MEDICAL ONCOLOGY NEWS IN BREAST CANCER 2014

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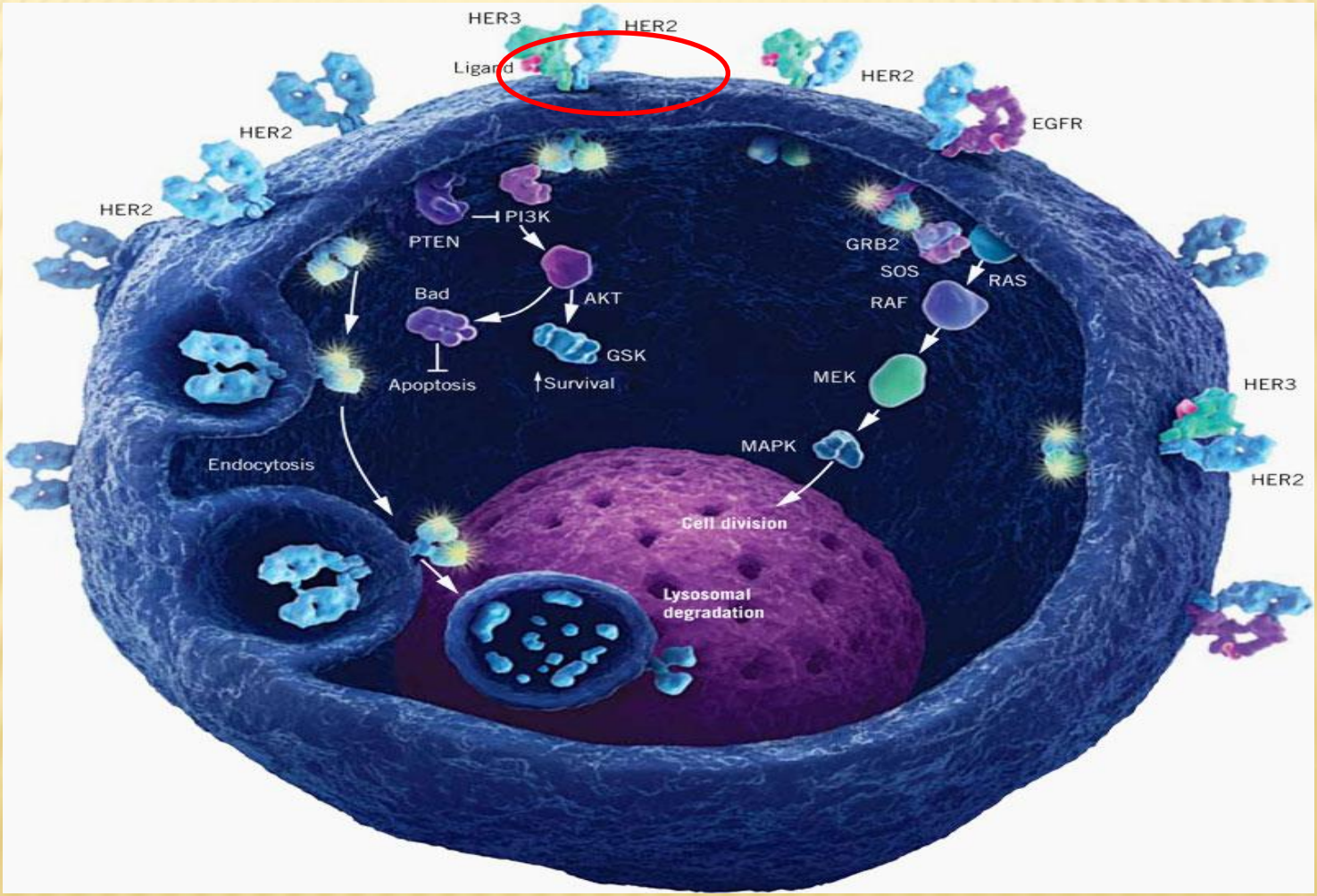
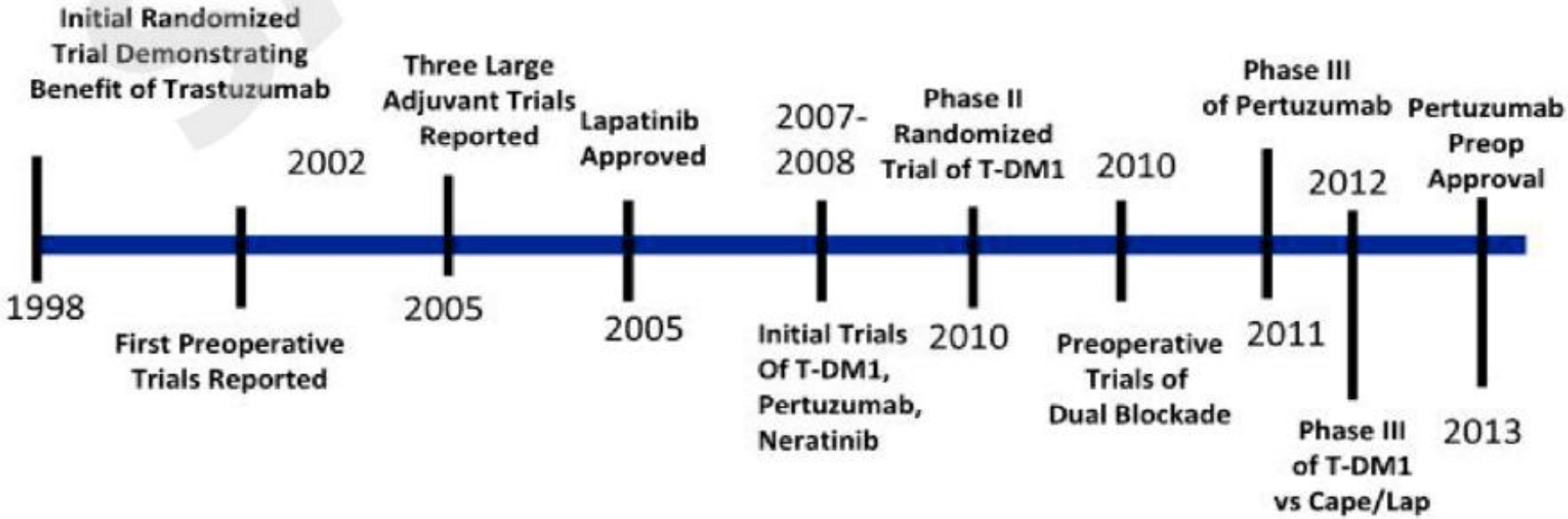
SUCCESS STORY OF IDENTIFYING *ANTI-HER-2 IN THE 1990S…*




Herceptin® 150 mg
Pulver zur Herstellung eines Infusionslösungskonzentrats
Trastuzumab
1 Durchstichflasche
Roche
Herceptin® 150 mg
Pulver zur Herstellung einer Infusionslösung

HER2+ Disease: Major Clinical Advances Over The Past 15 Years



META-ANALYSIS OF ADJUVANT TRASTUZUMAB IN HER2+ BREAST CANCER

Adjuvant trastuzumab vs no trastuzumab in patients with small HER2+ BC[1]

Trial	HER2+ Tumors	Trastuzumab Timing	Trastuzumab Duration	Chemotherapy Regimen	Median Follow-up, Yrs
HERA[2]	5102	Sequential	1 or 2 yrs	Any: 94% A; 26% A and T	8.0
NCCTG N9831[3]	3505	Concurrent or Sequential	1 yr	AC → w T AC → w TH AC → w T → H	8.7
NSABP B-31[3]	3222	Concurrent	1yr	AC →T AC → TH	9.4
PACS 04[4]	528	Sequential	1yr	FEC → H DE → H	5.0
FinHER[5]	232	Concurrent	9 wks	D ± H → FEC V ± H → FEC	5.6

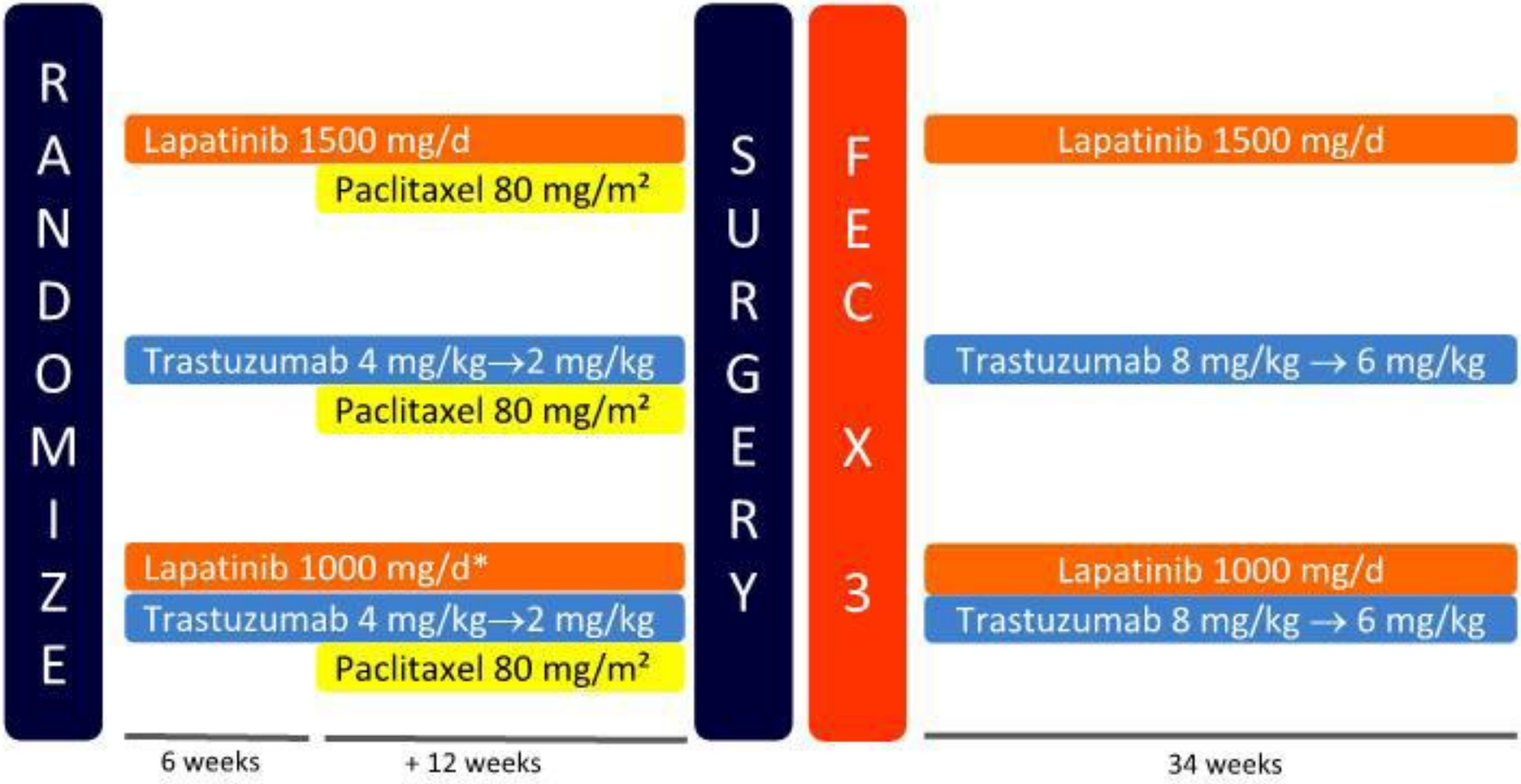
1. O'Sullivan C, et al. ASCO 2014. Abstract 508. 2. Goldhirsch A, et al. Lancet. 2013;382:1021-1028.
3. Perez EA, et al. J Clin Oncol. 2011;29:3366-3373. 4. Spielmann M, et al. J Clin Oncol. 2009;27:6129-6134.
5. Joensuu H, et al. J Clin Oncol. 2009;27:5685-5692.

CONCLUSIONS FROM META-ANALYSIS OF ADJUVANT TRASTUZUMAB IN HER2+ BC

- Trastuzumab therapy conferred substantial DFS and OS benefit to patients with tumors ≤ 2 cm
- Similar proportional benefit for hormone receptor–positive and hormone receptor–negative cohorts, but incidence and patterns of relapse appeared to differ over follow-up
- Trastuzumab therapy contributed to favorable outcomes previously reported for patients with hormone receptor–positive tumors ≤ 2 cm and 0-1 positive LN

1. O'Sullivan C, et al. ASCO 2014. Abstract 508. 2. O'Sullivan C, et al. SABCS 2013. Abstract S6-03.

NeoALTTO TRIAL in 455 WOMEN WITH HER2+ (ASCO/CAP 2007) BREAST CANCER ≥ 2 CM



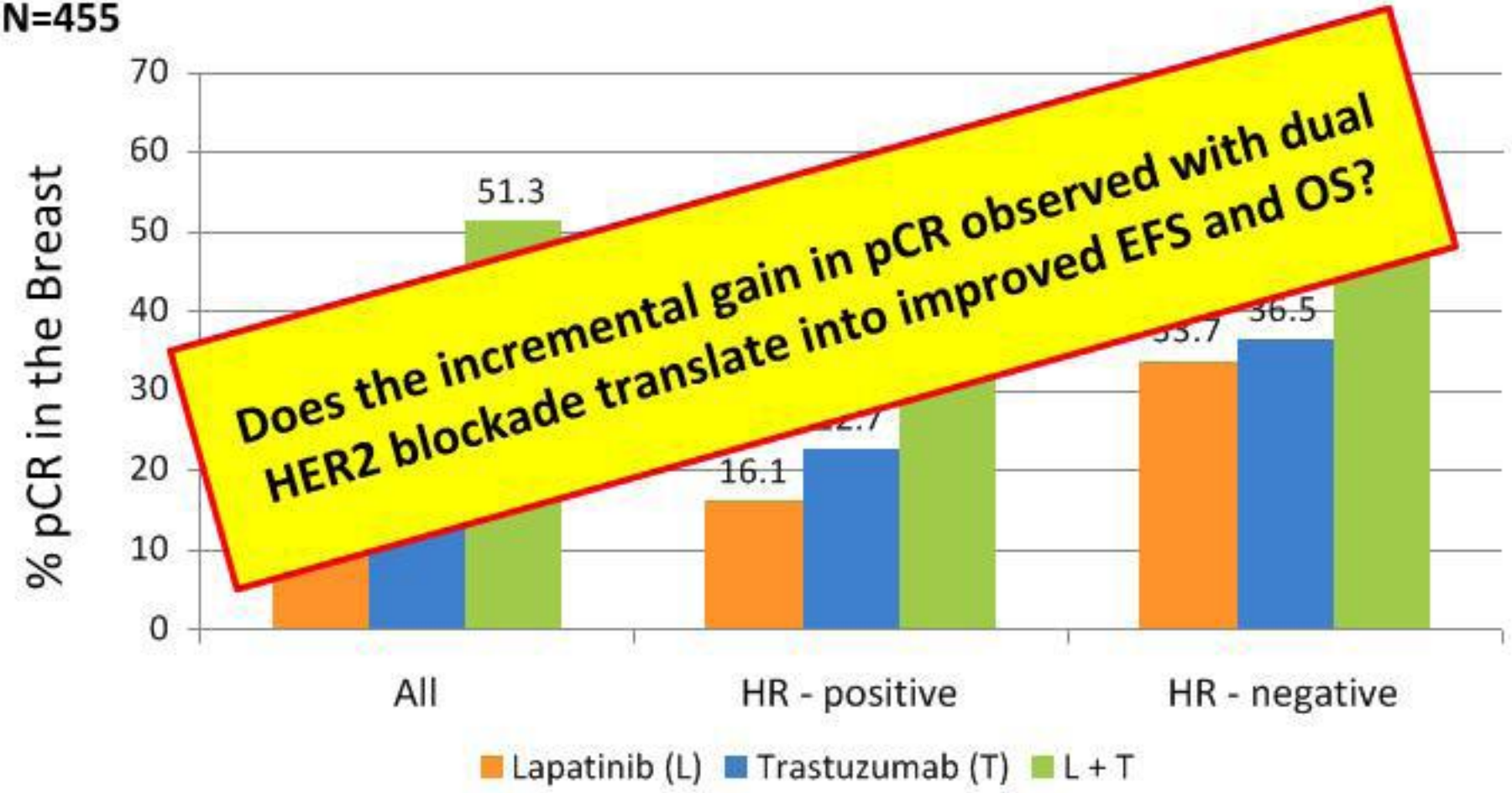
**Amendment-2 October 2008, reduced dose of lapatinib to 750 mg/d with paclitaxel*

54/152 had protocol-driven reduction

Baselga J et al; SABCS 2010; Lancet 2012

PRIMARY ENDPOINT BREAST PCR

N=455



Does the incremental gain in pCR observed with dual HER2 blockade translate into improved EFS and OS?

Baselga J et al; SABCS 2010; Lancet 2012

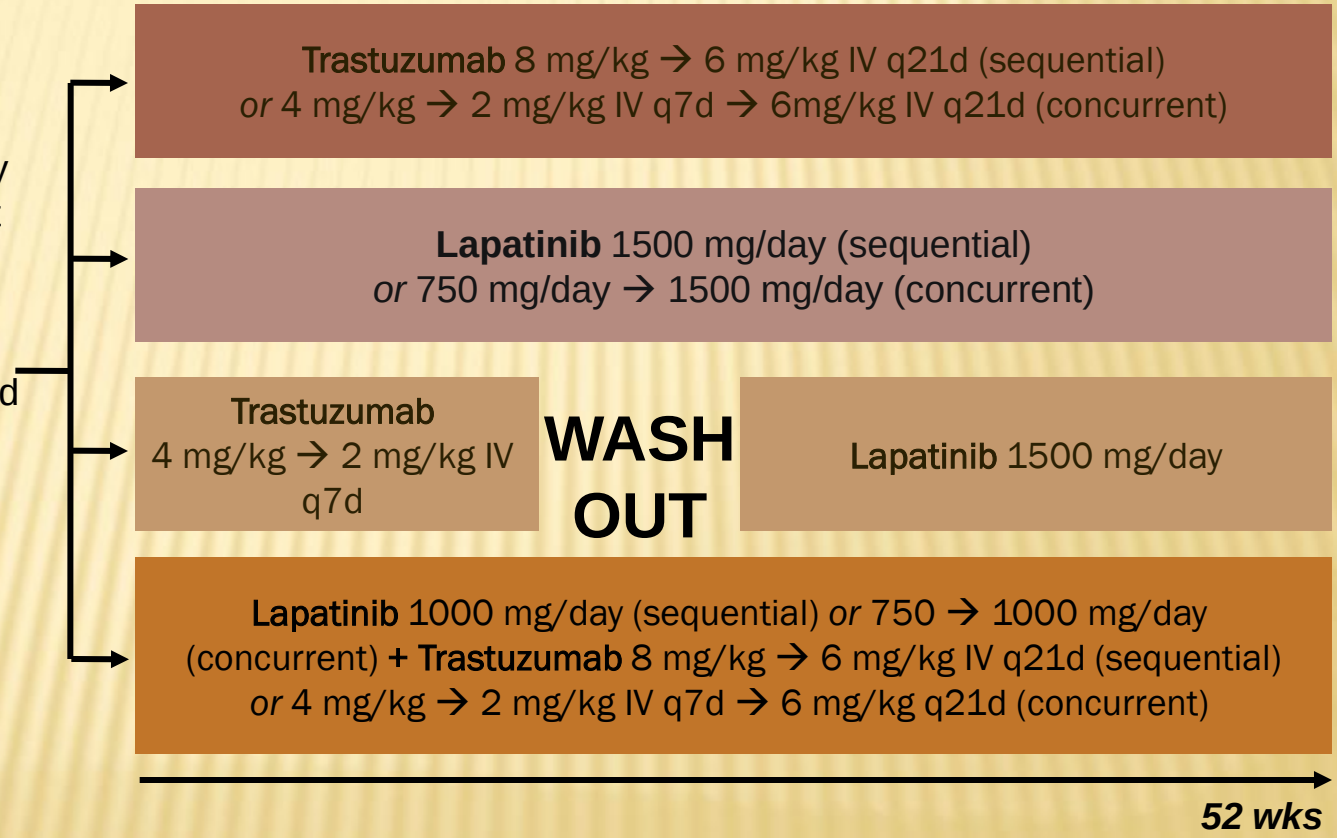
ALTTO TRIAL: COMPARING SEQUENTIAL AND COMBINATION LAPATINIB, TRASTUZUMAB TX

Early-stage HER2+ breast cancer patients in 3 groups:

Sequential:
(Neo)adjuvant chemotherapy prior to anti-HER2 treatment
(N = 4613)

Concurrent Anti-HER2+
12 wks of anthracycline-based chemotherapy
(paclitaxel or docetaxel)
(N = 3337)

Concurrent Anti-HER2+
18 wks of nonanthracycline-based chemotherapy
(docetaxel + carboplatin)
(N = 431)



Chemotherapy dosing: paclitaxel 80 mg/m^2/wk; docetaxel 70-100 mg/m^2 q3w; carboplatin AUC 6 q3wk

Piccart-Gebhart M, et al. ASCO 2014. Abstract LBA4.

ALTTO: NO DIFFERENCE IN 4-YR DFS OR OS WITH ADDITION OF LAPATINIB

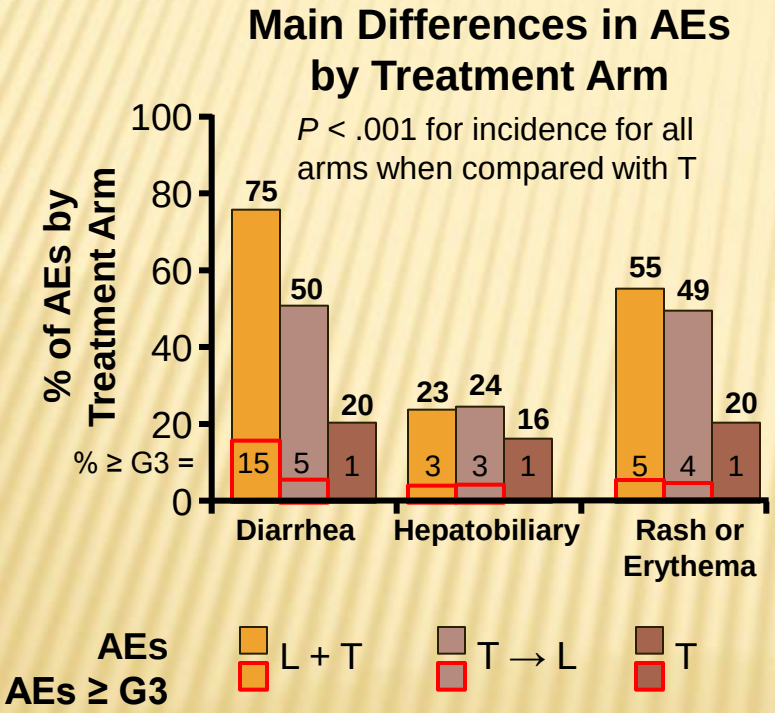
- High rate of 4-yr DFS and OS; no difference based on treatment group

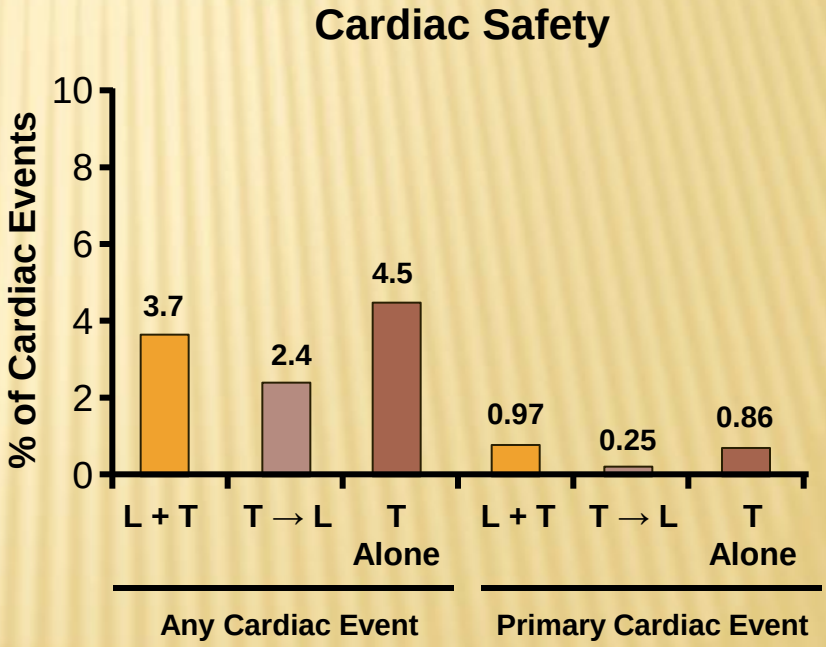
Result, %	L + T (n = 2093)	T → L (n = 2091)	T (n = 2097)
4-yr DFS	88	87	86
HR vs T (97.5% CI)	0.84 (0.70-1.02)	0.96 (0.80-1.15)	
P value	.048	.61	
4-yr OS	95	95	94
HR vs T (97.5% CI)	0.80 (0.62-1.03)	0.91 (0.71-1.16)	
P value	.078	.433	

4-Yr DFS Outcome, % (n/N)	L + T	T → L	T
Hormone receptor positive	90 (133/1203)	89 (141/1205)	88 (150/1200)
Hormone receptor negative	86 (121/890)	84 (143/886)	83 (151/897)
Sequential chemotherapy	86 (168/1155)	85 (184/1143)	83 (207/1147)
Concurrent chemotherapy	90 (86/938)	89 (100/948)	90 (94/950)

Piccart-Gebhart M, et al. ASCO 2014. Abstract LBA4.

ALTTO: SAFETY PROFILE WITH TRASTUZUMAB ± LAPATINIB





Piccart-Gebhart M, et al. ASCO 2014. Abstract LBA4. *Reprinted with permission.*

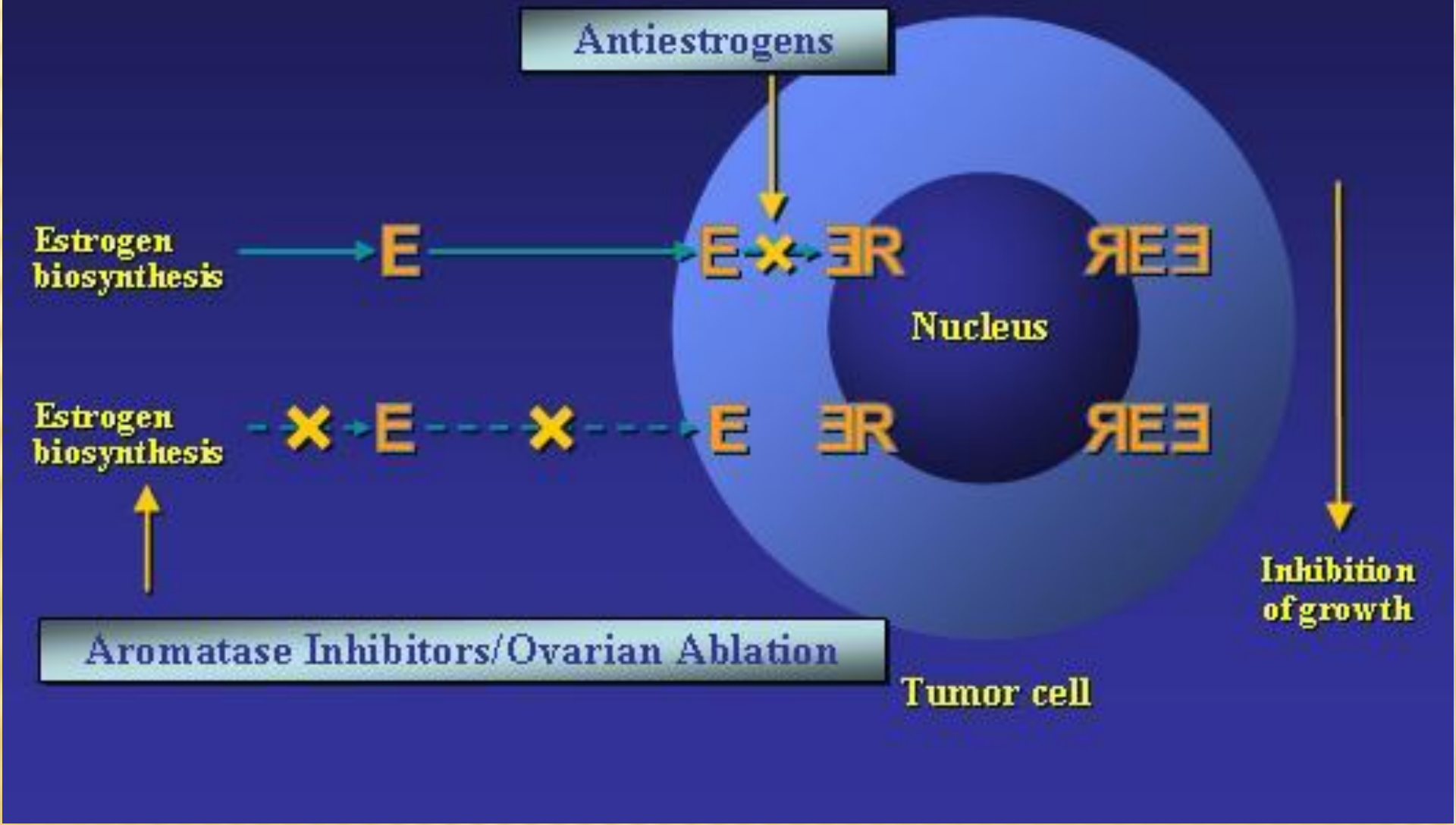
ALTTO: CONCLUSIONS

- Event rate lower than expected: at median follow-up 4.5 yrs, 555 DFS events for L + T vs T comparisons (target was 850 events)
- 4-yr DFS endpoint was not met for either pairwise comparison
  - L + T vs T: 88% vs 86% (HR: 0.84; 97.5% CI: 0.70-1.02)
  - T → L vs T: 87% vs 86% (HR: 0.93; 97.5% CI: 0.76-1.13)
- Lapatinib associated with significant increase in AEs of special interest vs trastuzumab alone (diarrhea, hepatobiliary, and rash or erythema)
  - 60% to 78% of pts in lapatinib arms received ≥ 85% of protocol specified dose
  - Cardiac toxicity low in all treatment groups
- Increase in pCR observed in NeoALTTO trial did not correspond with observed survival outcomes in ALTTO trial
  - Protocol-specified updated efficacy analysis is planned in 2 yrs

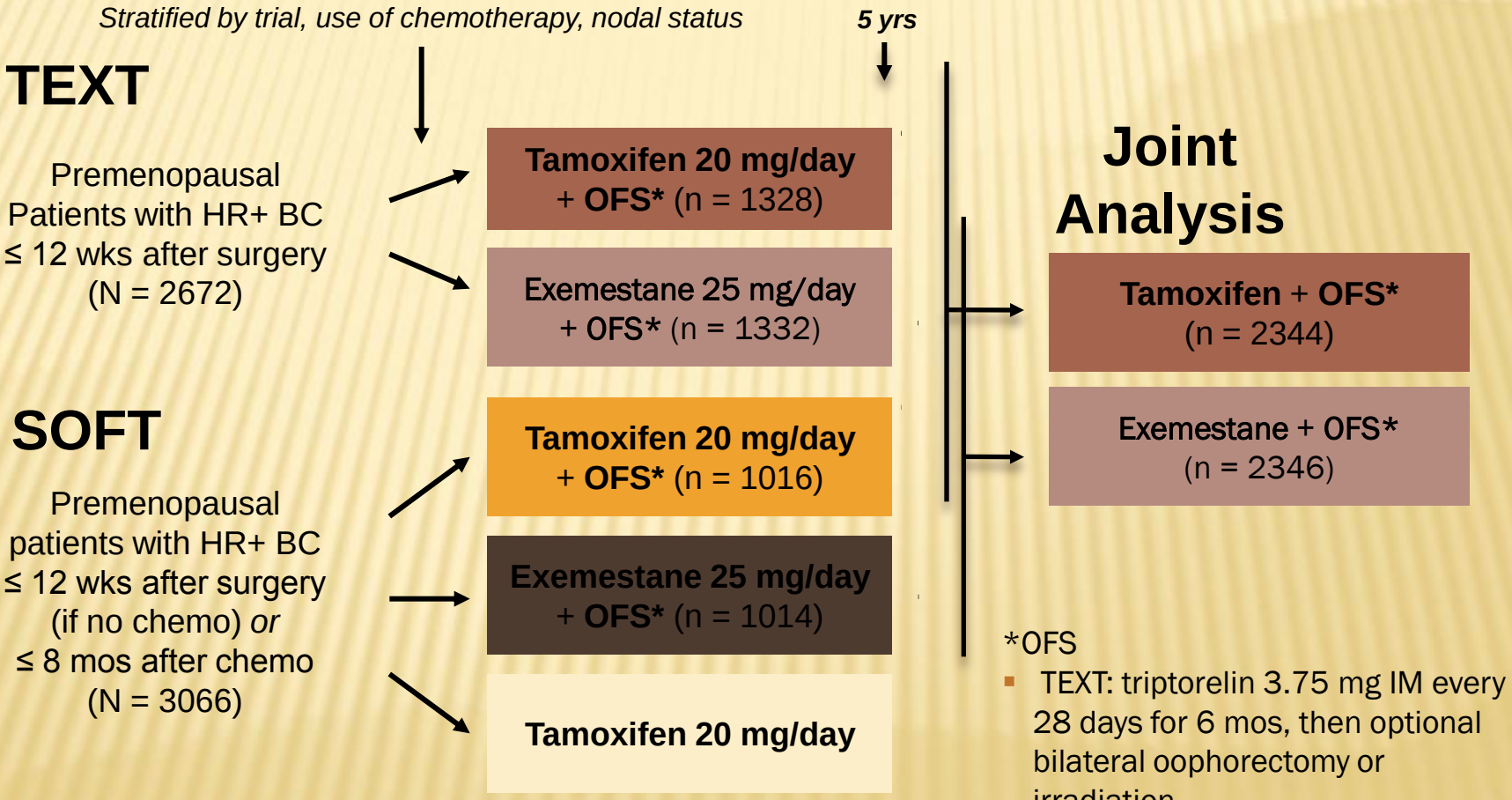
Piccart-Gebhart M, et al. ASCO 2014. Abstract LBA4.


Hormonal therapy

Inhibition of Estrogen-Dependent Growth



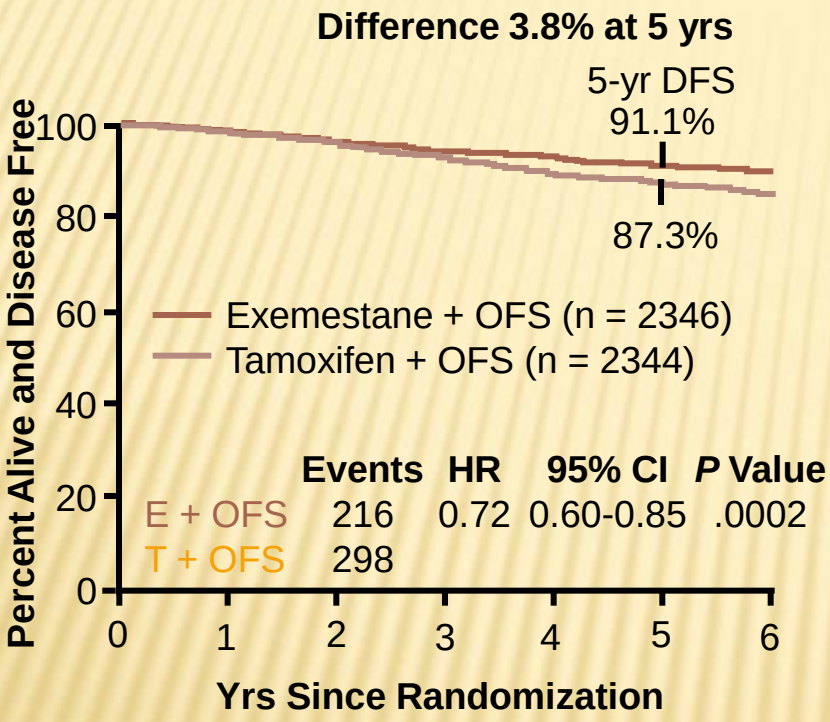
TEXT AND SOFT TRIALS: COMPARISON OF TAMOXIFEN OR EXEMESTANE WITH OFS

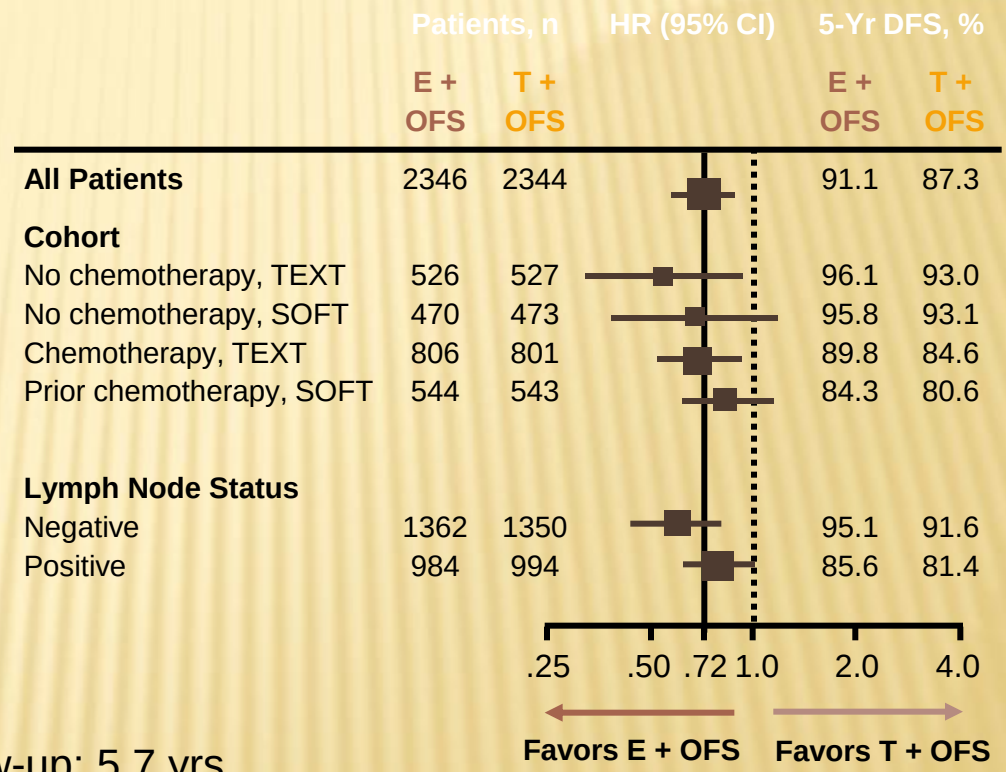


*OFS
- TEXT: triptorelin 3.75 mg IM every 28 days for 6 mos, then optional bilateral oophorectomy or irradiation
- SOFT: choice of method

Pagani O, et al. ASCO 2014. Abstract LBA1.

EXEMESTANE WITH OVARIAN FUNCTION SUPPRESSION IMPROVED DFS





Median follow-up: 5.7 yrs

- 60% of first failures involved distant sites, including soft tissue, bone, and viscera

Pagani O, et al. ASCO 2014. Abstract LBA1..

TEXT AND SOFT 5-YR EFFICACY OUTCOMES

Outcome, %	Exemestane + OFS (n = 2346)	Tamoxifen + OFS (n = 2344)	HR (95% CI)	*P* Value
5-yr BCFI	92.8	88.8	0.66 (0.55-0.80)	< .0001
5-yr DRFI	93.8	92.0	0.78 (0.62-0.97)	.02
5-yr OS	95.9	96.9	1.14 (0.86-1.51)	.37

Outcome, % (n/N)	Exemestane + OFS	Tamoxifen + OFS	HR (95% CI)
5-yr BCFI			
▪ TEXT	91.5 (78/806)	86.0 (118/801)	0.64 (0.48-0.85)
▪ SOFT	86.1 (72/544)	82.2 (90/543)	0.82 (0.60-1.12)
5-yr DFRI			
▪ TEXT	91.8 (69/806)	89.2 (88/801)	0.77 (0.56-1.06)
▪ SOFT	88.0 (61/544)	84.6 (77/543)	0.81 (0.58-1.13)

Pagani O, et al. ASCO 2014. Abstract LBA1.

TEXT AND SOFT: SELECTED ADVERSE EVENTS

CTCAE v3.0, %	Exemestane + OFS (N = 2318)		Tamoxifen + OFS (N = 2325)	
	Grades 1-4	Grades 3/4	Grades 1-4	Grades 3/4
Depression	50	3.8	50	4.4
Musculoskeletal	89	11	76	5.2
Osteoporosis ($\%T_{score} < -2.5$)	39 (13)	0.4	25 (6)	0.3
Fracture	6.8	1.3	5.2	0.8
Hypertension	23	6.5	22	7.3
Cardiac ischemia/infarction	0.7	0.3	0.3	0.1
Thrombosis/embolism	1.0	0.8	2.2	1.9
CNS ischemia	0.7	0.3	0.3	0.1
CNS bleeding	0.6	< 0.1	0.9	0.1
Hot flushes/flashes	92	10	93	12
Sweating	55	NR	59	NR
Vaginal dryness	52	NR	47	NR
Libido decrease	45	NR	41	NR
Dyspareunia	31	2.3	26	1.4
Urinary incontinence	13	0.3	18	0.3

Pagani O, et al. ASCO 2014. Abstract LBA1. *Reprinted with permission.*

TEXT AND SOFT: CONCLUSIONS

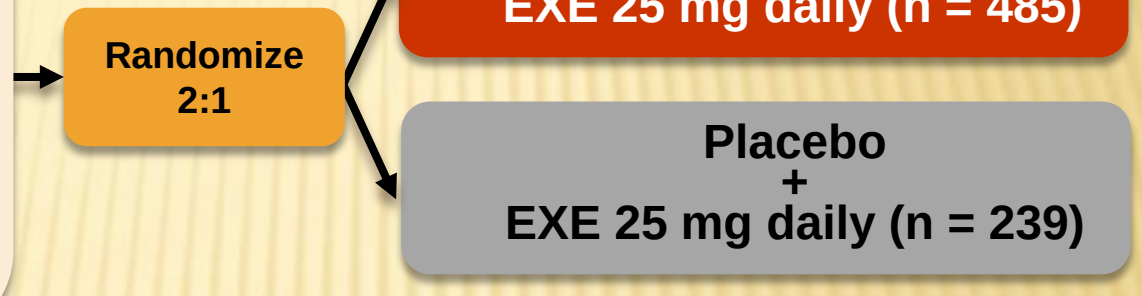
- Exemestane + OFS significantly improved DFS, BCFI, and DRFI vs tamoxifen + OFS, making it a new treatment option for postmenopausal women with early HR+ BC
- No significant difference in OS based on preliminary follow-up of HR+ BC
- Safety profile of exemestane + OFS similar to that seen with AIs in postmenopausal women
- Highly effective endocrine therapy alone offers excellent prognosis for some premenopausal women with HR+ BC
- Long-term follow-up is necessary

Pagani O, et al. ASCO 2014. Abstract LBA1.

BOLERO-2: STUDY DESIGN

N = 724

- Postmenopausal women
- ER^+, $HER2^-$ unresectable locally advanced or metastatic BC
- Recurrence or progression after letrozole or anastrozole



Stratification:

- **Sensitivity to prior hormone therapy**
- Presence of visceral metastases

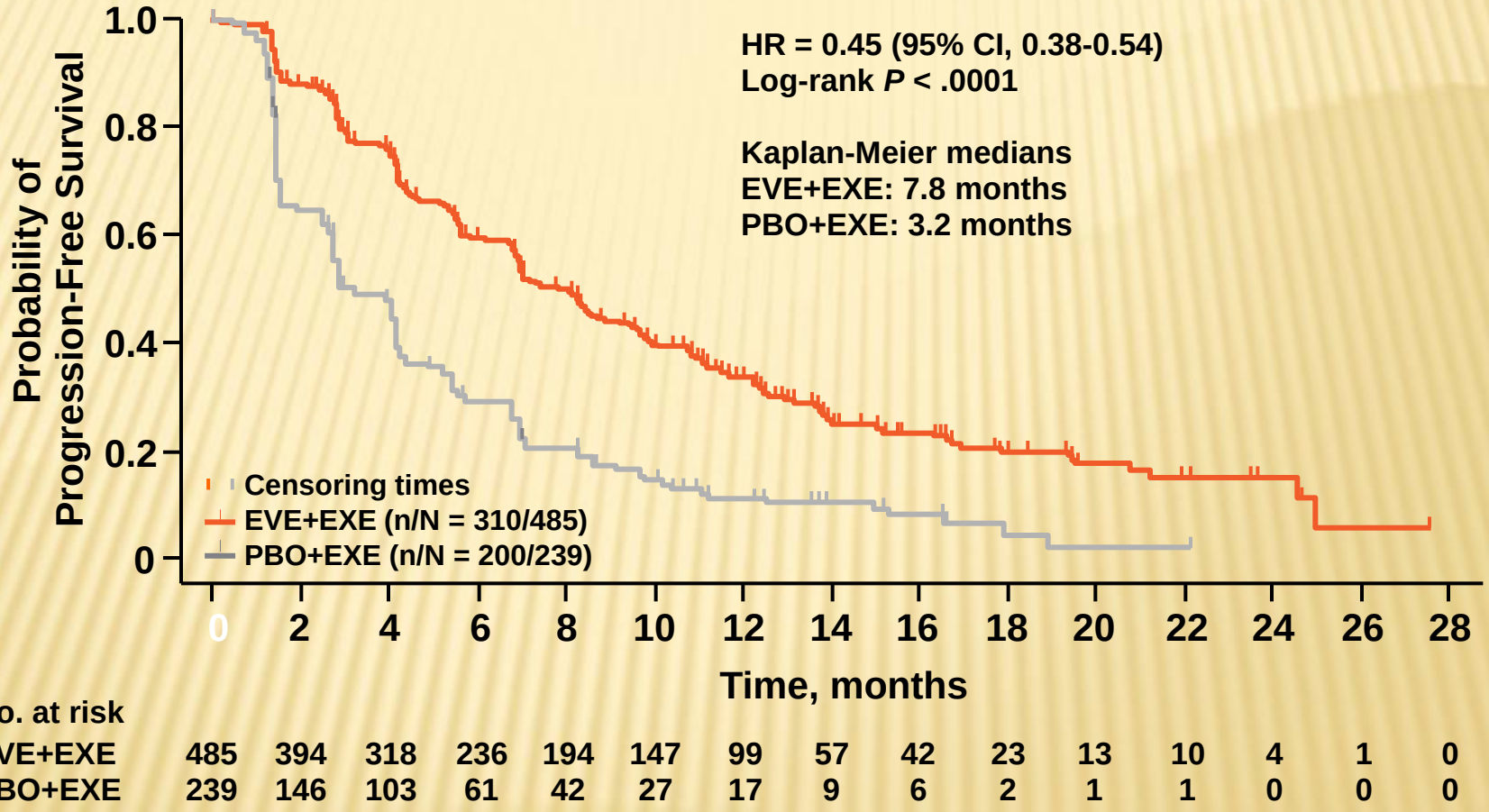
Endpoints

- **Primary**: PFS (local assessment)
- **Secondary**: **OS**, ORR, CBR, QOL, safety, PK
- **Exploratory**: Biomarkers

Abbreviations: BC, breast cancer; CBR, clinical benefit rate; ER^+, estrogen receptor-positive; EVE, everolimus; EXE, exemestane; $HER2^-$, human epidermal growth factor receptor-2–negative; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

BOLERO-2 MET PRIMARY ENDPOINT: FINAL PFS ANALYSIS (18-MO) BASED ON LOCAL ASSESSMENT DEMONSTRATED A 4.6-MO PROLONGATION OF PFS



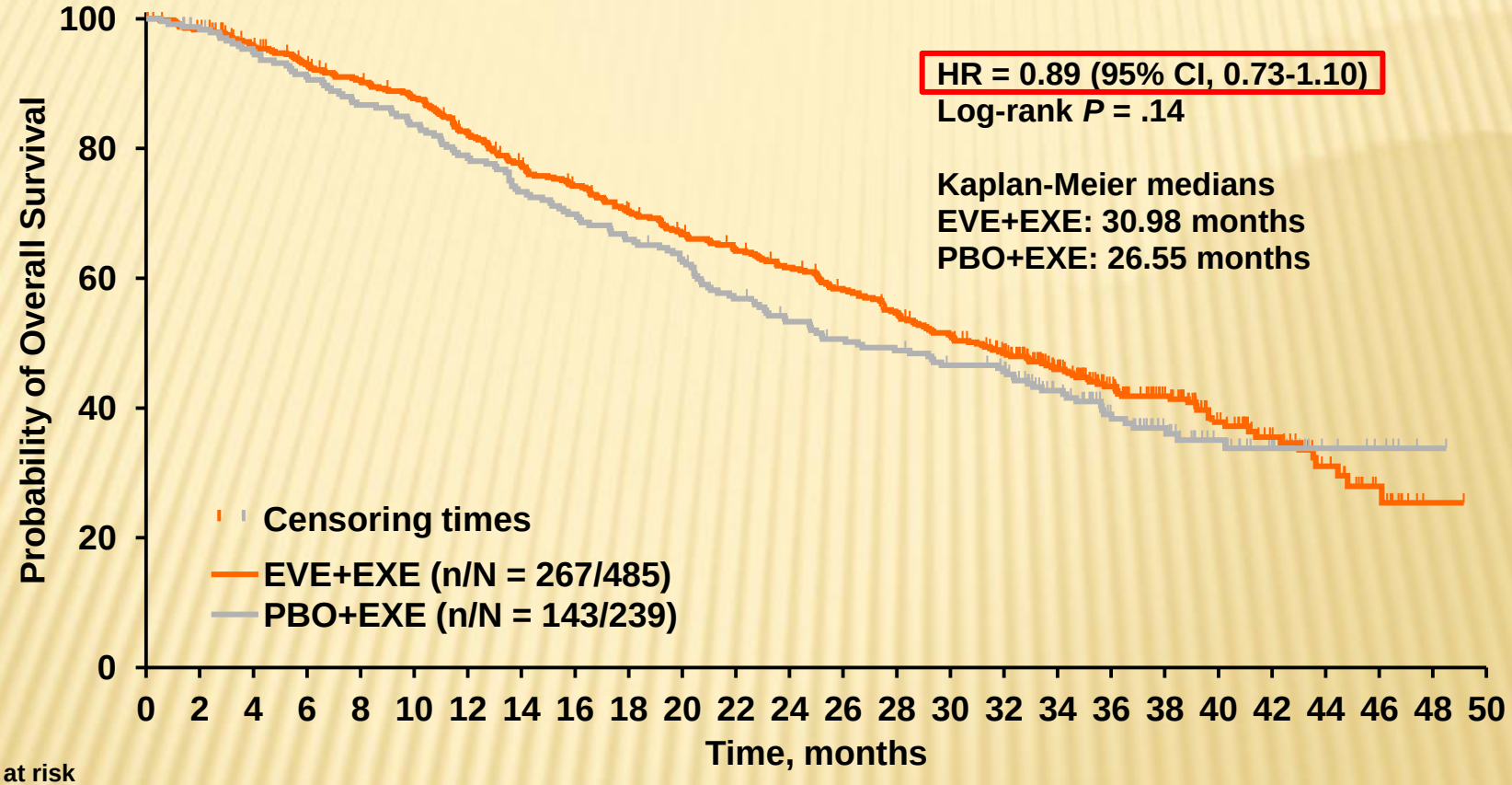
No. at risk

EVE+EXE	485	394	318	236	194	147	99	57	42	23	13	10	4	1	0
PBO+EXE	239	146	103	61	42	27	17	9	6	2	1	1	0	0	0

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

Yardley DA, et al. *Adv Ther*. 2013;30(10):870-884.

BOLERO-2 (39-MO): FINAL OS ANALYSIS



No. at risk

EVE+EXE	485	471	448	429	414	399	373	347	330	311	292	279	266	248	232	216	196	154	118	91	58	39	23	11	1	0
PBO+EXE	239	232	220	211	201	194	182	170	162	153	145	130	120	113	109	102	98	77	56	41	28	18	8	5	1	0

- At 39 months' median follow-up, 410 deaths had occurred (data cutoff date: 03 October 2013)
  - 55% deaths (n = 267) in the EVE+EXE arm vs 60% deaths (n = 143) in the PBO+EXE arm
  - 13 pts still on treatment

One-sided *P* value was obtained from the log-rank test stratified by sensitivity to prior hormonal therapy and presence of visceral metastasis from IXRS®. Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; IXRS®, Interactive Voice and Web Response System; PBO, placebo.

BOLERO-2 (39-MO): POST-STUDY TREATMENT ANTICANCER THERAPIES

Therapy Type	Everolimus + Exemestane (n = 485), %	Placebo + Exemestane (n = 239), %
Any posttreatment therapy	84	90
Chemotherapy	53	63
Hormonal therapy	47	44
Targeted therapy	10	11
Radiation therapy	9	11
Surgery	1	1
Immunotherapy	<1	0
Other	2	1
Chemotherapy	53	63
Taxane	28	36
Capecitabine	24	28
Anthracyclines	13	15
Cyclophosphamide	9	9
Vinorelbine	7	13
Platinum-based regimens	4	2
Gemcitabine	4	5

10% more patients in placebo arm received chemotherapy compared with the everolimus arm.

BOLERO-2 (39-MO): LONGER MEDIAN TIME FROM RANDOMIZATION TO FIRST CHEMOTHERAPY OR DEATH (EVEROLIMUS PLUS EXEMESTANE ARM)

Time From Randomization to First Chemotherapy or Death	Everolimus + Exemestane (n = 485)	Placebo + Exemestane (n = 239)
Number of events, n (%)	**366 (75.5)**	**192 (80.3)**
Chemotherapy	257 (53.0)	150 (62.8)
Death	109 (22.5)	42 (17.6)
Number censored, n (%)	**119 (24.5)**	**47 (19.7)**
Discontinued from study	105 (21.6)	45 (18.8)
Ongoing at data cutoff[a]	14 (2.9)	2 (0.8)
Time from randomization to first chemotherapy or death, months		
25th percentile (95% CI)	5.68 (5.03-6.57)	3.06 (2.53-3.48)
Median (95% CI)	11.86 (10.45-13.08)	5.98 (5.09-7.39)
75th percentile (95% CI)	25.10 (22.97-28.06)	14.16 (10.74-18.50)

[a] Ongoing without any chemotherapy by the cutoff date.

BOLERO-2 (39-MO): NO NEW SAFETY SIGNALS AT FINAL OS ANALYSIS (SAFETY SET)

	Everolimus + Exemestane (n = 482[a]), %	Placebo + Exemestane (n = 238[a]), %
All deaths	55	60
On-treatment deaths[b]	5	2
Disease progression as primary cause of death	3	1
AE as primary cause of death	2	<1
Serious AEs	33	16
Suspected to be drug-related	13	2
Grade 3/4 AEs	55	29
Suspected to be drug-related	41	8
AEs leading to discontinuation	29	5

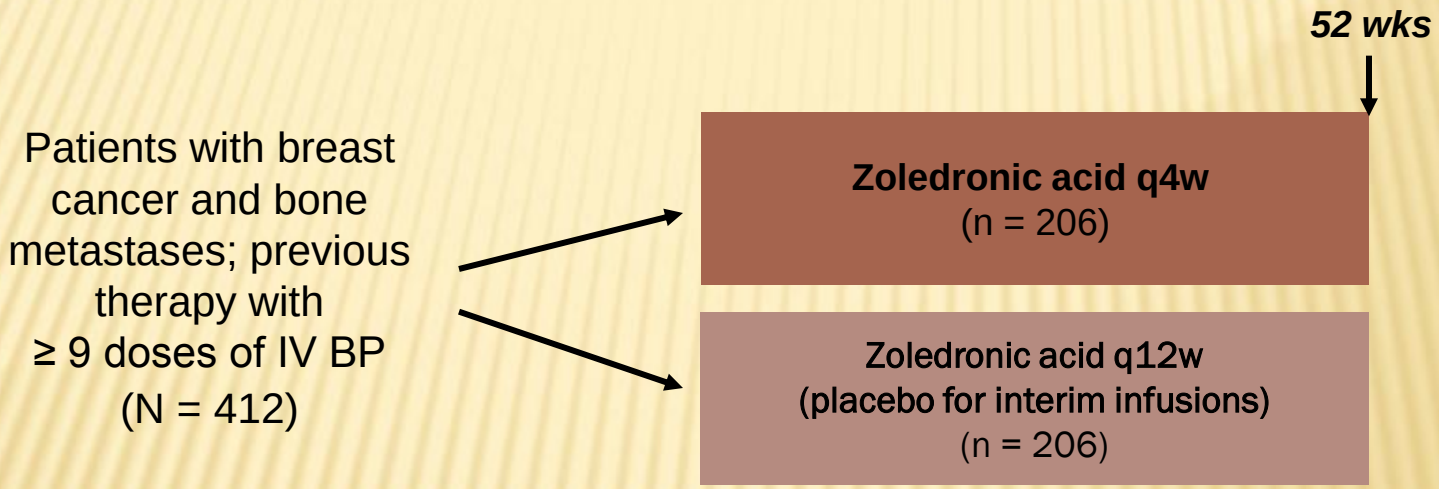
Categories are not mutually exclusive. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories.
[a]Safety set.
[b] Deaths occurring >28 days after end of treatment are not included.
Abbreviations: AE, adverse events; OS, overall survival.

BOLERO-2: CONCLUSIONS

- The PFS prolongation was clinically meaningful and statistically significant (median 4.6-month benefit; $P < .0001$) in patients with HR^+, $HER2^-$ advanced BC that progressed after previous NSAI therapy
- The secondary endpoint of OS did not reach statistical significance (median 31.0 months EVE+EXE vs median 26.6 months PBO+EXE; HR = 0.89; 95% CI, 0.73-1.10; $P = .14$)
- Slightly fewer patients (10%) in the everolimus arm received salvage chemotherapy after progression
- No new safety concerns were identified
- Ongoing translational research should further refine the benefit of mTOR inhibition and related pathways in this treatment setting

OPTIMIZE-2 STUDY: FREQUENCY OF CONTINUED ZOLEDRONIC ACID FOR BONE METS

- Prospective, double-blind, multicenter phase III clinical study



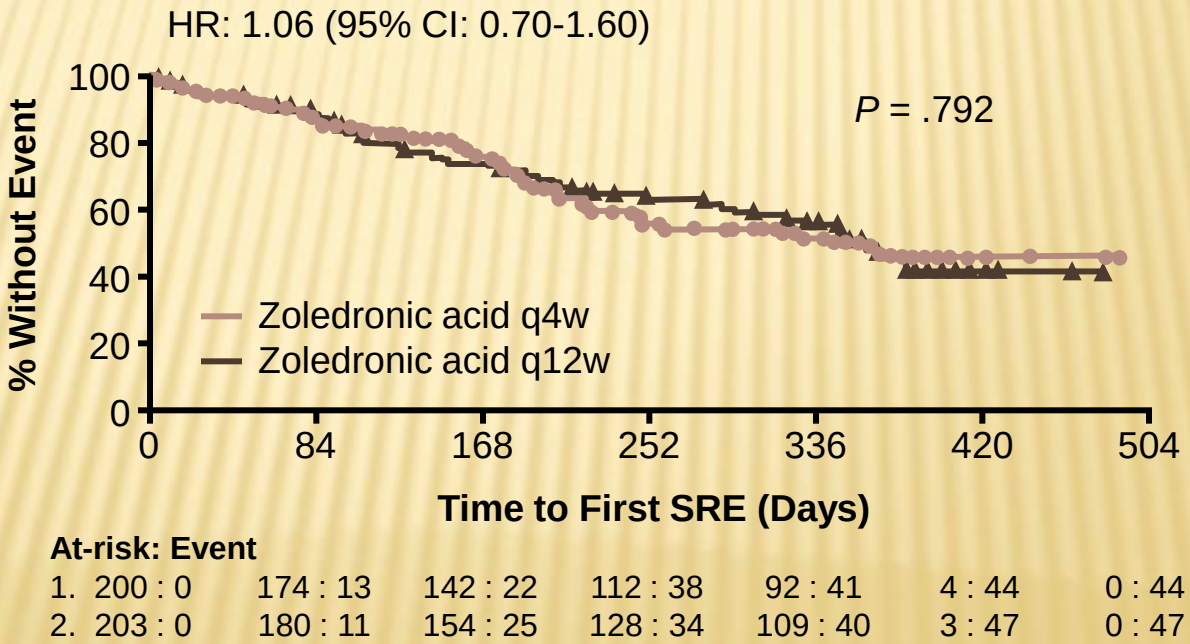
Protocol revisions during the course of the clinical trial

- Placebo arm was dropped early in the study secondary to poor accrual
- Sample size was reduced from 705 to 412, based on new data that became available (ZOOM trial)
- Statistical assumption of 10% noninferiority margin remained unchanged

Hortobagyi GN, et al. ASCO 2014. Abstract LBA9500.

OPTIMIZE-2: SRE WITH ZOLEDRONIC ACID

	Zoledronic Acid q4w	Zoledronic Acid q12w	Proportion Difference, % (95% CI)	*P* Value
≥ 1 SRE, % (n/N)	22 (44/200)	23.2 (47/203)	1.2 (-7.5 to 9.8)	.724



Hortobagyi GN, et al. ASCO 2014. Abstract LBA9500. *Reprinted with permission.*

OPTIMIZE-2: ADVERSE EVENTS WITH ZOLEDRONIC ACID TREATMENT

- Similar safety profiles for q4w or q12w dosing

Overall AEs, n (%)	Zoledronic Acid q4w (n = 198)	Zoledronic Acid q12w (n = 202)
AEs	189 (95.5%)	189 (93.6%)
Serious AEs	50 (25.3%)	51 (25.2%)
Grade 3/4 AEs	94 (47.5%)	86 (42.6%)
AEs leading to dose adjustment, interruption	21 (10.6%)	11 (5.4%)
AEs leading to study medication discontinuation	23 (11.6%)	18 (8.9%)
Deaths	10 (5.1%)	7 (3.5%)

AEs of Special Interest, n (%)	Zoledronic Acid q4w (n = 198)	Zoledronic Acid q12w (n = 202)
Renal AEs	19 (9.6%)	16 (7.9%)
ONJ (adjudicated) AEs	2 (1.0%)	0
Cardiac ischemic events	1 (0.5%)	2 (1.0%)
Atrial fibrillation events	1 (0.5%)	2 (1.0%)
Atypical subtrochanteric femoral fracture events (adjudicated)	0	0

- Median skeletal morbidity rate similar with q4w vs q12w dosing: 0.46 (SD: 1.063) vs 0.50 (SD: 1.500); *P* = .854

Hortobagyi GN, et al. ASCO 2014. Abstract LBA9500. *Reprinted with permission.*

OPTIMIZE-2: CONCLUSIONS

- Continuing zoledronic acid for an additional 1 yr at reduced dosing frequency of every 12 wks was noninferior to every 4 wks dosing (noninferiority margin: 10%)
- Similar safety profiles between the 2 arms
- Similar bone marker profiles between the 2 arms
- Results should be interpreted with caution due to study limitations, including:
  - Placebo arm dropped due to low accrual
  - Statistical concerns regarding noninferiority margin determination

Hortobagyi GN, et al. ASCO 2014. Abstract LBA9500.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EPISODE I

INVESTIGATIONAL AGENTS IN MBC

Agent	MOA	Phase	Patient Population	Response, % (n/N)
LY2835219 + fulvestrant[1]	CDK4/6 inhibitor	I	HR+ MBC	19.1 (9/47) PR; 29.8 (14/47) SD ≥ 24 wks; 21.3 (10/47) SD < 24 wks
LEE011 and/or BYL719 + letrozole[2]	CDK4/6 inhibitor or PI3K inhibitor	Ib	Postmenopausal ER+ HER2- MBC	Preliminary clinical activity Dose escalation continues
LEE011 + EVE + EXE[3]	CDK4/6 inhibitor	Ib/II	Postmenopausal ER+ MBC; refractory to NSAIs	7 (1/14) PR; 50 (7/14) SD
BYL719 + letrozole[4]	PI3K inhibitor	Ib	ER+ HER2- MBC	11 (3/26) PR; 27 (7/26) CBR
Sorafenib + letrozole[5]	Multitarget TKI	I/II	Postmenopausal HR+ MBC; no prior therapy for MBC	39 (16/41) PR; 41 (17/41) SD; Median OS: 51.5 mos
ABT-888[6]	PARP inhibitor	II	*BRCA*+ MBC; no prior platinum agents	*BRCA1*: 20 (4/20) CBR *BRCA2*: 42 (8/19) CBR

1. Patnaik A, et al. ASCO 2014. Abstract 534. 2. Munster PN, et al. ASCO 2014. Abstract 533. 3. Bardia A, et al. ASCO 2014. Abstract 535. 4. Mayer IA, et al. ASCO 2014. Abstract 516. 5. Tan AR, et al. ASCO 2014. Abstract 531. 6. Somlo G, et al. ASCO 2014. Abstract 1021.

OBESITY IN BREAST CANCER

- Early Breast Cancer Trialists' Collaborative Group collected data on 80,000 patients with early breast cancer to analyze independent effects of BMI on patient outcome
- Obesity independently associated with BC-related mortality in premenopausal pts with ER+ BC
  - In premenopausal obese (BMI ≥ 30) vs normal-weight women with ER+ disease (N = 20,000): 10-yr BC-relate mortality: 21.5% vs 16.6% (RR = 1.34; 95% CI: 1.22-1.47; 2P < .00001)
- Little effect in premenopausal women with ER-negative disease or in postmenopausal women
  - Postmenopausal ER+ (N = 40,000): RR = 1.06 (95% CI: 0.99-1.14)
  - Pre- or postmenopausal ER-negative (N = 20,000): RR: 1.00 (95% CI: 0.93-1.08)

Pan H, et al. ASCO 2014. Abstract 503.

WEIGHT LOSS HAS FAVORABLE EFFECT ON INFLAMMATORY AND METABOLIC BIOMARKERS

- Overweight/obese BC survivors (N = 97) randomized to usual care or weight loss counseling by a registered dietitian for 6 months in person or by phone
  - Pts with usual care achieved 2% weight loss while those with counseling lost approximately 6% (*P* < .05)
- Inflammatory biomarkers after intervention: statistically significant decrease in CRP (approximately 30%; *P* = .05); trend for decrease in leptin (*P* = .18); no difference in adiponectin (*P* = .71), IL-6 (*P* = .47), TNF-α (*P* = .99)
- Metabolic markers after intervention: trend for decrease in insulin (approximately 10%; *P* = .28); no difference in glucose or IGF-1 (*P* = .16, .36)
  - In the intervention cohort, patients with ≥ 5% weight loss (n = 27) compared with those with < 5% (n = 25):
    - Had statistically significant decrease in insulin (*P* = .048), IL-6 (*P* = .024), CRP (*P* = .021), and leptin (*P* = .002)
    - Had statistically significant increase in IGF-1 (*P* = .007)

Irwin M, et al. ASCO 2014. Abstract 1505.


Thank You