Prognostic Impact of Interval Breast Cancer Detection in pT1a N0M0 HER2-positive Breast Cancers

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La Sorveglianza Epidemiologica dello Screening
dei Tumori della Mammella nella Regione Emilia-Romagna

Bologna, 9 Marzo 2016

Epidemiology of Breast Cancer

•Breast cancer is the most frequently diagnosed malignant disease and the second leading cause of cancer deaths among women.

•Incidence increases with age, and the probability of a women developing breast cancer is 1 in 69 in her 40s, 1 in 38 in her 50s, and 1 in 27 in her 60s.

•Incidence has stabilized in recent years and mortality has decreased since 1990 because of many factors, including screening.

SEER Cancer Statistics Review 2009
American Cancer Society Statistics 2013

Pooled Relative Risks for Breast Cancer Mortality from Mammography Screening Trials for All Ages

Age	Trials Included, *n*	RR for Breast Cancer Mortality (95% CrI)	NNI to Prevent 1 Breast Cancer Death (95% CrI)
39–49 y	8*	0.85 (0.75–0.96)	1904 (929–6378)
50–59 y	6†	0.86 (0.75–0.99)	1339 (322–7455)
60–69 y	2‡	0.68 (0.54–0.87)	377 (230–1050)
70–74 y	1§	1.12 (0.73–1.72)	Not available

CrI = credible interval; NNI = number needed to invite to screening; RR = relative risk.

* Health Insurance Plan of Greater New York (27), Canadian National Breast Screening Study-1 (28), Stockholm (26), Malmö (26), Swedish Two-County trial (2 trials) (26, 31), Gothenburg trial (30), and Age trial (29).

† Canadian National Breast Screening Study-1 (28), Stockholm (26), Malmö (26), Swedish Two-County trial (2 trials) (26, 31), and Gothenburg trial (30).

‡ Malmö (26) and Swedish Two-County trial (Östergötland) (26).

§ Swedish Two-County trial (Östergötland) (26).

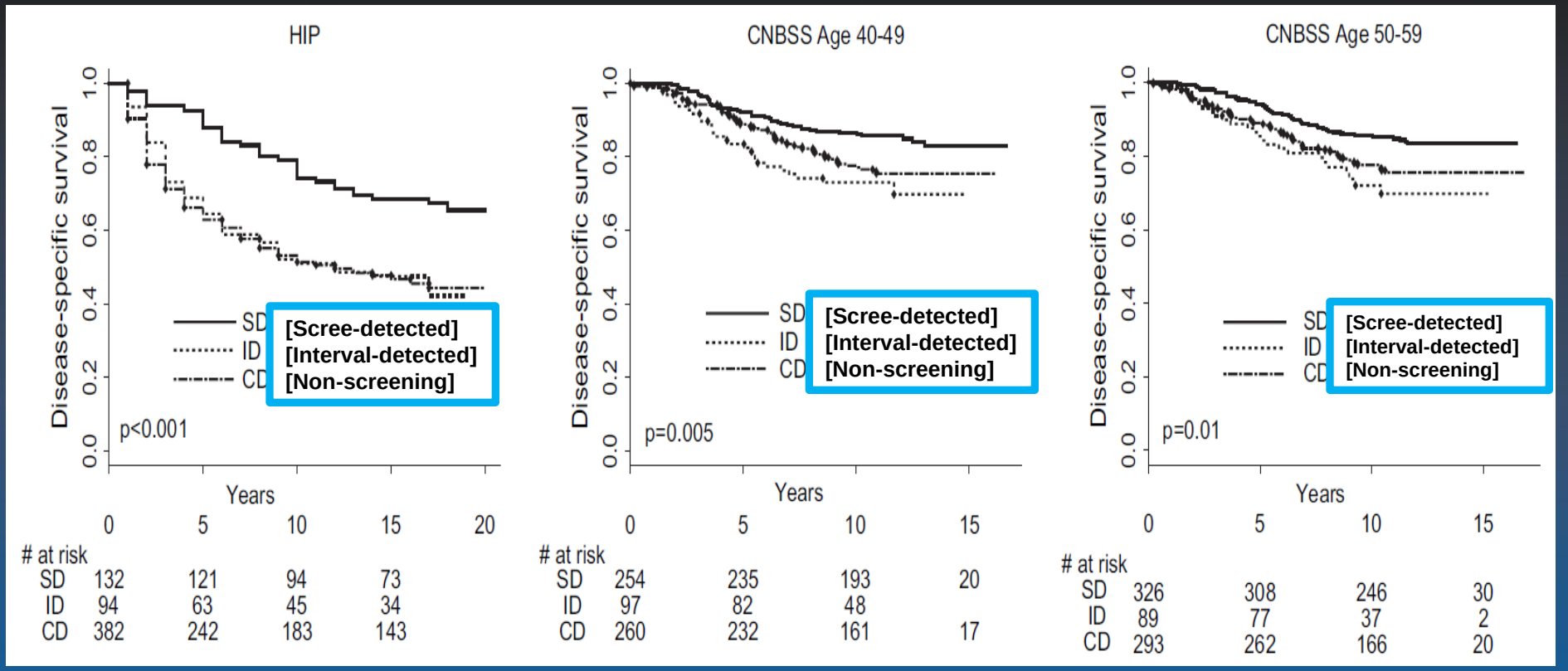
Nelson HD, Ann Intern Med 2009

Bias of Screening Mammography

- Stage shift (lead-time bias).

- Less aggressive tumors (length bias).

Disease-specific Survival Distribution by Method of Detection



Shen Y. J Natl Cancer Inst 2005

Limitations of Screening Mammography

- Approximately 10-20% of breast cancers are not routinely detected by mammography.

- Women who have interval cancers have tumors at a more advanced stage at diagnosis and have poorer survival than women with cancers detected by mammography.

- The high frequency and poorer outcomes of interval cancer may have a substantial effect on screening-related mortality reduction.

Holmberg LH, Lancet 1986
Porter PL, J Natl Cancer Inst 1999

Factors Contributing to Screening Mammography Failure

- Technical or interpretive errors.
- Mammographic characteristics of the breast or tumor.
- Rapidly growing cancers.

Porter PL, J Nal Cancer inst 1999
Gilliland FD, J Natl Cancer Inst 2000

Significant Differences Between Interval- and Screen-Detected Cancers

Author (year)	Number of screen-detected cancers	Number of Interval cancers	Age groups	Screening interval (years)	«True» interval cancer?	Analysis (univariate/ multivariate)	Significant differences
DeGroote (1983)	99	21	30–80	1	Yes	Univariate	Nodal status
Heuser (1984)	32	28	—	1	No	Univariate	Mammography Age
Frisell (1987)	222	60	40–64	2	Yes	Univariate	Tumor size Nodal status
Hatschek (1989)	212	98	40–74	2	No	Univariate	S-phase fraction
Bahnsen (1994)	163	22	36–75	2	No	Univariate[a]	Nodal status
Burrell (1996)	267	82	50–64	Varying	Yes	Univariate	Tumor size Nodal status Tumor grade
Klemi (1997)	385	100	40–74	Varying	No	Univariate	Age Tumor size Nodal status
Raja (2001)	625	230	50–64	3	Yes	Univariate	Tumor size Nodal status Tumor grade
Shen (2005)	712	280	40–64	1	No	Multivariate[b]	Nodal status
Pálka (2008)	258	48	45-65	2	No	Univariate	Tumor stage Tumor grade

[a]Adjusted for tumor size; [b]Adjusted for age and tumor size.

Significant Differences Between Interval- and Screen-Detected Cancers

Author (year)	Number of screen-detected Cancers	Number of Interval cancers	Age groups	Screening interval (years)	«True» interval cancer?	Analysis (univariate/ multivariate)	Significant differences
Crosier (1999)	84	51	50–64	3	Yes	Multivariate	ki-67 Her2/neu
Porter (1999)	279	150	40–80	Varying	No	Univariate[a]	Tumor grade ki-67 ER
Gilliland (2000)	64	63	40–80	Varying	No	Multivariate	P53 ki-67
Anttinen (2003)	79	39	> 50	Varying	No	Univariate[a]	Her2/neu
Collettt (2005)	95	95	50-74	2	No	Univariate	Basal-like
der Vegt (2010)	63	36	50–74	2	Yes	Univariate	ER
Domingo (2010)	115	34	50–69	2	Yes	Multivariate[a]	Breast density Triple negative
Kirsh (2011)	450	288	> 50	2	Yes	Univariate[a]	Mitotic score ER/PR
Mook (2011)	958	417	50–69	2	No	Univariate	ER
Chiarelli (2011)	995[b]	362	50–69	2	No	Univariate[a]	Mitotic score
Musolino (2012)	292	48	50–69	2	Yes	Univariate[a]	ki-67/ER Her2/neu
Caldarella (2013)	211	66	50–69	2	No	Multivariate[a]	Triple negative
Pollan (2013)	870	240	45-69	2	Yes	Univariate[a]	Breast density Her2/neu Triple negative

[a]Adjusted for age and tumor size; [b]Rescreen-detected breast cancer.

Significant Differences Between Symptomatic and Screen-Detected Cancers

Author (year)	Number of screen-detected cancers	Number of symptomatic cancers	Age groups	Screening interval (years)	Analysis (univariate/ multivariate)	Significant Differences
Joensuu (2004)	443	1540	40-74	2	Univariate	Tumor stage/grade
Dong (2008)	2387	3094	40-74	Varying	Multivariate[b]	Ki-67 ER/PR Her2/neu
Pálka (2008)	258	263	45–65	2	Univariate	Tumor stage/grade
Sihto (2008)	247	989	30–80	2	Univariate	ER/PR Her2/neu
Burke (2008)	100	100	30–80	Varying	Univariate	Tumor size/grade ER/PR
Dawson (2009)	610	769	50–70	2	Univariate	Tumor stage/grade ER/PR/Ki-67
Mook (2011)	958	1217	50-69	2	Univariate[b]	Tumor size/grade ER/PR
Chiarelli (2011)	995[c]	491	50-69	2	Univariate[b]	Tumor grade Mitotic score
Brewster (2011)	247	603	50-87	Varying	Univariate	Luminal-A Triple negative Her2/neu
Kim (2012)	1025	2116	30–80	2	Univariate	Triple negative
Crispo (2013)	114	334	50-69	2	Univariate	Triple negative

[a]Adjusted for age and tumor size; [b]Rescreen-detected breast cancer.

Association Between Method of Detection and Disease-free Survival After Adjusting for Clinical Variables

Factors adjusted for	HR (95% CI) for screen vs. symptom detected	Freedman statistic, %	Freedman statistic, *P*
None	0.65 (0.44–0.98)	–	–
Race	0.66 (0.43–0.99)	0	0.99
Histology	0.66 (0.44–0.99)	1.4	0.99
Tumor subtype	0.69 (0.45–1.08)	13.3	0.41
Ki67	0.69 (0.44–1.09)	11.9	0.55
Hormonal therapy	0.67 (0.45–1.01)	6.8	0.80
Nodal status	0.72 (0.48–1.09)	23.1	0.14
Chemotherapy	0.71 (0.46–1.09)	18.8	0.26
5 CNIs	0.72 (0.47–1.1)	22.1	0.16
Nuclear grade	0.71 (0.46–1.09)	17.4	0.35
Age at diagnosis	0.66 (0.44–0.98)	0.4	0.72
Tumor size	0.76 (0.49–1.19)	34.9	0.09
Tumor size + nodal status + age + grade + Ki67	0.75 (0.44–1.27)	31.7	0.11

Brewster P. Cancer Prev Res 2011

Study Population Selection

VOLUME 30 · NUMBER 19 · JULY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Human Epidermal Growth Factor Receptor 2 Status and Interval Breast Cancer in a Population-Based Cancer Registry Study

Antonino Musolino, Maria Michiara, Giovanni Maria Conti, Daniela Boggiani, Marella Zatelli, Dario Palleschi, Maria Angela Bella, Paolo Sgargi, Beatrice Di Blasio, and Andrea Ardizzoni

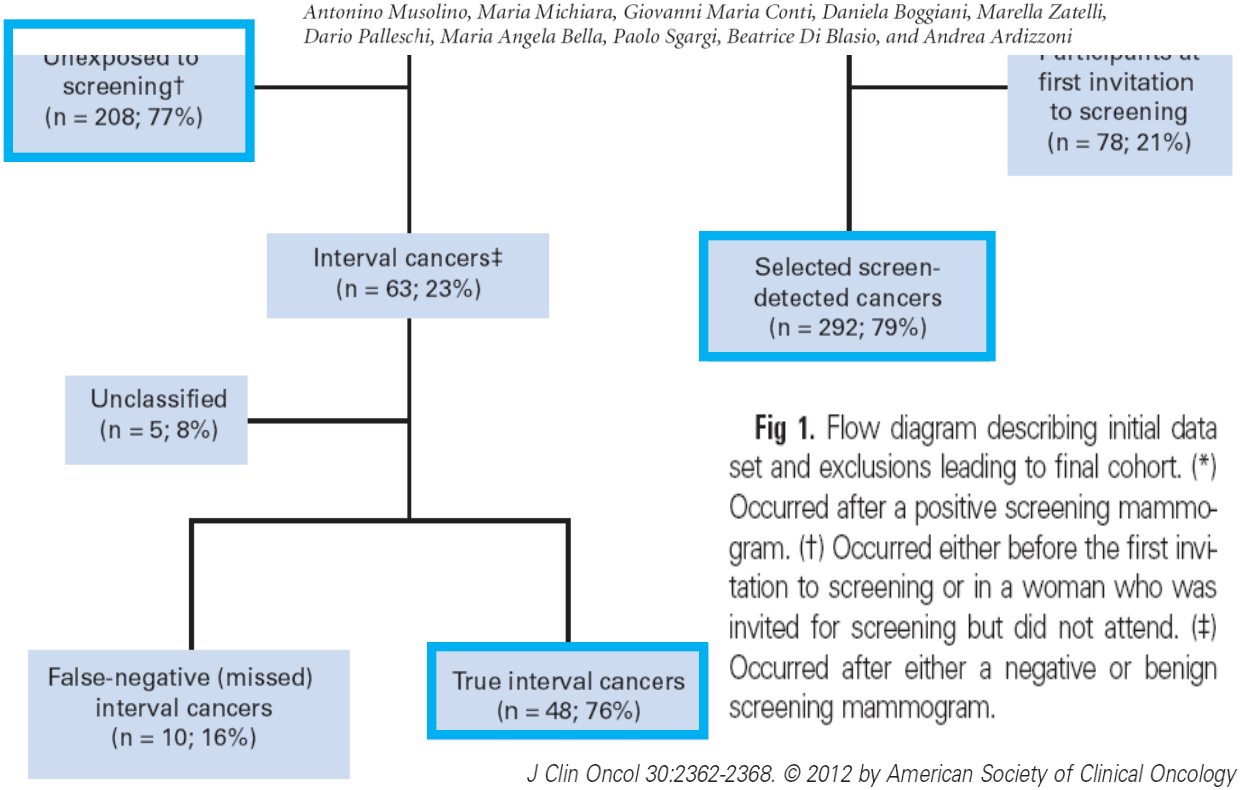


Fig 1. Flow diagram describing initial data set and exclusions leading to final cohort. (*) Occurred after a positive screening mammogram. (†) Occurred either before the first invitation to screening or in a woman who was invited for screening but did not attend. (‡) Occurred after either a negative or benign screening mammogram.

Musolino A. J Clin Oncol 2012

Age, Stage Distribution, and Clinical Characteristics by Mode of Breast Cancer Detection

Characteristic	True Interval Cancers (n = 48)		Screen-Detected Cancers (n = 292)		OR	95% CI	P	Unexposed Cases (n = 208)	
	No. of Patients	%	No. of Patients	%				No. of Patients	%
Age at screening, years									
50-54	12	25	29	10	1.0	Referent	< .001*	68	33
55-59	13	27	62	21	0.5	0.2 to 0.9		62	30
60-64	11	23	91	31	0.3	0.1 to 0.7		33	16
65-69	12	25	110	38	0.2	0.1 to 0.6		45	21
Tumor stage†‡									
I	24	52	207	71	1.0	Referent	< .001*	96	47
II	12	26	64	22	1.5	0.7 to 3.3		73	35
III-IV	10	22	21	7	4.8	1.9 to 10		38	18
Tumor size, cm†‡									
≤ 1.0	18	40	149	51	1.0	Referent	< .001*	48	23
> 1.0-2.0	14	30	99	34	1.2	0.6 to 2.4		85	41
> 2.0	14	30	44	15	2.8	1.3 to 5.6		74	36
Regional lymph nodes†§									
Negative	31	65	229	78	1.0	Referent	.57‖	155	75
Positive	16	35	63	22	1.0	0.7 to 1.9		52	25
Breast density†‡									
Low	26	58	164	62	1.0	Referent	.56‖	111	56
High	19	42	99	38	1.2	0.6 to 2.4		82	43
Menopausal status†									
Premenopausal	9	20	42	15	1.0	Referent	.35‖	45	24
Postmenopausal	35	80	238	85	1.0	0.3 to 2.8		143	76
Family history of breast cancer†									
None or second degree	38	83	209	78	1.0	Referent	.48‖	151	81
First degree	8	17	59	22	0.8	0.3 to 1.9		36	19

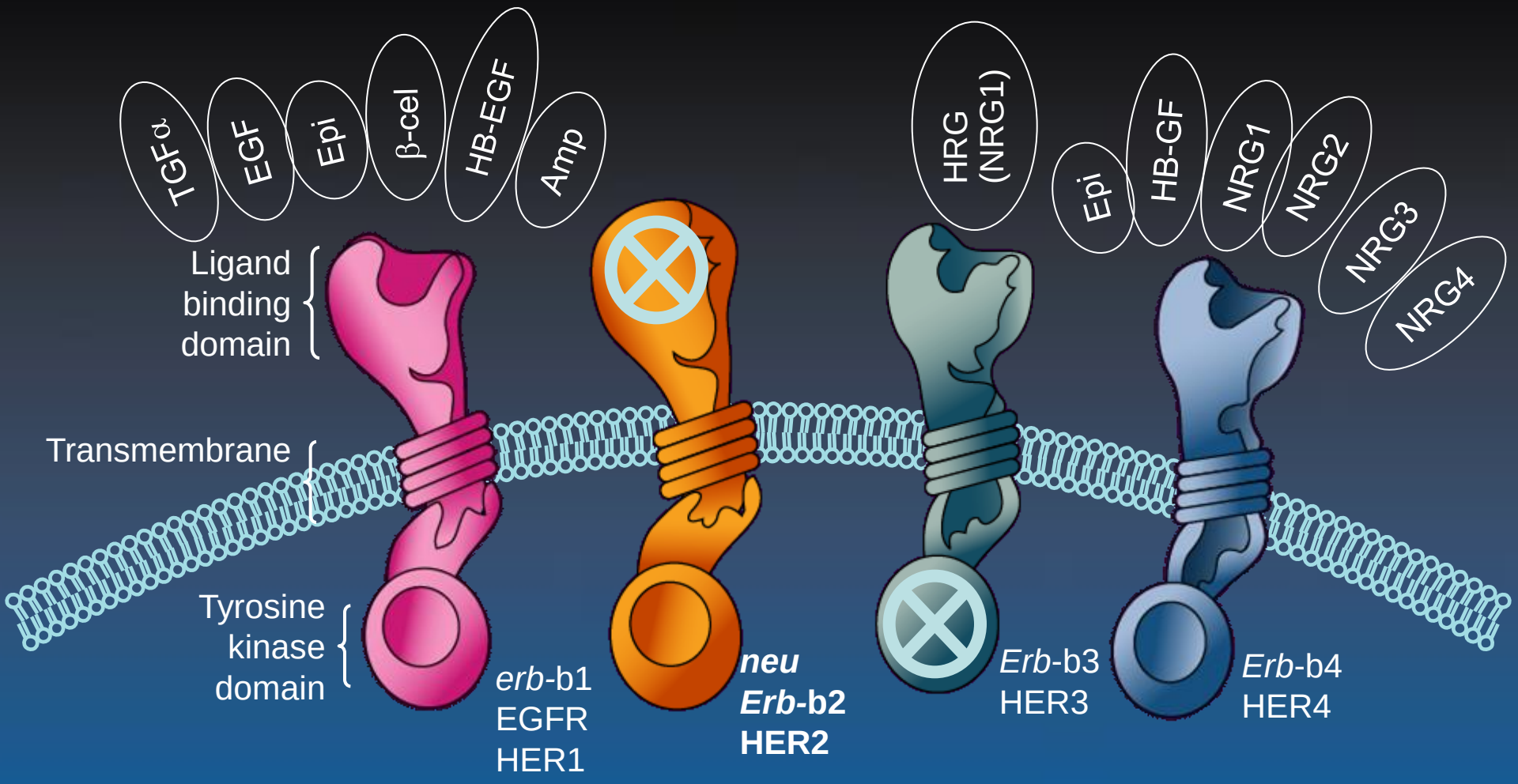
Musolino A. J Clin Oncol 2012

Tumor Characteristics of Interval-Detected and Screen-Detected Cancers

Characteristic	True Interval Cancers (n = 48)		Screen-Detected Cancers (n = 292)		OR*	95% CI	P	Unexposed Cases (n = 208)	
	No. of Patients	%	No. of Patients	%				No. of Patients	%
Histologic subtype									
Ductal, not otherwise specified	36	75	204	70	1.0	Referent		157	75
Tubular	2	4	9	3	1.4	0.1 to 6.9	.65†	4	2
Mucinous	1	2	6	2	1.0	0.1 to 8.3	.12†	6	3
Medullary	1	2	7	2	0.6	0.1 to 5.2	.69†	4	2
Lobular	6	13	58	20	0.57	0.2 to 1.4	.15‡	27	13
Other§	2	4	8	3	1.4	0.4 to 10	.59†	10	5
Histologic grade‖									
G1	10	24	97	36	1.0	Referent	< .001¶	40	22
G2	15	36	112	41	1.1	0.4 to 2.5		78	44
G3	17	40	62	23	1.8	1.2 to 3.8		61	34
Ki-67 proliferative index‖									
Low	19	44	193	68	1.0	Referent	< .001‡	107	57
High	24	56	90	32	2.4	1.2 to 4.5		81	43
Estrogen receptor‖									
Positive	32	71	247	86	1.0	Referent	.01‡	155	79
Negative	13	29	40	14	1.6	1.1 to 3.1		42	21
Progesterone receptor‖									
Positive	27	60	202	70	1.0	Referent	.162‡	136	69
Negative	18	40	85	30	1.2	0.3 to 1.5		61	31
HER2 status‖									
Negative	25	56	240	86	1.0	Referent	< .001‡	163	86
Positive	20	44	39	14	3.4	1.7 to 7.1		27	14

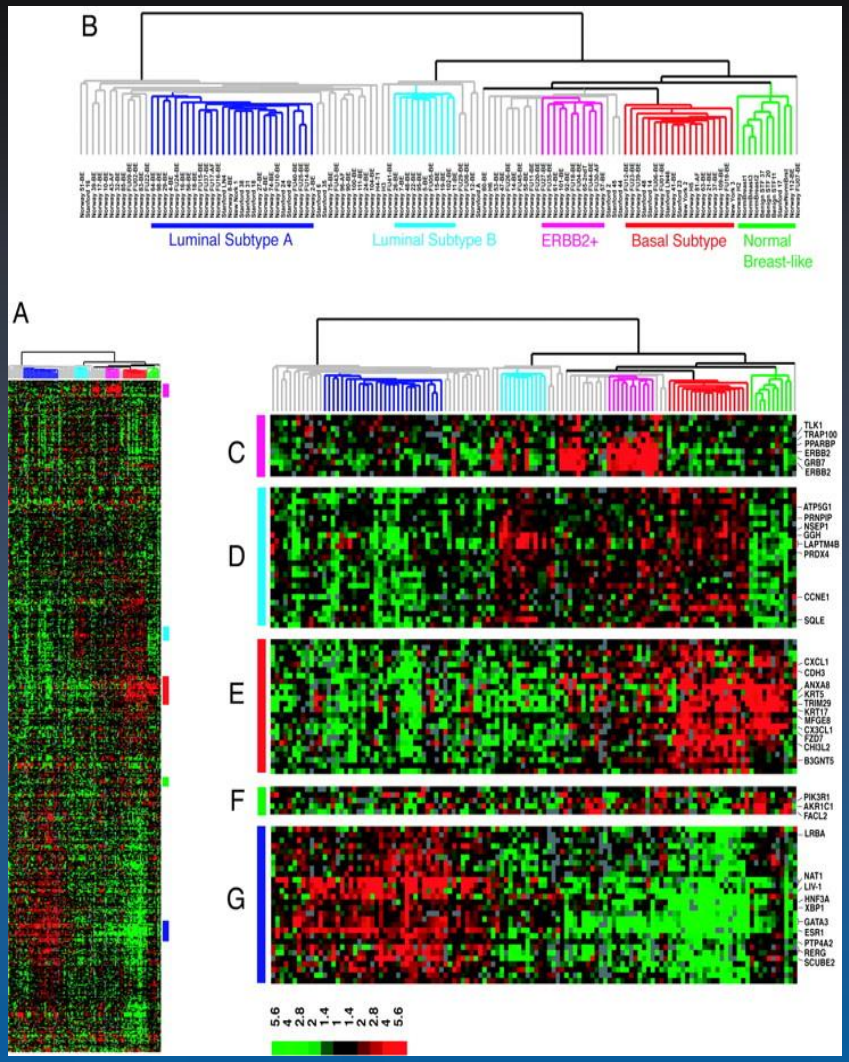
Musolino A. J Clin Oncol 2012

The EGFR/HER Family



Mendelsohn and Baselga. *Oncogene.* 2000;19:6550.
Olayioye et al. *EMBO J.* 2000;19:3159.
Prigent and Lemoine. *Prog Growth Factor Res.* 1992;4:1.
Harari and Yarden. *Oncogene*. 2000;19:6102.
Earp et al. *Breast Cancer Res Treat.* 1995;35:115.

Breast Cancer Subtypes



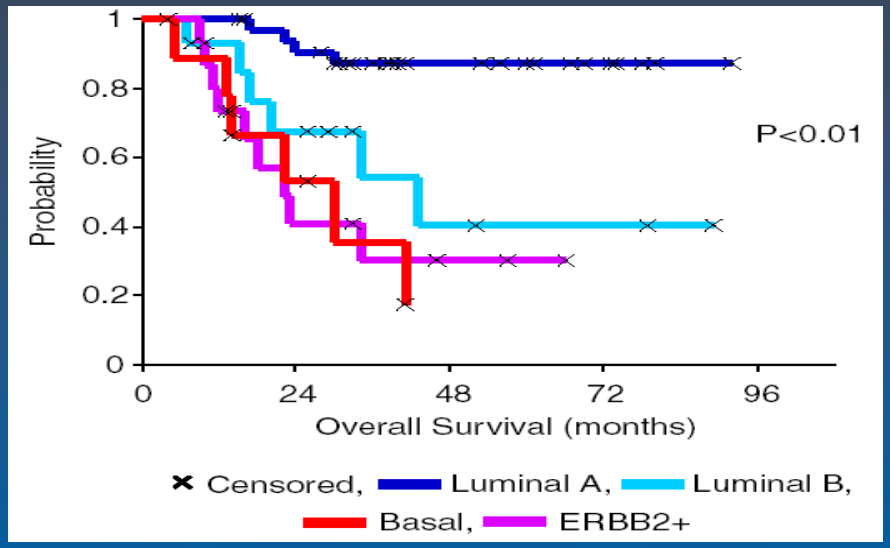
Luminal A

ER+ 65-75%

Luminal B

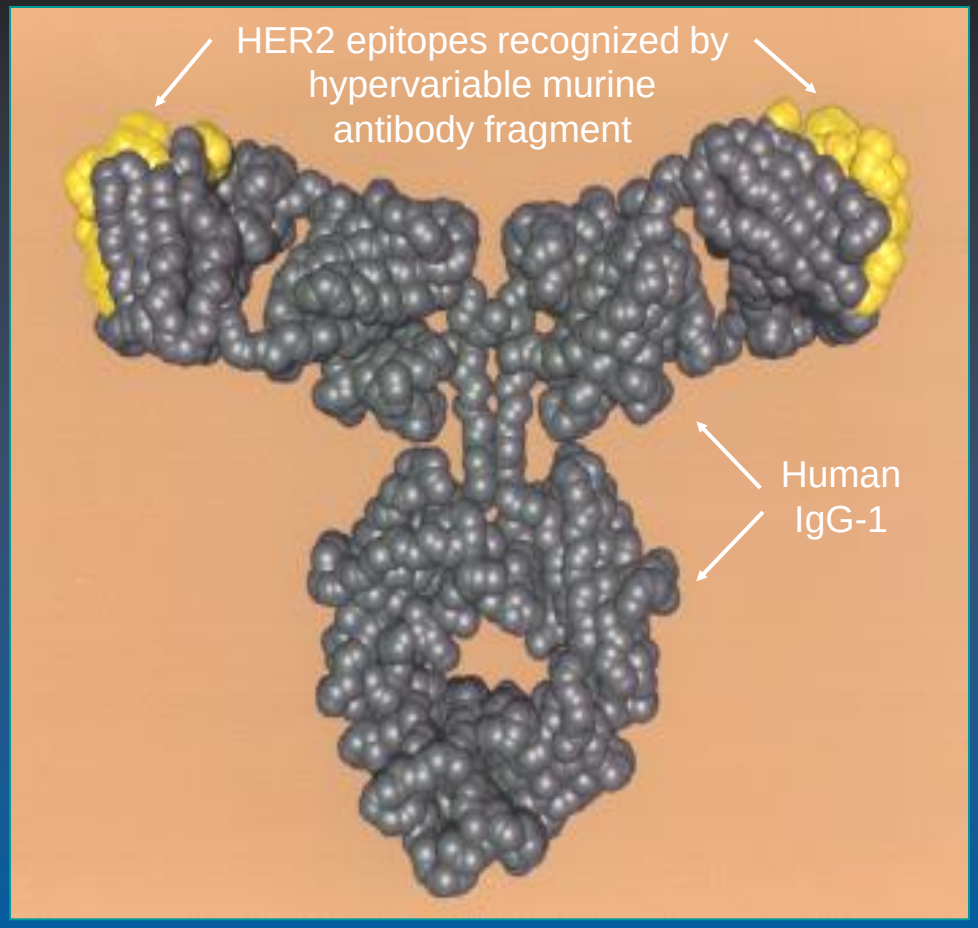
Basal-Like **ER- 15%**

HER2+ **ER- 15-20%**



Perou et al. Nature 2000
Sorlie et al. PNAS 2001

Trastuzumab: Humanized Anti-HER2 Antibody



- Targets HER2 protein
- High affinity (K_d = 0.1 nM) and specificity
- 95% human, 5% murine
  - Decreases potential for immunogenicity
  - Increases potential for recruiting immune effector mechanisms

BCIRG 006
Phase III Trial Comparing AC→T with AC→TH and with TCH in the Adjuvant Treatment of HER2-Amplified Early Breast Cancer Patients:

10-year Follow-up analysis

Slamon D, Eiermann W, Robert N, Giermerk J, Martin M, Jasiowka M, Mackey J, Chan A, Liu M, , Pinter T, Valero V, Falkson C, Fornander T, Shiftan T, Bensfia S, Hitier S, Xu N, Bee-Munteanu V, Drevot P, Press M, Crown J, on behalf of the BCIRG 006 Investigators.

Study sponsored by sanofi
Support from Genentech

San Antonio Breast Cancer Symposium, December 8-12, 2015

BCIRG 006 Trial Design

Her 2+
(Central FISH)

N+
or high
risk N-

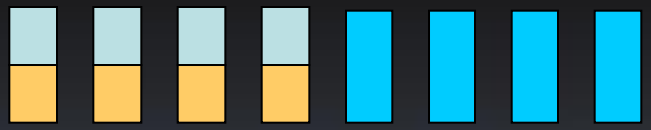
N=3,222

Stratified by Nodes and Hormonal Receptor Status

AC→T

4 x AC
60/600 mg/m²

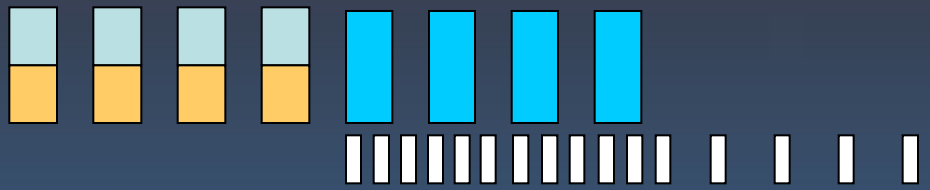
4 x Docetaxel
100 mg/m²



AC→TH

4 x AC
60/600 mg/m²

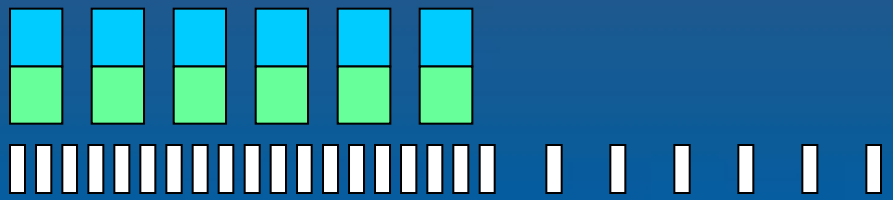
4 x Docetaxel
100 mg/m²



1 Year Trastuzumab

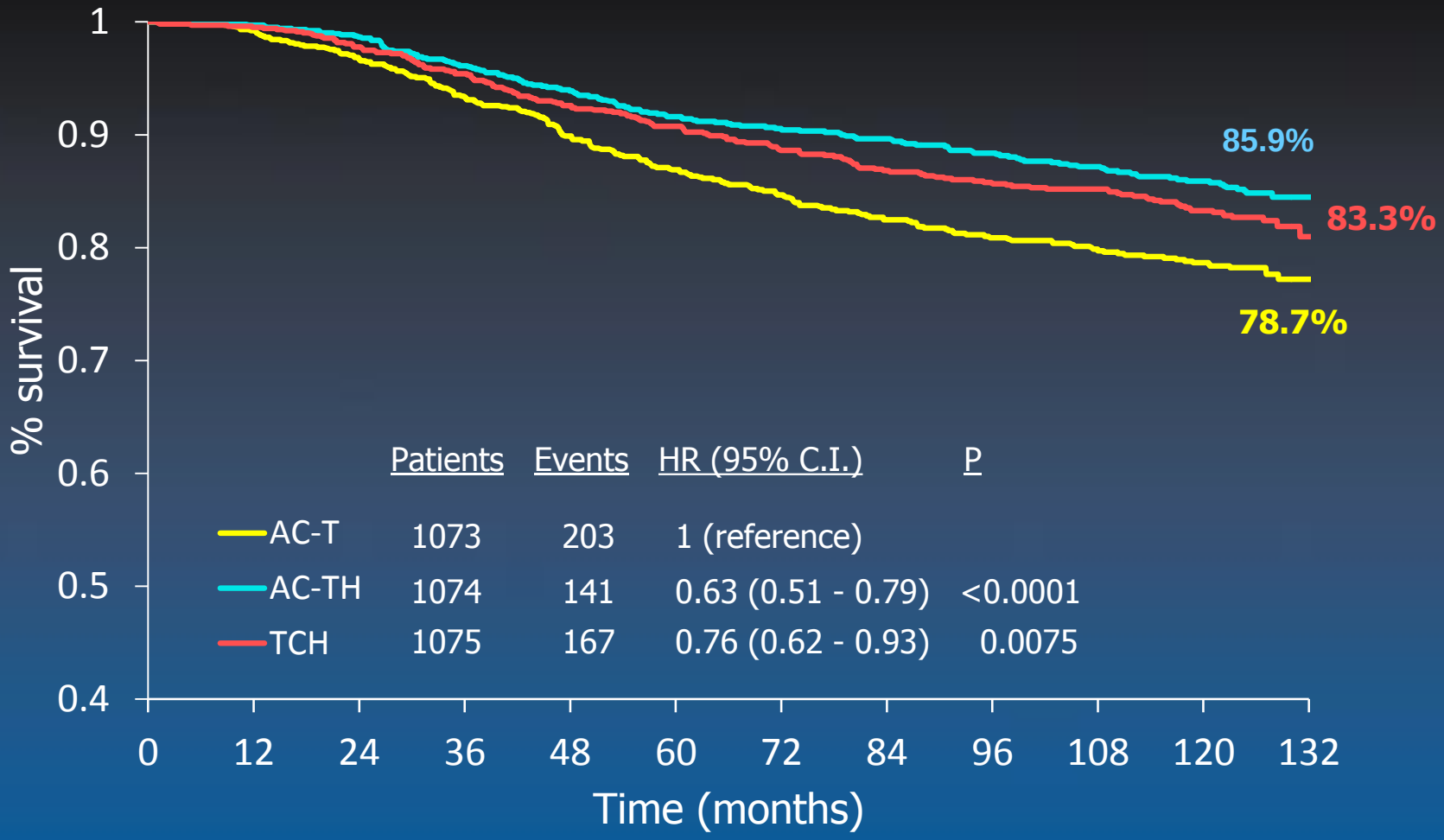
TCH

6 x Docetaxel and Carboplatin
75 mg/m² AUC 6



1 Year Trastuzumab

BCIRG 006 Overall Survival (10.3 yrs)



BCIRG 006
Grade 3/4 Non-Hematological Toxicity

	AC→T n=1,050	AC→TH n=1,068	TCH n=1,056
	%	%	%
Arthralgia	3.2	3.3	**1.4***
Myalgia	5.2	5.1	**1.8***
Fatigue	7.0	7.2	7.2
Hand-foot syndrome	1.9	1.4	**0.0***
Stomatitis	3.5	2.9	**1.4***
Diarrhea	3.0	5.6	5.4
Nausea	5.9	5.7	4.8
Vomiting	6.2	6.7	**3.5***
Irregular menses	27.3	24.5	26.7

BCIRG 006
Specific non-hematological toxicity (all grades)

	AC→T n=1,050	AC→TH n=1,068	TCH n=1,056
	%	%	%
Neuropathy-sensory	48.8	50.1	**36.1***
Neuropathy-motor	5.2	6.4	**4.3***
Nail changes	49.4	43.7	**28.7***
Myalgia	53.0	55.4	**38.9***
Renal failure	0.0	0.0	0.1
Creatinine Grade 3/4	0.6	0.3	0.1

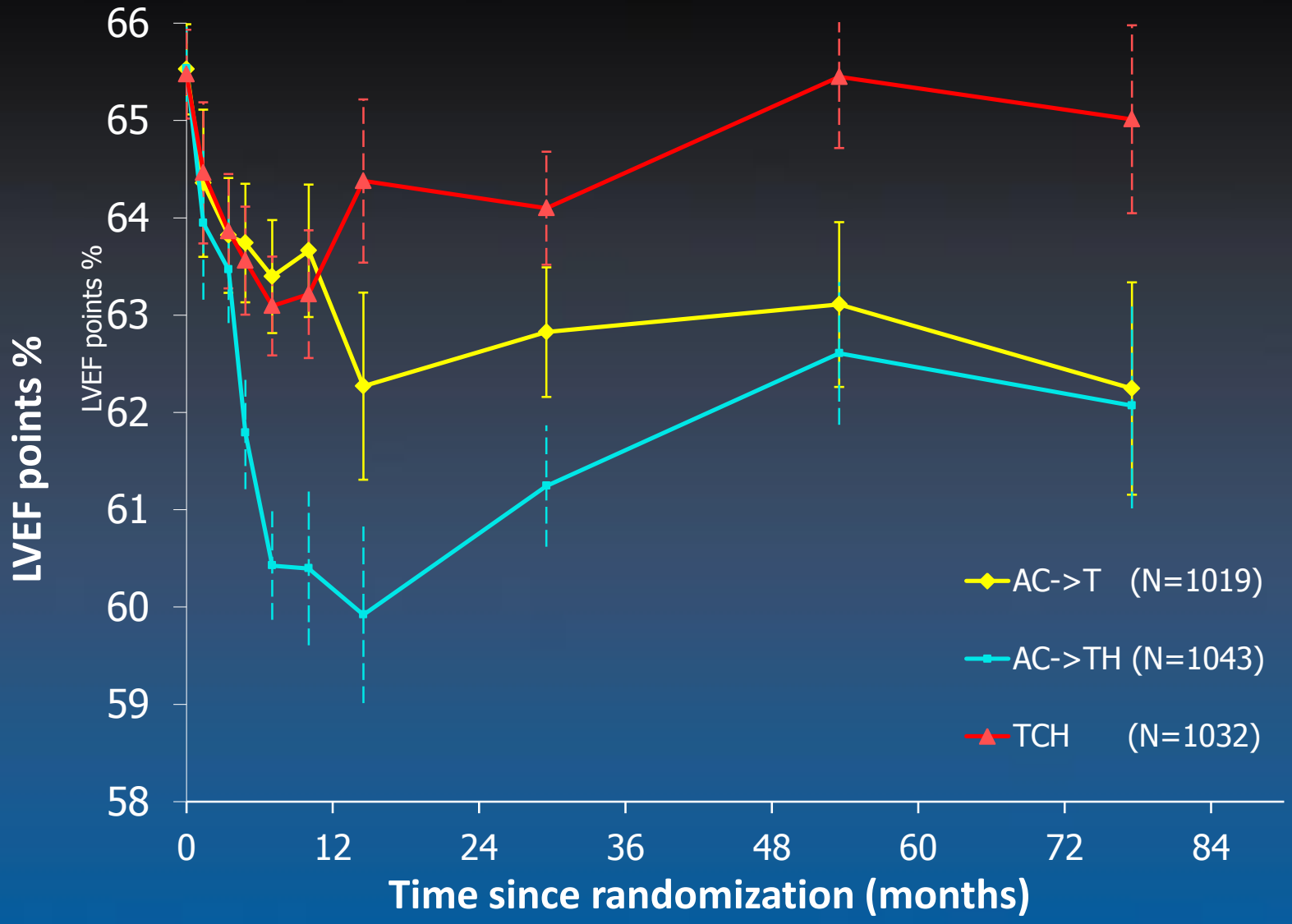
San Antonio Breast Cancer Symposium, December 8-12, 2015

BCIRG 006 Grade 3/4 Hematological Toxicity

	AC→T n=1,050	AC→TH n=1,068	TCH n=1,056
	%	%	%
Neutropenia	63.5	71.6	**66.2***
Leucopenia	51.9	60.4	**48.4***
Febrile neutropenia	9.3	11.0	9.6
Neutropenic infection	11.9	12.6	11.2
Anemia	2.3	**3.0***	5.4
Thrombocytopenia	1.6	**2.1***	6.1
Acute Leukemias	6 (0.6)	2 (0.1)	1 (0.1)

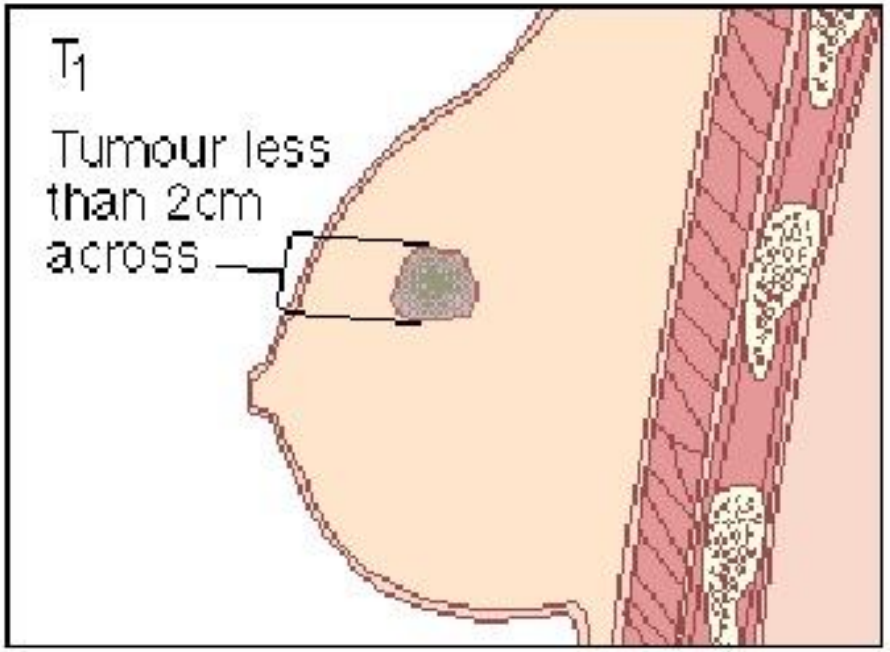
San Antonio Breast Cancer Symposium, December 8-12, 2015

BCIRG-006 Mean LVEF - Final Analysis



T1 Stage

- T1mic: <0.1 cm
- T1a:>0.1- ≤ 0.5 cm
- T1b: >0.5- ≤ 1.0 cm
- T1c: >1.0- ≤ 2.0 cm



pT1a,b incidence in Italy:

1988-1990: 9.6%

2005-2007: 21.4%

Ratio of pT1a/T1b: 1/5

Gori et al. BMC Cancer 2012

Bucchi et al. J Med Screen 2003

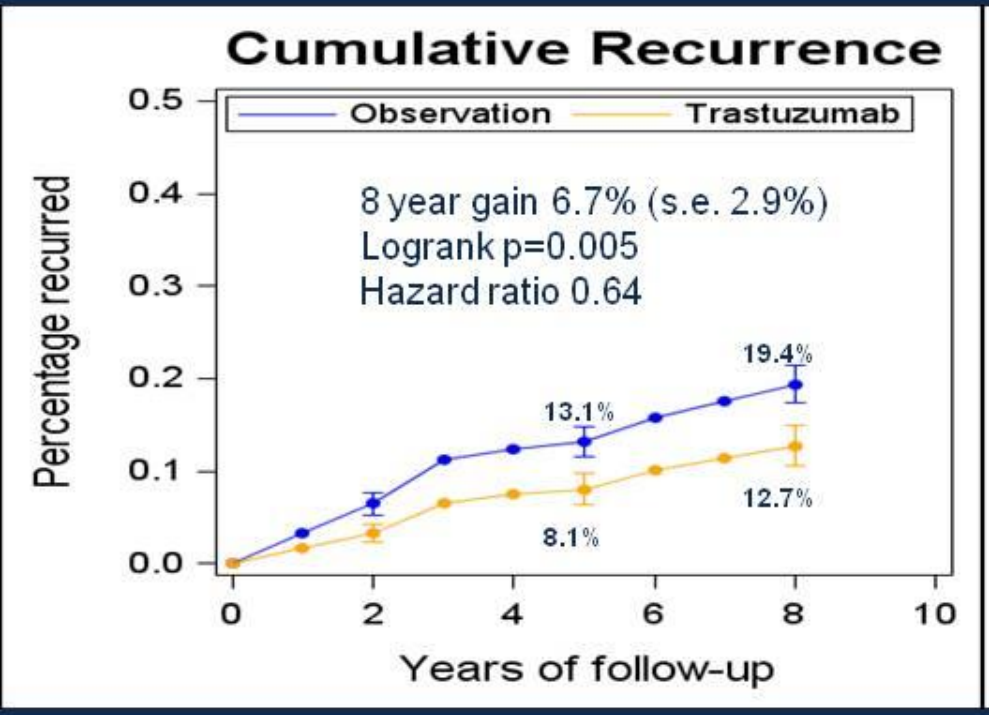
Efficacy Of Adjuvant Trastuzumab Compared With No Trastuzumab for Patients With HER2-Positive Breast Cancer And Tumors ≤ 2cm: A Meta-analysis Of The Randomized Trastuzumab Trials

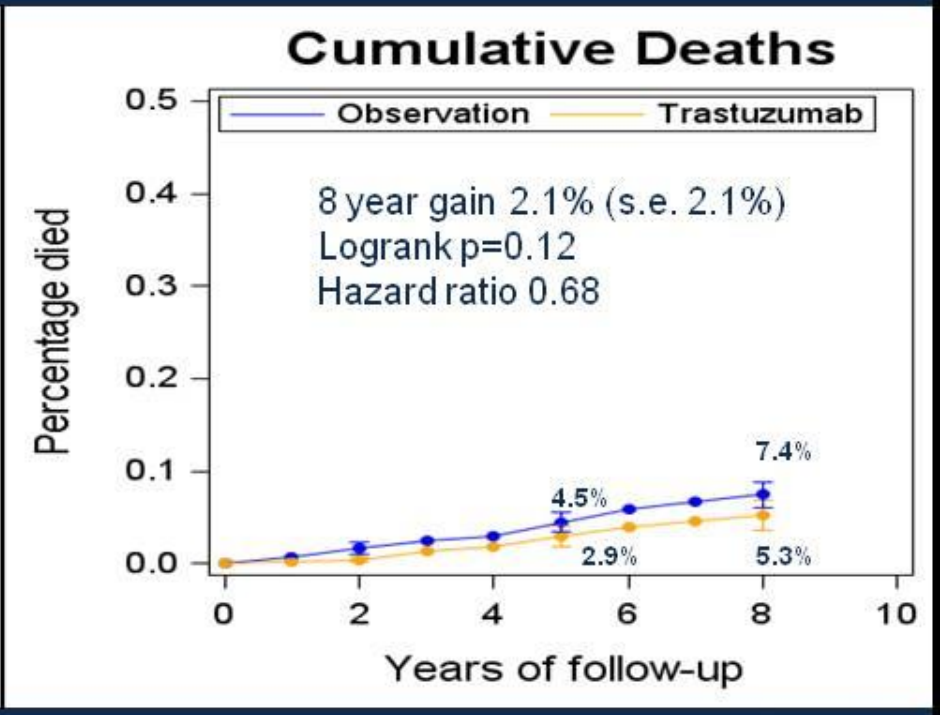
O'Sullivan CC, Bradbury I, de Azambuja E, Perez EA, Rastogi P, Spielmann M, Joensuu H, Ballman KV, Costantino JP, Delaloge S, Zardavas D, Piccart-Gebhart M, Zujewski JA, Holmes E, Gelber RD.

Long term follow up on behalf of the Trastuzumab Overview Group

PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.

Cumulative Incidence of Recurrence or Death: HR-Positive Disease with Tumors ≤ 2cm and N 0/1



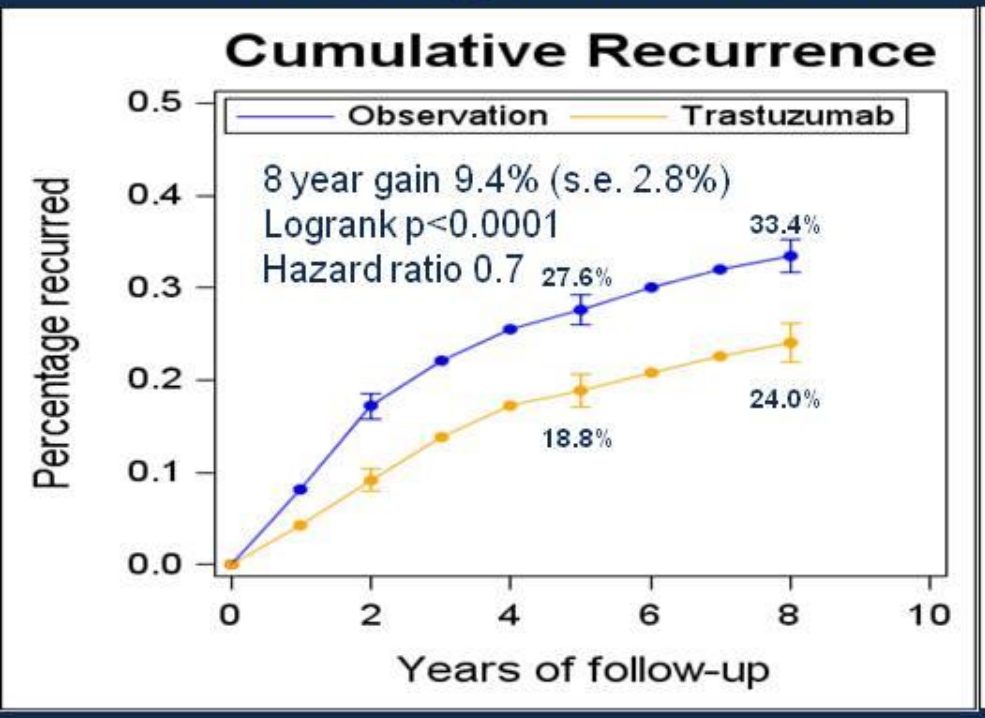


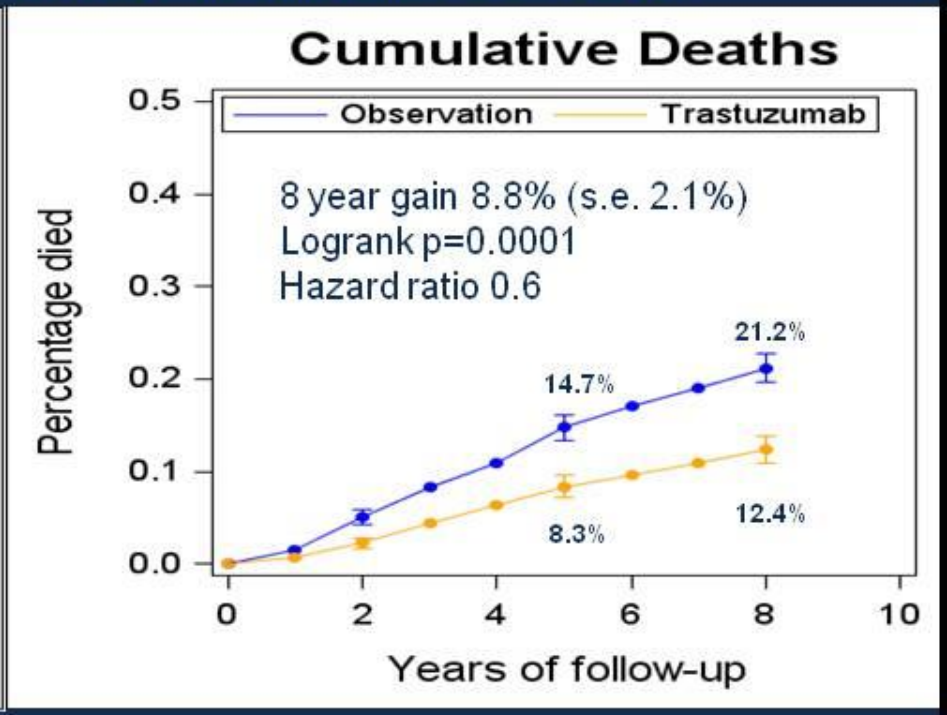
Presented by: Ciara C.O'Sullivan email: ciara.o'sullivan@nih.gov

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Ciara O'Sullivan at 2014 ASCO Annual Meeting

Cumulative Incidence of Recurrence or Death: HR-Negative Disease with Tumors ≤ 2cm





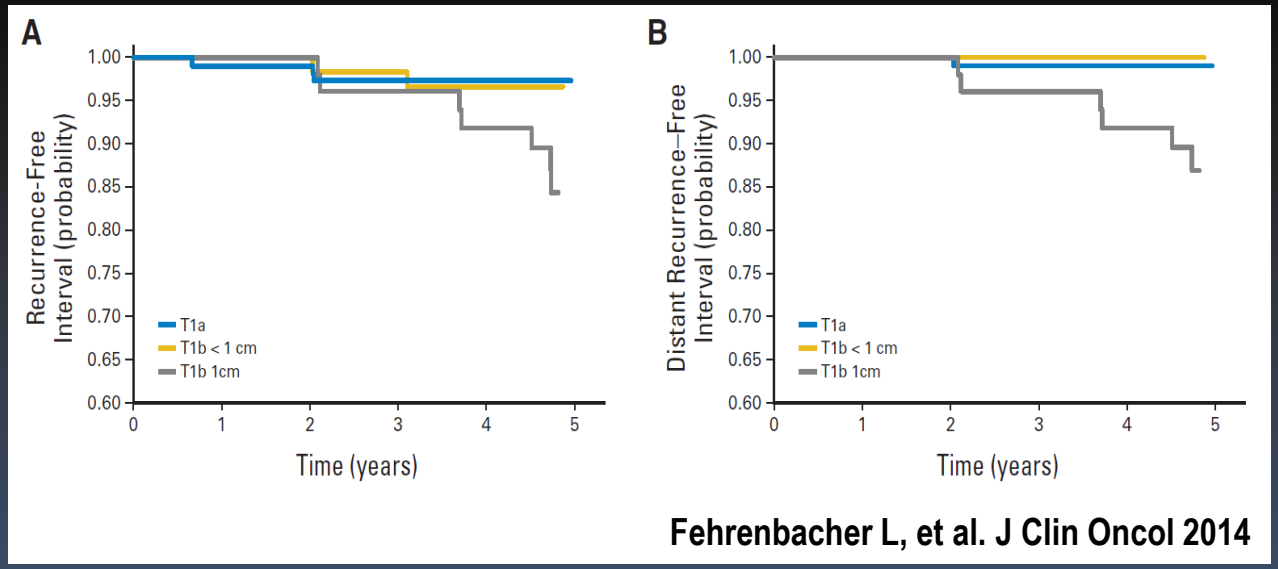
Presented by: Ciara C.O'Sullivan email:ciara.o'sullivan@nih.gov

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

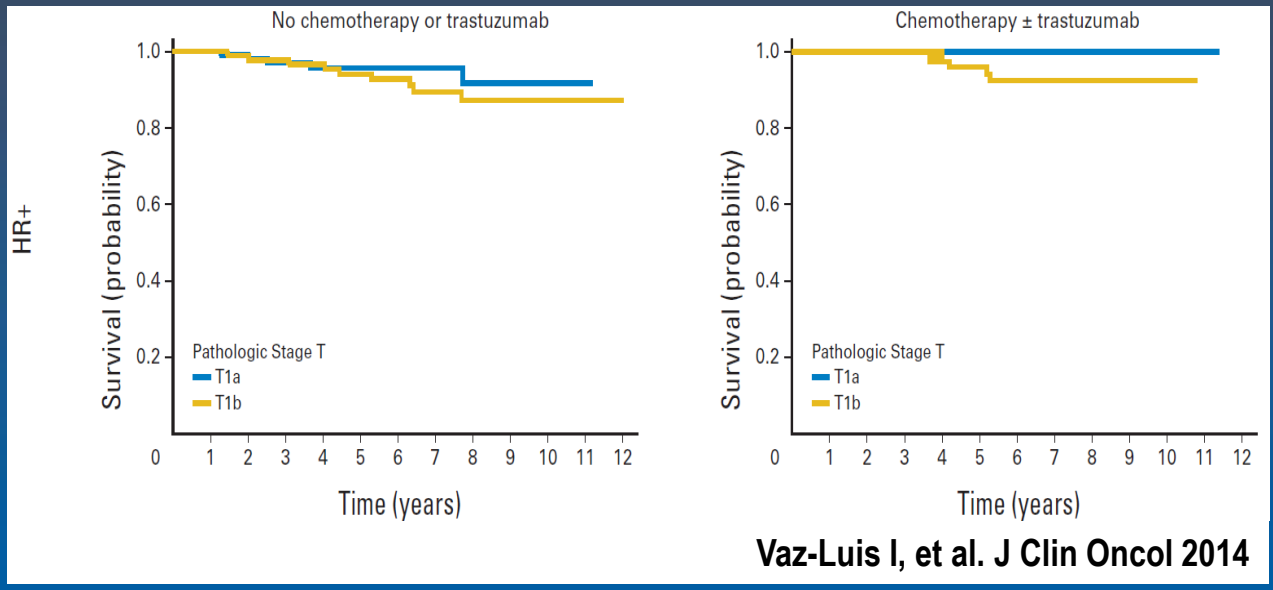
A more pressing question: Do patients with T1aN0 and T1bN0 disease warrant adjuvant tratuzumab?

- Only 75 T1aN0 and T1bN0 patients in this meta-analysis
- Risk : benefit ratio for this subset unknown

Outcome of pT1a,b HER2+ Breast cancers



Fehrenbacher L, et al. J Clin Oncol 2014



Vaz-Luis I, et al. J Clin Oncol 2014

Time Trends in The Use of Adjuvant Chemotherapy and Outcomes in Women with T1a/bN0 Breast Cancer in the National Comprehensive Cancer Network

Year of diagnosis	Percent of adjuvant CTX (± trastuzumab) (%)							
	HR+HER2- (T1a, b, c) N=6789		HR+HER2+ (T1a, b, c) N=738		HR-HER2+ (T1a, b, c) N=364		HR-HER2- (T1a, b, c) N=1026	
	T1a N=984	T1b N=2246	T1a N=135	T1b N=199	T1a N=81	T1b N=105	T1a N=99	T1b N=264
	P<0.0001		P<0.0001		P=0.0003		P=0.3600	
2003	3%	10%	13%	36%	50%	76%	18%	70%
2005	1%	11%	25%	50%	38%	77%	31%	50%
2009	2%	13%	47%	100%	56%	100%	50%	69%
5 Yr BC survival								
CTX (95 % CI)	100%	98.8 % (95.4-99.7)	100%	100%	100%	96.3% (88.8-98.8)	100%	97.9% (93.6-99.3)
No CTX (95 % CI)	99.9% (99.2-100)	99.4 % (98.9-99.7)	98.5% (89.9-99.8)	97.7% (91.1-99.4)	94.9 % (81-98.7)	100%	95.4% (86.4-98.5)	95.2% (87.6-98.2)

Vaz Duarte L, et al. J Clin Oncol 2014

Prognostic Impact of Interval Breast Cancer Detection in pT1a N0 M0 Early Breast Cancer with HER2-positive Status: A Multicenter, Population-Based Cancer Registry Study

Prognostic Impact of Interval Breast Cancer Detection in pT1a N0 M0 Early Breast Cancer with HER2-positive

- **HER2+ cases: 15% (<u>No adjuvant trastuzumab</u>)**
- **Screen-detected cancers: 53%**
- **Interval cancers: 18%**
- **Nonscreening-related cancers: 29%**

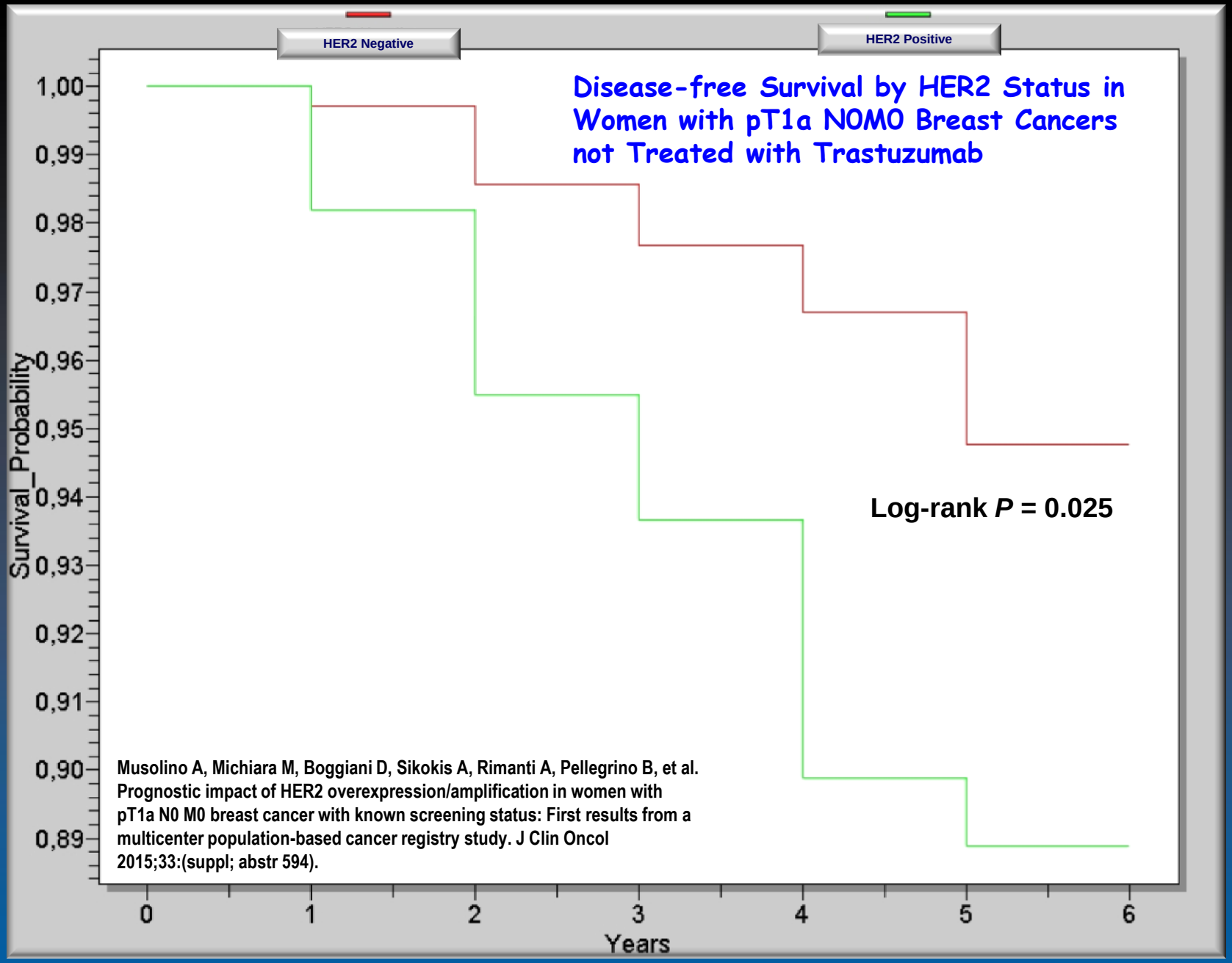
<u>Primary Endpoints</u>:

- **Evidence of poorer disease-free survival (DFS) and overall survival (OS) in pT1a N0 M0, HER2-positive interval cancers in comparison with pT1a N0 M0, HER2-positive screen-detected cancers.**

<u>Secondary Endpoints</u>:

- **No differences in outcome (DFS and OS) between pT1a N0 M0, HER2-positive screen-detected cancers and pT1a N0 M0, HER2-negative screen-detected cancers.**

Study financed by Programma di Ricerca Regione-Università 2010-2012 – Regione Emilia-Romagna (ER)



Musolino A, Michiara M, Boggiani D, Sikokis A, Rimanti A, Pellegrino B, et al. Prognostic impact of HER2 overexpression/amplification in women with pT1a N0 M0 breast cancer with known screening status: First results from a multicenter population-based cancer registry study. J Clin Oncol 2015;33:(suppl; abstr 594).

Conclusions

- Interval cancers have been shown to be biologically more aggressive than their screen-detected counterparts.
- In a general population of pT1a N0M0 early BCs with known screening status, HER2-positive tumors account for a substantial proportion of screening failure and have a significant risk of relapse.
- Final analysis of this study will evaluate if interval cancer detection may identify patients with HER2-positive pT1a N0M0 tumors in whom the rate of recurrence justifies consideration for systemic, anti-HER2, adjuvant therapy.

Cancer Treatment Reviews 43 (2016) 1–7

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journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Prognostic risk factors for treatment decision in pT1a,b N0M0 HER2-positive breast cancers

Antonino Musolino [a,*], Daniela Boggiani [a], Angelica Sikokis [a], Anita Rimanti [a], Benedetta Pellegrino [a], Rosa Vattiato [b], Paolo Sgargi [a], Fabio Falcini [b], Caterina Caminiti [c], Maria Michiara [a], Francesco Leonardi [a]

[a] Medical Oncology Unit and Cancer Registry of Parma Province, University Hospital of Parma, Italy
[b] Romagna Tumor Registry, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, IRCCS, Meldola, Italy
[c] Research and Innovation Unit, University Hospital of Parma, Italy

Regione Emila-Romagna
Breast Cancer Registry:

Fabio Falcini, M.D.
Lauro Bucchi, M.D.
Rosa Vattiato, Ph.D.

Regione Emilia-Romagna
Breast Cancer Screening
Program:

Carlo Naldoni, M.D.

Back-up slides

Adjuvant Paclitaxel and Trastuzumab for Node-Negative HER2+ Breast Cancer

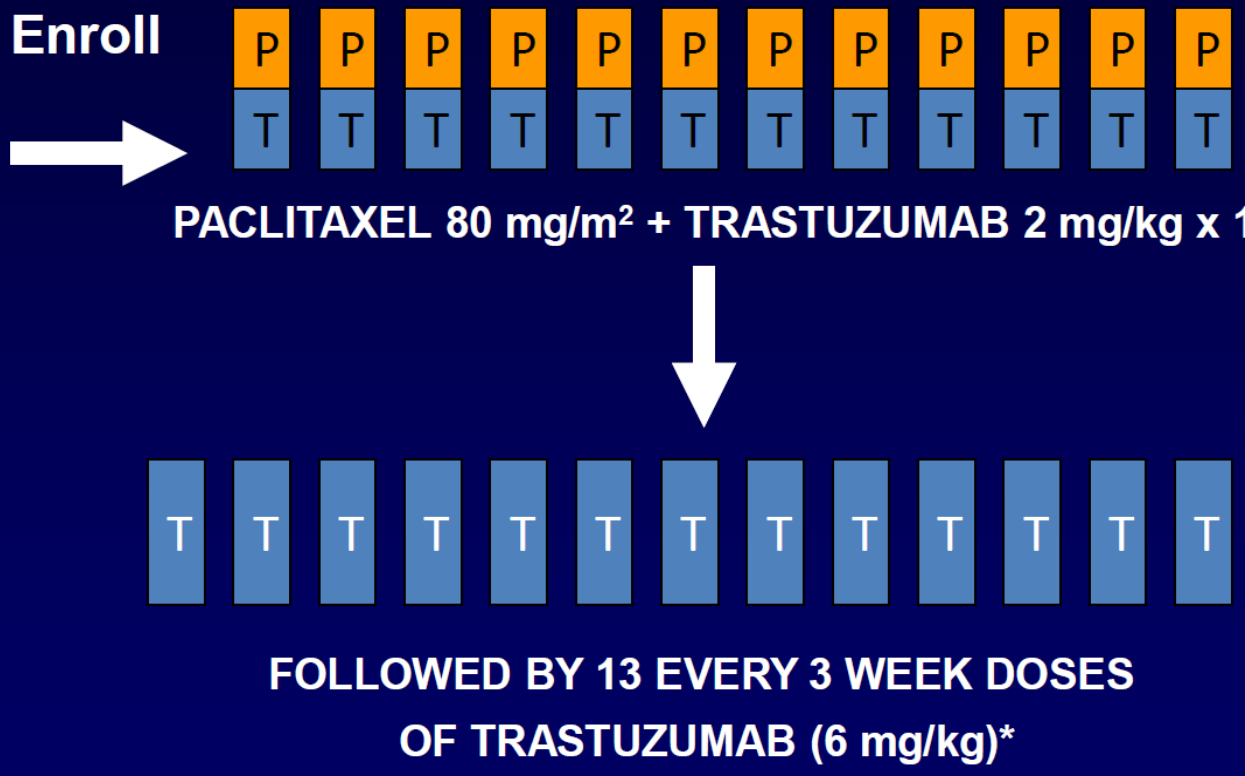
Abstract S1-04

Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, Albain KS, Rugo H, Ellis M, Shapira I, Wolff AC, Carey LA, Overmoyer BA, Partridge AH, Guo H, Hudis CA, Krop IE, Burstein HJ, Winer EP

Study Design (APT Trial)

HER2+
ER+ or ER-
node negative
≤3 cm

Planned N = 400



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

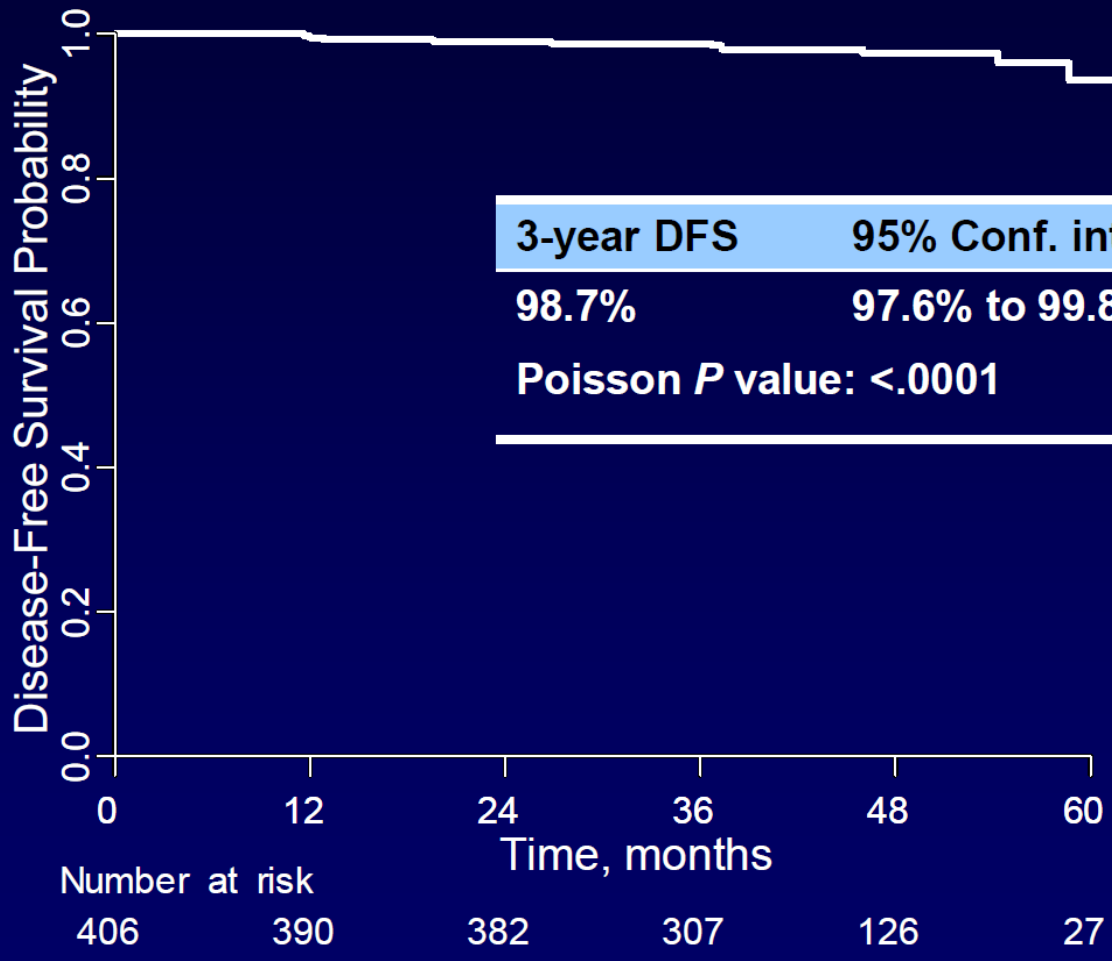
Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

Patient Characteristics

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

Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

Disease-Free Survival



3-year DFS	95% Conf. interval
98.7%	97.6% to 99.8%

Poisson *P* value: <.0001

Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

Will there be a role for TDM1 earlier in therapy? ATEMPT Trial

Stage I
HER2+
500 patients

3

Trastuzumab-DM1 q3weeks X17

N=375

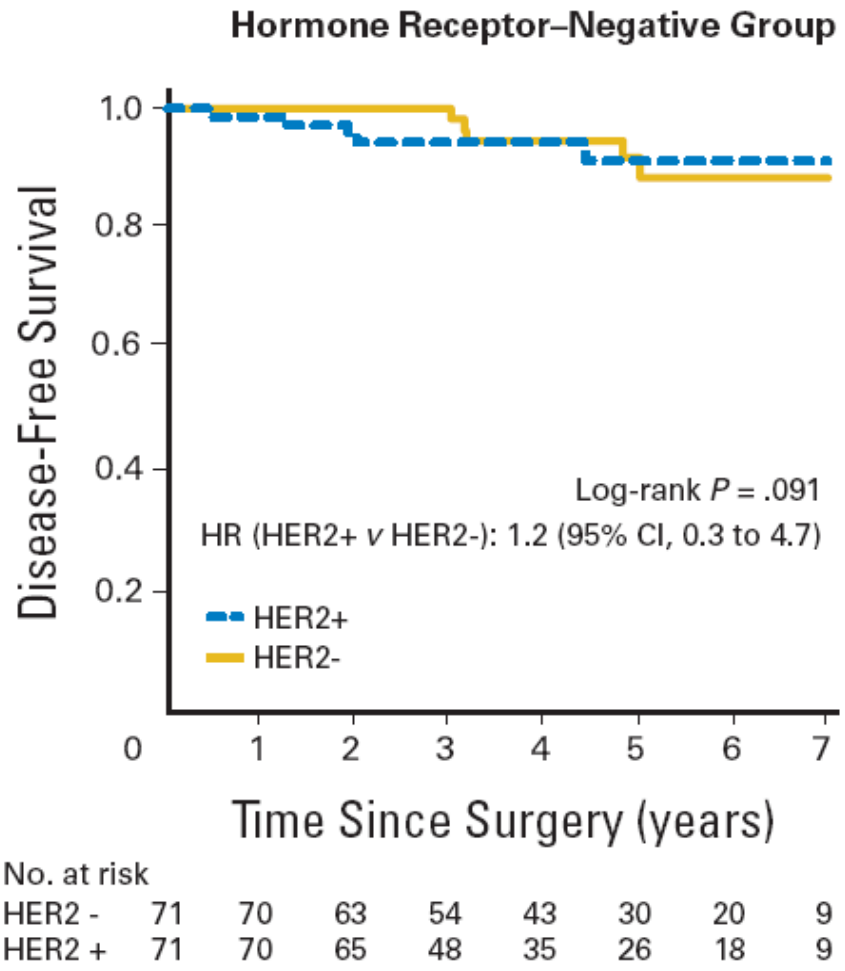
1

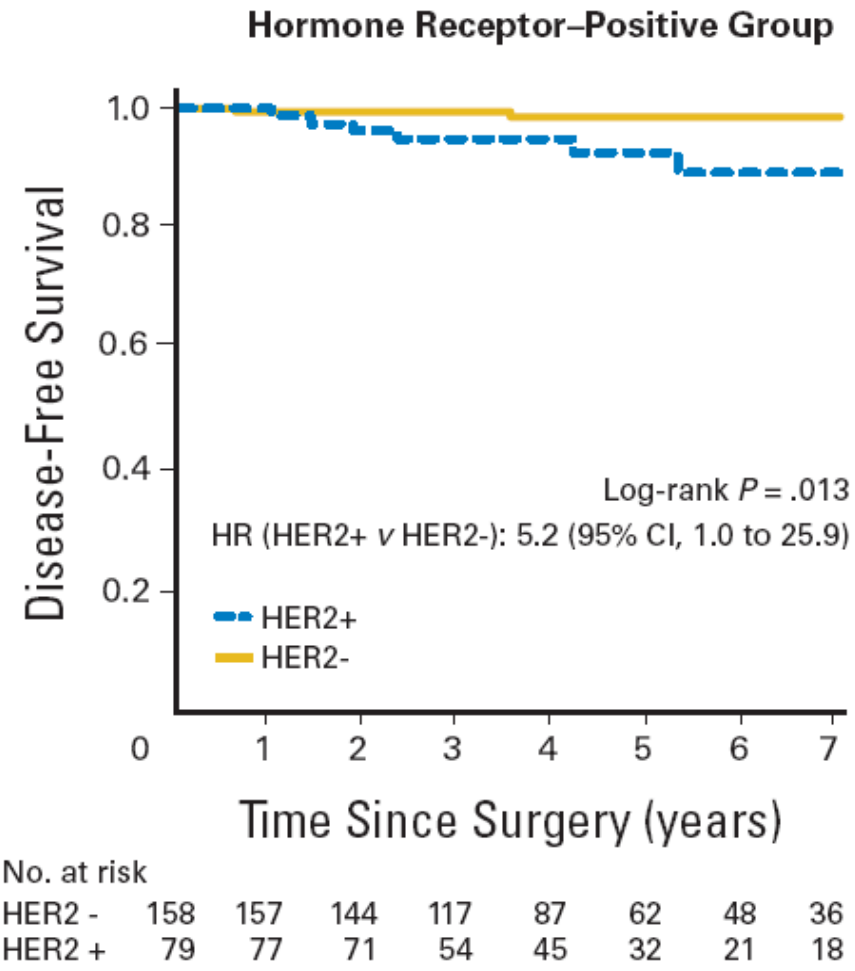
Paclitaxel + Trastuzumab x12→
Trastuzumab q3weeks x13

N=125

PI: Sara Tolaney, MD, MPH

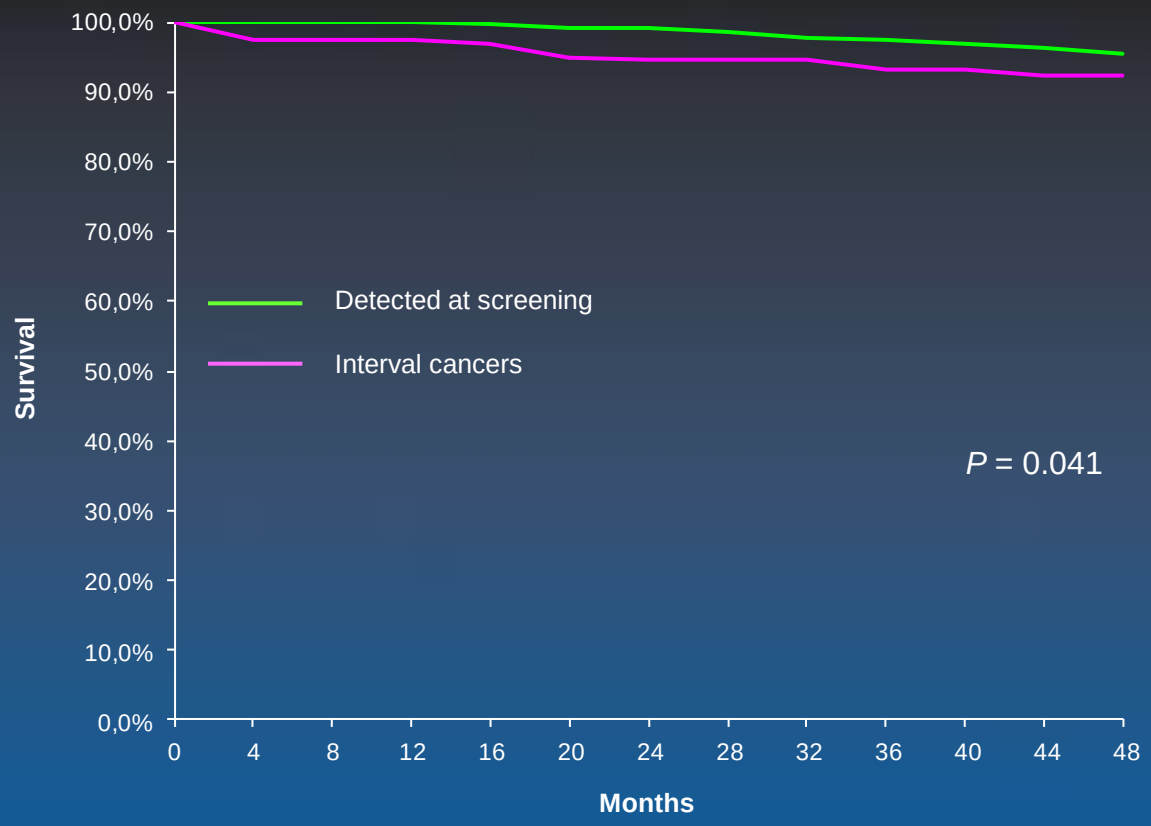
Disease-free survival in patients with pT1a-b N0 M0 Breast cancer by HER2 Status





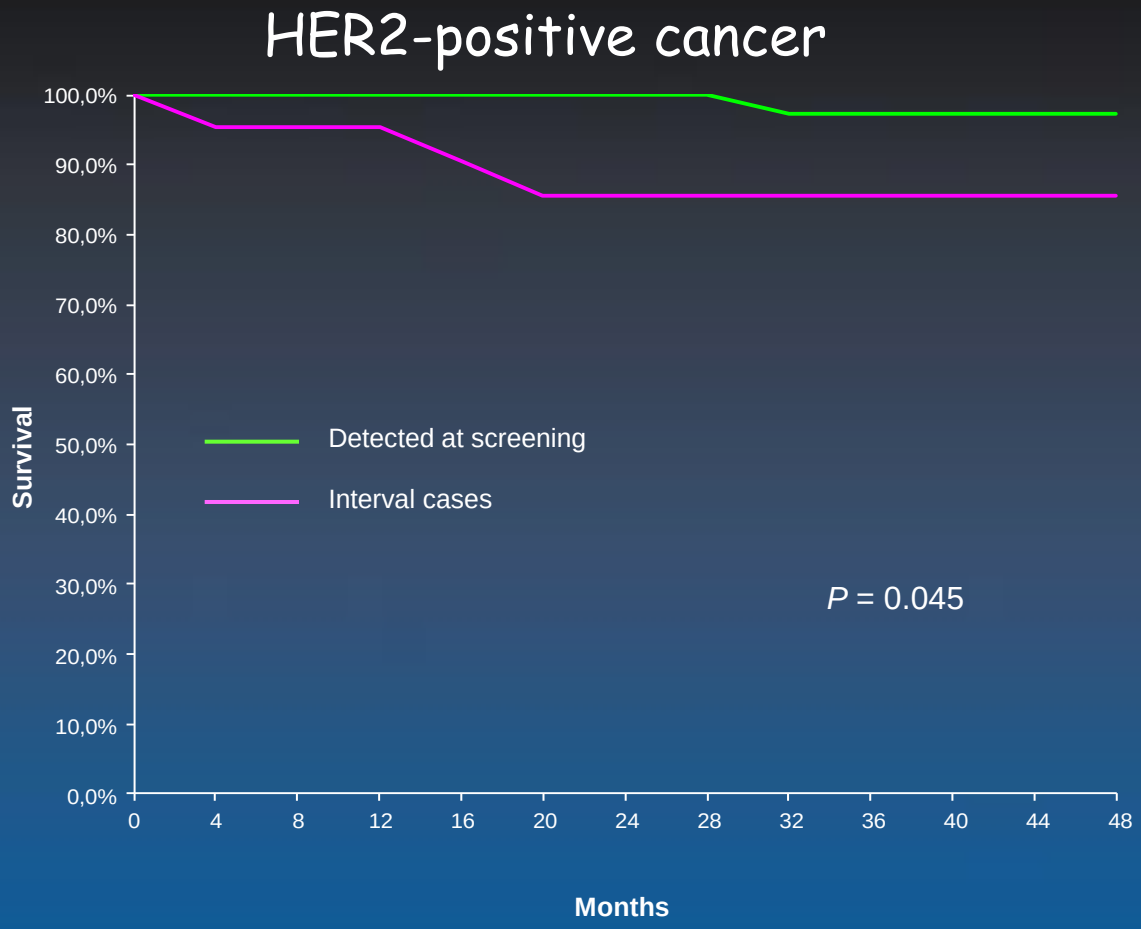
Curigliano. J Clin Oncol 2009

Overall Survival by Mode of Breast Cancer Detection



Musolino A. Unpublished data

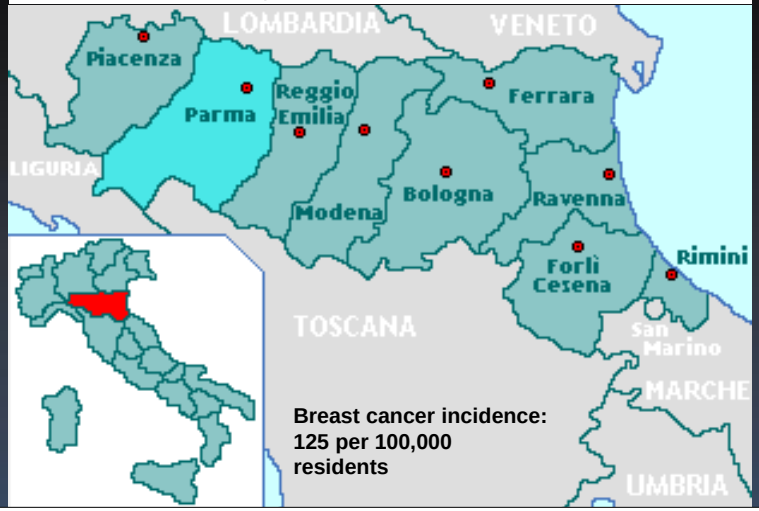
Disease-free Survival by Mode of Breast Cancer Detection

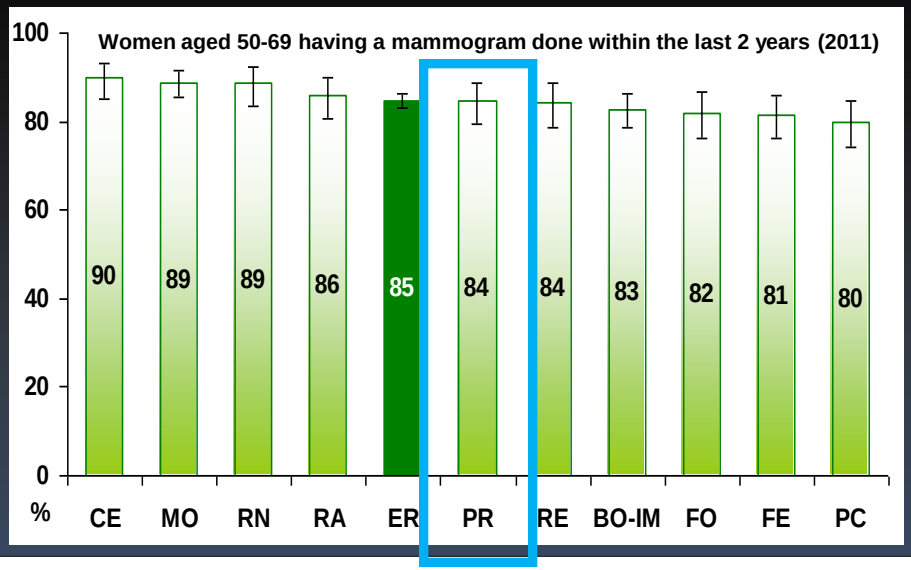


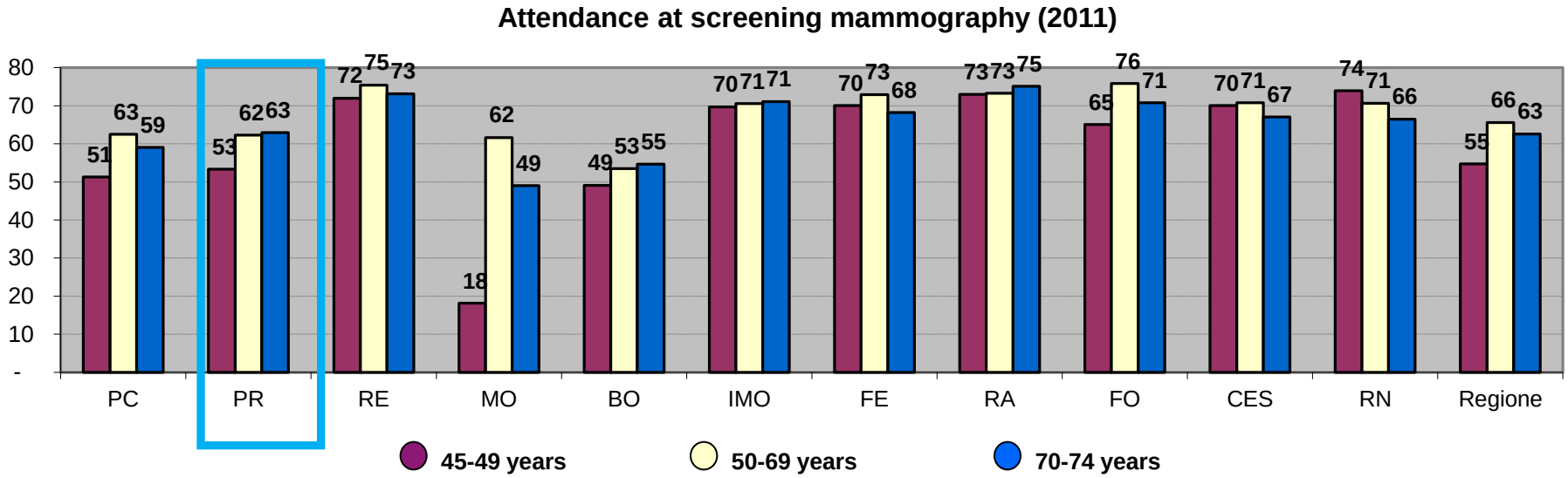
Musolino A. Unpublished data

Parma Province Cancer Registry and Breast Cancer Screening Program

The Province of Parma included a total of 392,976 residents (men, 189,548; women, 203,428) in the 2001 census.[20]

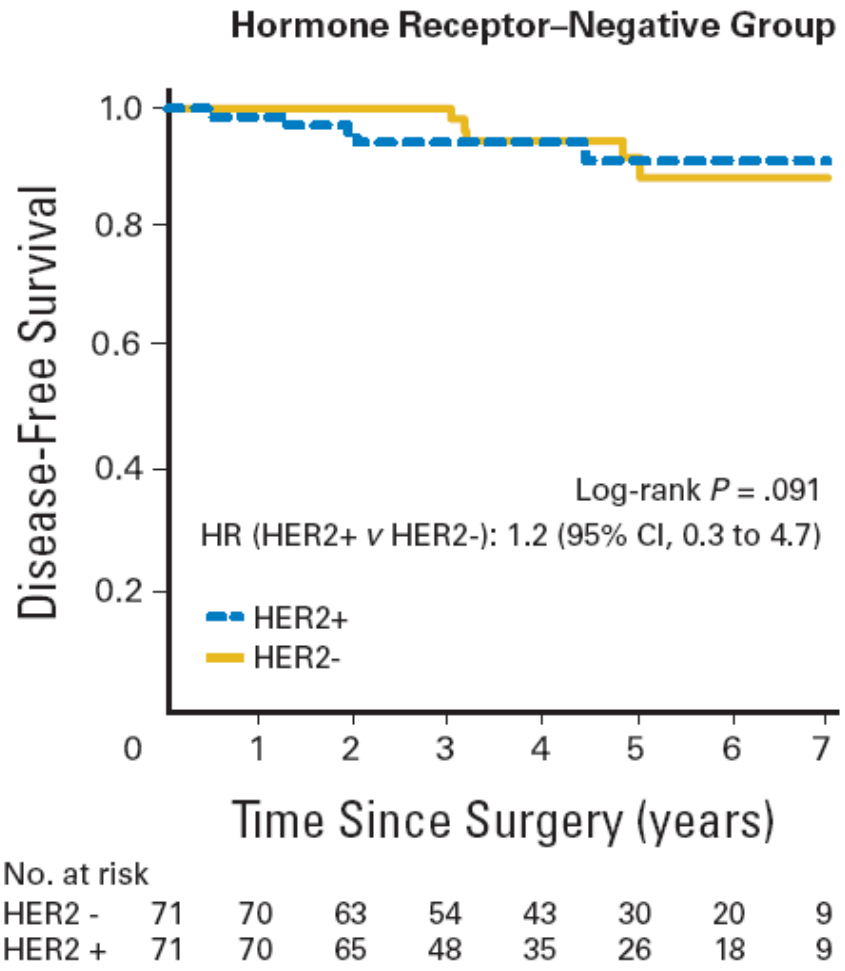


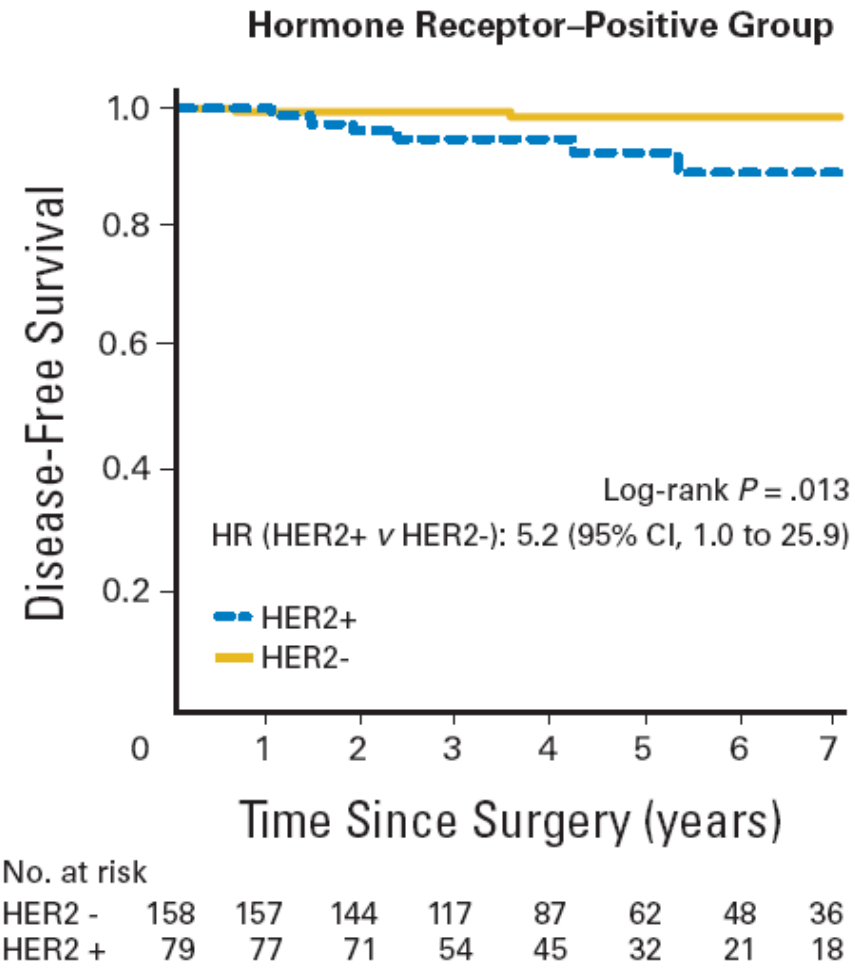




By courtesy of Dr. Carlo Naldoni, Regione Emilia-Romagna Breast Cancer Screening Program

Disease-free survival in patients with pT1a-b N0 M0 Breast cancer by HER2 Status



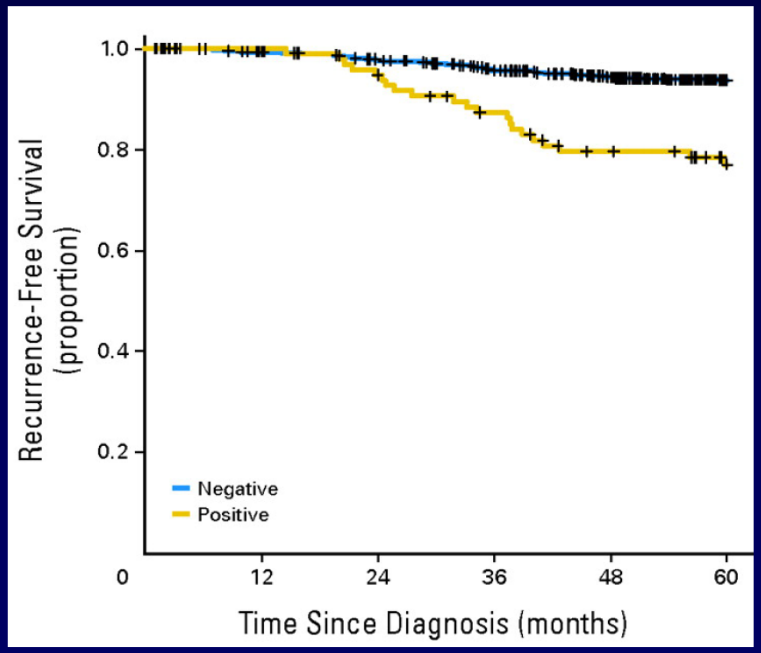


Curigliano. J Clin Oncol 2009

Outcomes for T1a/bN0 HER2+ Tumors

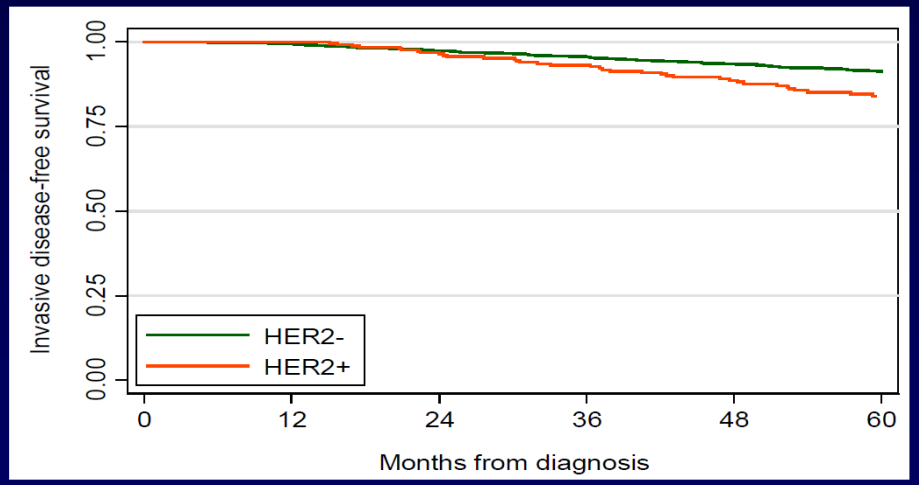
MD Anderson series

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



NCCN series

HER2 status	n	5 yr DFS
HER2+	255	83.3%
HER2-	3127	89.0%



Gonzalez-Angulo AM, et al. *J Clin Oncol.* 2009;27(34):5700-5706. Vaz Duarte Luis IM, et al. *J Clin Oncol.* 2013;31(Suppl): Abstract 1006.

Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

Significant Differences Between Interval- and Screen-Detected Cancers

Author (year)	Number of screen-detected cancers	Number of Interval cancers	Age groups	Screening interval (years)	«True» interval cancer?	Analysis (univariate/ multivariate)	Significant differences
DeGroote (1983)	99	21	30–80	1	Yes	Univariate	Nodal status
Heuser (1984)	32	28	—	1	No	Univariate	Mammography Age
Frisell (1987)	222	60	40–64	2	Yes	Univariate	Tumor size Nodal status
Hatschek (1989)	212	98	40–74	2	No	Univariate	S-phase fraction
Bahnsen (1994)	163	22	36–75	2	No	Univariate[a]	Nodal status
Burrell (1996)	267	82	50–64	Varying	Yes	Univariate	Tumor size Nodal status Tumor grade
Klemi (1997)	385	100	40–74	Varying	No	Univariate	Age Tumor size Nodal status
Raja (2001)	625	230	50–64	3	Yes	Univariate	Tumor size Nodal status Tumor grade
Shen (2005)	712	280	40–64	1	No	Multivariate[b]	Nodal status
Pálka (2008)	258	48	45-65	2	No	Univariate	Tumor stage Tumor grade

[a]Adjusted for tumor size; [b]Adjusted for age and tumor size.

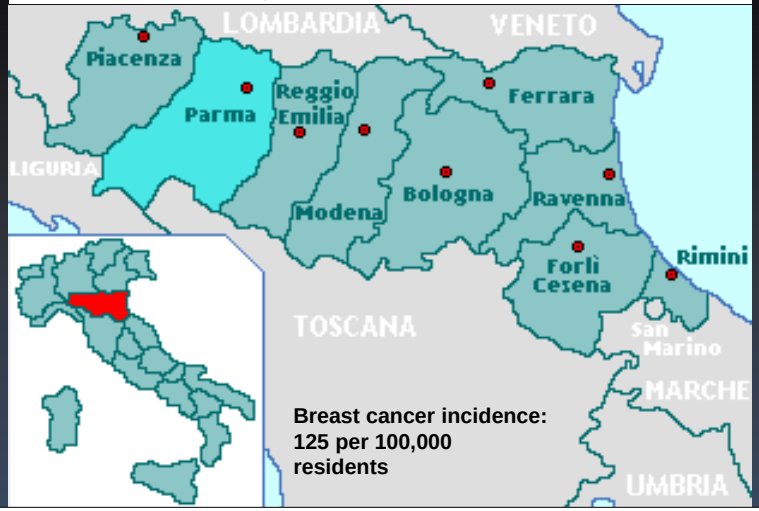
Significant Differences Between Interval- and Screen-Detected Cancers

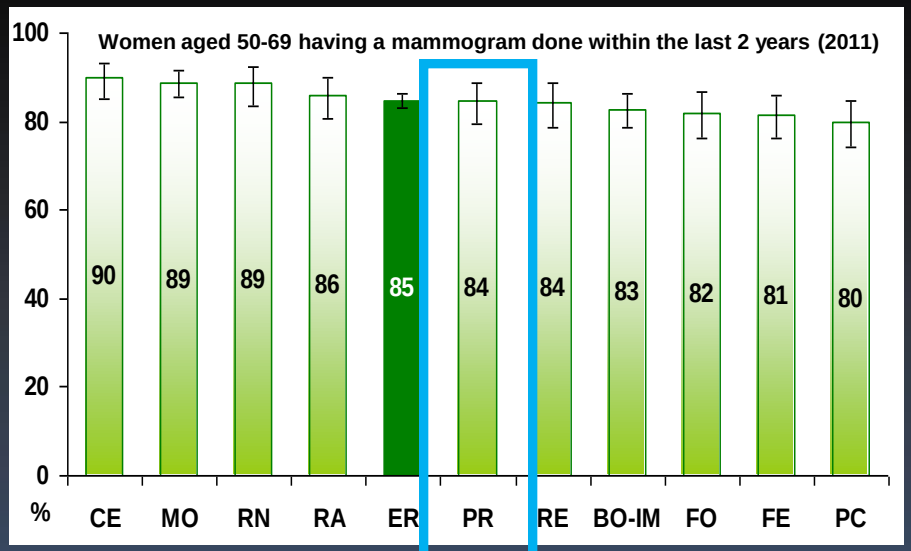
Author (year)	Number of screen-detected Cancers	Number of Interval cancers	Age groups	Screening interval (years)	«True» interval cancer?	Analysis (univariate/ multivariate)	Significant differences
Crosier (1999)	84	51	50–64	3	Yes	Multivariate	ki-67 Her2/neu
Porter (1999)	279	150	40–80	Varying	No	Univariate[a]	Tumor grade ki-67 ER
Gilliland (2000)	64	63	40–80	Varying	No	Multivariate	P53 ki-67
Anttinen (2003)	79	39	> 50	Varying	No	Univariate[a]	Her2/neu
Collettt (2005)	95	95	50-74	2	No	Univariate	Basal-like
der Vegt (2010)	63	36	50–74	2	Yes	Univariate	ER
Domingo (2010)	115	34	50–69	2	Yes	Multivariate[a]	Breast density Triple negative
Kirsh (2011)	450	288	> 50	2	Yes	Univariate[a]	Mitotic score ER/PR
Mook (2011)	958	417	50–69	2	No	Univariate	ER
Chiarelli (2011)	995[b]	362	50–69	2	No	Univariate[a]	Mitotic score
Musolino (2012)	292	48	50–69	2	Yes	Univariate[a]	ki-67/ER Her2/neu
Caldarella (2013)	211	66	50–69	2	No	Multivariate[a]	Triple negative
Pollan (2013)	870	240	45-69	2	Yes	Univariate[a]	Breast density Her2/neu Triple negative

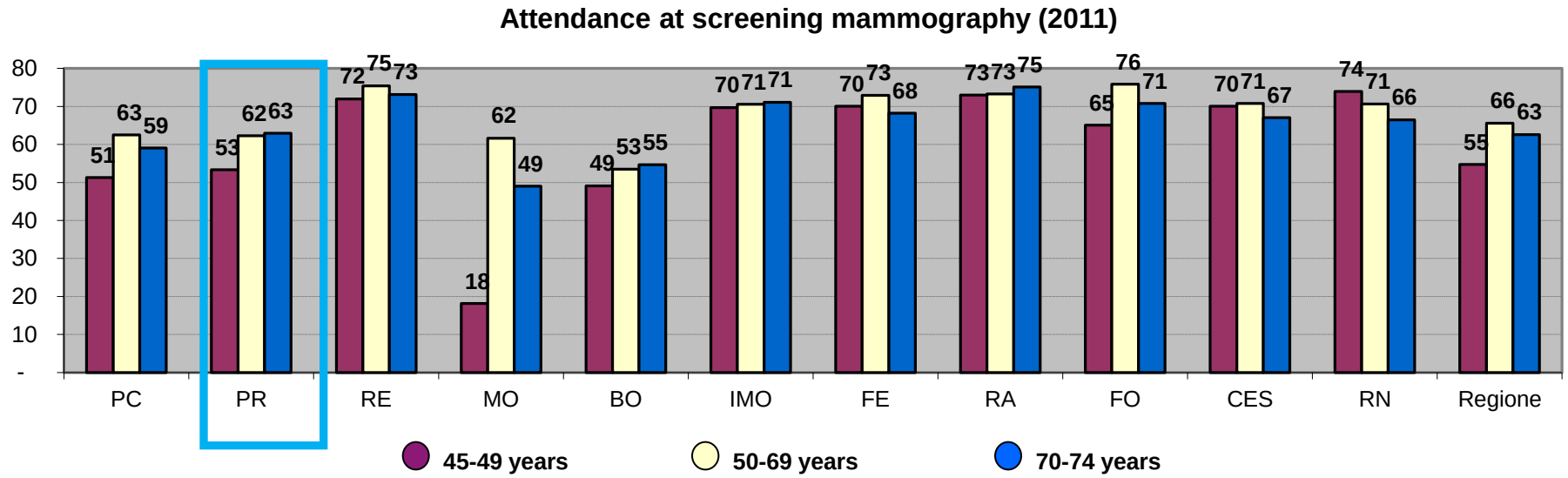
[a]Adjusted for age and tumor size; [b]Rescreen-detected breast cancer.

Parma Province Cancer Registry and Breast Cancer Screening Program

The Province of Parma included a total of 392,976 residents (men, 189,548; women, 203,428) in the 2001 census.[20]







By courtesy of Dr. Carlo Naldoni, Regione Emilia-Romagna Breast Cancer Screening Program

Adjuvant Paclitaxel and Trastuzumab for Node-Negative HER2+ Breast Cancer

Abstract S1-04

Tolaney SM, Barry WT, Dang CT, Yardley DA, Moy B, Marcom PK, Albain KS, Rugo H, Ellis M, Shapira I, Wolff AC, Carey LA, Overmoyer BA, Partridge AH, Guo H, Hudis CA, Krop IE, Burstein HJ, Winer EP

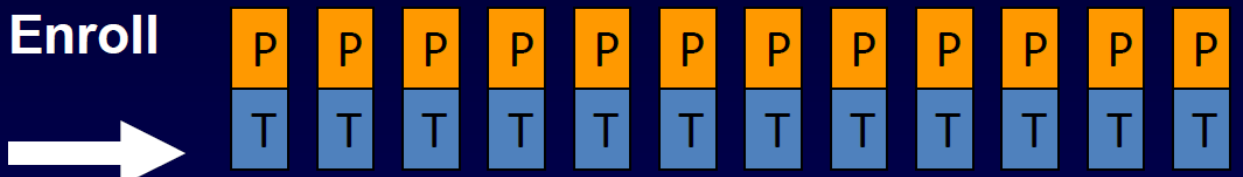
N Engl J Med 2015

Study Design (APT Trial)

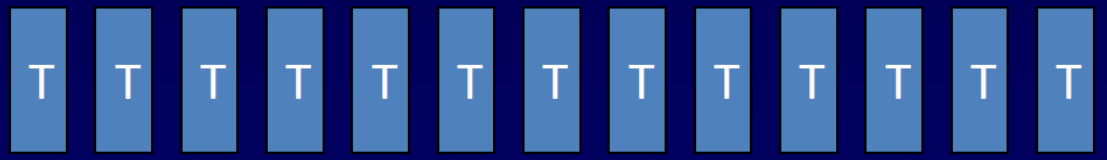
HER2+
ER+ or ER-
node negative
≤3 cm

Planned N = 400

Enroll



PACLITAXEL 80 mg/m² + TRASTUZUMAB 2 mg/kg x 12



FOLLOWED BY 13 EVERY 3 WEEK DOSES
OF TRASTUZUMAB (6 mg/kg)*

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

Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

N Engl J Med 2015

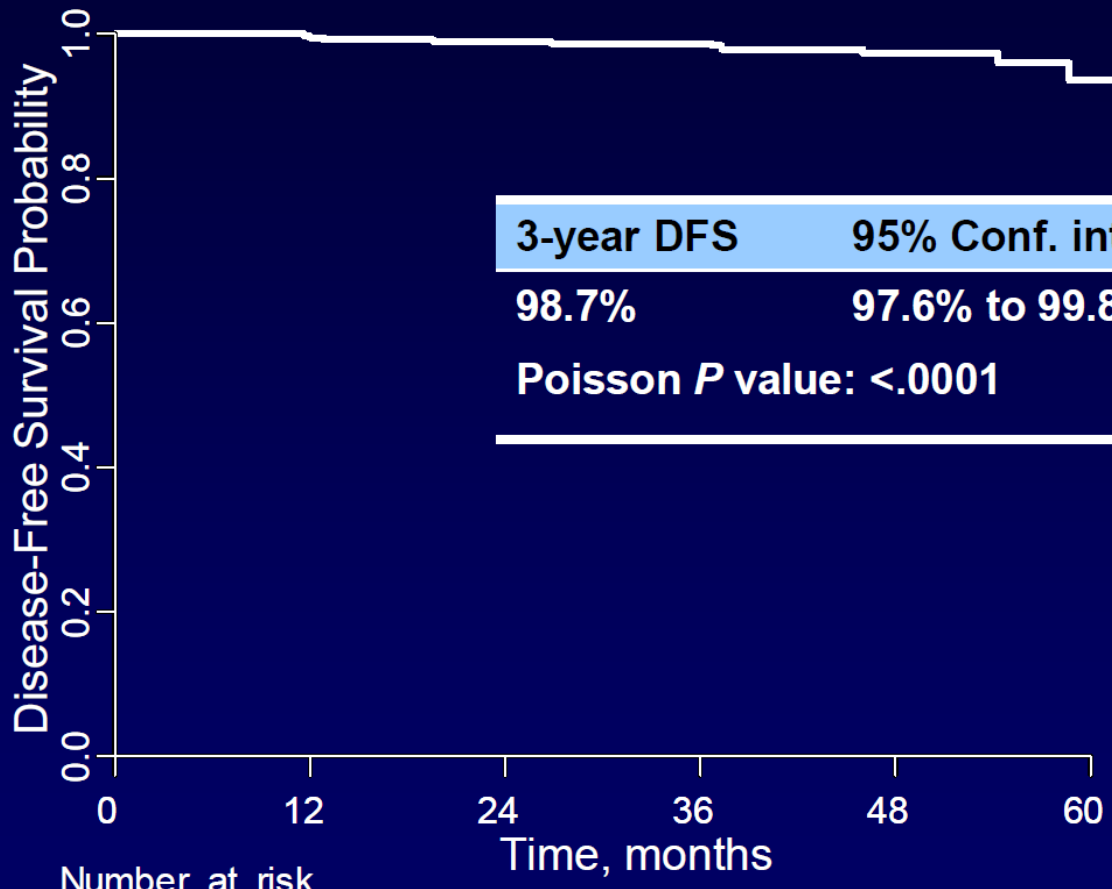
Patient Characteristics

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

Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

N Engl J Med 2015

Disease-Free Survival



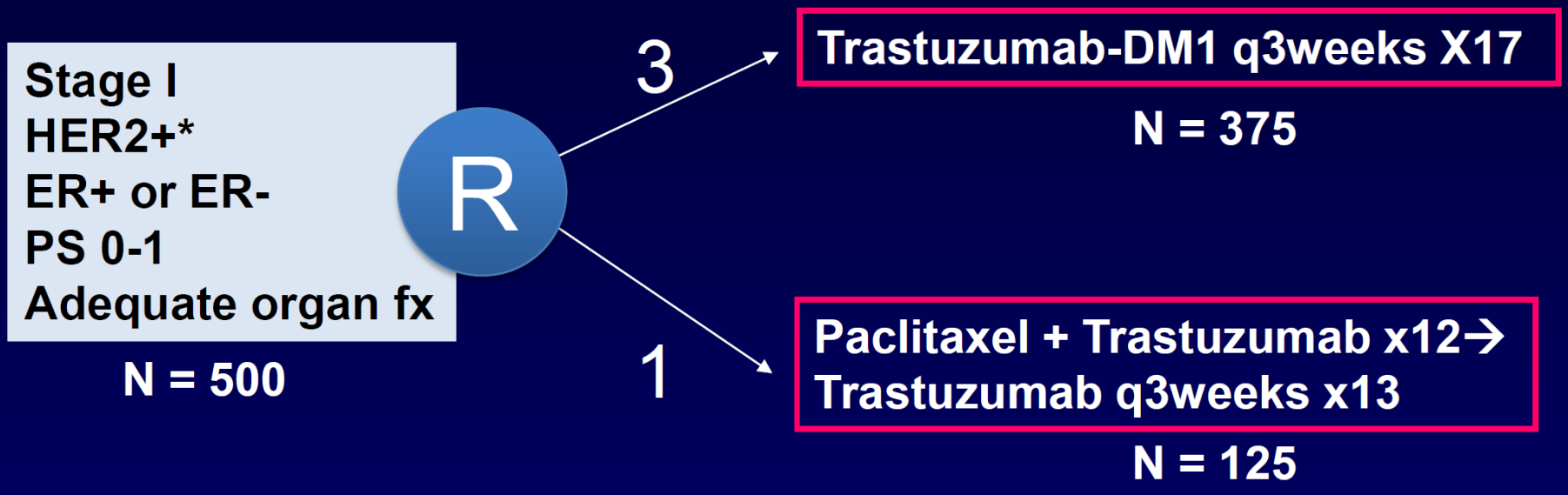
3-year DFS	95% Conf. interval
98.7%	97.6% to 99.8%

Poisson *P* value: <.0001

Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

N Engl J Med 2015

ATEMPT Trial Schema



*HER2-positive defined as IHC 3+ or FISH≥2.0; will be confirmed by central HER2 testing prior to study enrollment

Adjuvant endocrine therapy can be initiated after completion of 12 weeks of therapy.

Adjuvant radiation therapy can be administered concurrently with study treatment.

PI: Sara Tolaney, MD, MPH

Tolaney SM, et al. *Cancer Res.* 2013;73(24 Suppl): Abstract S1-04.

Cox Multivariate Analysis of Overall Survival

Covariate	Hazard Ratio	95% CI	S.E.	Z-score	*P*-Value
Detection outside screening	2.4	1.4-5.9	0.6	1.2	0.04
Hormone receptor negative	3.5	1.2-10.1	0.5	2.3	0.02
HER2+	2.5	1.2-5.2	0.4	2.6	0.009
Advanced tumor stage	7.1	2.5-20.7	0.5	3.6	< 0.001

Musolino A. Unpublished data

Conclusions

- Interval cancers have been shown to be biologically more aggressive than their screen-detected counterparts.
- Molecular subtype distribution of screen-detected breast cancer differs from that of interval cancers and may account, in part, for the better outcome of screen-detected cancer.
- Intervention studies aiming to optimize imaging technologies and screening intervals are warranted to improve the early detection of aggressive, fast-growing, breast cancer phenotypes.
- Screen detection has been found to be independently associated with better overall and breast cancer–specific survival, and the method of detection should be taken into account when estimating individual prognosis.