5 Minute JournalClub

Key SABCS Presentations

Issue 5, 2011

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Research To Practice®

CME Information

LEARNING OBJECTIVES

- Employ an understanding of new data to address concerns expressed by patients and providers over CYP2D6 genotype and the efficacy and tolerability of tamoxifen.
- Use new research findings to refine or validate current fulvestrant dosing and its sequential placement in the treatment of advanced breast cancer.
- Counsel patients who are diagnosed with breast cancer during pregnancy about the known benefits and risks of delivering treatment prior to or after delivery.
- Explain the emerging body of evidence correlating obesity with disease outcome to patients with early breast cancer.
- Compare and contrast rates of breast cancer relapse among obese, overweight and normal-weight patients receiving adjuvant exemestane or tamoxifen.
- Cite the disease-free survival (DFS) and overall survival for obese and nonobese patients according to hormone receptor and HER2/neu status subtype, as derived from a meta-analysis.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

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FACULTY DISCLOSURES

The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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No real or apparent conflicts of interest to disclose.

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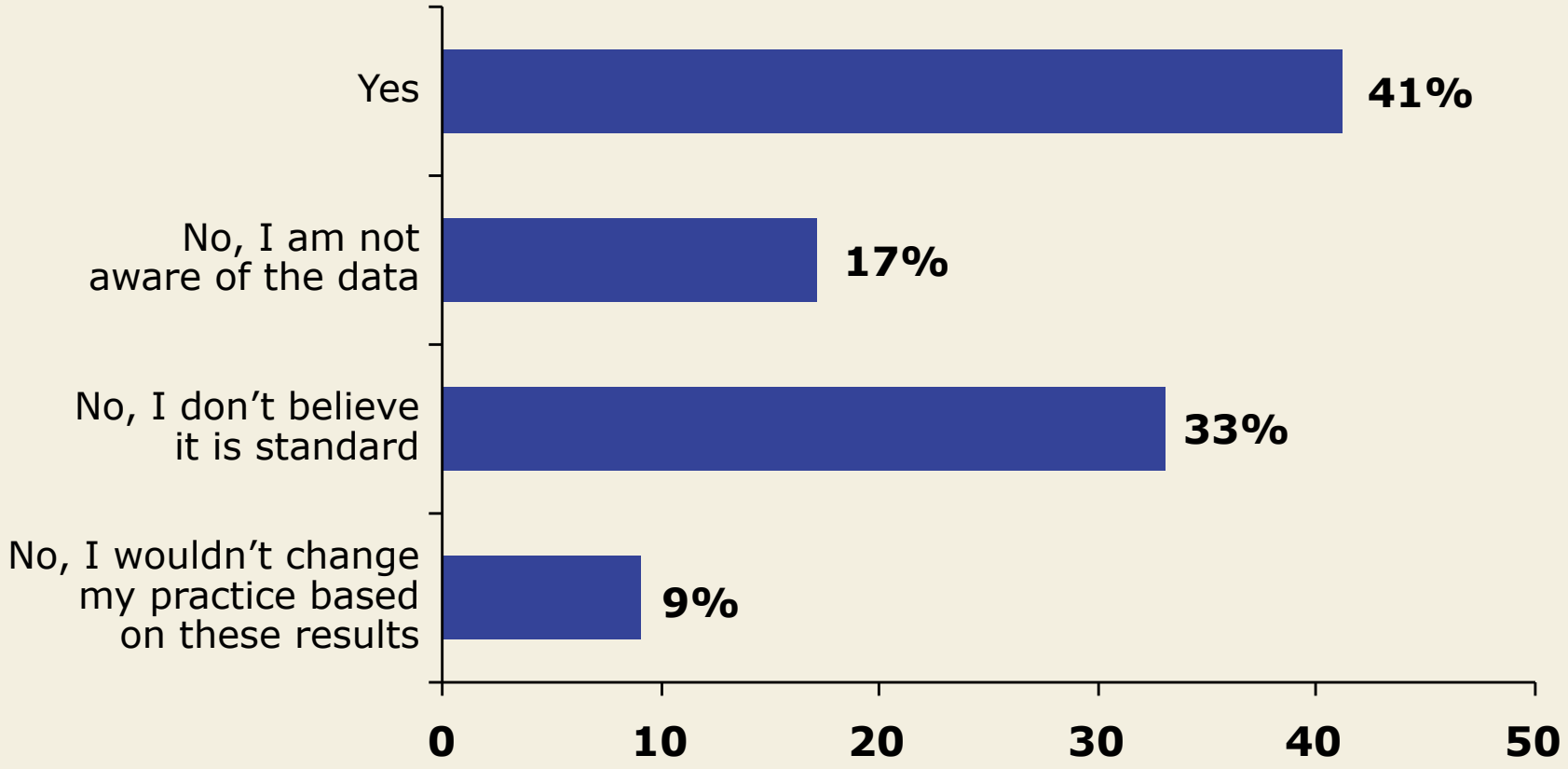
Outcome According to CYP2D6 Genotype Among Postmenopausal Women with Endocrine-Responsive Early Invasive Breast Cancer Randomized in the BIG 1-98 Trial[1]

Lack of Correlation between Gene Variants in Tamoxifen Metabolizing Enzymes with Primary Endpoints in the ATAC Trial[2]

[1]Leyland-Jones B et al.
Proc SABCS 2010;Abstract S1-8.

[2]Rae JM et al, on behalf of the ATAC Trialists.
Proc SABCS 2010;Abstract S1-7.

Have You Ordered CYP2D6 Genotyping for Patients with ER-Positive Breast Cancer?



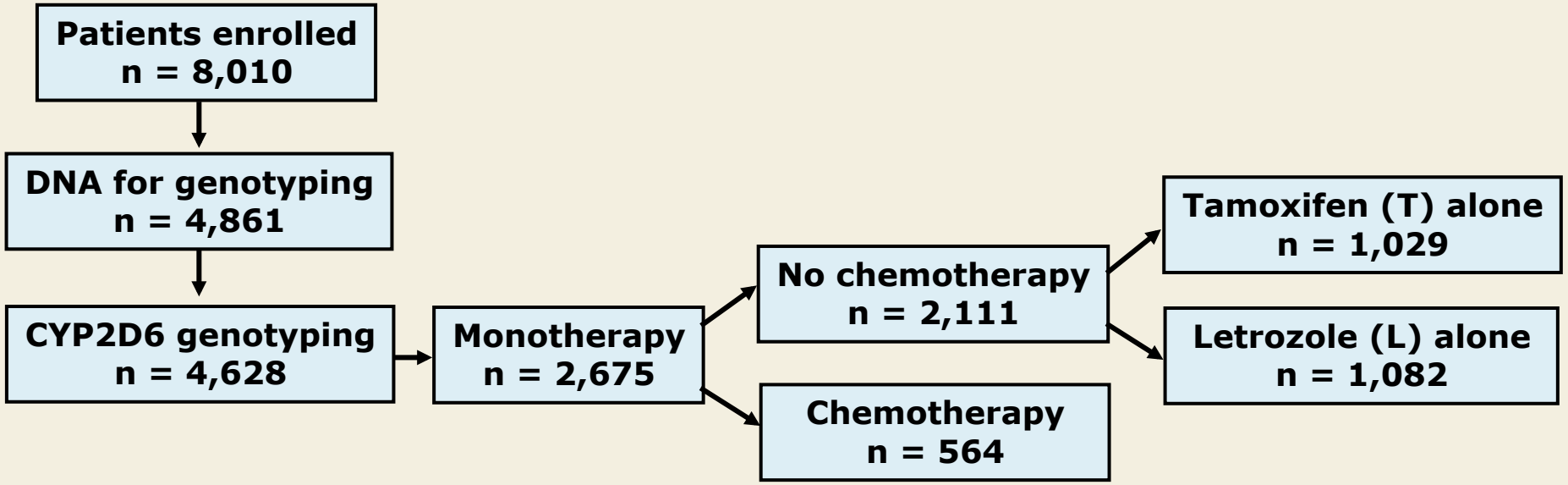
Patterns of Care in Breast Cancer, Research To Practice 2009.

Outcome According to CYP2D6 Genotype Among Postmenopausal Women with Endocrine-Responsive Early Invasive Breast Cancer Randomized in the BIG 1-98 Trial

Leyland-Jones B et al.

Proc SABCS 2010;Abstract S1-8.

BIG 1-98: Analytic Cohort



Patient characteristics: Caucasian: 98%, ER-positive: 100%, Node-negative: 57%, No chemotherapy (Chemo) received: 77%

Current analysis objectives:

- To investigate the association of CYP2D6 variants with breast cancer-free interval (BCFI) and onset of hot flashes/night sweats.
- To evaluate the role of adjuvant chemotherapy, which was administered in about one third of trial patients prior to randomization to adjuvant endocrine therapy.

Leyland-Jones B et al. *Proc SABCS* 2010;Abstract S1-8.

CYP2D6 Phenotype

- **Poor metabolizers (PM):**
  - Homozygous or compound heterozygous for null alleles (*3, *4, *6 or *7)
- **Intermediate metabolizers (IM):**
  - Homozygous for reduced-function alleles (*41) or heterozygous for reduced- and null-function alleles
  - hetEM: Heterozygous for one reduced- or null-function allele
- **Extensive metabolizers (EM):**
  - Absence of reduced- or null-function alleles

Leyland-Jones B et al. *Proc SABCS* 2010;Abstract S1-8.

CYP2D6 Phenotype is Not Associated with BCFI in Patients Treated with Tamoxifen +/- Chemo

Tamoxifen Alone				
CYP2D6 Phenotype	**Patients (n)**	**Events (n)**	**Adjusted HR (95% CI)**	***p*-value**
Poor metabolizers (PM)	86	8	0.58 (0.28-1.21)	0.35
Intermediate metabolizers (IM)	277	40	0.95 (0.50-1.40)	
Extensive metabolizers (EM)	610	75	Reference	

Chemotherapy plus Tamoxifen				
CYP2D6 Phenotype	**Patients (n)**	**Events (n)**	**Adjusted HR (95% CI)**	***p*-value**
PM	26	3	0.76 (0.23-2.48)	0.23
IM	77	12	0.57 (0.29-1.10)	
EM	167	37	Reference	

Leyland-Jones B et al. *Proc SABCS* 2010;Abstract S1-8.

CYP2D6 Phenotype is Not Associated with BCFI in Patients Treated with Letrozole +/- Chemo

Letrozole Alone				
CYP2D6 Phenotype	**Patients (n)**	**Events (n)**	**Adjusted HR (95% CI)**	***p*-value**
PM	99	11	0.95 (0.50-1.80)	0.98
IM	296	37	1.02 (0.69-1.53)	
EM	639	72	Reference	

Chemotherapy plus Letrozole				
CYP2D6 Phenotype	**Patients (n)**	**Events (n)**	**Adjusted HR (95% CI)**	***p*-value**
PM	25	3	1.00 (0.30-3.35)	0.34
IM	66	12	1.68 (0.83-3.39)	
EM	169	23	Reference	

Leyland-Jones B et al. *Proc SABCS* 2010;Abstract S1-8.

Author Conclusions and Clinical Implications

- Genotype analysis of postmenopausal women with endocrine-responsive early breast cancer (EBC) treated on the BIG 1-98 trial found CPY2D6 phenotypes of reduced enzyme activity (PM, IM) were:
  - NOT associated with worse disease control
  - NOT associated with reduced hot flashes (data not shown)

- For postmenopausal women with endocrine-responsive EBC:
  - CYP2D6 pharmacogenetics testing *is not* justified to determine whether to administer tamoxifen
  - Presence or absence of hot flashes *should not be used* as an indicator of tamoxifen efficacy

Leyland-Jones B et al. *Proc SABCS* 2010;Abstract S1-8.

Lack of Correlation between Gene Variants in Tamoxifen Metabolizing Enzymes with Primary Endpoints in the ATAC Trial

Rae JM et al, on behalf of the ATAC Trialists.

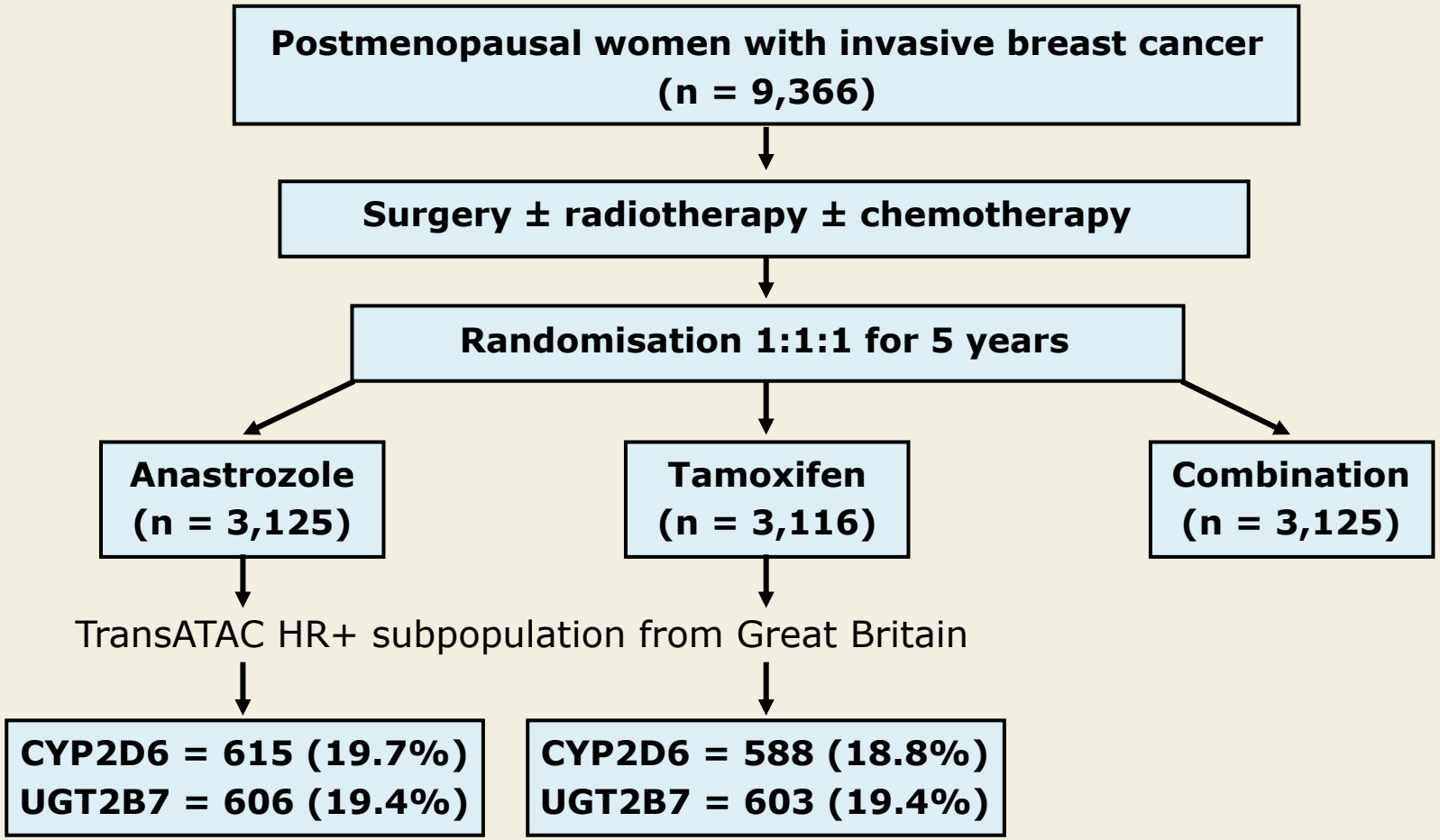
Proc SABCS 2010;Abstract S1-7.

Objective and Methods

- **Study Objective:**
  - Determine whether a correlation exists between single nucleotide polymorphisms (SNPs) in tamoxifen metabolizing enzymes and clinical outcomes in the ATAC trial of adjuvant anastrozole vs tamoxifen for five years.
- **Genetic Analysis in the ATAC Trial:**
  - Genotypes determined from leukocytic DNA present in formalin-fixed paraffin-embedded tumor samples
    - **CYP2D6 gene** - seven most common SNPs in Caucasians were genotyped and entered into the establishment of a CYP2D6 scoring system for predicting CYP2D6 phenotype, based on predicted allele activities: *1, *2, *3, *4, *6, *10, *41
    - **UGT2B7 gene** - common functional SNP in Caucasians was genotyped: *2

Rae JM et al. *Proc SABCS* 2010;Abstract S1-7.

ATAC Trial Design



Rae JM et al. *Proc SABCS* 2010;Abstract S1-7.

CYP2D6*4 Gene Variant Does Not Predict Recurrence in Patients Treated with Tamoxifen or Anastrozole

Tamoxifen Arm				
CYP2D6 Genotype	**Hazard Ratio**	**95% CI**	***p*-value**	**Overall *p* for Trend**
Wt/Wt (n = 402)	Ref	—	—	0.688
*4/Wt (n = 149)	1.19	0.79-1.80	0.397	
*4/*4 (n = 37)	0.98	0.45-2.14	0.972	

Anastrozole Arm				
Wt/Wt (n = 430)	Ref	—	—	0.22
*4/Wt (n = 146)	0.66	0.38-1.13	0.130	
*4/*4 (n = 39)	0.61	0.22-1.66	0.332	

Wt = wild type; the CYP2D6*4 variant is the most common and is associated with decreased tamoxifen activation.

Rae JM et al. *Proc SABCS* 2010;Abstract S1-7.

UGT2B7*2 Gene Variant Does Not Predict Recurrence in Patients Treated with Tamoxifen or Anastrozole

Tamoxifen Arm				
UGT2B7 Genotype	**Hazard Ratio**	**95% CI**	***p*-value**	**Overall *p* for Trend**
Wt/Wt	Ref	—	—	0.549
*2/Wt	1.29	0.79-2.09	0.310	
*2/*2	1.11	0.65-1.90	0.709	

Anastrozole Arm				
Wt/Wt	Ref	—	—	0.845
*2/Wt	0.88	0.52-1.49	0.640	
*2/*2	0.85	0.47-1.52	0.640	

The UGT2B7*2 variant is associated with decreased tamoxifen inactivation.

Rae JM et al. *Proc SABCS* 2010;Abstract S1-7.

Author Conclusions and Clinical Implications

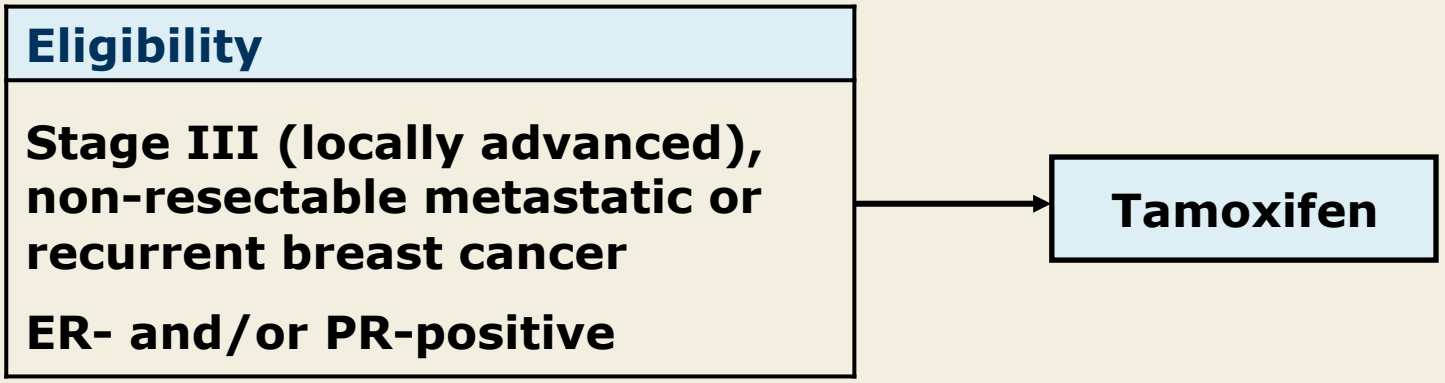
- The genotypes of CYP2D6 and UGT2B7 tamoxifen metabolizing enzymes were not associated with clinical outcomes in the ATAC trial.
- Use of concomitant CYP2D6 inhibitors (SSRI) does not affect outcomes.
- For adjuvant tamoxifen or anastrozole treatment, the evidence is NOT sufficient to recommend:
  - Genotyping for CYP2D6 and UGT2B7
  - Avoidance of the use of CYP2D6 inhibitors

Rae JM et al. *Proc SABCS* 2010;Abstract S1-7.

ECOG-E3108: A Phase II Multicenter Trial Correlating Progression-Free Survival and CYP2D6 Activity

Target Accrual: 240 (Open)

Trial Identifier: NCT01124695



Primary Objective: To correlate CYP2D6 score (0 vs 1-2) and progression-free survival in patients treated with tamoxifen

www.ClinicalTrials.gov, February 2011.

Investigator Commentary: CYP2D6 Genotyping and Clinical Outcome in Postmenopausal Women with Early BC

This has been an area of controversy as there has been mixed evidence on the use of CYP2D6 testing to make treatment decisions. The hypothesis that CYP2D6 genotype could predict response to tamoxifen was sound, but some past studies were positive and others were negative. This left us scratching our heads and sometimes left clinicians crossing within databases the writing of prescriptions for SSRIs that inhibit CYP2D6 against the tamoxifen prescriptions to see whether they were going to predict rates of recurrence.

Retrospective reanalysis of two large randomized trials — BIG 1-98 and ATAC — which evaluated tamoxifen versus aromatase inhibitors were presented at SABCS 2010. Investigators looked specifically at tamoxifen itself or tamoxifen relative to the aromatase inhibitors and attempted to determine whether germline CYP2D6 status had any bearing on the relative benefits of tamoxifen. CYP2D6 status did not allow clinicians to predict with any accuracy which patients did or did not benefit from tamoxifen.

These were clean data sets and well-studied, prospectively followed patient populations. This is likely the highest level of evidence we're ever going to get, and this is nearly a unique resource at this point. I believe this story is over.

Interview with Clifford Hudis, MD, January 12, 2011

A Comparison of Fulvestrant 500 mg with Anastrozole as First-line Treatment for Advanced Breast Cancer: Follow-up Analysis from the FIRST Study

Robertson JFR et al.

Proc SABCS 2010;Abstract S1-3.

Methods

- **Objective**
  - To report follow-up data for time to progression (TTP) and time to treatment failure (TTF) from the FIRST study of fulvestrant 500 mg versus anastrozole in the first-line metastatic setting
- FIRST: A Phase II, open-label study
  - **Eligibility**
    - ER-positive
    - Postmenopausal
    - Advanced disease
  - Patients were randomly assigned 1:1 to fulvestrant 500 mg (d0, 14, 28 and then q 4wk) or anastrozole 1 mg daily.

Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

FIRST Study Endpoints

- **Primary**
  - Clinical benefit rate
- **Secondary**
  - Objective response rate
  - Time to progression (TTP)
  - Duration of response
  - Duration of clinical benefit
  - Safety
- **Exploratory**
  - Best response to subsequent therapy

These endpoints were planned for the primary data cutoff

Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

Clinical Benefit Rate

Fulvestrant 500 mg n = 102	Anastrozole 1 mg n = 103	Odds ratio (95% CI)	Absolute difference (95% CI)
72.5%	67.0%	1.30 (0.72, 2.38)	5.6% (-7.8 to 15.8%)

Robertson JF et al. *J Clin Oncol* 2009;27(27):4530-5.

TTP Analysis

Patients experiencing disease progression	Fulvestrant 500 mg n = 102	Anastrozole 1 mg n = 103	Hazard ratio (95% CI)	*p*-value
At primary cutoff[1]	29.4%	41.7%	0.63 (0.39, 0.99)	0.05
Updated analysis[2]	61.8%	76.7%	0.66 (0.47, 0.92)	0.01

Primary analysis median follow-up
Fulvestrant 500 mg - 8.0 months
Anastrozole 1 mg - 5.9 months

Updated analysis median follow-up
Fulvestrant 500 mg - 18.8 months
Anastrozole 1 mg - 12.9 months

[1] Robertson JF et al. *J Clin Oncol* 2009;27(27):4530-5; [2] Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

TTP Analysis

Median time to progression	Fulvestrant 500 mg n = 102	Anastrozole 1 mg n = 103	Hazard ratio (95% CI)	*p*-value
At primary cutoff[1]	Not calculable	12.5 months	0.63 (0.39, 0.99)	0.05
Updated analysis[2]	23.4 months	13.1 months	0.66 (0.47, 0.92)	0.01

Primary analysis median follow-up
Fulvestrant 500 mg - 8.0 months
Anastrozole 1 mg - 5.9 months

Updated analysis median follow-up
Fulvestrant 500 mg - 18.8 months
Anastrozole 1 mg - 12.9 months

[1] Robertson JF et al. *J Clin Oncol* 2009;27(27):4530-5; [2] Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

TTF Analysis

Patients experiencing treatment failure[1]	Fulvestrant 500 mg n = 102	Anastrozole 1 mg n = 103	Hazard ratio (95% CI)	*p*-value
Treatment failures	74.5%	84.5%	0.73 (0.54, 1.00)	0.05
Median TTF (months)	17.6	12.7		

Updated analysis median follow-up
Fulvestrant 500 mg - 18.8 months; Anastrozole 1 mg - 12.9 months

[1] Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

Safety

- No significant differences between the groups in pre-specified adverse events[1]:
  - GI disturbances, joint disorders, hot flashes, urinary tract infections, weight gain, endometrial dysplasia, ischemic cardiovascular disorders, osteoporosis, thromboembolic events and vaginitis
- Total of 22 serious adverse events (SAEs) in updated analysis period (n = 14)[2]
  - 12 SAEs in fulvestrant group (n = 7)
  - 10 SAEs in anastrozole group (n = 7)
- No new safety concerns with fulvestrant 500 mg arising from SAEs reported with longer follow-up[2]

[1] Robertson JF et al. *J Clin Oncol* 2009;27(27):4530-5; [2] Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

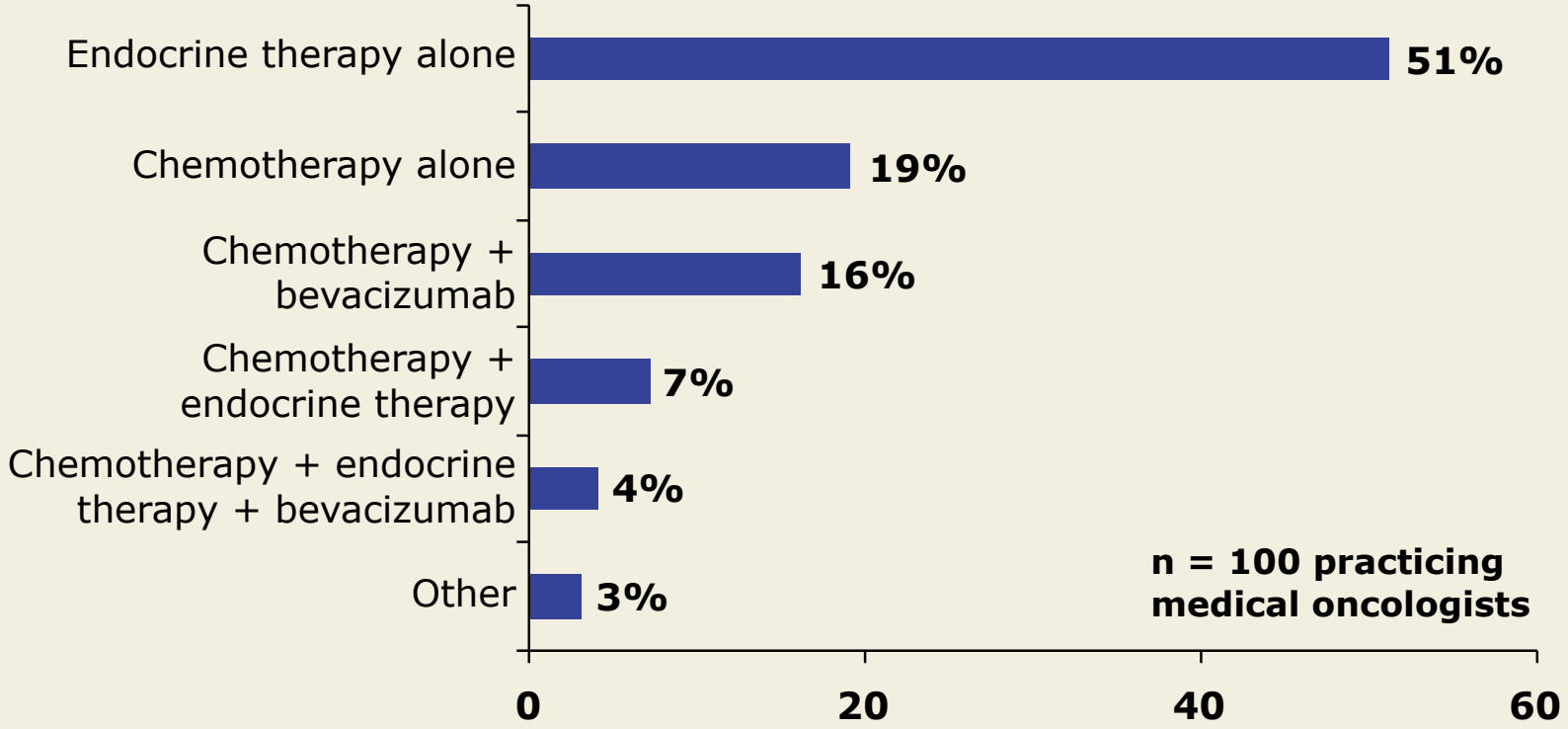
Author Summary

- TTP benefits for fulvestrant 500 mg were significantly greater than those of anastrozole 1 mg with longer follow-up.
  - Patients experiencing disease progression: 61.8% vs 76.7% (p = 0.01)
  - Median TTP: 23.4 months vs 13.1 months (p = 0.01)
- TTP benefit of fulvestrant 500 mg was consistent in all predefined subgroups (data not shown).
- Patients who experience disease progression on either fulvestrant or anastrozole remain sensitive to subsequent endocrine treatments.

Robertson JFR et al. *Proc SABCS* 2010;Abstract S1-3.

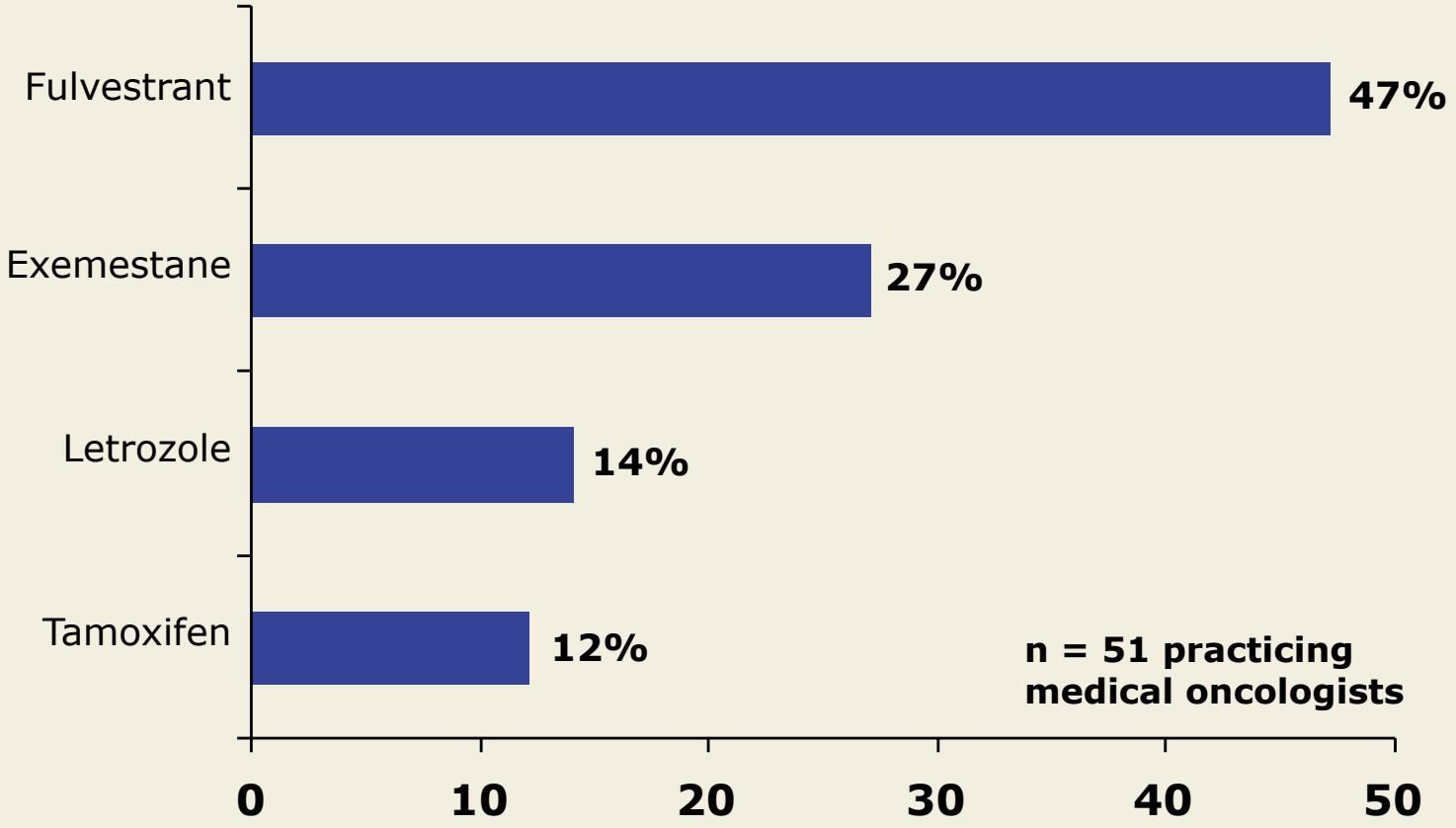
A 60-yo postmenopausal woman with a 2.1-cm ER+/PR+/HER2-, node+ IDC treated with ddAC → T followed by anastrozole develops asymptomatic lung and bone mets

In addition to bisphosphonates, which of the following systemic treatments would you recommend?



Patterns of Care in Breast Cancer, Research To Practice 2010.

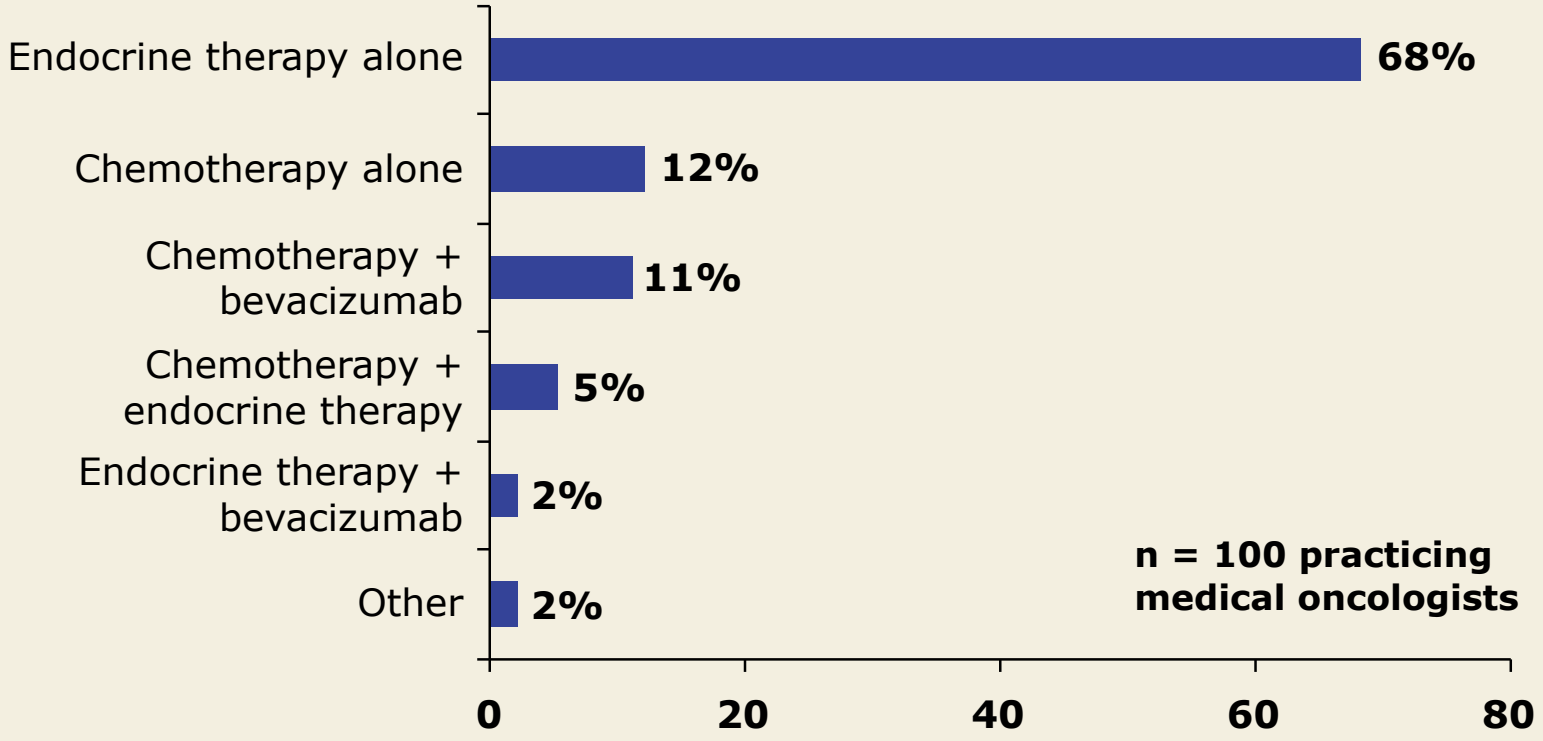
Which endocrine therapy would you recommend for the previous patient?



Patterns of Care in Breast Cancer, Research To Practice 2010.

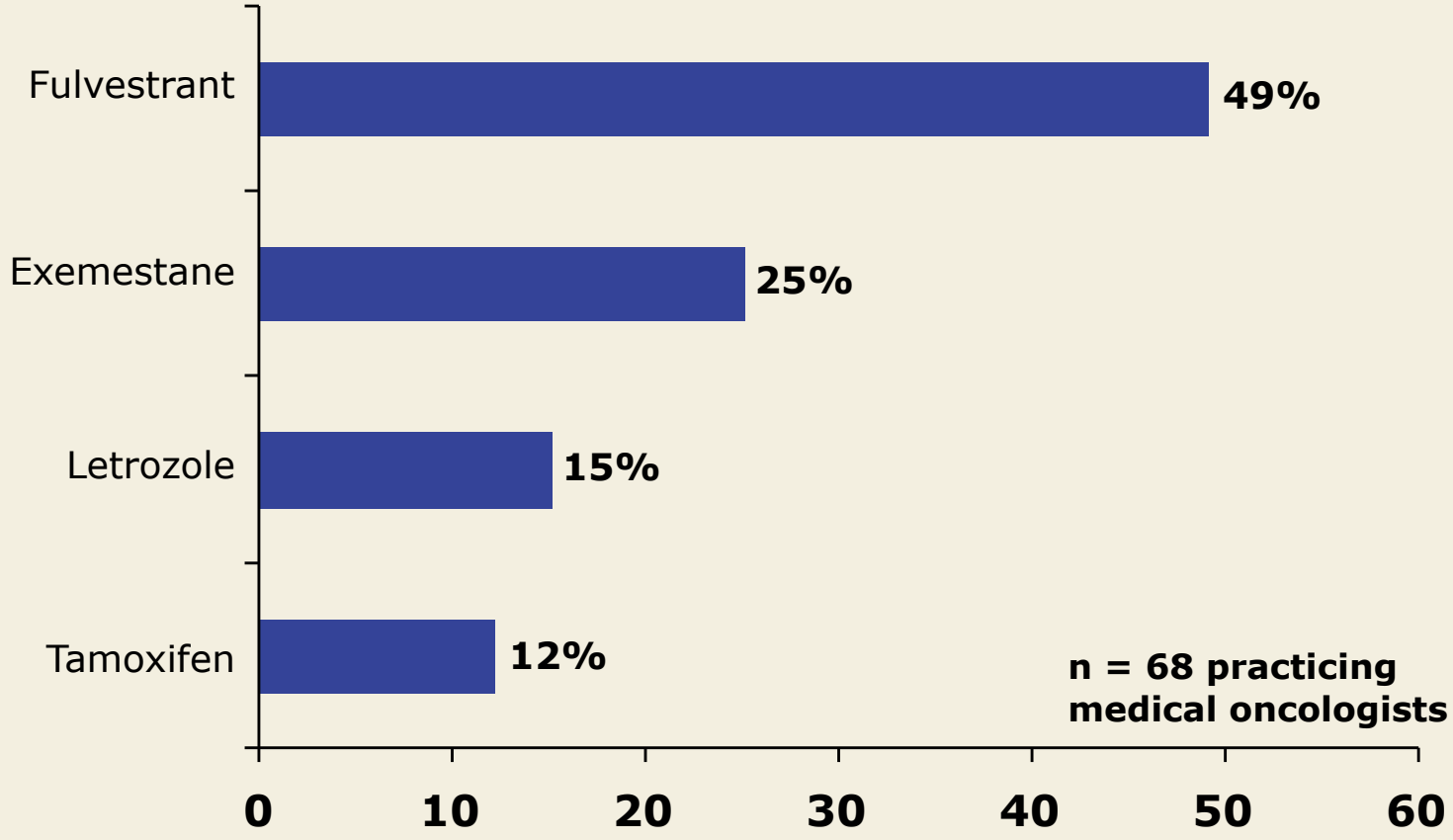
A 75-yo woman with a 2.1-cm ER+/PR+/ HER2-, node+ IDC treated with ddAC → T followed by anastrozole develops asymptomatic lung and bone mets

In addition to bisphosphonates, which of the following systemic treatments would you recommend?



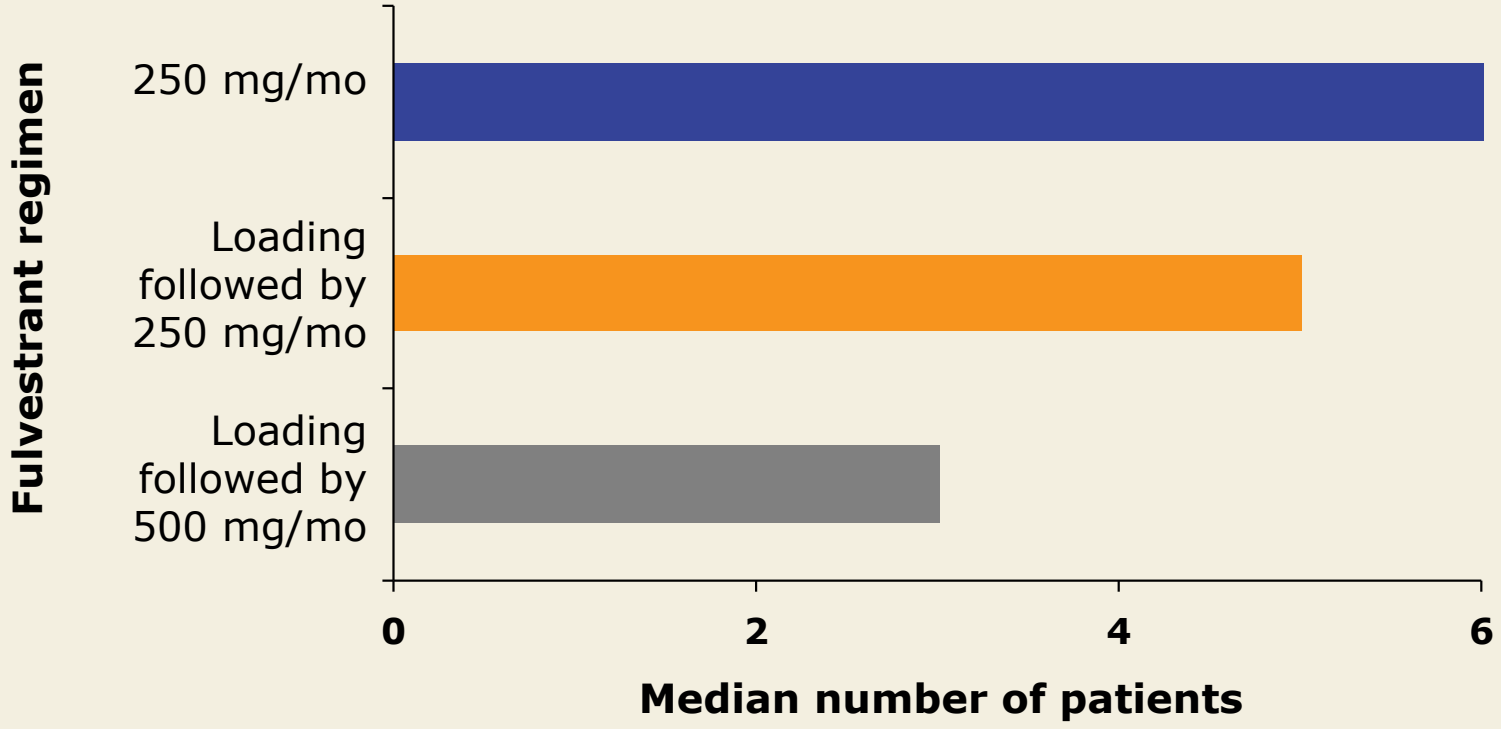
Patterns of Care in Breast Cancer, Research To Practice 2010.

Which endocrine therapy would you recommend for the previous patient?



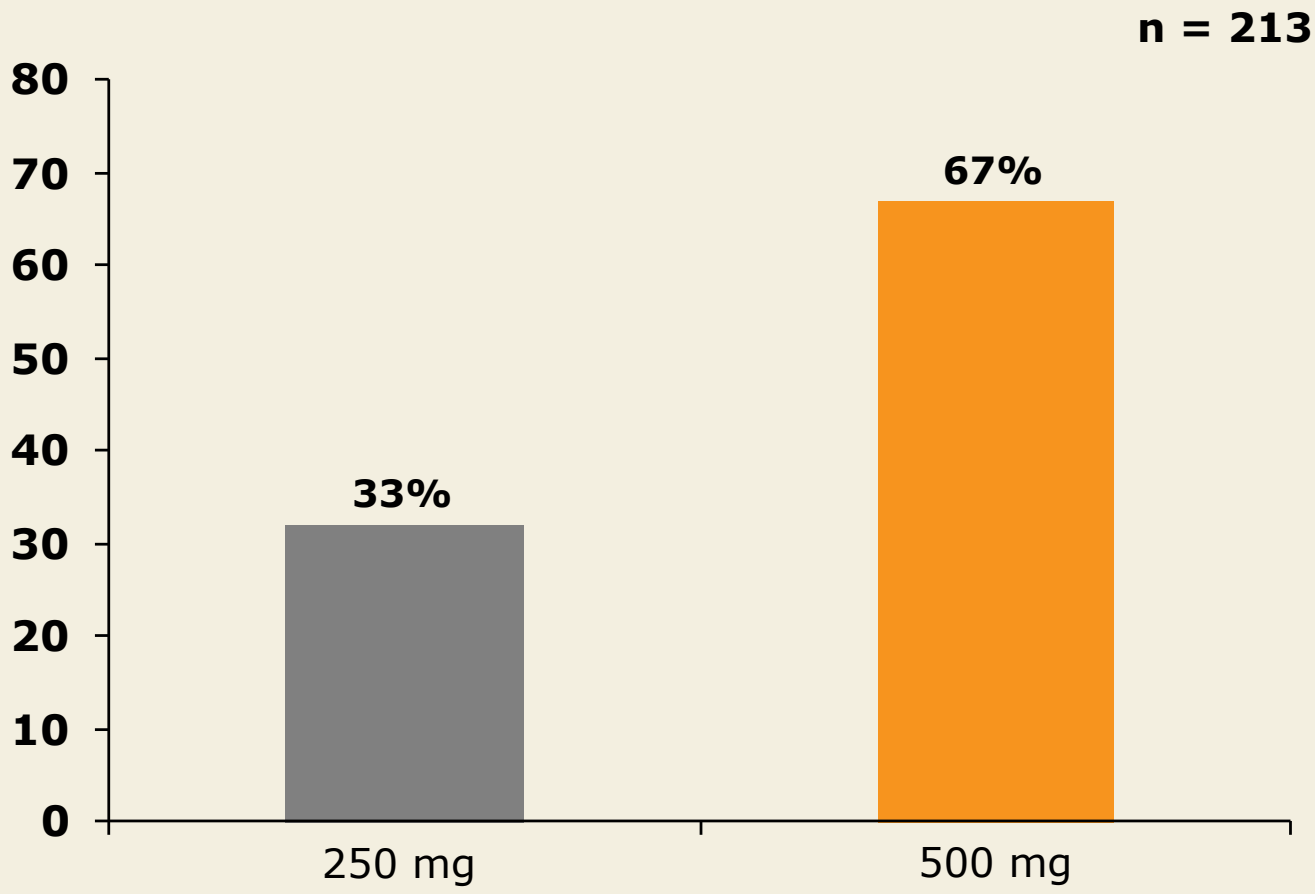
Patterns of Care in Breast Cancer, Research To Practice 2010.

For how many patients have you used the following fulvestrant regimens in the past year?



Patterns of Care in Breast Cancer, Research To Practice 2010.

What monthly dose of fulvestrant do you try to use in metastatic BC, regardless of whether you use a loading dose?



Research To Practice Premeeting Survey, *Real-Life Decisions: Practical Perspectives on the Management of Early and Advanced Breast Cancer*, held at SABCS 2010.

Investigator Commentary: FIRST Study of First-Line High-Dose Fulvestrant versus Anastrozole

FIRST was a randomized, Phase II trial that compared fulvestrant 500 mg to anastrozole as initial treatment for postmenopausal women with ER-positive metastatic breast cancer. In this medium-sized study, the investigators demonstrated that the higher dose of fulvestrant was at least as good as and maybe better than the aromatase inhibitor, with a median time to disease progression of 13 months for anastrozole and 23 months for fulvestrant. The overall response rates were comparable between fulvestrant and anastrozole.

This study provides an opportunity to use fulvestrant earlier in the treatment of ER-positive metastatic breast cancer, as so many of these patients have already received tamoxifen or an aromatase inhibitor as part of their adjuvant therapy. It's not clear if this study redefines the way we will conventionally use these agents, but it's a nice demonstration that fulvestrant is an active agent.

Interview with Harold J Burstein, MD, PhD, December 22, 2010

313 Patients with Breast Cancer During Pregnancy — Results from a Prospective and Retrospective Registry (GBG-20/BIG02-03)

Loibl S et al.

Proc SABCS 2010;Abstract S6-2.

Methods

- **Study design**
  - A registry of retrospectively and prospectively collected data
- **Objective**
  - To increase the evidence for treatment of breast cancer during pregnancy
- **Eligibility**
  - All patients diagnosed with breast cancer during pregnancy independent of treatment and gestational age

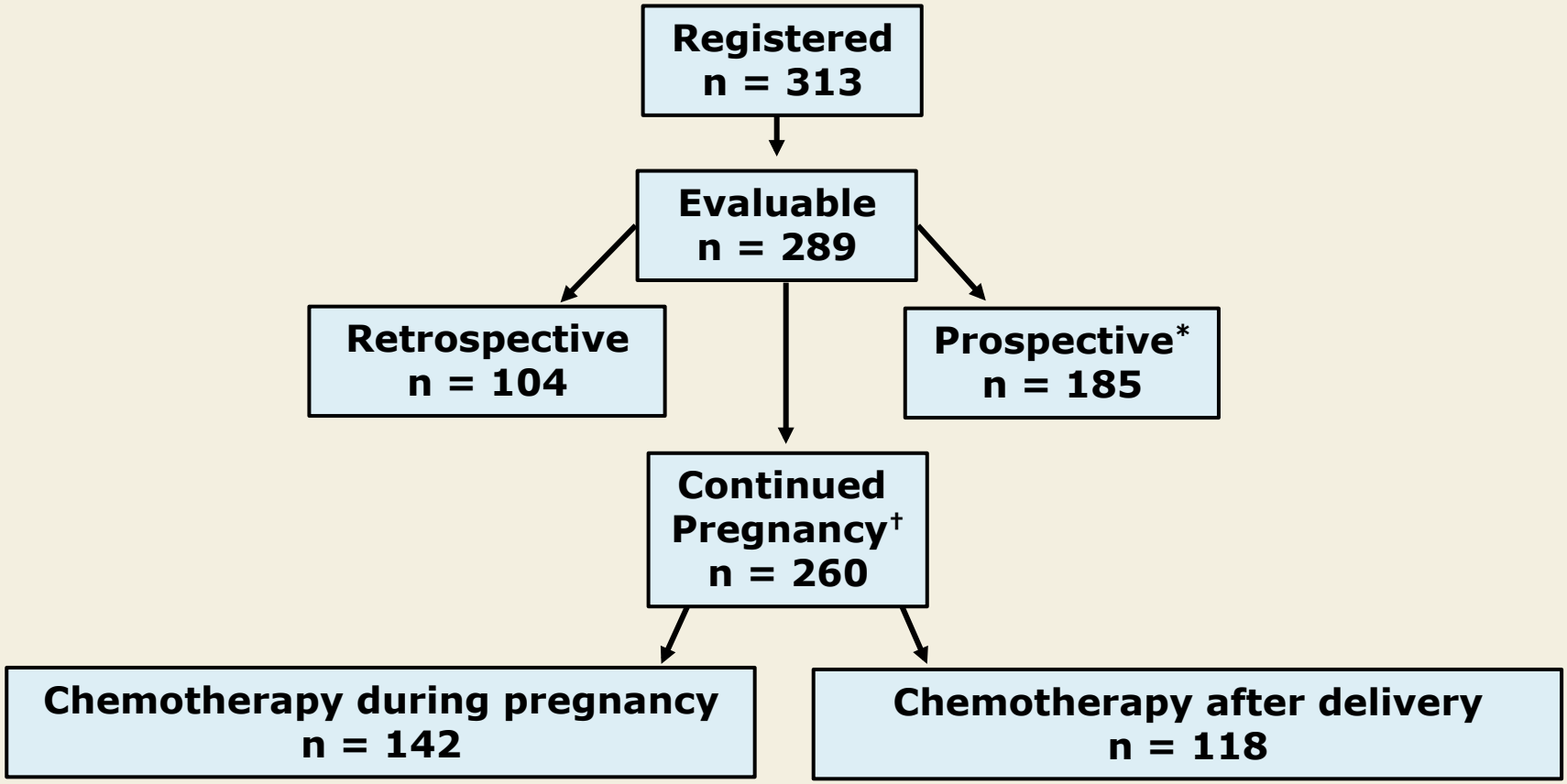
Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

Endpoints

- **Primary**
  - Fetal outcome 4 weeks after delivery
- **Secondary**
  - Maternal outcome of pregnancy
  - Stage at presentation and biological characteristics
  - Breast cancer therapy and type of surgery
  - Mode of delivery (vaginal vs caesarean)
  - Outcome of the newborn 5 years after delivery
  - Breast cancer outcome 5 years after diagnosis

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

Flow Diagram of Patients



* Patients diagnosed after April 2003 were defined as prospective
† Abortion or miscarriage (n = 29)

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

Baseline Characteristics

	All patients n = 260	Chemotherapy during pregnancy n = 142	Chemotherapy after delivery n = 118
Age, median	34 years	34 years	33 years
T-status 1 or 2	69.9%	62.8%	76.2%
Node-positive	48.1%	51.4%	40.0%
Ductal subtype	97.1%	98.6%	95.8%
Grade III	64.4%	63.9%	66.7%
ER-negative	60.9%	59.9%	63.9%
HER2-positive	42.2%	43.0%	42.2%

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

Obstetrical Characteristics

	All patients n = 289	Prospective n = 185	Retrospective n = 104
Time of diagnosis, gestation week	23 weeks	24 weeks	20 weeks
Abortion or miscarriage	10.0%	10.8%	8.7%
Caesarean delivery	48.7%	44.4%	56.1%
Mastectomy	50.4%	49.1%	52.7%

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

Chemotherapy During Pregnancy (n = 142)

Regimen	AC/EC	FE(A)C	CMF	Vinca alkaloids	E/A monotherapy	Taxanes
Patients, n	71	29	14	12	10	6

Cycles	1	2	3	4	5	6	8
Patients, n	8	25	23	52	14	19	1

- A total of 527 cycles were given.
- The median number of cycles was 4.

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

Delivery Outcome

	All patients n = 260	Chemotherapy during pregnancy n = 142	Chemotherapy after delivery n = 118
Time of diagnosis, gestation week	—	20 weeks	28 weeks
Median week of delivery, (range)	36 (30-42)	37 (31-42)	36 (30-42)
Median birth weight	2,772 grams	2,810 grams	2,730 grams
Premature deliveries*	24.0%	16.9%†	33.0%†

* Before 35th week

† $p = 0.009$ for chemotherapy during pregnancy vs after delivery

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

Selected Newborn Events

Events	Chemotherapy during pregnancy (n = 142)	Chemotherapy after delivery (n = 118)	*p*-value
Total*	17 (12%)	8 (6.7%)	0.16
Congenital malformations†	3	1	—
Trisomy-18	1	0	—
Persistent foramen ovale	2	0	—
Infections	4	0	—
Neutropenia	2	1	—
Anemia	2	0	—
Necrotic enterocolitis	1	0	—

*Eight and five newborns that were prematurely delivered experienced an event in the chemotherapy during versus chemotherapy after delivery groups, respectively;†Polydactylia (n = 2), rectal atresia (n = 1), hypospadia (n = 1)

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

Author Summary

- More than 50% of the patients received chemotherapy during pregnancy (median = 4 cycles)
- 77% received an anthracycline-based regimen
  - Only six patients received a taxane during pregnancy
- Premature deliveries were significantly greater in the no chemotherapy group compared to the chemotherapy group (p = 0.009), most likely to allow patients to begin treatment following delivery.
- Fetal outcomes were comparable between the groups treated during or after pregnancy.
  - Total newborn events, 17 vs 8 (p = 0.16)
- Survival outcomes are comparable between patients treated during or after pregnancy (data not shown).

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

Author Conclusions

- Premature delivery increasing fetal morbidity and unfavorable long-term outcome is unnecessary.
- Pregnant patients should receive treatment that follows as closely as possible the standard recommendations for non-pregnant women.

Loibl S et al. *Proc SABCS* 2010;Abstract S6-2.

Investigator Commentary: Breast Cancer During Pregnancy

There is probably no clinical circumstance in breast cancer medicine that's more frightening for the patient and for the doctor than breast cancer during pregnancy, because it can be tougher to diagnose the tumor due to the physiologic changes in the breast that accompany pregnancy and because of the risks that the cancer treatments and diagnostic evaluations might have on the baby. So little is known about breast cancer during pregnancy that almost any meaningful data are welcome.

The German Breast Group collected data from their registry experience to track outcomes of women who were diagnosed with breast cancer during pregnancy. They demonstrated that it is feasible to administer several chemotherapy regimens to patients who absolutely need it during their pregnancy, particularly in the second and third trimesters. The investigators also attempted to characterize how the infants fared who were born having been exposed to chemotherapy. For the most part, no major findings arose of congenital anomalies or major adverse events seen in those infants. Some infants had a variety of short-term medical issues, but we must be concerned that the small sample size makes it difficult to exclude the possibility that chemotherapy didn't have subtle adverse effects on these babies.

Interview with Harold J Burstein, MD, PhD, December 22, 2010

Obesity at Diagnosis Is Associated with Inferior Outcomes in Hormone Receptor Positive Breast Cancer[1]

The Impact of Body Mass Index (BMI) on the Efficacy of Adjuvant Endocrine Therapy in Postmenopausal Hormone Sensitive Breast Cancer Patients; Exploratory Analysis from the TEAM Study[2]

Multivariate Analysis of Obesity and Disease Free Survival in Patients with Nodal Positive Primary Breast Cancer – The ADEBAR Trial[3]

[1]**Sparano JA et al.**
Proc SABCS 2010;Abstract S2-1.
[2]**Seynaeve C et al.**
Proc SABCS 2010;Abstract S2-3.
[3]**Hepp P et al.**
Proc SABCS 2010;Abstract S2-2.

Obesity at Diagnosis is Associated with Inferior Outcomes in Hormone Receptor Positive Breast Cancer

Sparano JA et al.

Proc SABCS 2010;Abstract S2-1.

Objectives and Study Characteristics

Objectives: Determine relationship between obesity (BMI > 30 kg/m^2) and clinical characteristics, clinical outcomes (DFS and OS) and clinical outcomes by breast cancer subtypes

ECOG trials included in the meta-analysis			
Trial, (n)	E1199 (n = 3,484)	E5188 (n = 1,502)	E3189 (n = 613)
Population	Node-positive and high-risk node negative	ER-positive, node-positive; premenopausal	ER-negative, node-positive
Chemotherapy	AC-taxane	CAF	CAF vs 16-wk regimen
Endocrine therapy	TAM or TAM/AI	None vs goserelin vs goserelin + TAM	None
Median age (years)	52	43	47
Obese (BMI >30)	38%	25%	31%

AI = aromatase inhibitor; BMI = body mass index; DFS = disease-free survival; OS = overall survival; TAM = tamoxifen

Sparano JA et al. *Proc SABCS* 2010;Abstract S2-1.

Multivariate Analysis (E1199)

Obese vs nonobese	DFS, HR* (95% CI)	OS, HR (95% CI)
All patients	1.10 (0.96-1.26); $p = 0.14$	1.13 (0.96-1.33); $p = 0.15$
HR-positive, HER2-negative	1.23 (1.02-1.49); $p = 0.035$	1.46 (1.15-1.85); $p = 0.002$
HER2-positive	1.07 (0.77-1.47); $p = 0.70$	0.89 (0.60-1.31); $p = 0.55$
Triple-negative	1.01 (0.77-1.33); $p = 0.93$	1.05 (0.77-1.43); $p = 0.75$

* HR = hazard ratio. HR > 1 indicates a worse outcome.

Sparano JA et al. *Proc SABCS* 2010;Abstract S2-1.

Validation in E5188 and E3189

Obese vs nonobese	DFS, HR* (95% CI)	OS, HR (95% CI)
E5188 (n = 1,502) (premenopausal, ER-positive; node-positive)	1.41 (1.19-1.67); $p < 0.0001$	1.51 (1.24-1.83); $p < 0.0001$
E3189 (n = 613) (ER-negative; node-positive)	0.90 (0.70-1.16); $p = 0.41$	0.83 (0.63-1.09); $p = 0.18$

* HR > 1 indicates a worse outcome.

Sparano JA et al. *Proc SABCS* 2010;Abstract S2-1.

Author Conclusions

- Obese patients from E1199 who had ER-positive, HER2-negative disease had inferior outcomes compared to nonobese patients.
- A test for interaction showed obesity and ER-positive/ HER2-negative disease to interact significantly for OS but not DFS (data not shown).
- This observation was validated with data from the two other studies (E5188 and E3189).
- Obesity did not affect the delivery of AC or endocrine therapy (data not shown).
- Lower relative dose intensities were seen for paclitaxel but not docetaxel in obese patients compared to nonobese patients (data not shown).

Sparano JA et al. *Proc SABCS* 2010;Abstract S2-1.

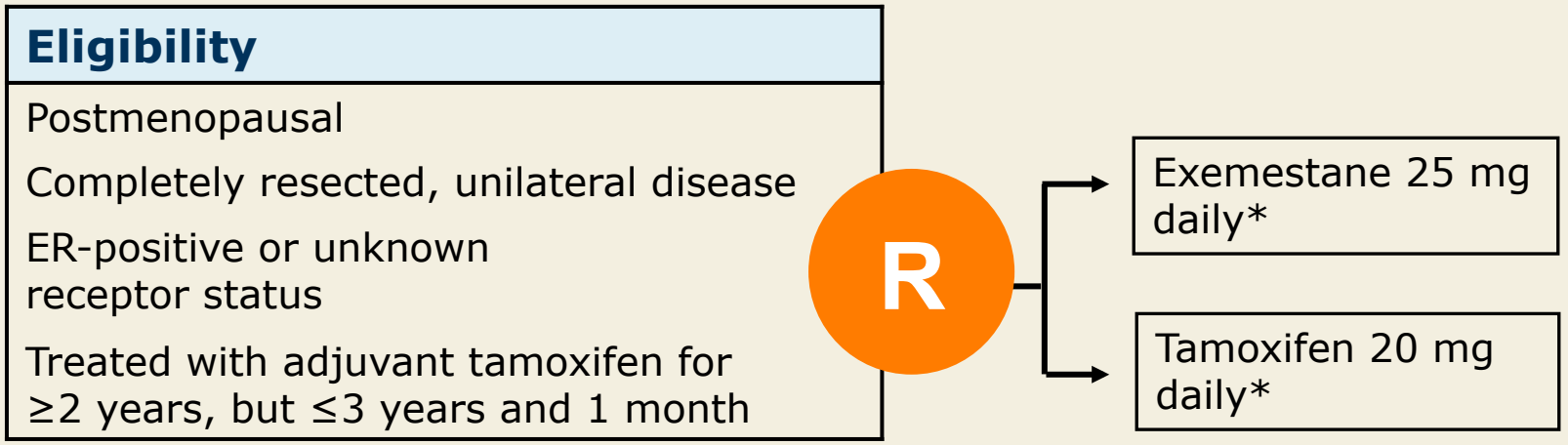
The Impact of Body Mass Index (BMI) on the Efficacy of Adjuvant Endocrine Therapy in Postmenopausal Hormone Sensitive Breast Cancer Patients; Exploratory Analysis from the TEAM Study

Seynaeve C et al.

Proc SABCS 2010;Abstract S2-3.

TEAM Study Design

Accrual: 4,742 (Closed)



Primary objective of current analysis: To conduct a retrospective exploratory analysis of efficacy in relation to BMI in patients from the TEAM study.

* For 2 to 3 years in order to complete a total of 5 years of adjuvant endocrine treatment (ie, prerandomization treatment plus treatment following randomization)

Seynaeve C et al. *Proc SABCS* 2010;Abstract S2-3; Coombes R et al. *N Eng J Med* 2004;350(11):1081-92.

Recurrence Rates (from Abstract)

2.75-year follow-up*	Normal weight	Overweight	Obese
Exemestane	8.1%	6.8%	7.5%
Tamoxifen	9.1%	8.8%	12.5%
HR (95% CI)	0.91 (0.66-1.24)	0.78 (0.55-1.09)	0.57 (0.39-0.84)†

5.1-year follow-up*	Normal weight	Overweight	Obese
Exemestane	14.8%	15.1%	15.1%
Tamoxifen	17.0%	16.9%	18.3%

* A total of 41 underweight patients were excluded from this analysis
† $p = 0.004$

Seynaeve C et al. *Proc SABCS* 2010;Abstract S2-3.

Author Conclusions

- At 2.75 years, significantly fewer obese patients treated with exemestane had recurrences compared to obese patients treated with tamoxifen (p = 0.004).
  - However, the differences in recurrence rate between the obese treatment groups disappeared by year five.
- There were no significant differences in overall survival or disease-free survival between the BMI groups for either treatment (data not shown).
- These data suggest that BMI may be an important determinant of recurrence rate between patients treated with tamoxifen vs exemestane.

Seynaeve C et al. *Proc SABCS* 2010;Abstract S2-3.

Multivariate Analysis of Obesity and Disease Free Survival in Patients with Nodal Positive Primary Breast Cancer – The ADEBAR Trial

Hepp P et al.

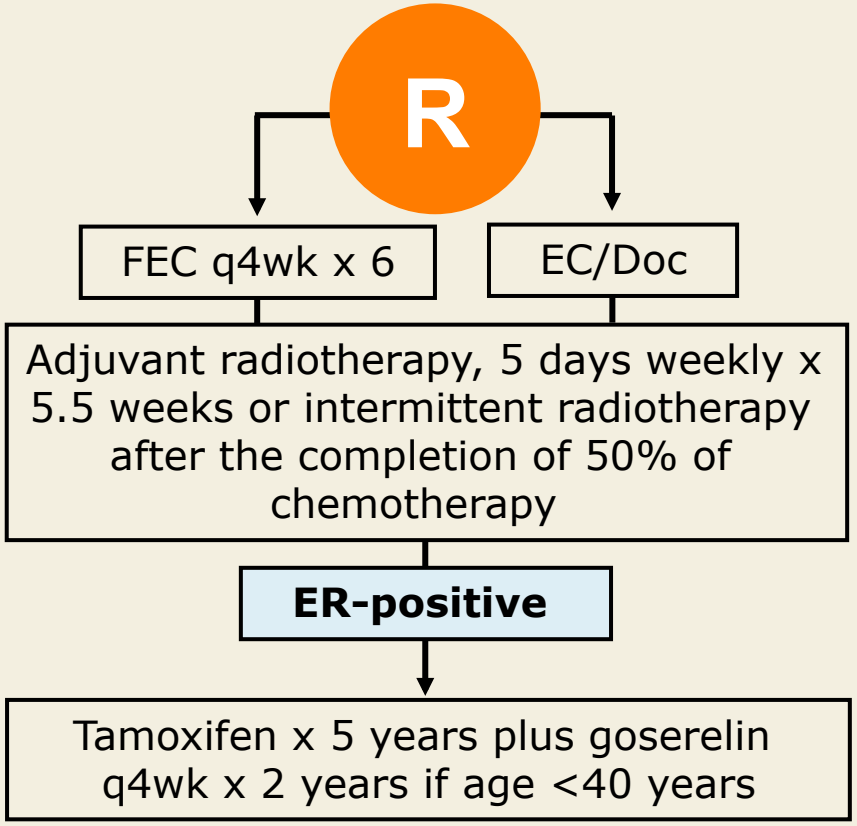
Proc SABCS 2010;Abstract S2-2.

ADEBAR Study Design

Targeted accrual: 447 (Closed)

Eligibility
No inflammatory disease
T1-4, N1-2, M0 with ≥4 metastatic axillary lymph nodes

Primary objective of current analysis:
Retrospective analysis of the ADEBAR trial to determine the impact of obesity on outcomes.



FEC: Fluorouracil and epirubicin on d 1, 8 and cyclophosphamide on d 1-14.
EC/Doc: Epirubicin and cyclophosphamide q3wks x 4, followed by docetaxel q3wks x 4.

Hepp P et al. *Proc SABCS* 2010;Abstract S2-2; ClinicalTrials.gov Identifier NCT00047099.

Results

Distribution of enrolled patients:
Underweight (BMI<18.5 kg/m^2), 1% (n = 13)
Normal weight (BMI 18.5-25.0 kg/m^2), 40.9% (n = 557)
Overweight (BMI >25 to <30 kg/m^2), 36.1% (n = 491)
Obese (BMI >30 kg/m^2), 22% (n = 300)

Groups compared	Disease-free survival	Overall survival
Normal BMI vs overweight	p = 0.786	p = 0.452
Overweight vs obese*	p = 0.008	p = 0.014

* Obese group showed statistically significant worse DFS and OS outcomes compared to the overweight group.

Comparisons between treatments (FEC versus EC/Doc) within each BMI group showed no significant differences for disease-free survival and overall survival.

Hepp P et al. *Proc SABCS* 2010;Abstract S2-2.

Author Summary and Conclusions

- Compared to overweight patients, obese patients had significantly decreased rates of disease-free survival (p = 0.008) and overall survival (p = 0.014).
- There were no significant differences between treatments (FEC versus EC/Doc) when comparisons were made within each BMI group for disease-free survival and overall survival.
- A multivariate analysis of overall survival indicated BMI >30 kg/m^2 to be an independent negative prognostic factor (data not shown).
  - Hazard ratio 1.67, p = 0.008
- This analysis implicates an effect of obesity on disease-free and overall survival in patients with early-stage node-positive breast cancer.

Hepp P et al. *Proc SABCS* 2010;Abstract S2-2.

Investigator Commentary: Obesity and Breast Cancer

A number of studies from randomized trials now suggest that obesity is associated with a poorer prognosis in patients with breast cancer and a higher risk of developing breast cancer. In addition, of course, obesity is related to a number of other adverse health outcomes. The pooled analysis from the ECOG investigators is quite striking, and it's clear that it's not good to be obese and have breast cancer.

In the prospective randomized ADEBAR trial of adjuvant chemotherapy, a multivariate analysis demonstrated that obesity was an independent negative prognostic factor, with obesity having a negative effect on survival in patients with node-positive breast cancer.

Data from the TEAM study suggest that obese patients may fare better with exemestane than with tamoxifen. It is interesting to note that data from ATAC indicate that the converse may be true, with higher-weight women faring less well with anastrozole than with tamoxifen. We are all "digging our teeth" into this, so at present I would wait to hear the whole story.

Interview with Kathleen I Pritchard, MD, December 30, 2010