Associazione Italiana Radioterapia Oncologica
Gruppo di Studio per la Patologia Mammaria

II Zoom Journal Club 2012

Coordinatore: Luigia Nardone

Centro Congressi EATALY

Roma, 25 Gennaio 2013

"News da San Antonio"
Nuovi dati clinici sul trattamento farmacologico del carcinoma mammario.

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Dipartimento di Oncologia-SC Oncologia Medica

ITT Istituto Toscano Tumori

SST Azienda Sanitaria Firenze

Servizio Sanitario della Toscana

“News da SABCS e del 2012”:
nuovi dati clinici sul trattamento farmacologico del carcinoma mammario.

❑ terapia adiuvante

- Ormonoterapia (TAM / LET)
- Anticorpi monoclonali (trastuzumab e bevacizumab)
- Chemioterapia adiuvante dopo recidiva di malattia

❑ terapia della malattia metastatica

- 2012: everolimus / pertuzumab / T-DM1
- SABCS: Fulvestrant / Bevacizumab / Eribulina
- Nuovi target: CDK PD 0332991

Terapia adiuvante

ATLAS - Adjuvant Tamoxifen: Longer Against Shorter

10 vs 5 years of adjuvant tamoxifen in ER+ disease: effects in the first & second decade after diagnosis

Presented on behalf of the

ATLAS collaborative group

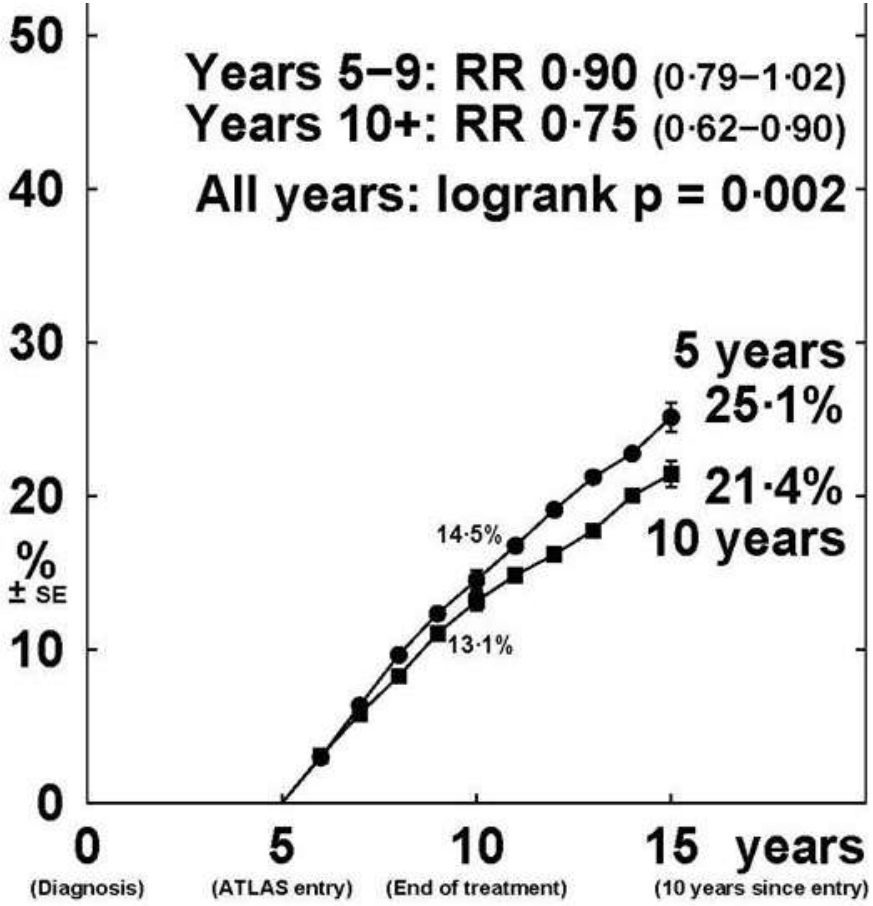
Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial

*Christina Davies, Hongchao Pan, Jon Godwin, Richard Gray, Rodrigo Arriagada, Vinod Raina, Mirta Abraham, Victor Hugo Medeiros Alencar, Atef Badran, Xavier Bonfill, Joan Bradbury, Michael Clarke, Rory Collins, Susan R Davis, Antonella Delmestri, John F Forbes, Peiman Haddad, Ming-Feng Hou, Moshe Inbar, Hussein Khaled, Joanna Kielanowska, Wing-Hong Kwan, Beela S Mathew, Bettina Müller, Antonio Nicolucci, Octavio Peralta, Fany Pernas, Lubos Petruzelka, Tadeusz Pienkowski, Balakrishnan Rajan, Maryna T Rubach, Sera Tort, Gerard Urrútia, Miriam Valentini, Yaochen Wang, Richard Peto, for the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group**

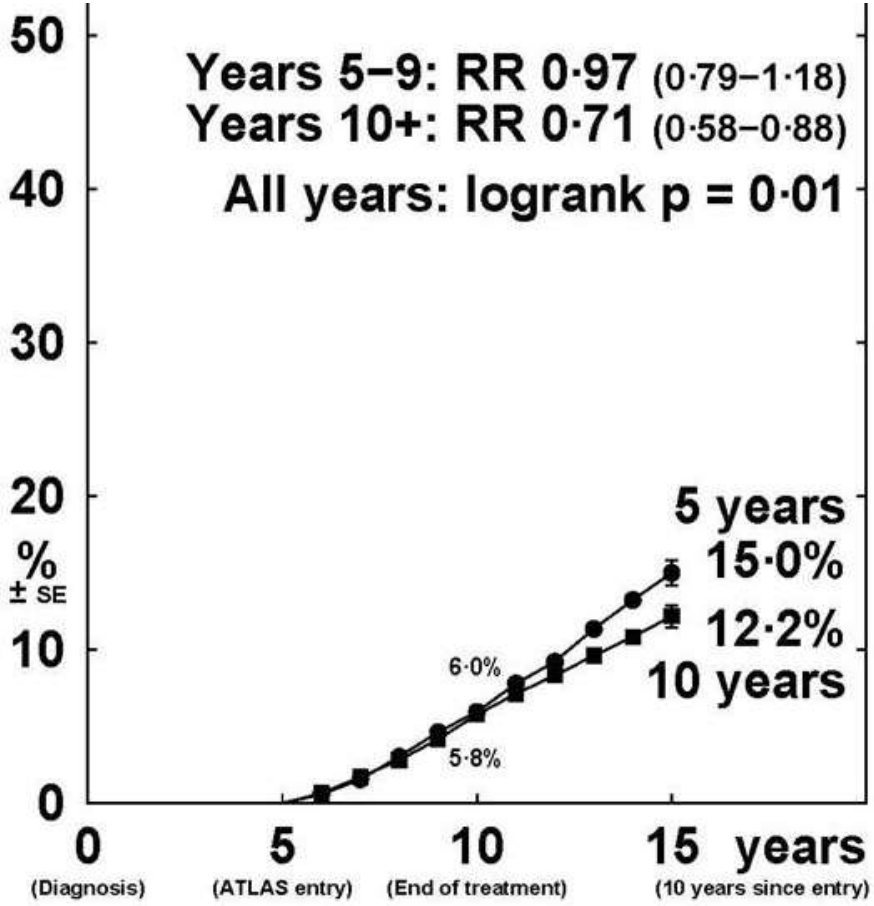
www.thelancet.com **Published online December 5, 2012 http://dx.doi.org/10.1016/S0140-6736(12)61963-1**

ATLAS: 6846 women, ER+, 10 vs 5 years tamoxifen

RECURRENCE



BREAST CANCER MORTALITY



Recurrence rates (% / year) and logrank analyses

Tamoxifen allocation	Years 5 – 9	Years 10 – 14	Year 15+
Continue to 10 years	2·83 (428 / 15115)	1·96 (165 / 8439)	2·54 (24 / 945)
Stop at 5 years	3·16 (471 / 14889)	2·66 (214 / 8038)	3·03 (26 / 859)
Rate ratio, from (O–E) / V	0·90 SE 0·06 −24·8 / 224·7	0·74 SE 0·09 −29·1 / 94·7	0·85 SE 0·26 −2·1 / 12·5

Death rates (% / year: total rate − rate in women without recurrence) & logrank analyses

Tamoxifen allocation	Years 5 – 9	Years 10 – 14	Year 15+
Continue to 10 years	1·17 SE 0·09	1·38 SE 0·12	1·64 SE 0·39
Stop at 5 years	1·21 SE 0·09	2·01 SE 0·15	2·29 SE 0·47
Rate ratio, from (O–E) / V	0·97 SE 0·10 −3·2 / 94·0	0·70 SE 0·10 −27·2 / 77·5	0·79 SE 0·27 −2·5 / 10·6

Analyses of events without prior recurrence‡, any ER status						
Death without recurrence						
Vascular death						
Stroke	62	59	0·8	30·2	1·03 (0·72–1·46)	0·89
Pulmonary embolus	10	8	0·8	4·5	1·21 (0·48–3·04)	0·69
Heart disease§	178	205	–16·1	95·7	0·85 (0·69–1·03)	0·10
Neoplastic death						
Endometrial cancer¶	17	11	2·8	7·0	1·49 (0·71–3·13)	0·29
Other neoplastic disease	78	75	0·4	38·2	1·01 (0·74–1·39)	0·94
Other death						
Specified cause	171	161	2·3	82·9	1·03 (0·83–1·28)	0·80
Unspecified cause	175	160	5·1	83·7	1·06 (0·86–1·32)	0·58
Second cancer incidence						
Contralateral breast cancer	419	467	–28·9	221·5	0·88 (0·77–1·00)	0·05
Endometrial cancer¶	116	63	24·8	44·8	1·74 (1·30–2·34)	0·0002
Primary liver cancer	3	3	–0·0	1·5	0·99 (0·20–4·90)	0·99
Colorectal cancer	46	52	–3·8	24·5	0·86 (0·58–1·27)	0·44
Unspecified site	254	251	–1·3	126·2	0·99 (0·83–1·18)	0·91
Non-neoplastic disease (ever hospitalised or died)						
Stroke	130	119	3·8	62·2	1·06 (0·83–1·36)	0·63
Pulmonary embolus	41	21	9·7	15·5	1·87 (1·13–3·07)	0·01
Ischaemic heart disease	127	63	–20·2	72·5	0·76 (0·60–0·95)	0·02
Gallstones	75	66	3·7	35·2	1·11 (0·80–1·54)	0·54
Cataract	72	63	3·5	33·7	1·11 (0·79–1·56)	0·54
Bone fracture	62	70	–4·9	33·0	0·86 (0·61–1·21)	0·39

Interpretation

The Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial, with a mean of 7·6 years of further follow-up after entry at year 5, shows that recurrence and breast cancer mortality during the second decade after diagnosis are reduced more effectively by 10 years of adjuvant tamoxifen than by 5 years. Although known side-effects were increased (at least in postmenopausal women) by longer treatment, the absolute reduction in breast cancer mortality was an order of magnitude greater than the absolute increase in mortality due to these side-effects. Taken together with the results from trials of 5 years of tamoxifen versus none, the results from ATLAS show that 10 years of effective endocrine therapy can approximately halve breast cancer mortality during years 10–14 after diagnosis. Longer follow-up of ATLAS (and a meta-analysis of all such trials) will be needed to assess the full benefits and hazards throughout the second decade.

Relative effectiveness of letrozole compared with tamoxifen for patients with lobular carcinoma in the BIG 1-98 trial

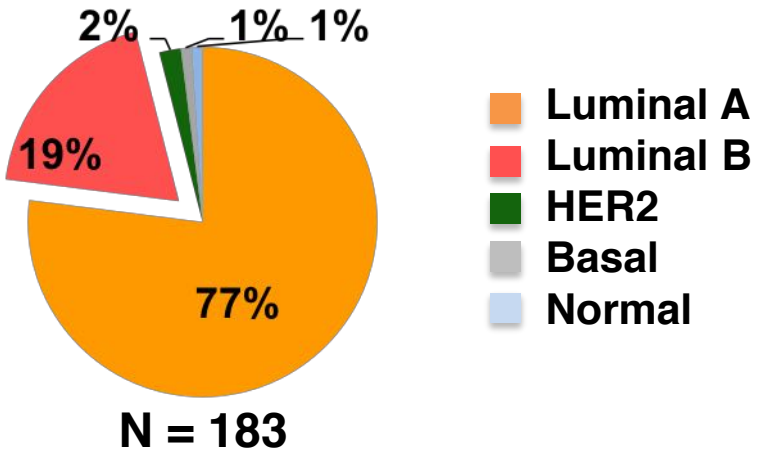
Otto Metzger Filho, Anita Giobbie-Hurder, Elizabeth Mallon, Giuseppe Viale, Eric P. Winer, Beat Thürlimann, Richard D. Gelber, Marco Colleoni, Bent Ejlertsen, Hervé Bonnefoi, Alan S. Coates, Aron Goldhirsch for the BIG 1-98 Collaborative Group

International Breast Cancer Study Group
IBCSG

BIG
BREASTINTERNATIONALGROUP

Background

- **Lobular carcinoma is mostly represented by Luminal A (low proliferative tumors) followed by Luminal B (high proliferative tumors) by gene expression profiling [1]**



- **In a previous analysis of BIG 1-98 the magnitude of benefit of letrozole vs. tamoxifen was greater among patients with high proliferative tumors (determined by Ki 67 labeling index) [2]**

1. *Metzger et al. SABCS 2011 P01-02-05*
2. *Viale et al.* JCO 2008

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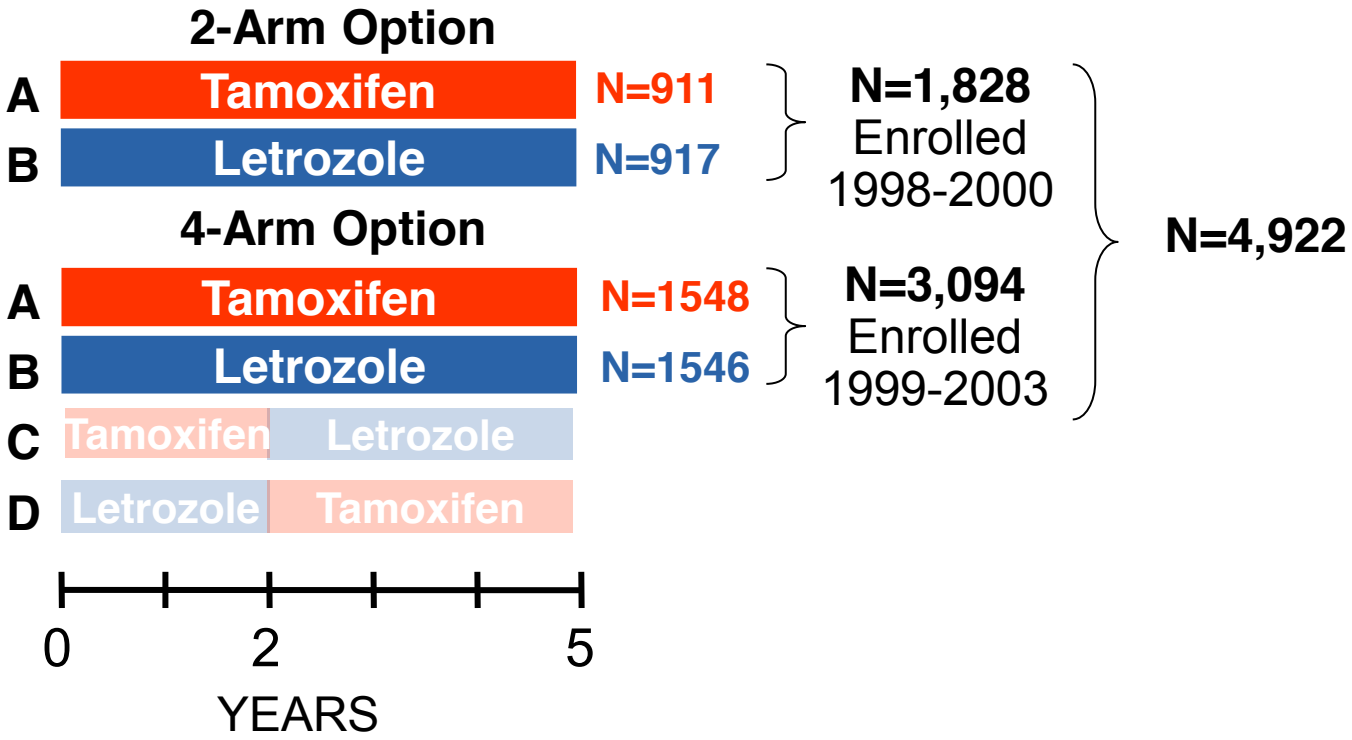
BIG 1-98 Analytic Cohort
Postmenopausal HR+ BC
12-year update (Lancet Oncol 2011)



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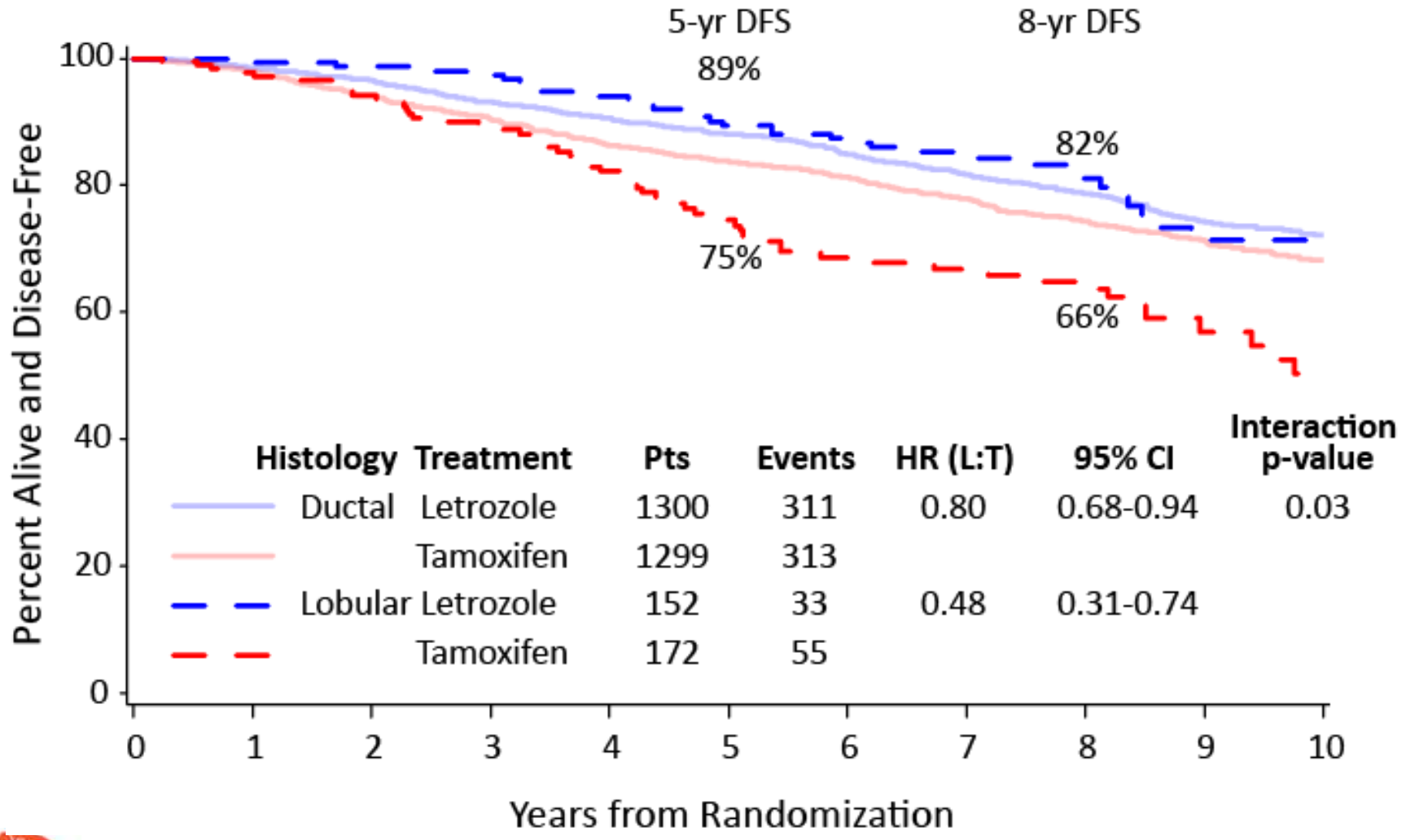
Disease-free survival



Histology	Treatment	Pts	Events	HR (L:T)	95% CI	Interaction p-value
Ductal	Letrozole	1300	311	0.80	0.68-0.94	0.03
	Tamoxifen	1299	313			
Lobular	Letrozole	152	33	0.48	0.31-0.74	
	Tamoxifen	172	55			

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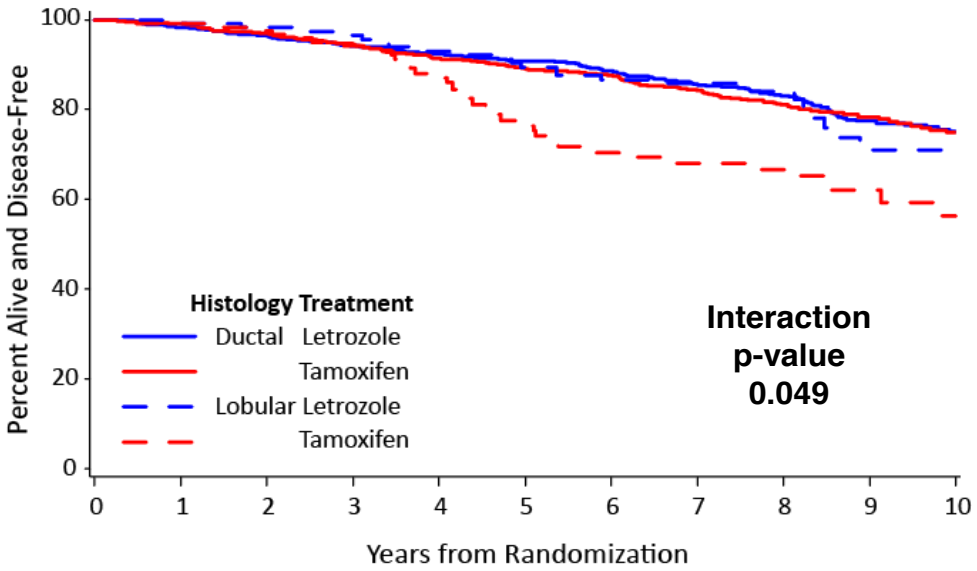
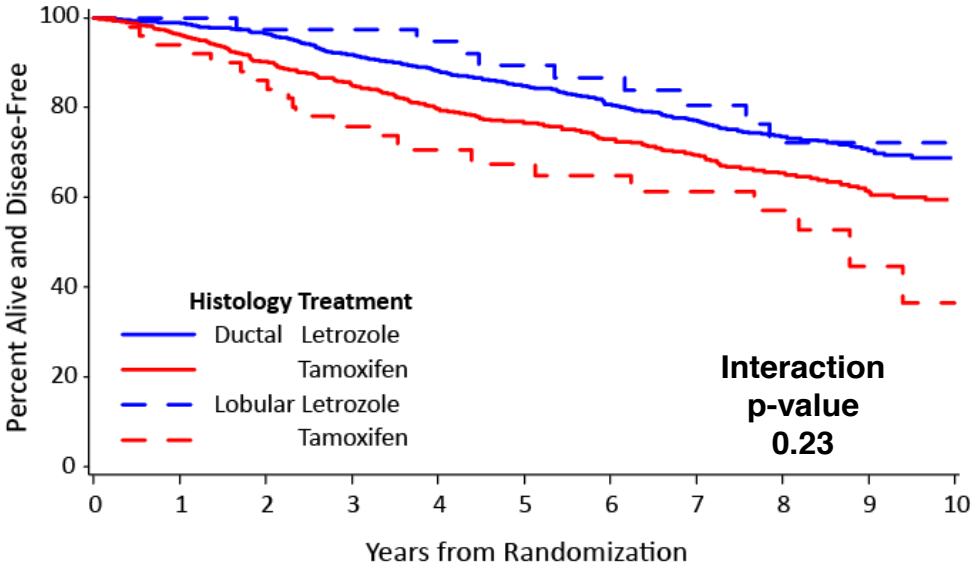
Disease-free survival

Luminal A



Luminal B



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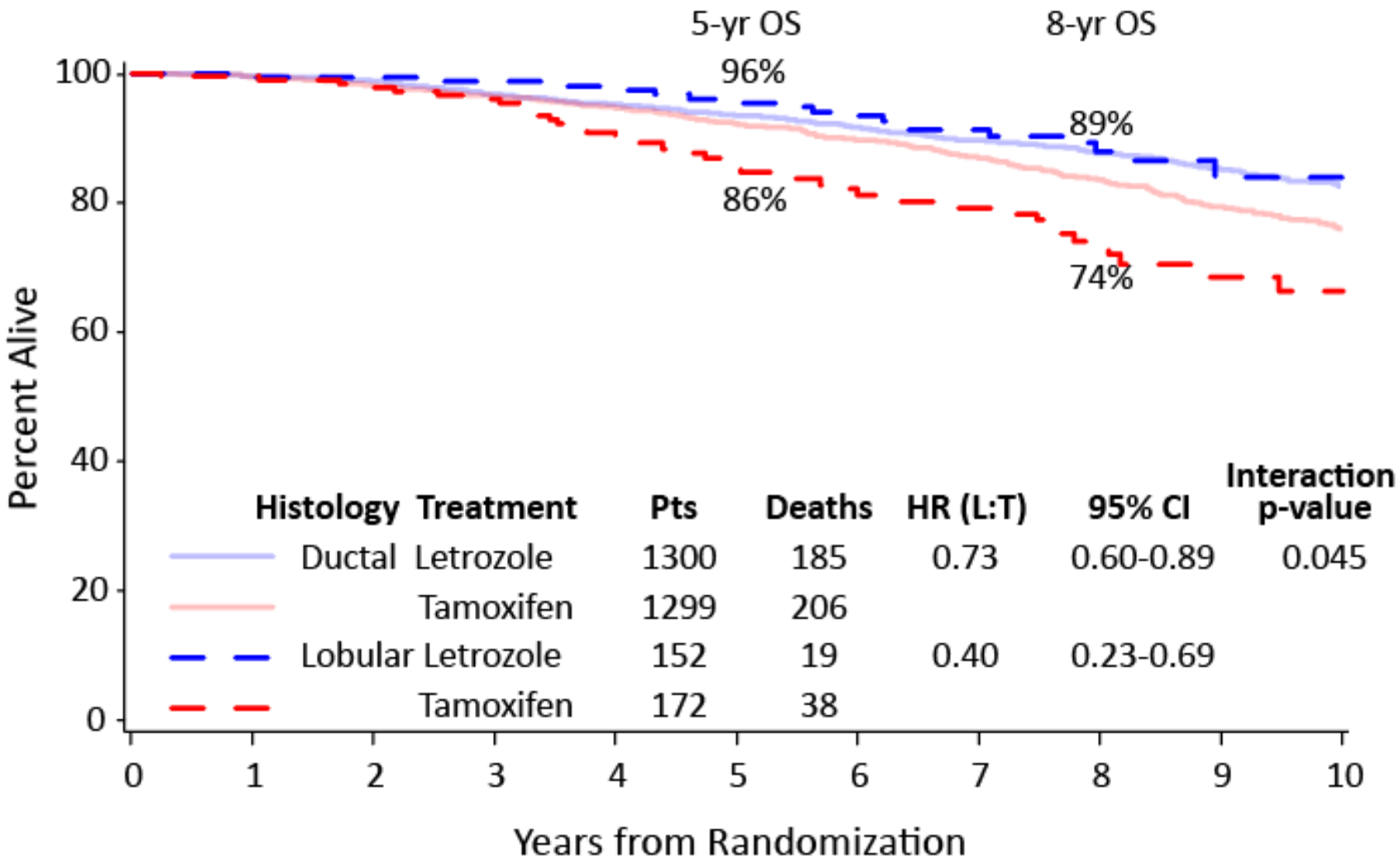
Overall survival



Histology	Treatment	Pts	Deaths	HR (L:T)	95% CI	Interaction p-value
Ductal	Letrozole	1300	185	0.73	0.60-0.89	0.045
	Tamoxifen	1299	206			
Lobular	Letrozole	152	19	0.40	0.23-0.69	
	Tamoxifen	172	38			

International Breast Cancer Study Group

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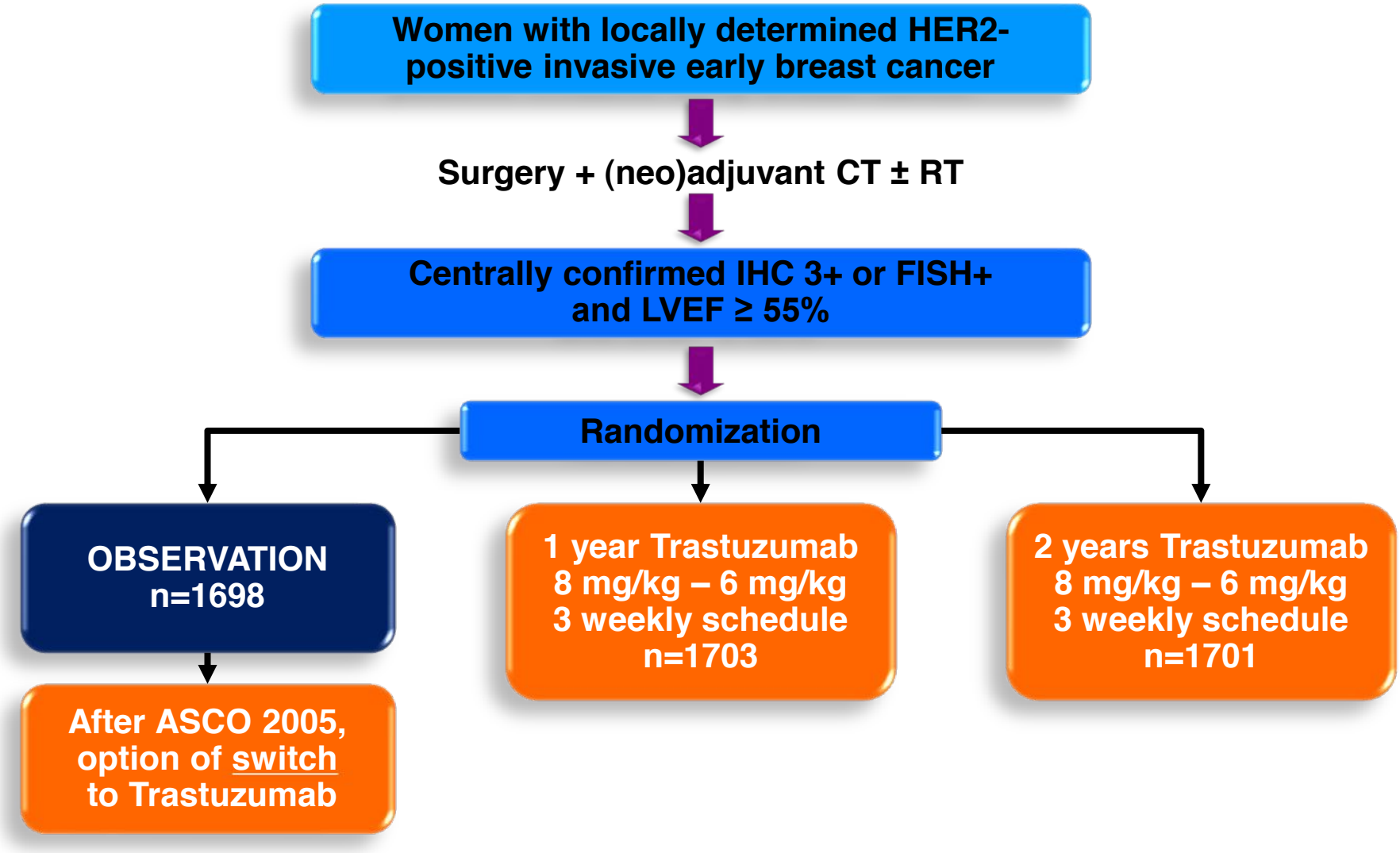
HERA TRIAL: 2 years versus 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow-up

HERA TRIAL DESIGN

ACCRUAL 2001 – 2005 (N=5102)



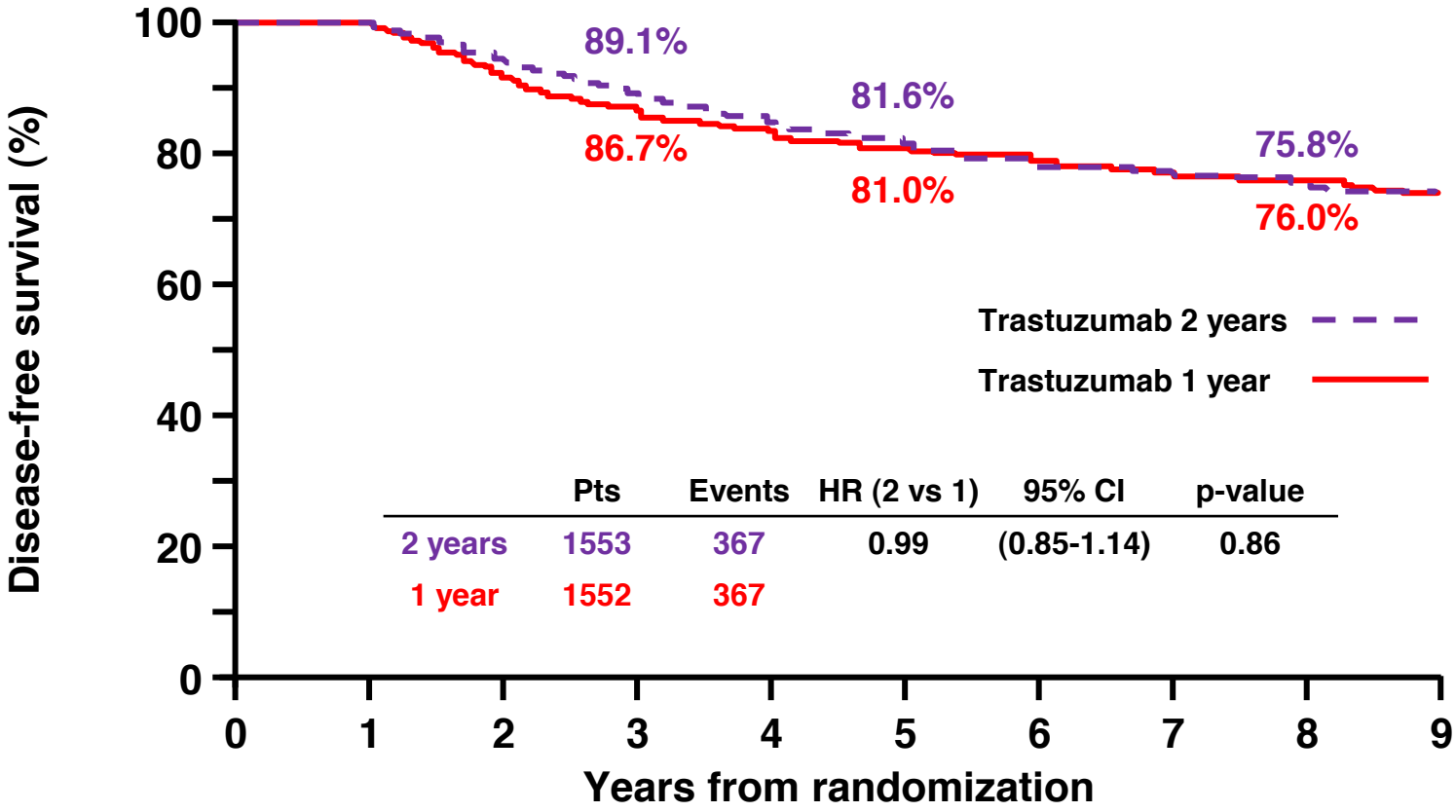
CT, chemotherapy; RT, radiotherapy

BASELINE CHARACTERISTICS

	Trastuzumab 1 Year N=1552	Trastuzumab 2 Years N=1553
Nodal Status		
Any Nodal Status, neo-adjuvant chemo	10.7%	10.8%
Node-negative, adjuvant chemo	32.9%	32.8%
1-3 Nodes Positive, adjuvant chemo	29.3%	29.6%
≥ 4 Nodes Positive, adjuvant chemo	27.1%	26.9%
Adjuvant Chemotherapy Regimen		
No Anthracyclines	6.1%	5.9%
Anthracyclines w/o Taxanes	68.5%	68.6%
Anthracyclines + Taxanes	25.5%	25.6%

HERA was a global trial with the exception of the United States

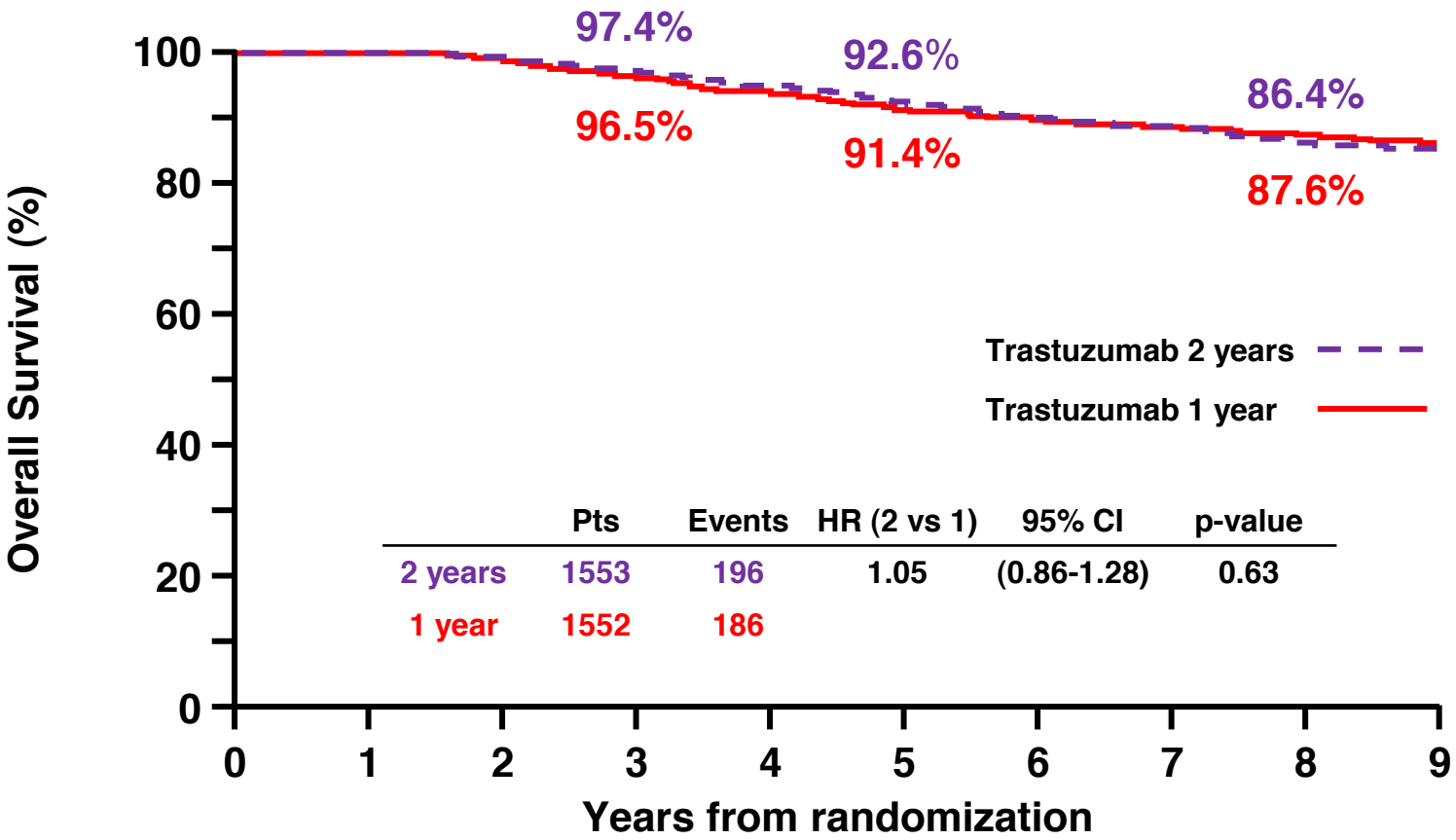
DFS FOR 2 YEARS VS. 1 YEAR TRASTUZUMAB AT 8 YRS MFU



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

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

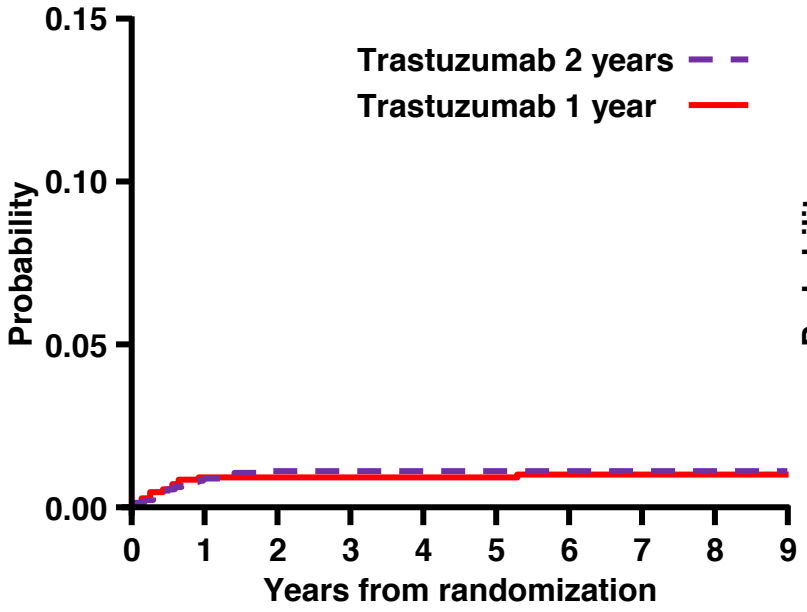


No. at risk

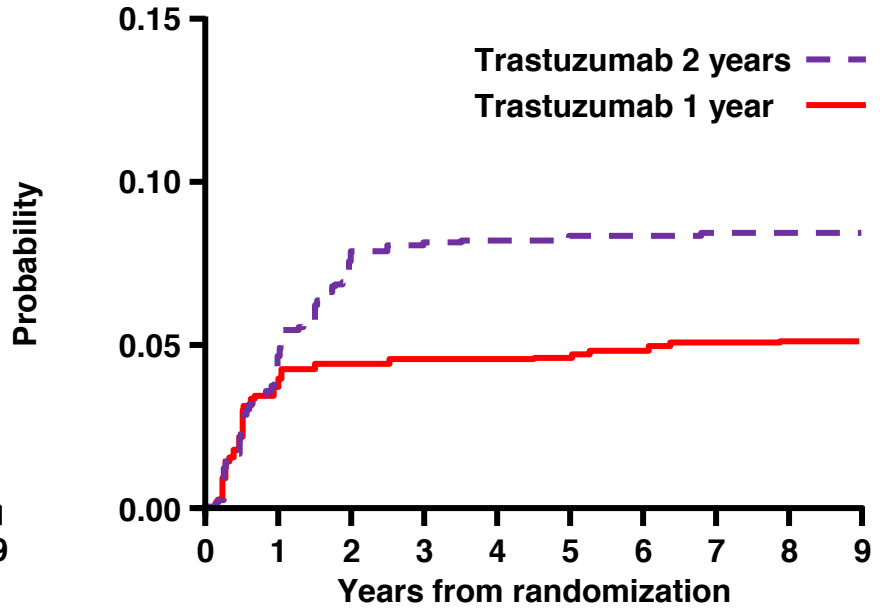
Trastuzumab 2 years	1553	1553	1525	1485	1438	1382	1317	1193	708	208
Trastuzumab 1 year	1552	1552	1513	1461	1413	1364	1329	1218	732	225

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)

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

EH Romond[1,2], VJ Suman[3], J-H Jeong[1,4], GW Sledge, Jr.[5], CE Geyer, Jr.[1,6], S Martino[7], P Rastogi[1,8], J Gralow[9], SM Swain[1,10], E Winer[11], G Colon-Otero[12], C Hudis[13], S Paik[1], N Davidson[8], EP Mamounas[14], JA Zujewski[15], N Wolmark[16], EA Perez[12]

[1]National Surgical Adjuvant Breast and Bowel Project Operations and Biostatistical Centers; [2]University of Kentucky; [3]Mayo Clinic; [4]Department of Biostatistics, University of Pittsburgh Graduate School of Public Health; [5]IU Simon Cancer Center; [6]University of Texas Southwestern Medical Center; [7]The Angeles Clinic and Research Institute; [8]University of Pittsburgh Cancer Institute; [9]University of Washington; [10]Medstar Washington Hospital Center; [11]Dana-Farber Cancer Institute; [12]Mayo Clinic, Jacksonville; [13]Memorial Sloan-Kettering Cancer Center; [14]Aultman Hospital; [15]Division of Cancer Therapy and Diagnosis, Cancer Therapy Evaluation Program, National Cancer Institute, National Institutes of Health, DHHS; [16]Allegheny Cancer Center Allegheny General Hospital

San Antonio Breast Cancer Symposium – December 4-8, 2012

Abstract #S5-5

NSABP B-31

Arm 1

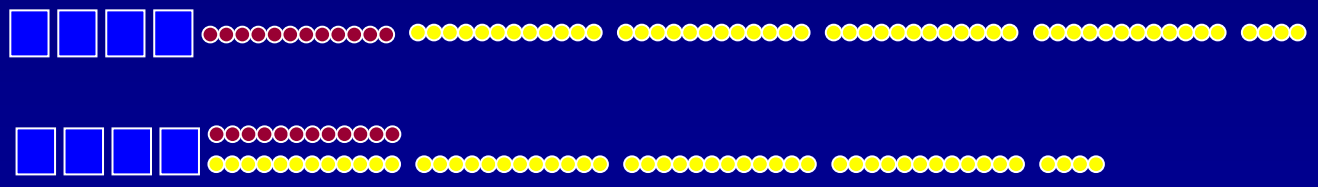
Arm 2

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

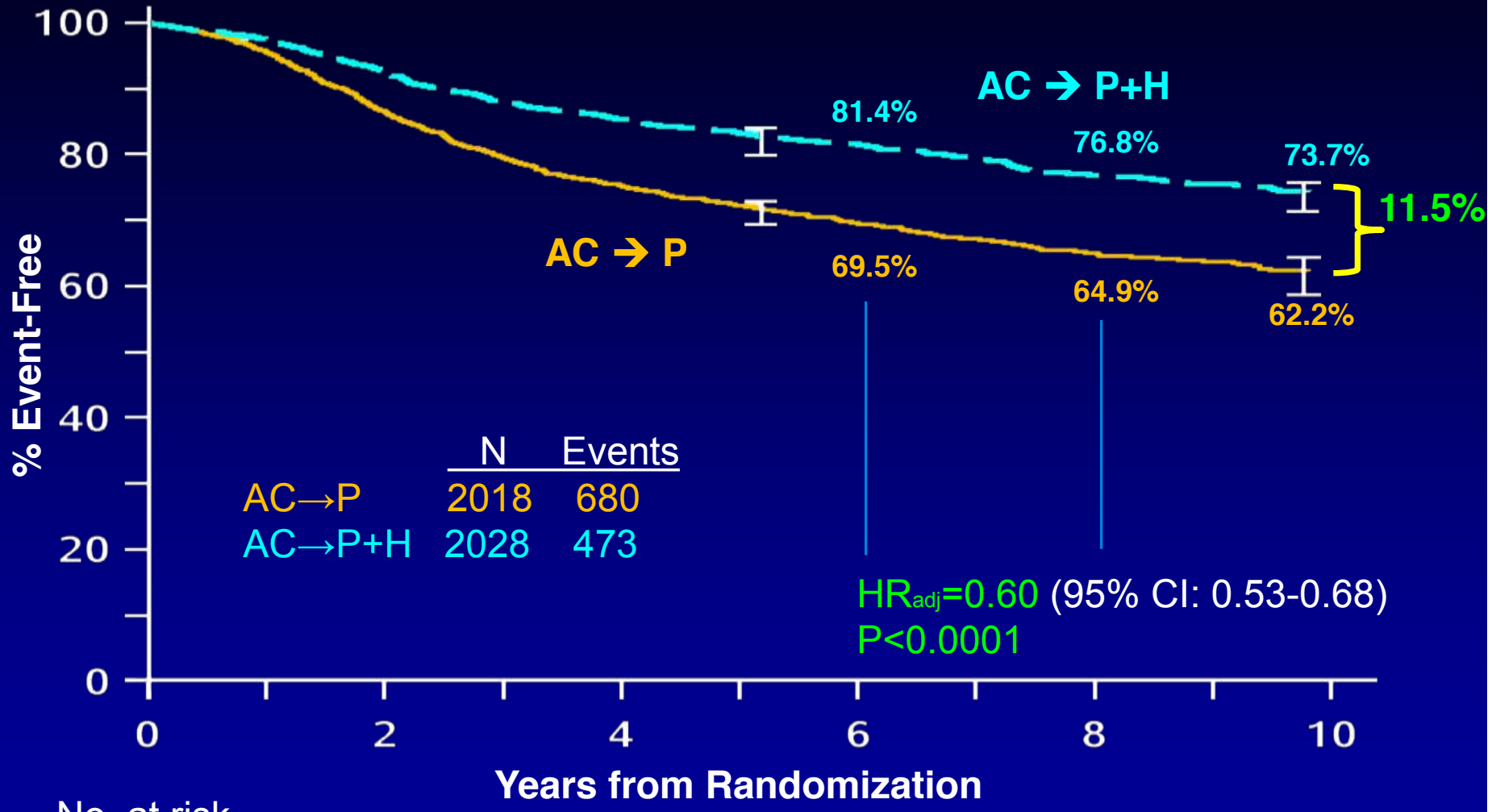
= trastuzumab (H) 4mg/kg LD + 2 mg/kg/wk x 51

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

- 102 women (5%) assigned to the treatment arm did not receive trastuzumab because of cardiac symptoms or decrease in LVEF that precluded initiation of the antibody. These are included in the trastuzumab arm in the ITT analysis.
- 413 women (20.4%) assigned to the control arm received trastuzumab after the first interim analysis reported positive results in 2005. These are included in the control arm in the ITT analysis.

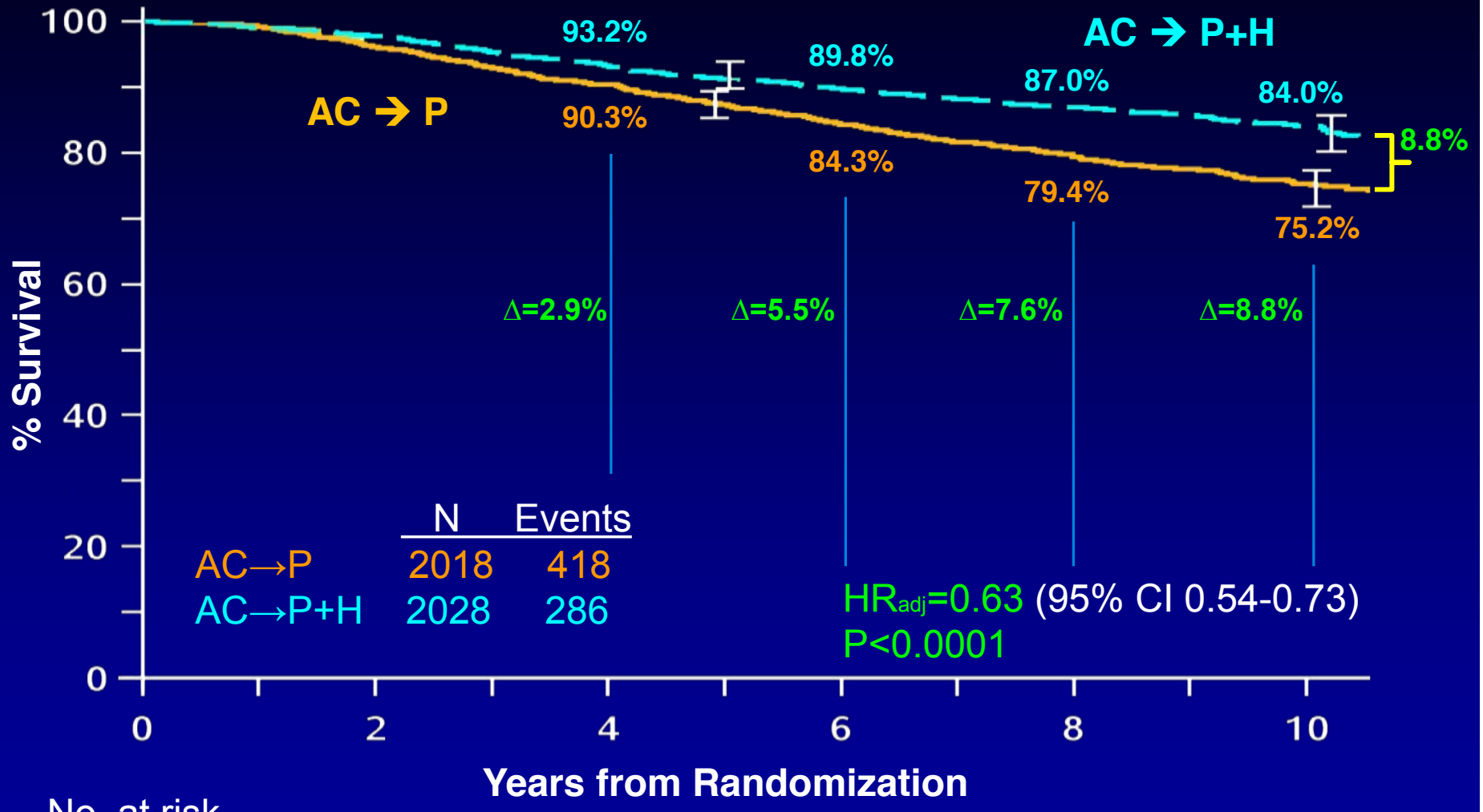
N9831/B-31 Disease-Free Survival



No. at risk

AC→P+H	2028	1959	1848	1747	1675	1611	1514	1293	910	619	350
AC→P	2018	1887	1689	1529	1423	1329	1232	1027	705	449	255

B-31/N9831 Overall Survival

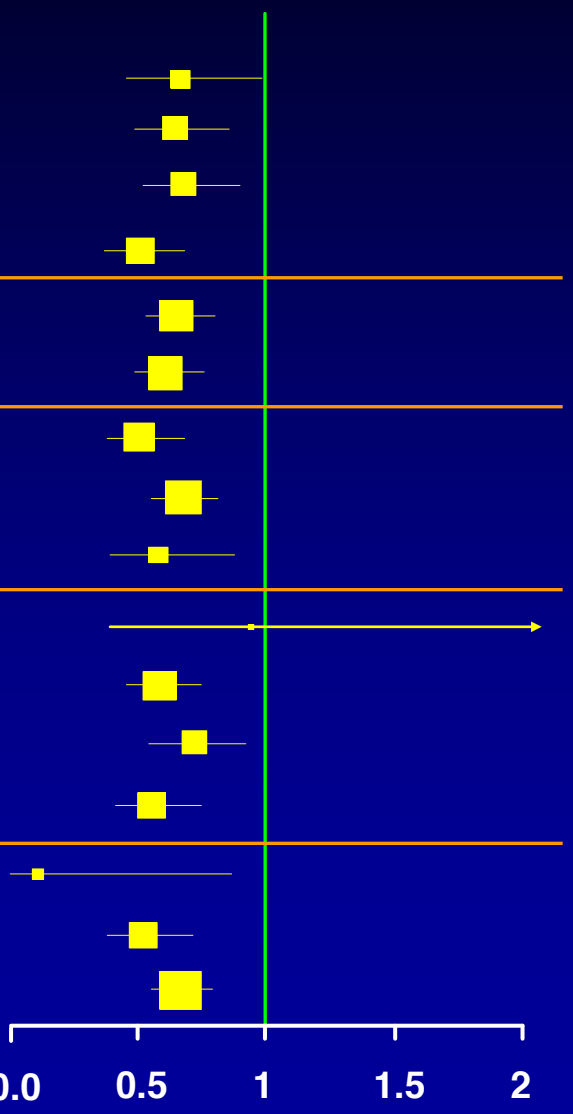


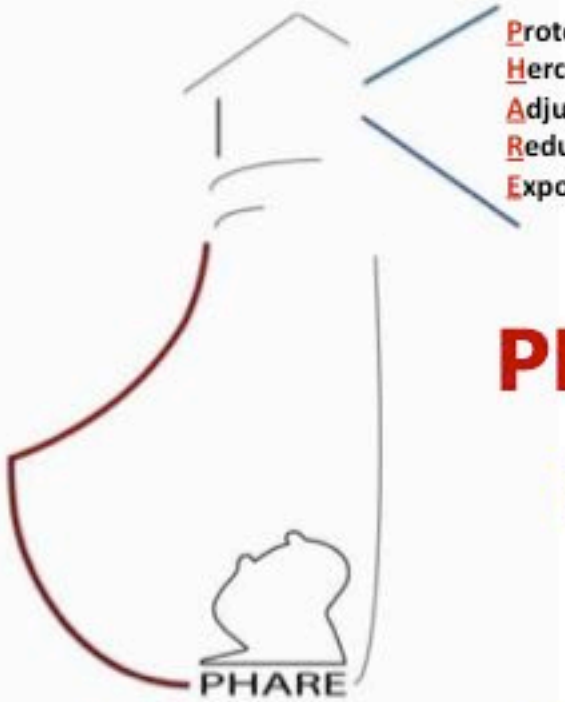
No. at risk

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

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





Protocol of
Herceptin®
Adjuvant with
Reduced
Exposure

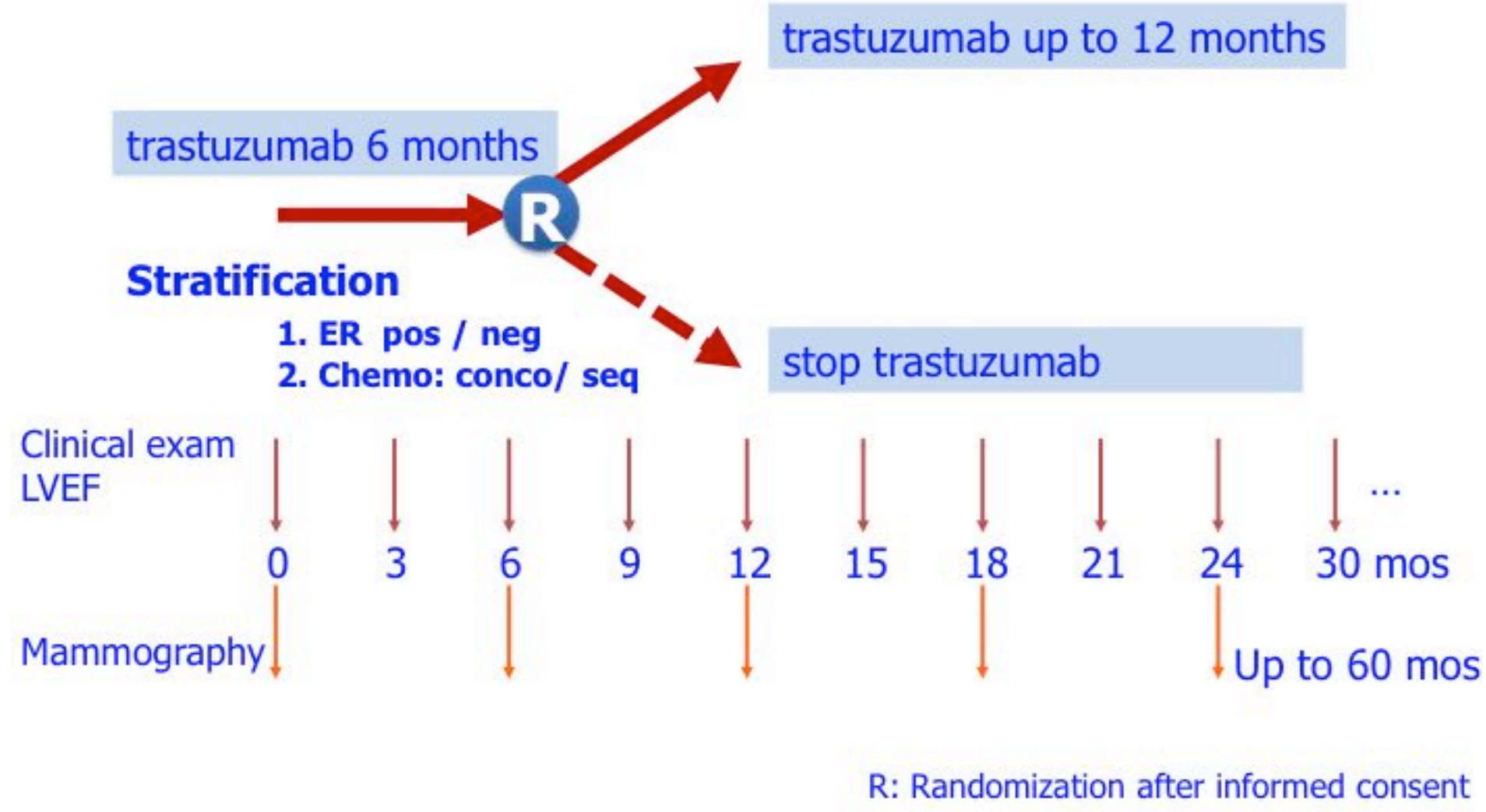
INSTITUT NATIONAL DU CANCER

PHARE* Trial results of subset analysis comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer

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.

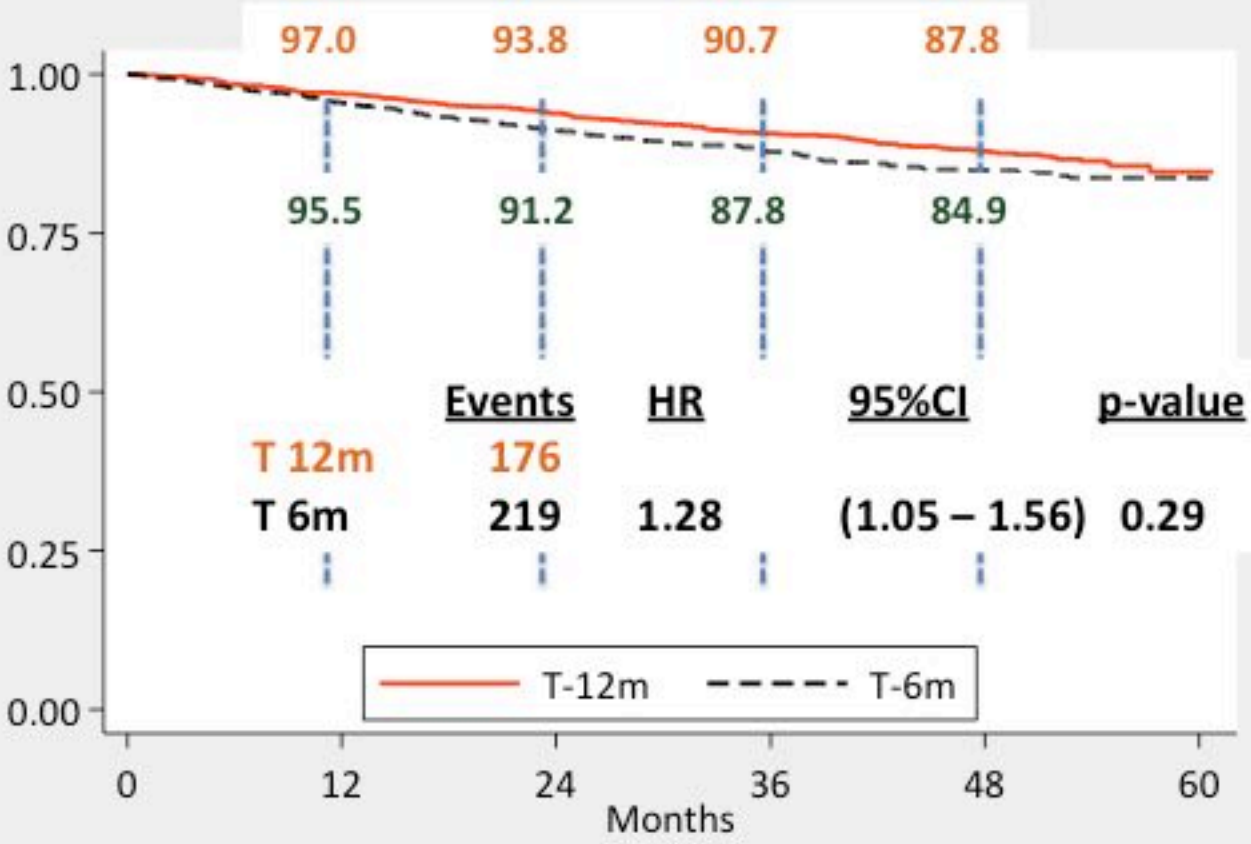
*lighthouse in French

Study design



R: Randomization after informed consent

Disease Free Survival

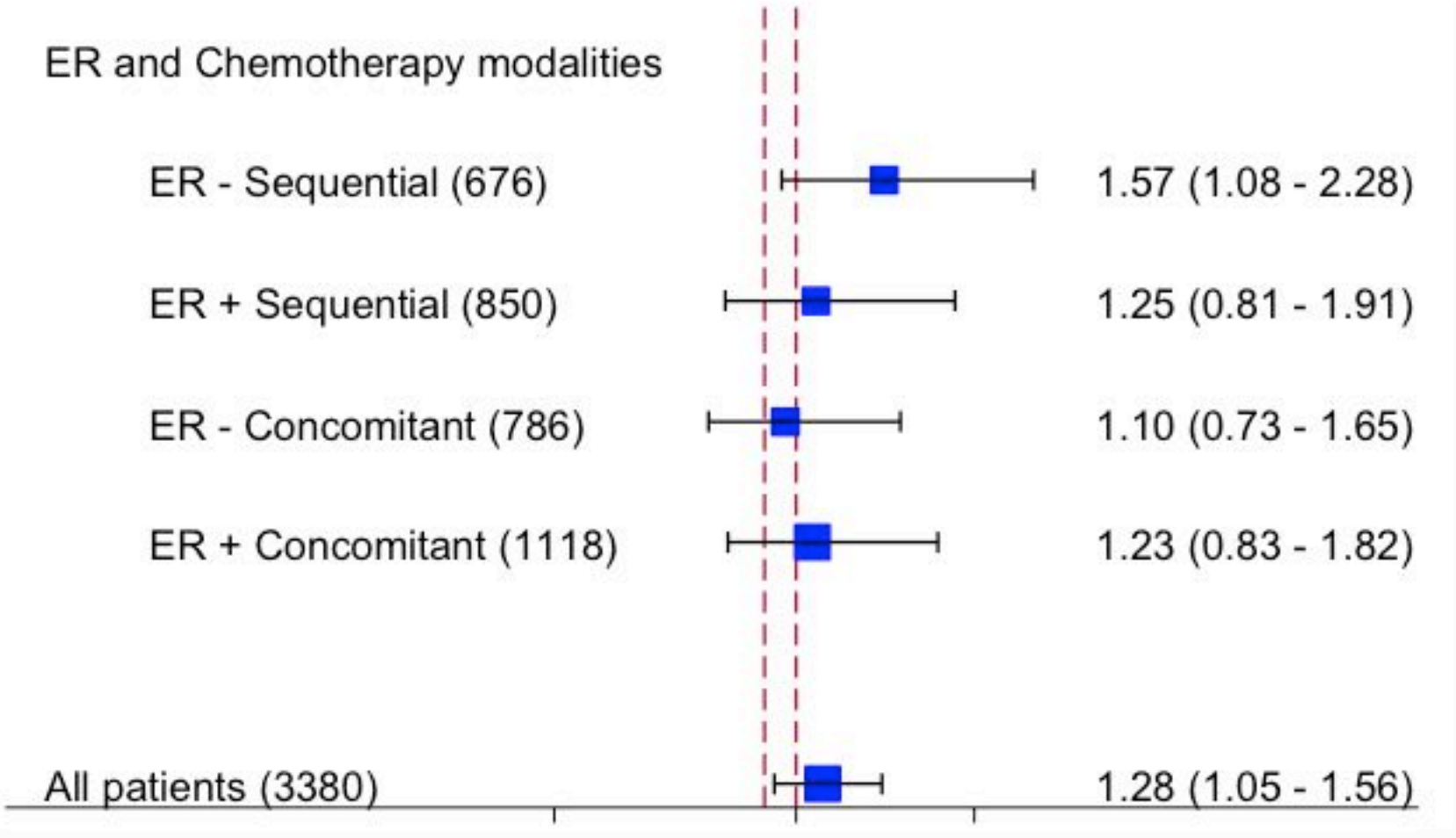


Trastuzumab

T-12m	1690	1613	1390	980	544	18
T-6m	1690	1586	1353	939	526	23

* Cox model stratified by ER status and concomitant chemotherapy

Conclusion


ER and Chemotherapy modalities
ER - Sequential (676)
1.57 (1.08 - 2.28)
ER + Sequential (850)
1.25 (0.81 - 1.91)
ER - Concomitant (786)
1.10 (0.73 - 1.65)
ER + Concomitant (1118)
1.23 (0.83 - 1.82)
All patients (3380)
1.28 (1.05 - 1.56)

Conclusion

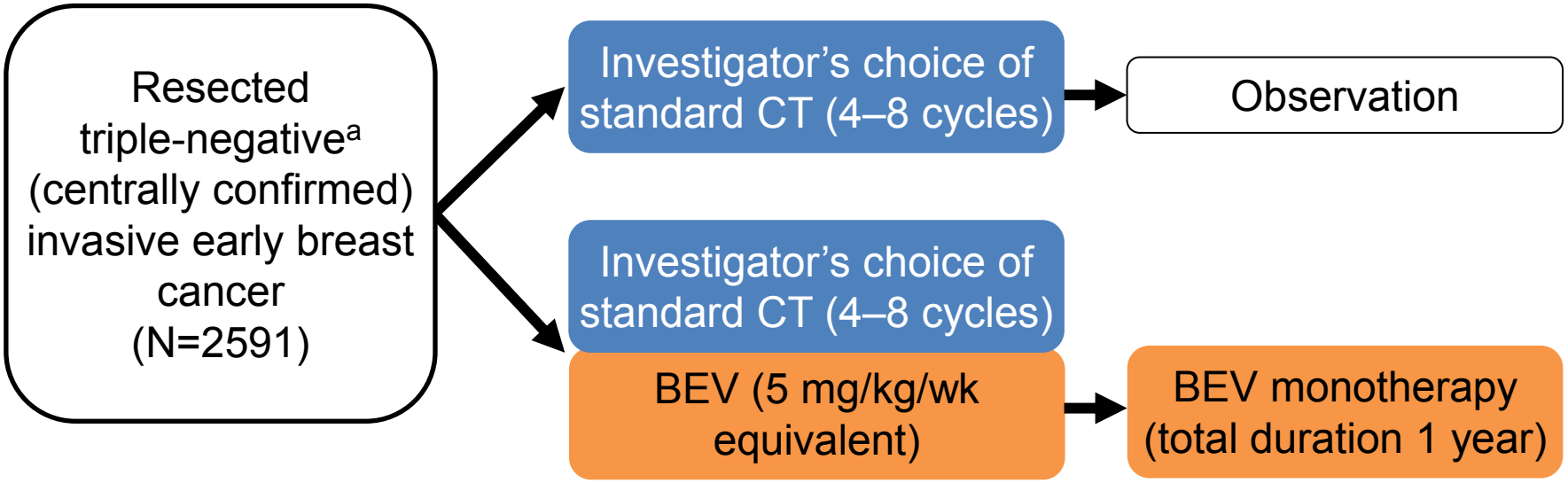
- PHARE failed to show that 6 months of trastuzumab is non inferior to 12 months
- Subgroups analysis suggested
  - Sequential modality for ER negative tumors impacted the overall results
  - Results in other groups seemed compatible with non-inferiority hypothesis
- PHARE longer FU & PERSEPHONE, SHORTHER & SOLD trial results are expected

Primary results of BEATRICE, a randomized phase III trial evaluating adjuvant bevacizumab-containing therapy in triple-negative breast cancer

D Cameron[1], J Brown[2], R Dent[3], C Jackisch[4], J Mackey[5], X Pivot[6], G Steger[7], T Suter[8], M Toi[9], M Parmar[10], L Bubuteishvili-Pacaud[11], V Henschel[11], R Laeufle[11], R Bell[12]

[1]University of Edinburgh and NHS Lothian, Edinburgh, UK; [2]University of Leeds, Leeds, UK; [3]Sunnybrook Health Sciences Center and University of Toronto, Toronto, ON, Canada and National Cancer Center, Singapore, Singapore; [4]Klinikum Offenbach, Offenbach, Germany; [5]Cross Center Institute, Edmonton, Canada; [6]University Hospital Jean Minjoz, Besançon, France; [7]Medical University of Vienna, Vienna, Austria; [8]Bern University Hospital, Inselspital, Switzerland; [9]Kyoto University, Kyoto, Japan; [10]MRC Clinical Trials Unit, London, UK; [11]F Hoffmann-La Roche Ltd, Basel, Switzerland; [12]Andrew Love Cancer Centre, Geelong, Australia

BEATRICE:
Randomized open-label multicenter phase III trial



Stratification factors:

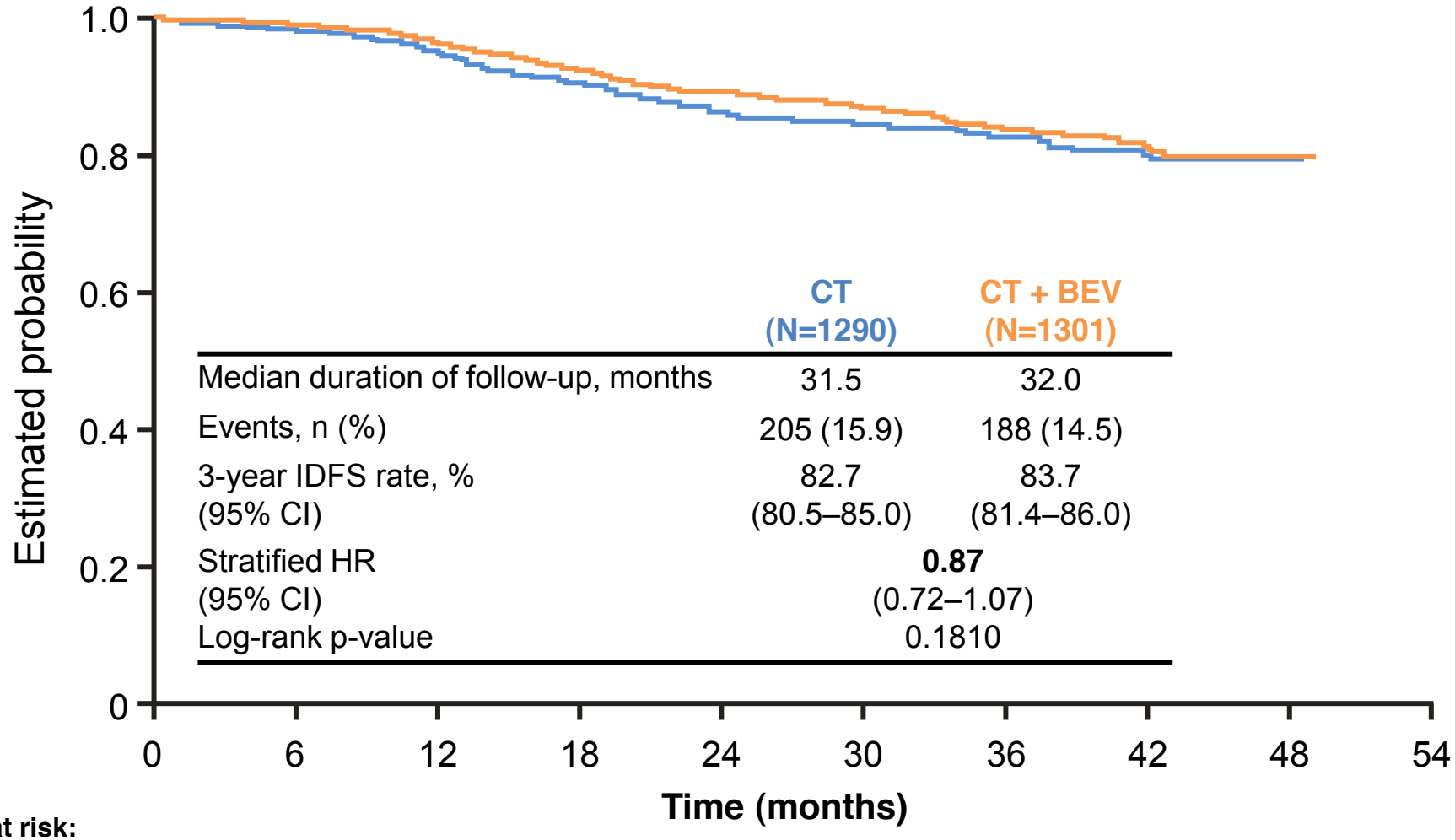
- Axillary nodal status (0 vs 1–3 vs ≥4)
- Adjuvant chemotherapy (anthracycline vs taxane vs anthracycline + taxane)
- Hormone receptor status (negative vs low)
- Surgery (breast-conserving vs mastectomy)

Chemotherapy options:

- Taxane based (≥4 cycles)
- Anthracycline based (≥4 cycles)
- Anthracycline + taxane (3–4 cycles each)

[a]HER2-negative and hormone receptor negative or low (total Allred score of 2 or 3; intensity score 1, proportion score 1 or 2)

Primary endpoint: IDFS[a]



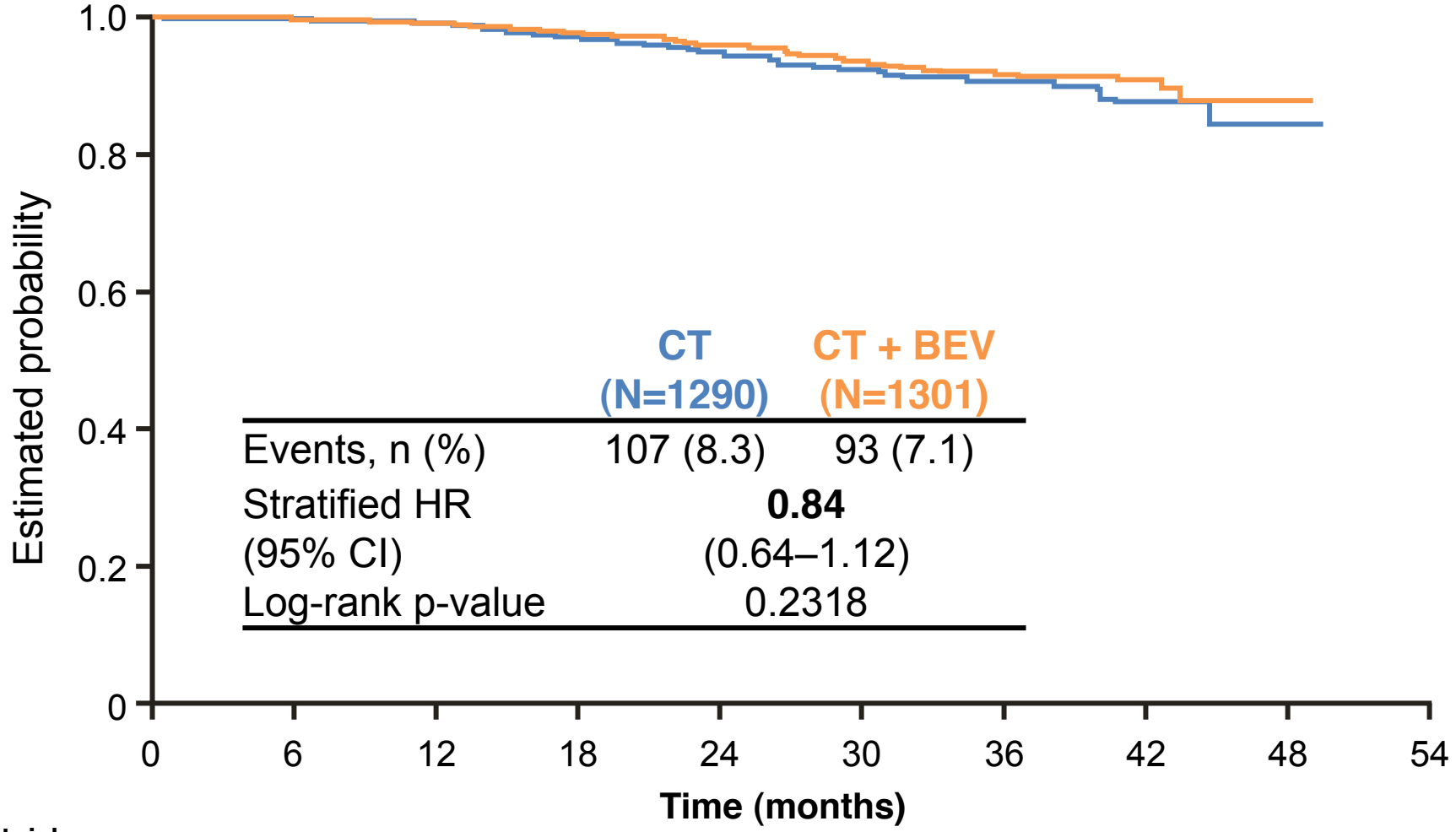
	CT (N=1290)	CT + BEV (N=1301)
Median duration of follow-up, months	31.5	32.0
Events, n (%)	205 (15.9)	188 (14.5)
3-year IDFS rate, % (95% CI)	82.7 (80.5–85.0)	83.7 (81.4–86.0)
Stratified HR (95% CI)	**0.87** (0.72–1.07)	
Log-rank p-value	0.1810	

No. at risk:

CT + BEV	1301	1244	1193	1129	1058	814	409	122	4	0
CT	1290	1221	1151	1086	994	772	383	105	2	0

[a]Intent to treat, not censored for non-protocol therapy

Interim OS (59% of required events)



No. at risk:

CT + BEV	1301	1264	1234	1196	1130	863	443	128	4	0
CT	1290	1248	1215	1169	1087	831	424	113	4	0

Grade ≥3 AEs of special interest by treatment phase

AE, No. of patients (%)	Chemotherapy phase		Observation or single-agent BEV phase	
	CT (N=1271)	CT + BEV (N=1288)	CT (N=1271)	CT + BEV (N=1288)
All grade ≥3 AESIs	33 (3)	143 (11)	12 (<1)	122 (9)
ATE	2 (<1)	2 (<1)	1 (<1)	4 (<1)
VTE	15 (1)	21 (2)	4 (<1)	1 (<1)
Bleeding	2 (<1)	8 (<1)	2 (<1)	0
CHF/LVD	3 (<1)	12 (<1)	1 (<1)	24 (2)
Hypertension	6 (<1)	88 (7)	4 (<1)	70 (5)
Fistula/abscess	2 (<1)	0	0	1 (<1)
Gastrointestinal perforation	0	6 (<1)	0	0
Proteinuria	1 (<1)	8 (<1)	0	24 (2)
RPLS	0	1 (<1)	0	1 (<1)
Wound-healing complication	3 (<1)	3 (<1)	0	1 (<1)

ATE = arterial thromboembolic event; CHF = congestive heart failure; LVD = left ventricular dysfunction; RPLS = reversible posterior leukoencephalopathy syndrome; VTE = venous thromboembolic event.

Conclusions

- First randomized phase III trial specifically in early TNBC
  - 3-year IDFS better than anticipated
- BEATRICE demonstrated no statistically significant improvement in invasive DFS with the addition of 1 year's BEV to adjuvant CT for TNBC
  - IDFS HR = 0.87 (95% CI: 0.72–1.07; p=0.1810)
- Adverse events overall consistent with the established safety profile in mBC[1]

[1]Cortes J, et al. Ann Oncol 2012
mBC = metastatic breast cancer

San Antonio Breast Cancer Symposium – December 4-8, 2012

NSABP
National Surgical Adjuvant Breast and Bowel Project

IBCSG
International Breast Cancer Study Group

BIG
BREASTINTERNATIONALGROUP

Chemotherapy Prolongs Survival for Isolated Local or Regional Recurrence of Breast Cancer: The CALOR Trial

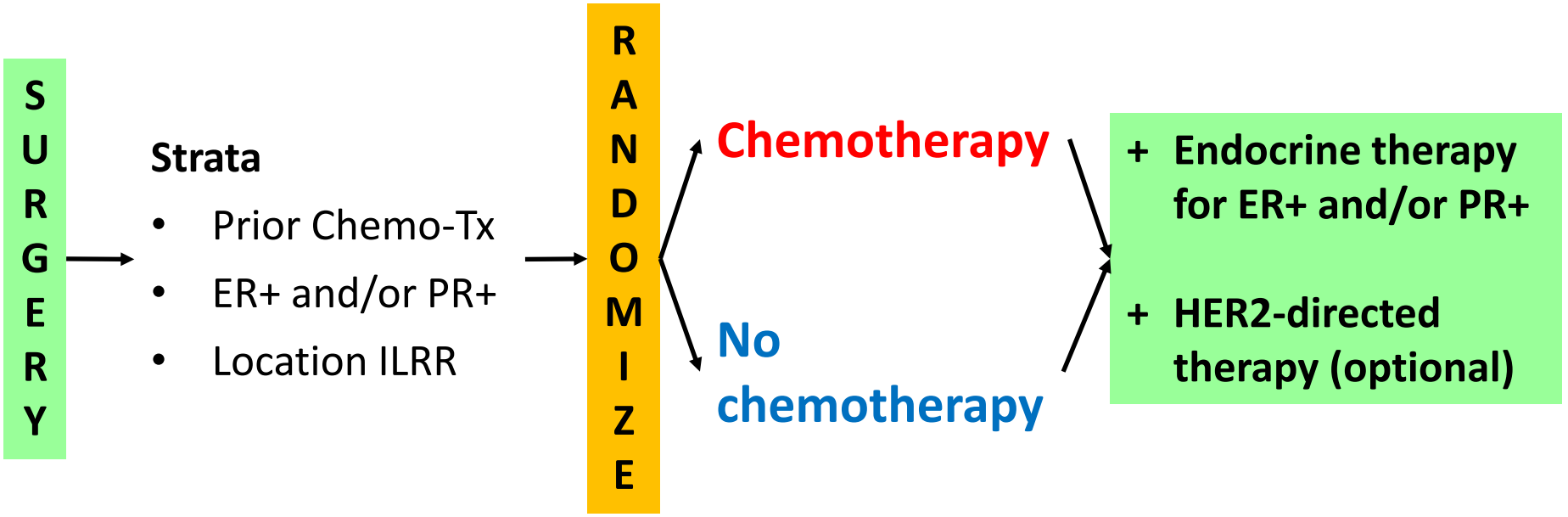
S. Aebi, S. Gelber, I. Láng, S.J. Anderson, A. Robidoux, M. Martín, J.W.R. Nortier, E.P. Mamounas, C.E. Geyer, Jr., R. Maibach, R.D. Gelber, N. Wolmark, I. Wapnir, for the **CALOR** Trial Investigators

Chemotherapy as **A**djuvant for **LO**cally **R**ecurrent Breast Cancer.
IBCSG 27–02, NSABP B–37, BIG 1–02 (BOOG, GEICAM, IBCSG)

CALOR Trial – Eligibility Criteria

- **First ipsilateral local and/or regional recurrence**
  - breast (IBTR)
  - chest wall
  - mastectomy scar and/or skin
  - axillary or internal mammary lymph nodes
- **Complete gross excision of recurrence**
  - Negative or microscopically involved margins
- **No evidence of supraclavicular lymph nodes**
- **No evidence of distant metastasis**

CALOR Trial



- **Chemotherapy chosen by investigators**
  Recommendation: ≥ 2 drugs, 3 to 6 months of therapy

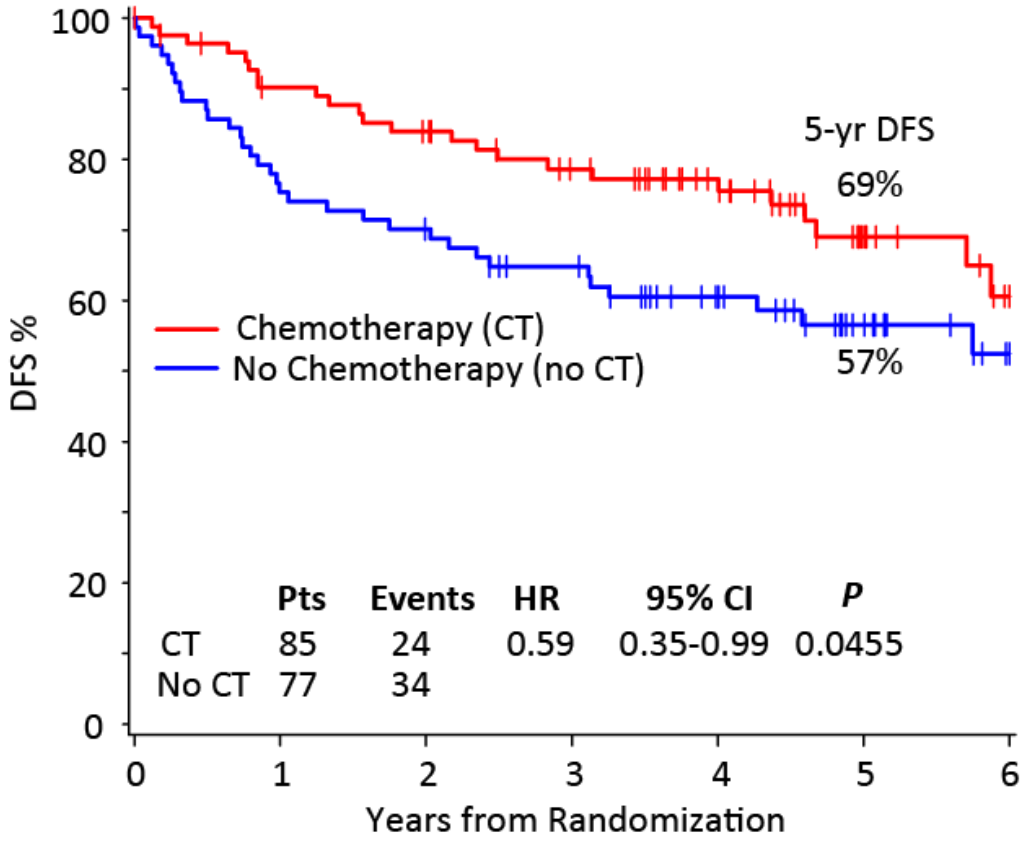
Statistical Considerations

- Original sample size for HR = 0.74
  977 patients, 347 DFS events
  - Low accrual rate
  - Newer, more effective chemotherapies
- Amendment 3, 2008:
  Revised sample size for HR = 0.6
  265 patients, 124 events
  - 5-year DFS for the observation group: 50%
  - 1-β = 0.8, logrank α = 0.05, 1 interim analysis

Statistical Considerations

- January 31, 2010
  Closure of the trial with 162 patients, no interim analysis
- Analysis plan (April, 2010)
  "…analyses to be conducted when the median follow up reaches four years with a minimum follow up of 2.5 years…"

CALOR Trial – Disease-free Survival

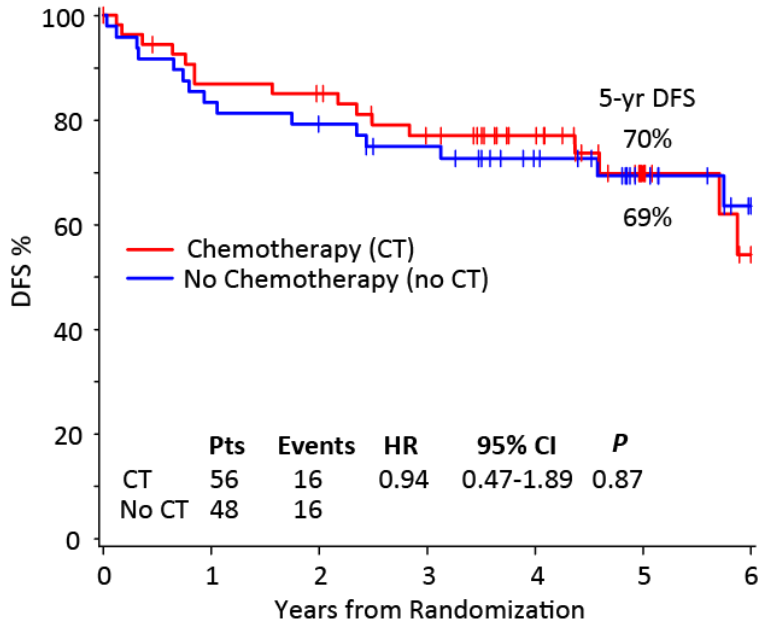


Number at Risk

Chemotherapy	85	72	66	57	45	23	12
No Chemotherapy	77	58	53	46	34	21	10

DFS ER Status

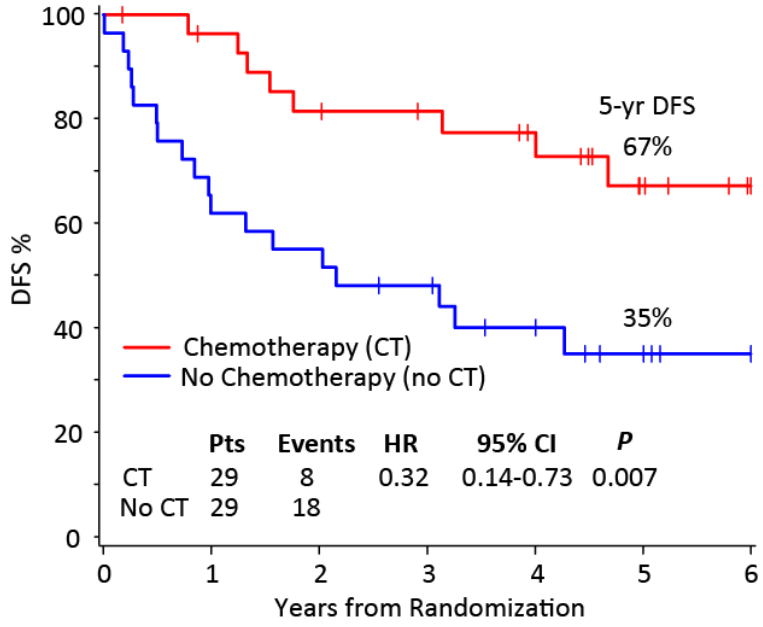
ER+



Number at Risk

Chemotherapy	56	47	44	37	28	13	6
No Chemotherapy	48	40	37	33	25	16	8

ER-

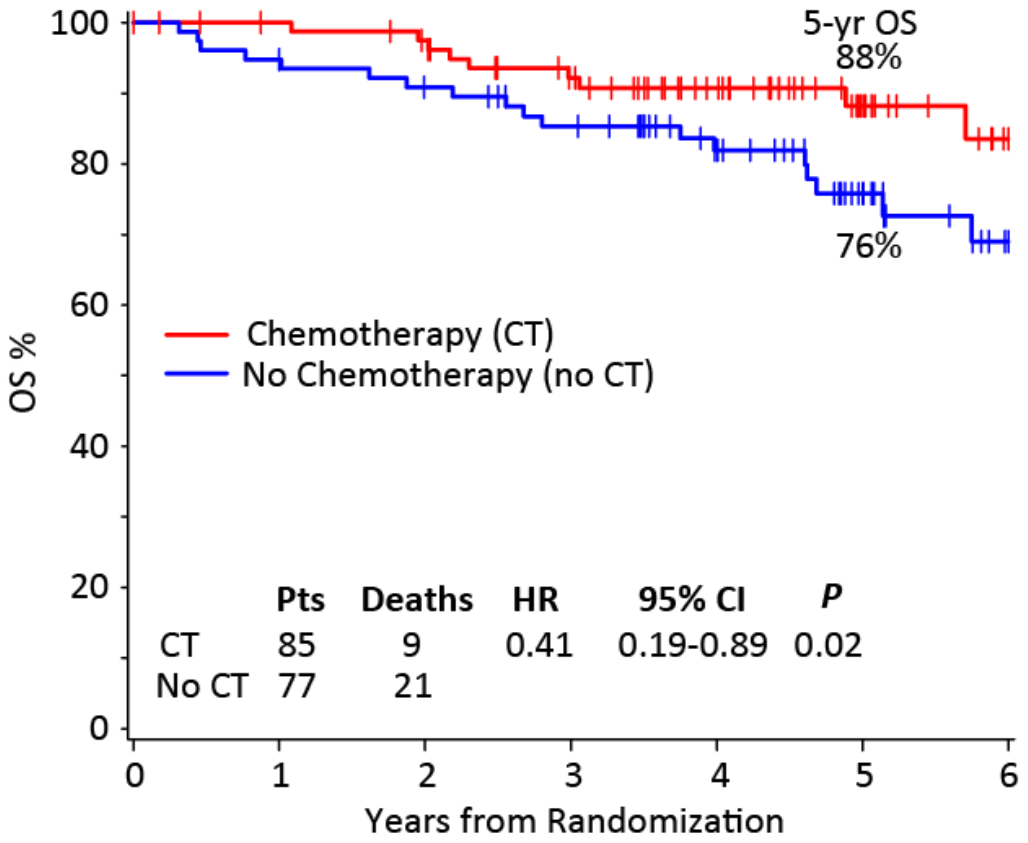


Number at Risk

Chemotherapy	29	26	22	20	17	10	6
No Chemotherapy	29	18	16	13	9	5	2

Univariate Interaction term: Treatment x ER: P = 0.044

CALOR Trial – Overall Survival



Number at Risk

Chemotherapy	85	80	76	65	51	29	14
No Chemotherapy	77	72	68	61	47	30	15

CALOR Trial – Conclusions

- Adjuvant chemotherapy reduced the risk of
  - DFS events by 41% (ER+ 6%; ER- 68%)
  - Death by 59% (ER+ 60%; ER- 57%)
- Adjuvant chemotherapy should be recommended for patients with completely resected isolated local or regional recurrence of breast cancer
  - The data are strongest for patients with ER-negative recurrences
  - Longer follow-up is needed for patients with ER-positive recurrences

Malattia metastatica

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

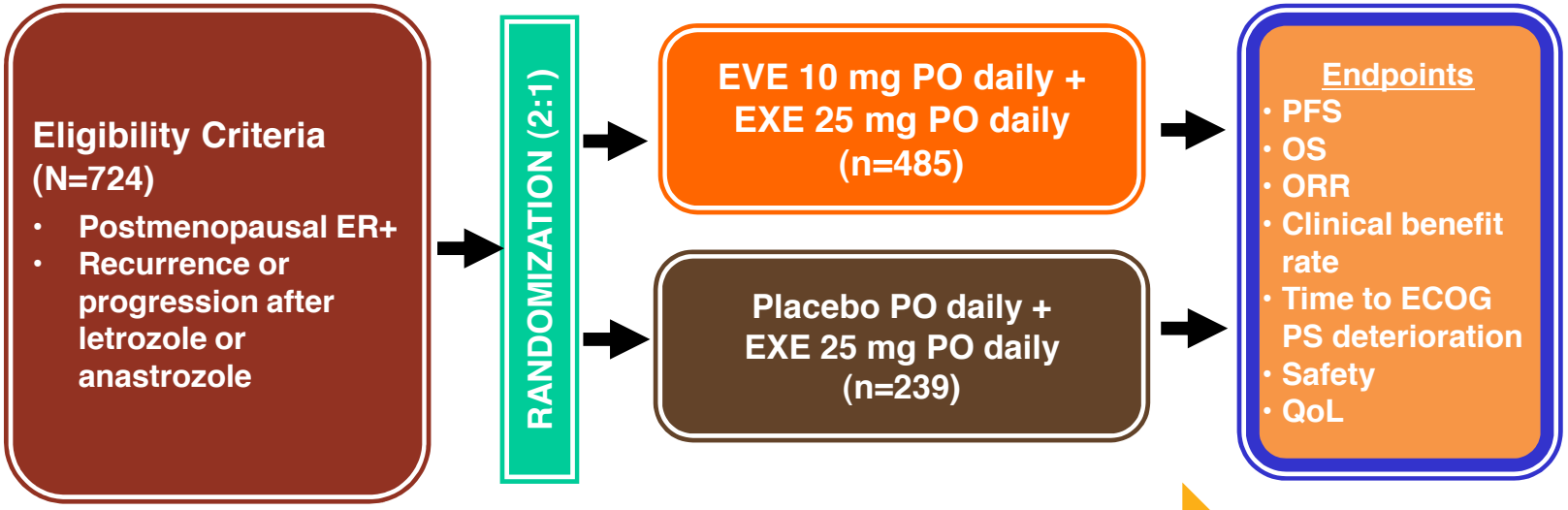
Everolimus in Postmenopausal Hormone-Receptor–Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D., Martine Piccart, M.D., Ph.D., Howard A. Burris III, M.D., Hope S. Rugo, M.D., Tarek Sahmoud, M.D., Ph.D., Shinzaburo Noguchi, M.D., Michael Gnant, M.D., Kathleen I. Pritchard, M.D., Fabienne Lebrun, M.D., J. Thaddeus Beck, M.D., Yoshinori Ito, M.D., Denise Yardley, M.D., Ines Deleu, M.D., Alejandra Perez, M.D., Thomas Bachelot, M.D., Ph.D., Luc Vittori, M.Sc., Zhiying Xu, Ph.D., Pabak Mukhopadhyay, Ph.D., David Lebwohl, M.D., and Gabriel N. Hortobagyi, M.D.

N Engl J Med 2012;366:520-9.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE
European Society for Medical Oncology

BOLERO-2: Phase III Trial of Exemestane ± Everolimus in ABC



Stratification by
- Sensitivity to prior endocrine therapy
- Visceral metastases

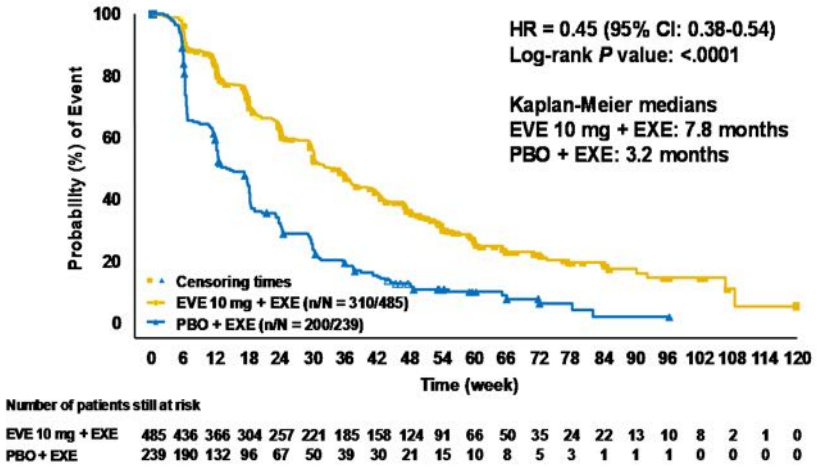
Treatment until disease progression or unacceptable toxicity

- Refractory to letrozole or anastrozole defined as:
  - Disease recurrence while on therapy or within 12 months after end of treatment, if letrozole or anastrozole received as adjuvant treatment *or*
  - Progression during therapy or within one month, if letrozole or anastrozole received as treatment for advanced disease

Baselga J et al. *N Engl J Med* 2012;366:520-529

BOLERO-2 (18-ms FU): PFS Local

BOLERO-2

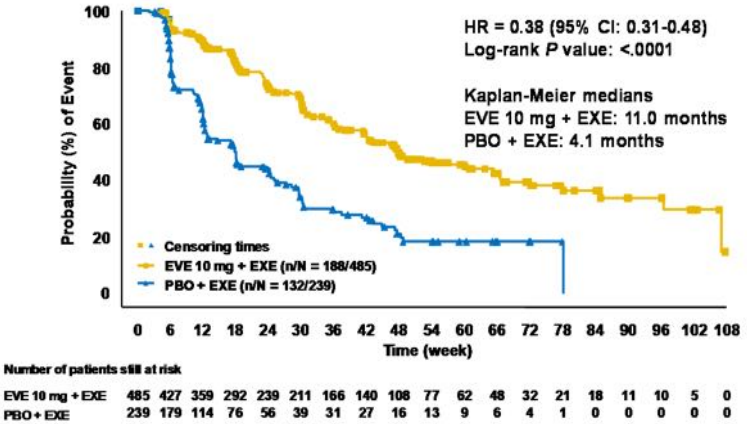


4.6 months benefit in PFS

BOLERO-2 (18-ms FU): PFS Central

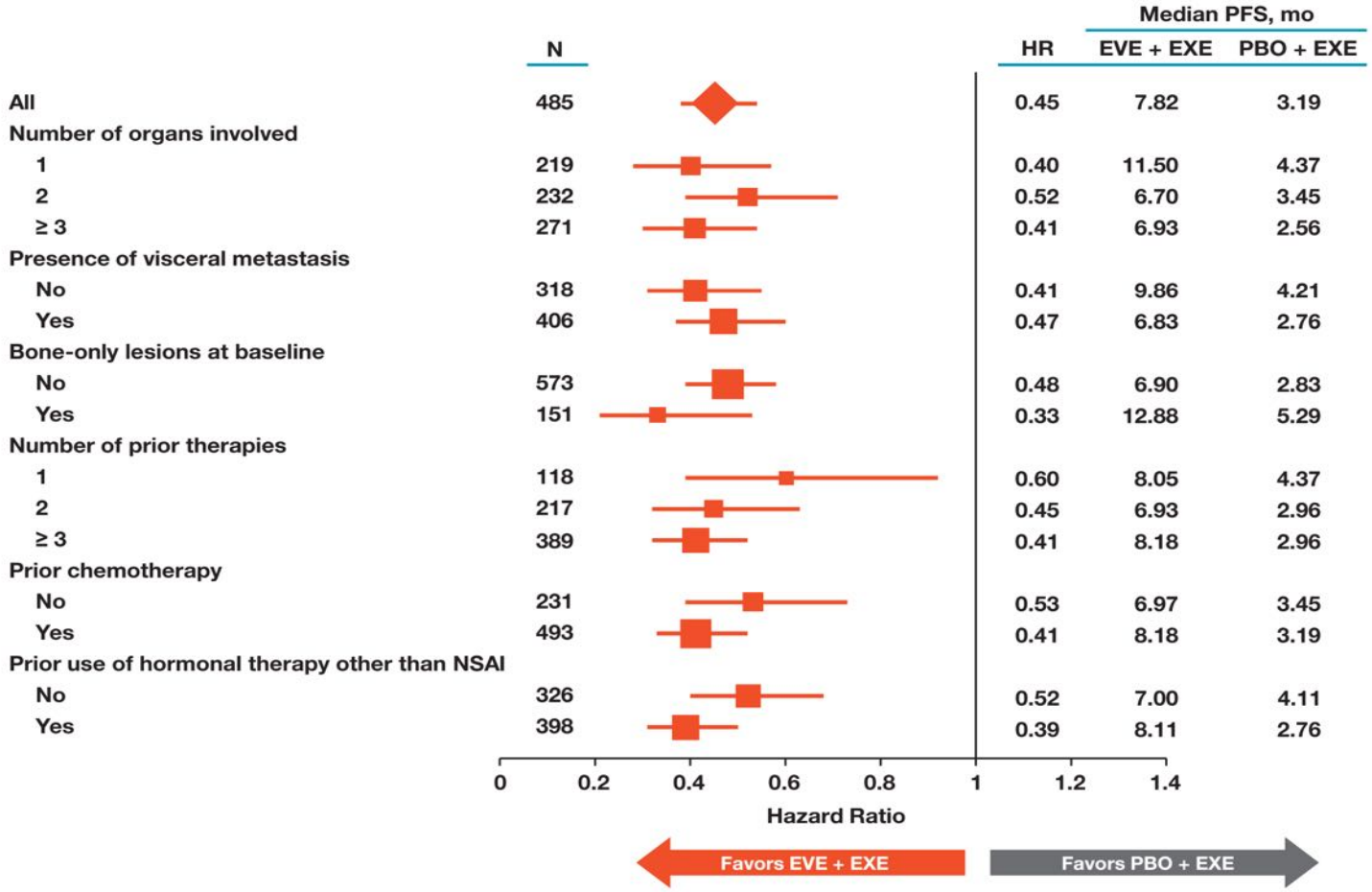
BOLERO-2

6.9 months benefit in PFS



Piccart-Gebhart M et al. Paper presented at: 2012 American Society of Clinical Oncology Annual Meeting; June 1-5, 2012; Chicago, IL.

BOLERO-2 (18-month follow-up): PFS in Subgroups

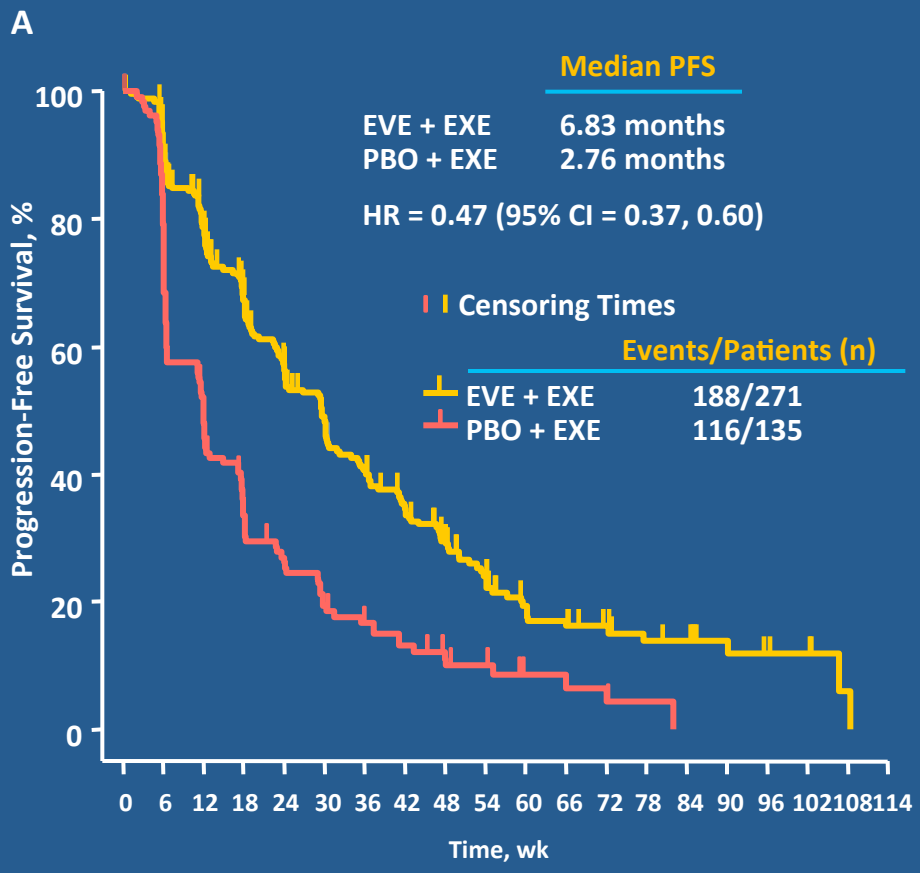


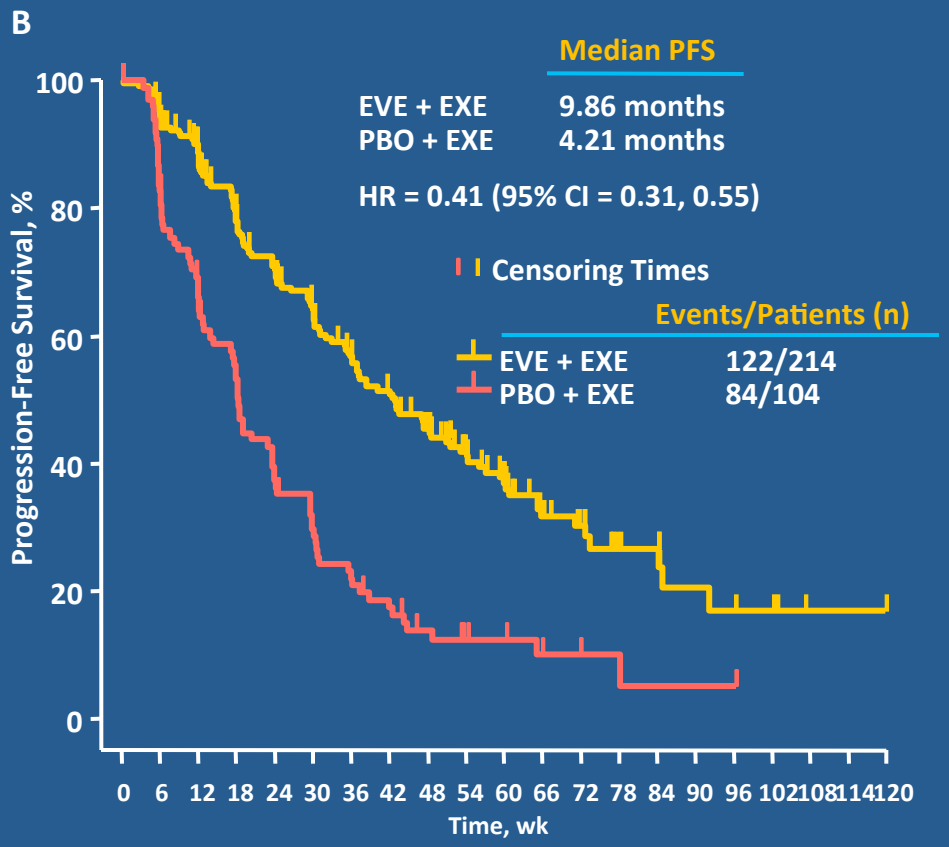
Piccart-Gebhart M et al. Paper presented at: 2012 American Society of Clinical Oncology Annual Meeting; June 1-5, 2012; Chicago, IL.

Campone et al ESMO 2012

RESULTS (continued)

Figure 1. Kaplan-Meier curve for PFS in patients (A) with and (B) without visceral involvement.





Number of Patients Still at Risk

EVE + EXE	271	240	192	157	128	107	88	72	52	38	25	22	16	12	11	7	5	4	1	0
PBO + EXE	135	108	66	44	32	23	18	14	11	8	4	4	3	1	0	0	0	0	0	0

Number of Patients Still at Risk

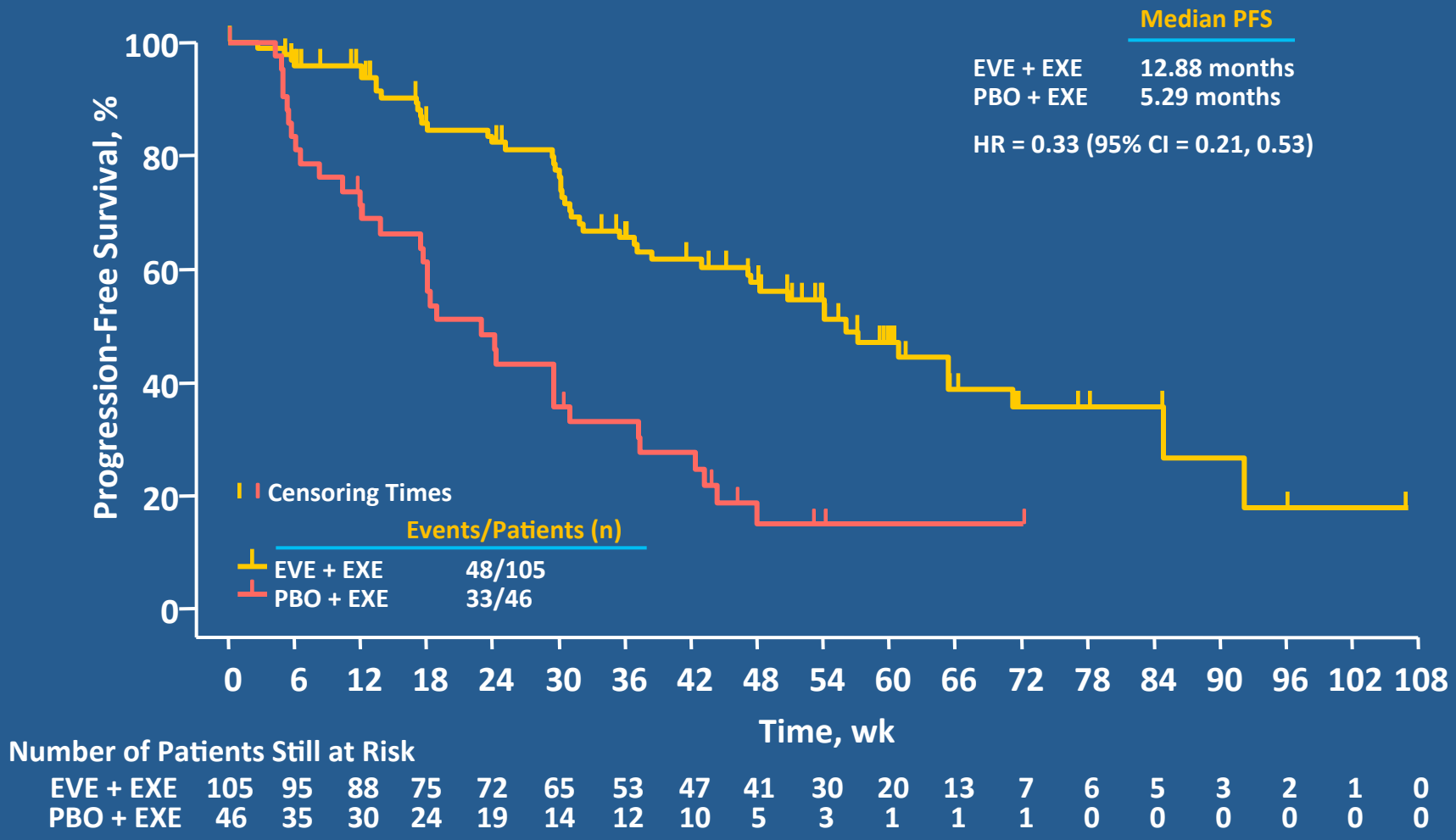
EVE + EXE	214	196	174	147	129	114	97	86	72	53	41	28	19	12	11	6	5	4	1	1	0
PBO + EXE	104	82	66	52	35	27	21	16	10	7	6	4	2	2	1	1	1	0	0	0	0

Abbreviations: CI, confidence interval; EVE, everolimus (10 mg/day); EXE, exemestane (25 mg/day); HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

Campone et al ESMO 2012

RESULTS (continued)

Figure 2. Kaplan-Meier curve for PFS in patients with bone-only metastases.



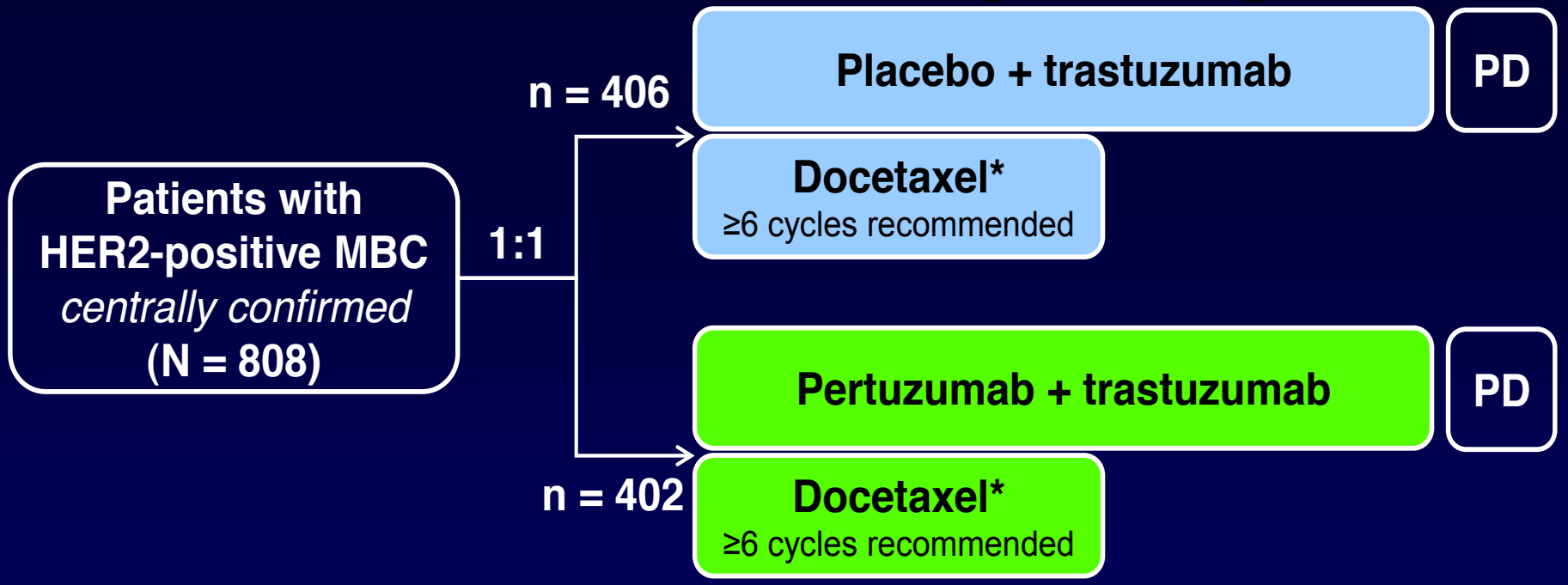
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 12, 2012 VOL. 366 NO. 2

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*

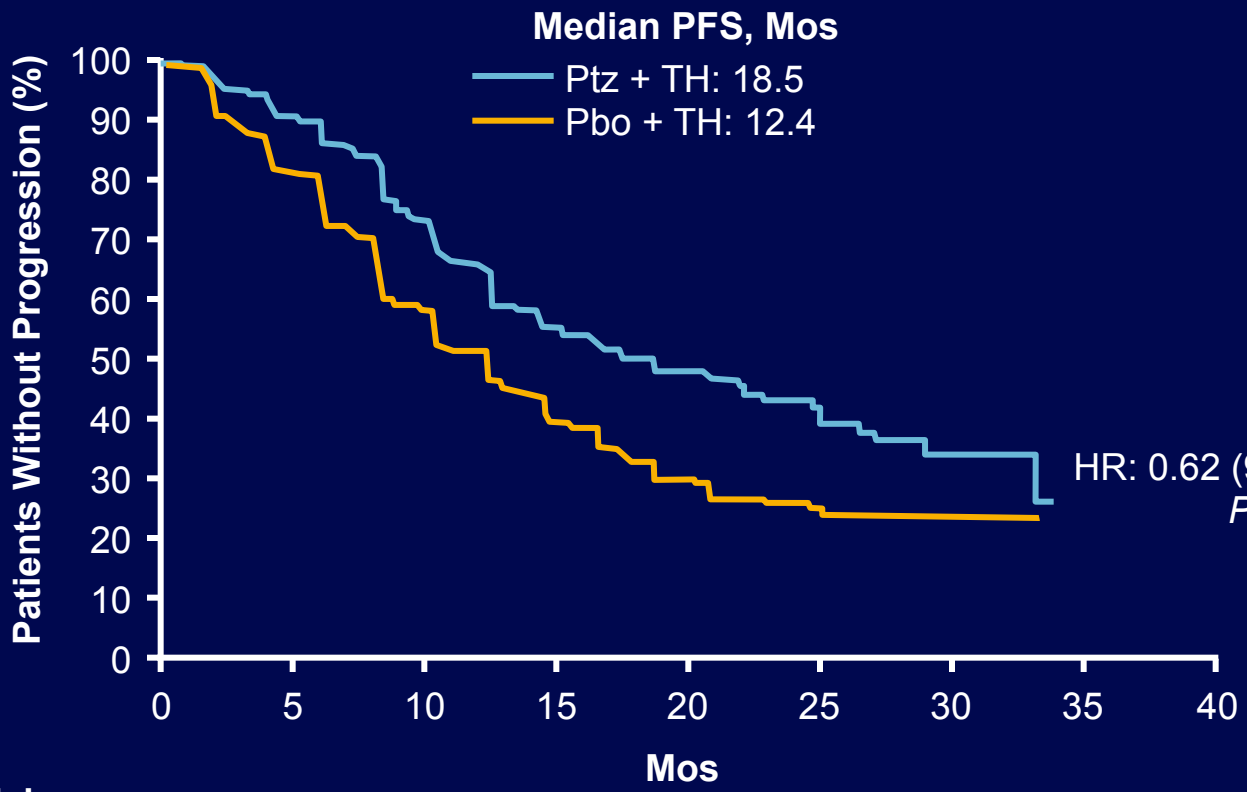
CLEOPATRA: Study Design



* <6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion

- Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)
- Study dosing q3w:
  - Pertuzumab/Placebo: 840 mg loading dose, 420 mg maintenance
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Docetaxel: 75 mg/m^2, escalating to 100 mg/m^2 if tolerated

CLEOPATRA: Independently Assessed PFS



Patients at Risk, n

Ptz + TH	402	345	267	139	83	32	10	0	0
Pbo + TH	406	311	209	93	42	17	7	0	0

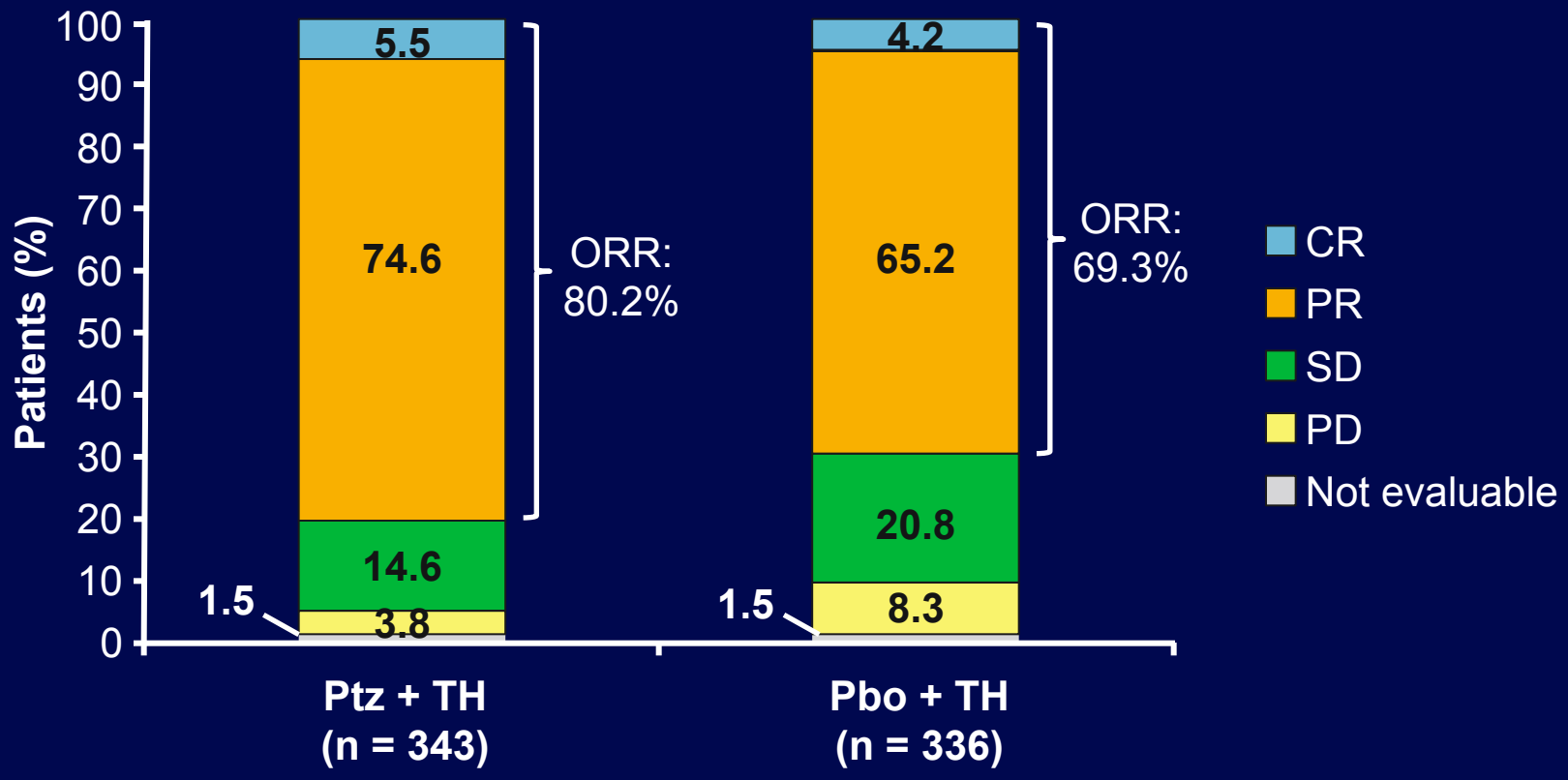
Baselga J, et al. N Engl J Med. 2012;366:109-119.

CLEOPATRA: PFS by Previous Trastuzumab Therapy

Patient Subgroup	Median PFS, Mos		HR (95% CI)
	Placebo + Trastuzumab + Docetaxel	Pertuzumab + Trastuzumab + Docetaxel	
Previous (neo)adjuvant trastuzumab treatment (n = 88)	10.4	16.9	0.62 (0.35-1.07)
No previous (neo)adjuvant trastuzumab treatment (n = 288)	12.6	21.6	0.60 (0.43-0.83)

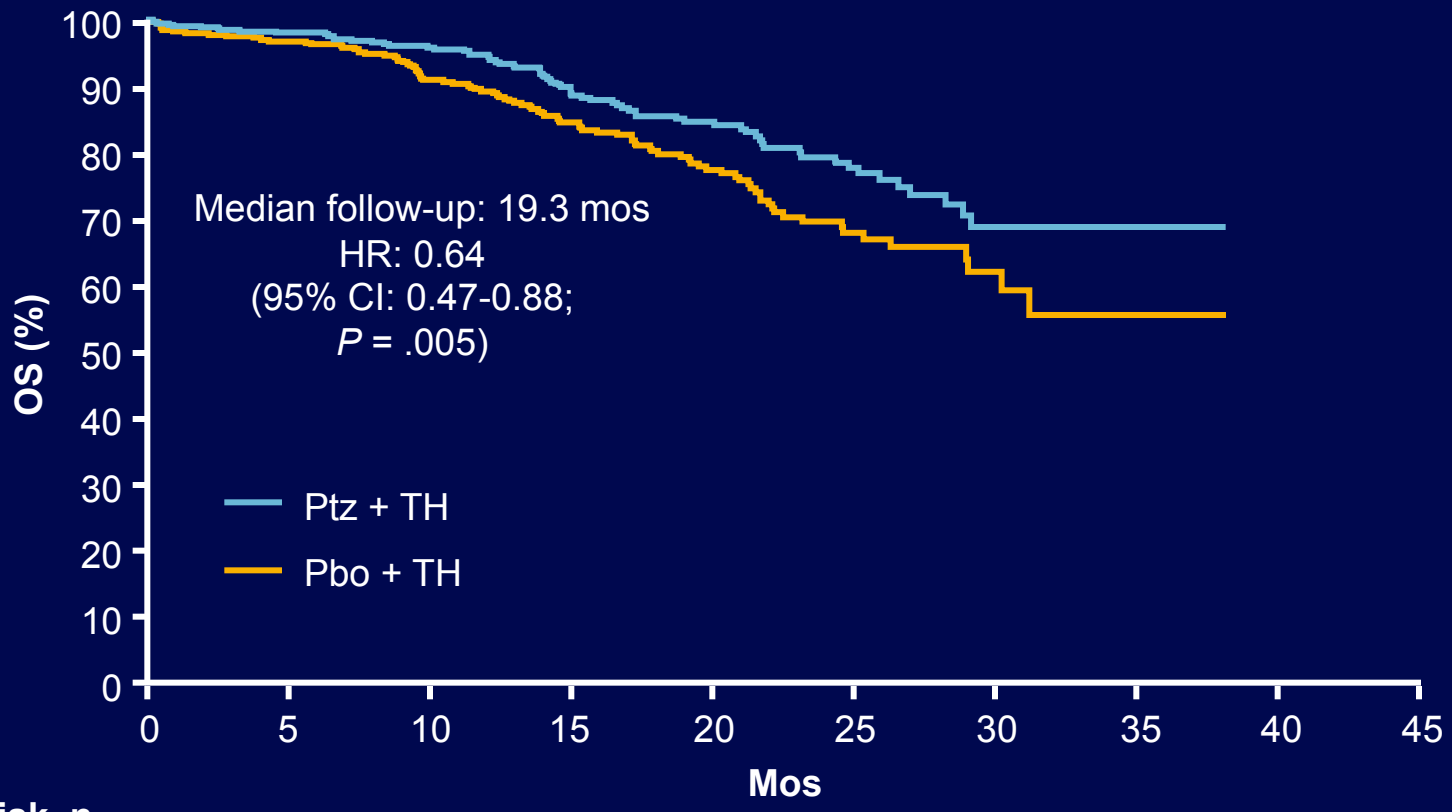
Baselga J, et al. N Engl J Med. 2012;366:109-119.

CLEOPATRA: Response Rates



Baselga J, et al. N Engl J Med. 2012;366:109-119.

OS: Predefined Interim Analysis

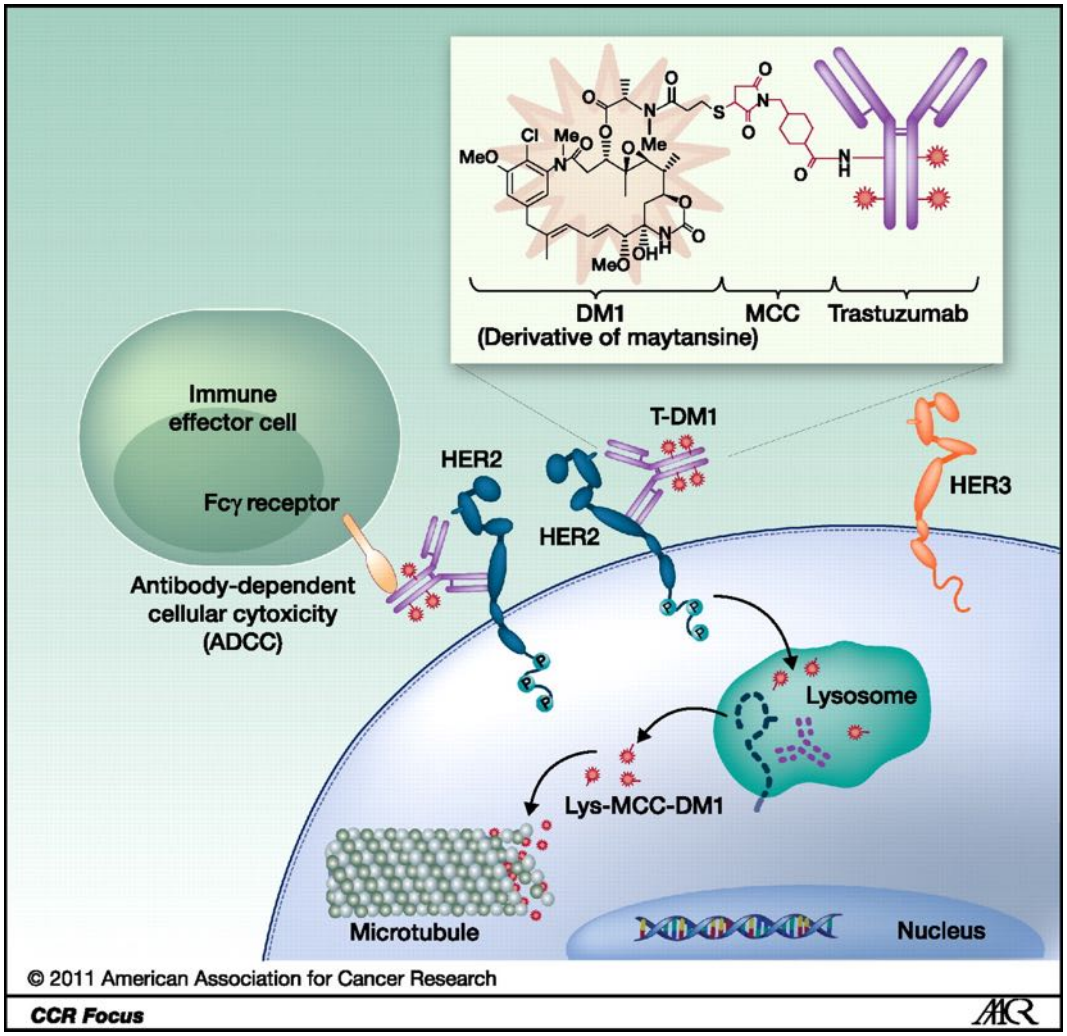


Patients at Risk, n

Ptz + TH	402	387	367	251	161	87	31	4	0	0
Pbo + TH	406	383	347	228	143	67	24	2	0	0

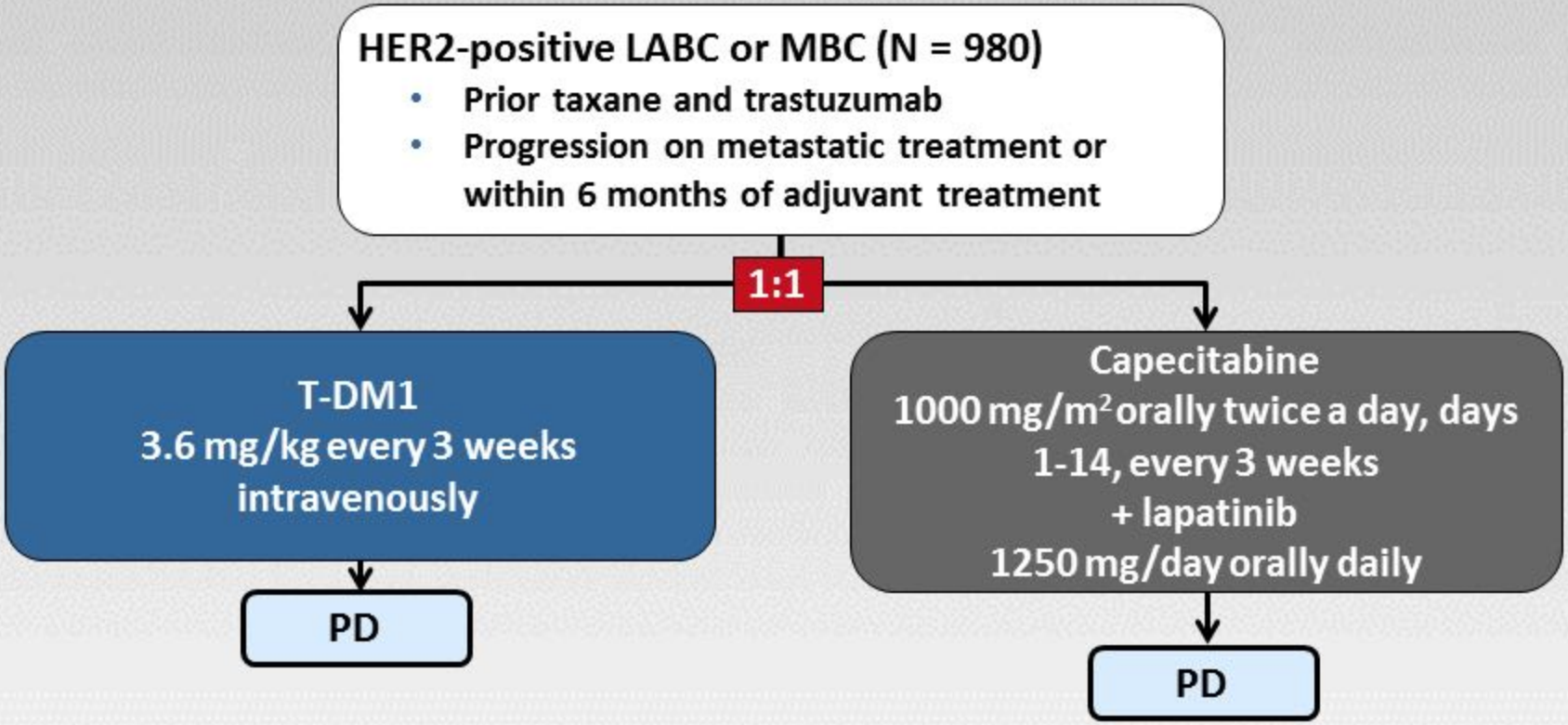
Baselga J, et al. N Engl J Med 2012;366:109-119.

Structure of T-DM1 and mechanisms of action.



LoRusso P M et al. Clin Cancer Res 2011;17:6437-6447

EMILIA Study Design



Stratification factors: World region, number of prior chemotherapy regimens for MBC or unresectable LABC, presence of visceral disease

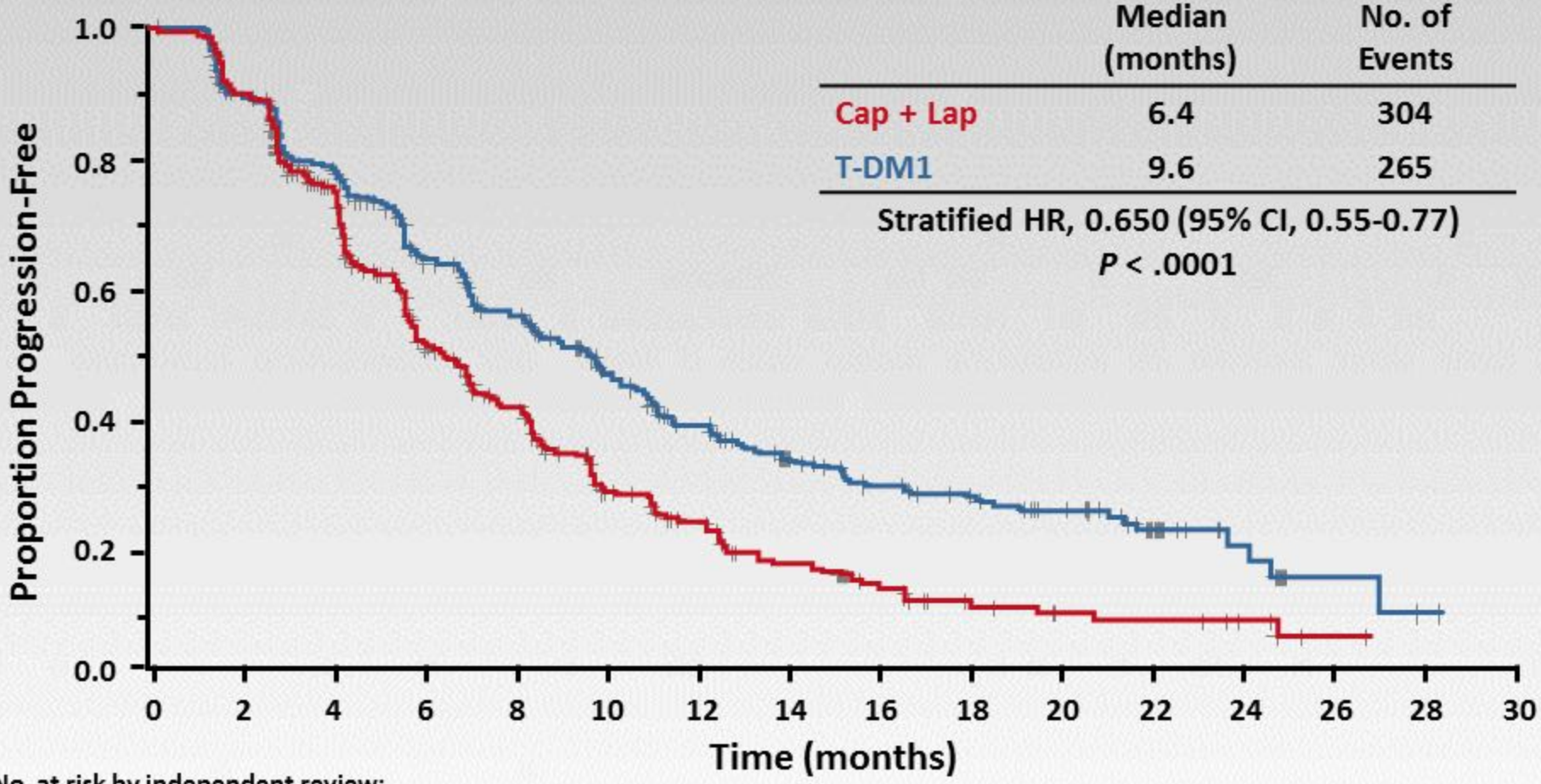
Primary endpoints: PFS by independent review, OS, and safety

Key secondary endpoints: PFS by investigator, ORR, DOR

DOR = duration of response; LABC = locally advanced breast cancer; MBC = metastatic breast cancer; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; T-DM1 = trastuzumab emtansine

Verma S, et al. *N Engl J Med.* 2012 Oct 1. [Epub ahead of print]

PFS by Independent Review



	Median (months)	No. of Events
Cap + Lap	6.4	304
T-DM1	9.6	265

Stratified HR, 0.650 (95% CI, 0.55-0.77)

P < .0001

No. at risk by independent review:

Cap + Lap	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0

Cap = capecitabine; CI = confidence interval; HR = hazard ratio; Lap = lapatinib

Medscape EDUCATION

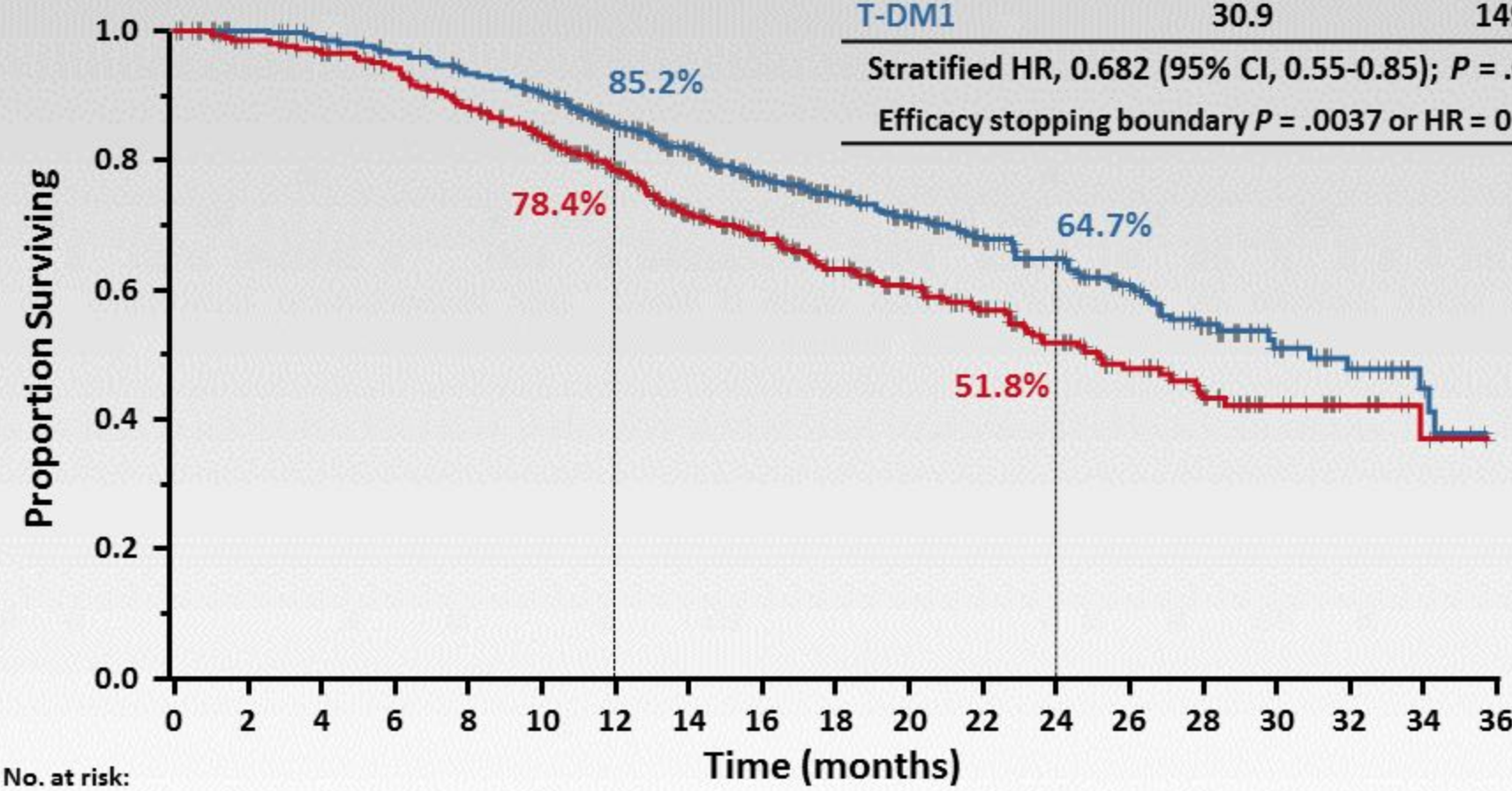
Verma S, et al. *N Engl J Med.* 2012 Oct 1. [Epub ahead of print]

OS: Confirmatory Analysis

	Median (months)	No. of Events
Cap + Lap	25.1	182
T-DM1	30.9	149

Stratified HR, 0.682 (95% CI, 0.55-0.85); *P* = .0006

Efficacy stopping boundary *P* = .0037 or HR = 0.727



No. at risk:																			
Cap + Lap	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

Medscape EDUCATION

Verma S, et al. *N Engl J Med.* 2012 Oct 1. [Epub ahead of print]

Adverse Events: Grade ≥ 3 Adverse Events with Incidence ≥ 2%

	Adverse Events Grade ≥ 3 with Incidence ≥ 2%	Adverse Events Grade ≥ 3 with Incidence < 2%
Cap + Lap (n = 488)	Diarrhea (20.7%) Hand-foot syndrome (16.4%) Vomiting (4.5%) Neutropenia (4.3%) Hypokalemia (4.1%) Fatigue (3.5%) Nausea (2.5%) Mucosal inflammation (2.3%)	Thrombocytopenia (0.2%) Increased AST (0.8%) Increased ALT (1.4%) Anemia (1.6%)
T-DM1 (n = 490)	Neutropenia (2.0%) Hypokalemia (2.2%) Fatigue (2.4%) Thrombocytopenia (12.9%) Increased AST (4.3%) Increased ALT (2.9%) Anemia (2.7%)	Diarrhea (1.6%) Hand-foot syndrome (0.0%) Vomiting (0.8%) Nausea (0.8%) Mucosal inflammation (0.2%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase

Verma S, et al. *N Engl J Med.* 2012 Oct 1. [Epub ahead of print]

San Antonio Breast Cancer Symposium – December 4–8, 2012. Abstract # 866

Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer – First efficacy results from the LEA study.

Miguel Martin[1*], Sibylle Loibl[2*], Gunter von Minckwitz[2], Serafín Morales[3],Carmen Crespo[4], Antonio Anton[5], Ángel Guerrero[6], Bahriye Aktas[7], Winfried Schoenegg[8], Montserrat Muñoz[9], José Ángel Garcia-Saenz[10], Miguel Gil[11], Manuel Ramos[12], Eva Carrasco[13], Cornelia Liedtke[14], Grischa Wachsmann[15], Keyur Mehta[2], Juan R De la Haba[16], On behalf of GEICAM (Spanish Breast Cancer Research Group) and GBG (German Breast Group).
***contributed equally**

[1]Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain; [2]GBG (German Breast Group), Neu-Isenburg, Germany; [3]H. Arnau Vilanova de Lérida, Spain; [4]Hospital U. Ramón y Cajal, Spain; [5]Hospital Universitario Miguel Servet, Spain; [6]Instituto Valenciano de Oncología, Spain; [7]University Women´s Hospital Essen, Germany; [8]Medical Practice Berlin, Germany; [9]Hospital Clinic i Provincial, Spain; [10]Hospital Clínico U. San Carlos, Spain; [11]Instituto Catala d' Oncología Hospitalet, Spain; [12]Centro Oncológico de Galicia, Spain; [13]GEICAM (Spanish Breast Cancer Research Group), Spain; [14]University Women´s Hospital Muenster, Germany; [15]Klinikum Boeblingen, Germany and [16]Hospital U. Reina Sofía, Spain.

Background

- Preclinical[1] and retrospective clinical[2,3,4] data suggest that high vascular endothelial growth factor (VEGF) levels in tumor tissue from breast cancer are associated with a decreased response to endocrine therapy.
- Clinical data suggest that the down regulation of VEGF may overcome resistance and improve efficacy to hormonal therapy[4].
- The combination of endocrine therapy and bevacizumab has shown to be safe and active in phase II trials[5,6]
- We designed the phase III LEA study to address the hypothesis that anti-VEGF treatment can delay resistance to endocrine therapy in patients with hormone-receptor positive advanced breast cancer.

1. De la Haba J, AACR 2011; 2. Linderholm B, JCO 2000; 3. Manders P, Cancer 2003; 4. Rydén L, JCO 2005; 5.Ferrero-Torres, CBC 2010; 6.Traina TA, JCO 2010

Study Design and treatment

Binational, multicentric, randomised, open label phase III study

N= 380 patients unresectable locally advanced or metastatic breast cancer HR+/HER2-

Stratification criteria:

- Adjuvant AI (yes/no)
- Nº lesions (one/multiple)
- Measurable lesions (yes/no)
- Country (Spain/Germany)

R

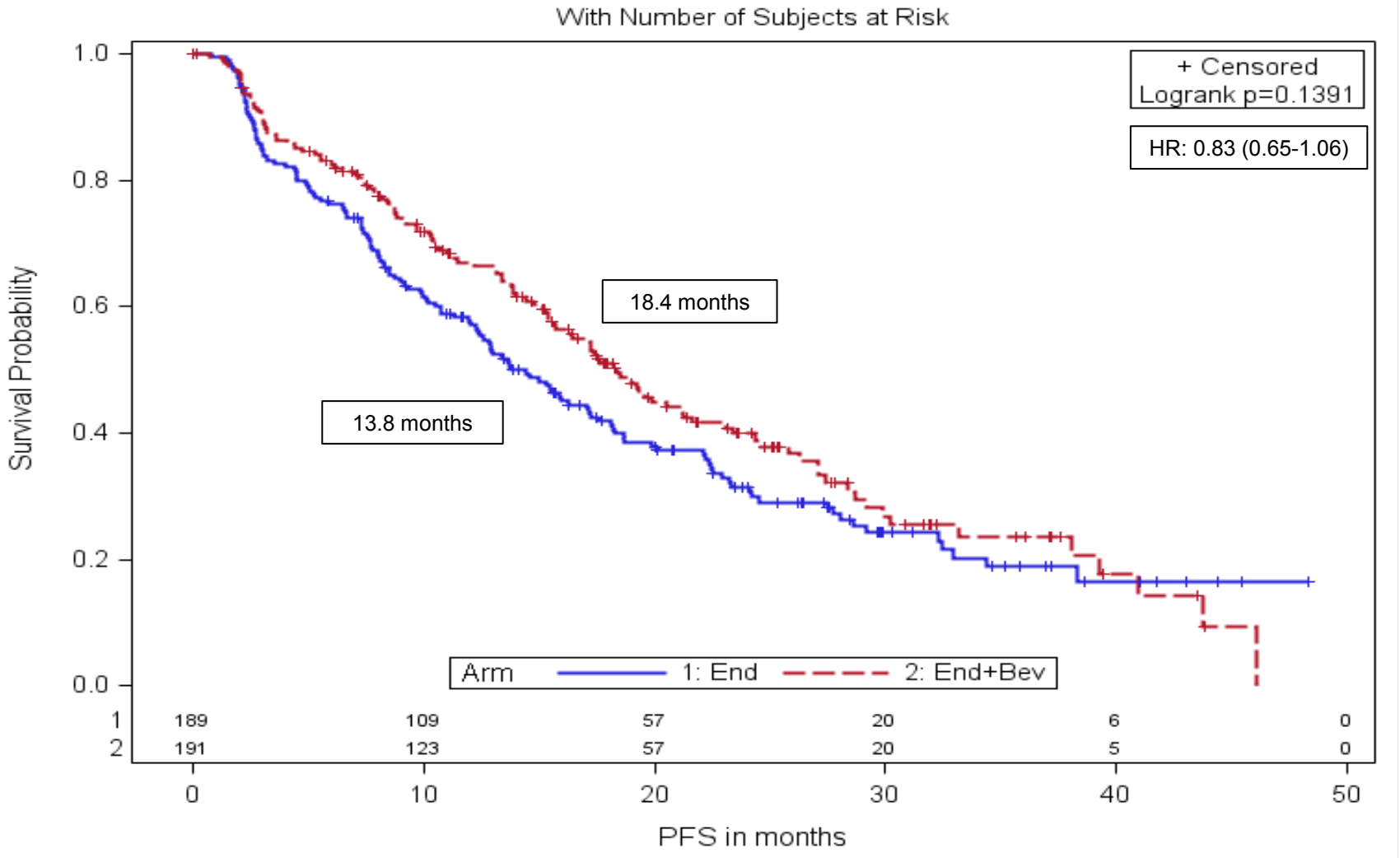
ET: Letrozole (2.5 mg/d) or Fulvestrant 250mg i.m. 1 q28

ET-B: Letrozole (2.5 mg/d) or Fulvestrant 250mg i.m. q28d + Bevacizumab (15 mg/kg q3w)

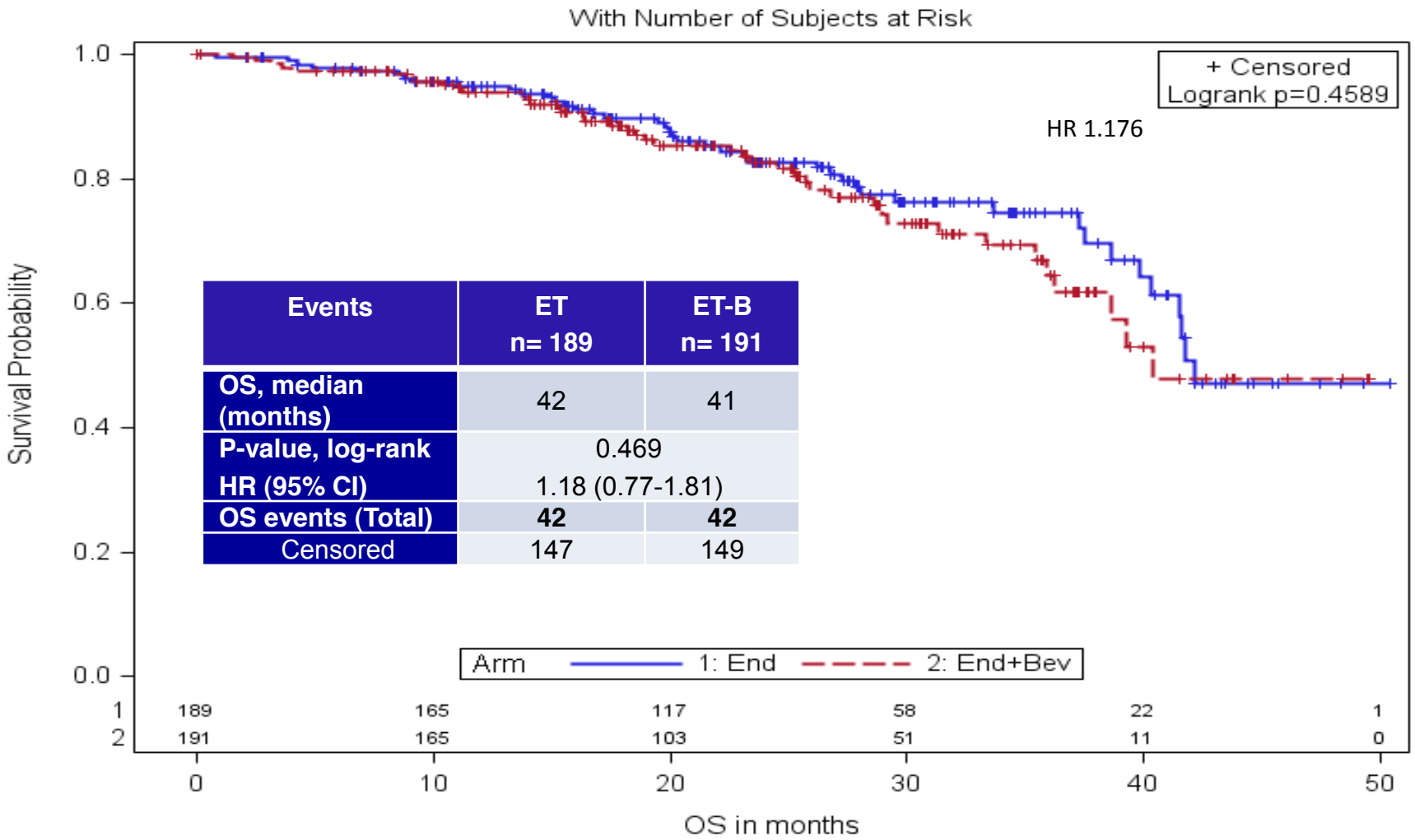
Till disease progression

ET: Endocrine Therapy; B: Bevacizumab

Progression-free Survival



Overall Survival



Events	ET n= 189	ET-B n= 191
OS, median (months)	42	41
P-value, log-rank	0.469	
HR (95% CI)	1.18 (0.77-1.81)	
OS events (Total)	**42**	**42**
Censored	147	149

Conclusions

- The LEA study fails to demonstrate a statistically significant increase in PFS for ET plus bevacizumab vs ET alone:
  - Median PFS: 18.4 months for ET-B vs 13.8 months for ET, p=0.14
  - HR: 0.83 (0.65-1.06)
- An increase of smaller magnitude (i.e. <31% reduction in PFS with bevacizumab) cannot be ruled out
- Adding bevacizumab to ET as first-line therapy had no impact on overall survival
- Biomarker studies can help to select the population that might benefit from bevacizumab in addition to hormonal treatment

A Phase III, Open-Label, Randomized, Multicenter Study Of Eribulin Mesylate Versus Capecitabine In Patients With Locally Advanced Or Metastatic Breast Cancer Previously Treated With Anthracyclines And Taxanes

Peter A. Kaufman,[1] Ahmad Awada,[2] Christopher Twelves,[3] Louise Yelle,[4] Edith A. Perez,[5] Jantien Wanders,[6] Martin S. Olivo,[7] Yi He,[7] Corina E. Dutcus,[7] Javier Cortes[8]

[1]Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; [2]Medical Oncology Clinic, Jules Bordet Institute, Brussels, Belgium; [3]Leeds Institute of Molecular Medicine and St James's Institute of Oncology, Leeds, UK; [4]Department of Medicine, University of Montreal, Montreal, Canada; [5]Mayo Medical Clinic, Jacksonville, FL, USA; [6]Eisai Ltd, Hatfield, UK; [7]Eisai Inc., Woodcliff Lake, NJ, USA; [8]Vall D'Hebron University Hospital, Barcelona, Spain

Study Rationale

- Eribulin is the only chemotherapeutic agent with a demonstrated survival benefit for patients with heavily pre-treated MBC
- Phase III EMBRACE trial (≥ 3rd-line† patients with MBC):
  - ≥ 2 chemotherapeutic regimens for MBC (≤5 regimens in total), including an anthracycline and a taxane in the adjuvant or metastatic setting
  - 2.5-month improvement in OS for eribulin versus treatment of physician's choice (13.1 vs 10.6 months; p=0.041; HR, 0.81; 95% CI 0.66, 0.99)
- Capecitabine is a widely used therapy in MBC, including 1st-, 2nd- and 3rd-line setting for MBC
  - Approved for the treatment of patients with MBC whose disease is resistant to both paclitaxel and an anthracycline-containing regimen

Cortes et al. Lancet 2011;377:914-23

Study Design

- Global, randomized, open-label Phase III trial (Study 301)

Patients (N=1102)

Locally advanced or MBC

- ≤3 prior chemotherapy regimens (≤2 for advanced disease)
- Prior anthracycline and taxane in (neo)adjuvant setting or for locally advanced or MBC

Eribulin mesylate
1.4 mg/m^{2†} 2- to 5-min IV
Day 1 & 8 q21 days

Randomization 1:1

Capecitabine
1250 mg/m^2 BID orally
Days 1-14, q21 days

Co-primary endpoint

- OS and PFS

Secondary endpoints

- Quality of life
- ORR
- Duration of response
- 1-, 2- and 3-year survival
- Tumor-related symptom assessments
- Safety parameters
- Population PK (eribulin arm only)

- Stratification:
  - Geographical region, HER2 status

†Equivalent to 1.23 mg/m^2 eribulin

Patient and Disease Characteristics

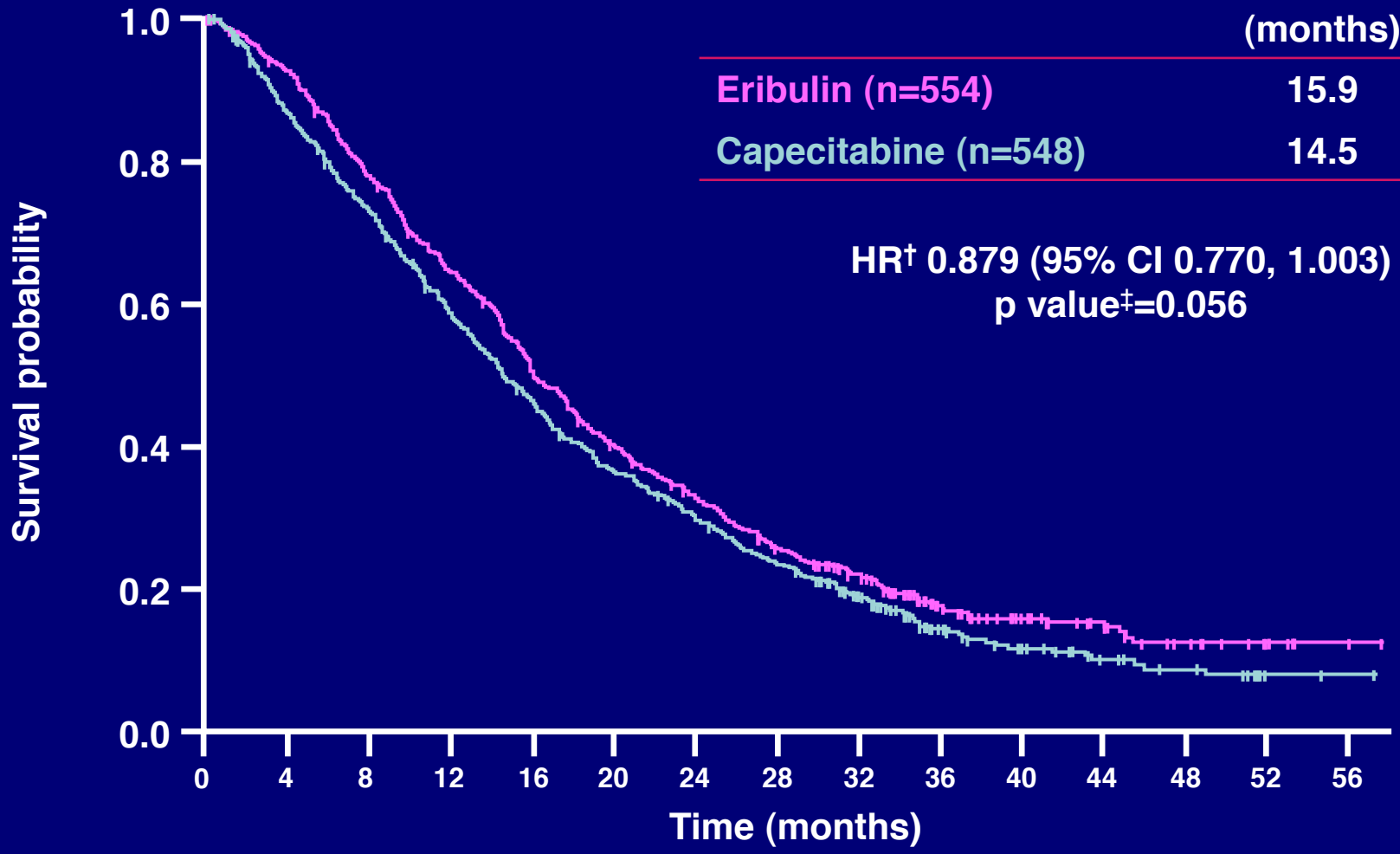
		Eribulin (n=554)	Capecitabine (n=548)
Median age (range)		54.0 (24-80)	53.0 (26-80)
ECOG performance, %	0	45	42
	1	53	55
	2+	2	3
Number of prior chemotherapy regimens for advanced disease, %	0	21	19
	1	50	53
	2	28	27
	>2	1	1
Sites of disease†, %	Visceral	84	88
	Non-visceral only	15	11
HER2 status‡, %	Positive	16	15
	Negative	68	69
ER status‡, %	Positive	47	51
	Negative	42	39
PR status‡, %	Positive	41	43
	Negative	47	45
Triple (ER/PR/HER2) negative, %		27	25

ITT population
†Determined by independent assessment; missing patients for sites of disease were 1% for eribulin and 1% for capecitabine
‡Assays carried out and defined locally
Unknown patients for eribulin and capecitabine were: HER2 status 17% and 16% ; ER status 11% and 10%; PR status 12% and 12%, respectively

Overall Survival

	Median OS (months)
Eribulin (n=554)	15.9
Capecitabine (n=548)	14.5

HR† 0.879 (95% CI 0.770, 1.003)
p value‡=0.056



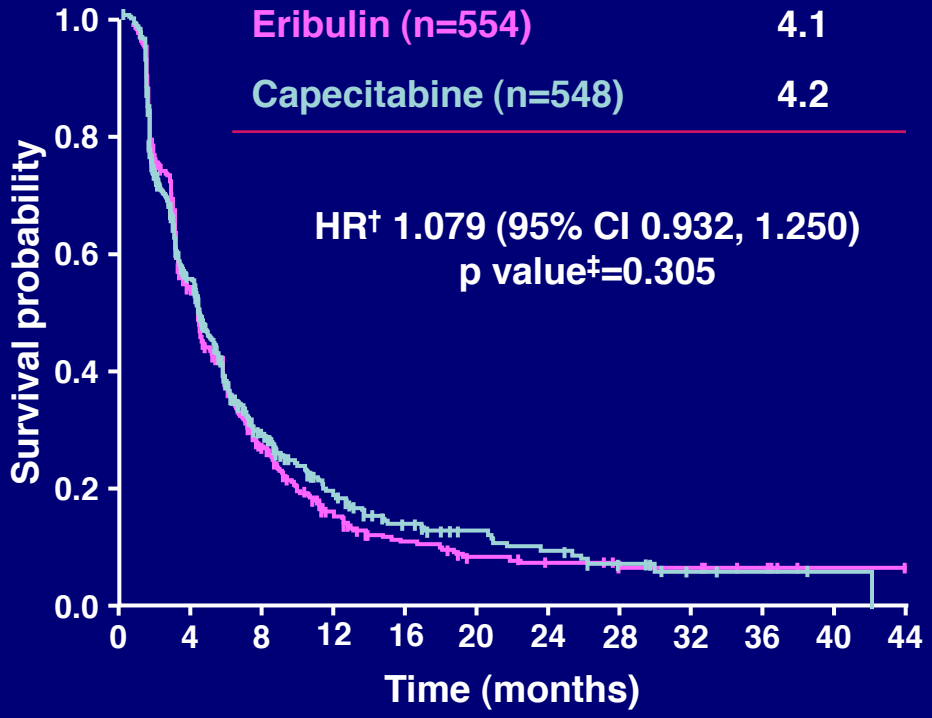
ITT population; †HR Cox model including geographic region and HER2 status as strata
‡p value from stratified log-rank test based on clinical database

Progression-Free Survival

Independent Review

	Median (months)
Eribulin (n=554)	4.1
Capecitabine (n=548)	4.2

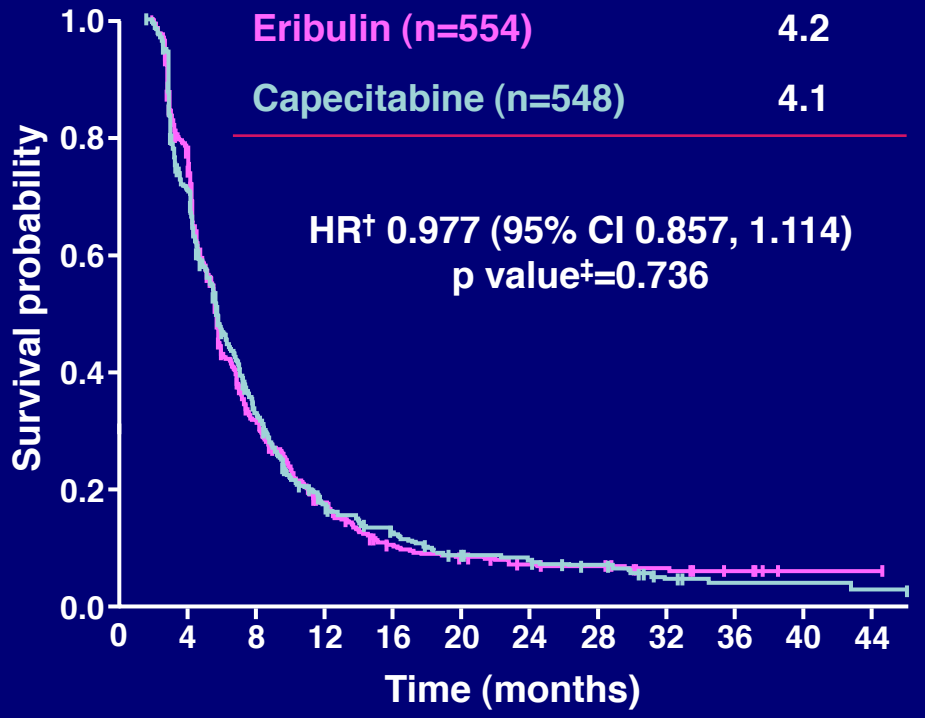
HR† 1.079 (95% CI 0.932, 1.250)
p value‡=0.305



Investigator Review

	Median (months)
Eribulin (n=554)	4.2
Capecitabine (n=548)	4.1

HR† 0.977 (95% CI 0.857, 1.114)
p value‡=0.736



ITT population; †HR Cox model including geographic region and HER2 status as strata
‡p value from stratified log-rank test based on clinical database

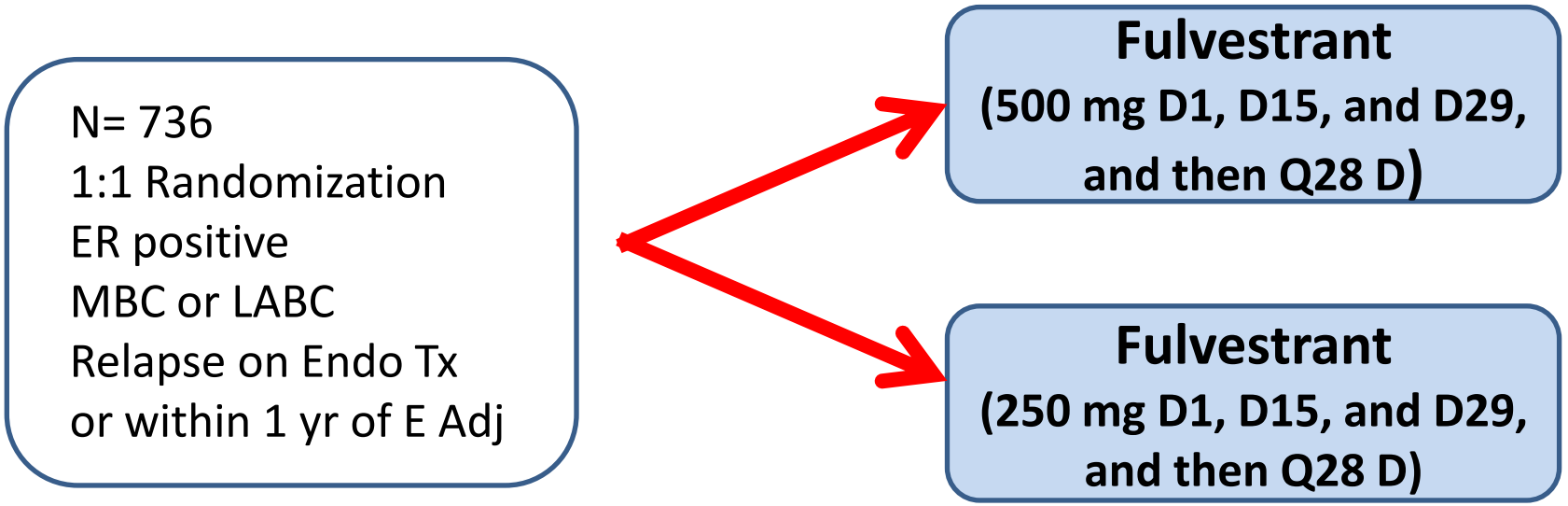
Conclusions

- This trial does not demonstrate a statistically significant superiority of eribulin vs capecitabine in either OS or PFS
  - Median OS: eribulin 15.9 months, capecitabine 14.5 months HR, 0.879 (95%CI: 0.770, 1.003)
- Pre-specified exploratory analyses suggest particular patient subgroups may have greater therapeutic benefit with eribulin and may warrant further study
  - Triple negative HR, 0.702 (95%CI: 0.545, 0.906)
  - ER negative HR, 0.779 (95%CI: 0.635, 0.955)
  - HER2 negative HR, 0.838 (95%CI: 0.715, 0.983)
- Eribulin and capecitabine have similar overall activity in this trial that included patients in the 1st-, 2nd-, or 3rd-line setting
  - The AE profiles of eribulin and capecitabine are consistent with their previously known side effects

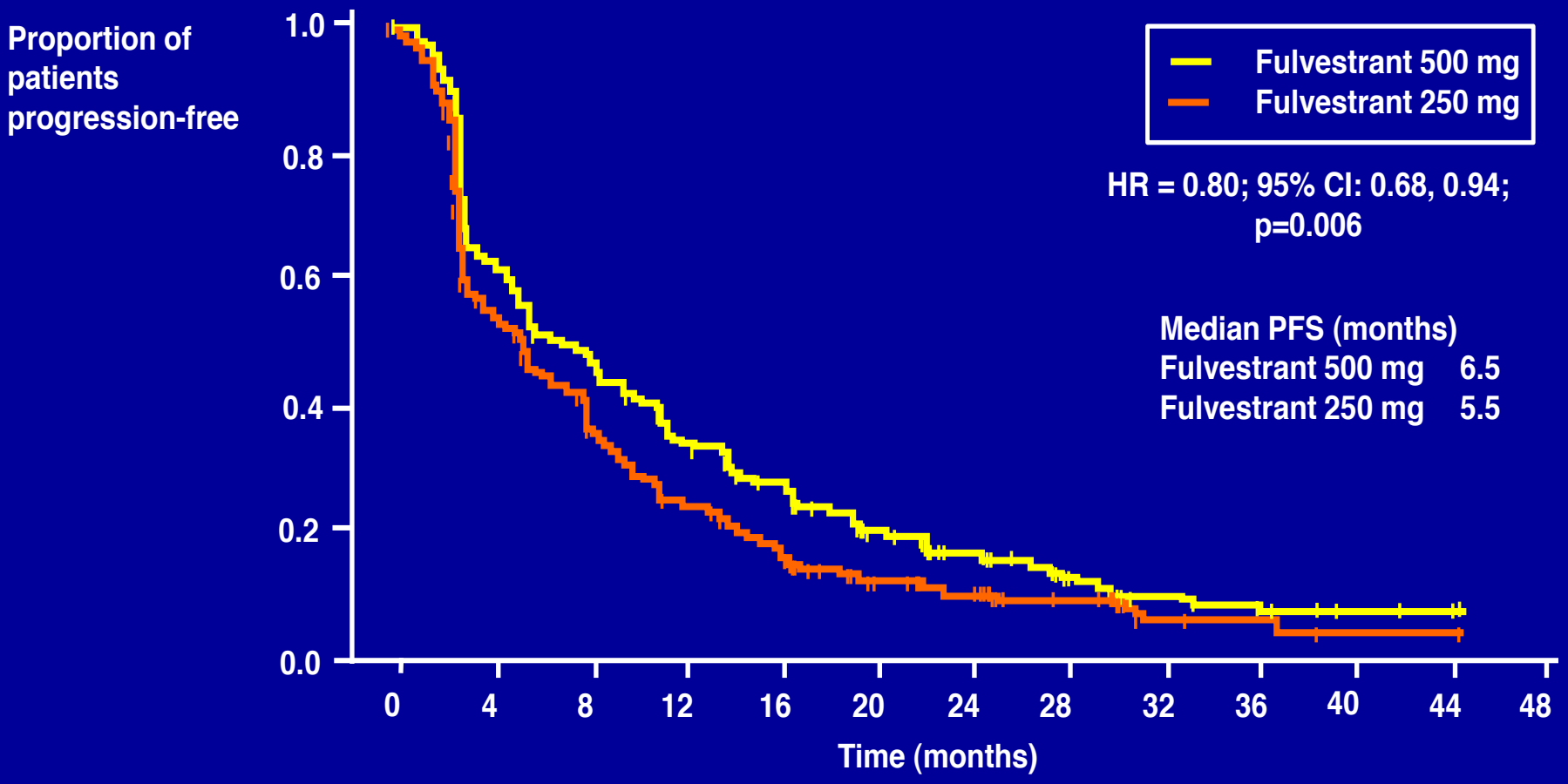
Final analysis of overall survival for the Phase III CONFIRM trial: fulvestrant 500 mg versus 250 mg

Angelo Di Leo, Guy Jerusalem, Lubos Petruzelka, Igor N. Bondarenko, Rustem Khasanov, Didier Verhoeven, José L. Pedrini, Iva Smirnova, Mikhail R. Lichinitser, Kelly Pendergrass, Sally Garnett, Yuri Rukazenkov, Miguel Martin, on behalf of the CONFIRM investigators

Phase III CONFIRM trial: Fulvestrant 500 mg versus 250 mg



Primary endpoint: progression-free survival



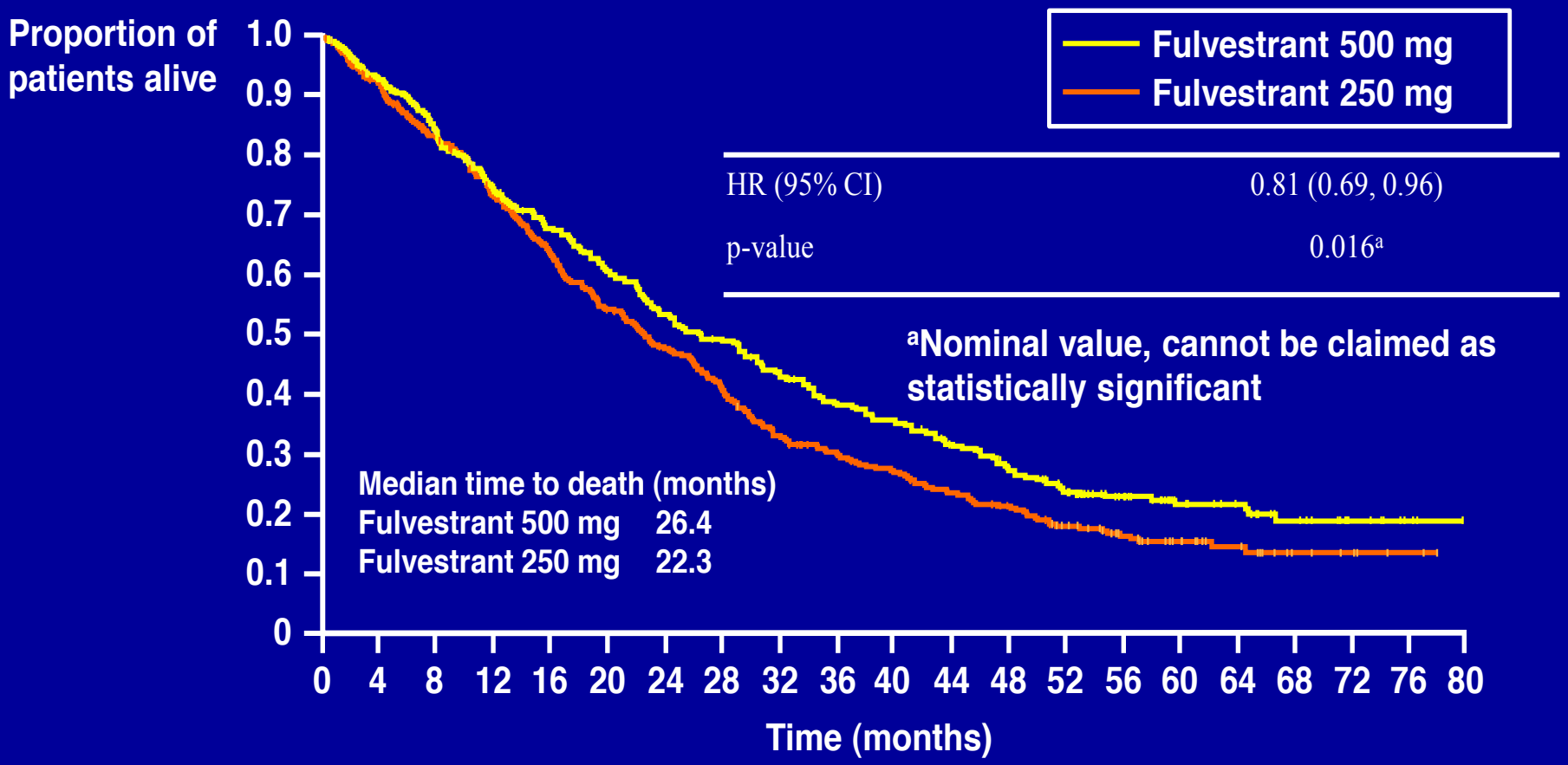
Patients at risk:

500 mg	362	216	163	113	90	54	37	19	12	7	3	2	0
250 mg	374	199	144	85	60	35	25	12	4	3	1	1	0

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Di Leo A et al. J Clin Oncol 2010; 28: 4594-4600

Overall survival (final analysis at 75% maturity – full analysis set)



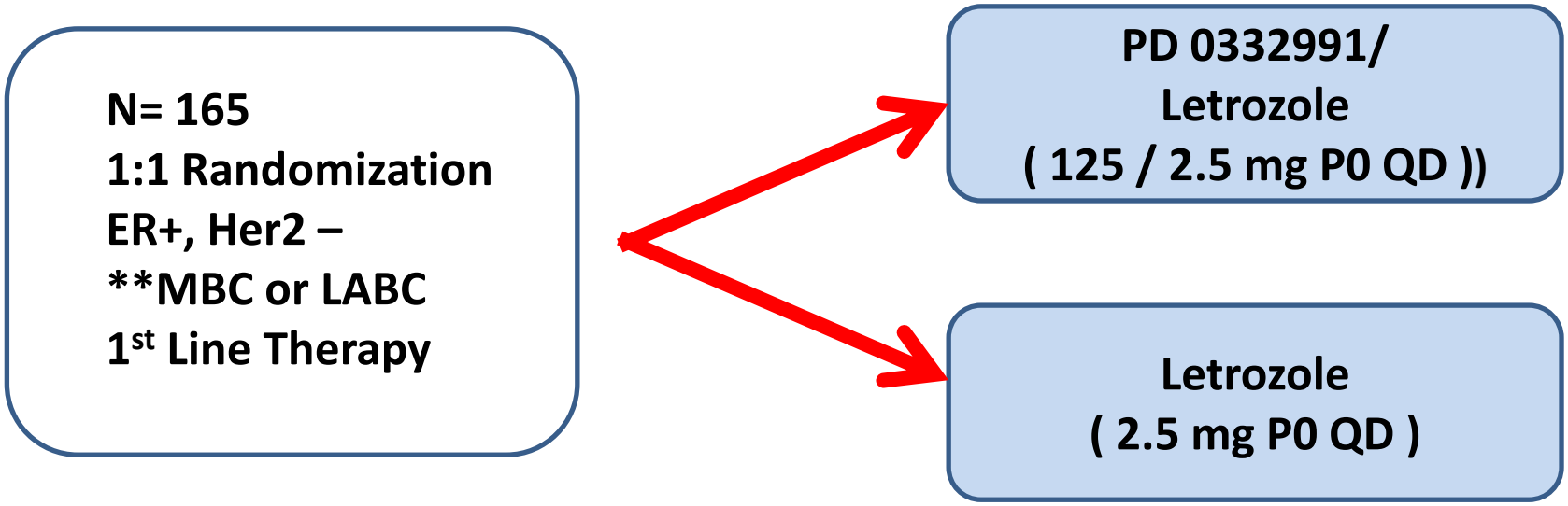
Patients at risk:

500 mg	362	333	288	254	227	202	178	163	141	123	114	98	81	64	47	30	26	15	8	1	0
250 mg	374	338	299	261	223	191	164	137	112	96	87	74	64	48	37	22	14	8	3	2	0

Conclusions

- Final OS analysis at 75% maturity shows that fulvestrant 500 mg is associated with 4.1-month increase in median OS and a 19% reduction in the risk of death compared with fulvestrant 250 mg
- These results are consistent with the previously reported PFS and OS data (J Clin Oncol. 28: 4594-00, 2010)
- Analysis of 1st subsequent therapies does not support any imbalance between the two study arms
- Only 2% of patients crossed-over from 250 to 500 mg. However, activity for 500 mg after pre-treatment with 250 mg is unknown
- The safety results do not support any clinically relevant difference between fulvestrant 250 and 500 mg and they are consistent with the previously reported safety profile of fulvestrant 500 mg

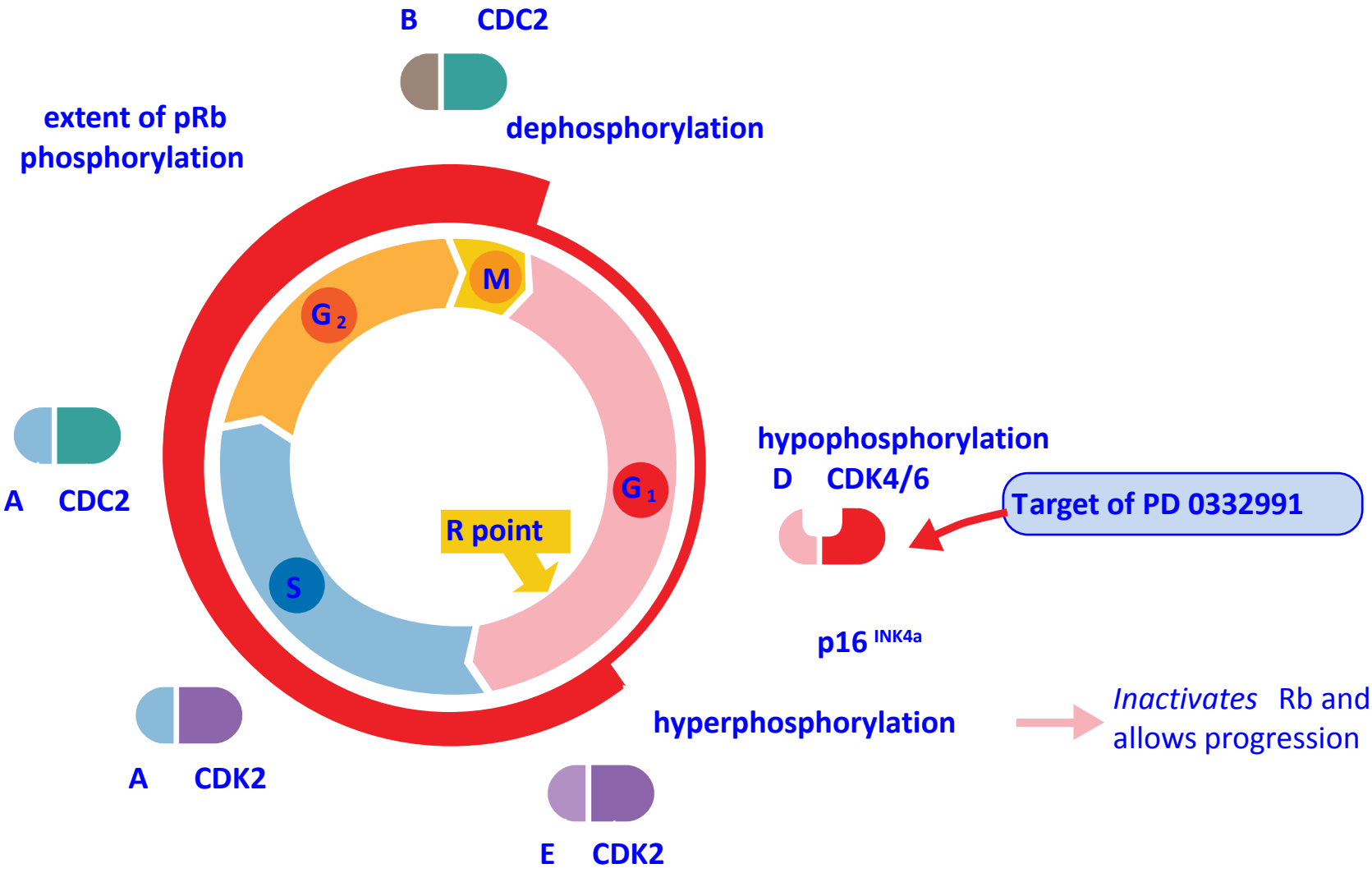
Phase Randomized II Trial of Letrozole ± PD 0332991



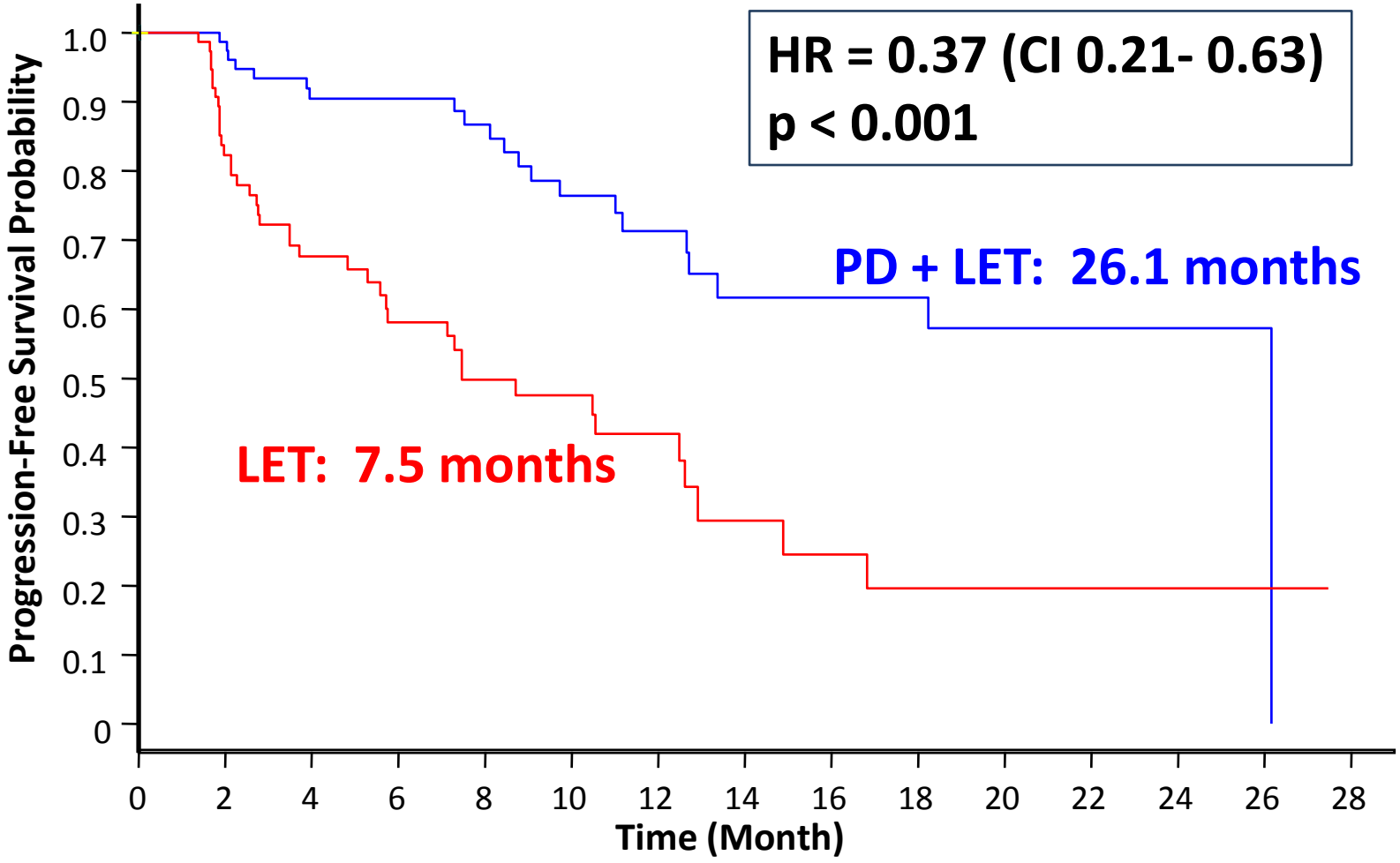
** All patients were ER+, Her2 -, but in the second phase of the study (n= 99) an additional restriction was that the patients had to have amplified CCND1 amp and/or loss of p16.

SABCS Abstract S1-6; 2012

An example of a new targeting agent
Targets A Cyclin Dependent Kinase PD 0332991



PD 0332991 + Letrozole
Progression Free Survival



PD 0332991 + Letrozole
Grade 3 / 4 Toxicity

	PD 991 + LET (n = 83)	LET (n = 77)
Neutropenia	51	1
Leukopenia	14	0
Fatigue	2	1
Anemia	4	1
Nausea	2	1
Hot flush	0	0
Alopecia	0	0
Arthralgia	0	1
Diarrhea	4	0

Conclusioni

Terapia adiuvante:

- 10 anni di TAM (..)
- LETROZOLO in lobulari
- durata del TRASTUZUMAB: 1 anno
- Chemioterapia diuvante dopo recidiva (ER neg ..)
- nessun ruolo di Bevacizumab TN

Terapia della malattia metastatica

- NUOVI FARMACI (coming soon) .. Everolimus / Pertuzumab / T-DM1
- Dose Fulvestrant 500 mg
- No Bevacizumab in I linea con OT
- Eribulina / Capecitabina
- NUOVO TARGET:

Grazie per l’attenzione