Post San Antonio 2011
Dr André Robidoux

Essai clinique avec bisphosphonate

- Gnant M et al: **ABCSG-12**
- Paterson AHG et al: **NSABP protocol B-34**
- Mobus V et al: **GAIN study**
- De Boer R et al: **ZO-FAST**

Thérapie néoadjuvante: Relation entre pCR et devenir chez les patientes Her2- et Her2+

- Minckwitz G et al: **GeparTrio Trial**
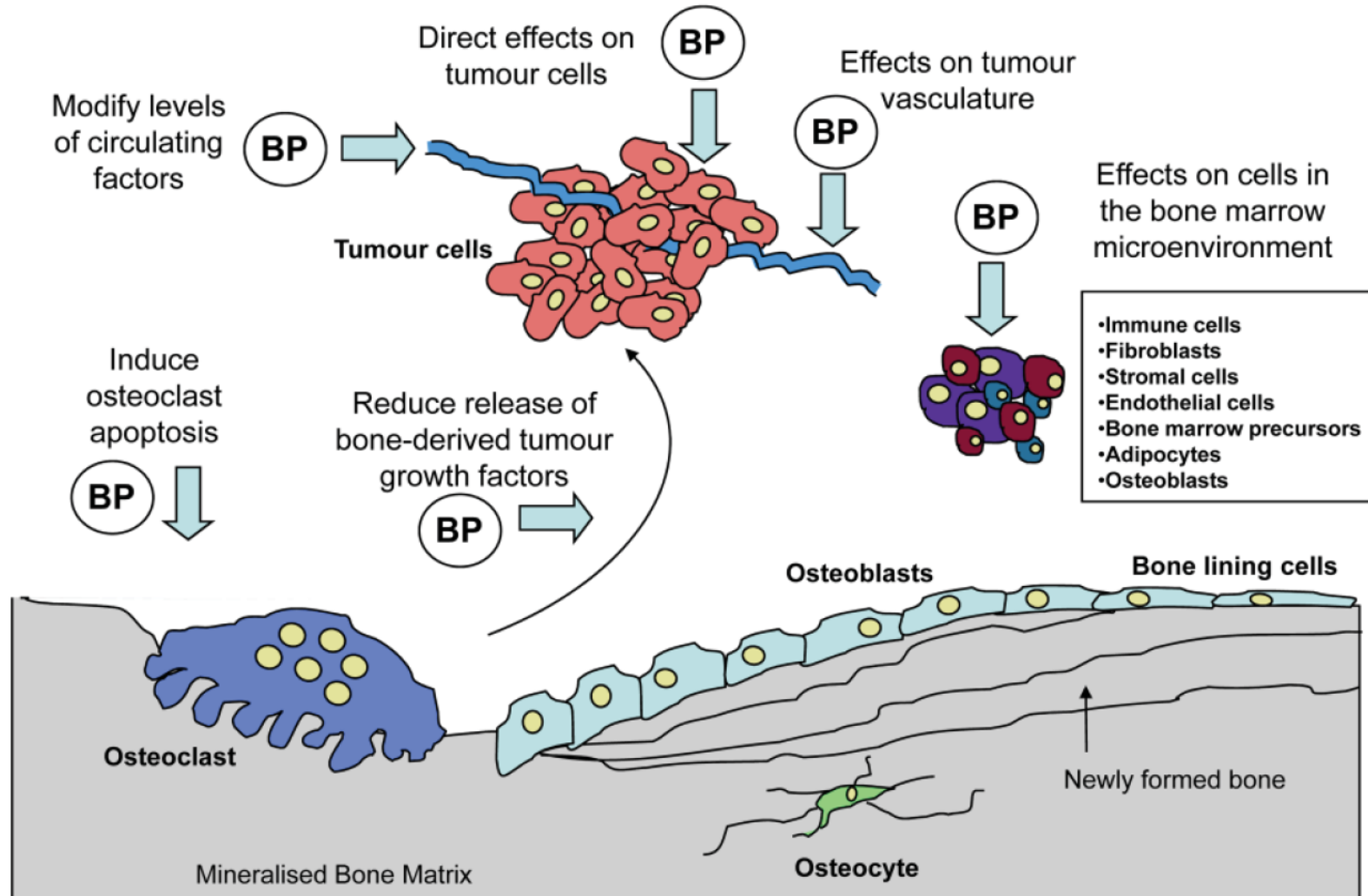- Loibl S et al: **Metanalysis of the German Oncology Group**

Oncotype Dx: DCIS recurrence score

- Solin LJ et al: DCIS recurrence score based on the results of ECOG5194
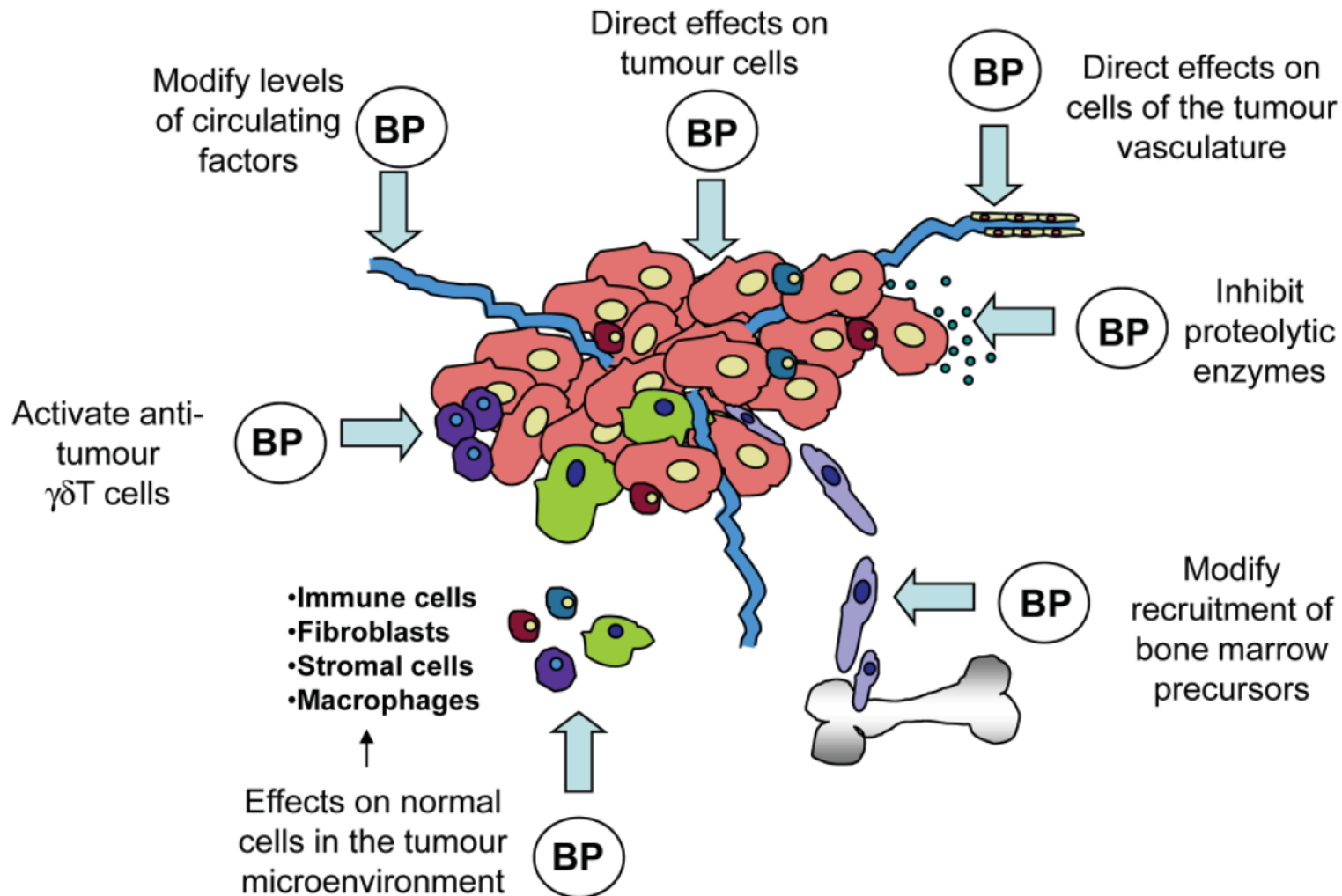
Overall Structure of Bisphosphonates

Osteoclast

R_2 Chain

PO_3H_2

R_1 Chain

C

PO_3H_2
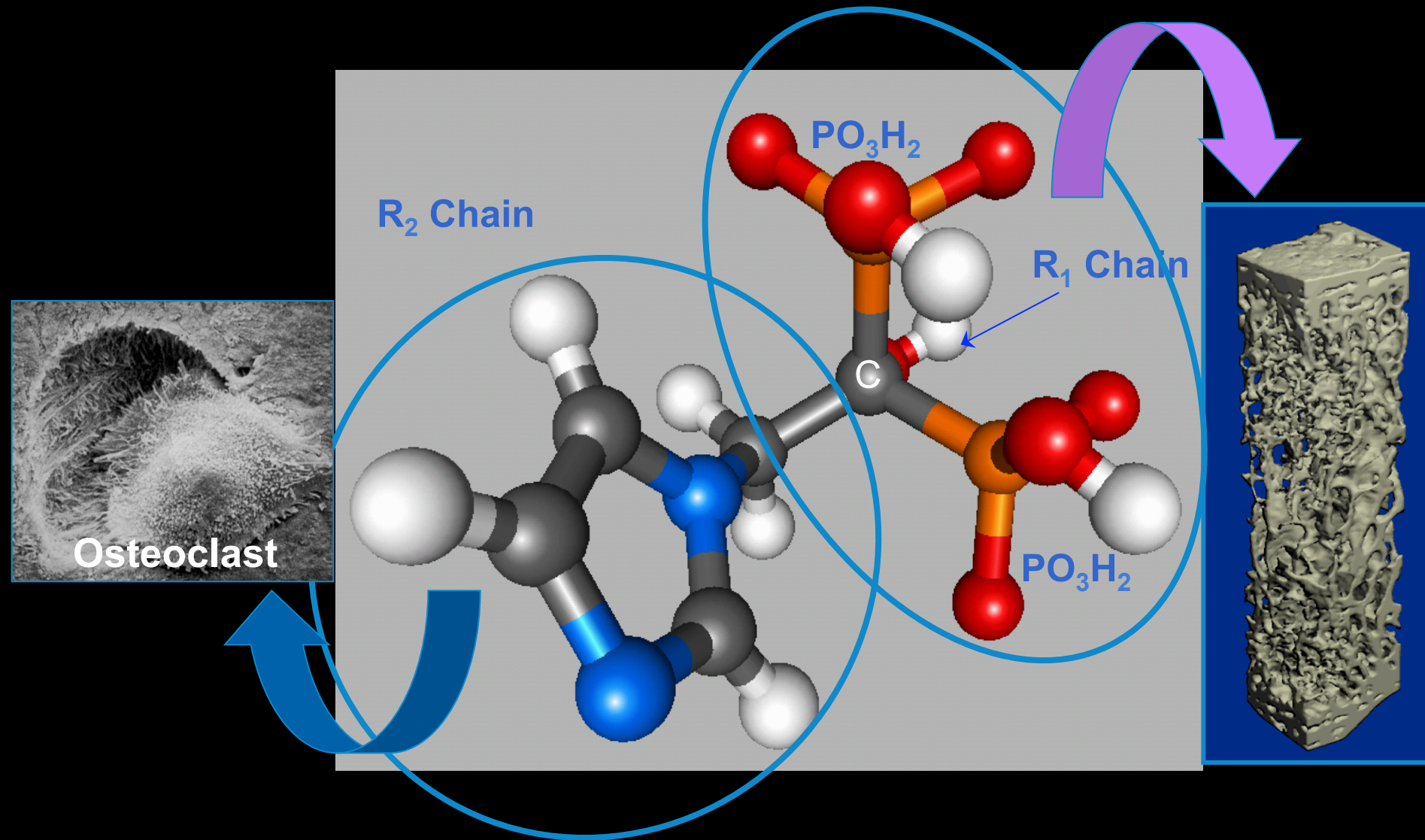
Multiple Potential Anti-tumor Effects of Bisphonates in Bone

Holan and Coleman, Breast Cancer Res 2010;12:214

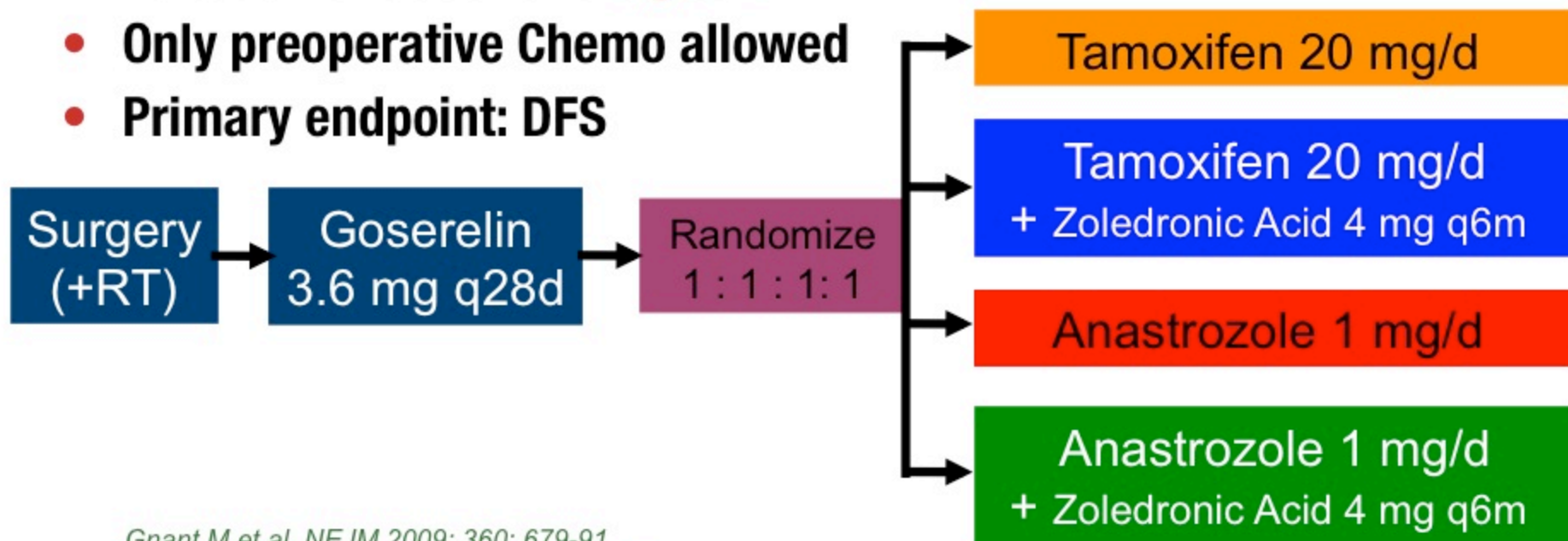# Potential Anti-tumor Effects of Bisphosphonates Outside the Skeleton

Holan and Coleman Breast Cancer Res 2010;12:214

ABCSG-12 Trial Design

- **Recruitment 1999-2006**
- **1,803 premenopausal patients**
- **Stage I&II, ER+ and/or PgR+**
- **Duration of treatment: 3 years**
- **Only preoperative Chemo allowed**
- **Primary endpoint: DFS**

Surgery (+RT) → Goserelin 3.6 mg q28d → Randomize 1 : 1 : 1 : 1

- Tamoxifen 20 mg/d
- Tamoxifen 20 mg/d + Zoledronic Acid 4 mg q6m
- Anastrozole 1 mg/d
- Anastrozole 1 mg/d + Zoledronic Acid 4 mg q6m

Gnant M et al. NEJM 2009; 360: 679-91
Gnant M et al. Lancet Oncol 2008; 9: 840-9
Gnant M et al. ASCO 2010 Proceedings; abs #533
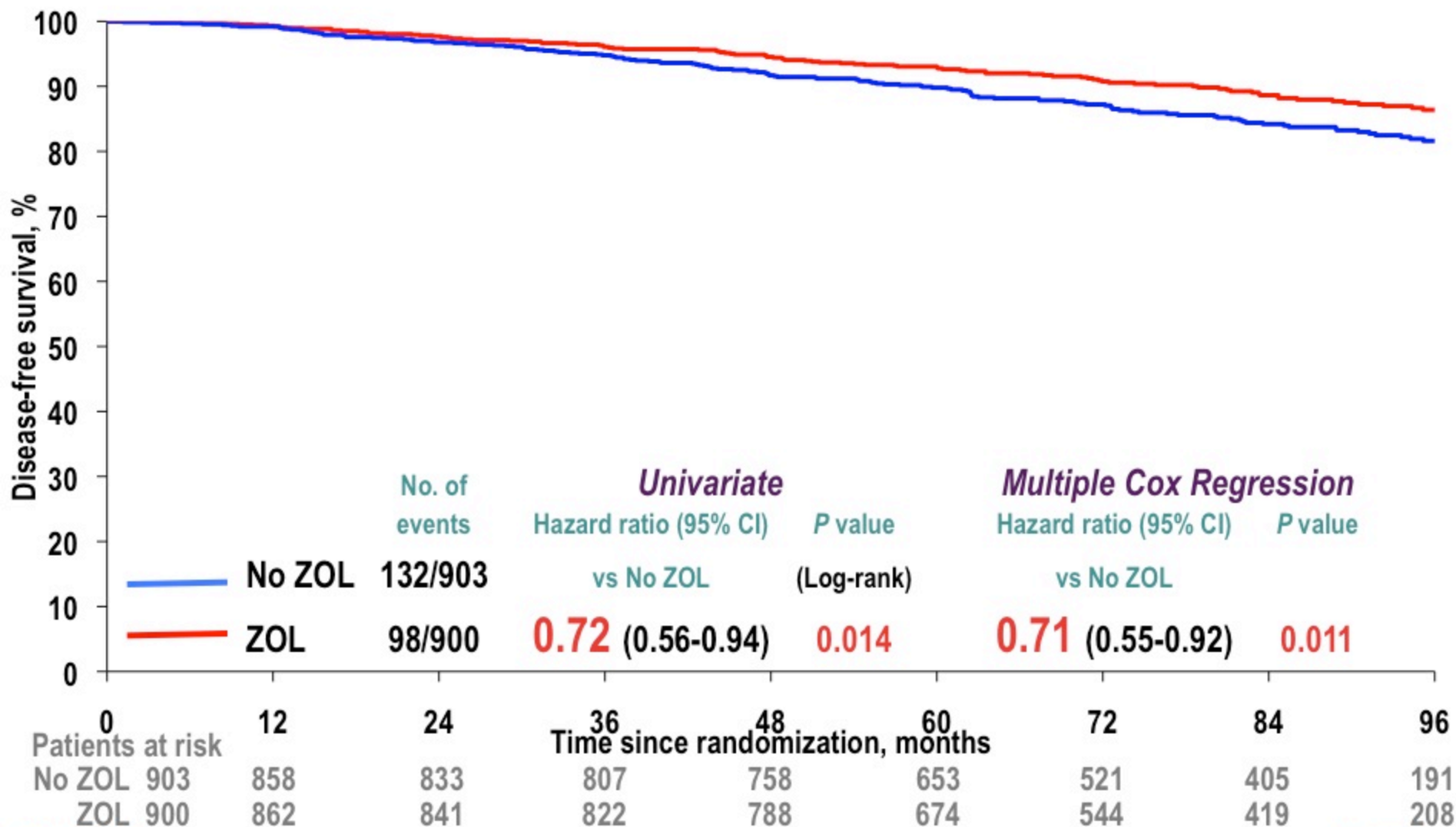Gnant M et al. Lancet Oncol 2011; 12: 631-41
Gnant M et al. ASCO 2011 Proceedings; abs #520

Patients

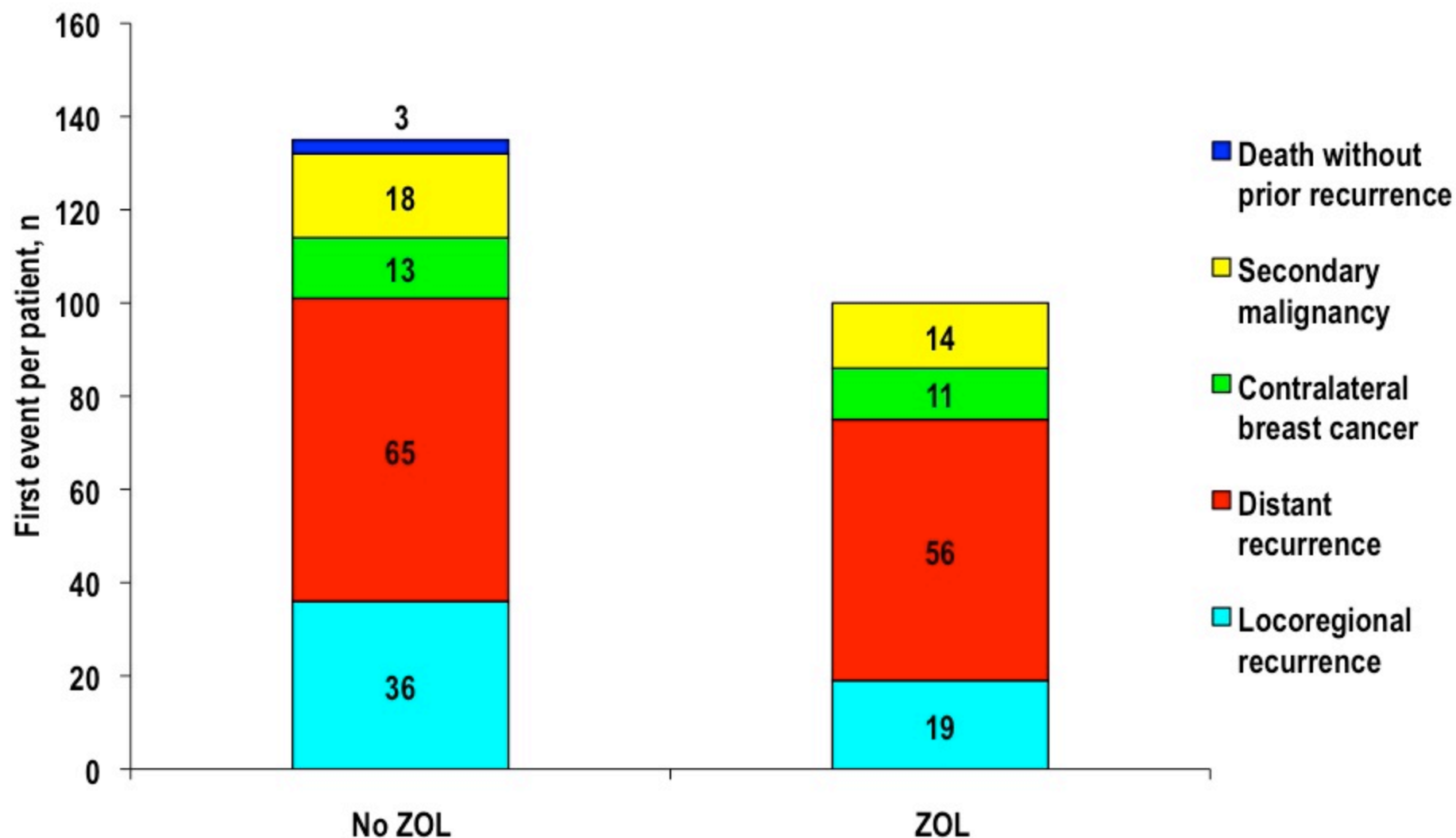|	All patients (n = 1,803)	TAM (n = 450)	TAM+ZOL (n = 450)	ANA (n = 453)	ANA+ZOL (n = 450)
Median age, y (range)	45 (25-58)	45 (27-56)	45 (27-54)	44 (25-58)	44 (28-56)
≤ 40 y, n (%)	413 (22.9)	101 (22.4)	84 (18.7)	112 (24.7)	116 (25.8)
> 40 y, n (%)	1390 (77.1)	349 (77.6)	366 (81.3)	341 (75.3)	334 (74.2)
Tumor stage, n (%)					
T1	1375 (76.3)	341 (75.8)	339 (75.3)	352 (77.7)	343 (76.2)
≥T2	386 (21.4)	98 (21.8)	97 (21.6)	93 (20.5)	98 (21.8)
Nodal status, n (%)					
Negative	1211 (67.2)	305 (67.8)	298 (66.2)	304 (67.1)	304 (67.6)
Positive	550 (30.5)	134 (29.8)	138 (30.7)	141 (31.1)	137 (30.4)
Histological grading, n (%)					
1,2,x	1381 (76.6)	346 (76.9)	347 (77.1)	347 (76.6)	341 (75.8)
3	352 (19.5)	85 (18.9)	85 (18.9)	89 (19.6)	93 (20.7)
Estrogen receptor, n (%)					
Negative	67 (3.7)	16 (3.6)	20 (4.4)	14 (3.1)	17 (3.8)
+	223 (12.4)	50 (11.1)	62 (13.8)	54 (11.9)	57 (12.7)
++	645 (35.8)	169 (37.6)	151 (33.6)	170 (37.5)	155 (34.4)
+++	826 (45.8)	204 (45.3)	203 (45.1)	207 (45.7)	212 (47.1)

Primary Endpoint: Disease-Free Survival
Zoledronic Acid Significantly Improves DFS Compared With Endocrine Therapy Alone

	No. of events	Univariate Hazard ratio (95% CI) vs No ZOL	P value (Log-rank)	Multiple Cox Regression Hazard ratio (95% CI) vs No ZOL	P value
No ZOL	132/903				
ZOL	98/900	0.72 (0.56-0.94)	0.014	0.71 (0.55-0.92)	0.011

Patients at risk

Time since randomization, months	0	12	24	36	48	60	72	84	96
No ZOL	903	858	833	807	758	653	521	405	191
ZOL	900	862	841	822	788	674	544	419	208

First DFS Events (ITT Population)

Zoledronic acid reduced disease recurrence at all sites

ABCSG-12 @ 48, 62, 76, and 84 months:
ZOL Significantly Improved DFS *vs.* no ZOL in All Analyses

48 months	62 months	76 months	84 months
HR = 0.74	HR = 0.68	HR = 0.73	HR = 0.72
p=0.01	p=0.008	p=0.02	p=0.01

— ZOL
— No ZOL

Shown are Kaplan-Meier analyses of DFS at median follow-up of 48, 62, 76, and 84 months, respectively. Abbreviations: CI, confidence interval; DFS, disease-free survival; ZOL, zoledronic acid.

Gnant M et al. NEJM 2009; 360: 679-91
Gnant M et al. ASCO 2010 Proceedings; abs #533
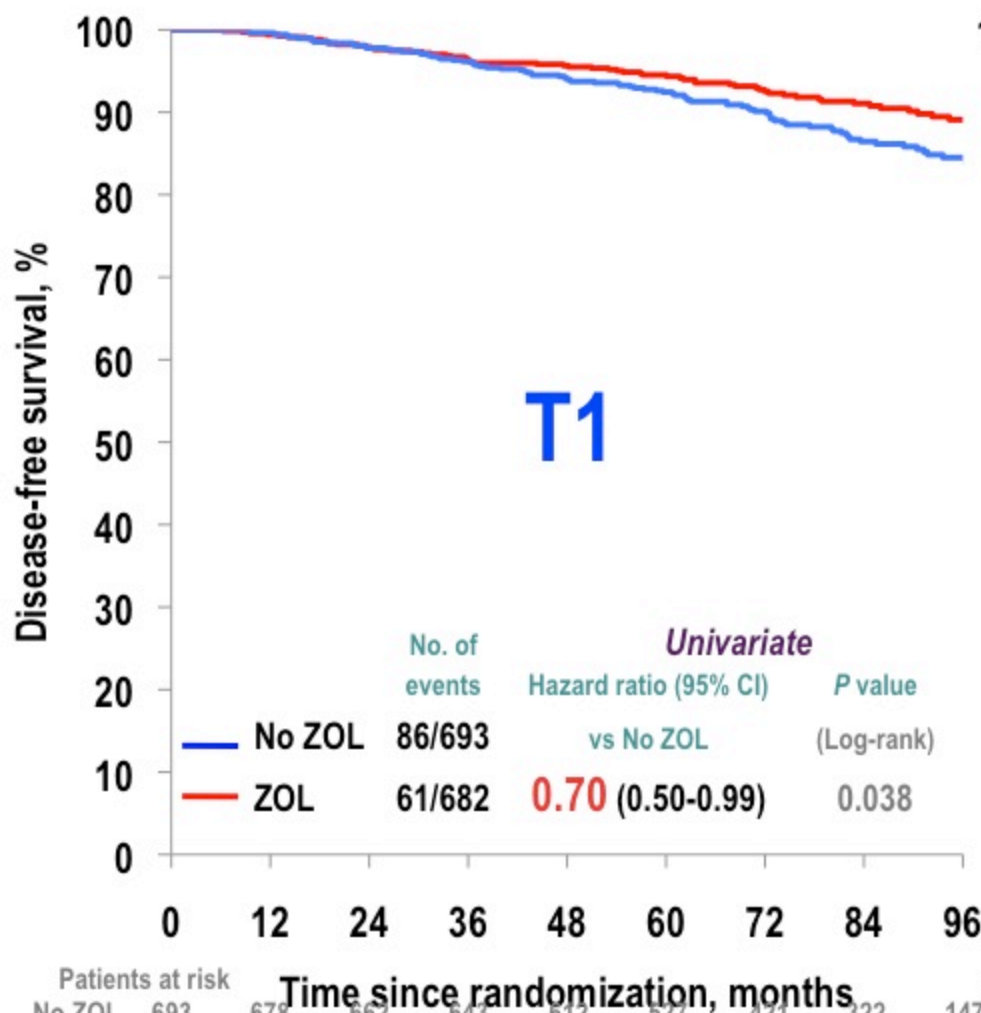Gnant M et al. Lancet Oncol 2011; 12: 631-41
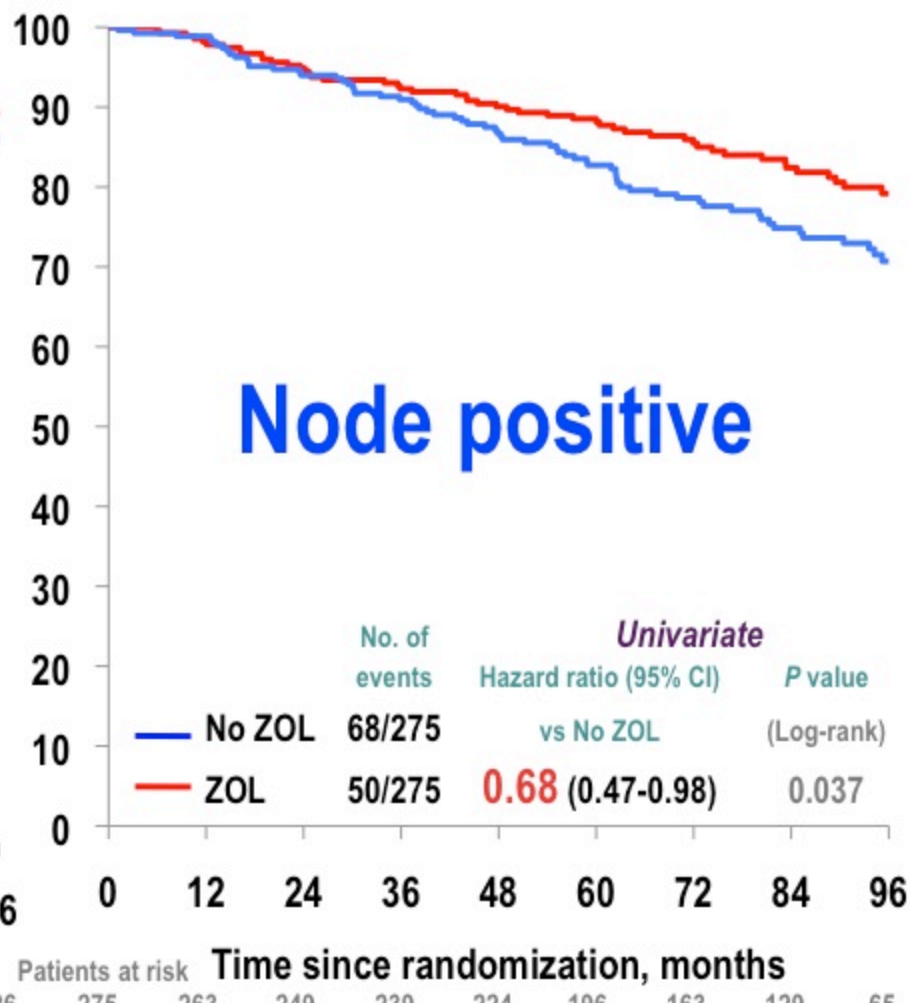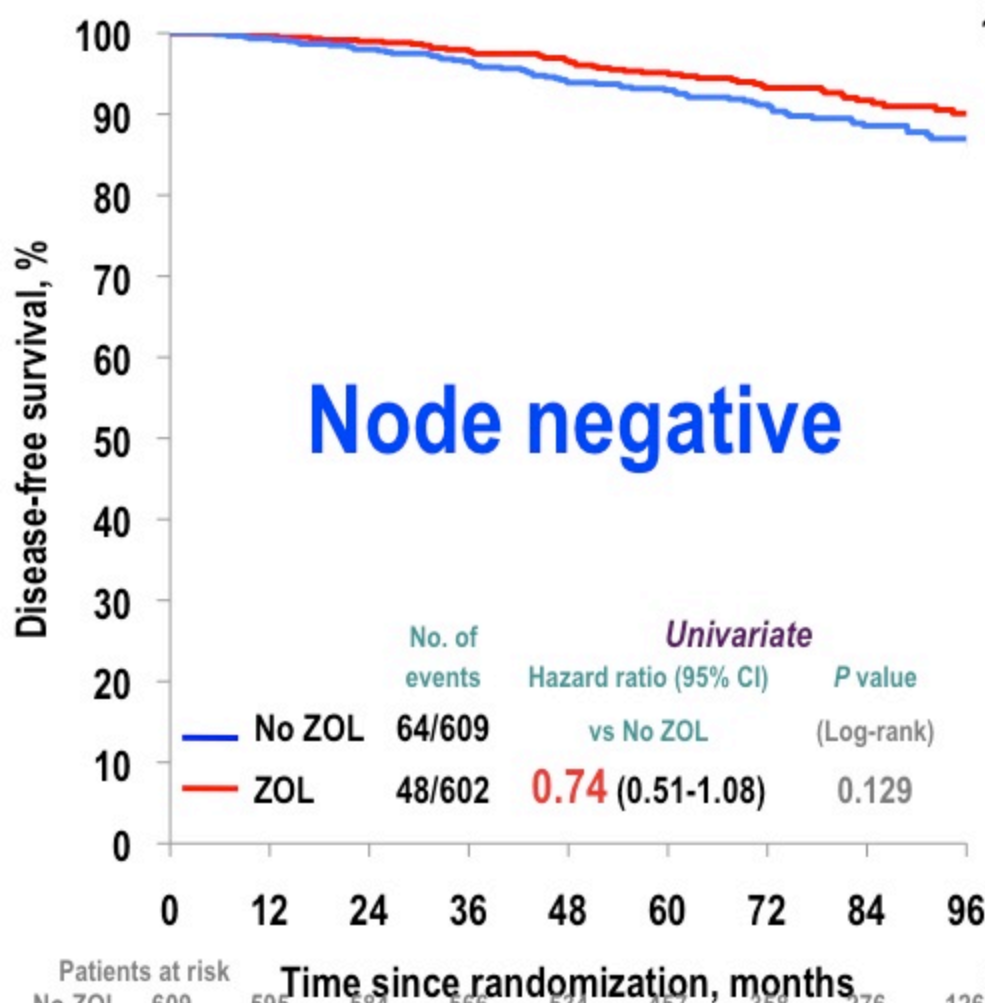Gnant M et al. ASCO 2011 Proceedings; abs #320

ZOL *vs.* No ZOL in T1 and T2/3
Disease-Free Survival

T1

	No. of events	Univariate		
		Hazard ratio (95% CI) vs No ZOL	P value (Log-rank)
No ZOL	86/693		
ZOL	61/682	**0.70** (0.50–0.99)	0.038

T2/3

	No. of events	Univariate		
		Hazard ratio (95% CI) vs No ZOL	P value (Log-rank)
No ZOL	43/182		
ZOL	34/186	**0.69** (0.44–1.09)	0.109

Time since randomization, months

Patients at risk									
No ZOL	693	678	662	643	612	527	421	322	
ZOL	682	669	654	639	617	529	428	329	

Patients at risk									
	147	182	171	163	154	139	120	95	78	41
	156	186	185	179	175	165	140	111	85	48

ZOL *vs.* No ZOL in N- and N+ Cohorts
Disease-Free Survival

ZOL *vs.* No ZOL in ANA and TAM Cohorts

Disease-Free Survival

ANA

	No. of events	Univariate Hazard ratio (95% CI) vs No ZOL	P value (Log-rank)
No ZOL	71/453		
ZOL	52/450	**0.71** (0.49-1.01)	0.057

Patients at risk

No ZOL	453	430	416	404	379	329	259	205	99
ZOL	450	436	427	417	397	342	279	209	103

TAM

	No. of events	Univariate Hazard ratio (95% CI) vs No ZOL	P value (Log-rank)
No ZOL	61/450		
ZOL	46/450	**0.73** (0.50-1.08)	0.121

Patients at risk

	450	428	417	401	379	324	262	200	92
	450	426	414	405	391	332	265	210	105

Time since randomization, months

ZOL *vs.* No ZOL by Age (≤40 and >40)

Disease-Free Survival

Age ≤ 40

	No. of events	Univariate Hazard ratio (95% CI) vs No ZOL	*P* value (Log-rank)
No ZOL	42/213		
ZOL	35/200	**0.87** (0.55-1.36)	0.525

Age > 40

	No. of events	Univariate Hazard ratio (95% CI) vs No ZOL	*P* value (Log-rank)
No ZOL	90/690		
ZOL	63/700	**0.66** (0.48-0.92)	0.013
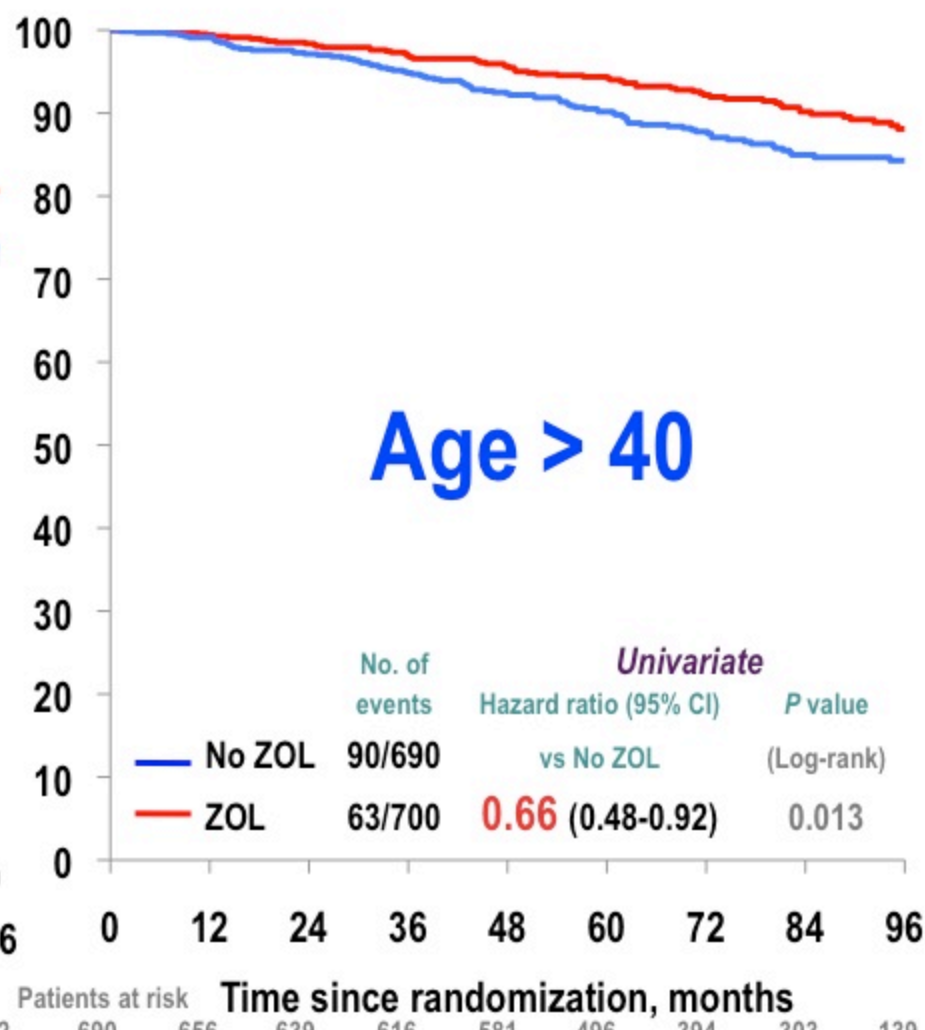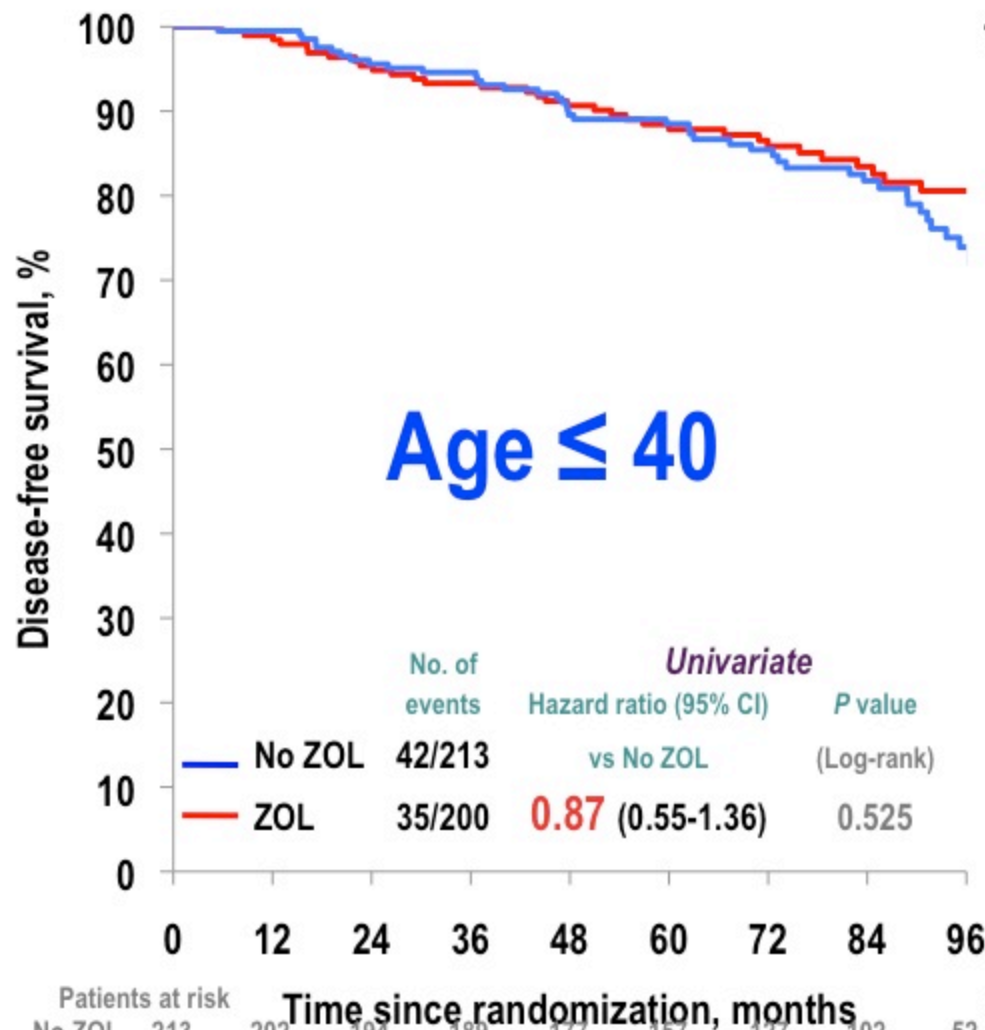
Patients at risk

No ZOL	213	202	194	189	177	157	127	102	52
ZOL	200	192	185	180	169	148	125	94	48

Patients at risk

No ZOL	690	656	639	616	581	496	394	303	139
ZOL	700	670	656	642	619	526	419	325	160

Overall Survival: All Patients

Adjuvant endocrine therapy based on ovarian function suppression yields excellent results in premenopausal patients with HR-positive breast cancer

3-yr OS
99.1%

5-yr OS
97.5%

7-yr OS
95.5%

Overall survival, %

Time since randomization, months

Patients at risk
1803 1732 1714 1688 1629 1413 1162 909 446
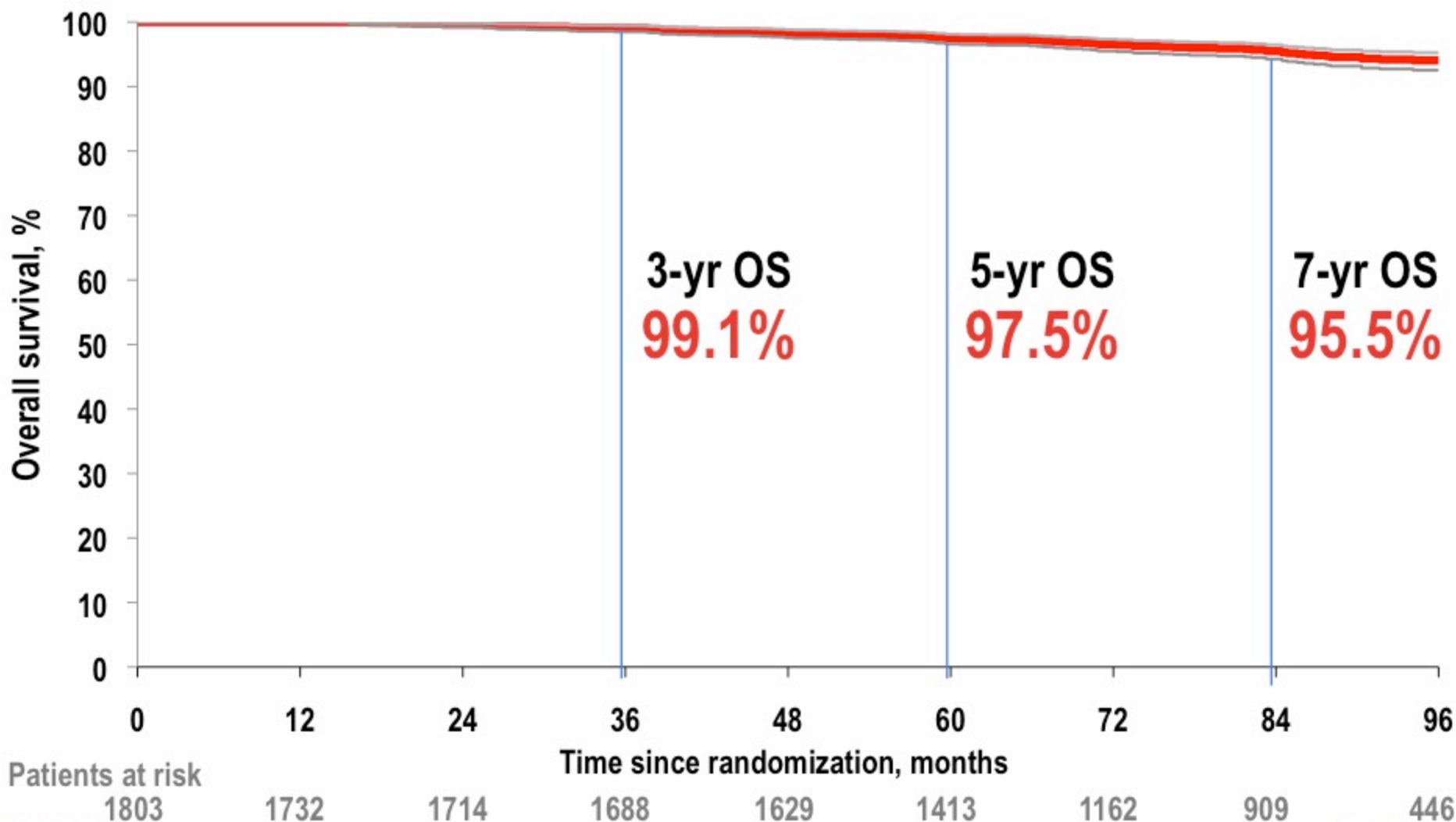
Overall Survival: Zol *vs* No ZOL

Zoledronic Acid Improves OS Compared With Endocrine Therapy Alone

Overall survival, %

	No. of events	Univariate		Multiple Cox Regression	
		Hazard ratio (95% CI) vs No ZOL	P value (Mantel-Cox)	Hazard ratio (95% CI) vs No ZOL	P value
No ZOL	49/903				
ZOL	33/900	**0.63** (0.40-0.99)	0.049	**0.61** (0.39-0.96)	0.033

Time since randomization, months

Patients at risk	0	12	24	36	48	60	72	84	96
No ZOL	903	864	856	839	811	706	576	456	215
ZOL	900	868	858	849	818	708	587	454	232
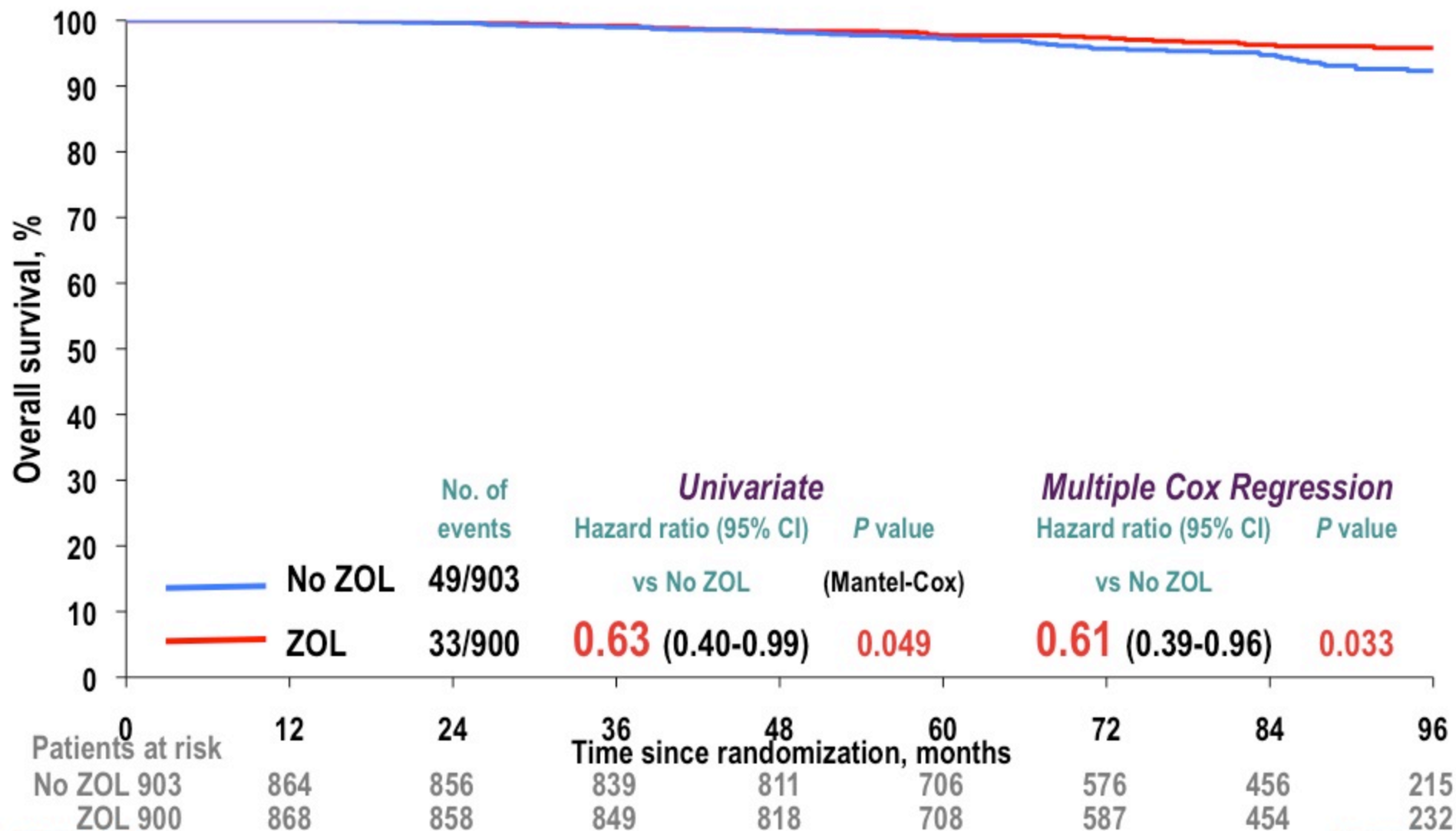
Summary

- **Overall survival >95% at 7 years of median follow-up supports the efficacy of endocrine therapy (without chemotherapy) in this premenopausal patient population**

- **DFS benefits of adjuvant ZOL, first observed at 48 months, are maintained (⇧28%) at 84 months (up to 4-5 years posttreatment) and now extend to OS (⇧37%), suggesting a sustained anticancer effect**

  - **Reassuring tolerability of ZOL in this study**

- **DFS and OS benefits are driven by patients >40 years old, suggesting that anticancer effects may be greatest in patients achieving maximal estrogen blockade**

B-34 Study Design

STRATIFICATION

- **Age (< 50, ≥ 50)**
- **Number of Positive Nodes (0, 1-3, 4+)**
- **ER / PgR Status**

RANDOMIZATION

GROUP 1
Clodronate*
1600 mg/day
x 3 years

GROUP 2
Placebo*
x 3 years

*At the discretion of the investigator, patients may receive adjuvant systemic chemotherapy and/or tamoxifen, or no adju

Study Population
3323 Patients Randomized

Characteristic	Placebo	Clodronate
Number randomized	1661	1662
Number ineligible	31	23
Number without follow-up	5	7
Number with follow-up	1656	1655
Median time on study (years)	8.41	8.41

Patient Characteristics (%)

Characteristic*	Placebo N=1661	Clodronate N=1662
Age at entry (years)†		
≤49	35.5	35.7
≥50	64.5	64.3
Race		
White	82.8	83.1
Black	7.6	7.0
Hispanic	5.4	5.8
Other	4.2	4.1
Number of positive nodes†		
Negative	75.4	75.7
1 – 3	17.8	17.8
4 or more	6.9	6.5
ER/PgR status†		
Both Negative	22.2	22.1
ER and/or PgR Positive	77.8	77.9
Adjuvant Therapy		
No adjuvant therapy	3.2	3.2
Chemotherapy only	21.0	20.7
Endocrine therapy only	31.9	31.6
Chemo and endocrine therapy	43.9	44.5

* Values are based on all patients entered into the study unless otherwise specified
† As reported at the time of randomization.

% on Protocol Therapy by Time
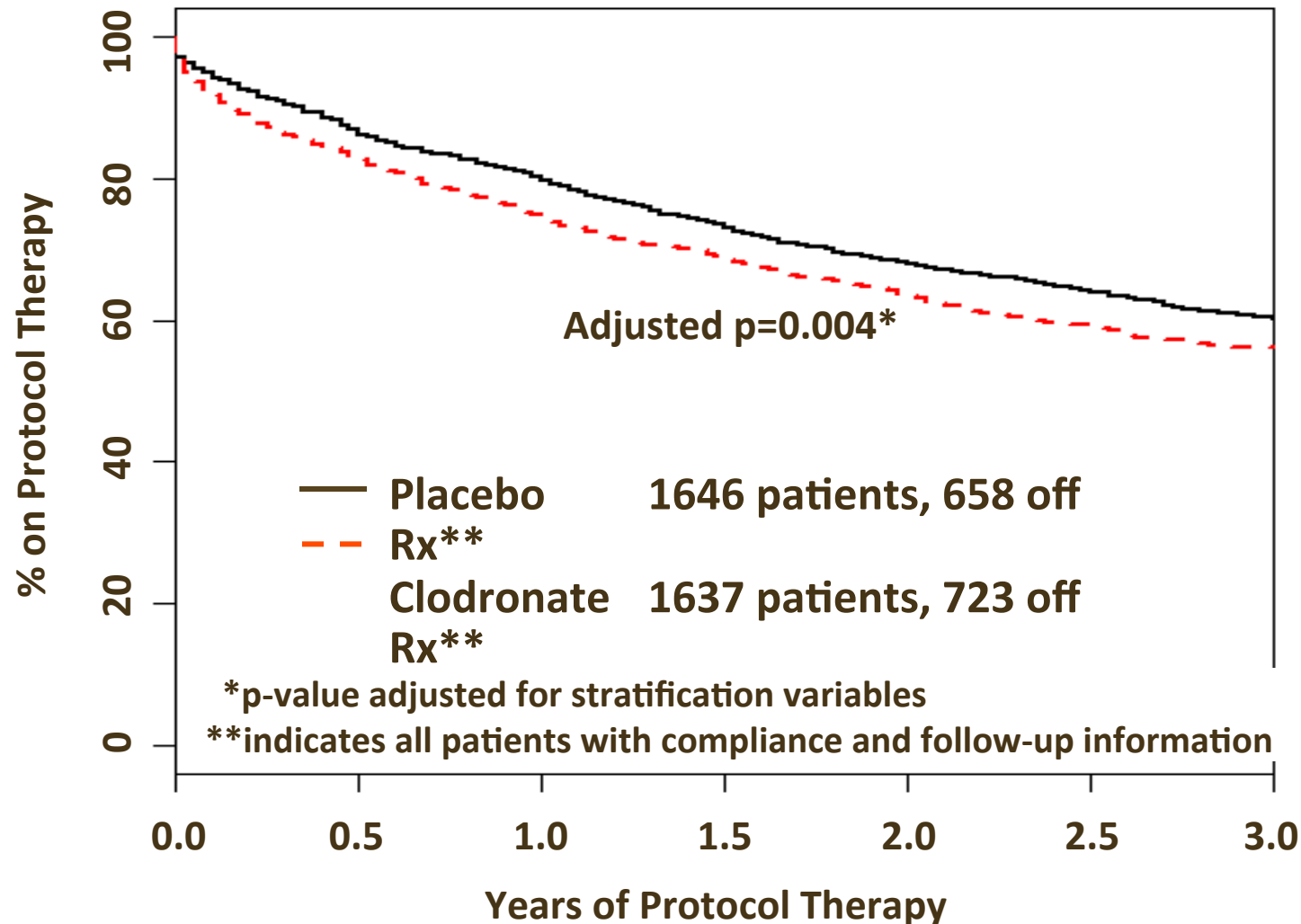
Toxicities and Side Effects (%)

Toxicity Grades	Clodronate N=1612			Placebo N=1623		
	3	4	5	3	4	5
Overall Toxicity	15	5	<1	14	7	1
Diarrhea	2	<1	0	1	0	0
SGOT/SGPT	<1	<1	0	<1	<1	0
Hypocalcemia	<1	0	0	<1	0	0
Creatinine	<1	<1	0	0	0	0
Thrombosis/Embolism	1	<1	0	1	1	0
Pancreatitis	<1	0	0	<1	0	0
Osteonecrosis of jaw	*1 case*			*0 cases*		
Death (cause unknown)	*1 case*			*5 cases*		

Time to Event Endpoints

ENDPOINT	ENDPOINT Abbrev.	Definition of Event
Disease free survival*	DFS	All recurrences, deaths and 2nd primary cancers
Overall survival**	OS	All deaths
Recurrence free interval**	RFI	All recurrences
Bone metastasis free interval**	BMFI	All skeletal metastases
Non-bone metastasis free interval**	NBMFI	All non-skeletal metastases

*Primary endpoint
**Specified secondary endpoints
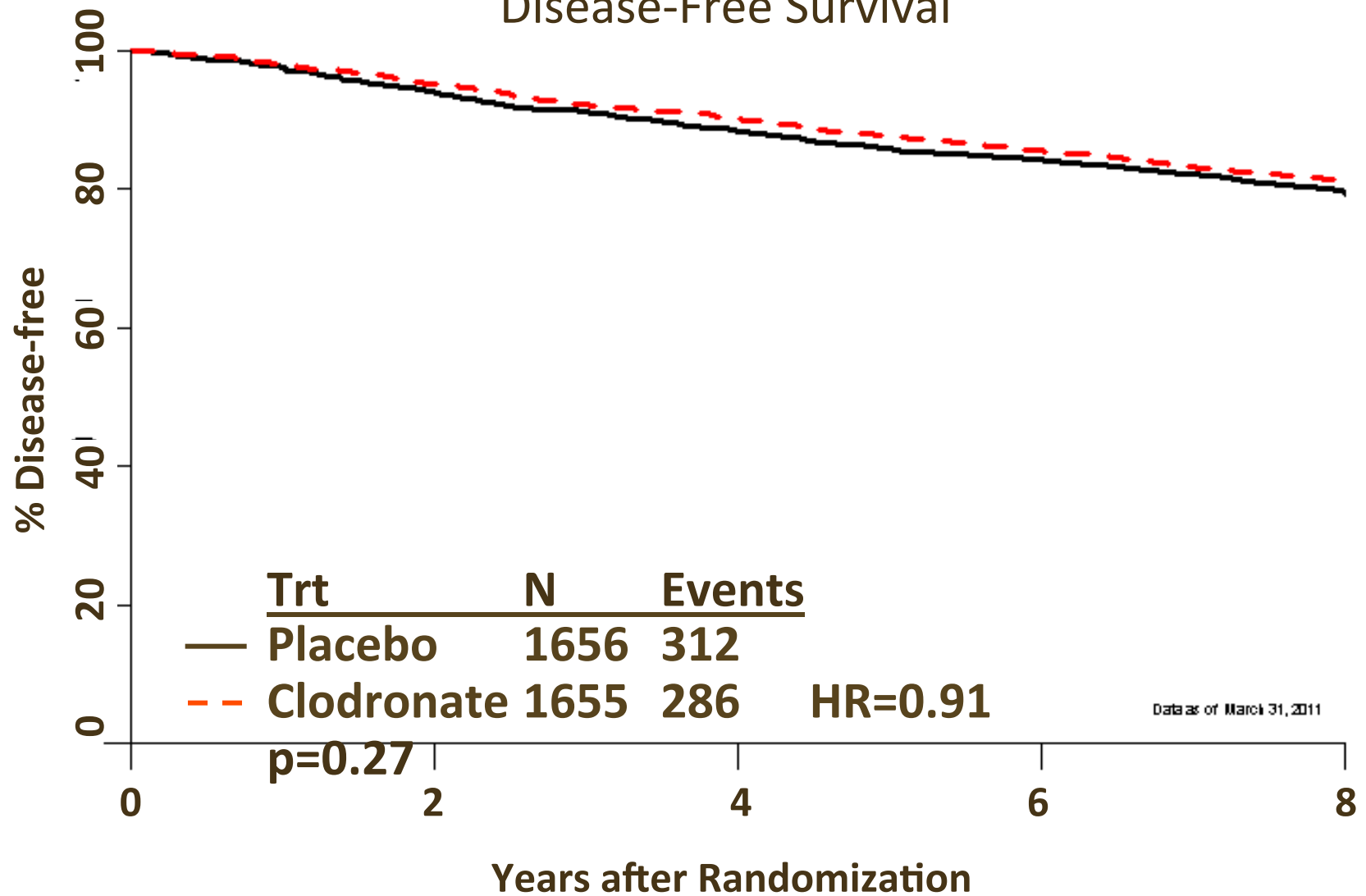
Analyses of Specified Endpoints

ENDPOINT	Hazard Ratio (HR)	95% confidence interval	p-value
DFS	0.913	0.778 – 1.072	0.266
OS	0.842	0.672 – 1.054	0.131
RFI	0.834	0.671 – 1.038	0.101
BMFI	0.765	0.548 – 1.068	0.114
NBMFI	***0.743***	***0.554 – 0.996***	***0.046***

NSABP B-34 Hazard Ratios of Bone Metastasis Free Interval between Groups According to Stratification Variables
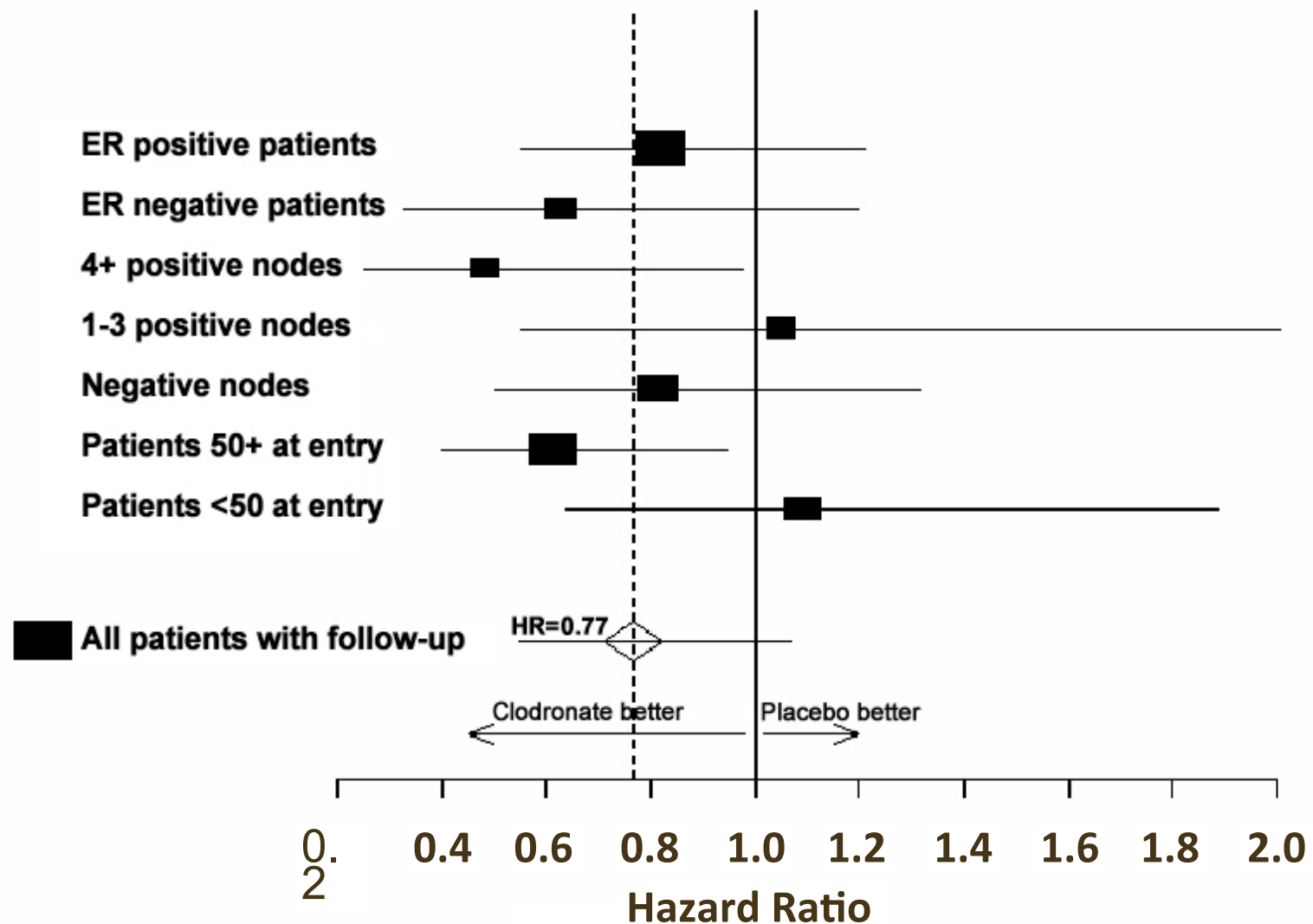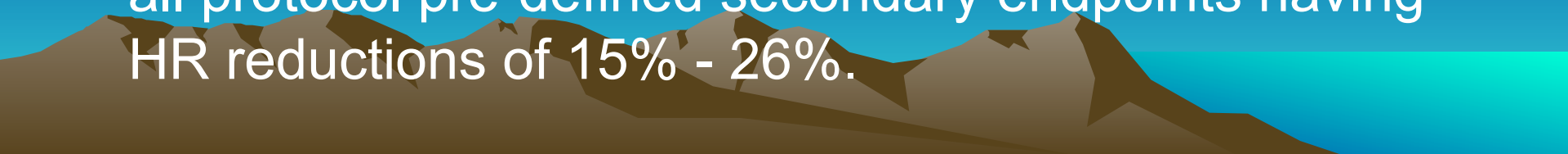
B-34 Post-hoc Analysis
Hazard Ratios of Non-Skeletal Metastases between Groups by Age Categories (<50, 50-59, 60+)

Patients 60+ at entry

Patients 50-59 at entry

Patients <50 at entry

■ All patients with follow-up

HR=0.74

Clodronate better   Placebo better

0.2   0.4   0.6   0.8   1.0   1.2   1.4

Hazard Ratio
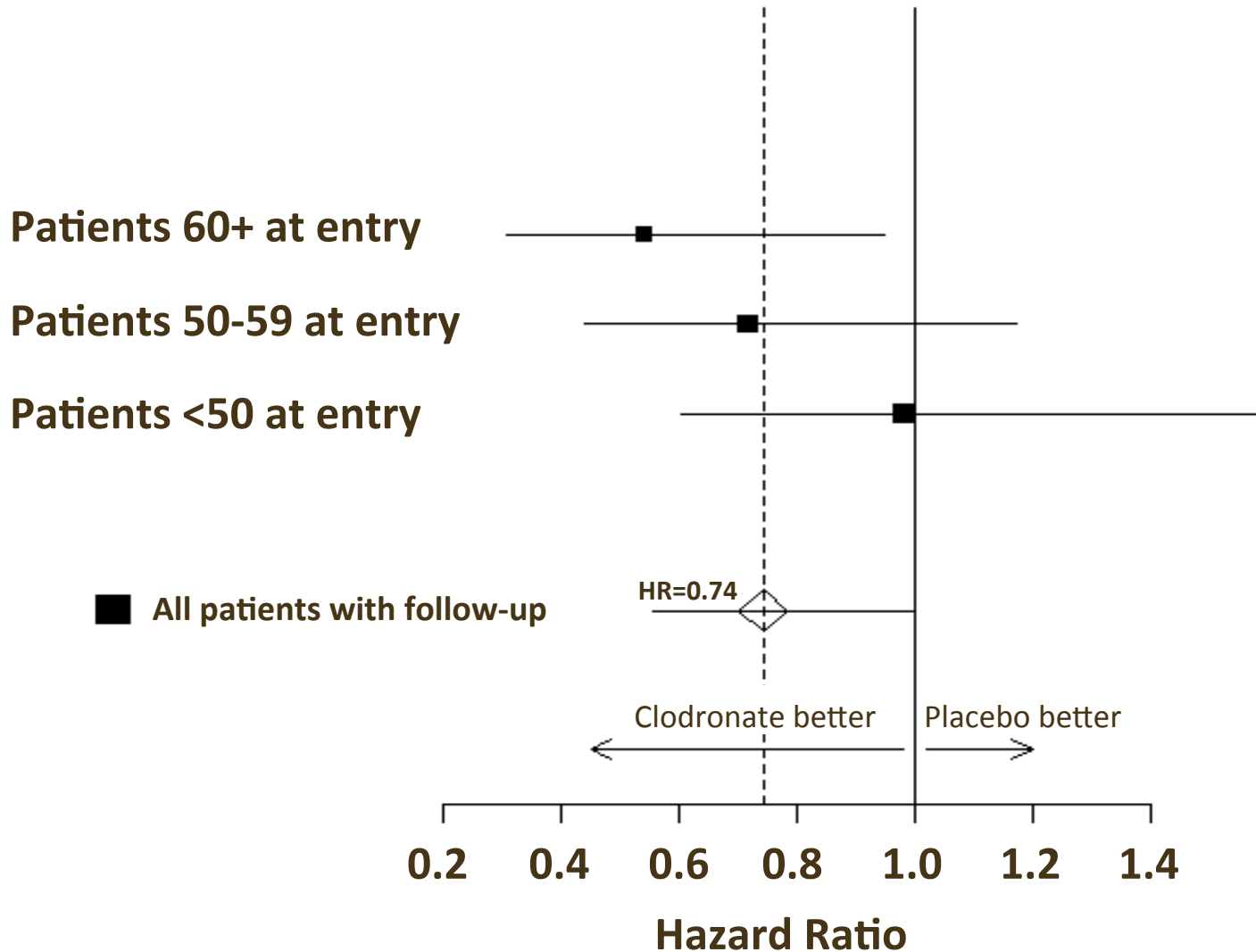
Conclusions (1)

- The primary objective of DFS was not met in this low event rate population.

- The DFS benefit was attenuated due to the equivalent event rates for 2nd primary cancers, contra-lateral cancers and local/regional relapses.

- 40% of patients did not complete 3 years of study therapy

- Side-effects/toxicity in the clodronate and placebo groups were low and similar. One case of possible ONJ.

- Clodronate provided benefit for distant metastases in all protocol pre-defined secondary endpoints having HR reductions of 15% - 26%.

Conclusions (2)

- Secondary protocol pre-defined endpoint reductions observed in women 50 years and older were even greater [20% - 39%]:

  - Breast cancer RFI - ages $\geq$ 50: HR=0.76 (p = 0.05)

  - Bone metastasis-free interval - ages $\geq$ 50: HR= 0.61 (p = 0.024)

  - Non-bone metastasis-free interval - ages $\geq$ 50: HR=0.63 (p = 0.015)

  - Overall survival - ages $\geq$ 50: HR = 0.80 (p = 0.1)

    - 125 deaths in placebo arm vs. 101 deaths in clodronate arm

GAIN STUDY: A PHASE III TRIAL TO COMPARE ETC VS. EC-TX AND IBANDRONATE VS. OBSERVATION IN PATIENTS WITH NODE-POSITIVE PRIMARY BREAST CANCER – 1ST INTERIM EFFICACY ANALYSIS

Möbus V, Diel IJ, Elling D, Harbeck N, Jackisch C, Thomssen C, Untch M, Conrad B, Schneeweiss A, Kreienberg R, Huober J, Müller V, Lück HJ, Bauerfeind I, Loibl S, Nekljudova V, von Minckwitz G

for the AGO-B/GBG/NOGGO study groups

Rationale

- ➢ **Dose-dense chemotherapy results in a superior DFS and OS compared to conventionally dosed EC-T in patients with early breast cancer** [1,2]

- ➢ **Intense dose-dense (IDD) chemotherapy with epirubicin (E), paclitaxel (T), cyclophosphamide (C) (ETC) might be able to further improve outcome in high-risk, node positive breast cancer patients** [1]

- ➢ **Bisphosphonates might be of additional benefit in the treatment of primary breast cancer patients** [3]

[1]Möbus V et al. J Clin Oncol 2010; [2]Citron M et al. J Clin Oncol 2003; [3]Diel I et al. New Engl J Med 1998

ETC Trial (≥4 LN+)
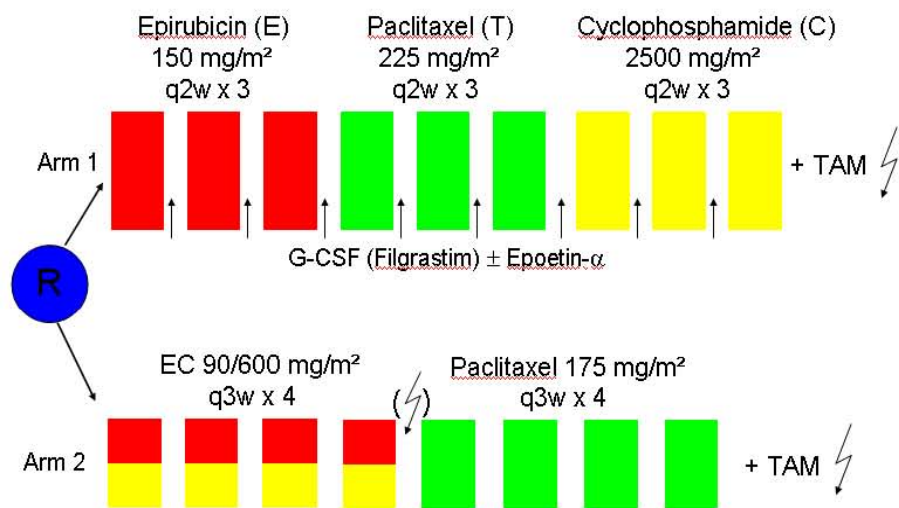
Möbus V et al. J Clin Oncol 2010
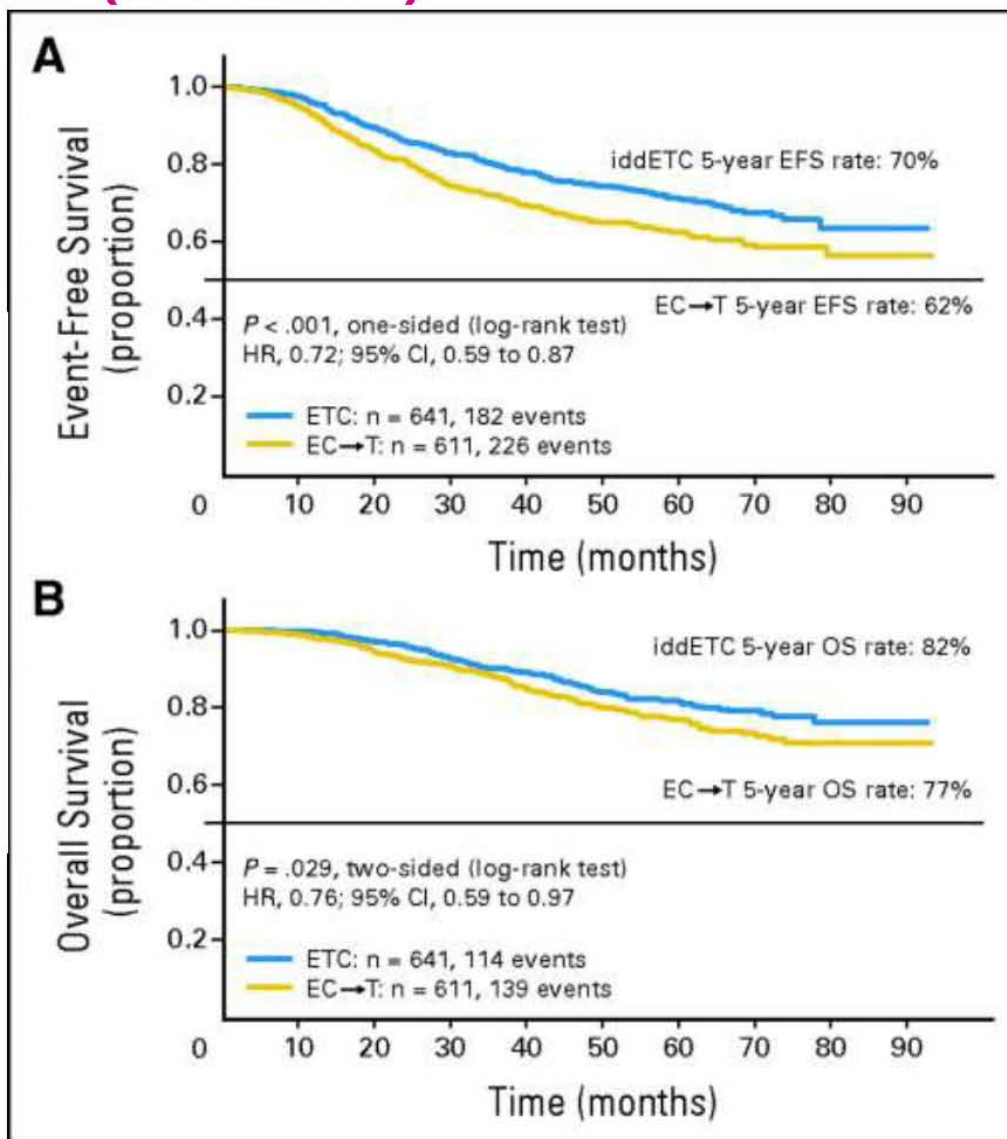
Trial Design

Arm A1:

Epirubicin 150 mg/m² q 2w
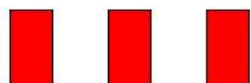
Paclitaxel 225 mg/m² q 2w
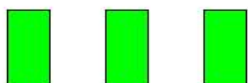
Cyclophosphamide 2000 mg/m² q 2w
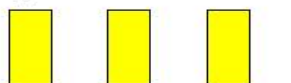
Ciprofloxacin

Pegfilgrastim
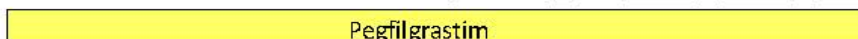
Darbepoetin alfa   or   Epoetin beta

Arm B1:

Ibandronate 50 mg daily p.o. 2 yrs.

Arm A2:

Epirubicin 112.5 mg/m² Cyclophosphamide 600 mg/m² q 2w
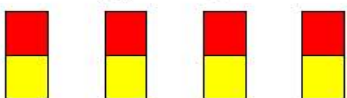
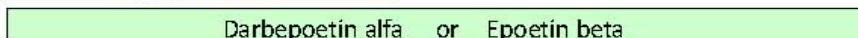Paclitaxel 67.5 mg/m² weekly Capecitabine 2000 mg/m² d1 – d14 q3w
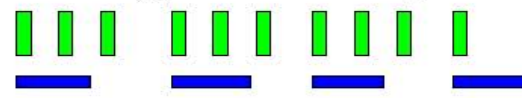
Ciprofloxacin

Pegfilgrastim
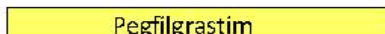
Darbepoetin alfa   or   Epoetin beta

Arm B2:

Observation

Objectives

Primary

➢ **Disease-free survival**
  ➢ ETC vs EC-TX
  ➢ **Ibandronate vs observation**

Secondary

➢ **Overall survival for** chemotherapy **and ibandronate**

➢ Compliance and side effects

➢ Incidence of secondary malignancies

➢ **Efficacy in HR (+/-) and different nodal risk groups (1-3, 4-9, ≥10) for** chemotherapy **and ibandronate**

Main Eligibility Criteria*

➤ **untreated, uni- / bilateral, primary breast cancer**

➤ **Node positive disease**

➤ **Biological age ≤ 65 years**

➤ **No distant metastases**

➤ **Normal organ function (incl. LVEF ≥55%)**

➤ **ECOG status <2**

➤ **Life expectancy ≥ 10 years**

Flow of Patients
(N=3023)

	Ibandronate	Observation
	N	**N**
Randomized	**2015**	**1008**
Started chemotherapy	**1996**	**998**
Started ibandronate	**1870**	**15**
Discontinued ibandronate	**18%**	**n.a.**
➤ Relapse or death	6.1%	n.a.
➤ AE	2.3%	n.a.
➤ Patient's wish	3.2%	n.a.
➤ Lost to FU	1.5%	n.a.
➤ Other	4.4%	n.a.

AGO-B
BREAST STUDY GROUP

GBG
GERMAN
BREAST
GROUP

Patients & Tumor Characteristics

	Ibandronate n=1996	Observation n=998
age (median yrs)	49	50
premenopausal	48.4%	47.2%
pT 4	2.1%	1.4%
pN1	38.1%	37.1%
pN2	34.9%	36.3%
pN3	27.0%	26.7%
mastectomy	44.5%	43.3%
ductal invasive	77.4%	77.1%
grade 3	47.3%	44.3%
hormone receptor positive	76.5%	77.7%
HER2 positive	22.1%	21.8%

DFS Ibandronate vs. Observation

Product-Limit Survival Estimates
With Number of Subjects at Risk

3 year DFS
  ibandronate 87.6%
  observation: 87.2%

Cox regression:
HR: 0.945, 95% CI (0.768, 1.16); p=0.59

OS Ibandronate vs. Observation

Product-Limit Survival Estimates
With Number of Subjects at Risk

3 year OS
   ibandronate 94.7%
   observation 94.1%

Cox regression:
HR: 1.04, 95% CI (0.763, 1.42);
p=0.80
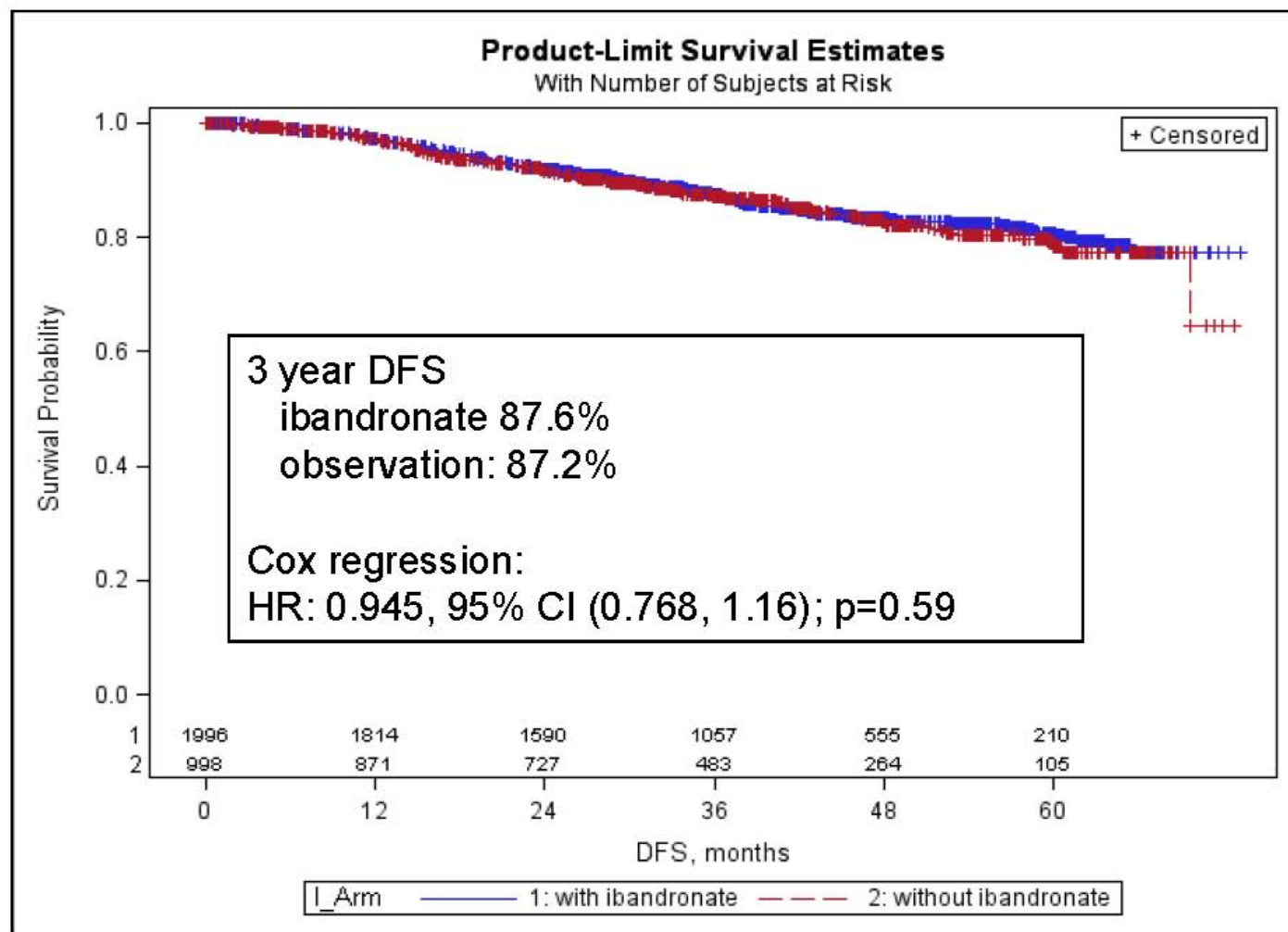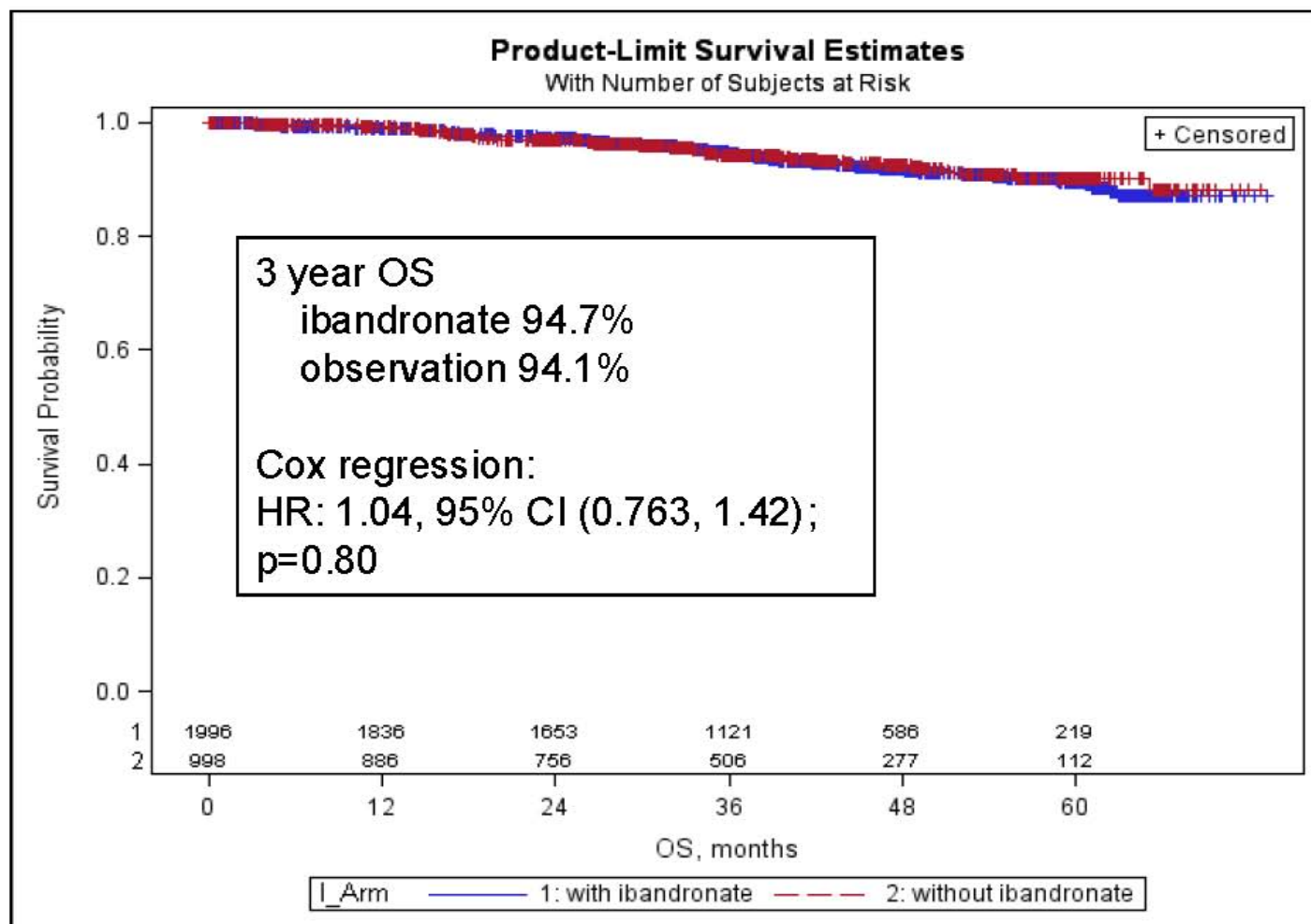
Summary and Conclusions

> ➤ **The interim futility boundary for chemotherapy was not crossed**

> ➤ **For the ibandronate question the futility boundary was reached**

> ➤ **There was no difference in DFS (p=0.59) and OS (p=0.80) between patients with ibandronate and observation**

> ➤ **There was no difference within subgroups**

> ➤ **The GAIN study demonstrated that adjuvant ibandronate does neither improve DFS nor OS in node positive early breast cancer after treatment with dose-dense chemotherapy**

Long-term Survival Outcomes Among Postmenopausal Women With Hormone Receptor-Positive Early Breast Cancer Receiving Adjuvant Letrozole and Zoledronic Acid:
5-year Follow-up of ZO-FAST

R.H. de Boer,[1] N. Bundred,[2] H. Eidtmann,[3] P. Neven,[4] G. von Minckwitz,[5] N. Martin,[6] A. Modi,[6] R. Coleman[7]

[1]Royal Melbourne Hospital, Victoria, Australia; [2]South Manchester University Hospital, Academic Surgery, Education and Research Center, Manchester, UK; [3]Universitäts Frauenklinik Kiel, Germany; [4]Breast Clinic, UZ Gasthuisberg, Leuven, Belgium; [5]German Breast Group, Frankfurt, Germany; [6]Novartis Pharma AG, Basel, Switzerland; [7]Academic Unit of Clinical Oncology, Weston Park Hospital, Sheffield, UK

ZO-FAST: Trial Design

Key endpoints

Primary: Bone mineral density (BMD) at 12 months

Secondary: BMD at 36 and 60 months, disease recurrence, fractures, safety

N = 1,065

Breast cancer
Stage I to IIIa
- Postmenopausal or amenorrhoeic due to cancer treatment
- ER+ and/or PgR+
- T-score ≥ –2.0

R

Letrozole +
immediate zoledronic acid (IM-ZOL)
(4 mg every 6 months)

Letrozole +

Delayed zoledronic acid (D-ZOL)
If 1 of the following occurs:
- BMD T-score < –2
- Clinical fracture
- Asymptomatic fracture at 36 months

Treatment duration: 5 years

Abbreviations: BMD, bone mineral density; ER, oestrogen receptor; PgR, progesterone receptor; R, randomisation.
http://www.clinicaltrials.gov. Identifier: NCT00050011.

ZO-FAST: Demographics and Baseline Disease Characteristics (All Randomized Patients)

Characteristic	IM-ZOL (n = 532)	D-ZOL (n = 533)
Median age, years (range)	57 (36 - 87)	58 (37 - 81)
Median BMI, kg/cm^2 (range)	26.6 (18.2 - 48.5)	26.7 (16.7 - 65.8)
ECOG PS, n (%)		
0	477 (89.7)	479 (89.9)
1	51 (9.6)	48 (9.0)
2	3 (0.6)	4 (0.8)
Unknown	1 (0.2)	2 (0.4)
Primary tumour size, n (%)		
T0 or T1	311 (58.5)	311 (58.3)
≥ T2	218 (41.0)	220 (41.3)
Not available	3 (0.6)	2 (0.4)
Regional lymph node involvement, n (%)		
N0	228 (42.9)	216 (40.5)
N1-3	302 (56.8)	315 (59.1)
Not available	2 (0.4)	2 (0.4)

Abbreviations: BMI, Body Mass Index; D-ZOL, delayed zoledronic acid; ECOG PS, Eastern Cooperative Oncology Group performance status; IM-ZOL, immediate zoledronic acid.

6

ZO-FAST: Primary Endpoint— Median Change in LS BMD
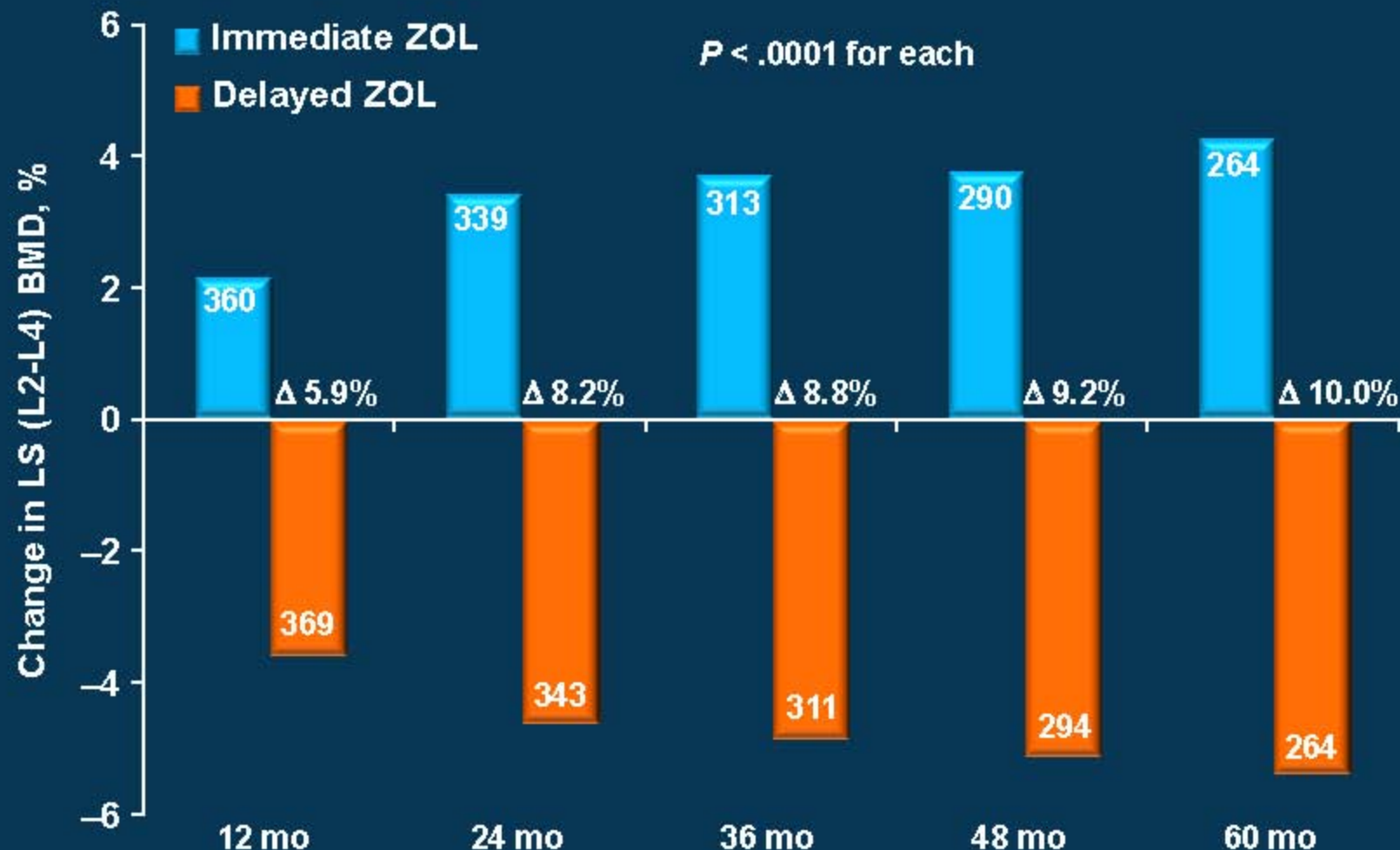
Abbreviations: BMD, bone mineral density; LS, lumbar spine; ZOL, zoledronic acid.

7

ZO-FAST: Disease-Free Survival

ITT Population

HR = 0.66; log-rank *P* value = .0375

— IM-ZOL 4 mg (42 events)
— D-ZOL 4 mg (62 events)

Number at risk		Time on Study, months				
IM-ZOL	532	518	500	488	475	376
D-ZOL	533	511	491	475	463	368

Censored Analysis[a]

HR = 0.62; log-rank *P* value = .024

— IM-ZOL 4 mg (42 events)
— D-ZOL 4 mg (53 events)

Number at risk		Time on Study, months				
IM-ZOL	532	518	500	488	475	376
D-ZOL	533	459	402	376	350	267

[a] Censored patients at initiation of delayed ZOL (n=144).
Abbreviations: DFS, disease-free survival; D-ZOL, delayed zoledronic acid; HR, hazard ratio; IM-ZOL, immediate zoledronic acid.

9

ZO-FAST: Disease Recurrence (ITT Population)

Disease Recurrence

Key Sites of Distant Recurrence[a]

10

ZO-FAST: Overall Survival (ITT Population)

HR = 0.69; log-rank *P* value = .196

— IM-ZOL 4 mg (26 events)
— D-ZOL 4 mg (36 events)

Time on Study, months

Number at risk

IM-ZOL	532	522	511	502	485	406
D-ZOL	533	519	505	491	480	407
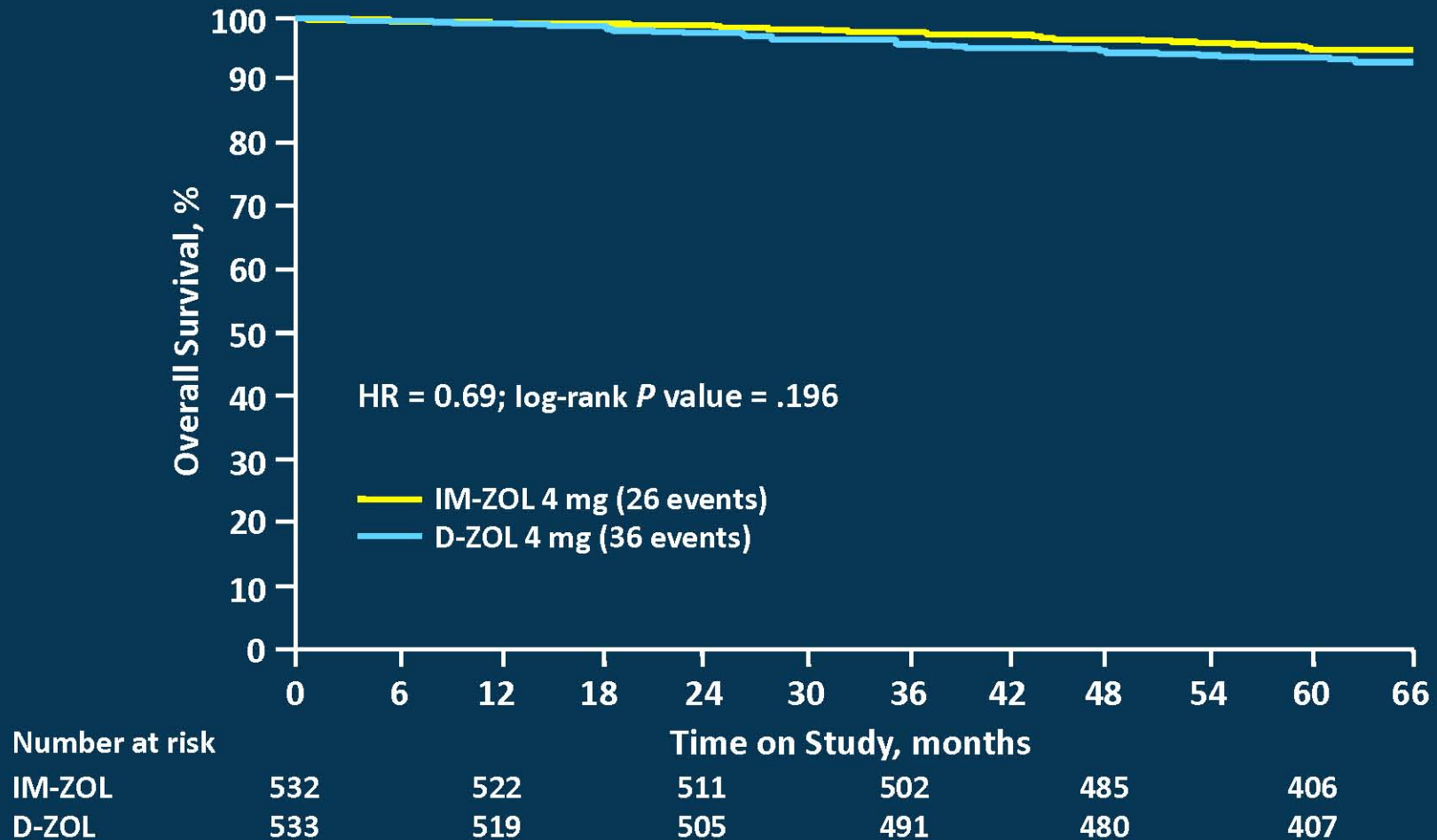
Abbreviations: D-ZOL, delayed zoledronic acid; HR, hazard ratio; IM-ZOL, immediate zoledronic acid.

ZO-FAST: Stratification Factors

- ## Protocol-defined
  - ### Recently postmenopausal (n=177)[a]
  - ### Truly postmenopausal (n=888)[b]

- ## Exploratory
  - ### Delayed Zoledronic acid initiation (n= 144/533 [27%])
    - #### (Coleman et al. Poster P2-17-01)

[a] Defined as chemotherapy- or ovarian suppression-induced premature menopause; standard biochemical criteria for menopause
[b] Defined as naturally occurring menopause prior to diagnosis

ZO-FAST: DFS Exploratory Analyses[a]

Hazard Ratio (95% Confidence Interval)

P value

Overall population
(N = 1,065; 42 vs 62 events)

0.66

.0375

Recently postmenopausal[b]
(n = 177; 3 vs 9 events)

0.34

.0942

Truly postmenopausal[c]
(n = 888; 39 vs 53 events)

0.71

.0998

0.1   1   10

Reduced Risk With Immediate ZOL → Increased Risk With Immediate ZOL
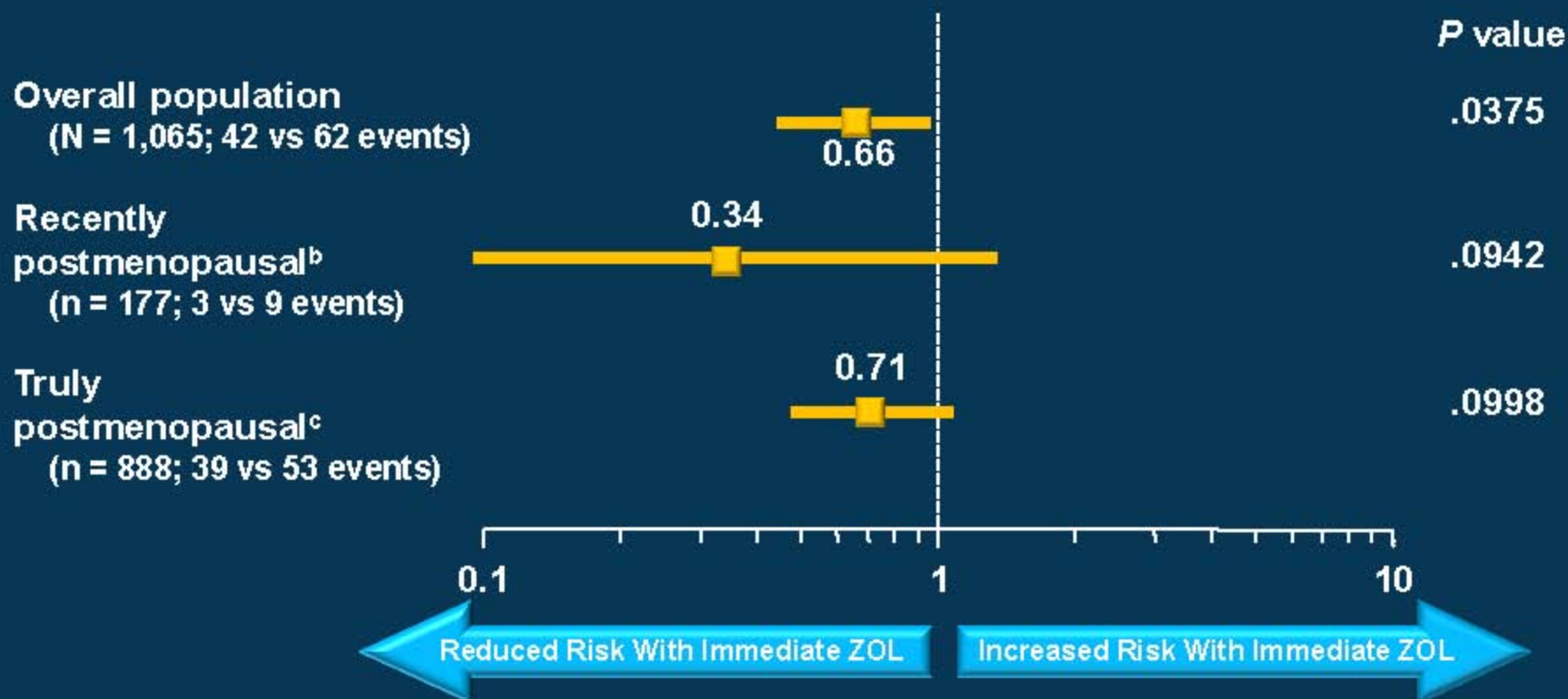
Among women who were postmenopausal for >5 years or >60 years old at study entry (n=670), IMZOL prolonged DFS (HR=0.63; 95% CI, 0.39-1.01; P=.052) vs DZOL

[a] Cox regression analyses.
[b] Defined as chemotherapy- or ovarian suppression-induced premature menopause.
[c] Defined as naturally occurring menopause prior to diagnosis.

13

ZO-FAST: OS Exploratory Analyses[a]

Hazard Ratio (95% Confidence Interval)

P value

Overall population
(N = 1,065; 26 vs 36 events)

0.69

.1463

Recently postmenopausal[b]
(n = 177; 3 vs 2 events)

1.41

.7046

Truly postmenopausal[c]
(n = 888; 23 vs 34 events)

0.65

.1035

0.1   1   10

Reduced Risk With Immediate ZOL   Increased Risk With Immediate ZOL
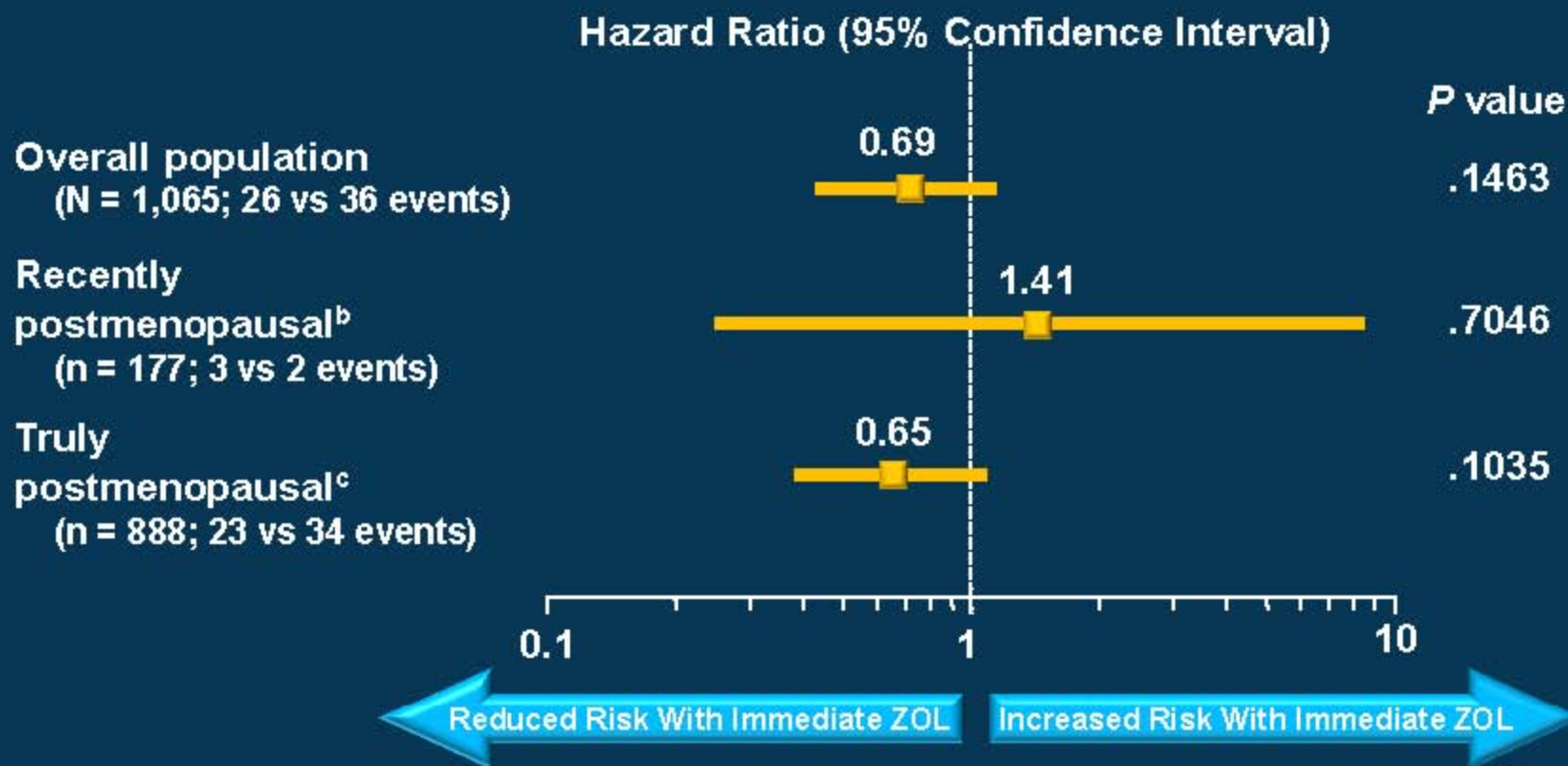
Among women who were postmenopausal for >5 years or >60 years old at study entry (n=670), IMZOL significantly prolonged OS (HR=0.50; 95% CI, 0.27-0.92; P=.022) vs DZOL

[a] Cox regression analyses.
[b] Defined as chemotherapy- or ovarian suppression-induced premature menopause.
[c] Defined as naturally occurring menopause prior to diagnosis

14

ZO-FAST: Osteonecrosis of the Jaw

- **ZO-FAST** (N = 1,065; 5-year follow-up)
  - 3 confirmed cases (0.56%)[a]

- Other adjuvant ZOL trials
  - Z-FAST (N = 601; 5-year follow-up)[1]
    - No confirmed cases
  - E-ZO-FAST (N = 527; 3-year follow-up)[2]
    - 1 confirmed case (0.19%)
  - ABCSG-12 (N = 1,803; > 5-year follow-up)[3]
    - No confirmed cases
  - AZURE (N = 3,360; 5-year follow-up)[4]
    - 17 confirmed cases (1.1%)

[a] A total of 9 potential ONJ events from 7 patients were reported and independently adjudicated by an external panel; 3 were confirmed, 2 had insufficient data, the remaining events were excluded.

1. Brufsky A, et al. SABCS 2009. Abstract 4083; 2. Llombart A, et al. ASCO-BC 2009. Abstract 213; 3. Gnant M, et al. ASCO 2011. Abstract 520; 4. Coleman RE, et al. *N Engl J Med*. 2011;365:1396-1405.

Conclusions

- The 60-month follow-up of ZO-FAST trial confirms and extends the BMD improvement seen with immediate zoledronic acid as reported at earlier time points

- There is a 34% improvement in DFS at 5 years between the immediate and delayed zoledronic acid groups, with a 3.6% absolute difference (91.9% vs 88.3%, respectively)

- As per the improved DFS results seen in the ABCSG-12 and AZURE trials (> 5 years postmenopausal subset), the data support the hypothesis that the anticancer potential of zoledronic acid might be best realized in a low-estrogen environment

Abbreviations: BMD, bone mineral density; DFS, disease-free survival;

Neoadjuvant chemotherapy adapted by interim response improves overall survival of primary breast cancer patients – Results of the GeparTrio trial.

Gunter von Minckwitz, Jens Uwe Blohmer, Serban Dan Costa, Carsten Denkert, Holger Eidtmann, Wolfgang Eiermann, Bernd Gerber, Claus Hanusch, Jörn Hilfrich, Jens Huober, Christian Jackisch, Manfred Kaufmann, Sherko Kümmel, Stefan Paepke, Andreas Schneeweiss, Michael Untch, Dirk Michael Zahm, Keyur Mehta, Sibylle Loibl

Aims

➤ **To take advantage from the *in vivo* chemo-sensitivity test situation of neoadjuvant treatment**

➤ **To develop specific treatment strategies for patients with or without response to 2 cycles TAC:**

   ➤ **Responding patients:**

   → treatment intensification by increased cycle number

   ➤ **Non-responding patients:**

   → switch to non-cross resistant treatment

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GeparTrio Trial Design

N=2072

Core biopsy:
uni/bilateral
cT2-4a-d
cN0-3
size ≥ 2 cm*

Sonography

NC   R

NX

OP

TACx6

OP

conventional
arms

CR/
PR   R

TACx6

OP

TACx8

OP

response-
guided
arms
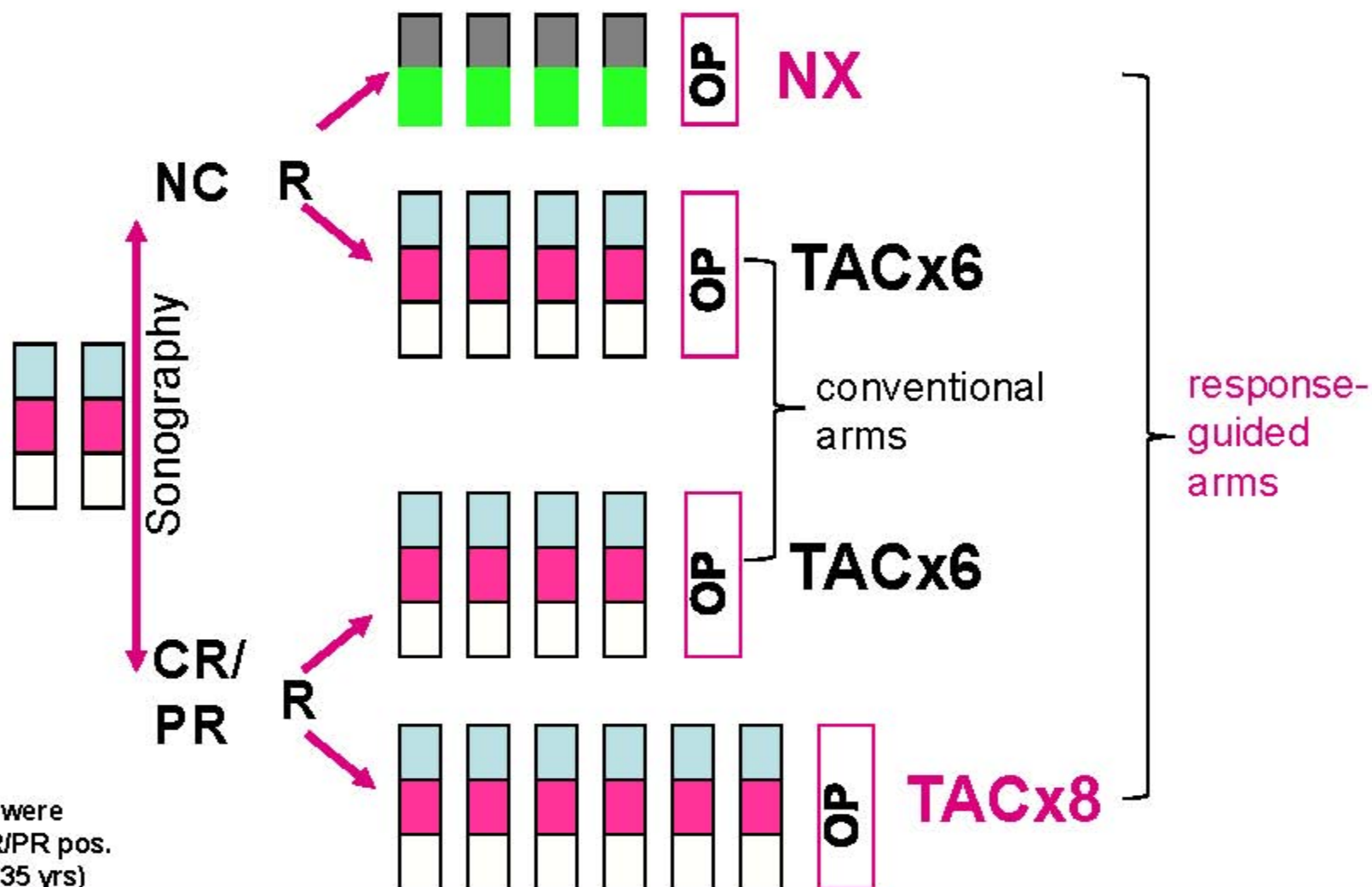
*low risk patients were
excluded (T2 + ER/PR pos.
+ cNO + G1/2 + > 35 yrs)

von Minckwitz et al, JNCI 100: 542, 2008
von Minckwitz et al. JNCI 100; 552, 2008

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Short Term Efficacy
(pCR = ypT0 ypN0)

Responder
N=1344

Non-Responder
N=604
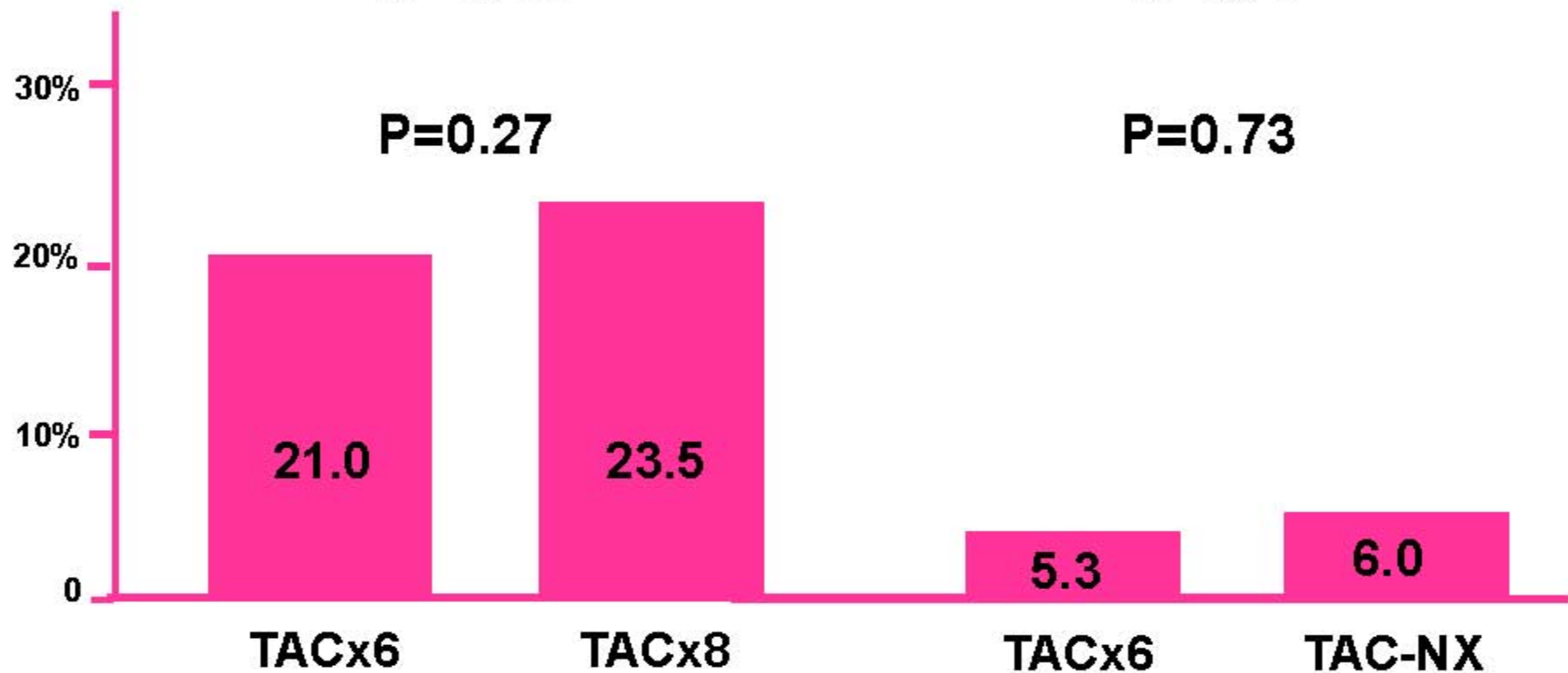
P=0.27

P=0.73

30%

20%

10%

0

21.0

23.5

5.3

6.0

TACx6

TACx8

TACx6

TAC-NX

von Minckwitz et al, JNCI 100: 542, 2008
von Minckwitz et al. JNCI 100; 552, 2008

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Objectives

Primary:

> Pathologic response (responder)

> Sonographic response (non-responder)

Secondary (actual with median follow up of 62 months):

> **To determine 5-year DFS and OS**

> **To examine treatment effects by breast cancer phenotype (post-hoc analysis)**

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Study Population

Characteristic	Conventional TACx6 N=1025 %	Response-guided TACx8 or TAC-NX N=987 %
Age < 40 years	16.9	18.2
cT> 40 mm	60.5	61.5
cT4a-c	9.0	8.7
cT4d	4.6	4.3
cN +	55.3	54.7
Lobular type	13.8	13.1
Grade 3	41.0	35.1
HR-negative	36.8	34.4
HER2-positive	30.5	29.1

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DFS and OS after
conventional (TACx6) vs. response-guided (TACx8/TAC-NX) treatment
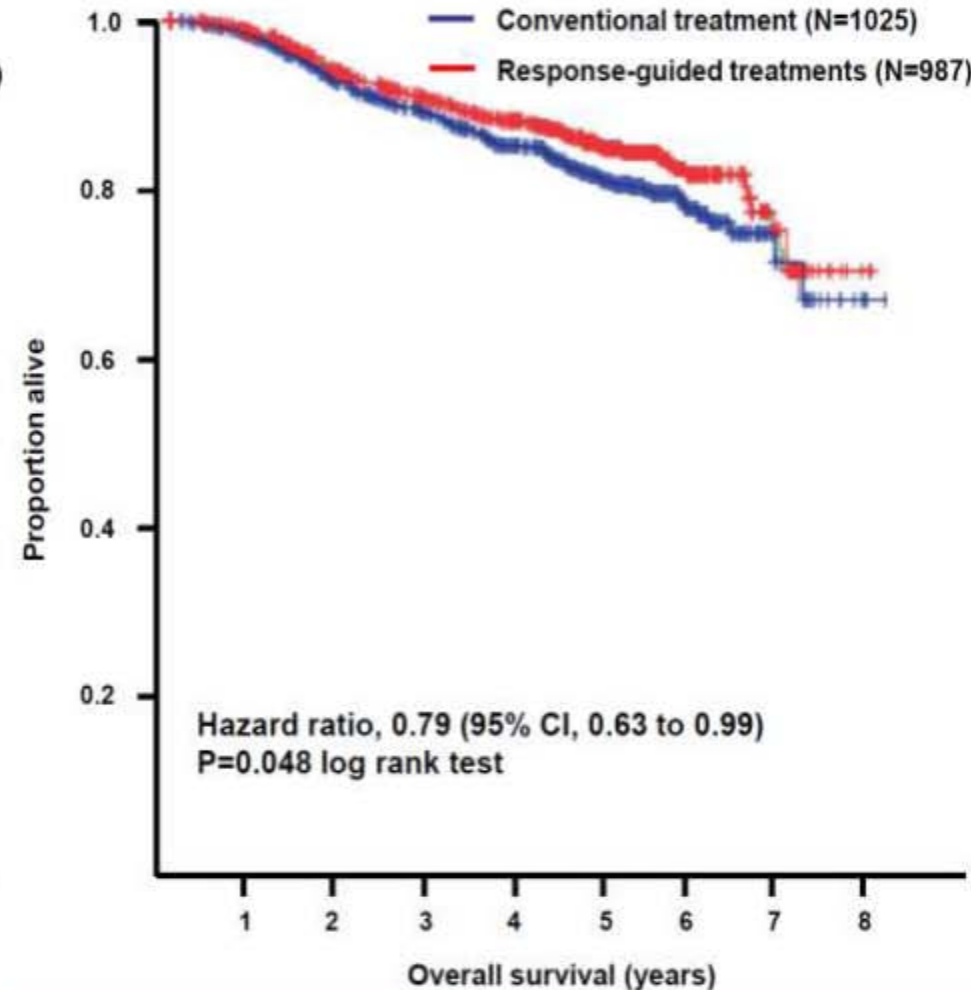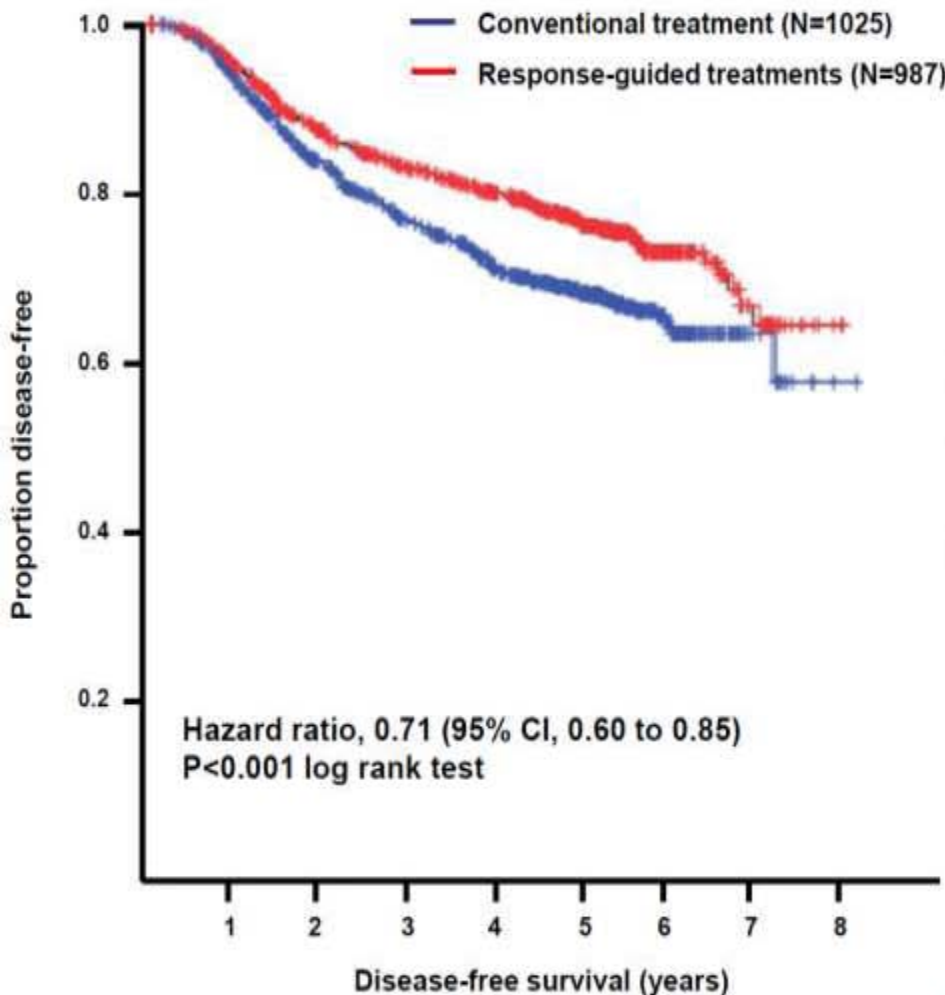
Median follow up 62 months

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DFS after TACx6 vs TACx8 in responding patients

Conventional treatment (TACx6) (N=704)
Response-guided treatment (TACx8) (N=686)

Hazard ratio, 0.78 (95% CI, 0.62 to 0.97)
P=0.026 log rank test

Proportion disease-free

Disease-free survival (years)

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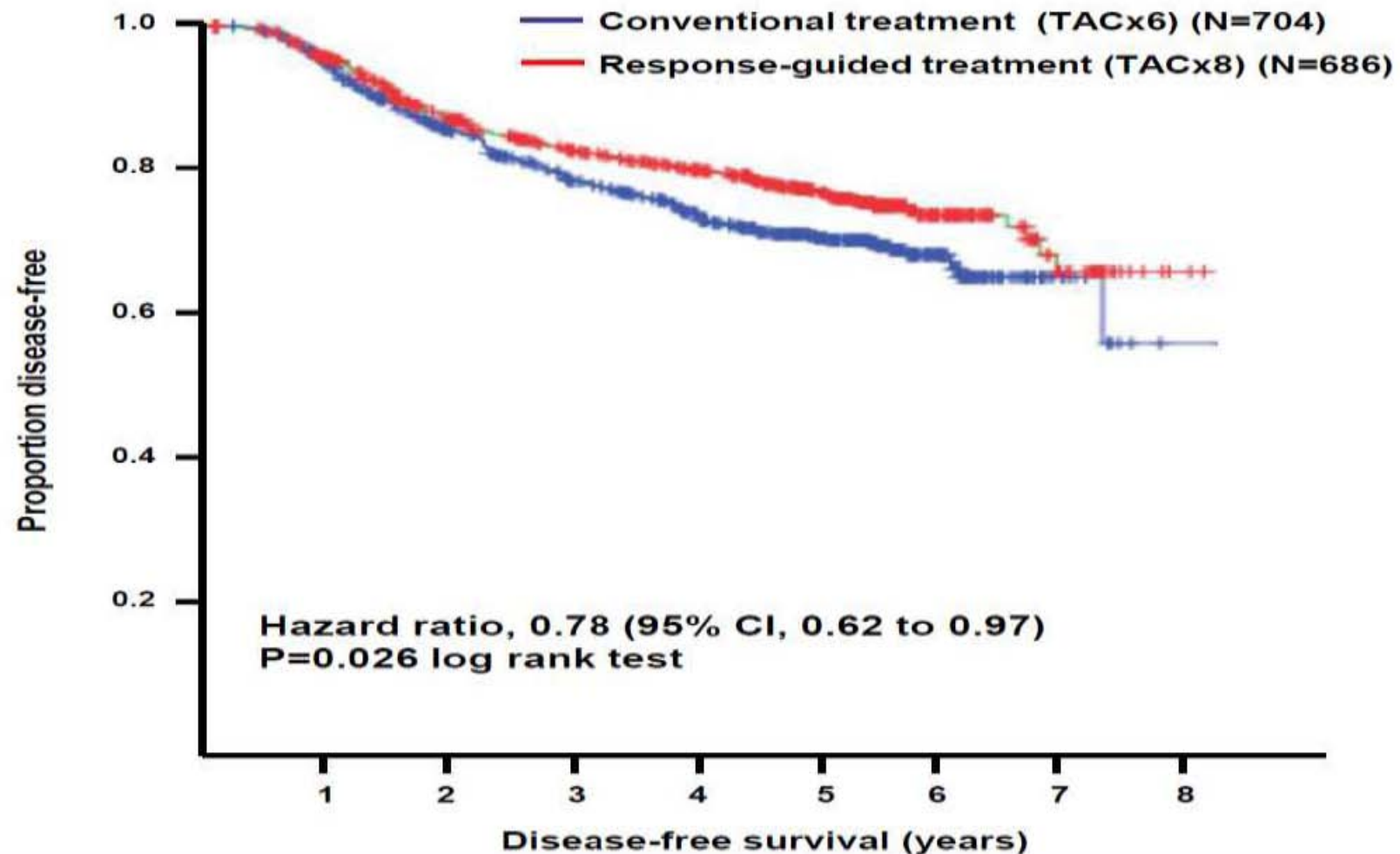
DFS after TACx6 vs TAC-NX in non-responding patients

— Conventional treatment (TACx6) (N=321)
— Response-guided treatment (TAC-NX) (N=301)

Hazard ratio, 0.59 (95% CI, 0.49 to 0.82)
P=0.001 log rank test

Proportion disease-free

Disease-free survival (years)

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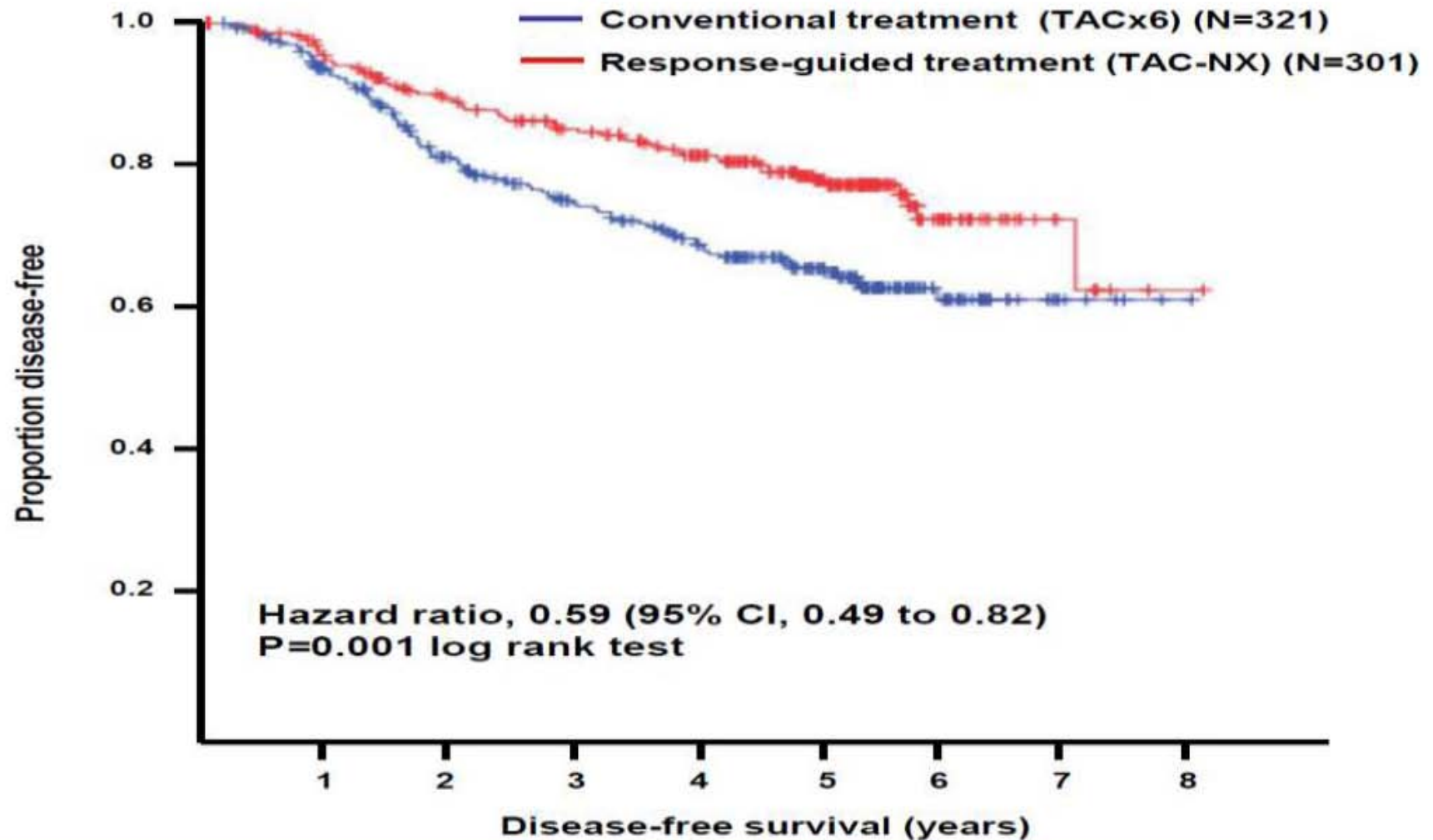
The Magic Triangle
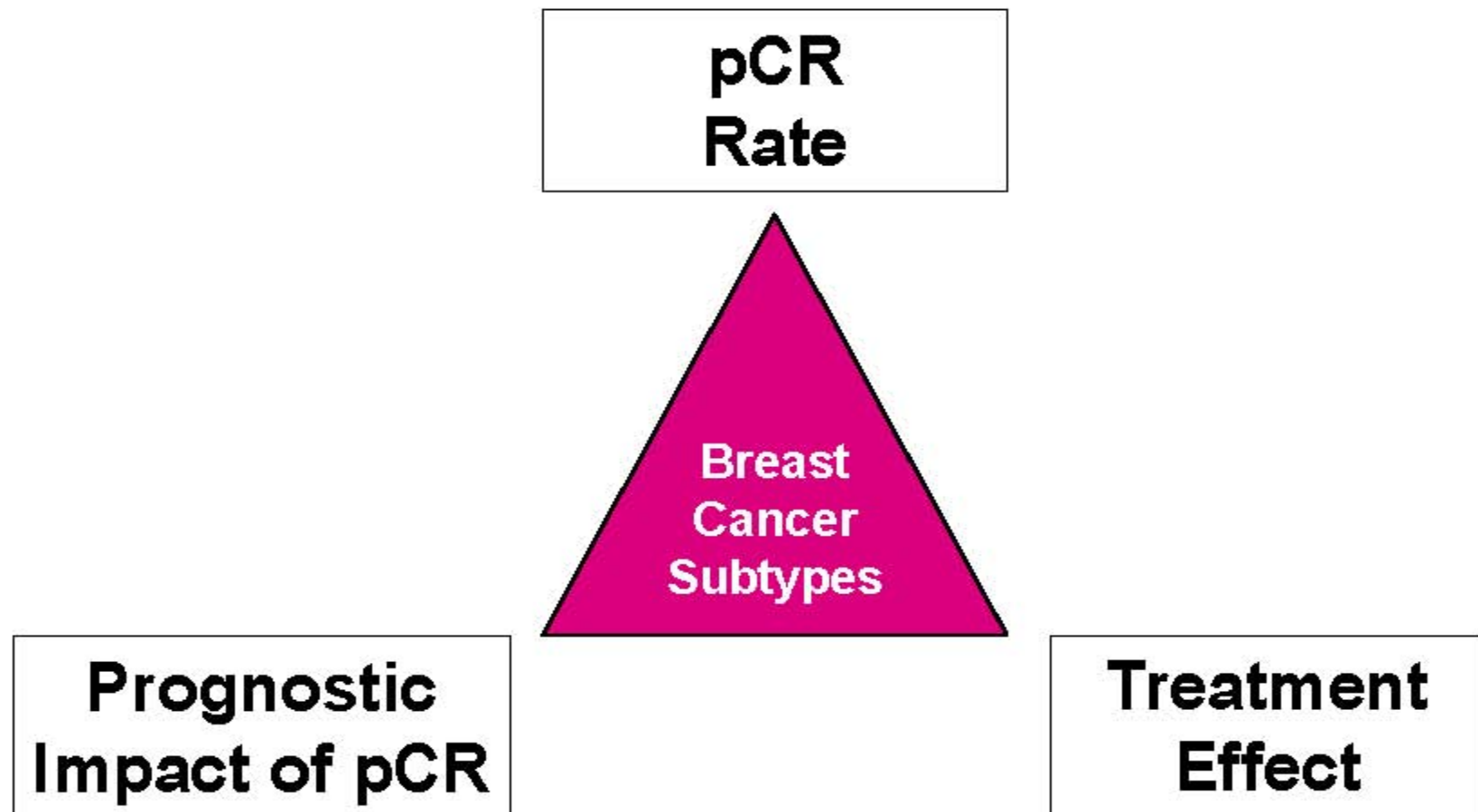
Breast Cancer phenotypes
(St. Gallen definition*)

Phenotype	Definition	Conventional %	Response-guided %
Luminal A	HR+, HER2-, G1/2	34.4	37.1
Luminal B (HER2-)	HR+, HER2-, G3	13.5	12.8
Luminal B (HER2+)	HR+, HER2+	17.3	17.8
HER2+ (non-luminal)	HR-, HER2+	11.7	10.4
Triple-negative	HR-, HER2-	23.1	22.0
Missing		N=181	N=227

*Goldhirsch A, Ann Oncol 2011

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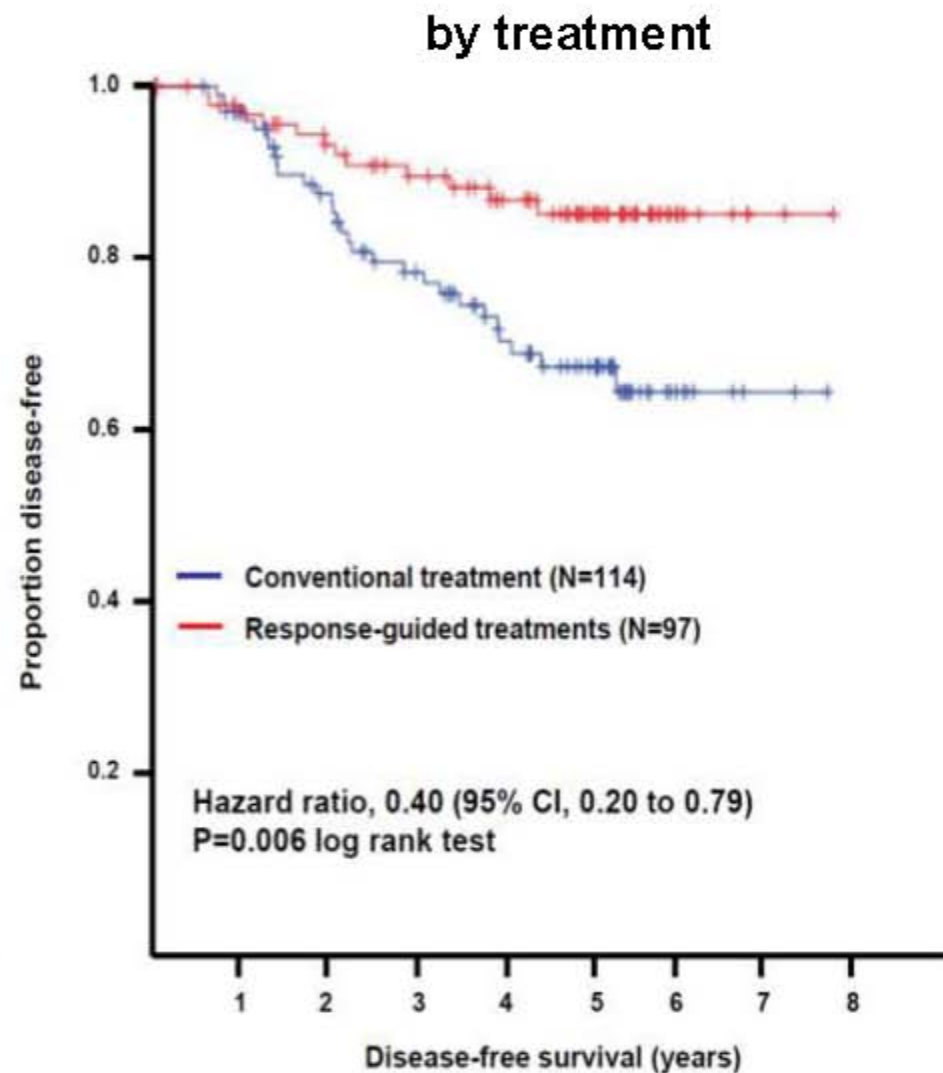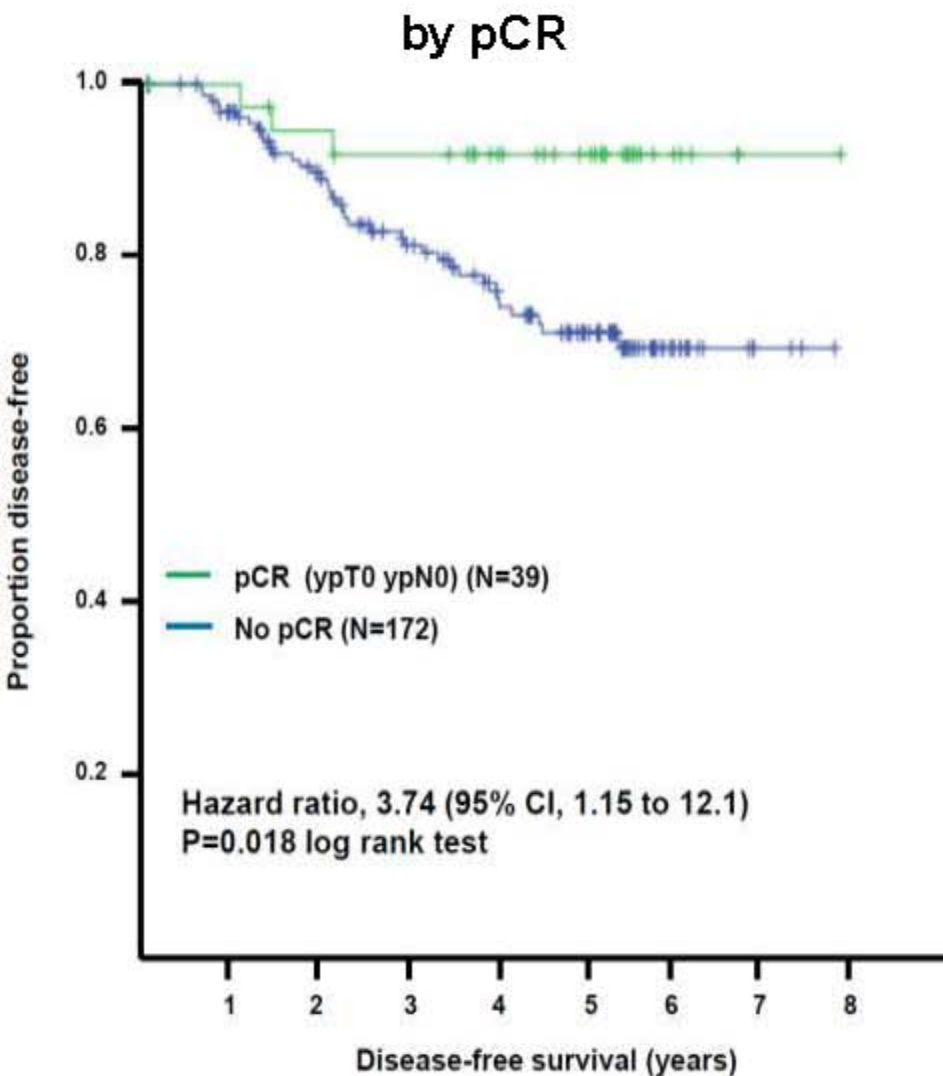# pCR Rates by Subtype

pCR (%)

DFS in Luminal A tumors

DFS in Luminal B (HER2-)

by pCR

pCR (ypT0 ypN0) (N=39)
No pCR (N=172)

Hazard ratio, 3.74 (95% CI, 1.15 to 12.1)
P=0.018 log rank test

by treatment

Conventional treatment (N=114)
Response-guided treatments (N=97)

Hazard ratio, 0.40 (95% CI, 0.20 to 0.79)
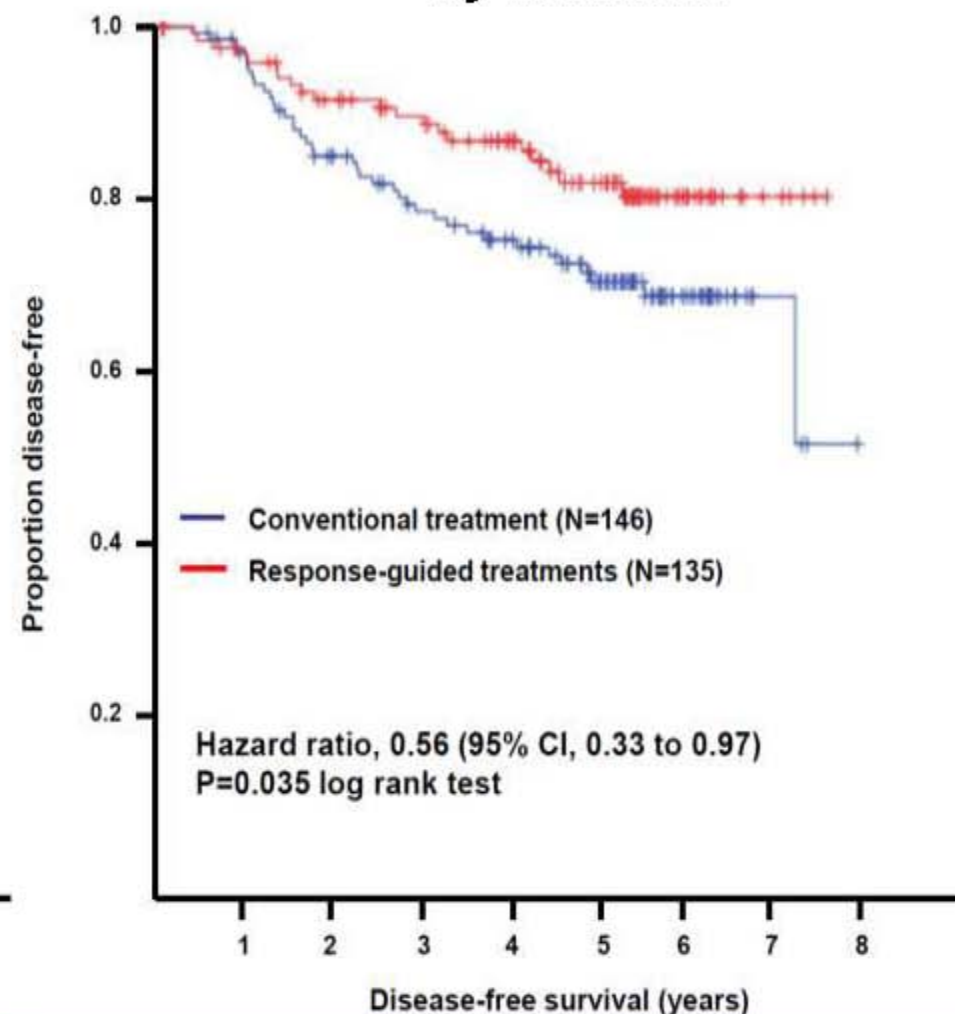P=0.006 log rank test

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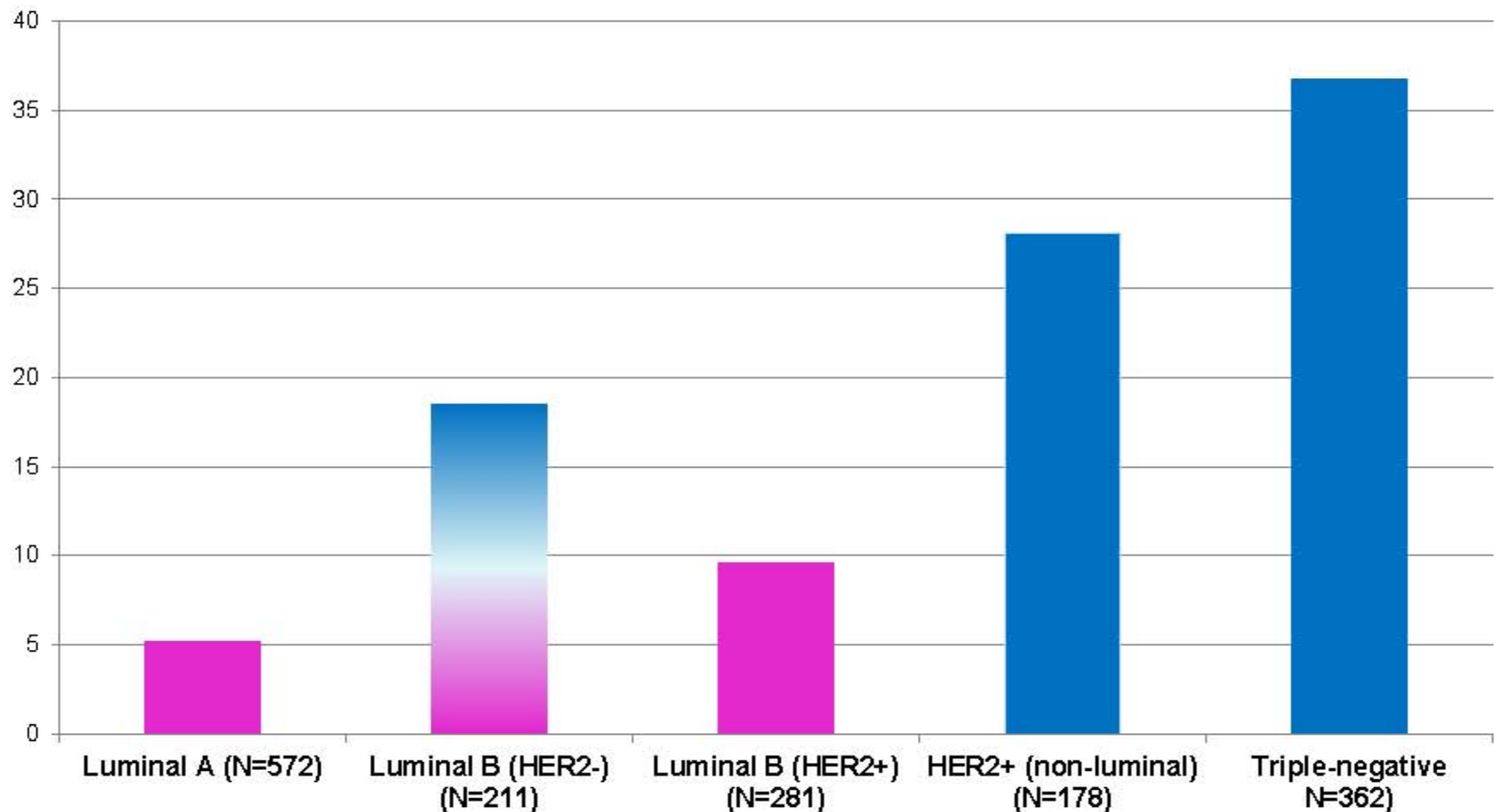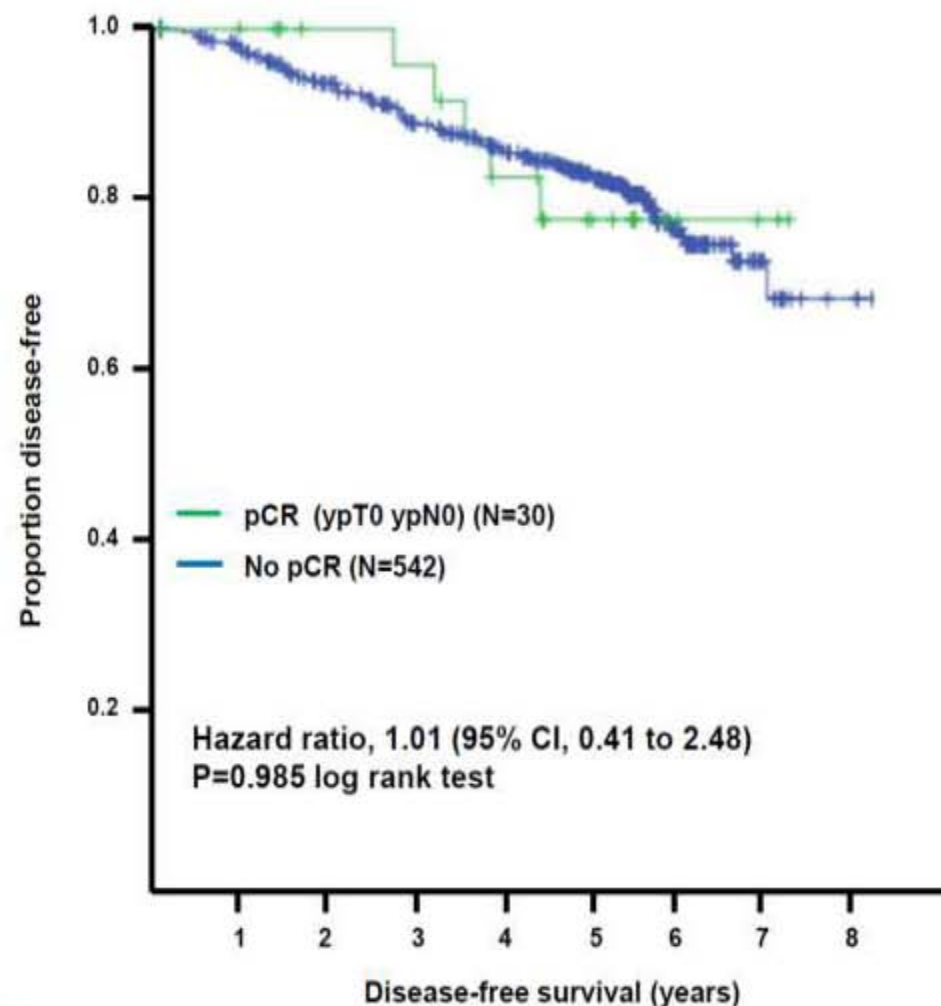
DFS in Luminal B (HER2+) tumors

by pCR

by treatment

pCR (ypT0 ypN0) (N=27)
No pCR (N=254)

Hazard ratio, 0.88 (95% CI, 0.38 to 2.06)
P=0.775 log rank test

Conventional treatment (N=146)
Response-guided treatments (N=135)

Hazard ratio, 0.56 (95% CI, 0.33 to 0.97)
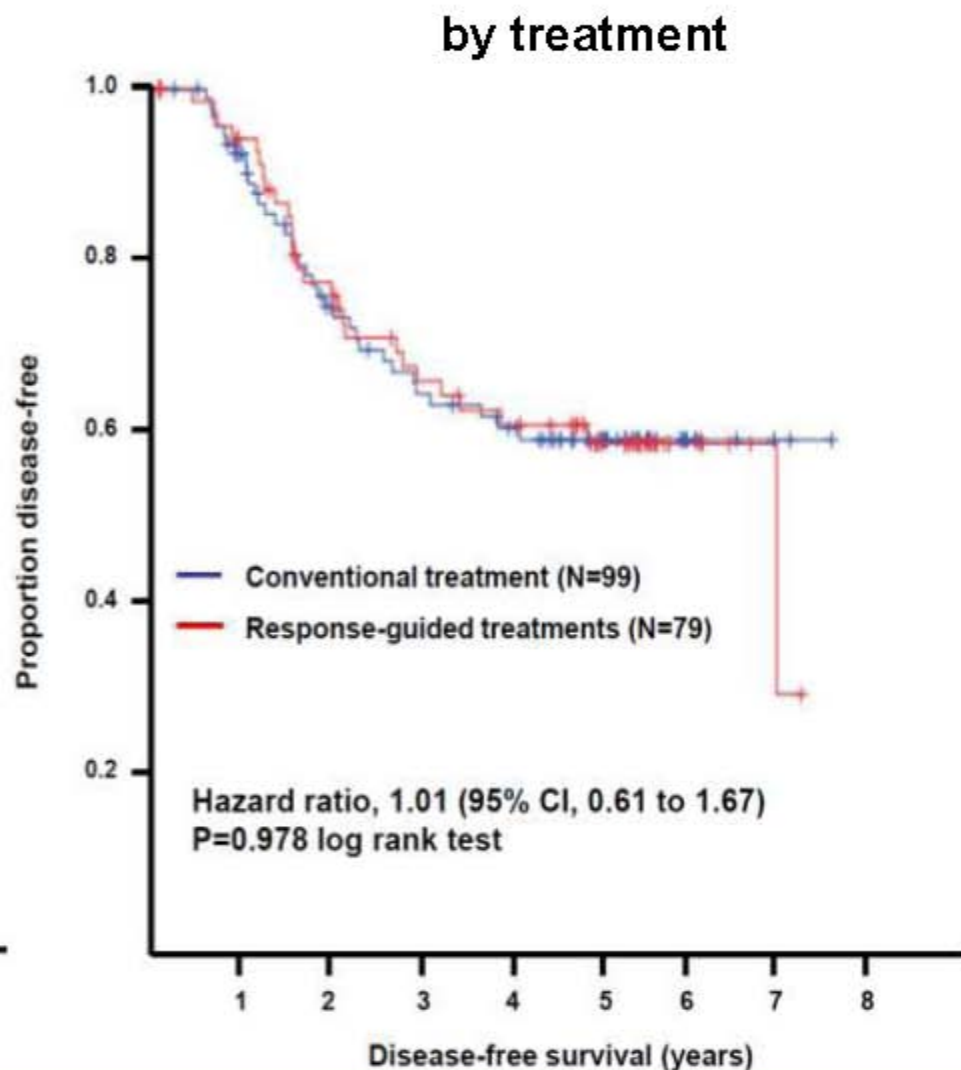P=0.035 log rank test

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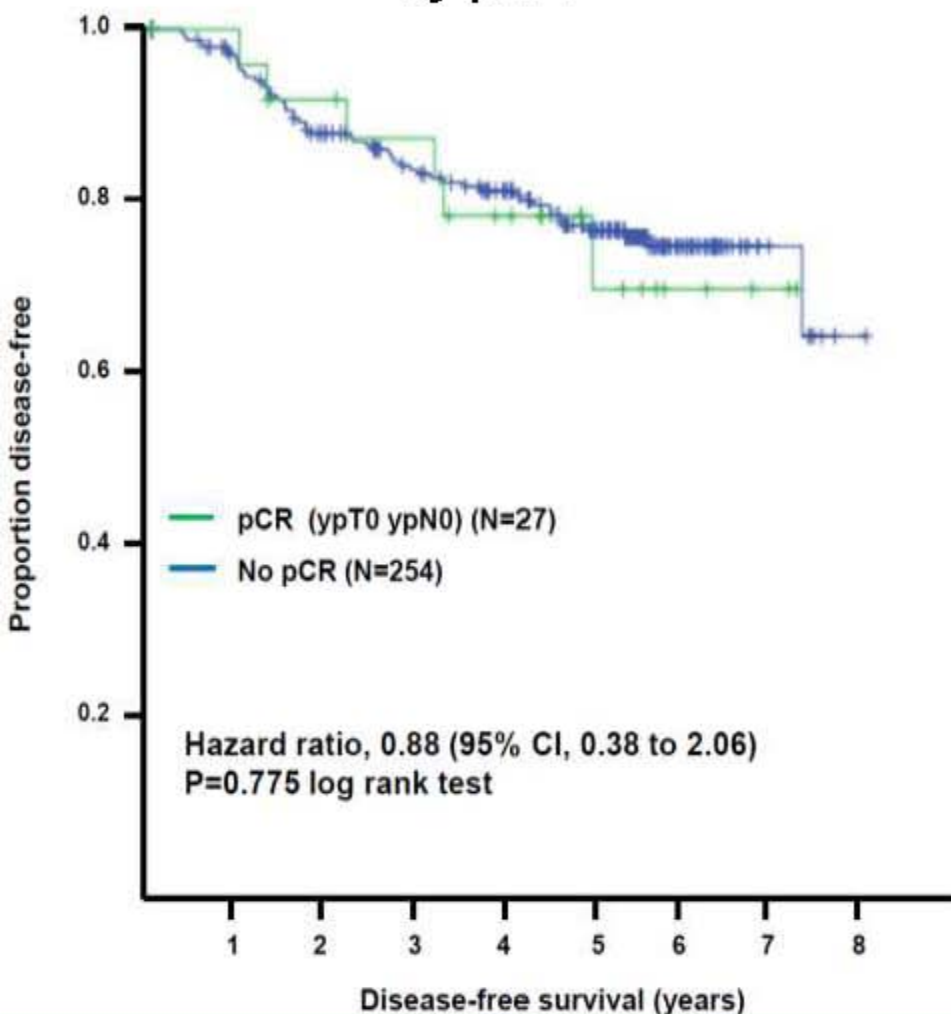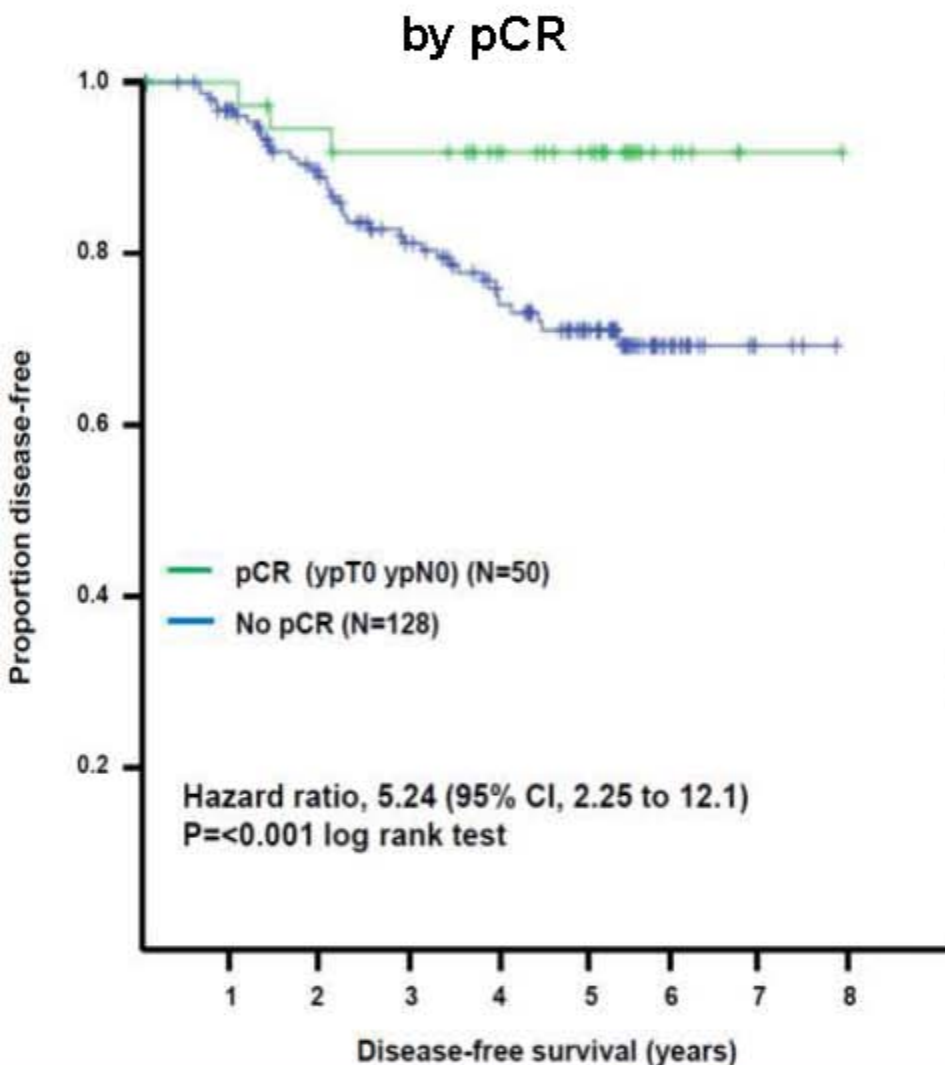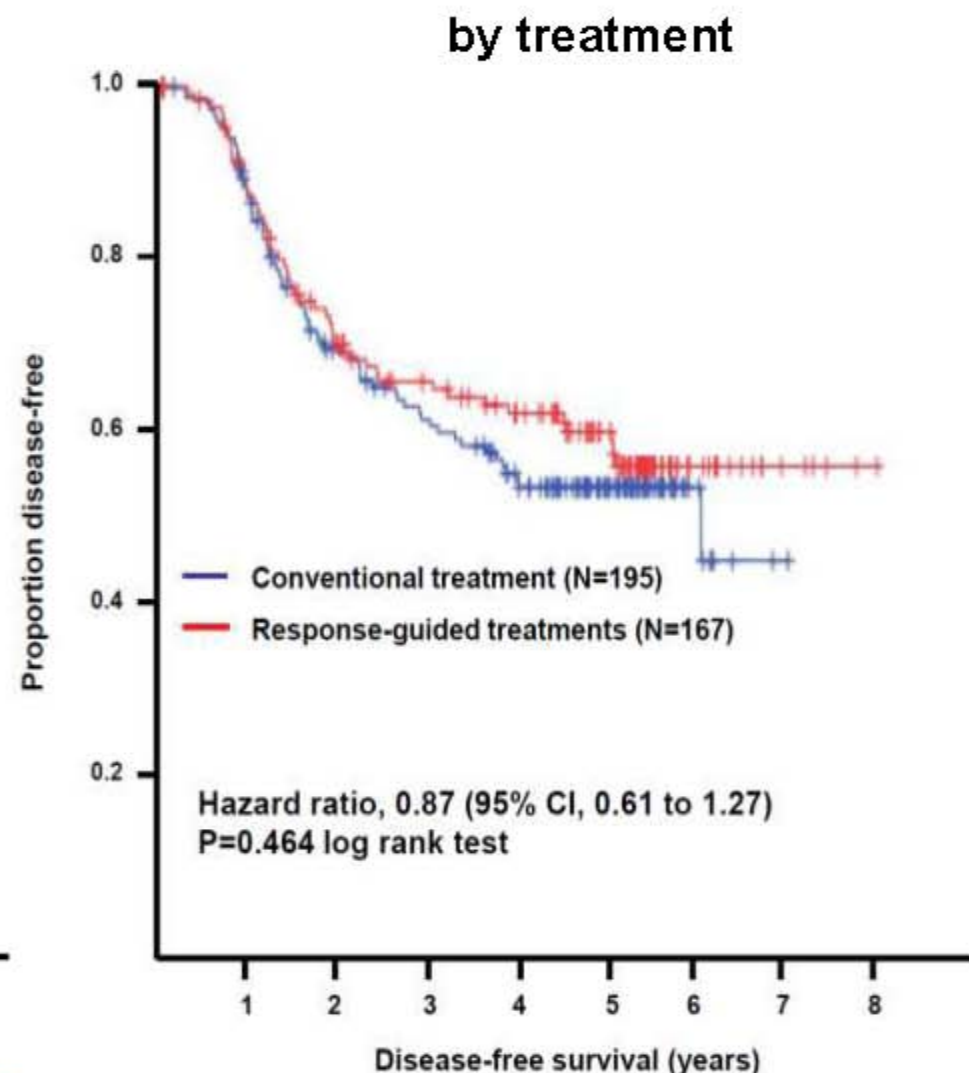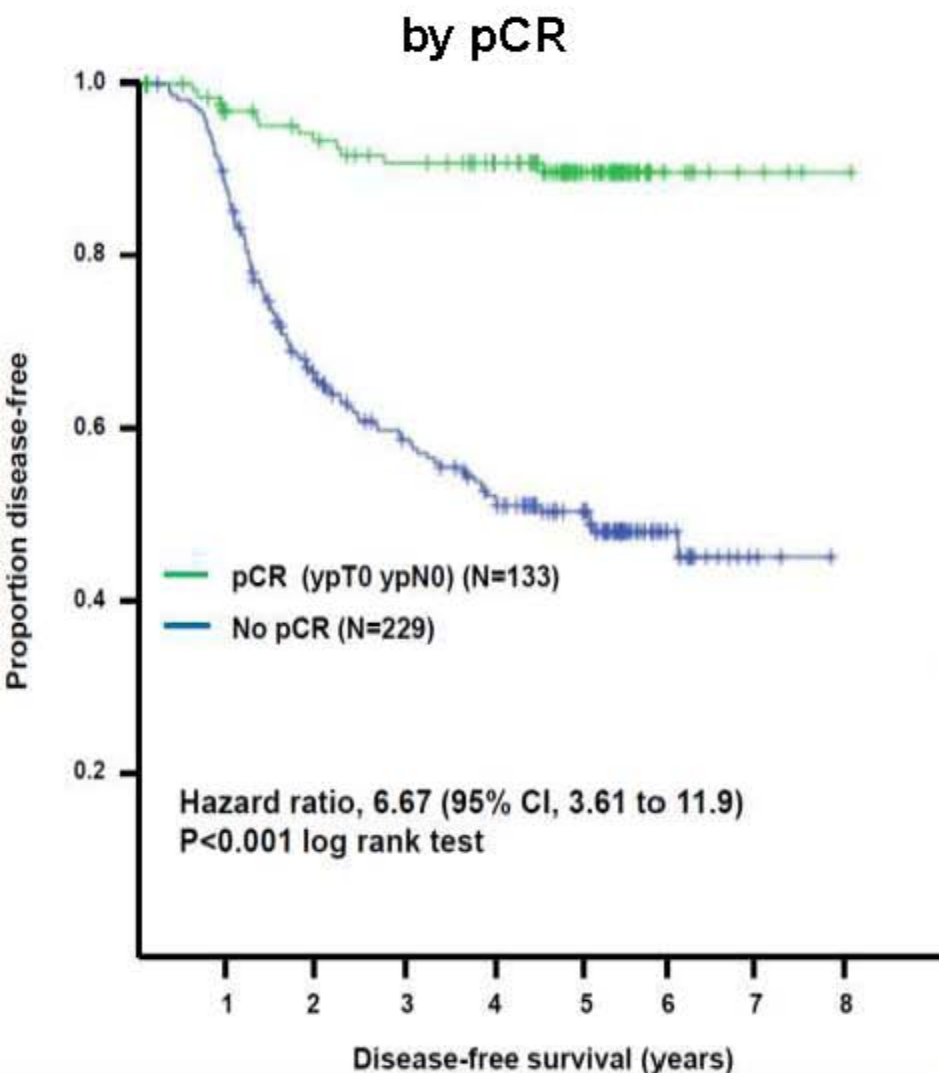
DFS in HER2+(non-luminal) tumors

DFS in Triple Negative Tumors

Conclusion

➢ **Interim response-guided (longer or sequential) neoadjuvant chemotherapy improved survival.**

➢ **Treatment effects on survival derived from luminal-type tumors.**

  ➢ **This treatment effect could not be predicted by pCR as these tumors have lower pCR rates and their prognosis does not depend on pCR.**

➢ **Patients with HER2+ or triple-negative tumors did not benefit from response-guided treatment.**

  ➢ **pCR is highly prognostic in these subgroups.**

  ➢ **Lack of treatment effect on pCR rate corresponds to lack of long term treatment.**

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Comparison of survival according to pathological complete response (pCR) in patients with HER2-positive breast cancer receiving neoadjuvant chemotherapy with and w/o trastuzumab compared to patients with HER2-negative tumors

Loibl S, von Minckwitz G, Blohmer JU, Costa SD, Eidtmann H, Fasching P, Gerber B, Hilfrich J, Huober J, Jackisch C, Kaufmann M, Konecny G, Denkert C, Nekljudova V, Mehta K, Untch M

for the GBG and AGO-B study groups

AGO-B
BREAST STUDY GROUP
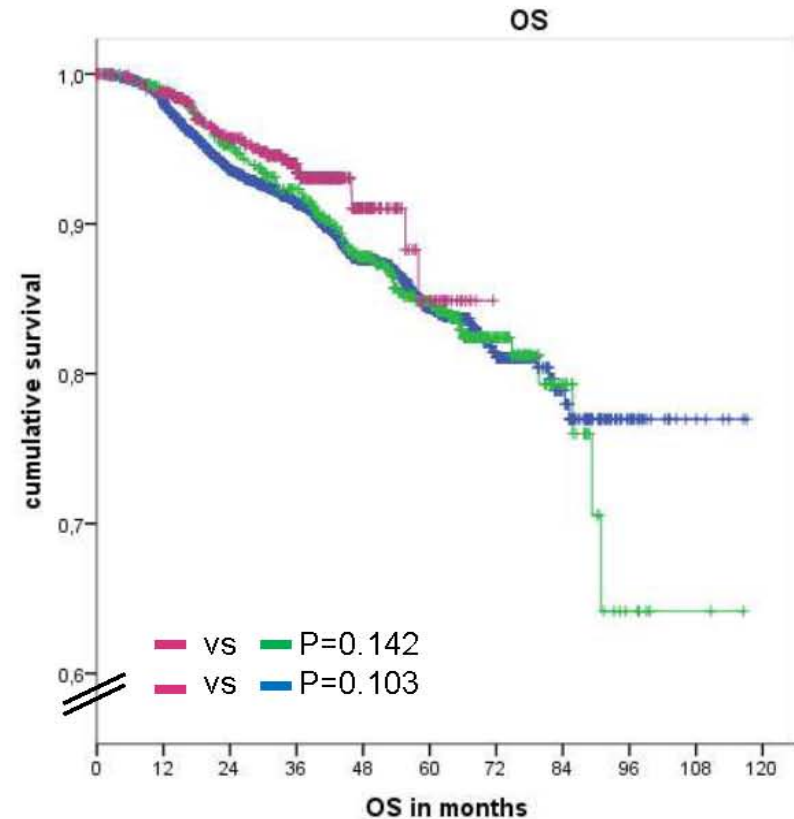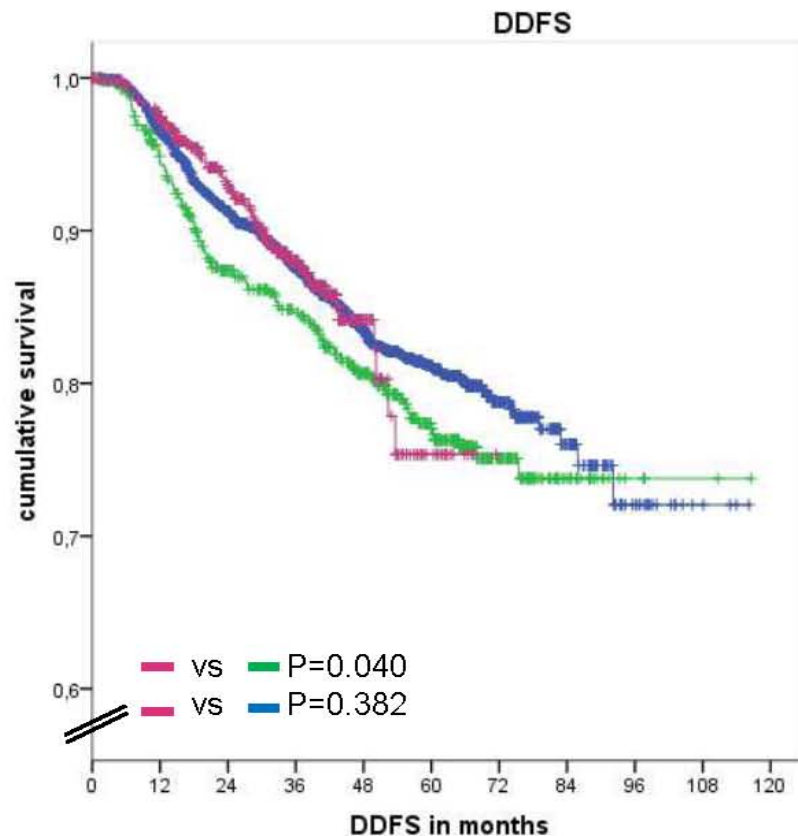
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Objectives

Definition of three subgroups:

> **HER2-positive with trastuzumab**

> **HER2-positive without trastuzumab**

> **HER2-negative**

Compare DDFS and OS in these subgroups:

> **pCR vs. no pCR**

> **hormone receptor positive and -negative tumors**
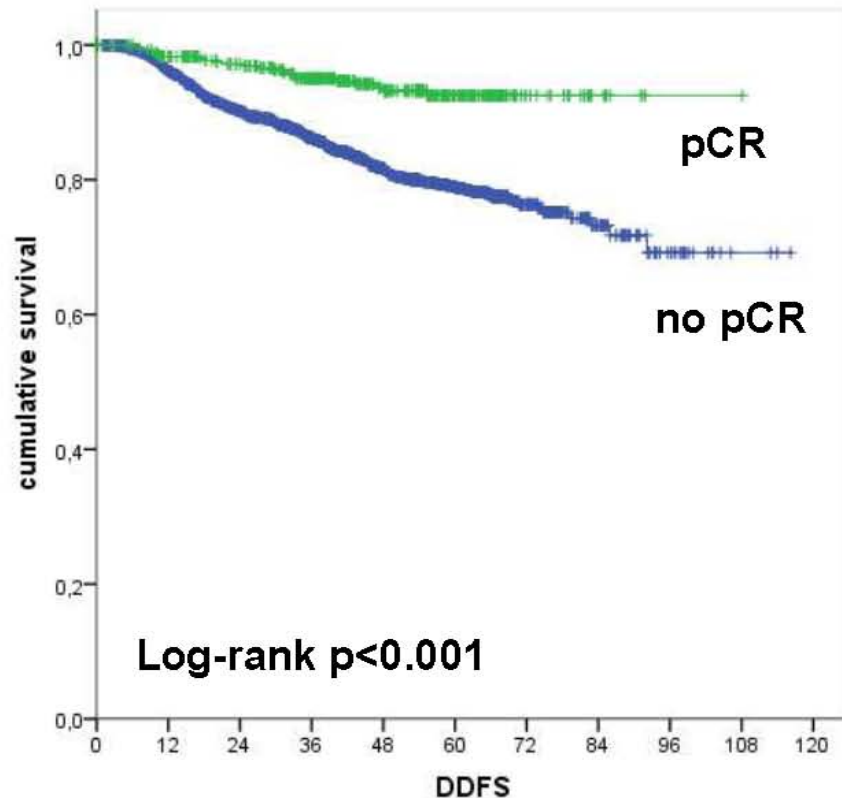
DDFS and OS in the three subgroups
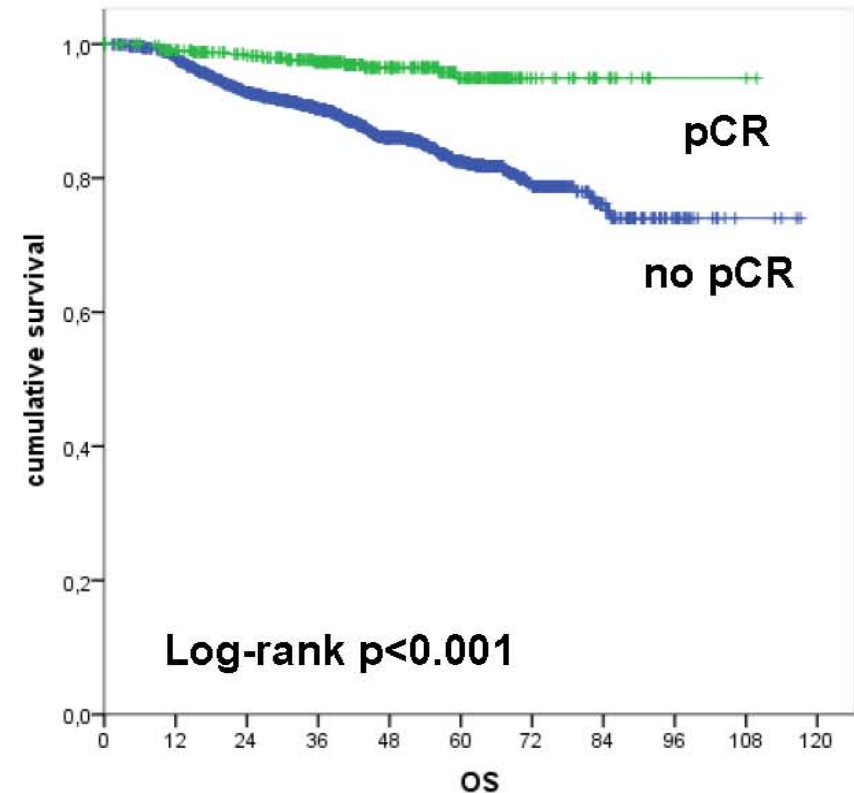

n= 662   HER2+ with trastuzumab
n= 3060 HER2 negative
n= 665   HER2+; no trastuzumab

DDFS and OS by pCR – HER2-negative

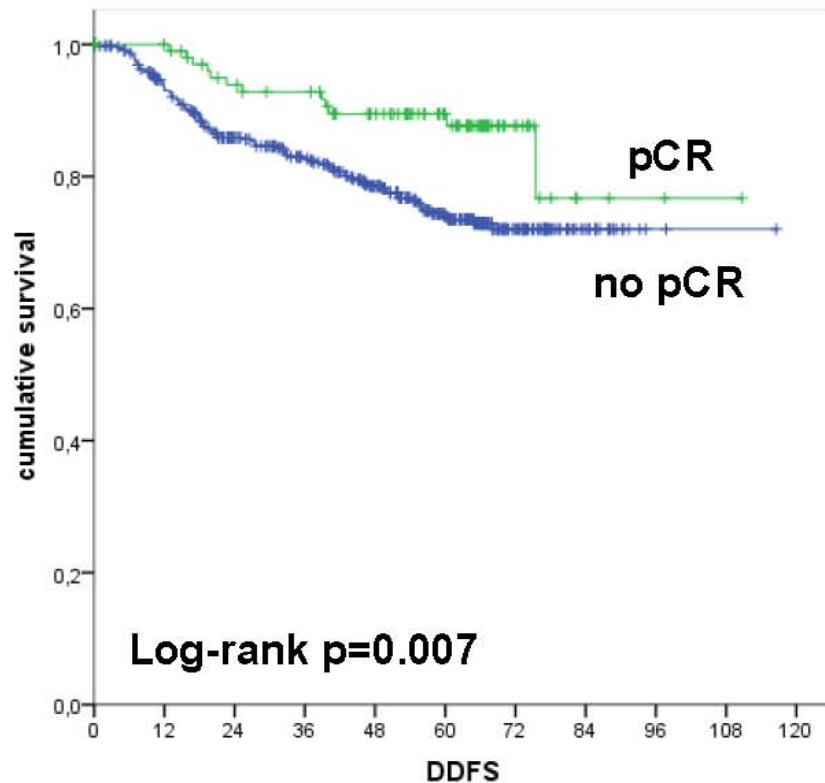# DDFS and OS by pCR – HER2-positive Without Trastuzumab
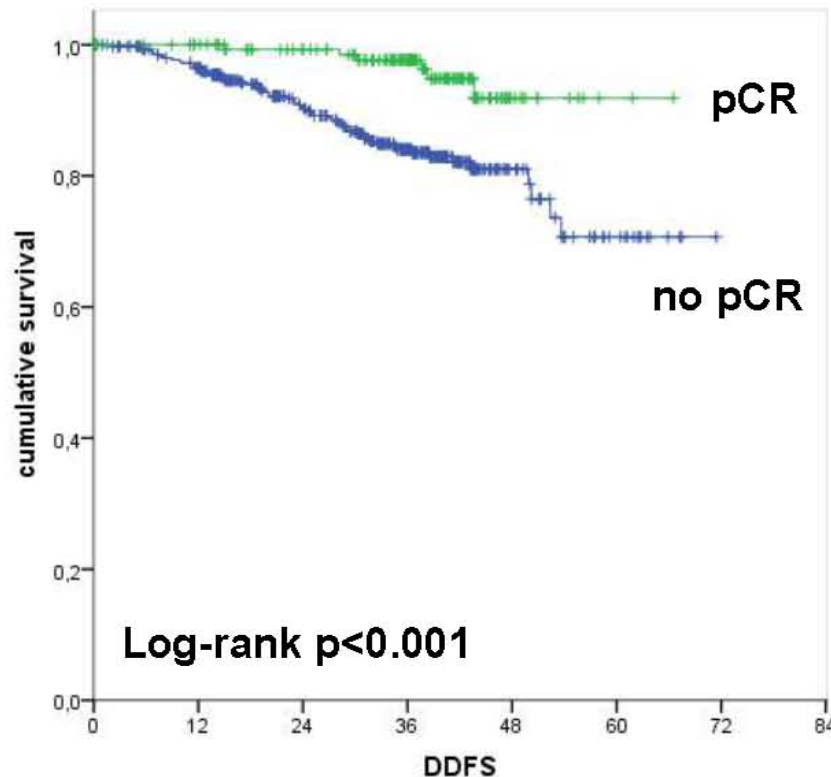
DDFS and OS by pCR – HER2-positive with Trastuzumab
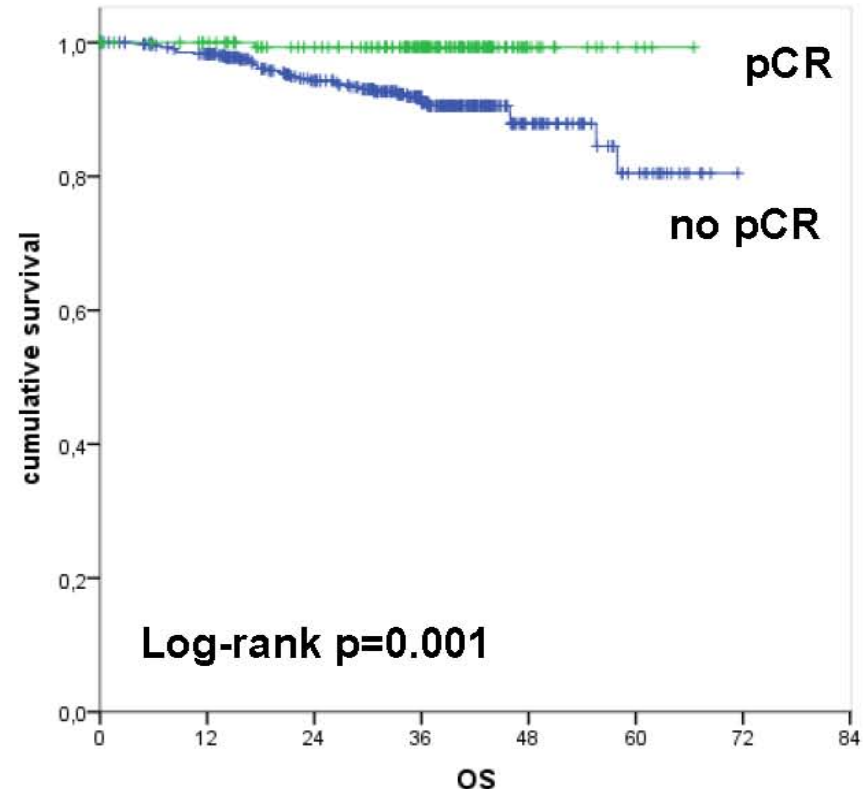
OS analysis by pCR

No pCR

pCR

Arm		N	Events
positive w trast	—	481	35
positive w/o trast	—	546	75
negative	—	2606	310

vs — p=0.295
vs — p=0.384

Log-rank
vs — p=0.058
vs — p=0.134

Arm		N	Events
positive w trast	—	181	1
positive w/o trast	—	119	9
negative	—	454	14
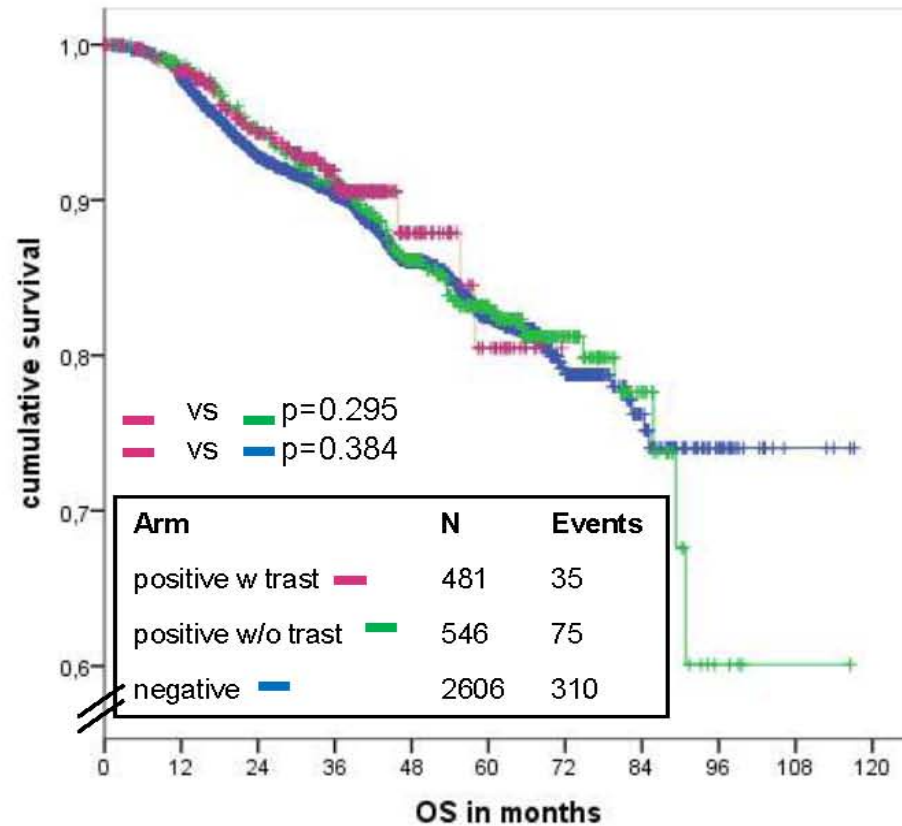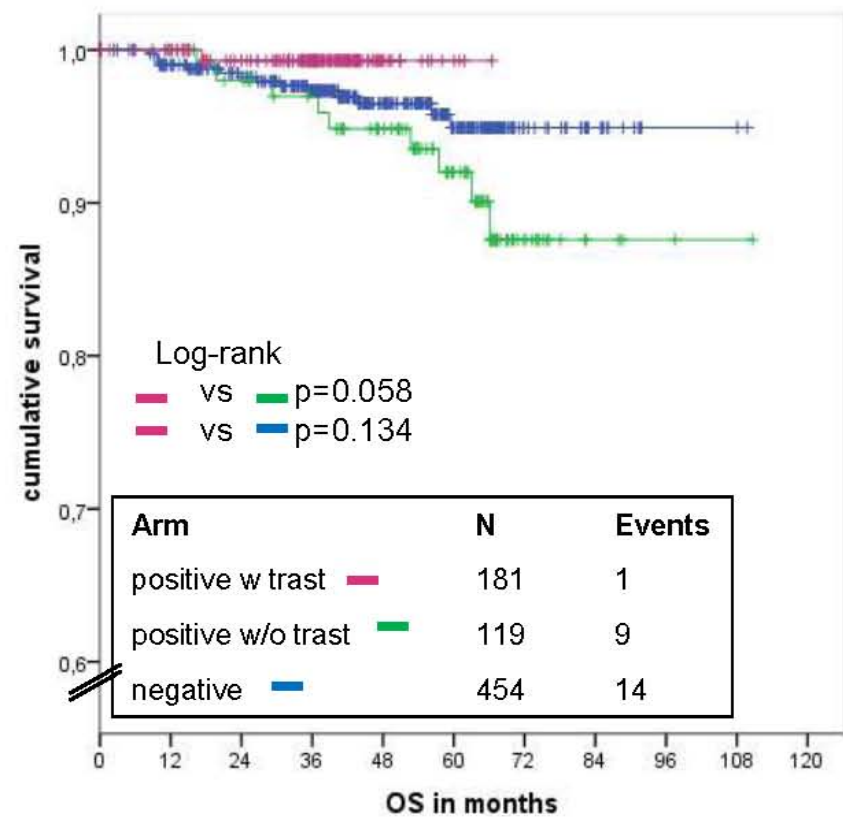
— n= 662   HER2+ with trastuzumab
— n= 3060 HER2 negative
— n= 665   HER2+; no trastuzumab

Summary

➢ **Patients with HER2-positive primary breast cancer treated with trastuzumab and chemotherapy achieve a higher pCR rate**

➢ **DDFS and OS was significantly better with pCR in HER2-negative, HER2-positive non- trastuzumab and HER2-positive trastuzumab patients**

➢ **In pCR patients OS tended to be superior with trastuzumab compared to HER2-positive, non-trastuzumab and HER2-negative patients**

➢ **In particular HER2-positive, hormone receptor negative patients have a better DDFS and OS compared to HER2-positive, non-trastuzumab and HER2-negative patients**

The Present and Future of Genomics in DCIS

On Demand Post-SABCS 2011 Update

Steve Shak, MD

Chief Medical Officer

Key Radiation Trials in DCIS

Year code, study name (reference)	Entry dates	No. of women randomized	No. of women eligible for analysis†	Median follow-up (yr)	Mammographic detection (%)	Breast and axillary surgery	Negative surgical margins required	Central pathological review	Breast radiotherapy
Data available for overview									
NSABP B-17 (3, 4, 5)	1985–1990	818	798	16.5	80	Local excision (37% axillary dissection)	Yes (13% involved or unknown)‡	623 (76%)	50 Gy (2 Gy/f) 9% with boost
EORTC 10853 (6, 7, 8, 9)	1986–1996	1010	918	10.4	72	Local excision (20% axillary dissection)	Yes (16% "not free," <1mm, involved or unknown)‡	824 (82%)	50 Gy (2 Gy/f) 5% with boost
SweDCIS (10, 11, 12)	1987–1999	1067	1011	8.4	79	Sector resection (17% axillary dissection)	No (11% positive, 9% unknown)‡	271 (25%)	50 Gy (2 Gy/f) (80%) or 48 Gy (2.4 Gy/f) (13%) or 54 Gy (2 Gy/f) then 2 wk gap (7%) Boost not recommended
UK/ANZ DCIS§(13)	1990–1998	1030	1002	4.8	100	Local excision (No axillary dissection)	Yes	0 (0%)	50 Gy (2 Gy/f) Boost not recommended
Data not yet available									
RTOG 9804	1999–2006	636	–	–	ns	Local excision (No axillary dissection)	Yes	0 (0%)	50.4 Gy (1.8 Gy/f) or 50 Gy (2 Gy/f) or 42.5 Gy (2.7 Gy/f) Boost not recommended

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *J Natl Cancer Inst Monogr* 2010; 162-177.

Unmet Need

- Reliable methods for making treatment decisions based upon patient specific tumor biology in DCIS have not been previously established

- There is a need to quantitatively assess the risk of invasive breast cancer recurrence in newly-diagnosed patients with DCIS

- There is a significant unmet need for validated tests that identify:

  - low risk disease which may be treated with surgery alone, avoiding toxicities and costs associated with radiation

  - high risk disease for which the addition of radiation may be considered

DCIS Score™: Gene Selection

Proliferation	Hormone Receptor Group	Reference
Ki-67 **STK15** **Survivin** **Cyclin B1** **MYBL2**	**PR** **GSTM1**	**Beta-actin** **GAPDH** **RPLPO** **GUS** **TFRC**

DCIS Score:
- Continuous variable
- Number between 0 – 100

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A QUANTITATIVE MULTIGENE RT-PCR ASSAY FOR PREDICTING RECURRENCE RISK AFTER SURGICAL EXCISION ALONE WITHOUT IRRADIATION FOR DUCTAL CARCINOMA IN SITU (DCIS): A PROSPECTIVE VALIDATION STUDY OF THE DCIS SCORE FROM ECOG E5194

Solin LJ, Gray R, Baehner FL, Butler S, Badve S, Yoshizawa C, Shak S, Hughes L, Sledge G, Davidson N, Perez EA, Ingle J, Sparano J, Wood W

Eastern Cooperative Oncology Group (ECOG)
North Central Cancer Treatment Group (NCCTG)
Genomic Health, Inc (GHI)

2011 San Antonio Breast Cancer Symposium

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ECOG E5194 (PARENT STUDY)

Prospective multicenter study 1997-2000 (n = 670)
Cohort 1: Low/intermediate grade, size $\leq$ 2.5 cm
Cohort 2: High grade, size $\leq$ 1 cm

Study treatment
- Surgical excision
- Minimum 3 mm negative margin width
- No radiation
- Tamoxifen option beginning May 2000

Reported outcomes at 5 and 7 years (Hughes, JCO, 2009)
- Currently 10-year outcomes

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Solin LJ et al, *San Antonio Breast Cancer Symposium* 2011; Abstract S4-6.

DCIS SCORE: 10-YEAR IPSILATERAL BREAST EVENTS (IBE) BY RISK GROUP

ANY IBE

Solin LJ et al, *San Antonio Breast Cancer Symposium* 2011; Abstract S4-6.
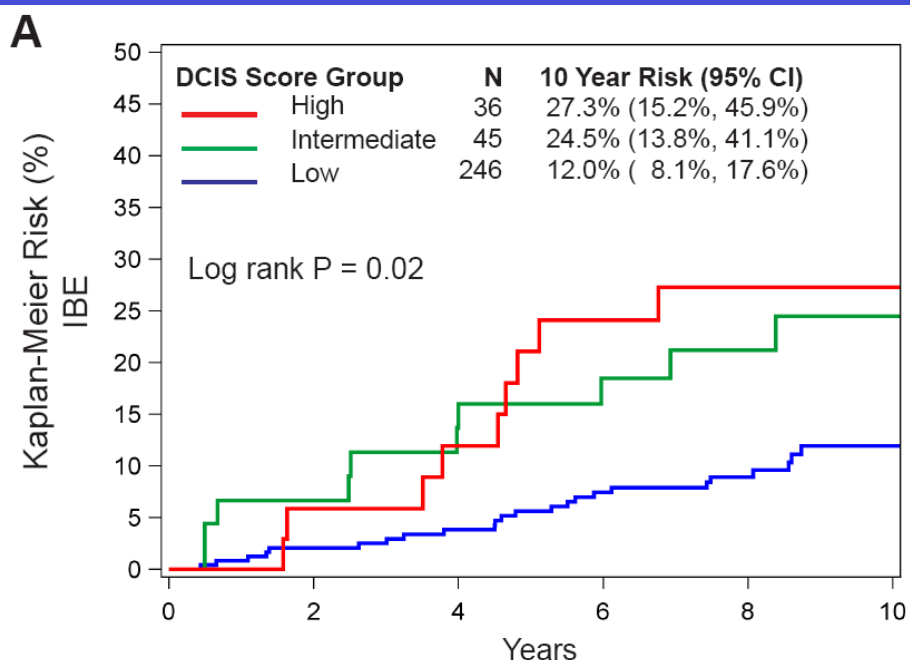
DCIS SCORE: 10-YEAR IPSILATERAL BREAST EVENTS (IBE) BY RISK GROUP

ANY IBE

INVASIVE IBE
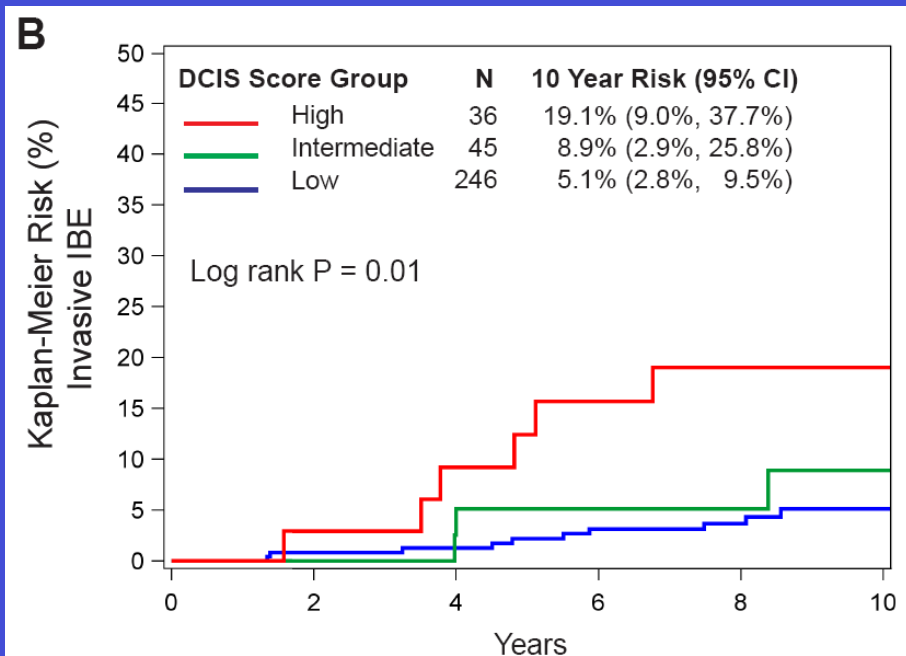
Solin LJ et al, *San Antonio Breast Cancer Symposium* 2011; Abstract S4-6.

DCIS SCORE: 10-YEAR RISK OF AN IPSILATERAL BREAST EVENT (IBE)

ANY IBE

Solin LJ et al, *San Antonio Breast Cancer Symposium* 2011; Abstract S4-6.

DCIS SCORE: 10-YEAR RISK OF AN IPSILATERAL BREAST EVENT (IBE)

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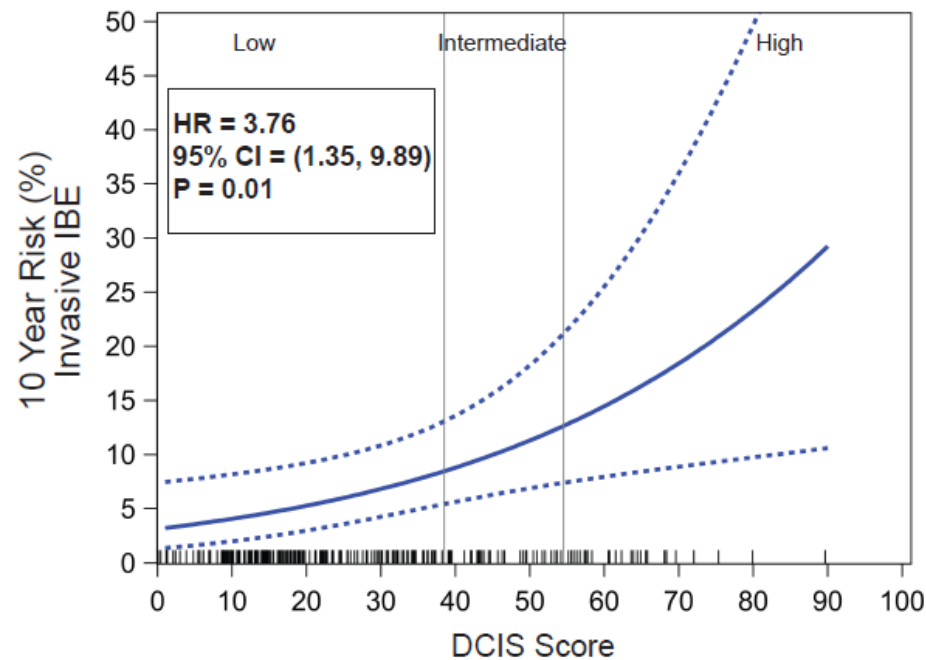
INVASIVE IBE

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    - Including tamoxifen, grade, and negative margin width
    - Identifies underlying tumor biology

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4. **DCIS Score provides a new clinical tool to guide treatment selection for patients with newly diagnosed DCIS**

Solin LJ et al, *San Antonio Breast Cancer Symposium* 2011; Abstract S4-6.

Résultats de ABCSG-12

- Design: étude de AZ (4mg q 6 mo pour 3 ans) ou non (et tamoxifen vs anastrozole)

- Objectif: comparé DFS: objectif principal

  OS: objectif secondaire

- Éligibilité: stage I, II, ER+ et/ou PGR+, prémenopausées recevant goserelin, pas de chimio adjuvante

Résultats ABCGS-12

- Plusieurs analyses de sous groupes manque de puissance et sujet à plusieurs controverses :

  - Âge 40 ans?

Conclusion concernant ABCGS-12 chez les femmes prémenopausées

- ABCGS-12: données probantes de niveau 1 sur la valeur ajoutée de AZ comme traitement adjuvant chez les patientes prémenopausées

- ABCGS-12 a rencontré ses objectif primaires et secondaires

- Résultats de SOFT en attente

- Questions: impact de l'âge (ex: <40 ans), degré de suppression ovarienne, chimio adjuvante et durée optimale

Conclusion concernant ZO-FAST et bisphosphonate chez les patientes ménopausées

- Résultats de ZO-FAST sont en ligne avec d᾽autres études récentes sur AZ:
  - ZO-FAST: 3.6% ↑ de DFS à 5 ans
  - ABCGS-12: 4% ↑ de DFS à 7 ans
  - AZURE: 7.1% ↑ de DFS à 5 ans

  - B-34: 24% ↑ de RFI à 8 ans (HR: 0.76 pour âge > 50

  - NB: bénéfices dans le même ordre que traitement endocrinien:
    - MA-17: 4.6% ↑ DFS à 4 ans
    - EBTCG: 2.9% ↓ des récidives avec un IA vs tamoxifene à 5 ans (méta-analyse)

Conclusions Regarding ZA in Postmenopausal Women

<u>ZO-FAST</u>: Demonstrated value of ZA in postmenopausal women but based on unplanned analyses. **Thus, insufficient to support ZA as standard of care in postmenopausal women.**

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97

Conclusions Regarding ZA Postmenopausal Women

<u>ZO-FAST</u>: Demonstrated value of ZA in postmenopausal women but based on unplanned analyses. **Thus, insufficient to support ZA as standard of care in postmenopausal women.**

Are premenopausal women treated with ovarian function suppression (as in ABCSG-12) the same as postmenopausal women?
Perhaps but not necessarily; cannot directly extrapolate ABCSG-12 results to postmenopausal women

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98

Comments Regarding ZA Trials
-Postmenopausal-

Numerous questions remain: e.g.,
- type of bisphosphonate
- schedule and duration of therapy
- impact of chemotherapy

Other studies will provide data, e.g.,
- B-34 (clodronate vs placebo, for 3 yrs)
- GAIN (ibandronate vs observation, for 2 yrs)
- S0307 (ZA vs clodronate vs ibandronate, for 3 yrs), future

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99

Comments Regarding ZA in Postmenopausal Women

Mounting evidence suggests that bisphosphonates will become established as efficacious in adjuvant therapy of postmenopausal women with early stage breast cancer.

Chimiothérapie néoadjuvante: Relation entre pCR et devenir des patientes

- HER2 négatif

  - Changement de pratique?
  - Ré-évaluation de réponse par echo aux 2 cycles
  - Changement de traitement ami-parcours
  - 8 cycles de chimio de routine?

- HER2+

  - Traitement anti-HER2 précoce est préférable
  - Marqueurs ER/PR et HER2 sur biopsie de principe
  - Cancer invasif HER2+ seront les premiers guéris

DCIS score

- Premier outil prédicteur de façon objective de la récidive locale dans le DCIS
  - Variable continue

- Applications?
  - Valeur prédictive du bénéfice de la radiothérapie indéterminée

- Recherche additionnelle nécessaire:
  - DCIS HER2+
  - Gènes prédicteurs des bénéfices de la radiothérapie
  - Gènes prédicteurs de la récidive sous forme invasive