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2011 San Antonio Breast Cancer Symposium Review

Metastatic HR+, TNBC, & Bisphosphonates Abstracts

Georgia Health Sciences University
New name. Same commitment to better health.

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January 7, 2012

Disclosure

- Potential Conflicts of Interest:
  - Principal Investigator:
    - *Novartis*
    - *ImClone*
    - *Exelesis*
  - Sub-Investigator:
    - *GHSU MB-CCOP*

GHSU Cancer Research Center

GHSU Cancer Outpatient Center

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- Metastatic HR+:
  - S1-1: SWOG S0226
  - S3-7: BOLERO-2
- Triple Negative:
  - S3-5: Next gen sequencing for TNBC
- Bisphosphonates:
  - S1-2: ABSCG-12
  - S1-3: ZOFAST
  - S2-3: NSABP B-34
  - S2-4: GAIN

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S1-1: SWOG S0226

A phase III randomized trial of anastrozole versus anastrozole and fulvestrant as first-line therapy for postmenopausal women with metastatic breast cancer.

Mehta RS, Barlow WE, Albain KS, Vandenberg TA, Dakhil SR, Tirumali NR, Lew DL, Hayes DF, Gralow JR, Livingston RB, and Hortobagyi GN

Background

- Anastrozole lowers estrogen levels and fulvestrant down-regulates the estrogen receptor
- The combination of anastrozole and fulvestrant may be additive in postmenopausal breast cancer
- Fulvestrant has a high efficacy in low-estrogen *in vivo* model (Osborne JNCI 1995)
- The combination of fulvestrant and anastrozole down-regulates several resistance proteins in *in vivo* model (Macedo et al. Cancer research 2008)

S0226: Main Eligibility Criteria

- Postmenopausal women with metastatic breast cancer (measurable or non-measurable)
- ER-positive or PgR-positive by local institutional standards
- No prior chemotherapy, hormonal therapy, or immunotherapy for metastatic disease
- Prior adjuvant tamoxifen allowed (stratification factor)
- Prior adjuvant AI allowed if completed 12 months earlier
- Neoadjuvant or adjuvant chemotherapy completed more than 12 months prior
- Patients were not allowed chemotherapy or other hormone therapy while on treatment
- Must have given informed consent

S0226: Schema

RANDOMIZE

Arm 1

Anastrozole only: 1 mg PO daily

Treat until progression; crossover to fulvestrant strongly encouraged after progression

Arm 2

Anastrozole: 1 mg PO daily

First cycle of 28 days:

Fulvestrant 500mg IM (2 x 5 mL) Day 1
Fulvestrant 250mg IM (1 x 5 mL) Day 14
Fulvestrant 250mg IM (1 x 5 mL) Day 28

Subsequent cycles of 28 days:

Fulvestrant 250mg IM (1 x 5 mL) Day 28

Treat until progression

- **690 eligible patients stratified by use of adjuvant tamoxifen**
- **Primary endpoint: Progression-free survival (PFS)**
- **Overall survival is a secondary endpoint**

Primary Comparisons

- Intent-to-treat analysis of eligible patients
- Analysis stratified by prior adjuvant tamoxifen
- Results presented:
  - Population characteristics
    - 707 patients randomized in the period June 2004 to June 2009
    - 694 analyzed excluding 12 ineligible patients and one who withdrew consent
  - Progression-free survival
  - Overall survival
  - Toxicity

Patient Characteristics

Characteristic	Anastrozole	Anastrozole + Fulvestrant	Total
Randomized	352	355	707
Ineligible or withdrew consent	7 (2.0%)	6 (1.7%)	13 (1.8%)
Analyzed	345	349	694
Age median (range)	65 (36-91)	65 (27-92)	65 (27-92)
Prior adjuvant tamoxifen	139 (40.3%)	141 (40.4%)	280 (40.3%)
Prior adjuvant chemo	103 (29.9%)	129 (37.0%)	232 (33.4%)
Disease characteristics			
Measurable	54.5%	53.9%	54.2%
Bone only	22.0%	21.5%	21.8%
De novo metastatic disease	41.8%	36.0%	38.9%
> 10 years since previous dx	26.1%	30.7%	28.4%
HER2-positive	8.5%	10.4%	9.5%

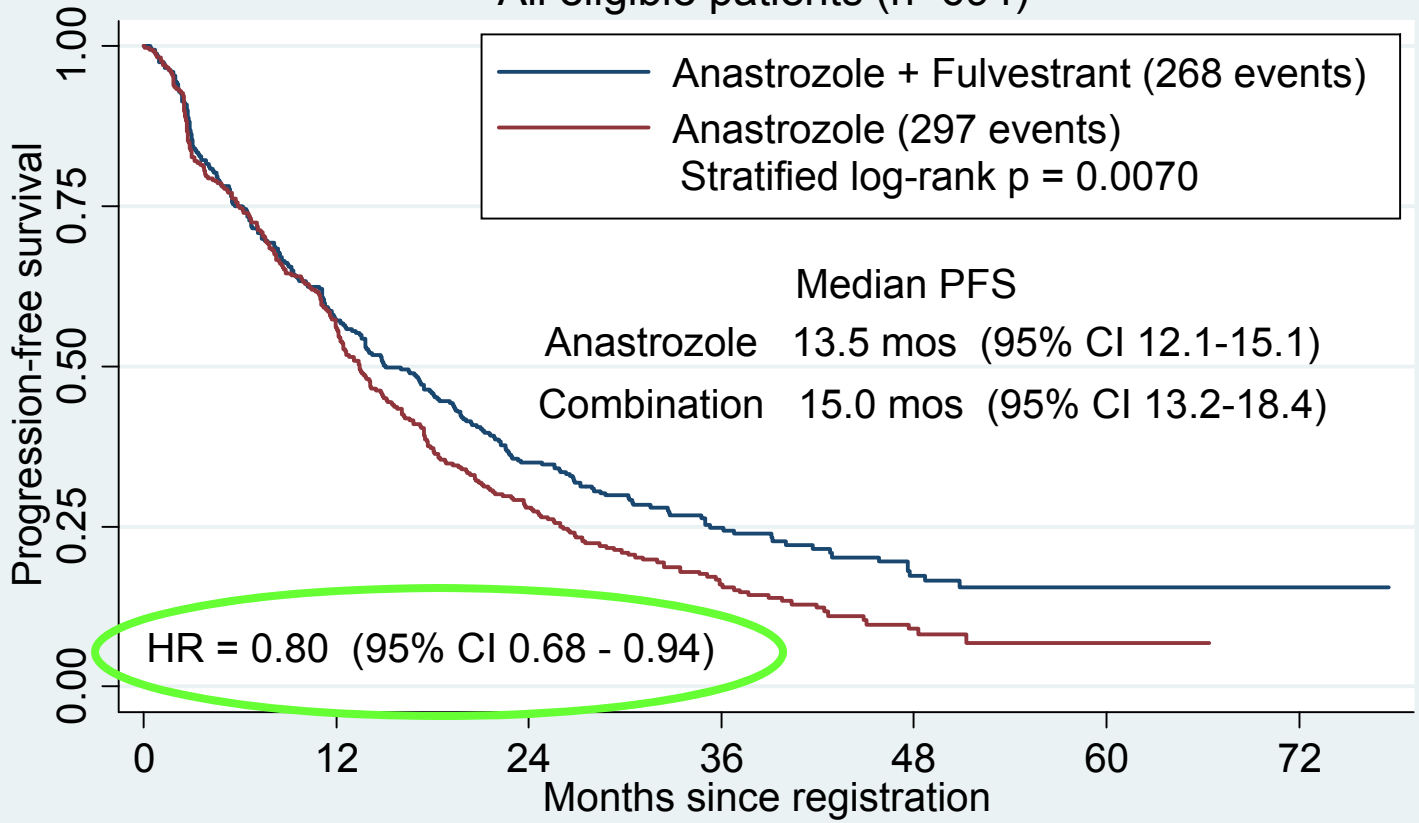
Use of adjuvant AI is being determined retrospectively, but only 12 users of adjuvant AI's have been identified.

Crossover

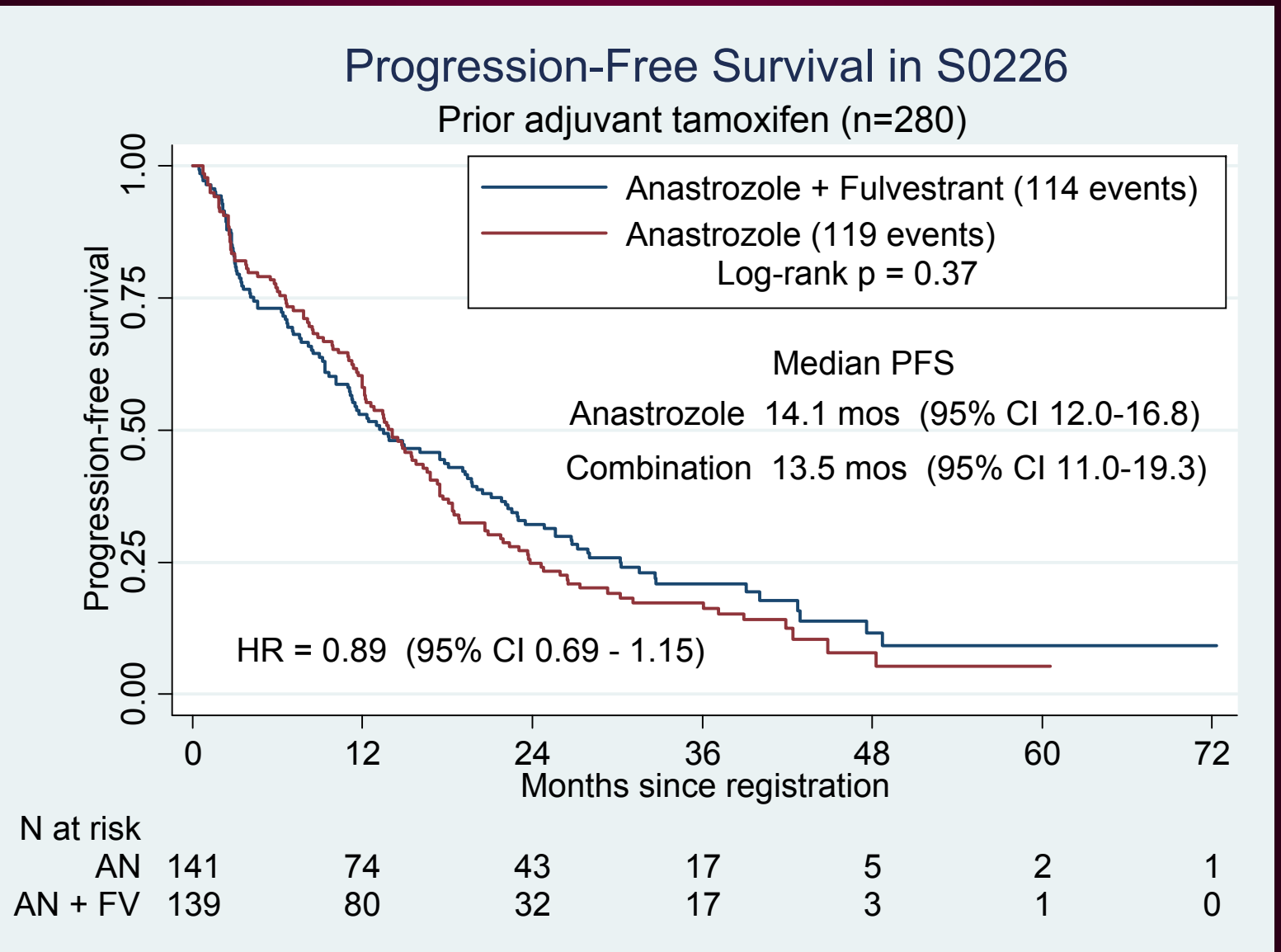
- ***Patients in the anastrozole arm were strongly encouraged to crossover to fulvestrant after progression***
- ***After Feb 15, 2011 patients on either arm could crossover to 500 mg fulvestrant dosing after progression***
- ***143 of 345 patients (41%) on anastrozole did crossover to fulvestrant after progression (including 5 who took the 500 mg dosing)***
- ***9 of 349 patients on the combination took 500 mg dosing after progression***

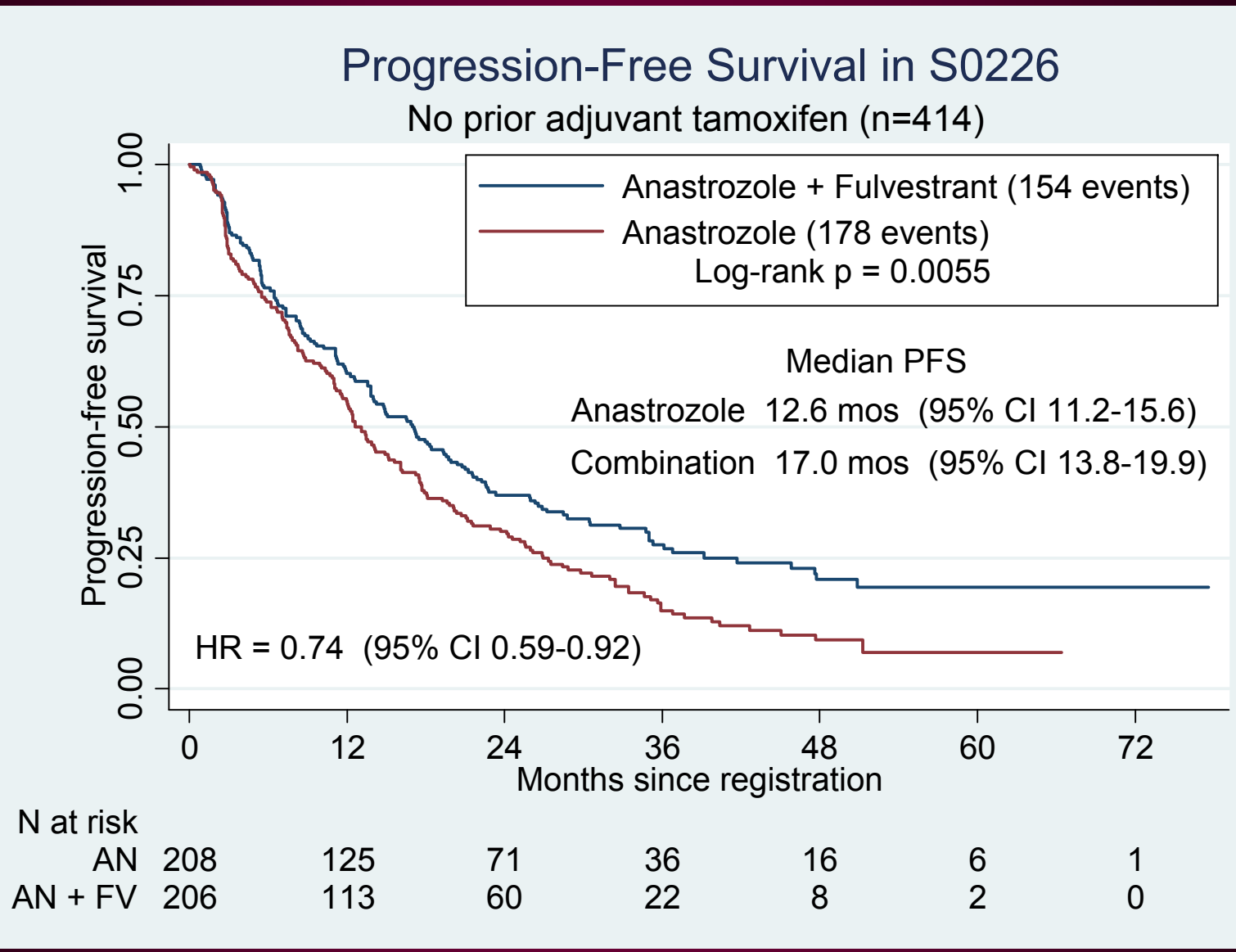
Progression-Free Survival in S0226

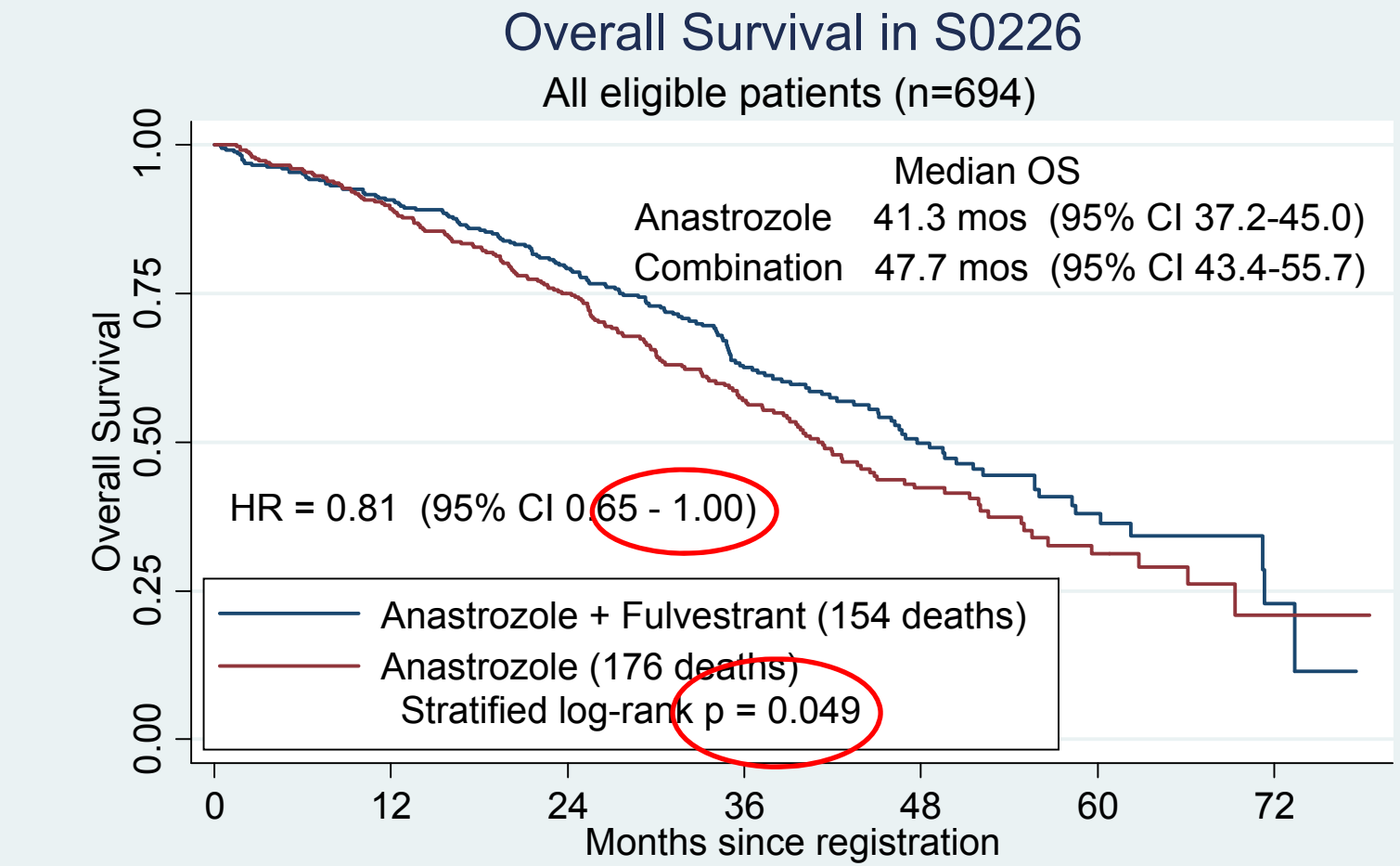
All eligible patients (n=694)



N at risk							
AN	349	199	114	53	21	8	2
AN + FV	345	193	92	39	11	3	0

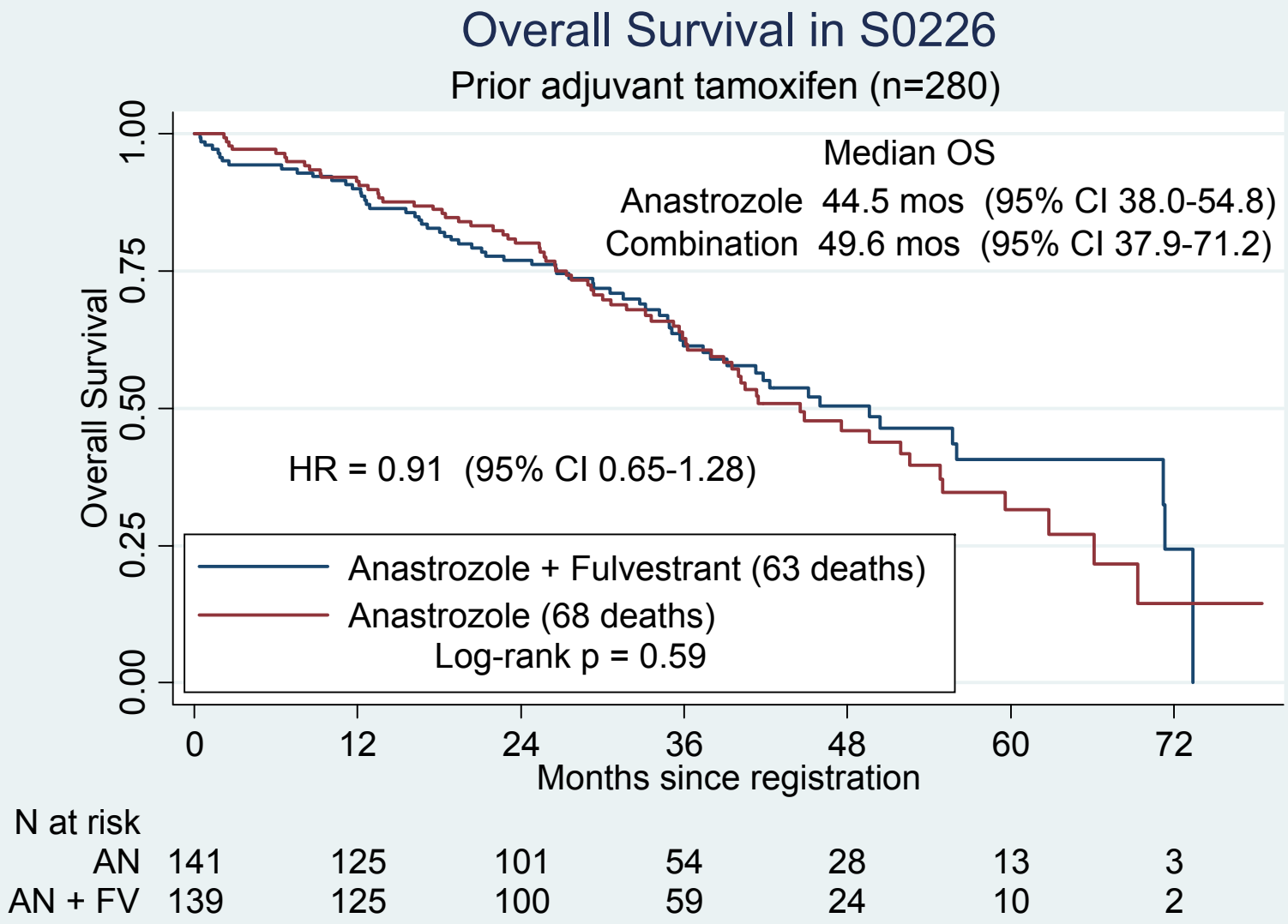

Progression-Free Survival in S0226
Prior adjuvant tamoxifen (n=280)
Anastrozole + Fulvestrant (114 events)
Anastrozole (119 events)
Log-rank p = 0.37
Median PFS
Anastrozole 14.1 mos (95% CI 12.0-16.8)
Combination 13.5 mos (95% CI 11.0-19.3)
HR = 0.89 (95% CI 0.69 - 1.15)
Progression-free survival
0.00
0.25
0.50
0.75
1.00
0
12
24
36
48
60
72
Months since registration
N at risk
AN 141 74 43 17 5 2 1
AN + FV 139 80 32 17 3 1 0


Progression-Free Survival in S0226
No prior adjuvant tamoxifen (n=414)
Anastrozole + Fulvestrant (154 events)
Anastrozole (178 events)
Log-rank p = 0.0055
Median PFS
Anastrozole 12.6 mos (95% CI 11.2-15.6)
Combination 17.0 mos (95% CI 13.8-19.9)
HR = 0.74 (95% CI 0.59-0.92)
Progression-free survival
0.00
0.25
0.50
0.75
1.00
0
12
24
36
48
60
72
Months since registration
N at risk
AN 208 125 71 36 16 6 1
AN + FV 206 113 60 22 8 2 0



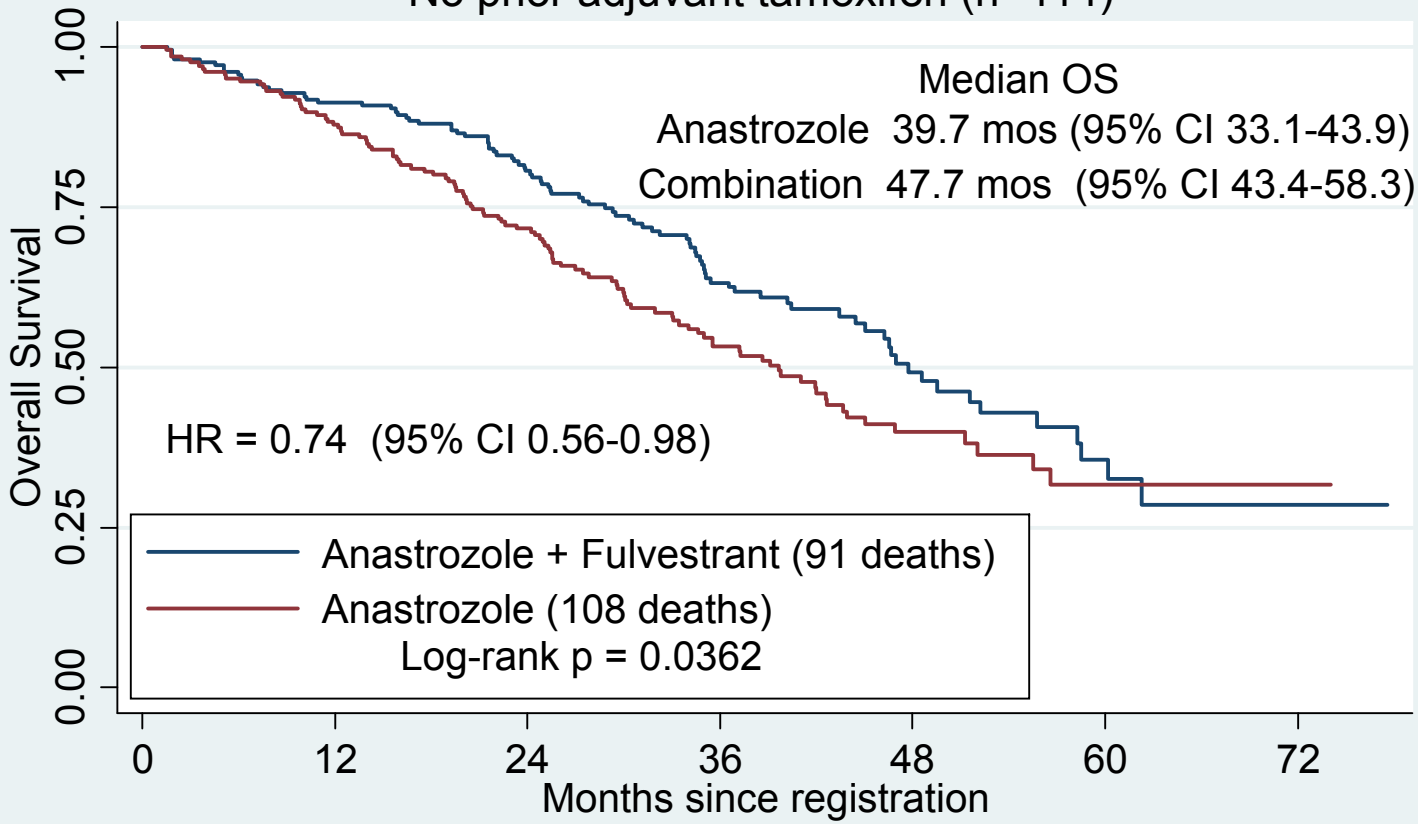
N at risk

AN	349	315	259	145	62	26	4
AN + FV	345	306	239	136	54	22	4


Overall Survival in S0226
Prior adjuvant tamoxifen (n=280)
Median OS
Anastrozole 44.5 mos (95% CI 38.0-54.8)
Combination 49.6 mos (95% CI 37.9-71.2)
HR = 0.91 (95% CI 0.65-1.28)
Anastrozole + Fulvestrant (63 deaths)
Anastrozole (68 deaths)
Log-rank p = 0.59
Overall Survival
0.00
0.25
0.50
0.75
1.00
0
12
24
36
48
60
72
Months since registration
N at risk
AN 141 125 101 54 28 13 3
AN + FV 139 125 100 59 24 10 2

Overall Survival in S0226

No prior adjuvant tamoxifen (n=414)

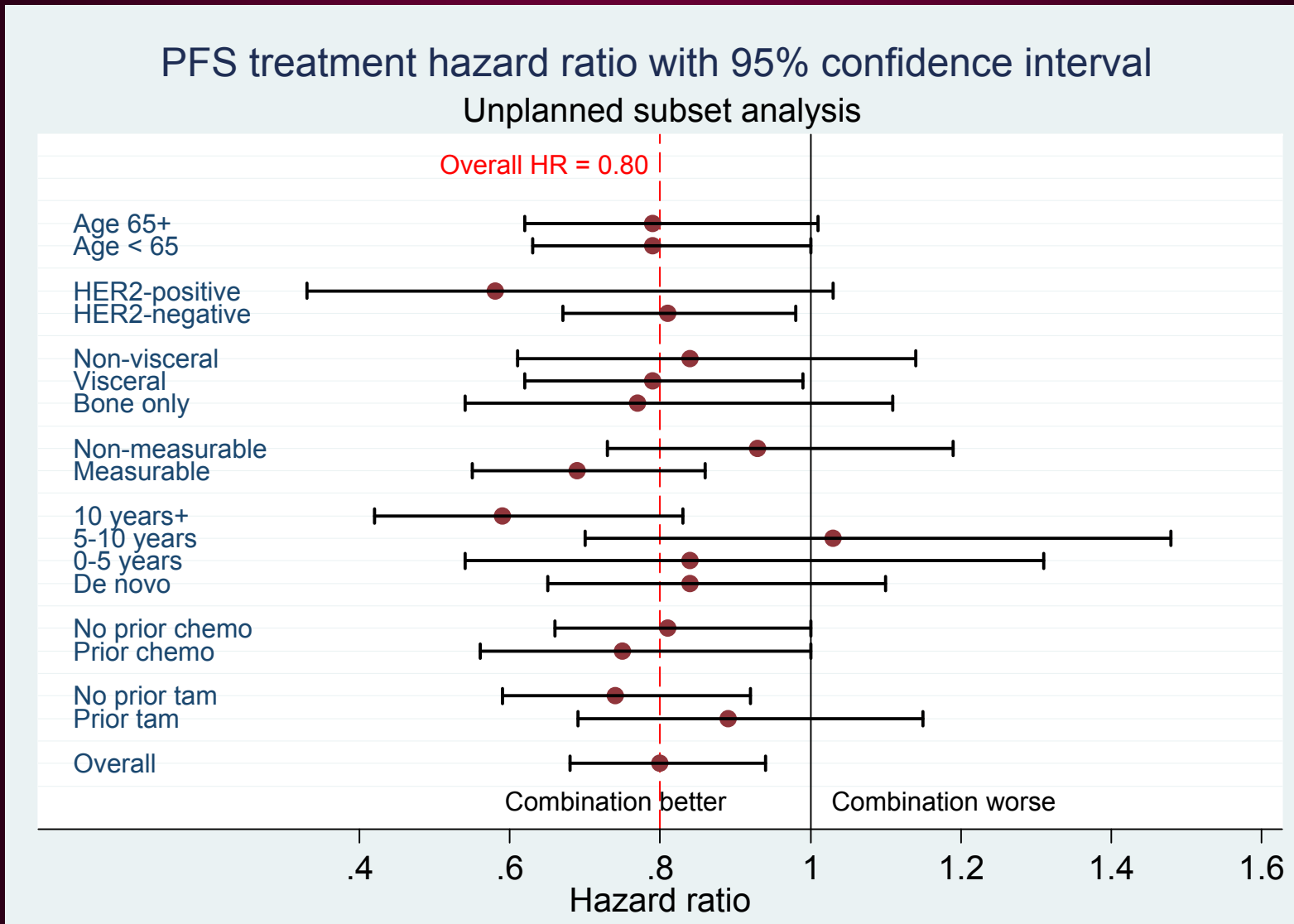


N at risk							
AN	208	190	158	91	34	13	1
AN + FV	206	181	139	77	30	12	2

Prior tamoxifen as a predictive factor?

- Overall planned analysis is highly significant
- ***Unplanned analysis*** by prior tamoxifen may suggest benefit only in the tamoxifen naive group
- Prior tamoxifen use is confounded with time between adjuvant diagnosis and metastatic diagnosis
- Need to better understand other possible predictive factors since the prior tamoxifen factor could be a false lead from an unplanned analysis

Forest Plot


PFS treatment hazard ratio with 95% confidence interval
Unplanned subset analysis
Overall HR = 0.80
Age 65+
Age < 65
HER2-positive
HER2-negative
Non-visceral
Visceral
Bone only
Non-measurable
Measurable
10 years+
5-10 years
0-5 years
De novo
No prior chemo
Prior chemo
No prior tam
Prior tam
Overall
Combination better
Combination worse
.4
.6
.8
1
1.2
1.4
1.6
Hazard ratio

S0226 Toxicity: Grade 4 and 5

- Three patients on the combination had grade 5 toxicities:
  - two had pulmonary embolism
  - one had cerebrovascular ischemia
- Two other patients on the combination had grade 4 toxicities:
  - one had pulmonary embolism
  - one had neutropenia and lymphopenia
- Four patients on anastrozole alone had Grade 4 toxicities (thrombosis/embolism, arthralgia, thrombocytopenia, dyspnea)

First-Line Hormonal Agent Phase-III Studies in Breast Cancer: Overall Survival

Study	N	Control Arm (months)	Experimental Arm (months)	HR for OS	P-value
S0226	694	Anastrozole (→fulvestrant (41.3)	Anastrozole + Fulvestrant (47.7)	0.80	0.049
Bergh SABCS 2009 (FACT)	514	Anastrozole (38.2)	Anastrozole + Fulvestrant (37.8)	1.00	1.00
Nabholtz 2003 Eur J C	1021	Tamoxifen (40.1)	Anastrozole (39.2)	0.97	?
Mouridsen 2003 JCO	916	Tamoxifen (30)	Letrozole (34)	?	0.53
Paridaens JCO 2008	371	Tamoxifen (43.3)	Exemestane (37.2)	1.04	0.82
Howell JCO 2004	587	Tamoxifen (38.7)	Fulvestrant (36.9)	1.29	0.04

S0226 Conclusions:

- The combination of anastrozole and fulvestrant improves PFS and OS, the primary and secondary endpoints, respectively, in first-line therapy of hormone receptor positive breast cancer in postmenopausal women
- The toxicity of the combination treatment is comparable to single agent treatment though Grade 5 toxicity was seen only with the combination

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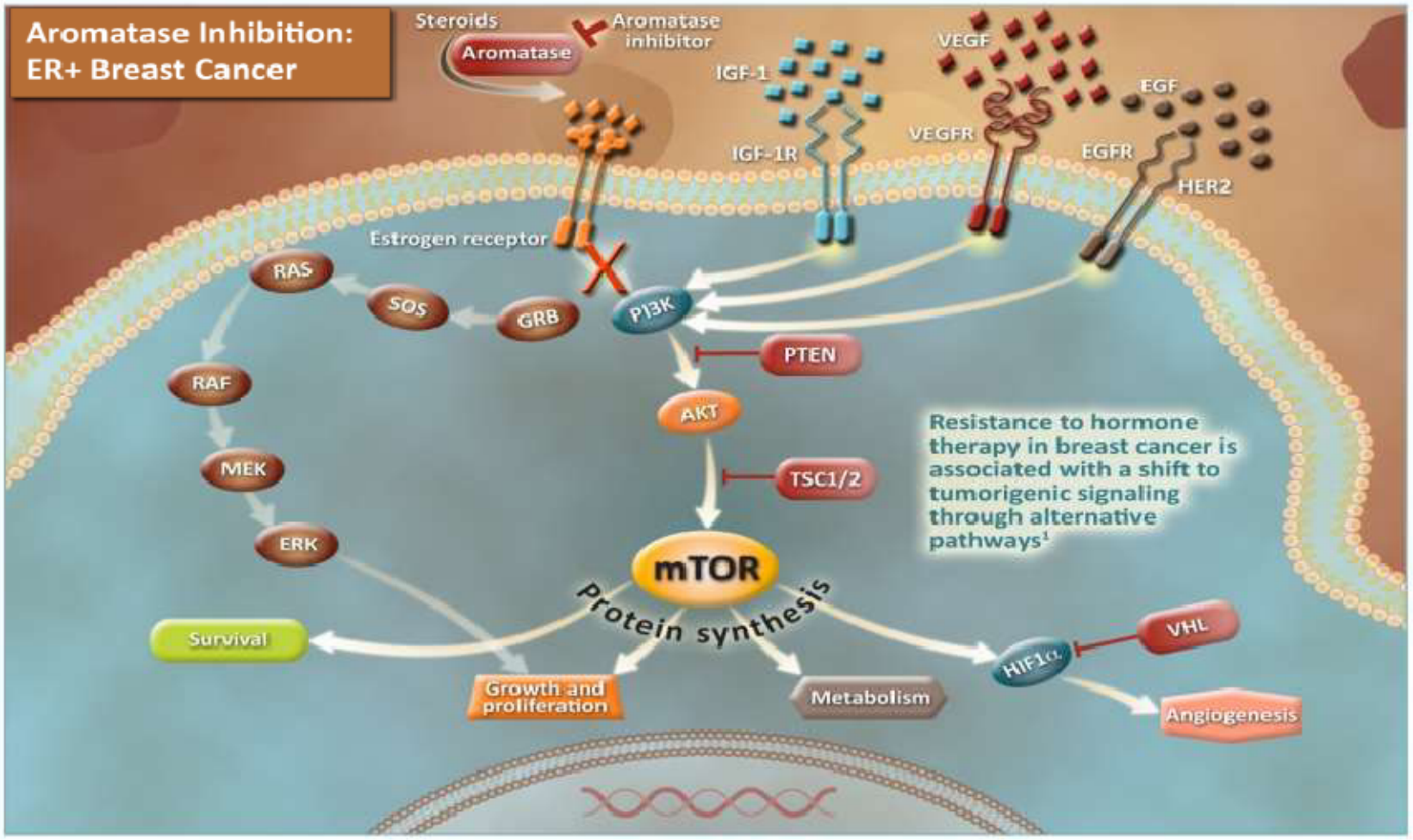
S3-7: BOLERO-2

Everolimus for postmenopausal women with advanced breast cancer: updated results of the BOLERO-2 trial

G. N. Hortobagyi, M. Piccart, H. Rugo, H. Burris, M. Campone, S. Noguchi, M. Gnant, K. I. Pritchard, L. Vittori, P. Mukhopadhyay, T. Sahmoud, D. Lebwohl, J. Baselga

On behalf of the BOLERO-2 Investigators

Aromatase Inhibition: ER+ Breast Cancer



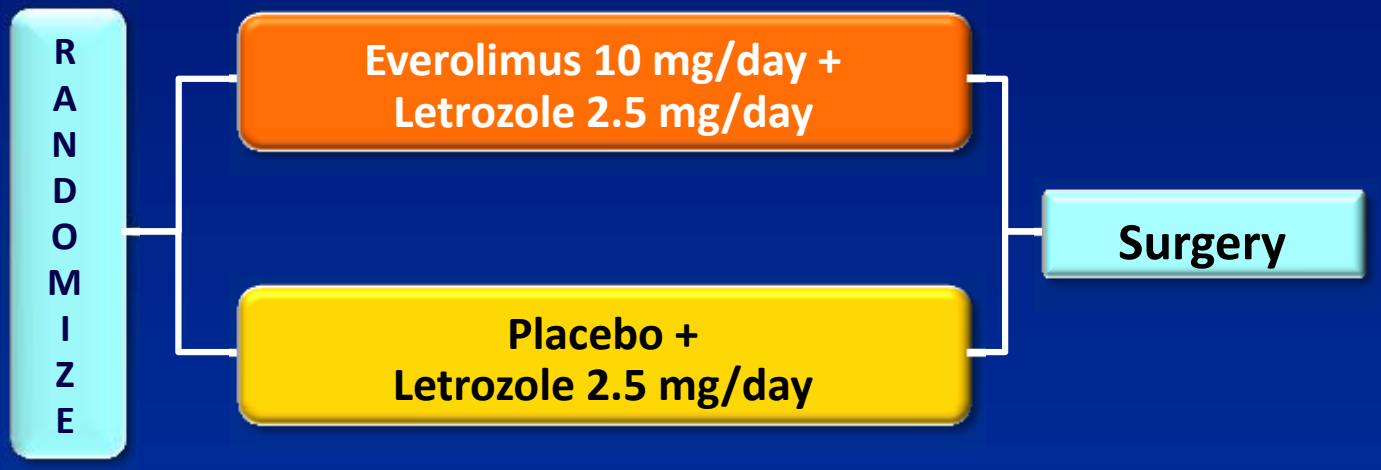
ER+ = estrogen receptor-positive.

Moy B et al. Clin Cancer Res. 2006;12:4790-4793

Neoadjuvant (Ph II): Letrozole ± Everolimus

Primary endpoint: RR at 16 weeks (palpation)

270 postmenopausal women with ER+ early BC

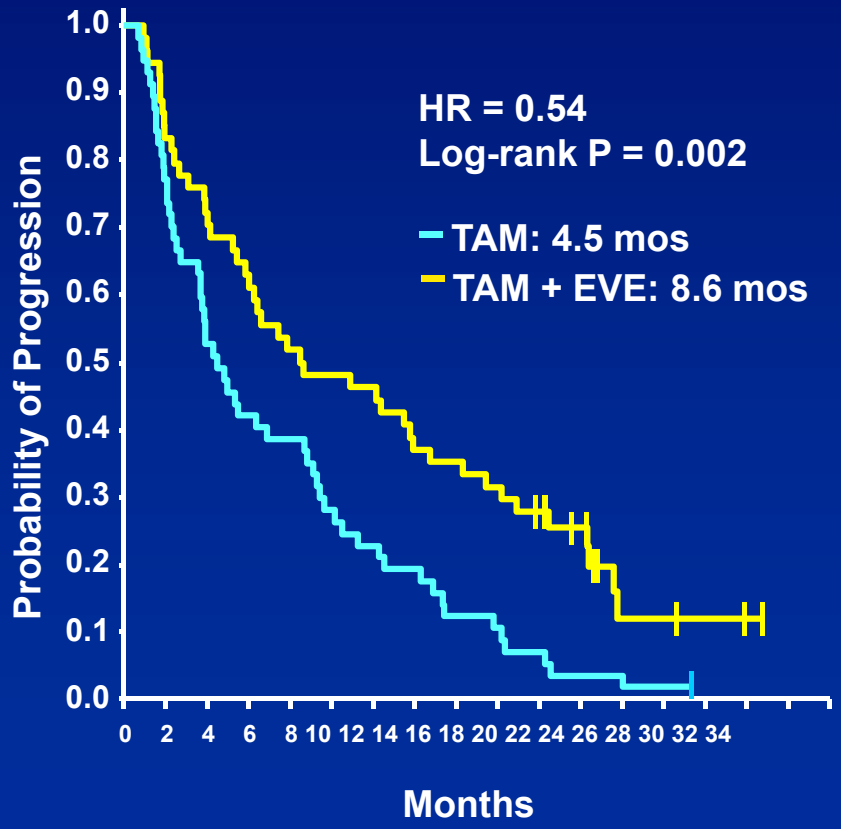


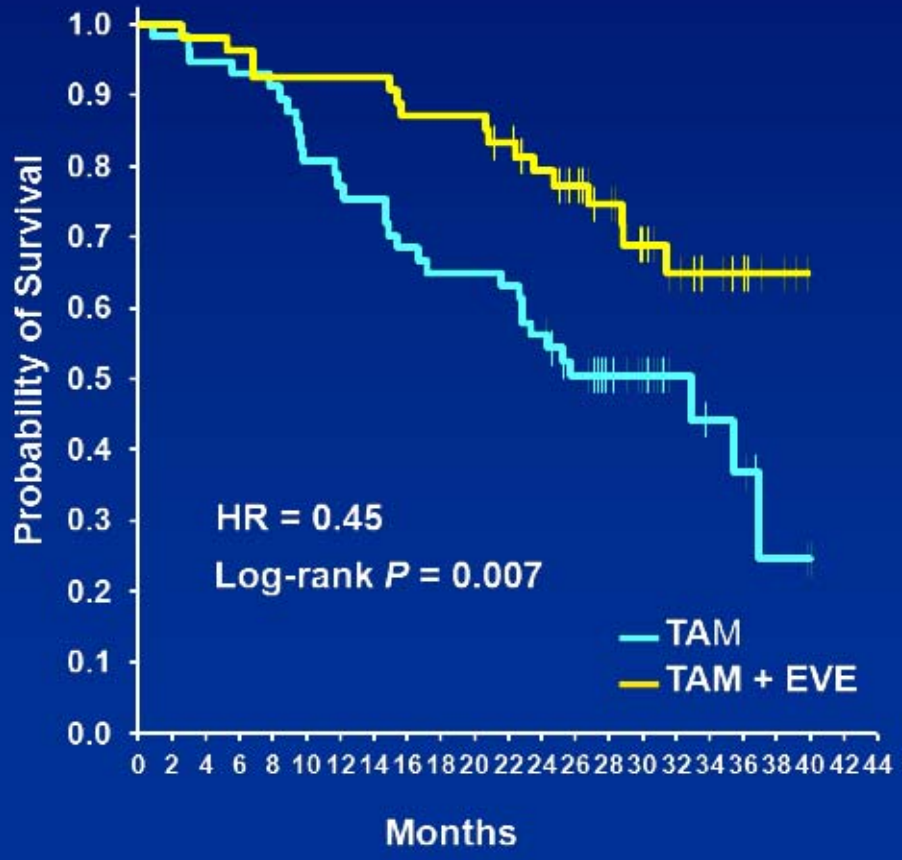
- Higher RR: 68% vs. 59% (P = 0.062)
- Greater antiproliferative response: ↓ Ki67 by 57% vs. 30% (P < 0.01)

BC = breast cancer; ER+ = estrogen receptor-positive; RR = response rate.
Baselga J et al. JCO. 2009;27:2630-2637

TAMRAD (Ph II): Tamoxifen ± Everolimus in Advanced BC

- 111 postmenopausal women with ER+ advanced BC previously **treated with an AI were randomized in a phase II trial**





AI = aromatase inhibitor; BC = breast cancer; ER+ = estrogen receptor-positive; EVE = everolimus; TAM = tamoxifen.
Bourgier C et al. ECCO/ESMO 2011 (Abstract #5005)

BOLERO-2 (Ph III): Everolimus in Advanced BC

N = 724

- Postmenopausal ER+
- Unresectable locally **advanced or metastatic BC**
- Recurrence or progression **after letrozole or anastrozole**

R
2:1

EVE 10 mg daily
+
EXE 25 mg daily (n = 485)

Placebo
+
EXE 25 mg daily (n = 239)

Stratification: Sensitivity to prior hormone therapy and presence of visceral metastases

Endpoints

- Primary: PFS (local assessment)
- Secondary: OS, ORR, QOL, safety, bone markers, PK

BC = breast cancer; ER+ = estrogen receptor-positive; EVE = everolimus; EXE = exemestane; ORR, overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; QOL = quality of life.
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2: Statistical Design

- Primary endpoint: PFS
  - Design: HR = 0.74, 528 events, 90% power
  - Interim analysis after 359 events, O'Brien-Fleming **boundary**

PFS crossed boundary at interim analysis (local and central)

- Cut-off date for this update: July 8, 2011
  - Median duration of follow-up: 12.5 months
  - 457 PFS events based on local radiology review
  - 282 PFS events based on central radiology review

HR = hazard ratio; PFS = progression-free survival.
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2: Baseline Characteristics

	Everolimus + Exemestane (n = 485), %	Placebo + Exemestane (n = 239), %
Median age (range), years	62 (34-93)	61 (28-90)
Race		
Caucasian	74	78
Asian	20	19
Performance status 0	60	59
Liver involvement	33	31
Lung involvement	29	33
Measurable disease[a]	70	68

[a]All other patients had ≥1 bone lesion.

Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2: Prior Therapy

	Everolimus + Exemestane (n = 485), %	Placebo + Exemestane (n = 239), %
Sensitivity to prior hormonal therapy	84	84
Last treatment: LET/ ANA	74	75
Last treatment		
Adjuvant	21	15
Metastatic	79	85
Prior tamoxifen	47	50
Prior fulvestrant	17	16
Prior chemotherapy for metastatic BC	26	26
Number of prior therapies: ≥3	54	53

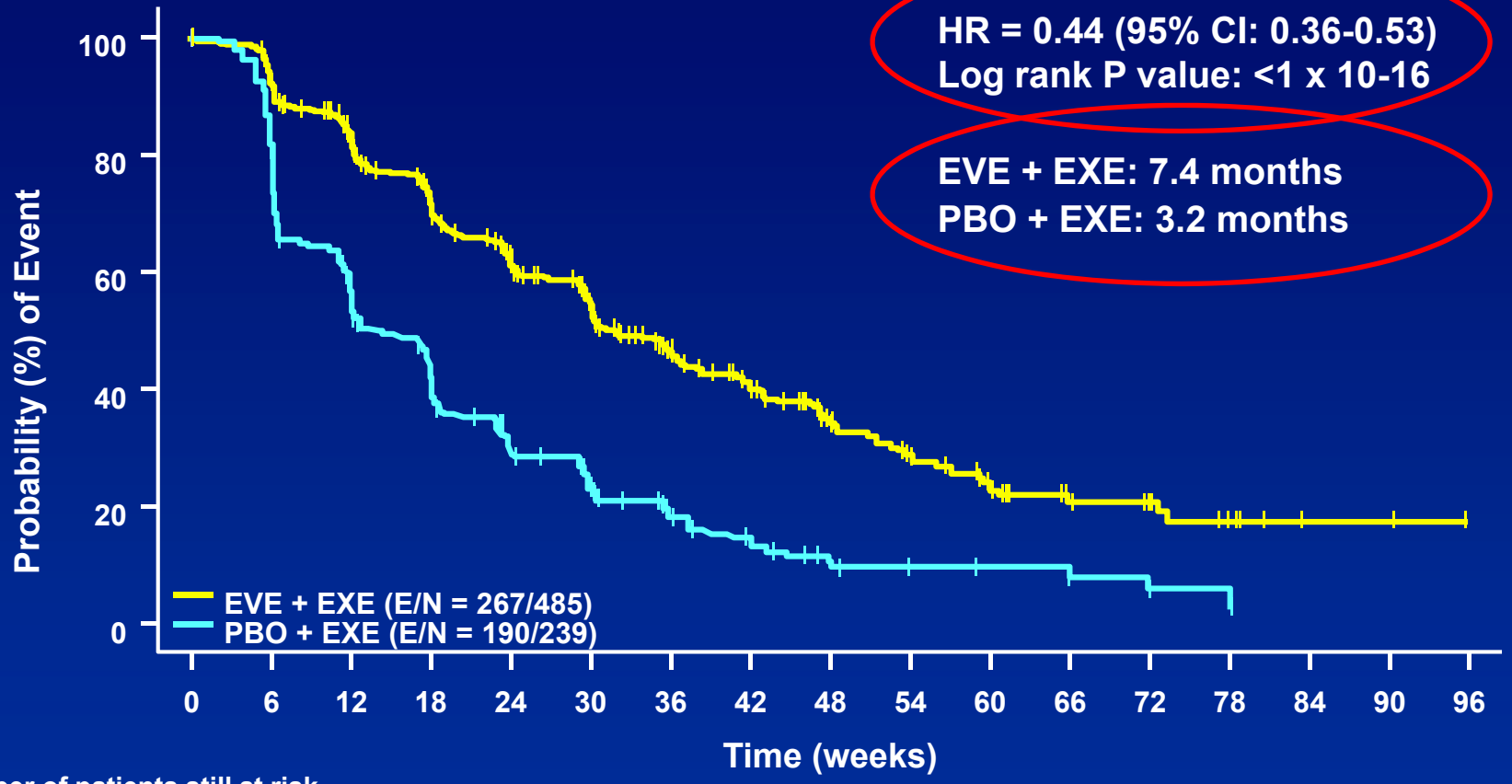
ANA = anastrozole; BC = breast cancer; LET = letrozole.
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2 (12 mo f/up): Patient Disposition

Disposition	Everolimus + Exemestane (n = 485), %	Placebo + Exemestane (n = 239), %
Protocol therapy ongoing	29	10
Discontinued	71	90
Disease progression	52	83
Adverse event	8	3
Subject withdrew consent	9	3
Death due to AE	1	<1
New cancer therapy	<1	<1
Protocol deviation	<1	0
Administrative problems	<1	0

AE = adverse event.
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2 (12-month f/up): PFS Local

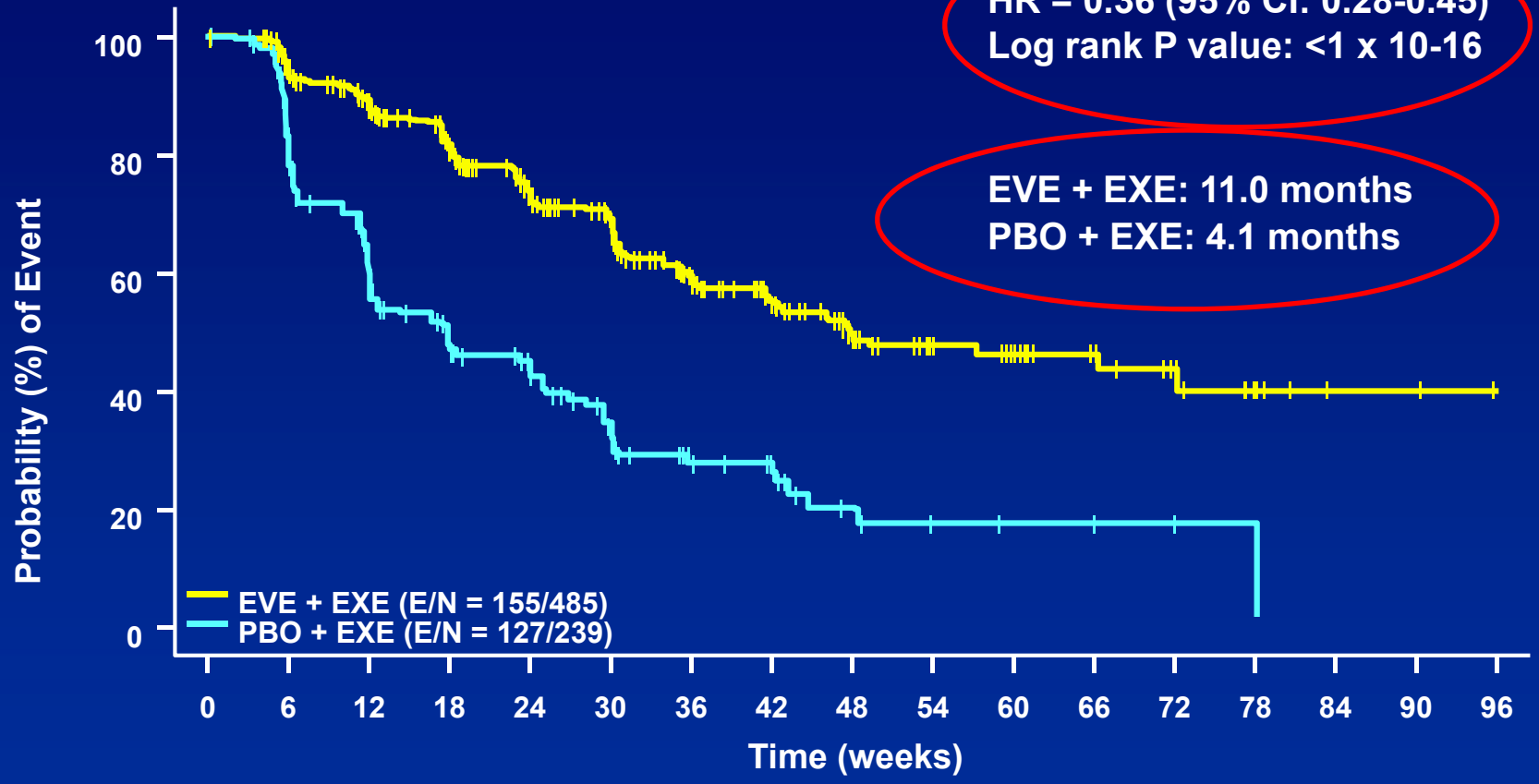


Number of patients still at risk

Everolimus	485	436	365	303	246	188	136	96	64	45	34	21	13	9	2	2	0
Placebo	239	190	131	95	63	45	29	19	12	8	6	6	4	2	0	0	0

CI = confidence interval; EVE = everolimus; EXE = exemestane; HR = hazard ratio; PBO = placebo; PFS = progression-free survival.
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2 (12 mo f/up): PFS Central



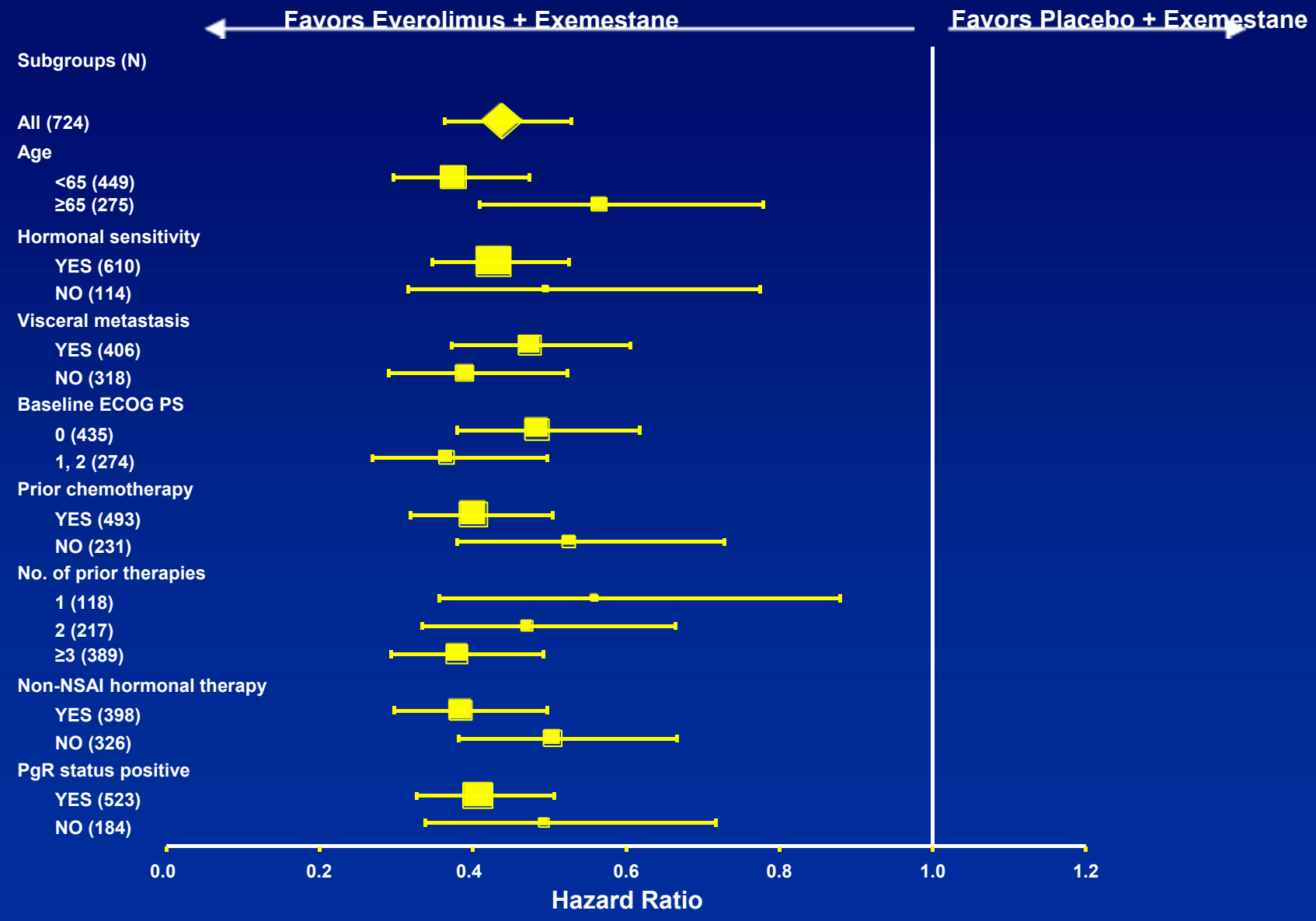
Number of patients still at risk

Everolimus	485	422	351	284	224	176	119	86	57	38	32	22	12	7	2	2	0
Placebo	239	179	112	74	56	36	23	18	8	5	4	4	3	1	0	0	0

CI = confidence interval; EVE = everolimus; EXE = exemestane; HR = hazard ratio; PBO = placebo; PFS = progression-free survival.

Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

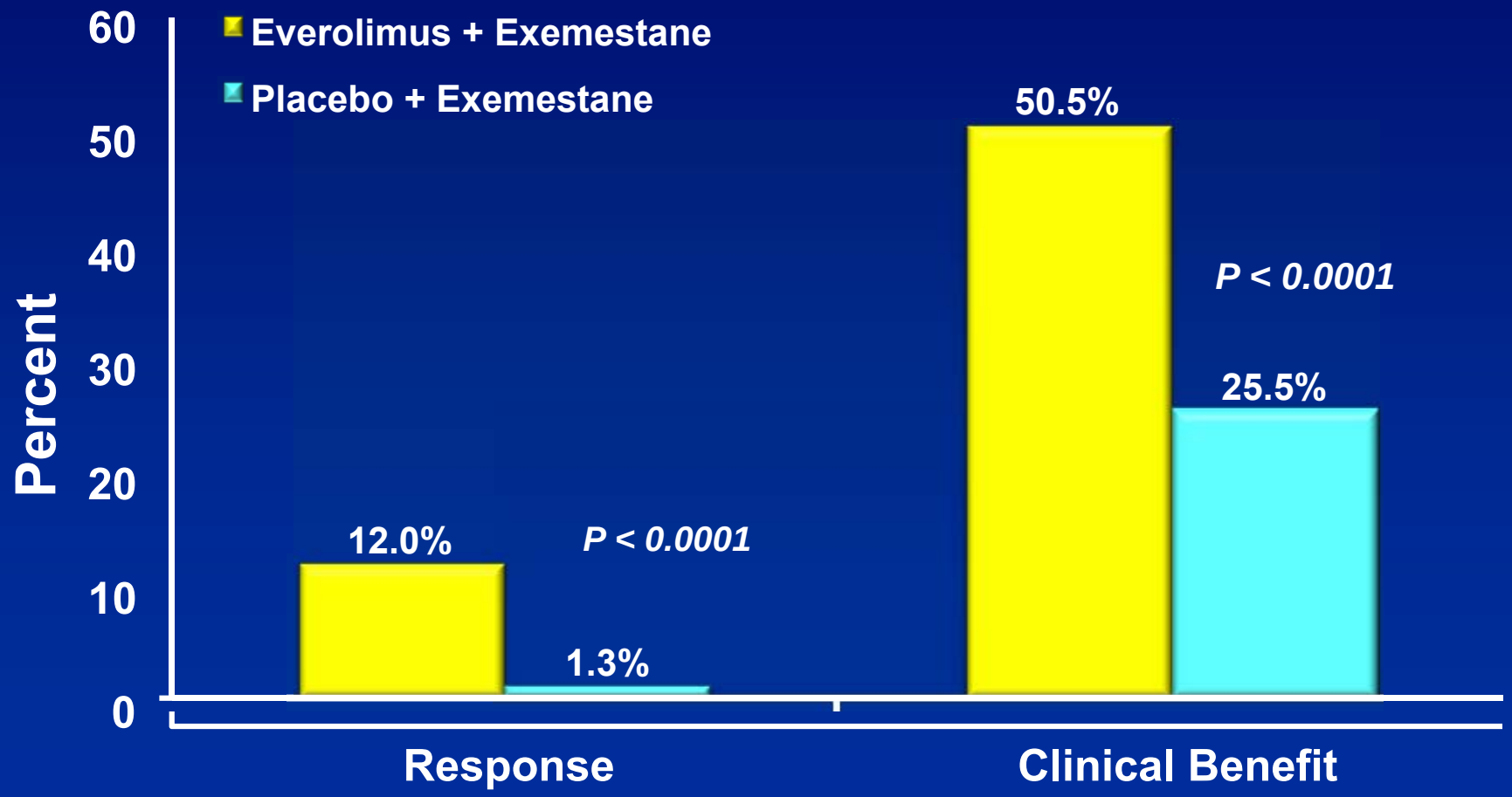
BOLERO-2 (12 mo f/up): PFS in Subgroups



PFS = progression-free survival; PgR = progesterone receptor; NSAI = nonsteroidal aromatase inhibitor; ECOG PS = Eastern Cooperative OncologyGroup performance status.

Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2 (12 mo f/up): Response and Clinical Benefit



Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2 (12 mo f/up): Overall Survival

As of July 8, 2011: 137 deaths

- 17.2% in everolimus arm
- 22.7% in placebo arm

OS final analysis at 392 events

- 80% power to detect 26% reduction in risk

OS = overall survival; PFS = progression-free survival.
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2 (12 mo f/up): Most Common Adverse Events

	Everolimus + Exemestane (n = 482), %			Placebo + Exemestane (n = 238), %		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Stomatitis	59	8	0	11	<1	0
Rash	39	1	0	6	0	0
Fatigue	36	4	<1	27	1	0
Diarrhea	33	2	<1	19	<1	0
Appetite decreased	30	1	0	12	<1	0
Nausea	29	<1	<1	28	1	0
Non-infectious Pneumonitis*	15	3	0	0	0	0
Hyperglycemia*	14	5	<1	2	<1	0

*Adverse Events of clinical interest
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2 (12 mo f/up): Summary

- Addition of everolimus to exemestane prolongs

  PFS in patients with ER+ HER2- breast cancer refractory to nonsteroidal aromatase inhibitors

  – Local: median 7.4 vs. 3.2 months,

  HR = 0.44, P < 1 x 10-16

  – Central: median 11.0 vs. 4.1 months,

  HR = 0.36, P < 1 x 10-16

- Benefit is observed in all subgroups

ER+ = estrogen receptor-positive; HER2- = human epidermal growth factor receptor 2-negative; HR = hazard ratio; PFS = progression-free survival.
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

BOLERO-2 (12 mo f/up): Conclusion

- Everolimus is the first agent to significantly **enhance the efficacy of hormonal therapy in patients with ER+, HER2- breast cancer**

- The addition of everolimus in advanced breast **cancer could represent a paradigm shift in the management of this patient population**

BC = breast cancer; ER+ = estrogen receptor-positive.
Hortobagyi G et al. SABCS 2011 (Abstract #S3-7)

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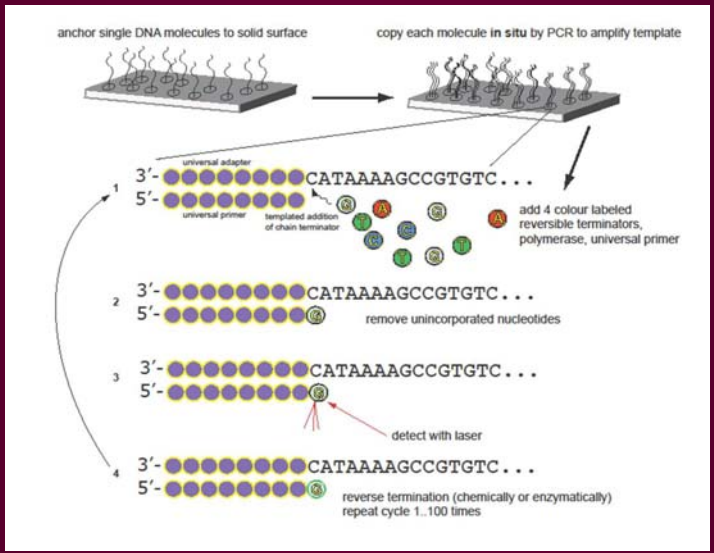
TNBC

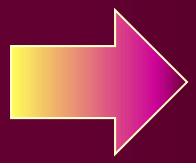
S3-5:
NextGen Sequencing of mTNBC
O'Shaugnessy et al.

- Use of genome sequencing technology to characterize driving mutations in mTNBC
- 7 samples from 14 pts w/ TNBC now with genome sequencing complete



TNBC

- Mutations discovered:
  - MAPK pathway activation
    - BRAF amplification/ overexpression
    - NF1 homozygous deletion
  - PI3KT/AKT pathway activation
    - PTEN homozygous deletion
    - INPP4B downregulation
    - ERAS overexpression



Trial design & development

TNBC

- PD3-2: Prognostic & Predictive Predictors for TNBC (Karn, T et al)
- PD3-8: BRCA1-like TNBC: Clinicopathological Variables & Chemosensitivity to Alkylating Agents (Wesseling, J et al.)

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    - 7-yr update
  - S1-3: ZOFAST
    - 5-yr update
  - S2-3: NSABP B-34
    - clodronate vs placebo
  - S2-4: GAIN
    - ibandronate vs placebo

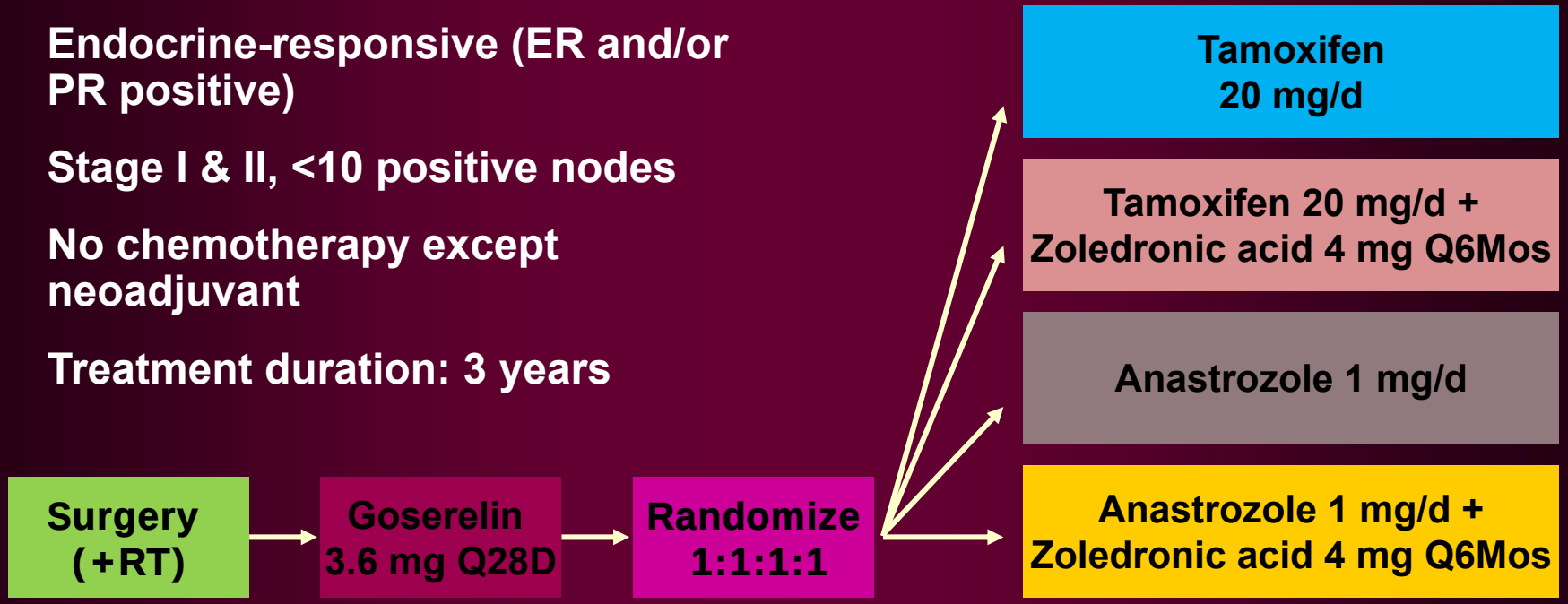
S1-2: 7 year update of ABCSG-12:

Significantly Improved Survival with Adjuvant Zolendronic Acid in Premenopausal Patients with Endocrine-Receptor Positive Early Breast Cancer

Gnant M, Mlineritsch B, Luschin-Ebengreuth G, Stoeger H, Dubsky P, Jakesz R, Singer C, Eidtmann H, Fesl C, Eiermann W, Marth C, Greil R.

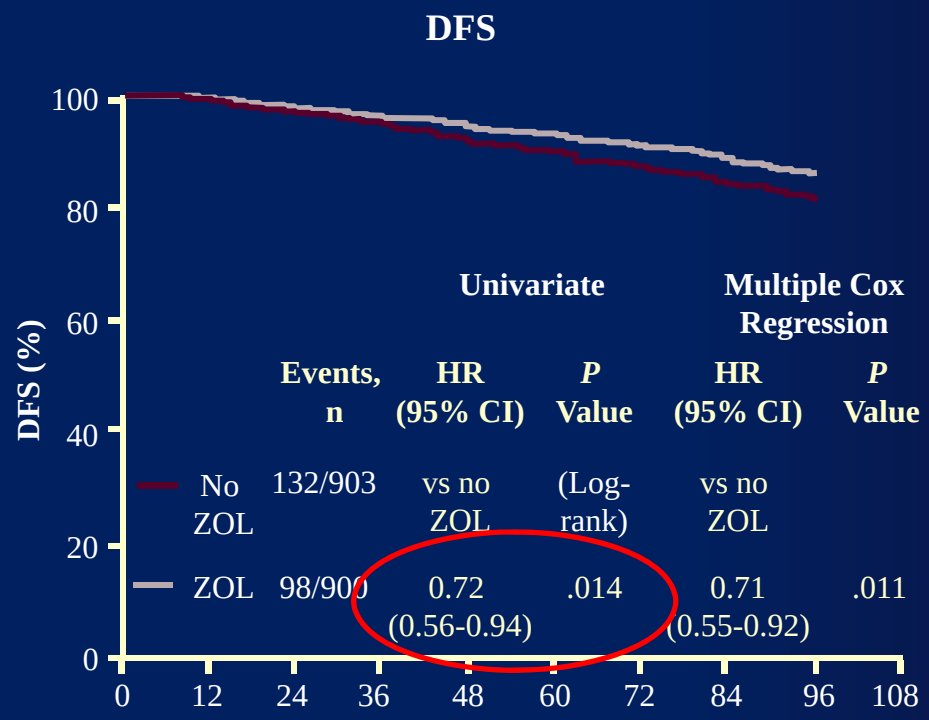
Ovarian Suppression Plus TAM or ANA +/- ZA: ABCSG-12 Trial Design

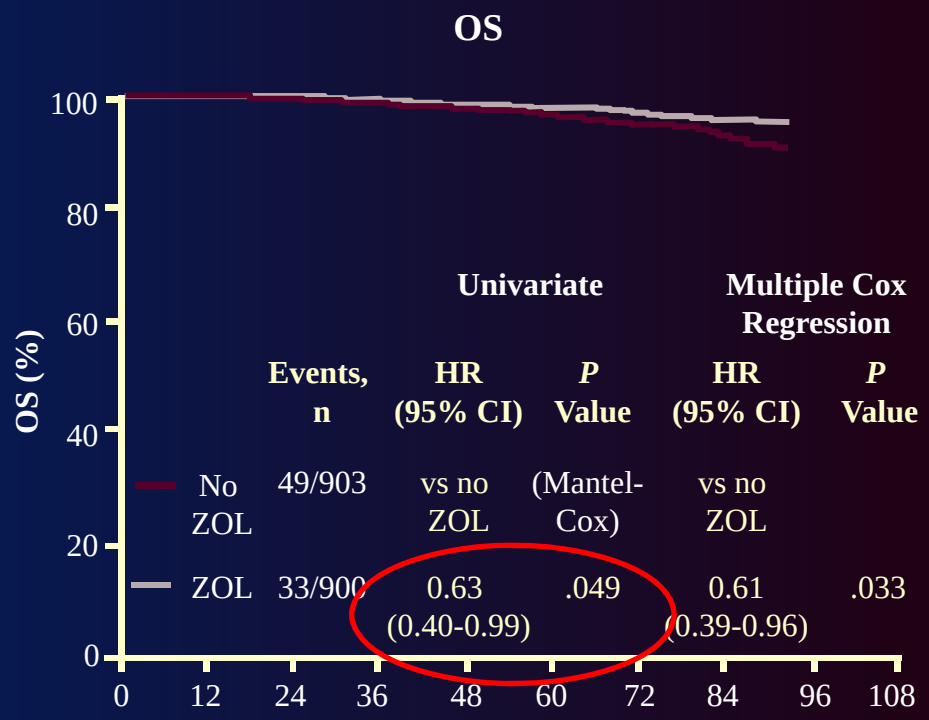
- Accrual 1999-2006
- 1,803 premenopausal breast cancer patients
- Endocrine-responsive (ER and/or PR positive)
- Stage I & II, <10 positive nodes
- No chemotherapy except neoadjuvant
- Treatment duration: 3 years



Gnant M, et al. ASCO 2008. Abstract LBA4.

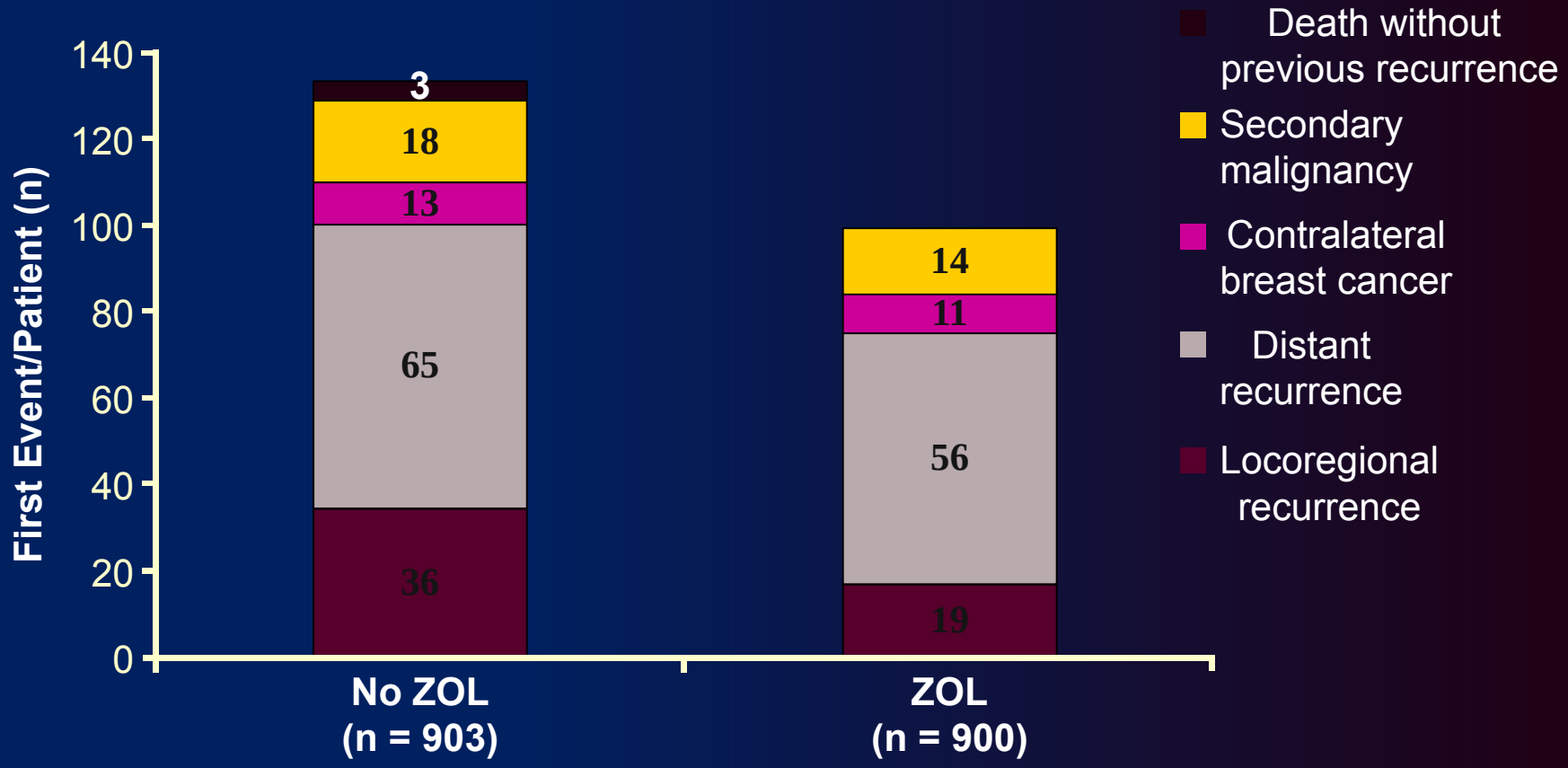
ABCSG-12 (84 Mos): Efficacy





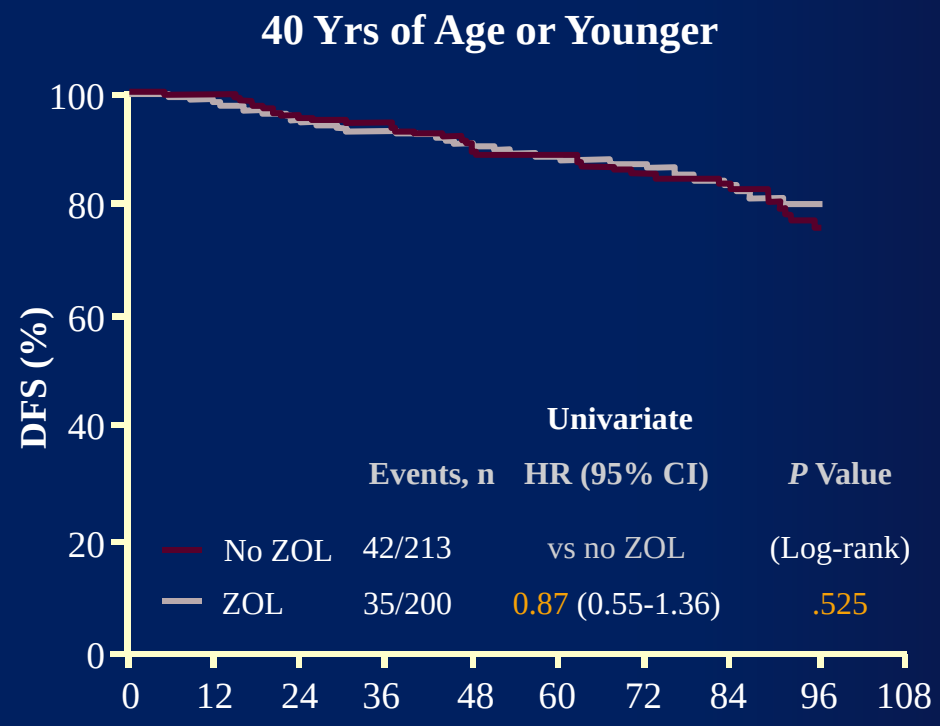
Gnant M, et al. SABCS 2011. Abstract S1-2

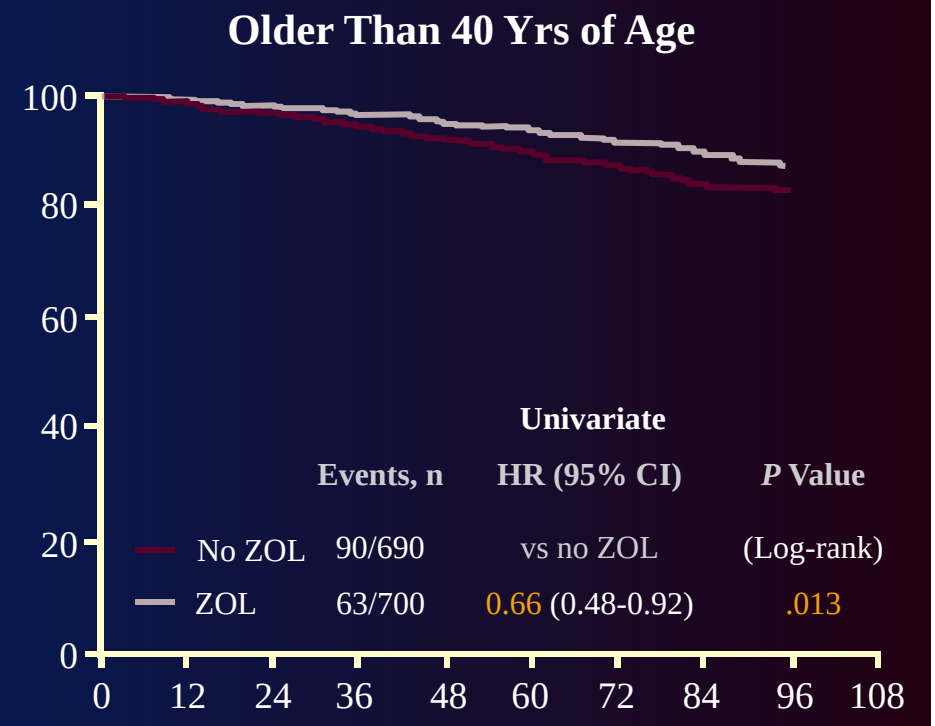
ABCSG-12 (84 Mos): First DFS Events



Gnant M, et al. SABCS 2011. Abstract S1-2

ABCSG-12 (84 Mos): Age Effect on DFS





Gnant M, et al. SABCS 2011. Abstract S1-2.

ABCSG-12: Conclusions

- Survival benefits with addition of ZOL to endocrine therapy first reported at median follow-up of 48 months are still present at 84 months
  - Significant improvement in DFS
    - Relative risk reduction: 28%
  - Significant improvement in OS
    - Relative risk reduction: **37%**
- ***Subanalysis suggests that survival benefits of ZOL may be restricted to patients older than 40 yrs of age***

Gnant M, et al. SABCS 2011. Abstract S1-2.

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- Metastatic HR+:
  - S1-1: SWOG S0226
  - S3-7: BOLERO-2
- Triple Negative:
  - S3-5: Next gen sequencing for TNBC
- Bisphosphonates:
  - S1-2: ABSCG-12
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    - 5-yr update
  - S2-3: NSABP B-34
    - clodronate vs placebo
  - S2-4: GAIN
    - ibandronate vs placebo

S1-3: 5 year update of ZO-FAST

Long-term Survival Outcomes Among Postmenopausal Women With Hormone Receptor-Positive Early Breast Cancer Receiving Adjuvant Letrozole and Zoledronic Acid:

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. Coleman7

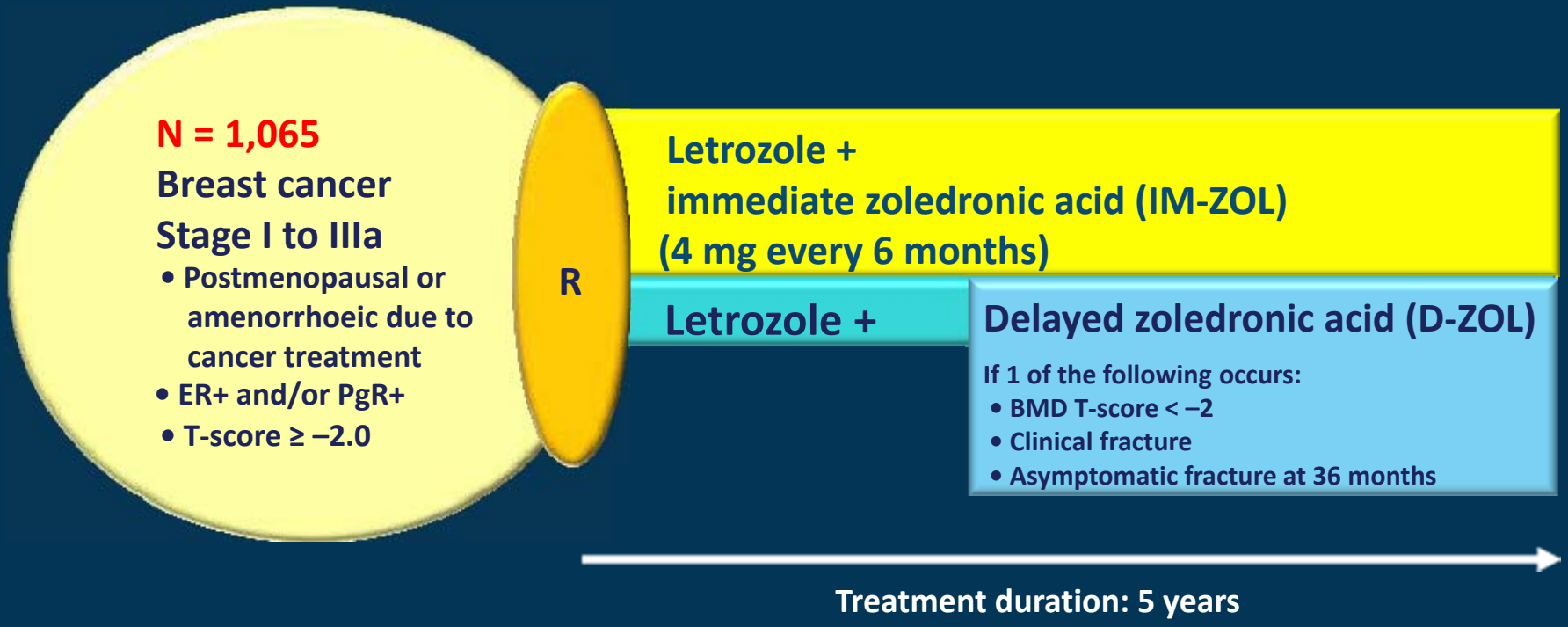
1Royal Melbourne Hospital, Victoria, Australia; 2South Manchester University Hospital, Academic Surgery, Education and Research Center, Manchester, UK; 3Universitäts Frauenklinik Kiel, Germany; 4Breast Clinic, UZ Gasthuisberg, Leuven, Belgium; 5German Breast Group, Frankfurt, Germany; 6Novartis Pharma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

ZO-FAST: Trial Design

Key endpoints

Primary: Bone mineral density (BMD) at 12 months

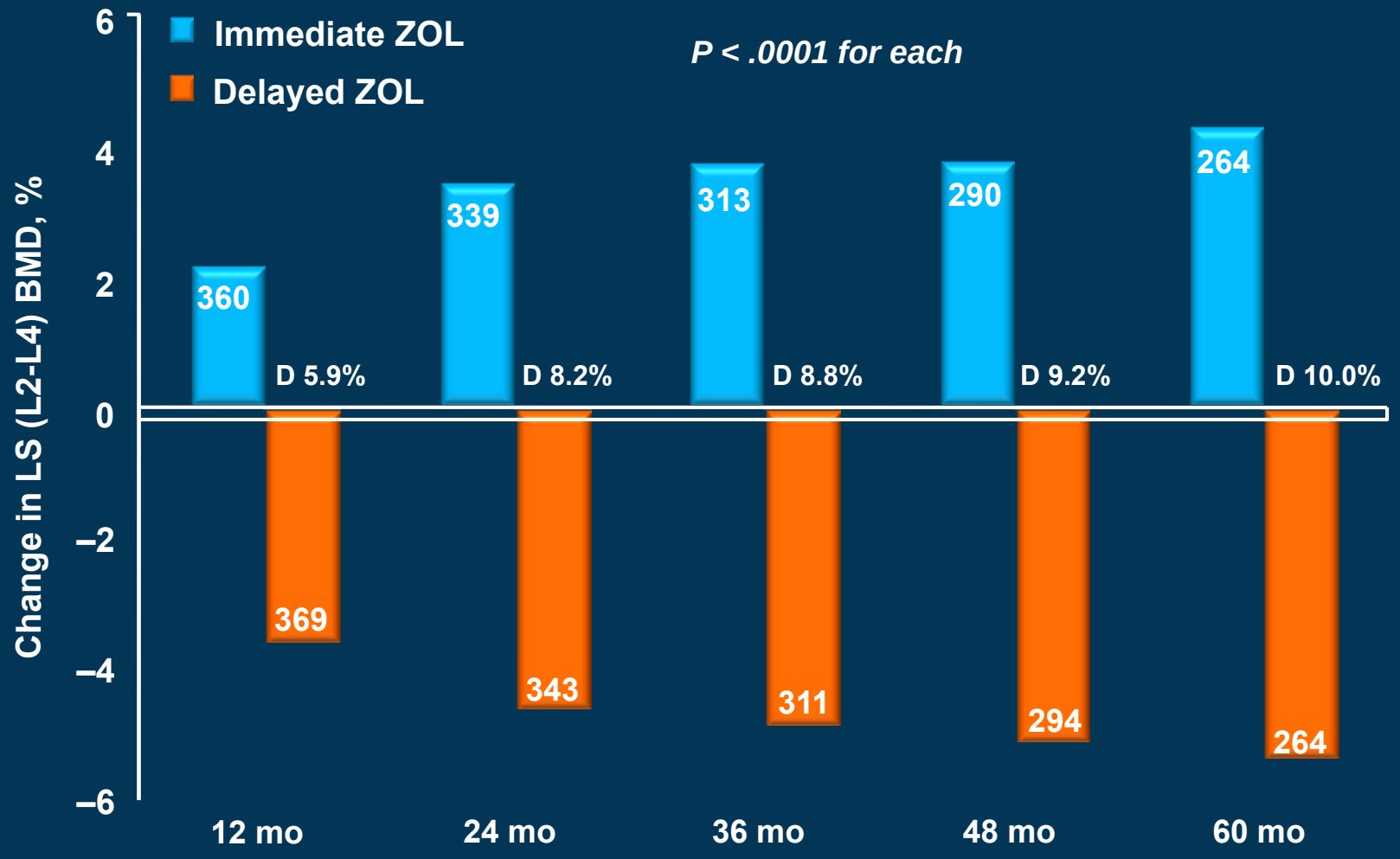
Secondary: BMD at 36 and 60 months, disease recurrence, fractures, safety



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

San Antonio Breast Cancer Symposium – December 6-10, 2011. Abstract S1-3.

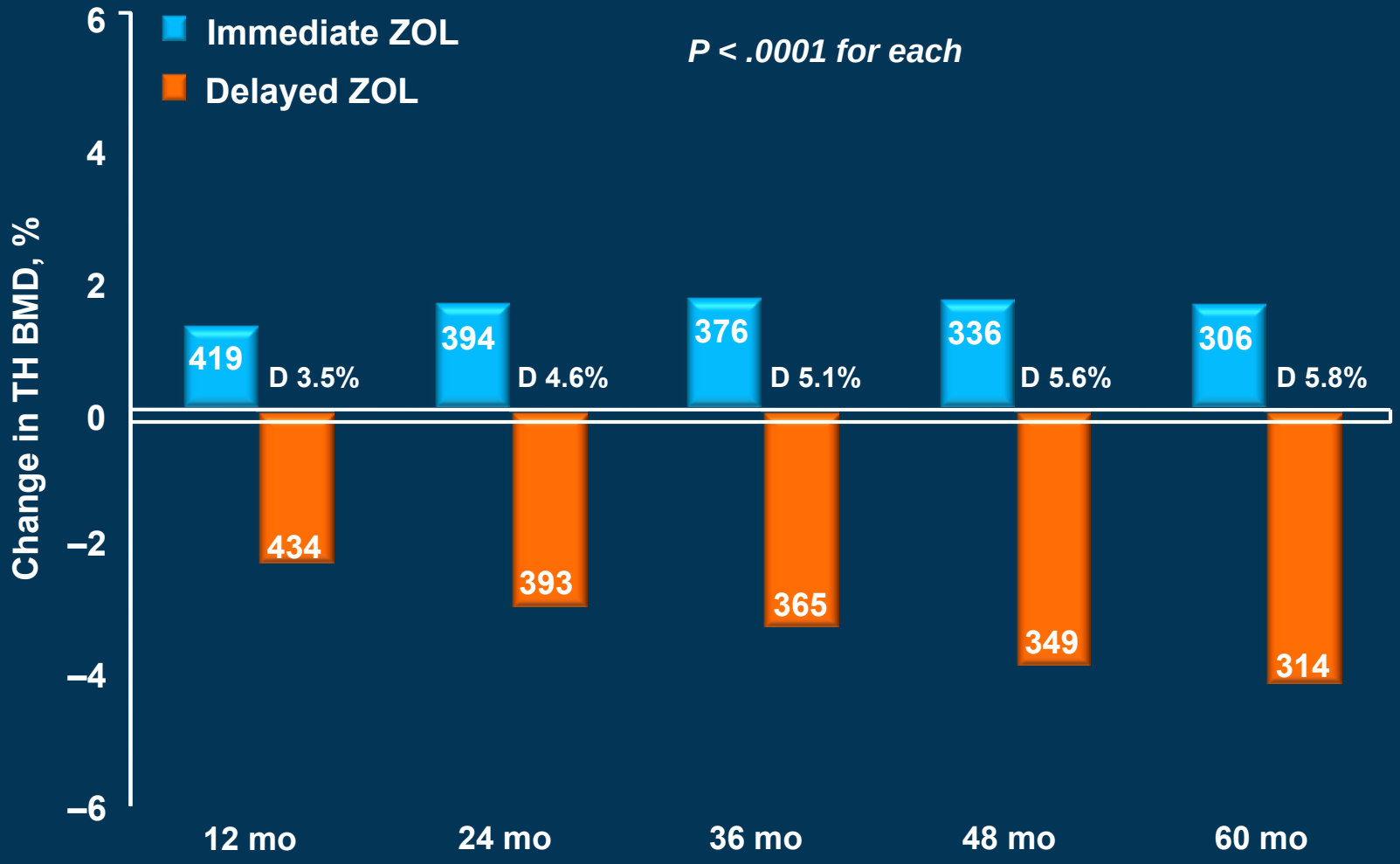
ZO-FAST: Primary Endpoint—Median Change in LS BMD



Abbreviations: BMD, bone mineral density; LS, lumbar spine; ZOL, zoledronic acid.

San Antonio Breast Cancer Symposium – December 6-10, 2011. Abstract S1-3.

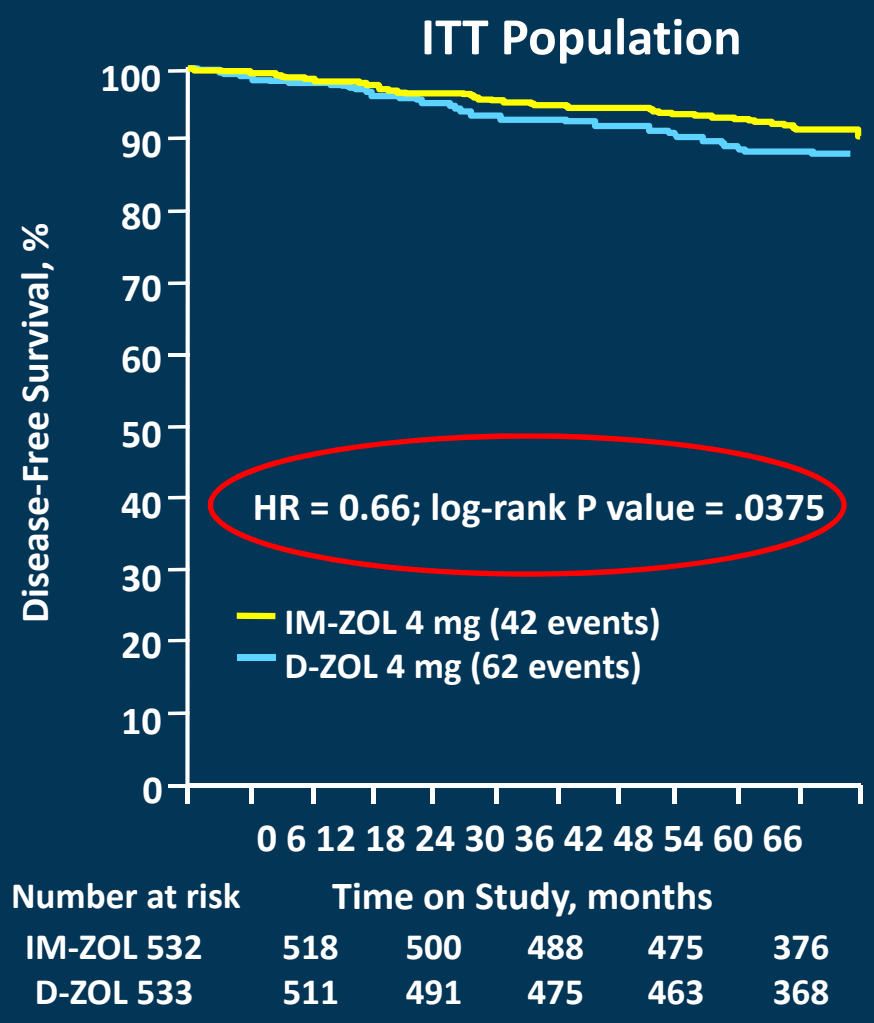
ZO-FAST: Secondary Endpoint—Median Change in TH BMD

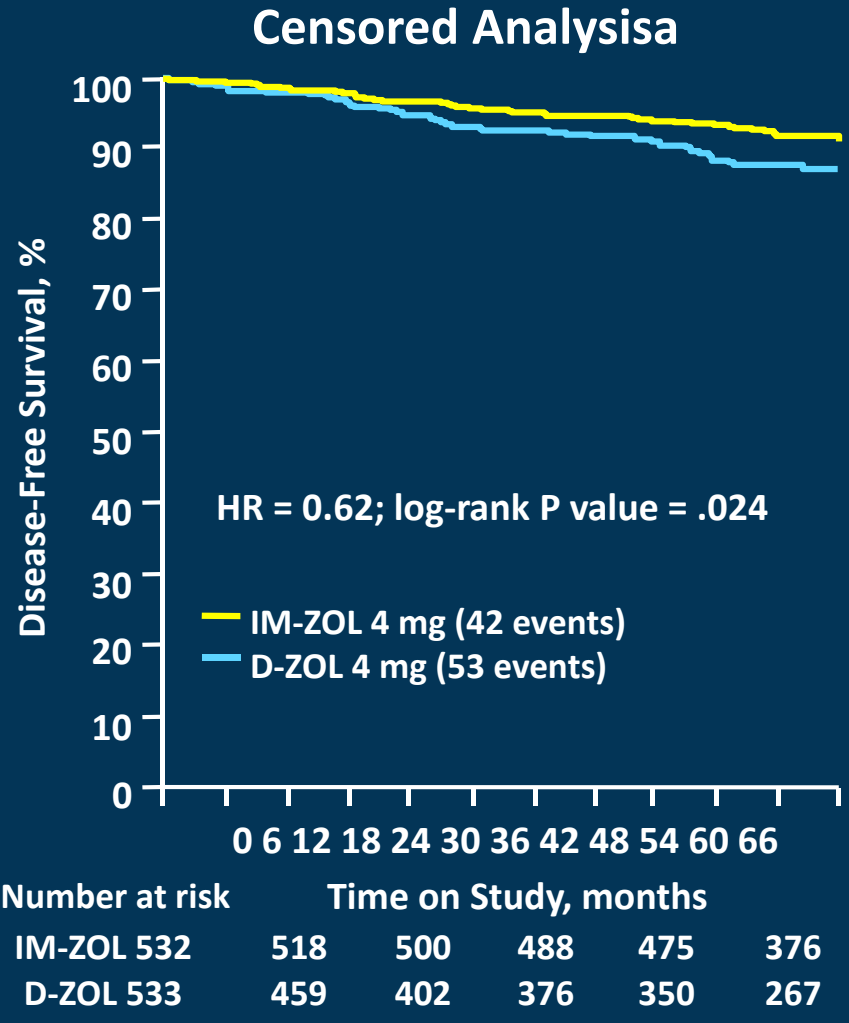


Abbreviations: BMD, bone mineral density; TH, total hip; ZOL, zoledronic acid.

San Antonio Breast Cancer Symposium – December 6-10, 2011. Abstract S1-3.

ZO-FAST: Disease-Free Survival



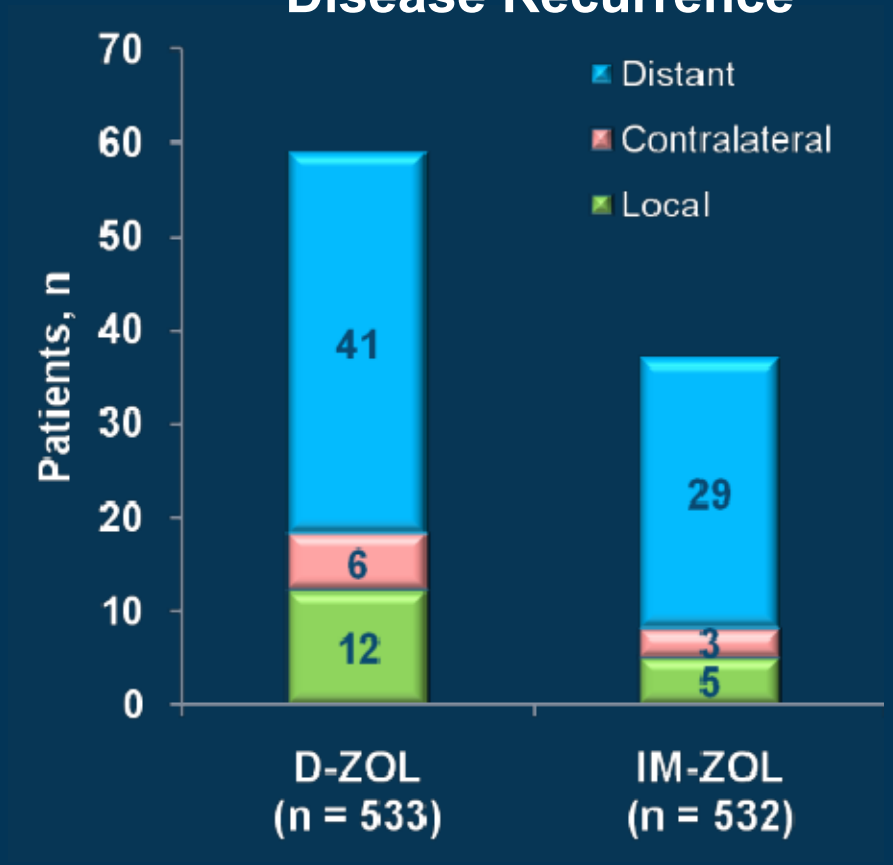


a Censored patients at initiation of delayed ZOL (n=144).

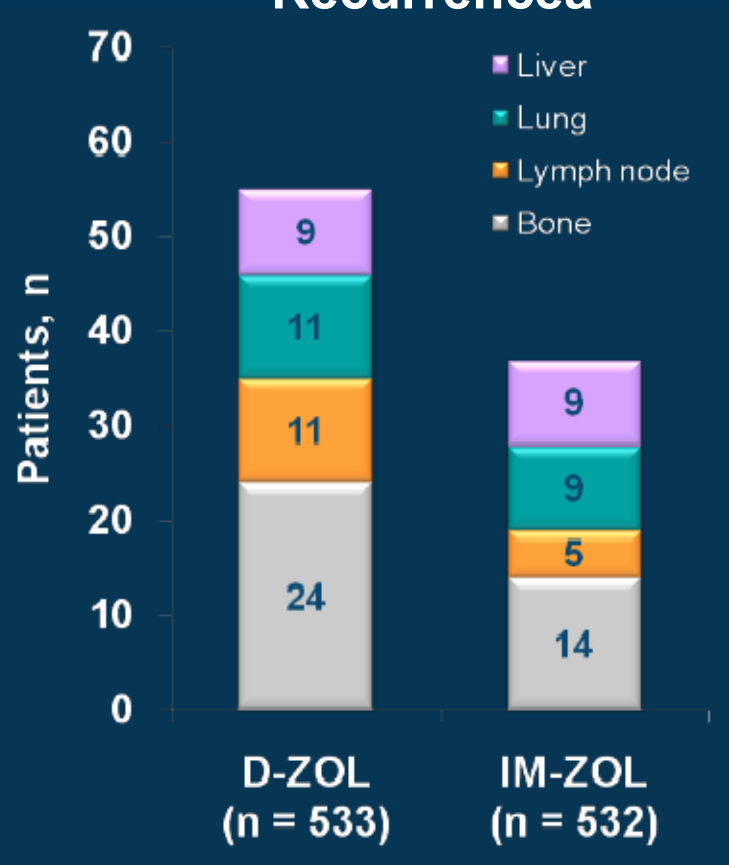
Abbreviations: DFS, disease-free survival; D-ZOL, delayed zoledronic acid; HR, hazard ratio; IM-ZOL, immediate zoledronic acid.

ZO-FAST: Disease Recurrence (ITT Population)

Disease Recurrence



Key Sites of Distant Recurrencea

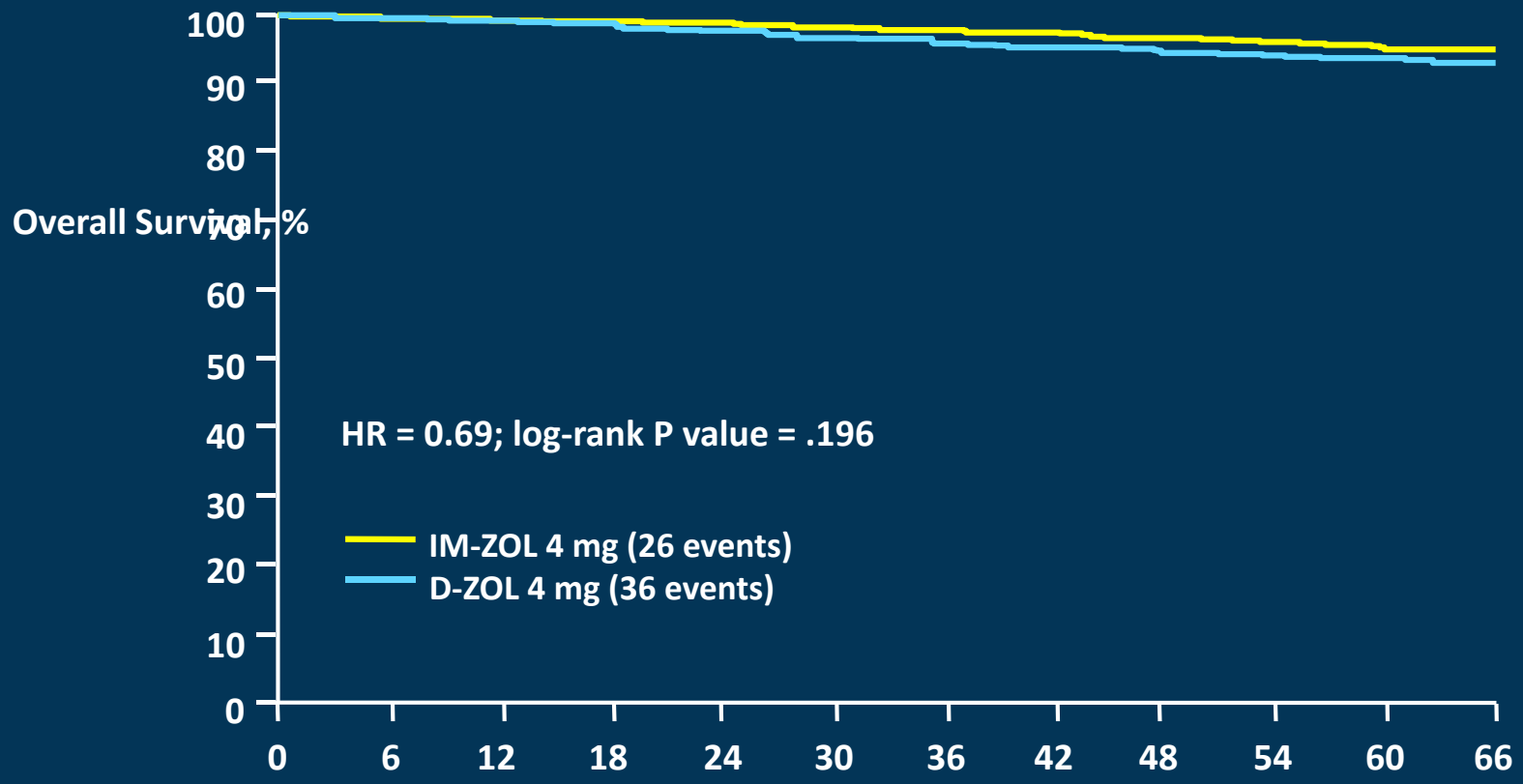


Abbreviations: DFS, disease-free survival; D-ZOL, delayed zoledronic acid; IM-ZOL, immediate zoledronic acid.

a Multiple sites may be reported for the same patient. Distant metastases include bone, brain, liver, lung, skin, lymph node, and other.

San Antonio Breast Cancer Symposium – December 6-10, 2011. Abstract S1-3.

ZO-FAST: Overall Survival (ITT Population)



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: 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%)

aA 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

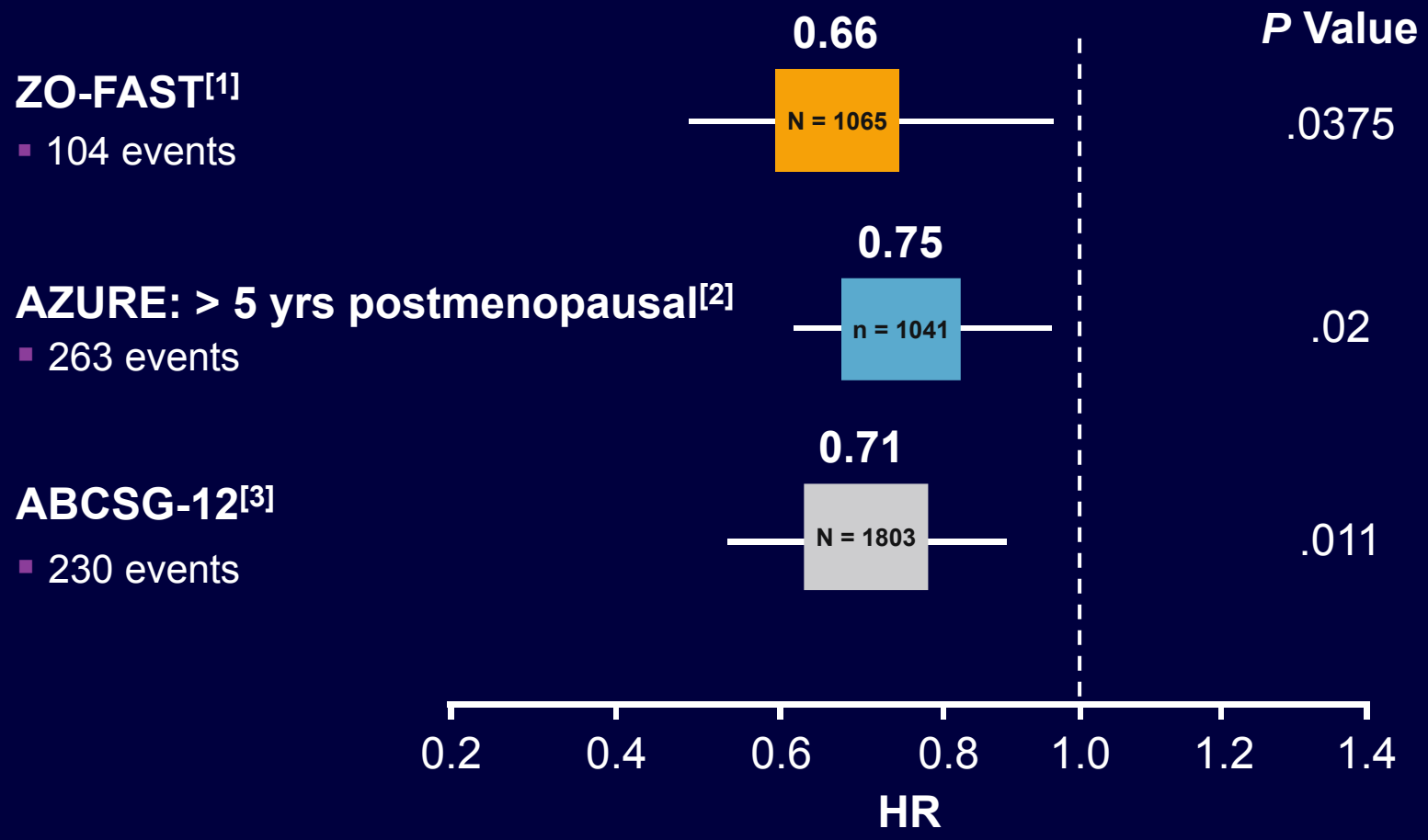
- The 60-month follow-up of ZO-FAST trial confirms and extends the BMD improvement seen with immediate zoledronic acid as reported at earlier time points

- 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;

Zoledronic Acid Studies: DFS Comparison



ZO-FAST[1]
- 104 events

AZURE: > 5 yrs postmenopausal[2]
- 263 events

ABCSG-12[3]
- 230 events

1. De Boer R, et al. SABCS 2011. Abstract S1-3. 2. Coleman RE, et al. N Engl J Med. 2011;365:1396-1405.
3. Gnant M, et al. SABCS 2011. Abstract S1-2.

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    - 5-yr update
  - S2-3: NSABP B-34
    - clodronate vs placebo
  - S2-4: GAIN
    - ibandronate vs placebo

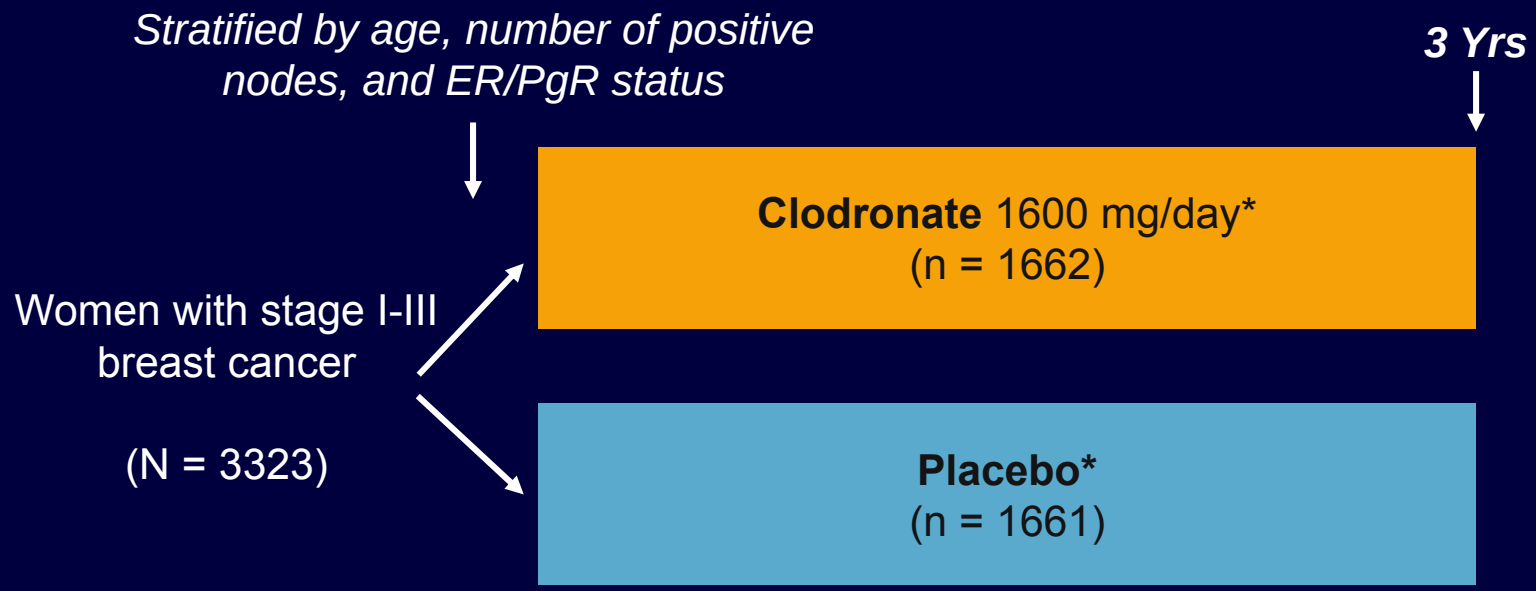
S2-3: NSABP Protocol B-34:

A Clinical Trial Comparing Adjuvant Clodronate vs. Placebo In Early Stage Breast Cancer Patients Receiving Systemic Chemotherapy and/or Tamoxifen or No Therapy – Final Analysis

AHG Paterson[1,2], SJ Anderson[1,3], BC Lembersky[1,4], L Fehrenbacher[1,5], CI Falkson[1,6], KM King[1,7], LM Weir[1,8], AM Brufsky[1,9], S Dakhil[1,10], T Lad[1,11], L Baez-Diaz[1,12], JR Gralow[13], A Robidoux[1,14], EA Perez[15], P Zheng[1,3], CE Geyer[1,16], SM Swain[1,17], JP Costantino[1,3], EP Mamounas[1,18], Norman Wolmark[1,19]

NSABP B-34: Phase III Study of Adjuvant Clodronate in Breast Cancer

- Primary endpoint: DFS (mean follow-up: 8.4 yrs)
- Two thirds aged 50 yrs or older; 25% node positive



*All patients could receive adjuvant systemic chemotherapy with or without tamoxifen or no adjuvant therapy at investigator discretion.

Paterson A, et al. SABCS 2011. Abstract S2-3.

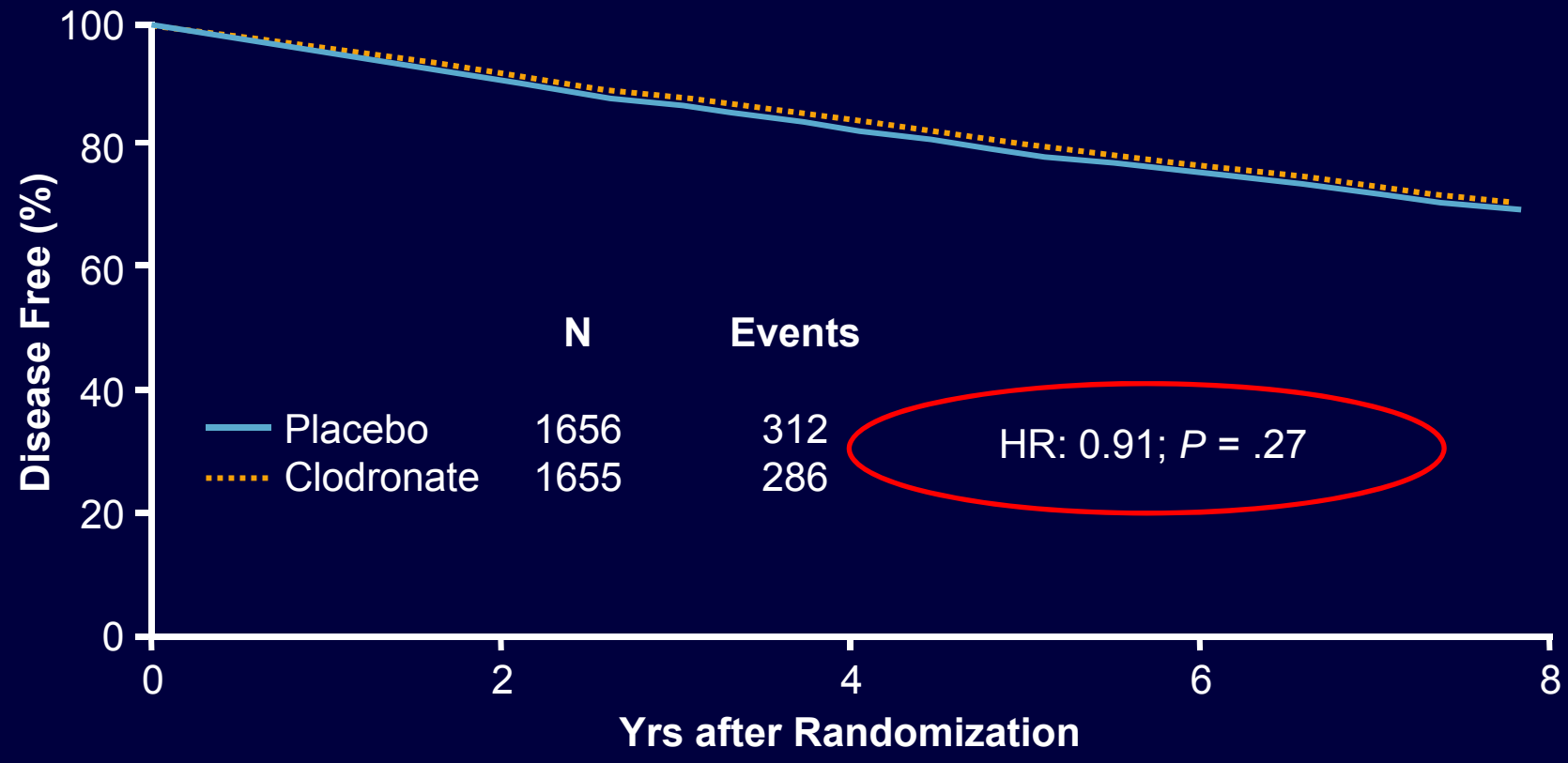
Patient Characteristics (%)

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.

NSABP B-34: Disease-Free Survival



Paterson A, et al. SABCS 2011. Abstract S2-3.

NSABP B-34: Analysis of Specified Endpoints

Endpoint	Events, n		HR (95% CI)	*P* Value
	Clodronate (n = 1655)	Placebo (n = 1656)		
DFS	286	312	0.913 (0.778-1.072)	.266
OS	140	167	0.842 (0.672-1.054)	.131
RFI	148	177	0.834 (0.671-1.038)	.101
BMFI	61	80	0.765 (0.548-1.068)	.114
NBMFI	78	105	0.743 (0.554-0.996)	.046

BMFI, bone metastasis–free interval; NBMFI: non–bone metastasis–free interval; RFI, relapse-free interval.

Paterson A, et al. SABCS 2011. Abstract S2-3.

NSABP B-34 Subset Analysis: DMFI, RFI, BMFI, NBMFI in Pts Aged > 50 Yrs

Endpoint for Patients Aged 50 Yrs or Older	HR	*P* Value
DMFI	0.62	.003
RFI	0.76	.05
BMFI	0.61	.024
NBMFI	0.63	.015

BMFI, bone metastasis–free interval; DMFI, distant metastasis-free interval; NBMFI: non–bone metastasis–free interval; RFI, relapse-free interval.

Paterson A, et al. SABCS 2011. Abstract S2-3.

NSABP B-34: Conclusions

- No significant benefit in DFS (primary endpoint) with oral clodronate in women with early breast cancer[1]
- Clodronate significantly reduced NBMFI vs placebo[1]
  - HR: 0.743; 95% CI: 0.554-0.996; *P* = .046
- In patients aged 50 yrs or older, clodronate associated with significant improvements in RFI, BMFI, NBMFI vs placebo[1]
  - Findings consistent with those observed in older, postmenopausal women in other adjuvant bisphosphonate studies[2-4]
- Adverse events similar in clodronate and placebo arms[1]

1. Paterson A, et al. SABCS 2011. Abstract S2-3. 2. De Boer R, et al. SABCS 2011. Abstract S1-3.
3. Coleman RE, et al. N Engl J Med. 2011;365:1396-1405. 4. Gnant M, et al. SABCS 2011. Abstract S1-2.

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- Metastatic HR+:
  - S1-1: SWOG S0226
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    - 5-yr update
  - S2-3: NSABP B-34
    - clodronate vs placebo
  - S2-4: GAIN
    - ibandronate vs placebo

S2-4: GAIN Study:
CTX +/- Ibandronate

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 Ch, 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

AGO-B
BREAST STUDY GROUP

GBG
GERMAN
BREAST
GROUP

GAIN
GERMAN ADJUVANT INTERGROUP NODE-POSITIVE STUDY

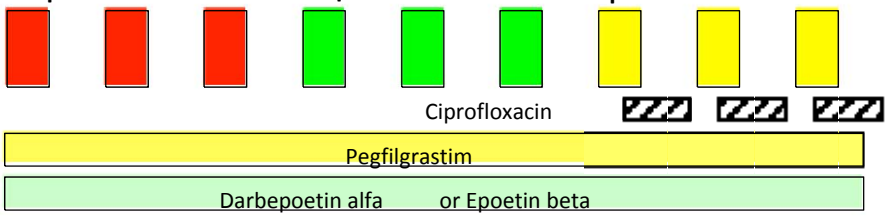
Trial Design

Arm A1:

Epirubicin
150 mg/m²
q 2w

Paclitaxel
225 mg/m²
q 2w

Cyclophosphamide
2000 mg/m²
q 2w



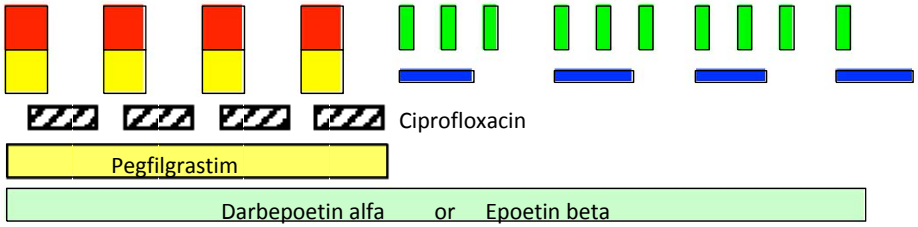
Arm B1:

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



Arm B2:

Observation

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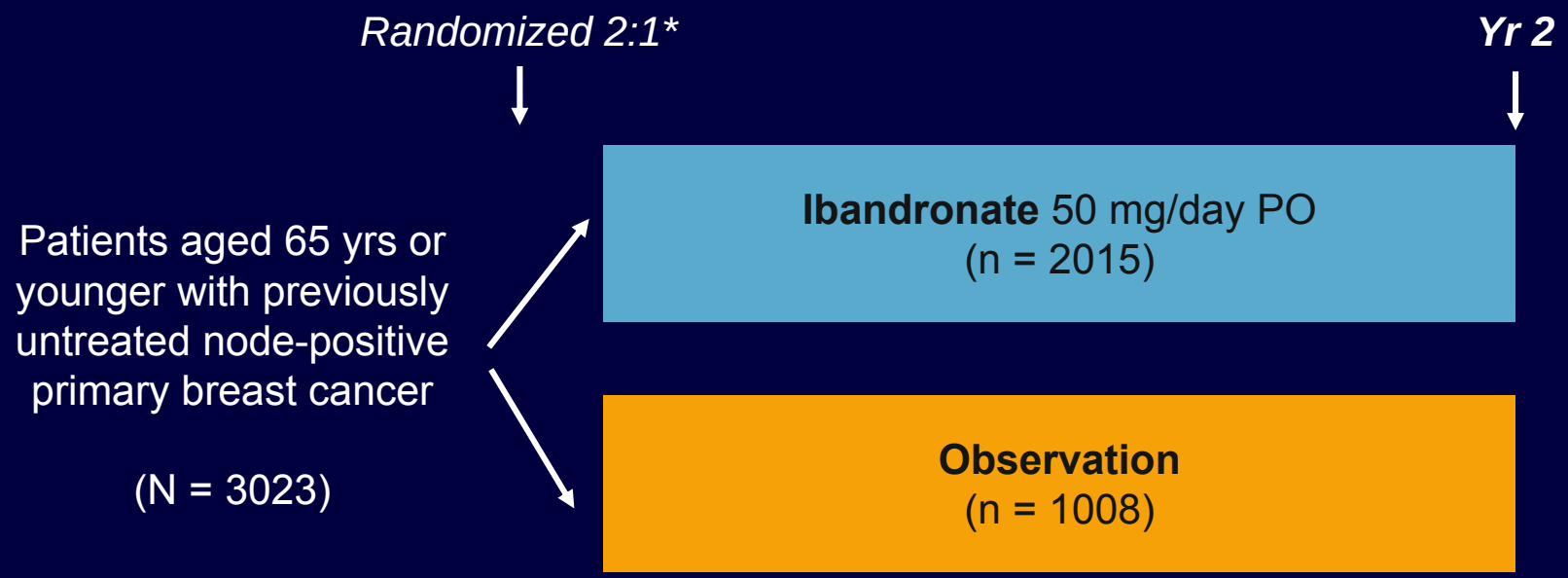
German GAIN Trial: Study Design



*Patients in trial also randomized 1:1 to receive ETC vs epirubicin/cyclophosphamide followed by paclitaxel/capecitabine (EC-TX).
ECT regimen: epirubicin 150 mg/m^2 every 2 wks for 3 cycles, followed by paclitaxel 225 mg/m^2 every 2 wks for 3 cycles, followed by cyclophosphamide 2000 mg/m^2 every 2 wks for 3 cycles.
EC-TX regimen: concurrent epirubicin 112.5 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 wks for 4 cycles, followed by concurrent paclitaxel 67.5 mg/m^2 wkly for 10 wks and capecitabine 2000 mg/m^2 on Days 1-14 every 3 wks for 4 cycles.
During chemotherapy, all patients received primary prophylaxis with pegfilgrastim and either epoetin or darbepoetin.

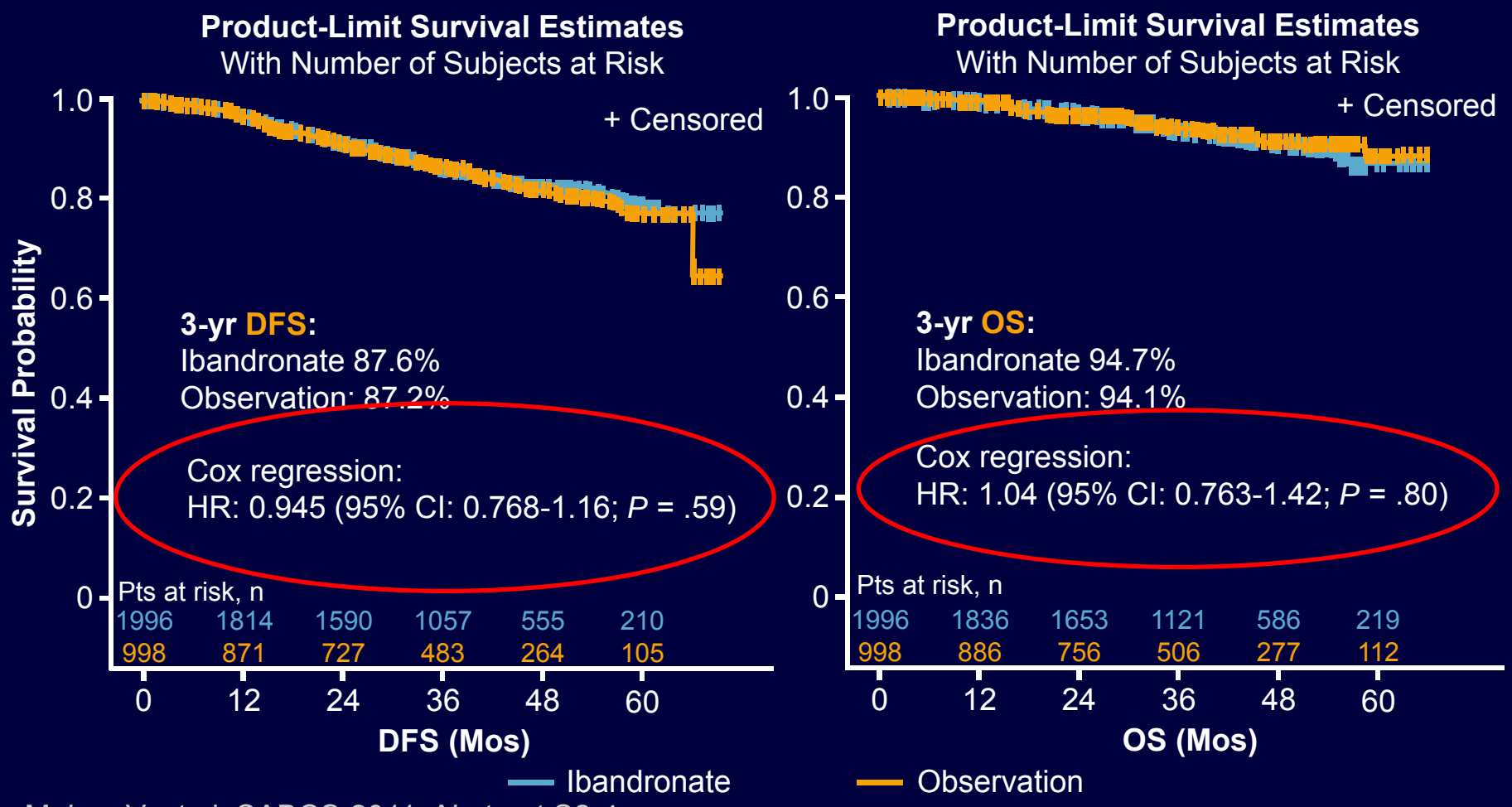
Mobus V, et al. SABCS 2011. Abstract S2-4.

GAIN: Patient Characteristics

Characteristic	Ibandronate (n = 1996)	Observation (n = 998)
Age, median yrs	49	50
Premenopausal, %	48.4	47.2
pT4, %	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

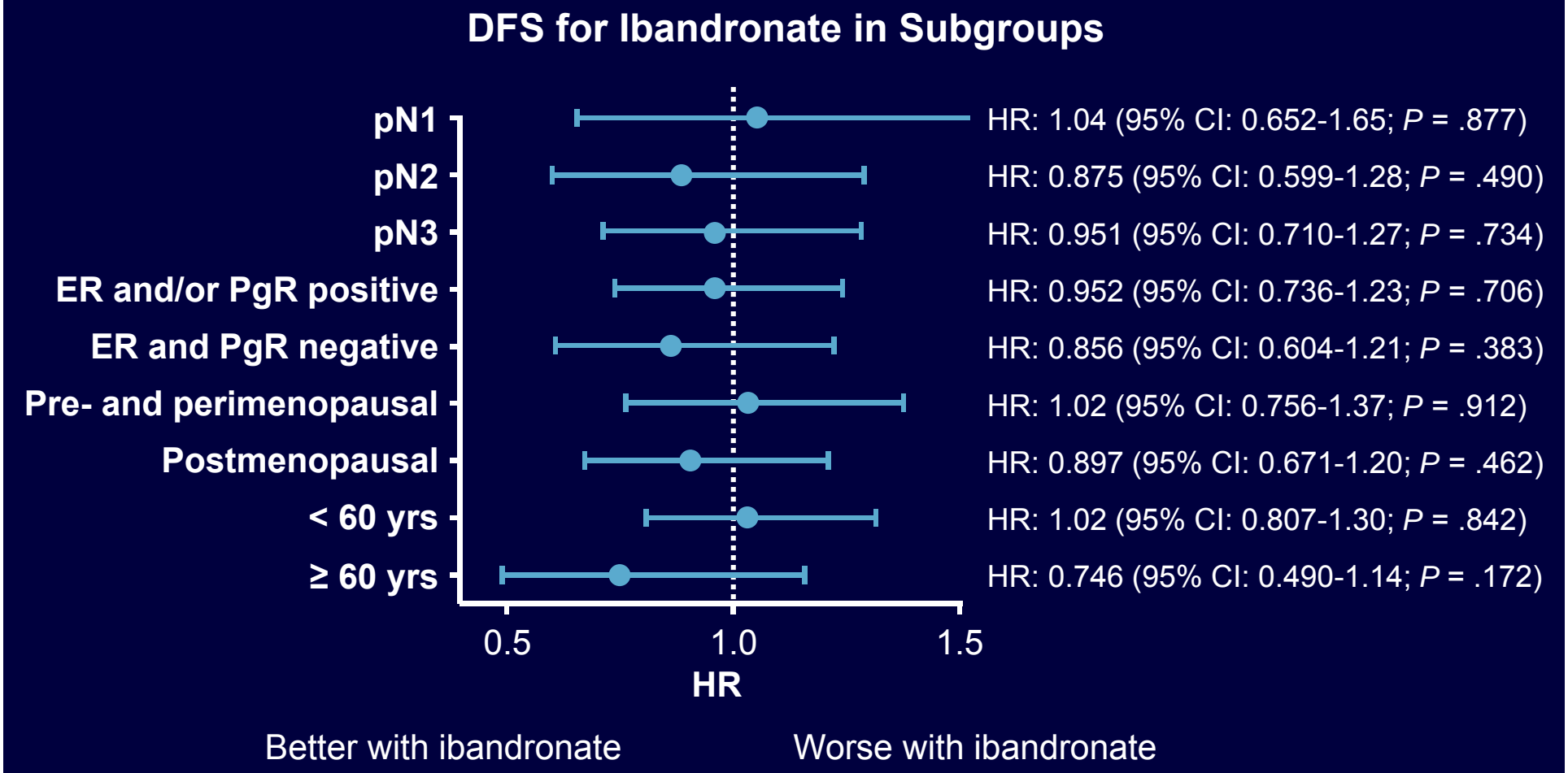
Mobus V, et al. SABCS 2011. Abstract S2-4.

GAIN: DFS and OS (ITT)



Mobus V, et al. SABCS 2011. Abstract S2-4.

GAIN: Subgroup Analyses



Mobus V, et al. SABCS 2011. Abstract S2-4.

GAIN: Conclusions

- Adjuvant ibandronate did not improve DFS nor OS following dose-dense chemotherapy in patients with node-positive primary breast cancer
- GAIN trial still ongoing to compare the 2 different dose-dense chemotherapy regimens

Mobus V, et al. SABCS 2011. Abstract S2-4.

Ongoing Phase III Trials of Antitumor Properties of Bone-Targeted Agents

Trial	Regimen	Primary Outcomes
SWOG 0307	ZOL vs clodronate vs ibandronate	DFS, OS
NATAN	ZOL after neoadjuvant chemo	EFS
D-CARE	Dmab 120 mg/mo for 6 mos, then 120 mg q3m vs placebo	Bone metastasis–free survival
HOBOE	Triptorelin + tamoxifen vs triptorelin + letrozole vs triptorelin + letrozole + ZOL	DFS
SUCCESS	FEC-D vs FEC-DG → 2 yrs ZOL vs 5 yrs ZOL	DFS
ABCSG-18	Dmab 60 mg q6m vs placebo	Time to first fracture

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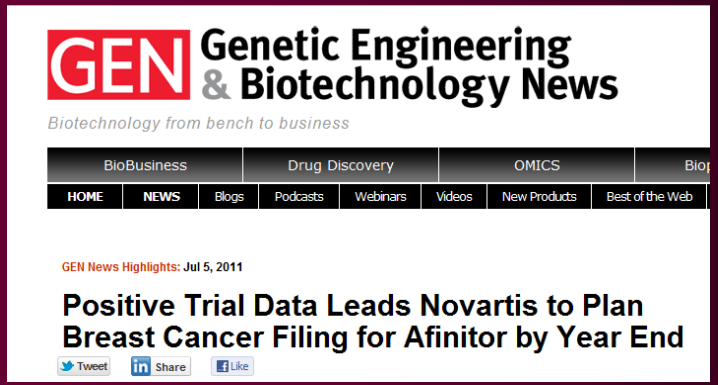
Summary Conclusions

- Metastatic HR+:
  - S1-1: SWOG S0226
    - Is ANA + FUL > ANA ?
      - » Maybe, but probably in TAM naïve pts only
  - S3-7: BOLERO-2
    - Is EVE + EXE a new SOC for MBC pts progressing on AI therapy?
      - » Probably, would strongly consider this option in the right patient



GASCO
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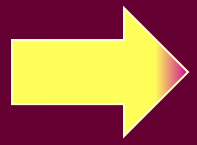
Summary Conclusions

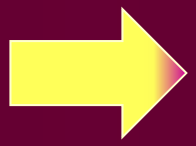
- Bisphosphonates:
  - S1-2: ABSCG-12
  - S1-3: ZO-FAST



Do we give zolendronate to EBC?

Probably yes, or at least low threshold to start especially in postmenopausal women at risk

  - S2-3: NSABP B-34
  - S2-4: GAIN



And clodronate or ibandronate in EBC?

Not yet, need to define susceptible populations better

Georgia Health Sciences University

New name. Same commitment to better health.

GHSU Multidisciplinary Breast Cancer Program

Surgical Oncology

E. James Kruse, DO

Medical Oncology

Thomas Samuel, MD

Radiation Oncology

Catherine Ferguson, MD

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GHSU Multidisciplinary Breast Cancer Program

GHSU Cancer Center

Phase I Trials Unit:

Pam Bourbo

Nicole Aenchbacher, RN, BSN

GHSU Breast Cancer Risk Assessment Program

GHSU Cancer Center

MB-CCOP Unit:

Melanie Kumrow

"Find out how much God has given you and from it take what you need; the remainder is needed by others."

~Augustine~

Alayna Samuel & Her Grandma,

Aleyamma Samuel- 15 year breast cancer survivor

Jake, Alayna, & Mark Samuel