La durata del trastuzumab adiuvante nel 2013

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Trastuzumab plus Adjuvant Chemotherapy for HER2-positive Breast Cancer: Final Planned Joint Analysis of Overall Survival from NSABP B-31 and NCCTG N9831

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NSABP B-31

Arm 1

Arm 2

NCCTG N9831

Arm A

Arm B

Arm C

= doxorubicin/cyclophosphamide (AC) 60/600 mg/m^2 q 3 wk x 4

= paclitaxel (P) 175 mg/m^2 q 3 wk x 4

= paclitaxel (P) 80 mg/m^2/wk x 12

= trastuzumab (H) 4mg/kg LD + 2 mg/kg/wk x 51

NSABP B-31

Control: AC→P

Arm 1

Arm A

Note.
Vast Majority of pts = N+

NCCTG N9831

Investigational: AC→P+H

Arm 2

Arm C

= doxorubicin/cyclophosphamide (AC) 60/600 mg/m² q 3 wk x 4

= paclitaxel (P) 175 mg/m² q 3 wk x 4

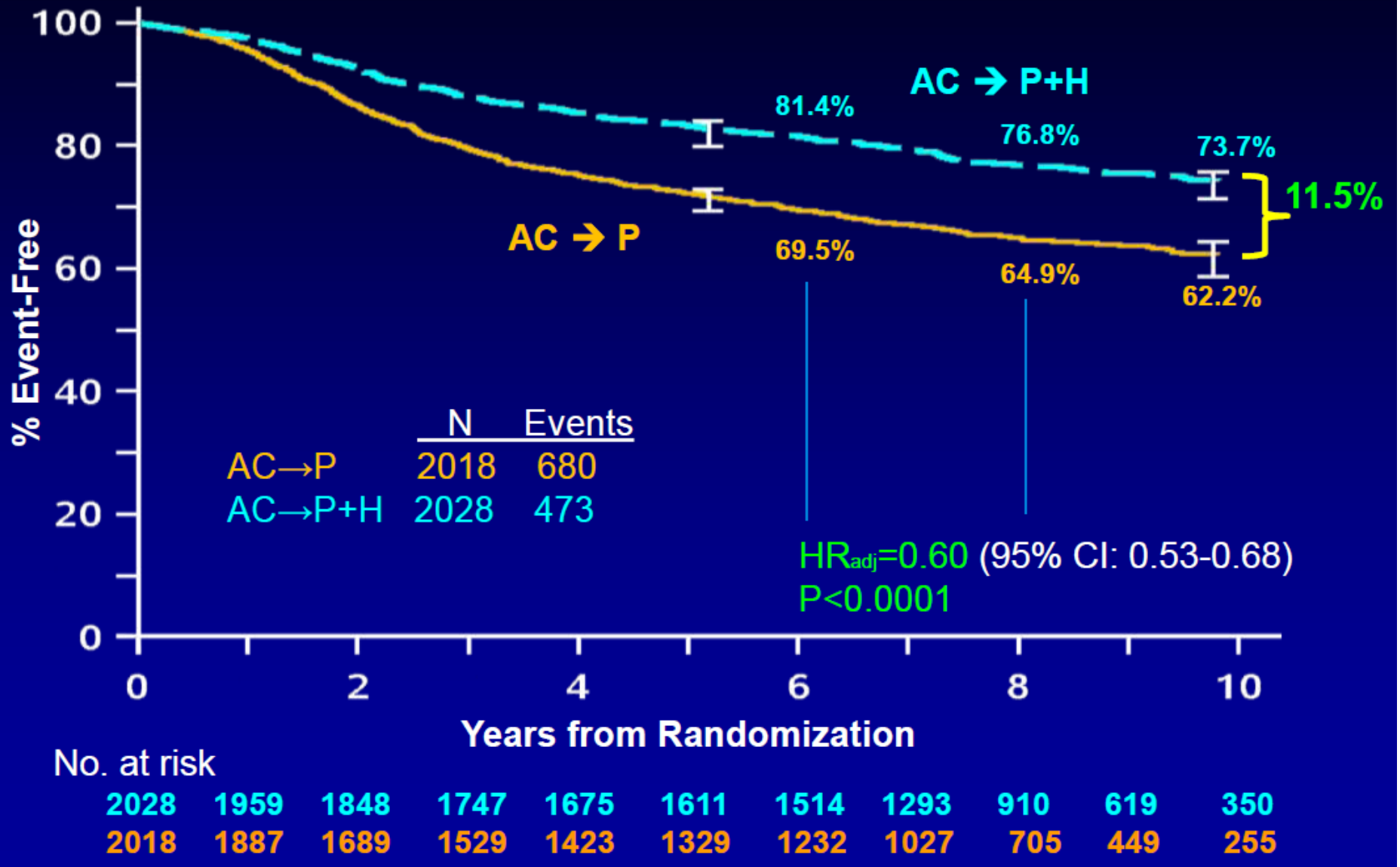
= paclitaxel (P) 80 mg/m²/wk x 12

= trastuzumab (H) 4mg/kg LD + 2 mg/kg/wk x 51

Joint Statistical Analysis

- Median follow-up: 8.4 years
  - Data lock: 15 Sept 2012
- Primary endpoint: DFS
  - analyzed by intent-to-treat
- Secondary endpoint: OS
  - analyzed by intent-to-treat
- First interim analysis occurred in 2005 after 355 DFS events
- Definitive survival analysis at 710 OS events

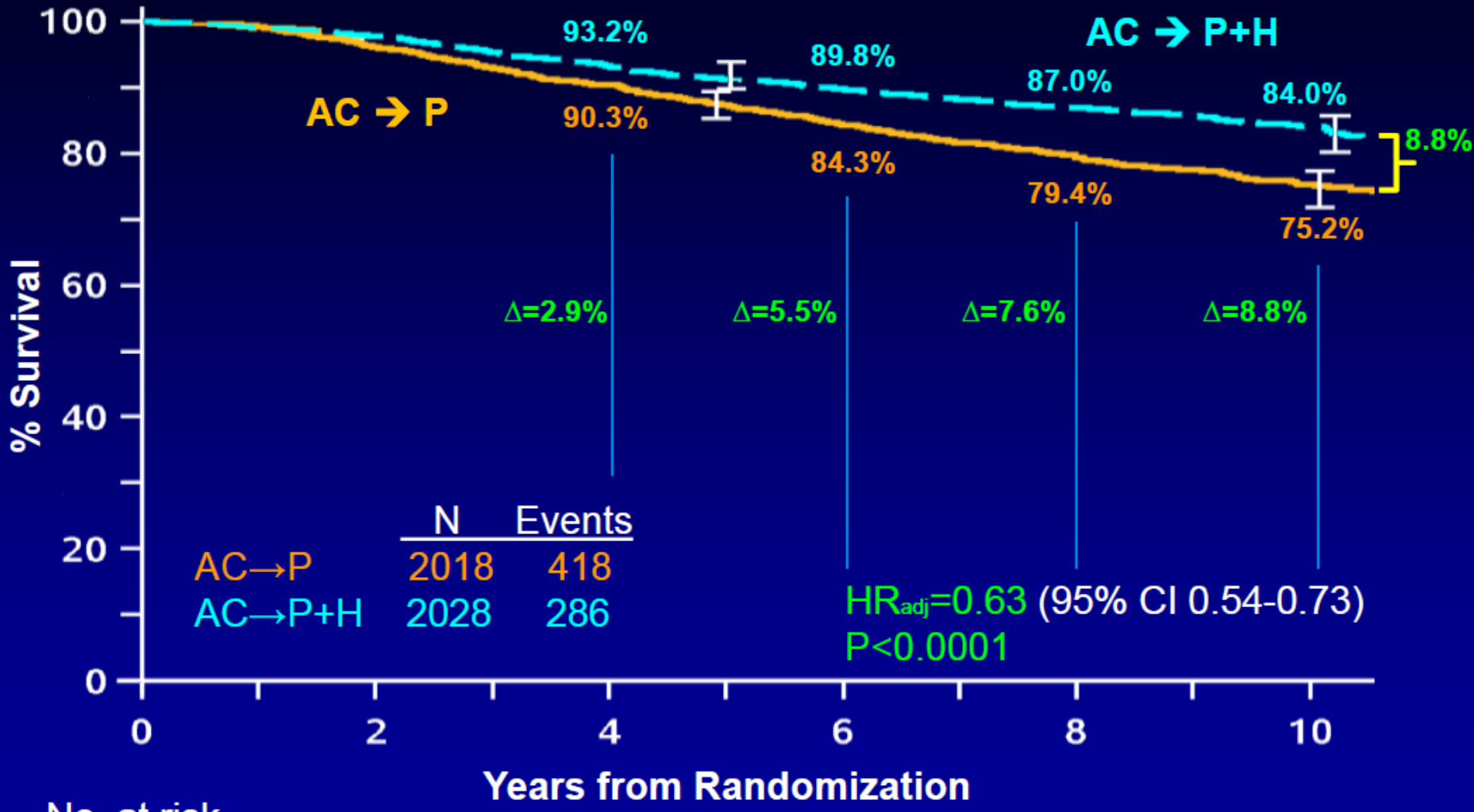
N9831/B-31 Disease-Free Survival



N9831/B-31 Joint Analysis
First DFS Events (%)

	AC ➡ T+H (n=2,028)	AC ➡ T (n=2,018)
Distant Recurrence	227 (11.2%)	391 (19.4%)
Local/Regional Recurrence	84 (4.1%)	124 (6.1%)
Contralateral Breast Disease	46 (2.3%)	40 (2.0%)
Other Second Primary Cancer	67 (3.3%)	74 (3.7%)
Death without Recurrence	38 (1.9%)	31 (1.5%)

B-31/N9831 Overall Survival



No. at risk

2028	1995	1959	1897	1843	1785	1709	1506	1085	735	439
2018	1962	1883	1806	1730	1640	1534	1336	944	604	353

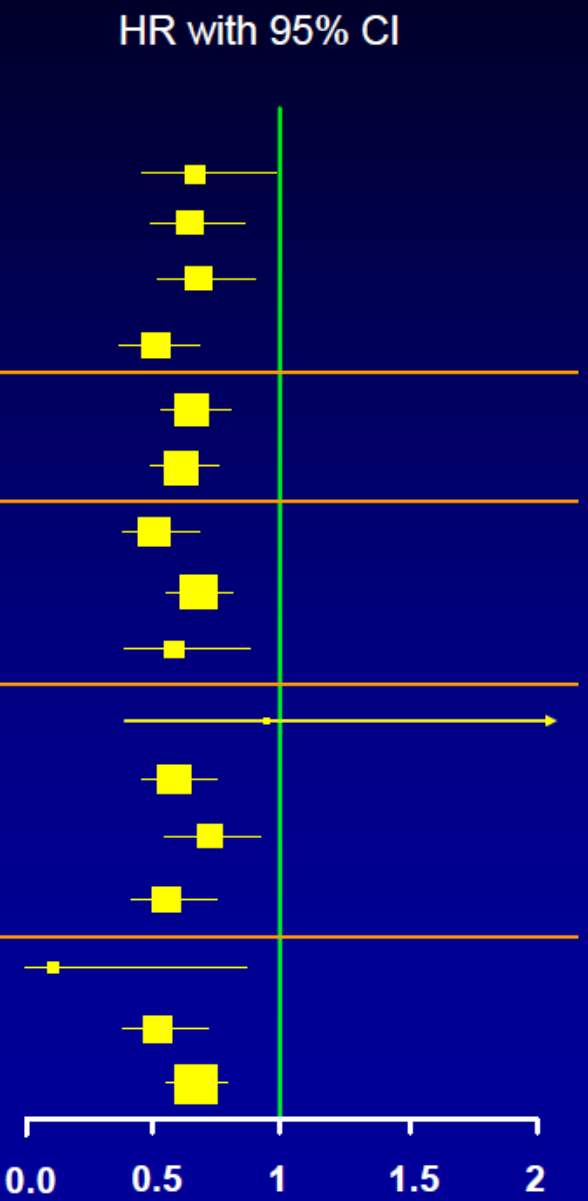
N9831/B-31 Joint Analysis

Overall Survival Events

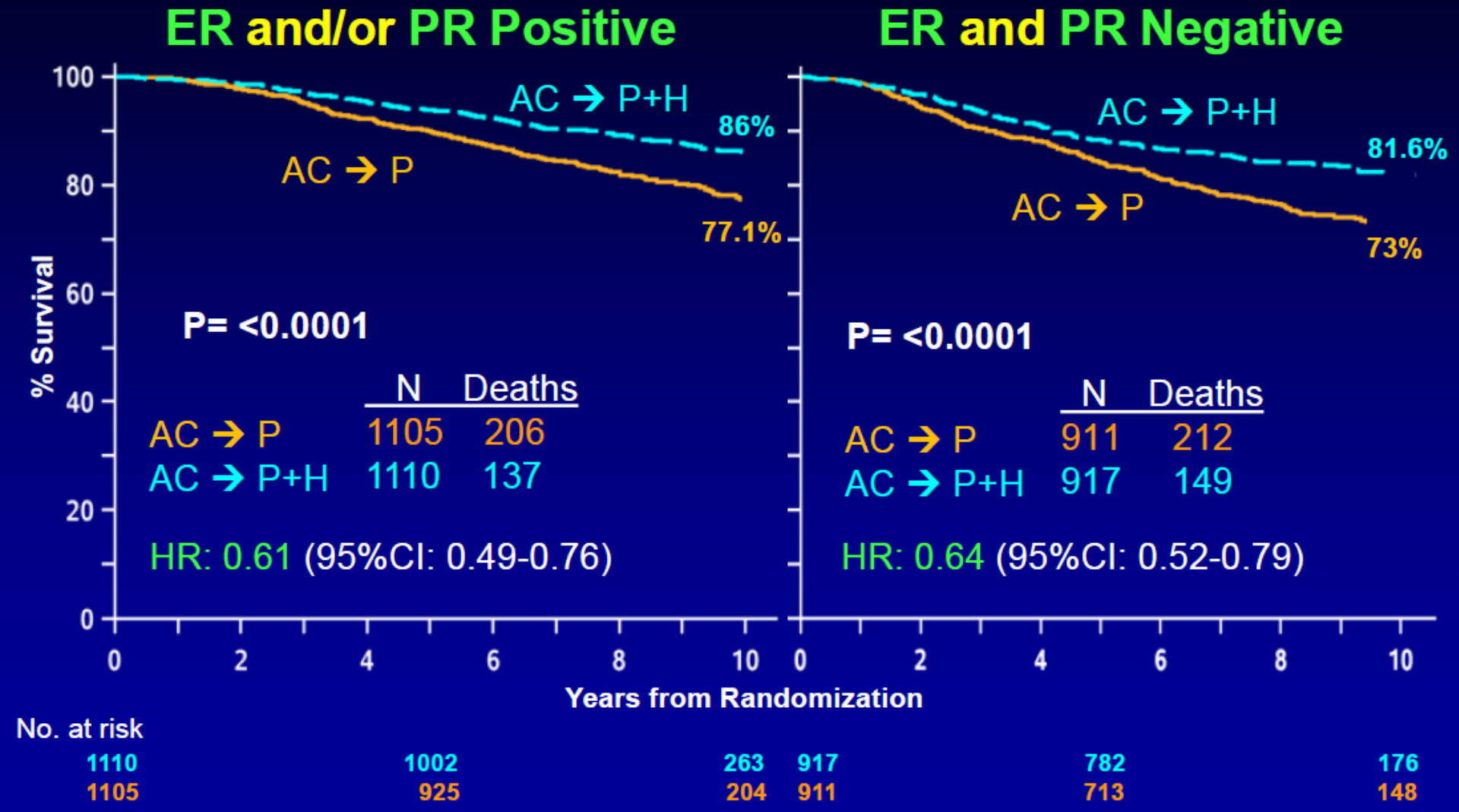
	AC ➡ T + H (%) n=2,028	AC ➡ T (%) n=2,018
Total Number who have died	286 (14.1)	418 (20.7)
Due to this breast cancer	209 (10.3)	340 (16.8)
Due to second primary	25 (1.2)	41 (2.0)
Due to other causes	20 (0.9)	15 (0.7)
Cause unknown	32 (1.6)	22 (1.1)

OS According to Subgroups
ACTH vs. ACT (reference group)

			No. of Events		
	Factor	N	ACT	ACTH	HR
Age	<40 years	654	65	45	0.67
	40-49	1373	121	87	0.65
	50-59	1336	129	90	0.68
	60+ years	683	103	64	0.51
Hormone Receptor	ER- and PR-	1828	212	149	0.65
	ER+ or PR+	2215	206	137	0.61
Tumor Size	0-2cm	1598	129	67	0.51
	2.1-5.0cm	2096	239	176	0.68
	5.1cm+	345	50	42	0.58
Nodal Status	LN 0	282	11	9	0.94
	LN 1-3	2144	161	104	0.59
	LN 4-9	1084	133	103	0.72
	LN 10+	536	113	70	0.56
Histologic Grade	Good	76	8	1	0.11
	Intermediate	1123	108	59	0.52
	Poor	2801	299	219	0.67



B-31/N9831 Overall Survival



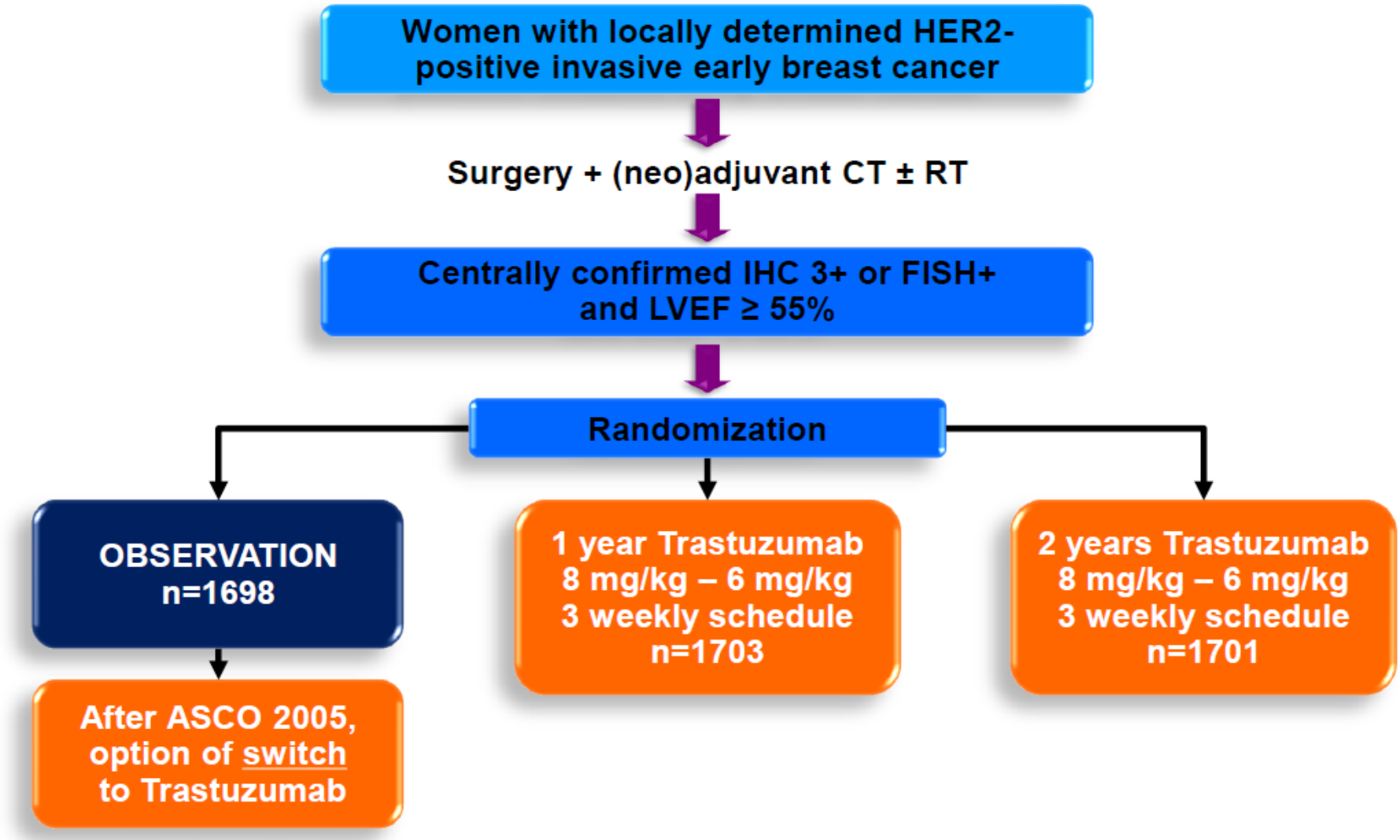
Conclusions

- At a median follow-up of 8.4 years the addition of trastuzumab to paclitaxel following AC chemotherapy is associated with a significant and substantial improvement in overall survival with a relative risk reduction of 37% (HR 0.63).
- For patients with high risk HER2-positive breast cancer, treatment with this regimen reduces the risk of a DFS event at 10 years by 40% (HR 0.60).
- The relative risk reduction benefit for both DFS and OS was present and of similar magnitude in virtually all subsets of patients analyzed.

HERA TRIAL: 2 years versus 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow-up

HERA TRIAL DESIGN

ACCRUAL 2001 – 2005 (N=5102)

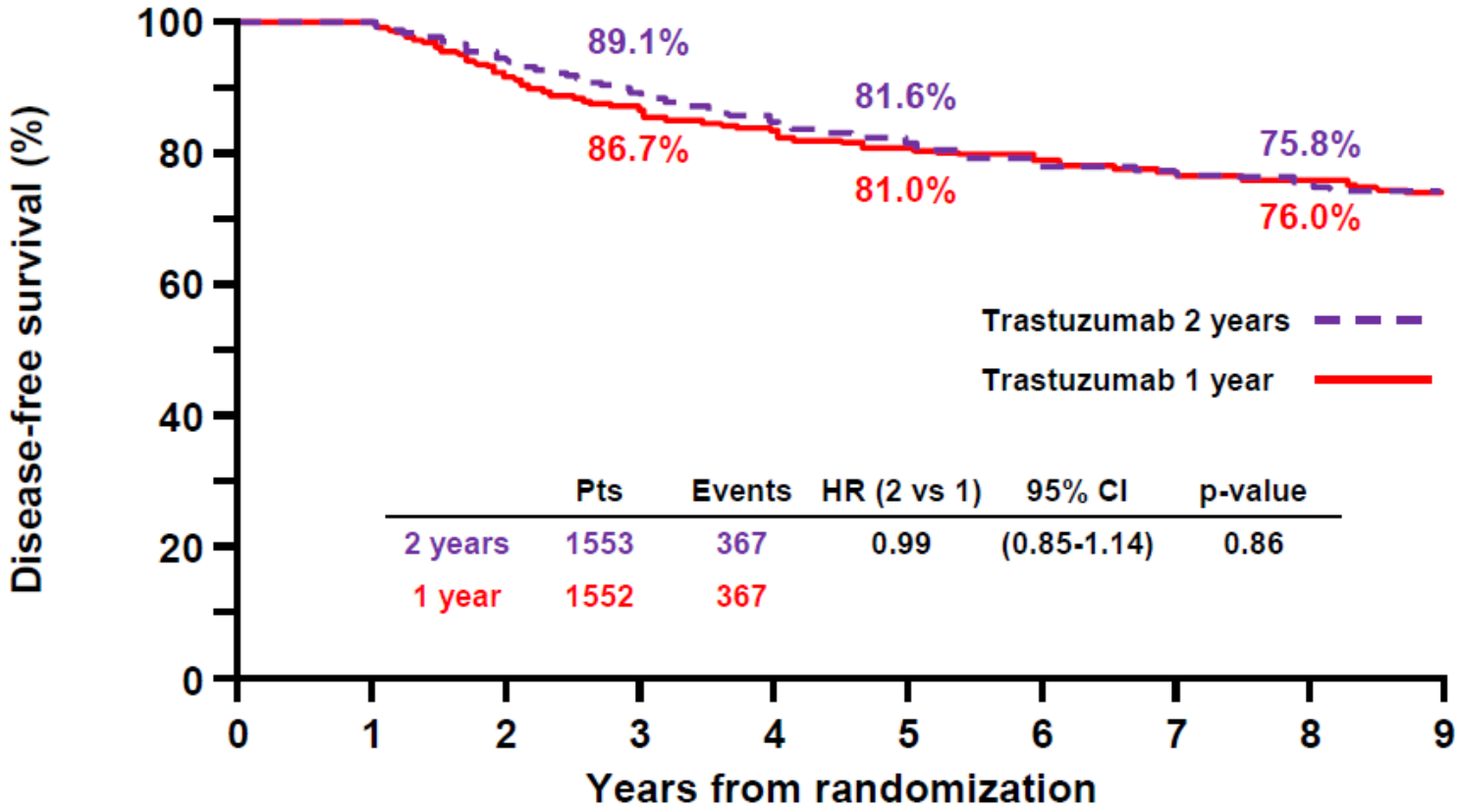


CT, chemotherapy; RT, radiotherapy

LANDMARK ANALYSIS OF 2 YEARS VS. 1 YEAR TRASTUZUMAB

- Population: Patients randomized to trastuzumab who remained disease-free for at least 366 days from randomisation: 1553 pts for 2 years arm and 1552 pts for 1 year arm.
- Two interim and one final analyses were planned.
- Final analysis planned for 725 disease-free survival (DFS) events to obtain 80% power to detect a true hazard ratio of 0.80.
- The current analysis is being reported today with 734 DFS events at 8 years' median follow up.

DFS FOR 2 YEARS VS. 1 YEAR TRASTUZUMAB AT 8 YRS MFU

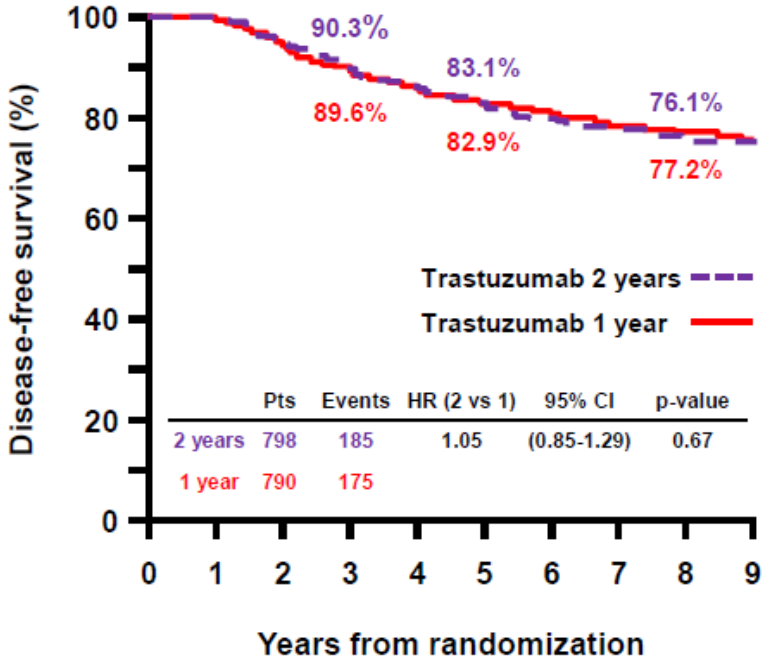


No. at risk										
Trastuzumab 2 years	1553	1553	1442	1361	1292	1223	1153	1051	633	194
Trastuzumab 1 year	1552	1552	1413	1319	1265	1214	1180	1071	649	205

DFS BY HORMONE RECEPTOR STATUS AT 8 YRS MFU

Hormone receptor positive

92.6% received endocrine therapy

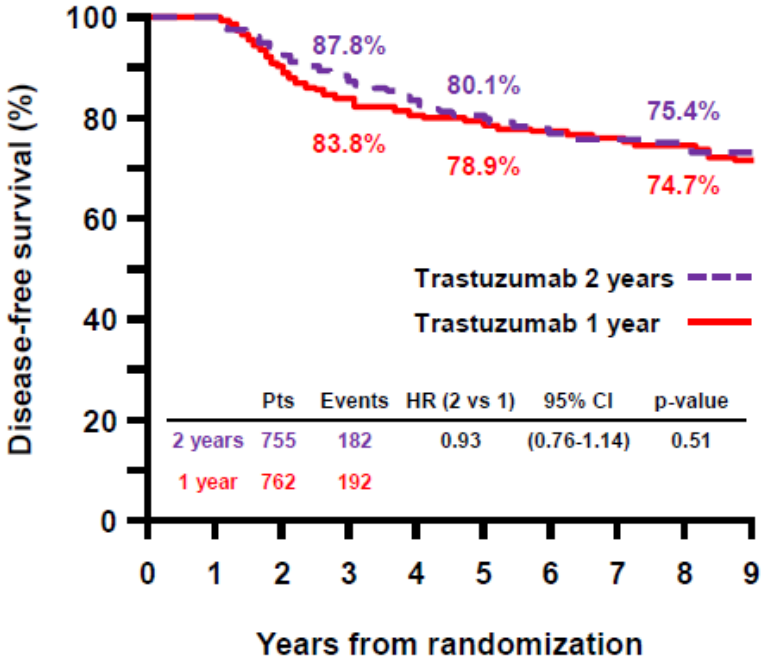


No. at risk

Trastuzumab 2 years	798	798	747	710	673	642	597	544	321	97
Trastuzumab 1 year	790	790	736	691	663	634	617	559	337	106

Hormone receptor negative

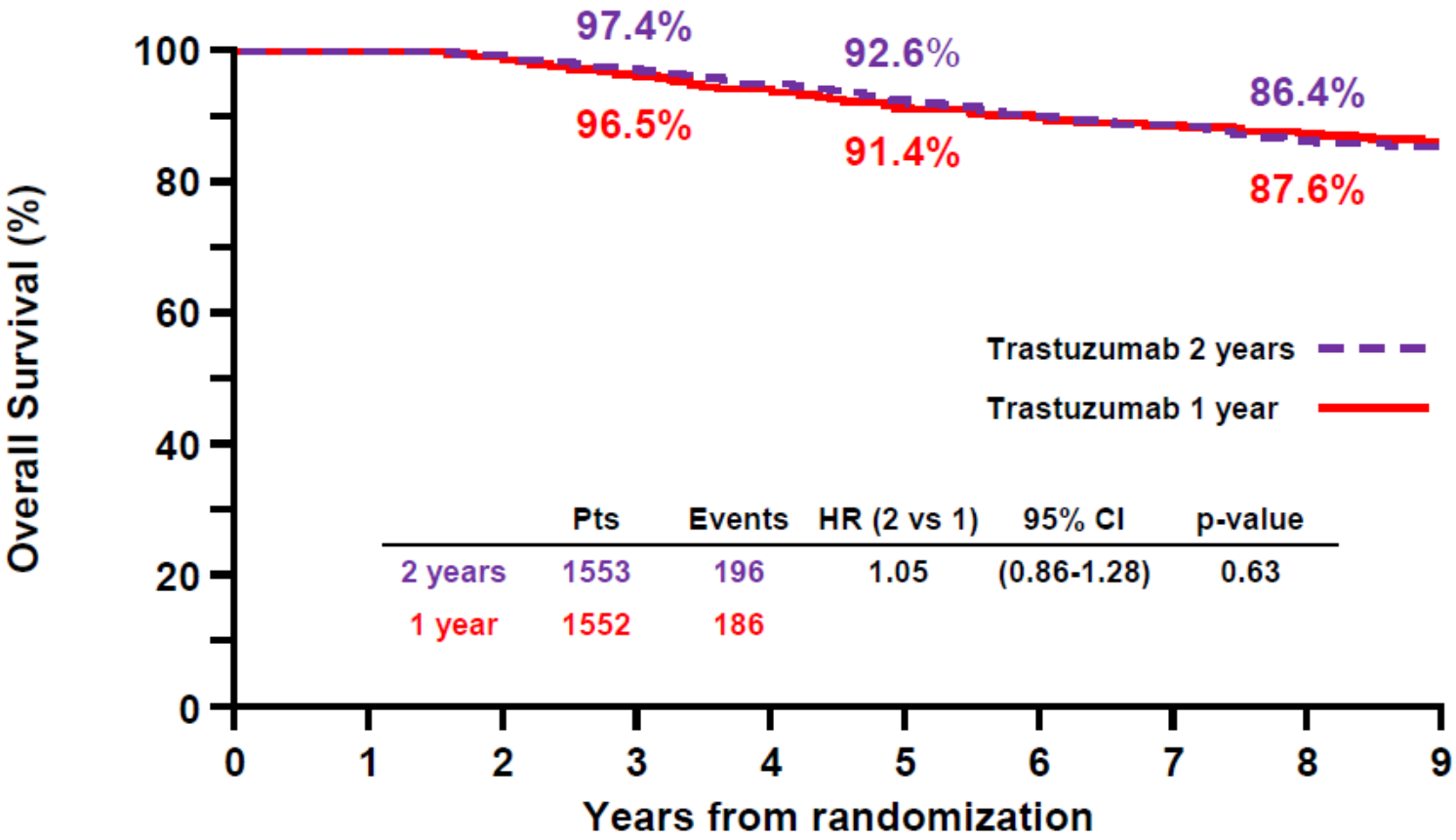
2.8% received endocrine therapy



No. at risk

Trastuzumab 2 years	755	755	695	651	619	581	556	507	312	97
Trastuzumab 1 year	762	762	677	628	602	580	563	512	312	99

OS FOR 2 YEARS VS. 1 YEAR TRASTUZUMAB AT 8 YRS MFU



No. at risk

Trastuzumab 2 years	1553	1553	1525	1485	1438	1382	1317	1193	708	208
Trastuzumab 1 year	1552	1552	1513	1461	1413	1364	1329	1218	732	225

HER2+ EBC - Adjuvant Trastuzumab Trials

Figure 7. Disease-free survival: all studies.

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
B31 (1)	-0.73	0.11	1672	1679	21.8%	0.48 [0.39, 0.60]
BCIRG006	-0.45	0.1	1074	1073	23.2%	0.64 [0.52, 0.78]
Buzdar	-2.27	1.11	23	19	0.6%	0.10 [0.01, 0.91]
FinHer	-0.87	0.35	115	118	5.2%	0.42 [0.21, 0.83]
HERA	-0.46	0.09	1703	1698	24.7%	0.63 [0.53, 0.75]
NOAH	-0.53	0.22	117	118	10.7%	0.59 [0.38, 0.91]
PACS-04	-0.15	0.18	260	268	13.8%	0.86 [0.60, 1.22]
Total (95% CI)			4964	4971	100.0%	**0.60 [0.50, 0.71]**

Heterogeneity: Tau² = 0.02; Chi² = 12.25, df = 6 (P = 0.06); I² = 51%
Test for overall effect: Z = 5.89 (P < 0.00001)

Hazard Ratio IV, Random, 95% CI

0.01 0.1 1 10 100
Favours experimental Favours control

40% relative RR for relapse

Standard adjuvant treatment for HER2+ EBC patients: 1 yr trastuzumab added to chemotherapy

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
B31 (1)	-0.4	0.17	1672	1679	22.0%	0.67 [0.48, 0.94]
BCIRG006	-0.46	0.13	1074	1073	37.7%	0.63 [0.49, 0.81]
Buzdar	0	0	23	19		Not estimable
FinHer	-0.6	0.36	115	118	4.9%	0.55 [0.27, 1.11]
HERA	-0.46	0.17	1703	1698	22.0%	0.63 [0.45, 0.88]
NOAH	-0.48	0.3	117	118	7.1%	0.62 [0.34, 1.11]
PACS-04	0.24	0.32	260	268	6.2%	1.27 [0.68, 2.38]
Total (95% CI)			4964	4971	100.0%	**0.66 [0.57, 0.77]**

Heterogeneity: Tau² = 0.00; Chi² = 4.70, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 5.16 (P < 0.00001)

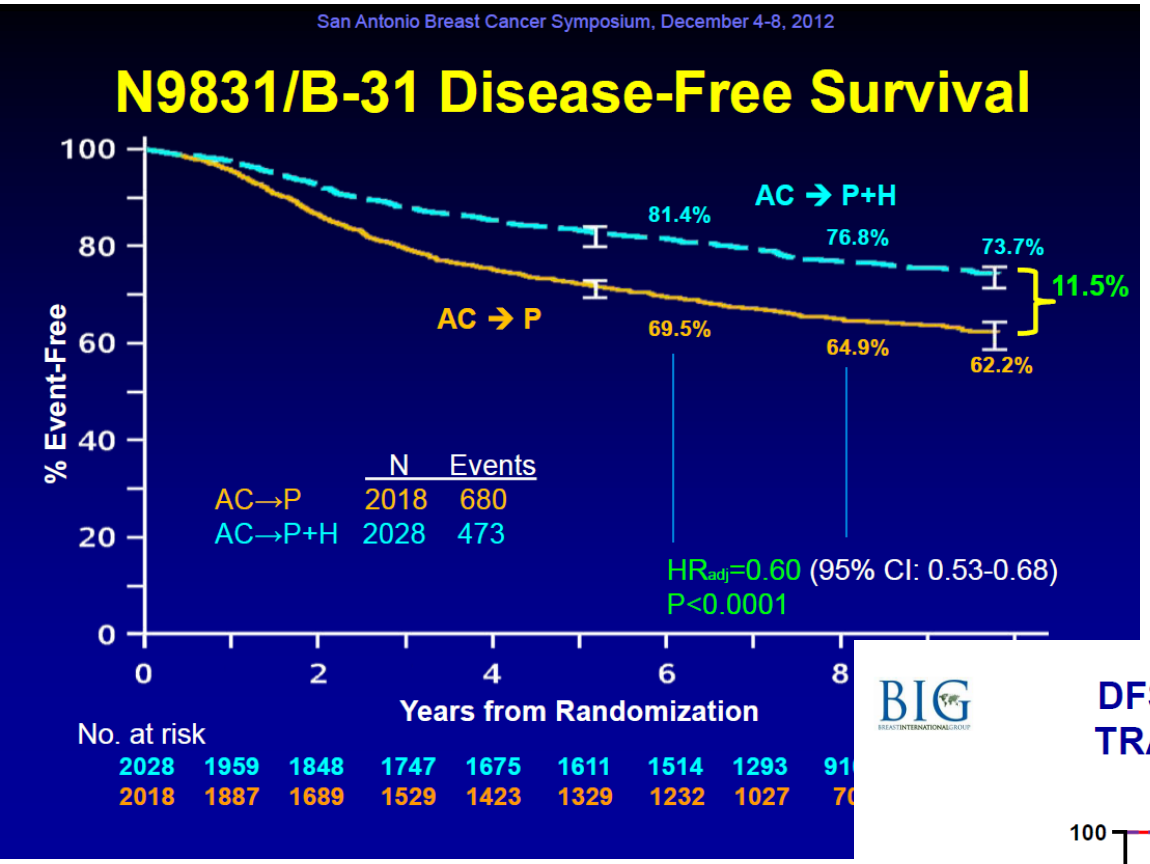
Hazard Ratio IV, Random, 95% CI

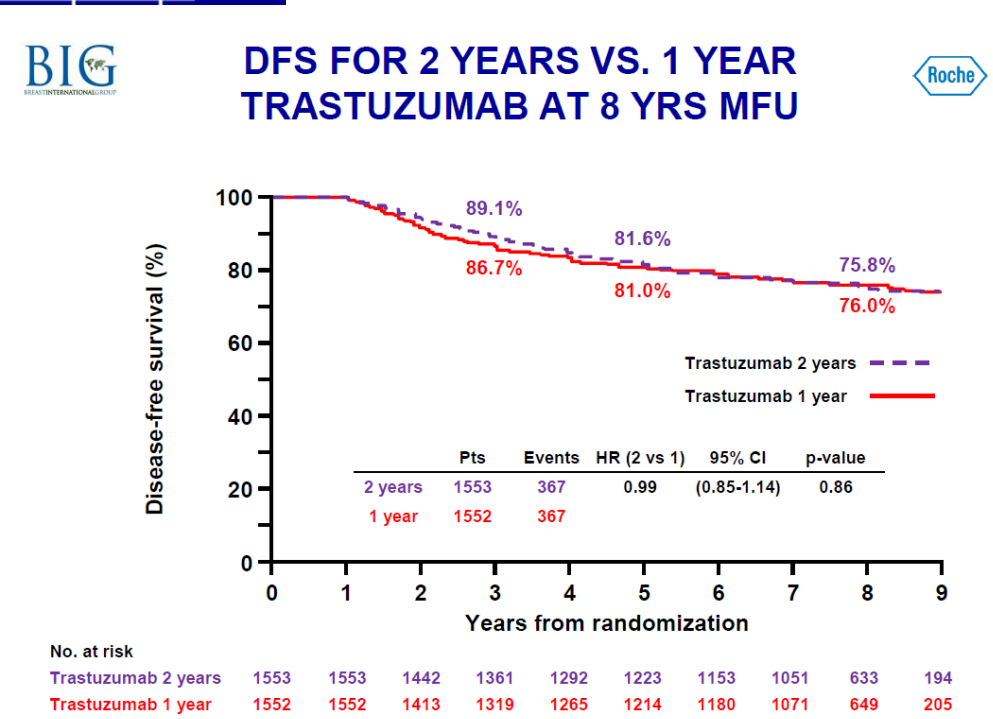
0.01 0.1 1 10 100
Favours experimental Favours control

(1) B31+N9831

34% relative RR for death

Moja L, et al. The Cochrane Library 2012, Issue 4


San Antonio Breast Cancer Symposium, December 4-8, 2012
N9831/B-31 Disease-Free Survival
% Event-Free
100
80
60
40
20
0
AC → P+H
81.4%
76.8%
73.7%
11.5%
AC → P
69.5%
64.9%
62.2%
N Events
AC→P 2018 680
AC→P+H 2028 473
HRadj=0.60 (95% CI: 0.53-0.68)
P<0.0001
0
2
4
6
8
Years from Randomization
No. at risk
2028 1959 1848 1747 1675 1611 1514 1293 91
2018 1887 1689 1529 1423 1329 1232 1027 70


BIG
DFS FOR 2 YEARS VS. 1 YEAR
TRASTUZUMAB AT 8 YRS MFU
Roche
Disease-free survival (%)
100
80
60
40
20
0
89.1%
86.7%
81.6%
81.0%
75.8%
76.0%
Trastuzumab 2 years
Trastuzumab 1 year
Pts Events HR (2 vs 1) 95% CI p-value
2 years 1553 367 0.99 (0.85-1.14) 0.86
1 year 1552 367
0
1
2
3
4
5
6
7
8
9
Years from randomization
No. at risk
Trastuzumab 2 years 1553 1553 1442 1361 1292 1223 1153 1051 633 194
Trastuzumab 1 year 1552 1552 1413 1319 1265 1214 1180 1071 649 205

ADVERSE EVENTS (SAFETY ANALYSIS POPULATION)

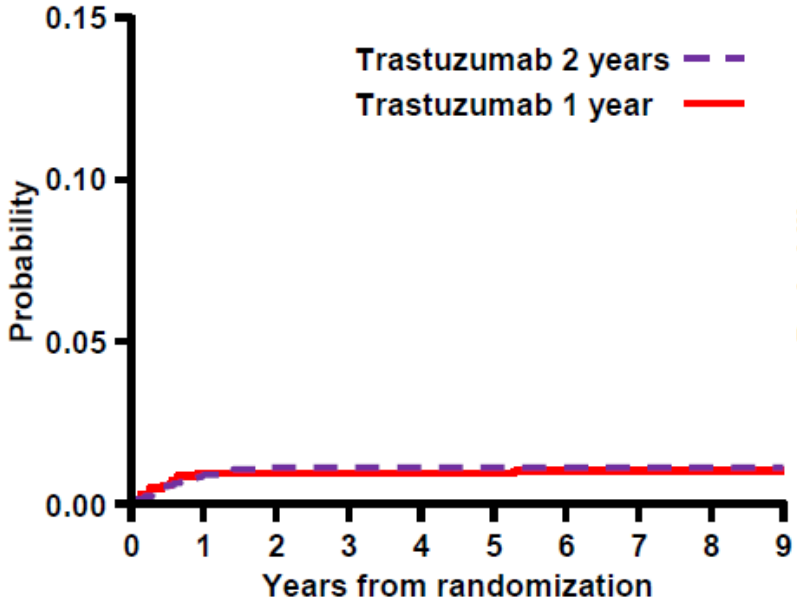
	Observation Only N=1744	Trastuzumab 1 Year N=1682	Trastuzumab 2 Years N=1673
≥ 1 grade 3 or 4 AE	8.2%	16.3%	20.4%
Secondary Cardiac[1]	0.9%	4.1%	7.2%
Primary Cardiac[2]	0.1%	0.8%	1.0%
Fatal adverse event	0.4%	1.1%	1.2%

[1] LVEF < 50% and ≥ 10% below baseline confirmed by repeat assessment, excluding patients with a primary cardiac endpoint.

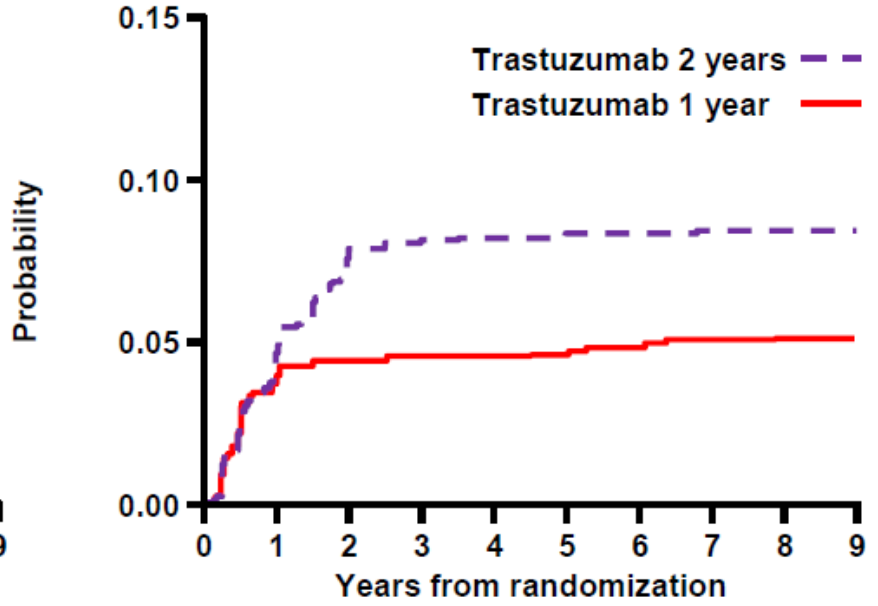
[2] NYHA class III or IV, confirmed by a cardiologist, and LVEF < 50% and ≥ 10% below baseline, OR cardiac death.

CUMULATIVE INCIDENCE OF CARDIAC ENDPOINTS*

Primary



Primary or Secondary



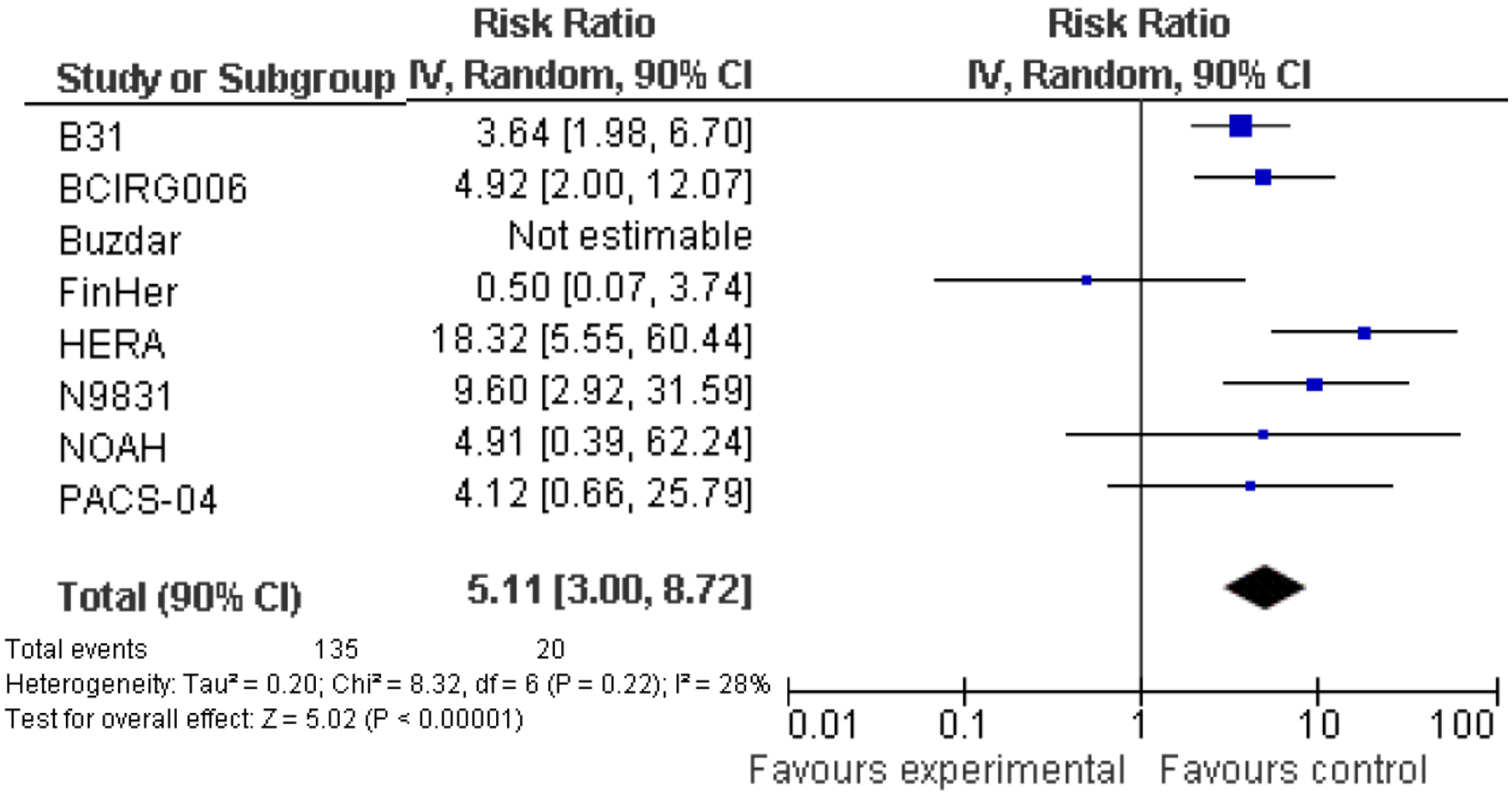
No. at risk

Trastuzumab 2 years	1673	1533	1423	1345	1276	1207	1137	1038	637	186
Trastuzumab 1 year	1682	1536	1399	1306	1254	1203	1169	1063	659	203

Trastuzumab 2 years	1673	1466	1323	1248	1182	1116	1047	952	589	171
Trastuzumab 1 year	1682	1488	1350	1257	1206	1158	1125	1017	629	190

* Competing risk analysis with disease-free survival events considered as competing risks
The majority of cardiac events are reversible (Procter et al. JCO 2010)

Adjuvant Trastuzumab
Congestive heart failure (CHF): all studies.



Moja L, et al. The Cochrane Library 2012, Issue 4

Adjuvant Trastuzumab (1 year) and Cardiotoxicity

		HERA (1year) (SABCS 2012)	BCIRG 006 (NEJM 2011)	NSABP B31 (JCO 2012)	COHORT ST. (JNCI 2012)	Older pts (>66) (JACC 2012)
CT ALONE						
	Grade III-IV	0.1%	0.7%*			
	Subclinical	0.9%	11.2%*			
	CE			1.3%*		
	HF/CM				4.3%*	32.1%°
CT + TRASTUZUMAB						
	Grade III-IV	0.8%	2.0% *- 0.4%^			
	Subclinical	4.1%	18.6% *- 9.4%^			
	CE			4.0%*		
	HF/CM				20.1%*	41.9%°

* Anthra; ^ TCH; ° 3-yr incidence (vs 18.1% for no therapy)

Risk of HF in BC patients after adjuvant anthracycline and trastuzumab: a retrospective study

- Cancer Research Network: 14 institutions
- Observation period: jan 1st 1999 – dec 31st 2007
- Admissions for HF/CM (ICD-9 code)
- 12,500 women

(diagnosis of HF/CM prior to or within 70 days from breast cancer diagnosis excluded)

Treatment	pts #	**HF/CM HR**	**5y incidence %**
No chemotherapy	5807	**1**	**3.1**
ChemoRx (no anthra)	2442	**1.49** (1.25-1.77)	**4.5**
Anthra-based chemo	3697	**1.40** (1.11-1.76)	**4.3**
Trastuzumab (no anthra)	112	**4.12** (2.30-7.42)	**12.1**
Anthra-based + Trastuzumab	442	**7.19** (5.0-10.35)	**20.1**

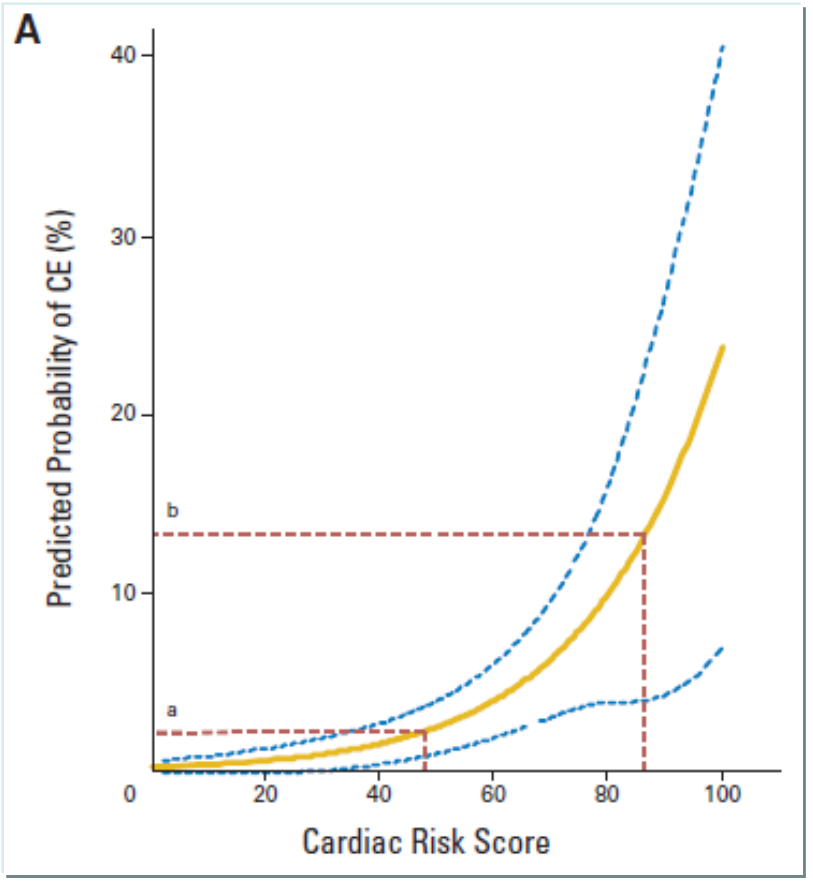
EJ Aiello Bowles et al, JNCI 104:1293-1305, 2012

NSABP B-31: risk factors for CHF

Age	CHF %	HR	P value
< 50	2.3	**1**	-
50-59	5.5	**2.43**	0.022
60+	6.1	**2.73**	0.025
Hypertensive medications			
yes	3.2	**1**	-
no	6.7	**2.1**	0.03
Baseline LVEF			
≥ 65	2.1	**1**	-
55-64	4.2	**1.98**	0.092
50-54	12.9	**6.72**	< 0.001
Post AC LVEF			
≥ 65	1.1	**1**	-
55-64	4.0	**3.58**	0.02
50-54	12.6	**11.84**	< 0.001

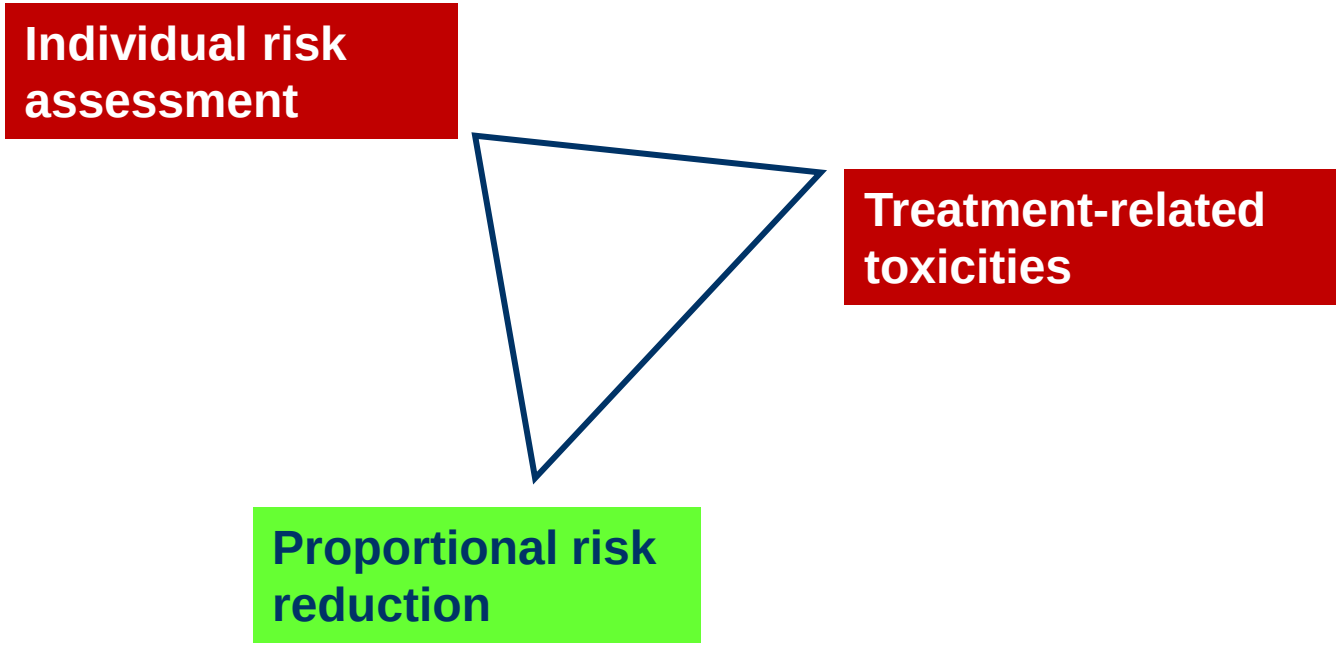
CRS

$$\frac{[7+0.04 \times \text{age})-(0.1 \times \text{baseline LVEF}] \times 100}{4.76}$$



Romond EH et al, JCO 2012

Adjuvant treatment for EBC
The elements of the risk/benefit equation



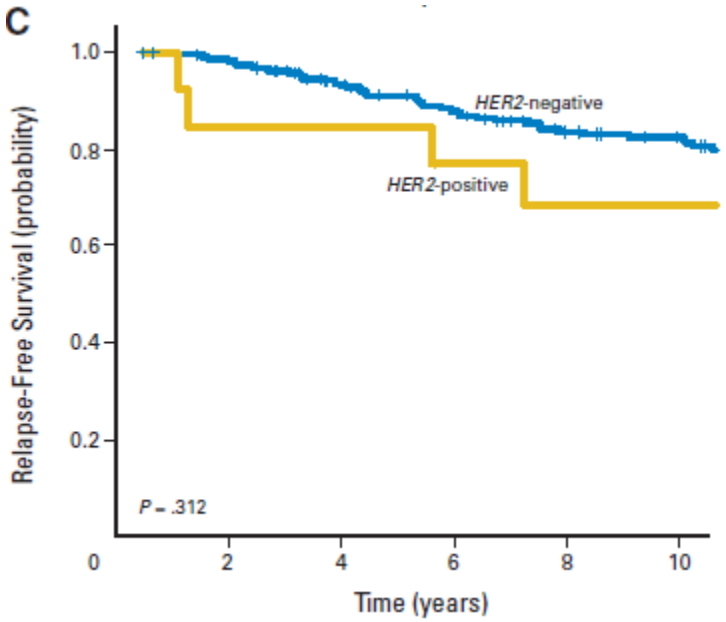
ABSOLUTE BENEFIT =
baseline risk/proportional risk reduction
MINUS
treatment-related toxicities

Very small tumors

- T1mi: microinvasive < 1mm
- T1a: 1-5 mm
- T1b: 6-10 mm

Node negative

RFS in patients with T1bN0 tumors who did not receive adjuvant systemic therapy



212 pts; RFS: 82%

13 pts; RFS: 68%

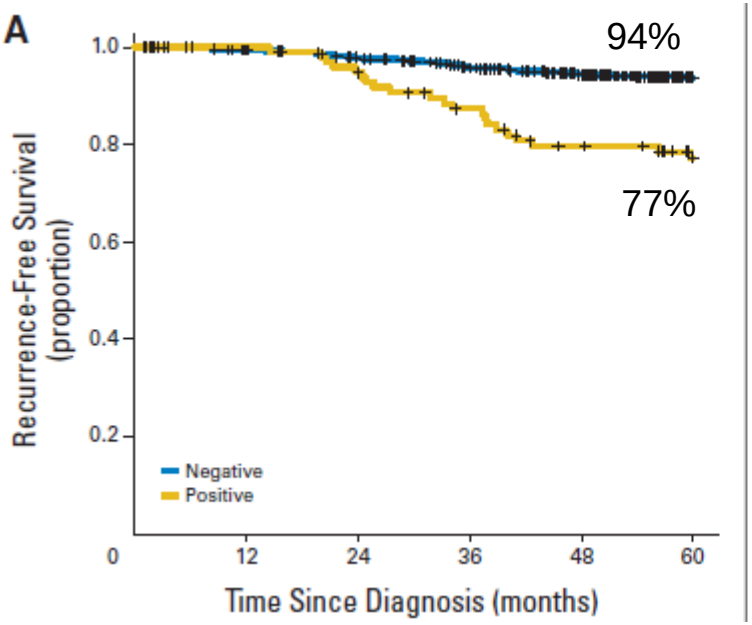
Chia *J Clin Oncol 26:5697-5704. © 2008*

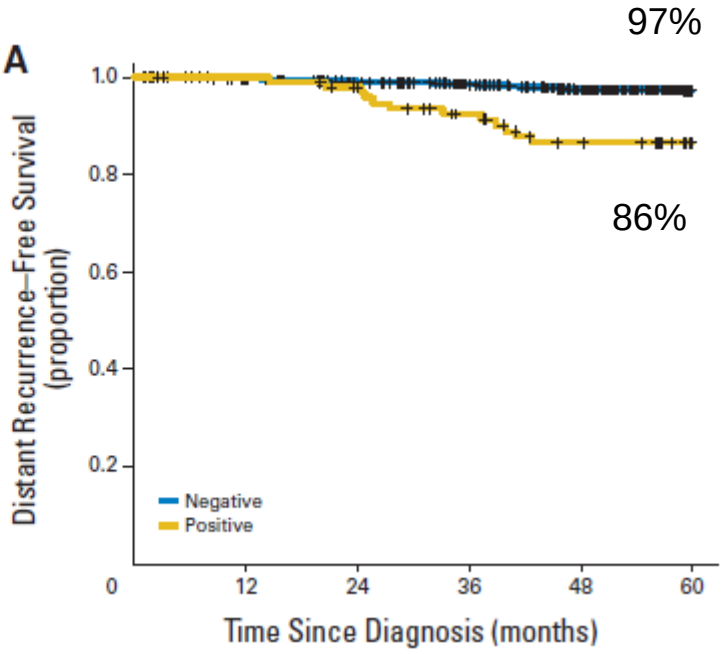
High Risk of Recurrence for Patients With Breast Cancer Who Have Human Epidermal Growth Factor Receptor 2–Positive, Node-Negative Tumors 1 cm or Smaller

Ana M. Gonzalez-Angulo, Jennifer K. Litton, Kristine R. Broglio, Funda Meric-Bernstam, Ronjay Rakkhit, Fatima Cardoso, Florentia Peintinger, Emer O. Hanrahan, Aysegul Sahin, Merih Guray, Denis Larsimont, Francesco Feoli, Heidi Stranzl, Thomas A. Buchholz, Vicente Valero, Richard Theriault, Martine Piccart-Gebhart, Peter M. Ravdin, Donald A. Berry, and Gabriel N. Hortobagyi

J Clin Oncol 27:5700-5706. © 2009

- N= 965; 98 (10%) HER2+
- No patient got chemo or trastuzumab
- 32% (31 pts) of HER2+ patients received ET (tamoxifen or AI)
- Median follow up: 6.2 years





SUPPLEMENT Table 1B

Analysis of Disease-Free Survival (DFS) by Tumor Size at Randomization

Size < 1 cm					
	# patients	# DFS Events	HR (95% C.I)	p value	5-year DFS (%)
AC→T	58	16	1 (ref)		72
AC→TH	46	6	0.36 (0.14-0.93)	0.034	86
TCH	44	6	0.45 (0.17-1.16)	0.096	86

Supplement to: Slamon et al., NEJM 2011; 365:1273-83

Trials exploring different duration of trastuzumab administration

Trial	Sponsor	Trastuzumab		CT regimen	sample size	status
		months	schedule			
HERA	BIG	12 v 24	All **S**	Center's choice	3,387	completed & reported
PHARE	INCA	6 v 12	**S** or **C**	Center's choice	3,400	completed & reported
Hellenic Oncology	University of Heraklion	6 v 12	All **C**	ddFEC/D	478	completed 12/2011
PERSEPHONE	University of Warwick	6 v 12	All **S**	Center's choice	4,000	ongoing
SHORTHER	University of Modena	2 v12	All **C**	A+T vs. T+FEC	1,250	ongoing
SOLD	Finnish BCG	2 v 12	All **C**	T+FEC	3,000	ongoing

S= sequential trastuzumab
C= concomitant trastuzumab

SUMMARY: ANALYSIS OF DFS AND OS FOR 1 YEAR TRASTUZUMAB VS. OBSERVATION AT 8 YRS MFU

- HERA results at 8 yrs MFU show sustained and statistically significant DFS and OS benefit for 1 year trastuzumab versus observation in ITT analyses despite selective crossover.
- 1 year of trastuzumab remains the standard of care as part of an adjuvant therapy for patients with HER2-positive early breast cancer.
- Benefit for 1 year trastuzumab, compared to observation, was shown across hormone receptor positive and negative cohorts.

Overall Best vs Personalized Best

HER2 +

- **Anthra → Taxane + Trastuzumab → Trastuzumab ± HT**

HER2 +

- **CT → Trastuzumab**
- **TCH**
- **Trastuzumab <1 y??**