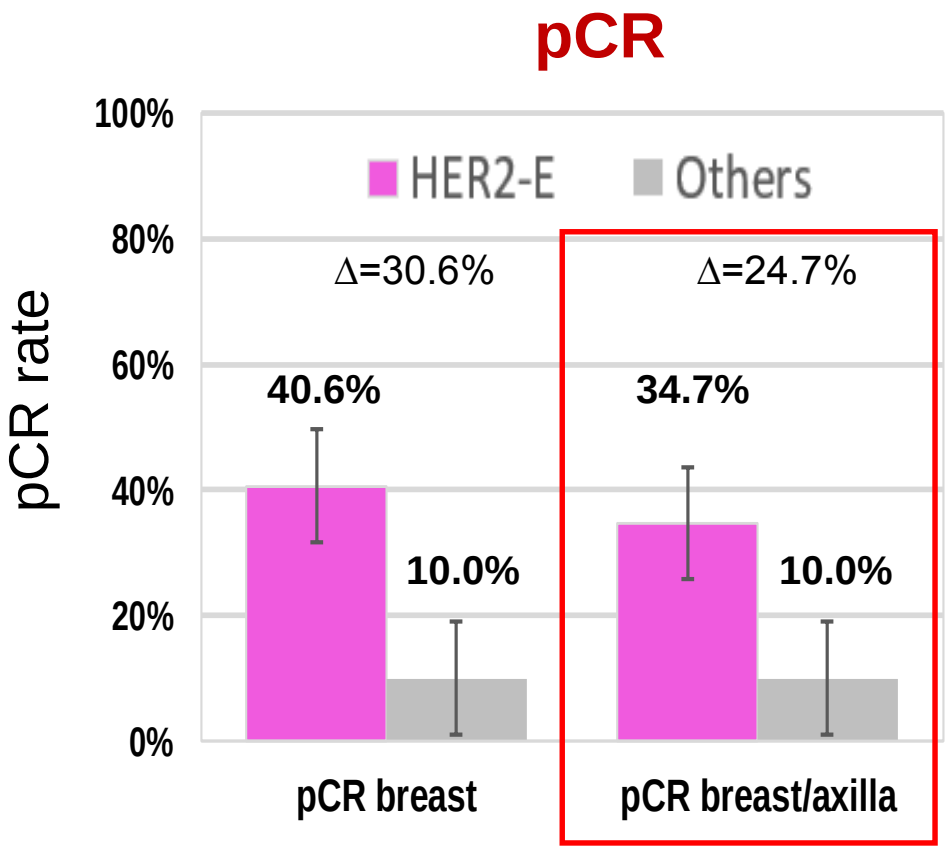


Increased pCR in the HER-2 enriched subtype

SOLTI

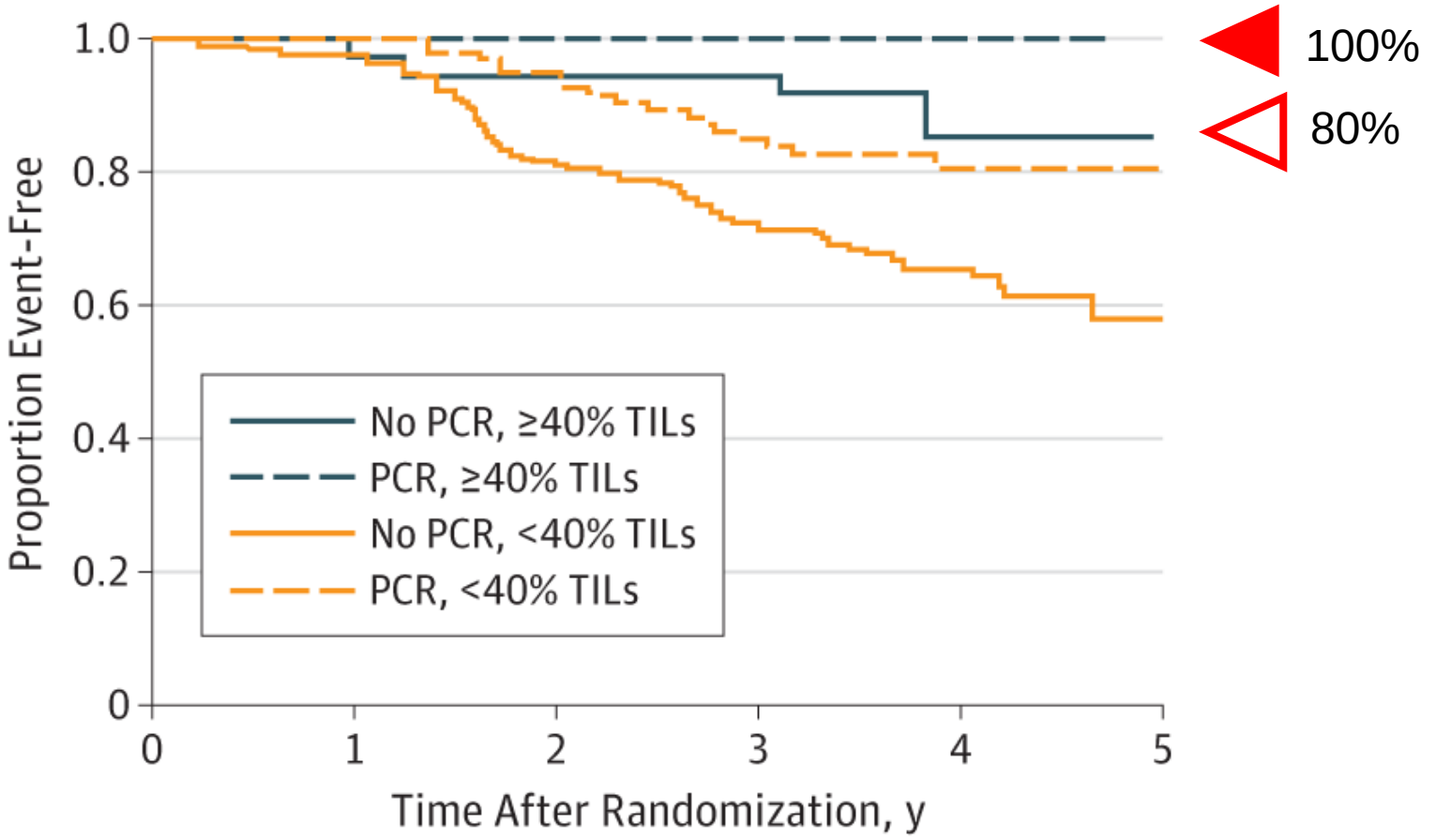
All samples
N=151





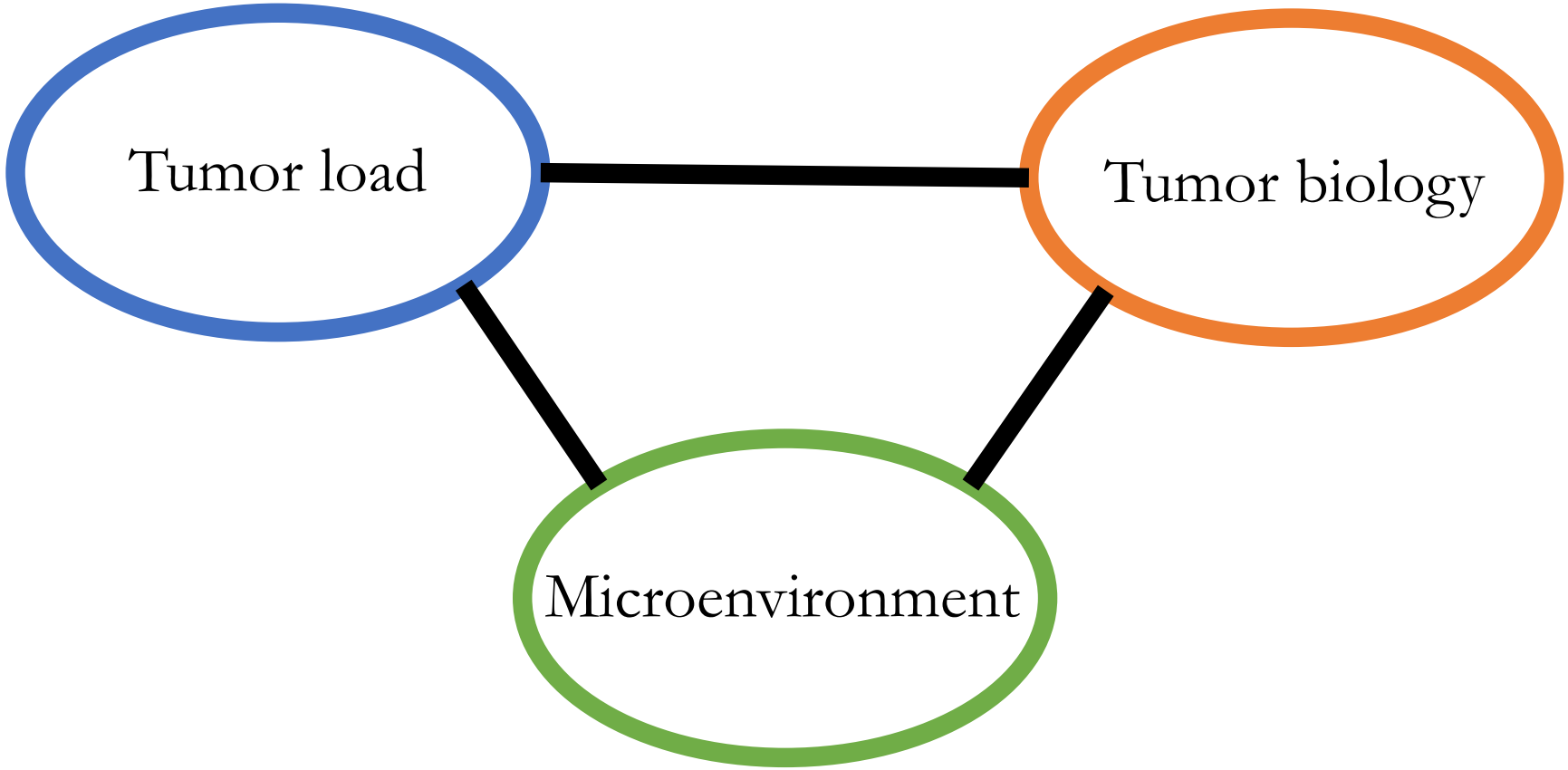
LumA LumB HER2-E Basal-like Normal-like

Attempts to identify biomarkers: tumor infiltrating lymphocytes (TILs) better outcomes with > TILs in the initial tumor (NeoALLTO)



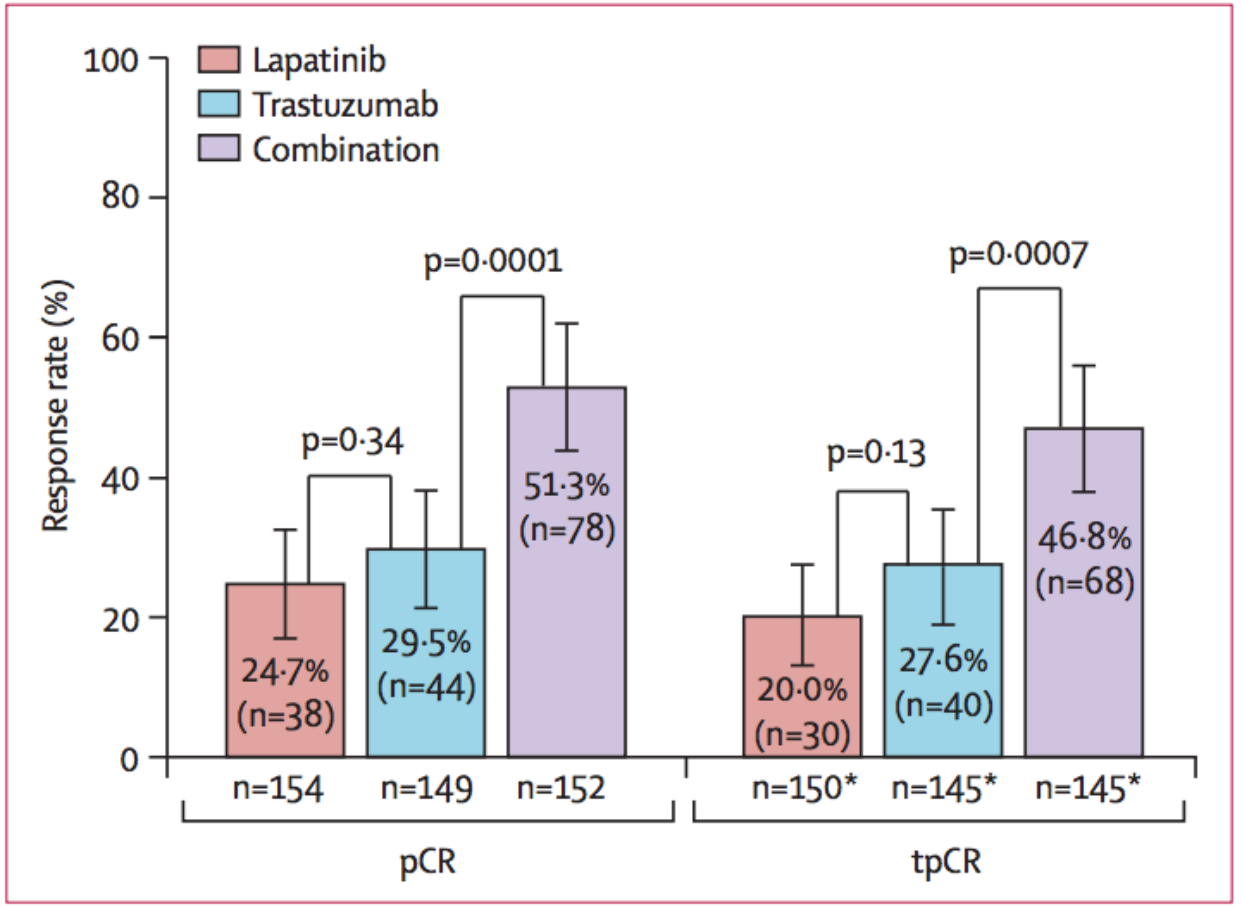
Salgado R. JAMA Oncol 2015

Important actors that interact and modify disease behavior



Modified after Prat A

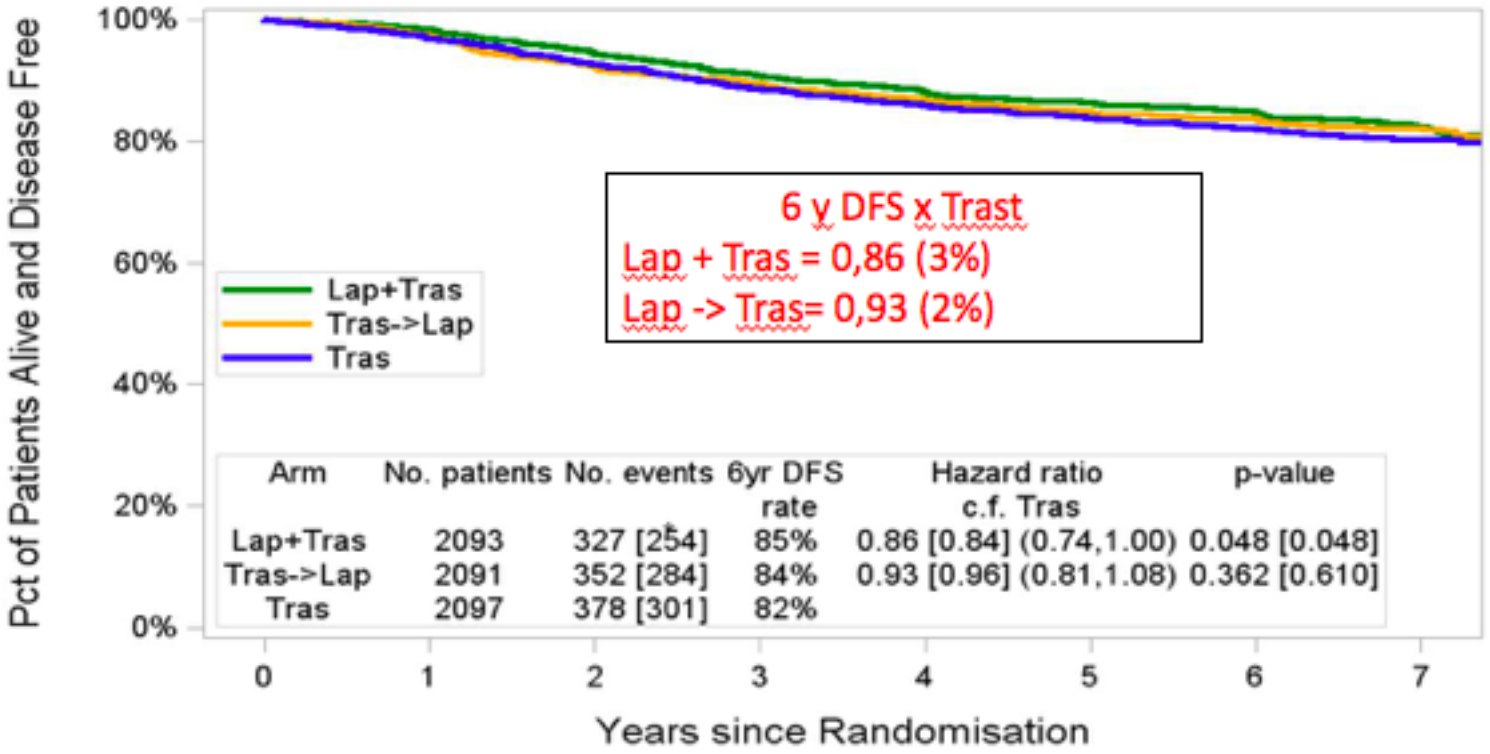
NeoALLTO
Increased pCR with the combination of trastuzumab and lapatinib



Lapatinib toxicity included diarrhea, transaminase elevation, without increase in cardiac toxicity

J. Baselga, Lancet 2012

ALLTO study
Trastuzumab + Lapatinib showed no significant increase in PFS



Moreno-Aspitia A. ASCO 2017

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2017
Invasive Breast Cancer

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-NEGATIVE - HER2-POSITIVE DISEASE[c]

Node positive (one or more metastases >2 mm to one or more ipsilateral axillary lymph nodes) → **Adjuvant chemotherapy[cc,ii] with trastuzumab[z] (category 1)**
or
Adjuvant chemotherapy[cc,ii] with trastuzumab[z] + pertuzumab

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Invasive Breast Cancer

SYSTEMIC ADJUVANT TREATMENT - HORMONE RECEPTOR-POSITIVE - HER2-POSITIVE DISEASE[c]

Node positive (one or more metastases >2 mm to one or more ipsilateral axillary lymph nodes) → **Adjuvant chemotherapy[bb,cc] with trastuzumab[dd] (category 1) and endocrine therapy[z,aa,ff]**
or
Adjuvant chemotherapy[bb,cc] with trastuzumab[dd] + pertuzumab and endocrine therapy[z,aa,ff]

[ff] Consider extended adjuvant neratinib after traztuzumab-containing therapy in HR-positive patients with a perceived high risk of recurrence (such as stage II-III). The benefits or toxicities associated with extended neratinib in patients who have received pertuzumab is unknown.